European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Sovrima

International Nonproprietary Name: idebenone

Procedure No. EMEA/H/C/000908

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

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1 BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Santhera Pharmaceuticals (Deutschland) GmbH submitted on 26 July 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Sovrima, which was designated as an orphan medicinal product EU/3/04/189 on 08 March 2004. Sovrima was designated as an orphan medicinal product in the following indication: treatment of Friedreich's Ataxia. The calculated prevalence of this condition was 5 per 10,000 EU population.

The applicant applied for the following indication: "treatment of Friedreich's Ataxia in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years. Sovrima is also indicated in adult Friedreich's Ataxia patients with cardiomyopathy."

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, known active substance.

Protocol Assistance:
The applicant received Protocol Assistance from the CHMP on 28 May 2005. The Protocol Assistance pertained to sought on pre-clinical and clinical development programmes of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:
Rapporteur: Tomas P Salmonson Co-Rapporteur: Concepción Prieto Yerro

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 26 July 2007.
- The procedure started on 15 August 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 01 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 05 November 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 10-13 December 2007 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 December 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 04 April 2008.
- During the CHMP meeting on 21-24 April 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 26 May 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues s to all CHMP members on 09 June 2008.
- During the CHMP meeting on 22-26 June 2008, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.

- During the CHMP meeting on 22-26 June 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21-24 July 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Sovrima on 24 July 2008.

1.3 Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMEA on 7 August 2008 to request a re-examination of the Sovrima CHMP opinion of 24 July 2008.
- During its meeting on 22-25 September 2008, the CHMP appointed Dr. K. Broich as Rapporteur and Dr P. Demolis as Co-Rapporteur.
- The detailed grounds for the re-examination request were submitted by the applicant on 19 September 2008 (Appendix 2 of Final Opinion). The re-examination procedure started on 20 September 2008.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 14 October 2008. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 13 October 2008.
- The CHMP adopted a List of Participants for the Scientific Advisory Group meeting on Central Nervous System (SAG-CNS) meeting to be held on 5 November 2008 together with the List of Question to be addressed by the experts, through written procedure 23 October 2008.
- During a meeting of the SAG-CNS meeting on 5 November 2008, experts were convened to consider the grounds for re-examination. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP.
- The Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 20 October 2008.
- During the CHMP meeting on 17-20 November 2008, the applicant presented an oral explanation before the CHMP on 17 November 2008.
- During the meeting on 17-20 November 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final Opinion recommending the refusal a Marketing Authorisation for Sovrima.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Friedreich's ataxia (FRDA) is a hereditary, neurodegenerative and cardiodegenerative disorder that primarily affects the central nervous system, spinal cord and peripheral nerves, as well the heart and pancreas. Although rare, is the most prevalent inherited ataxia with an overall prevalence in Europe of approximately 1 in 100,000. Review of the literature suggests that there is a North-South gradient in the prevalence, with a higher prevalence in the South of Europe (e.g. Spain 1:21,000) compared to the North of Europe (e.g. Norway 1:100,000). In the North-East of Europe prevalence is even lower (e.g. Finland 1:1,000,000). Males and females are equally affected.
The condition has an autosomal recessive mode of inheritance and is caused by expansions of GAA triplet repeats in the first intron of the frataxin gene. Normal alleles have 40 or fewer GAA repeats, while disease alleles have from around 100 to more than 1700 repeats. The frataxin protein has been shown to be involved in the assembly of iron-sulfur cluster containing enzymes of the mitochondrial respiratory chain which contribute to the generation of cellular energy. Lack of frataxin protein in FRDA patients has been linked to cell-damaging oxidative stress as well as reduced mitochondrial ATP output.
The major manifestations of FRDA are neurological dysfunction, cardiomyopathy and diabetes mellitus. The manifestations vary in part with the number of GAA expansions. Larger GAA expansions, particularly on the smaller allele, correlate with early age of onset, shorter times to loss ambulation, a greater frequency of cardiomyopathy, and loss of reflexes in the upper limbs. Symptoms usually begin between the ages of 5 and 15 but can appear as early as 18 months or as late as 30 years of age. The first symptom is usually difficulty in walking. The ataxia gradually worsens and slowly spreads to the arms and the trunk. Foot deformities such as clubfoot, flexion of the toes, hammer toes or foot inversion may be early signs. Rapid, rhythmic, involuntary movements of the eyeball are common. Most people with FRDA develop scoliosis, which, if severe, may impair breathing. Other symptoms may occur as a result of the hypertrophic cardiomyopathy, especially serious rhythm abnormalities such as tachycardia and heart block. About 20 percent of people with Friedreich's ataxia develop carbohydrate intolerance and 10 percent develop diabetes mellitus.
The rate of progression varies from person to person. Generally, within 10 to 20 years after the appearance of the first symptoms, the person is confined to a wheelchair, and in later stages of the disease individuals become completely incapacitated. Life expectancy may be affected, and many people with FRDA die in adulthood from the associated heart disease, the most common cause of death. However, some people with less severe symptoms of FRDA live much longer, sometimes into their sixties or seventies.

As with many degenerative diseases of the nervous system, there is currently no cure or effective treatment for FRDA. Therefore, there is no approved specific therapy for such condition. However, many of the symptoms and accompanying complications can be treated to help patients maintain optimal functioning as long as possible. Diabetes, if present, can be treated with diet and medications such as insulin. Orthopedic problems such as foot deformities and scoliosis can be treated with braces or surgery. Physical therapy may prolong use of the arms and legs.

As the frataxin abnormality appears to be associated with increased oxidative stress that can be detected by measuring markers of oxidative injury, it is hypothesized that the administration of antioxidants could decrease these markers. However, it remains to be demonstrated that such a change is clinically relevant.
Idebenone [2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone] is a synthetic short chain analogue of ubiquinone (Coenzyme Q10), the vital cell membrane antioxidant and essential constituent of the cellular energy (ATP)-producing mitochondrial electron transport chain (ETC). Idebenone appears to act as an anti-oxidant that also enhances the flux of electrons along the ETC, thereby facilitating the generation of ATP. Based on these effects it has been postulated as a potential therapeutic agent for FRDA. It is an antioxidant with the ability to operate under low oxygen tension situations. Because of its ability to inhibit lipid peroxidation, idebenone could protect cell membranes

and mitochondria from oxidative damage and its antioxidant properties could protect against cerebral ischaemia and nerve damage in the central nervous system.

Takeda Pharmaceuticals initially developed idebenone for the treatment of cognitive disturbances and Alzheimer's disease, approval being granted in Japan in 1986. Due to lack of proven efficacy in Alzheimer's disease in later clinical trials, it was subsequently withdrawn from the Japanese market in 1998. Idebenone was also introduced into the Italian and Portuguese markets for the treatment of cognitive disturbances in 1993. In several European countries FRDA patients can obtain idebenone on a "named patient" basis. The product has also received a limited provisional approval in Switzerland for the treatment of cardiomyopathy in FRDA, where the maximum daily dose is 15 mg/kg.

Data on toxicology, pharmacokinetics, clinical pharmacology as well as safety and efficacy in patients with either Alzheimer's disease or FRDA were generated by Takeda. Santhera Pharmaceuticals (Switzerland) Ltd was granted access to these data by Takeda. This information covers approximately 1000 patients with Alzheimer's disease treated in clinical trials for between 6 and 24 months, and 290 FRDA patients treated in several open and double-blind studies with Idebenone for periods of between 6 and 12 months.

This is a complete application submitted in accordance with Article 8.3 of Directive 2001/83/EC, known active substance. Idebenone has been assigned Orphan Drug Status (EU/3/04/189) by the European Commission on 8 March 2004. According to the COMP, Friedreich's Ataxia was estimated to affect approximately 0.7 in 10,000 persons in the Community at the time when the application was made. The condition was perceived as a chronically debilitating and life threatening due to severe neurological and cardiac complications and short life expectation. In addition, no satisfactory treatment has been authorised in the Community for patients affected by this condition.

The indication for which the applicant initially applied is "*Treatment of Friedreich's Ataxia*".
During the procedure the applicant proposed the following amended indication: "*Sovrima is indicated for the treatment of Friedreich's Ataxia in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years. Sovrima is also indicated in adult Friedreich's Ataxia patients with cardiomyopathy*."

The proposed posology was:

"Patients weighing 45 kg or under: 150 mg three times a day
Patients weighing over 45 kg: 300 mg three times a day

Available clinical data indicate that some patients may benefit from a higher dose as indicated below:

Patients weighing 45 kg or under: 450 mg three times a day.
Patients weighing over 45 kg: 750 mg three times a day."

"Treatment should be initiated by prescribers with experience in FRDA. Adults: If symptoms do not improve or stabilize within 12 months, treatment in adult patients should be reassessed."

2.2 Quality aspects

Introduction

Sovrima is presented as film-coated tablets containing 150 mg of idebenone as active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone K25, magnesium stearate, colloidal silicon dioxide and purified water.
The film coating consists of polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, aluminum lake and purified water.
The primary container consists of high density polyethylene (HDPE) bottles with polypropylene (PP) twist off cap.

Active Substance

The Active substance is idebenone its chemical name is 2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-2,5-cyclohexadiene-1,4-dione according to the IUPAC nomenclature.

Idebenone is yellow-orange crystalline powder. In fact two polymorphs of idebenone are known (form A and B) with different X-ray diffraction patterns and different melting point. It was verified that crystallization leads constantly to form A, whatever the nature of the solvent. Form B is obtained only after melting and re-solidification. Furthermore, it was noticed that with the current manufacturing process only form A is obtained. It can be concluded that polymorphism is not an issue since the two forms are distinguishable by their melting point and their IR spectra and both of these characteristics are controlled at release of the drug substance.

Idebenone is insoluble in water, freely soluble in ethanol, chloroform, diethyl ether and dioxane and slightly soluble in n-hexane. Idebenone is achiral.

Manufacture

Idebenone is synthesised in two reaction steps following purification by re-crystallisation. The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included. Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented.
Structure elucidation has been performed by infrared absorption spectroscopy, mass spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy and ultraviolet spectroscopy. The molecular weight was determined by elemental analysis which is in agreement with the expected molecular weight. The proposed molecular structure was confirmed by X-ray powder diffraction.

Specification

The active substance specifications include tests for appearance (crystalline powder), color (yellow-orange), appearance of a solution 10% in ethyl acetate, identification (IR-KBr, m.p), content of water (Ph.Eur), sulfated ash (Ph.Eur), heavy metals (Ph.Eur), residual catalysts (plasma atomic emission spectroscopy), residual solvents (GC), impurities (HPLC), assay, particle size (laser diffraction) and microbiological limit tests.
It was verified that all specifications reflect the relevant quality attributes of the active substance. The non-pharmacopoeia analytical methods, which were used in the routine controls, were well described and their validations are in accordance with the relevant ICH Guidelines. Impurities were described, classified as process related impurities and possible degradation products, and qualified. Residual solvents were satisfactorily controlled in the active substance according to the relevant ICH requirements. Certificates of analyses for the active substances were provided and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

Stability

The stability results from long-term and accelerated studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. During the stability studies the following parameters were controlled: appearance, content of water, related substances and assay. It was noticed that the test methods applied are those used for release of the drug substance. Following the stability studies was concluded that the active substance is very stable substance, in particular in the solid state. However, in aqueous buffers, degradation was observed at high pH-values, but after irradiation with a Xenon light source no decomposition was observed in solid state. The results of the long-term and accelerated studies fulfil the proposed specification. Therefore, the results justify a retest period proposed by the company in the intended packaging

Finished Product

Pharmaceutical Development

All information regarding the choice of the drug substance and the excipients are sufficiently justified.
Sovrima film-coated tablets were developed in two tablet strengths (60 mg, 150 mg) which were used in clinical trials. However, only one tablet strength (150 mg) was applied for with the present Marketing Authorisation application.

Idebenone was previously developed for the treatment of cognitive disorders (45 mg). This dosage form has been on the market for many years without any known problems related to manufacture, dissolution and stability. Therefore, as a starting point a 45 mg film-coated tablet of idebenone was developed, with cores of the same qualitative composition as the previous tablets. It was noticed that the use of a classical mixture of iron oxides was not adequate for the film-coat, since patients suffering from Friedrich's ataxia typically show a modification of their iron metabolism. In this context, other mixture (polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide, aluminum lake and purified water) was selected for the film-coat. However, this mixture contains sunset yellow as colorant, which shows a similar color as idebenone. Therefore, the obtained film-coat was sufficient for blinding of formulations used in clinical trials and to avoid potential discoloration of the film-coat by the active substance. Nevertheless, during the assessment a concern was raised with regard to the use of this particular colorant, since Sovrima might be used in the paediatric population. In this context it was ultimately agreed that, in the event of a positive opinion and authorization, the applicant had to commit to search for and evaluate possible alternatives to the azo-dye sunset yellow. For the clinical development and for commercialization, a film-coated tablet containing 150 mg idebenone was developed. The coating parameters were optimized in order to minimize an increase of hardness and of disintegration time and a decrease of the dissolution rate. The relevant process parameters were investigated in order to achieve acceptable dissolution rates. Furthermore, for the clinical trials a formulation of a film-coated tablet containing 60 mg was developed as well.

It was noticed that all the excipients used are well known and commonly used in the pharmaceutical industry. Statements of the suppliers of lactose on the risk of BSE/TSE were provided.

Manufacture of the Product

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as mixing, blending, compressing and coating.
Furthermore, the equipment used is commonly available in the pharmaceutical industry. It was demonstrated that there are no critical steps in the manufacturing process.
The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

Product Specification

The finished product specifications were established according the ICH guidelines and include the following tests: shape, colour, average mass, identification, assay, impurities (HPLC), uniformity of weigh (PhEur), dissolution and microbial limits (Ph Eur).
It was verified that no new impurities have been arising compared to the active substance and the specifications have been justified.
All analytical procedures that were used for testing the finished product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the relevant ICH guidelines.
The batch analysis data for three pilot scale batches confirm that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of the finished product.

Stability of the Product

The stability studies were conducted according to the relevant ICH guidelines. Three full-scale batches have been stored at long term, intermediate and accelerated conditions. All batches were packed in the proposed market packaging. It was verified that the following parameters were controlled: colour, content of water, related substances and assay were determined and the same analytical procedures as for the release analysis were used. It was noticed that the stability of the active substance was investigated under stress conditions (high temperature, light oxygen and influence of pH).

One production batch per strength was stored for photostability at ICH conditions and the results obtained justify, that no labelled storage condition concerning exposure to light is required.

Discussion on chemical and pharmaceutical aspects

Information on development, manufacture, control of the active substance and the finished product has been presented in a satisfactory manner. The results of the tests carried out indicated satisfactory consistency and uniformity of important product quality characteristics. The inclusion of the azo-dye in the tablets composition remained an unresolved issue at the time of the opinion.

Non-clinical aspects

Introduction

Idebenone was originally developed by Takeda Pharmaceutical Company Limited, which evaluated the non-clinical aspects of the product to support its use in cognitive impairment. Many of these studies are described in the published literature. In addition, Santhera Pharmaceuticals GmbH recently performed additional non-clinical studies covering a package of Safety Pharmacology studies in compliance with GLP and designed to conform with ICH Guideline S7A, two 28 day repeat dose toxicity studies in rats and dogs, and a standard battery of genotoxicity tests conforming to the ICH Guidelines S2A and S2B.
All pivotal toxicity studies, including new safety pharmacology studies, were performed in accordance with Good Laboratory Practice (GLP) principles. Most toxicology studies were conducted in accordance with applicable study guidelines and in compliance with regulations.

Pharmacology

Idebenone is a synthetic analogue of ubiquinone (coenzyme Q10) and functions as an electron carrier in the mitochondrial ETC, thus increasing the production of ATP (Sugiyama and Fujita, 1985; James *et al.*, 2005). Idebenone also inhibits lipid peroxidation and protects cell membranes and mitochondria from oxidative damage (Suno and Nagaoka, 1984a, 1984b). The proposed mode of action, which was supported by the data submitted, is that idebenone is reduced by complex I to 2H-idebenone which can return electrons to complex III, thereby facilitating the generation of ATP.

Primary pharmacodynamics

The pharmacodynamic effect was supported in appropriate *in vitro* and *in vivo* models at clinically relevant concentrations/dosages including a genetically-modified mouse model of FRDA.
In *in vitro* phamacodynamic studies using isolated mitochondria from heart and brain tissue, the reduced form of idebenone inhibited lipid peroxidation and swelling of mitochondria. Almost complete inhibition lipid peroxidation was observed at a concentration of 200 μM (EC_{50} 50 μM). None of idebenone main metabolites (QS-4, QS-6, QS-10) could prevent lipid peroxidation to the same extent. The inhibition of lipid peroxidation by idebenone was improved in the presence of the substrates for mitochondrial respiration.
In relation to the intended indication, a study in the ischemic rat heart model showed that idebenone can activate the energy metabolism of cardiac muscle and also improve cardiac function after reperfusion. *In vitro* studies further showed that idebenone can protect cultured fibroblasts derived from FRDA patients from cell-damaging oxidative stress thereby increasing cellular survival. Idebenone restored enzyme activities of the mitochondrial respiratory chain in heart biopsies of FRDA patients.
In vivo, the systemic effect of idebenone was tested in a genetically-modified mouse model of FRDA generated by targeted deletion of the frataxin gene in striated muscle. The Frda/MCK mutant mouse, like FRDA patients, develops a hypertrophic cardiomyopathy which eventually evolves into a dilated cardiomyopathy. Idebenone-treated Frda/MCK mutant mice exhibited a reduction in the left ventricular hypertrophic process (-24% measured as left ventricular mass; $p<0.01$) and a reduction of the left ventricular diameter (-16%; $p<0.01$) at Week 6 (i.e. after 3 weeks of 90 mg/kg/day of idebenone) compared to placebo-treated Frda/MCK mutant mice. The delay in the onset of the cardiac alterations was about 1 week and idebenone increased the life span of the Frda/MCK mutant mice by 10% ($p<0.012$; N=15/group) with an average survival rate of 79±9 days versus 71±9 days for placebo-treated animals. The results from this study indicated that idebenone improves cardiac parameters in FRDA mutant mice in a precise time window (5-6 weeks old FRDA mutant mice), after the onset of the disease but just before the collapse of Fe-S enzyme activities. In summary, idebenone showed an effect on mitochondrial function in the FRDA mouse model. The administered effect dose (90 mg/kg/day) in the FRDA mouse model is in the same range as the clinical dosages (32-50 mg/kg/day).

In addition, the protective actions of idebenone on ischemic cardiac muscle were investigated in anesthetized dogs with coronary stenosis**.** Idebenone, administered intravenously for 30 minutes after stenosis was initiated, dose-dependently reduced the S-T interval. At 5 mg/kg idebenone, suppression was nearly complete reaching levels approaching those of pre-stenosis conditions almost immediately after drug application. These reduced levels were maintained for the duration of the experiment (60 minutes). Since idebenone suppressed the increase of the S-T interval in the ischemic region of the heart but did not show an effect on systemic blood pressure, heart rate and coronary flow, it can be concluded that idebenone seems to improve the energy metabolism of the cardiac muscle mitochondria in the ischemic region of the dog heart.

Secondary pharmacodynamics

Secondary pharmacodynamic studies (in various animal models).
Such studies showed that idebenone inhibits the development of stroke and renal vascular lesions associated with severe hypertension. Idebenone had an ameliorating effect on neurological deficits (i.e. onset of stroke, survival time) related to cerebral ischemia. In normal rats, idebenone did not alter brain concentrations of acetylcholine (ACh) or choline in a dose range of 10-100 mg/kg, i.p. However, a significant decrease in ACh and an increase in choline occurred in various brain regions of ischemic rats. Pre-treatment with idebenone (10 mg/kg, i.p.) inhibited these changes due to ischemia in forebrain regions.

Safety pharmacology programme

No safety concerns of relevance for the human situation were observed in animal safety pharmacology studies. Idebenone (300-1000mg/kg) had no or only minor effects on either the central nervous system or somatic nervous systems. There were not remarkable undesired effects in behaviour, spontaneous locomotor activity, skeletal muscle coordination, barbiturate sleeping time, electroshock or metrazol-induced seizures, pain responses, spontaneous EEG and behaviour in conscious cats, spontaneous EEG in gallamine-immobilized cats, spinal reflex in anaesthetised cats and neuromuscular junction in rat isolated phrenic nerve-diaphragm preparations.
The only finding was a slight decrease in body temperature observed at 300 mg/kg, orally, assessed of low clinical relevance. No effects were seen on intestinal transport in mice and on gastric secretion in rats. Spasmolytic effects of Idebenone were observed in vitro in smooth muscle preparations at high concentrations (10^{-5} – 10^{-4} M), which over (> 140 times) the maximum human plasma concentration of parent Idebenone following a dose of 750 mg (23.6 ng/ml) three times a day (t.i.d.). However, idebenone significantly inhibited the tail currents of the hERG channel with an approximate IC20 of 0.17 µM a concentration of >7.4 times the maximum idebenone plasma concentrations following 750 t.i.d. in humans. *In vivo*, in the dog telemetry study, no effects on QT interval or other ECG parameters were observed at doses up to 500 mg/kg. The bioavailability of idebenone was, however, low in this study. In a 28-day repeated-dose toxicity study in dogs with oral dosing of 500 mg/kg, ECGs recorded at T_{max} 3h after dosing in Week 4, demonstrated no effect on the QTc interval. No adverse cardiovascular effects were noted in the safety pharmacology studies.

Pharmacodynamic drug interactions

No specific non-clinical (or clinical) pharmacodynamic drug interaction studies were performed.

Pharmacokinetics

Absorption

Idebenone was well and rapidly absorbed in the species tested (rat, mouse and dog). After a single dose 91% was found to be absorbed in rats and 62% in dogs, t_{max} occurred within 1 hour. However, due to a high first pass metabolism, less than 1% of parent idebenone reaches the systemic circulation. Concentrations of parent idebenone in plasma were considerably lower than the concentrations of metabolites, and detectable in plasma only during a short period of time. Thus, no half life was calculated on parent idebenone in any species. The terminal half lives of total radioactivity in plasma of rats and dogs after oral administration of [^{14}C]idebenone were 4.5 and 15.4 hrs, respectively.
At higher doses, systemic exposure did not increase in proportion to dose. The dose levels at which this nonlinearity started differed between species and studies. In dogs, systemic exposure in terms of AUC_{0-24} increased proportionally to the dose, up to 100 mg/kg, while C_{max} did not increase

proportionally, in the dose range 10 to 500 mg/kg. In rats, C_{max} increased proportionally up to 500 or 1000 mg/kg depending on study. Different analytical methods together with large variability in exposure data make the interpretations of nonlinearity highly uncertain. No time dependent effect on systemic exposure was shown and no difference between gender was seen with regard to parent idebenone. Administration of idebenone suspension in fed condition increased bioavailability considerably in dogs, the rate of absorption increased (t_{max} = 8h) and the systemic exposure in terms of mean C_{max} and AUC_{0-24} increased 14-and 45-fold, respectively. This was also seen in humans given fat rich food although the increase in bioavailability was not as pronounced.

Distribution

More than 99% of idebenone is bound to plasma proteins in all species tested including humans. A smaller fraction <25% was bound to lipoproteins and the remainder to albumin and other protein(s). The distribution radioactivity to erythrocytes was ≤ 10% in rats and dogs.
Highest concentrations of radioactivity after oral administration of [^{14}C]idebenone, were found in liver, kidney, blood, lung, spleen, skeletal muscle, thymus, stomach and intestine. No accumulation was seen in any tissue studied after repeated dosing. Parent idebenone distributed to brain and the highest concentration of idebenone and the active metabolite QS-10 was evident in cerebellum. Conjugated idebenone and metabolites were also detected in brain at concentrations approx 10 times higher than the parent idebenone. Distribution of idebenone and/or its metabolites to placenta and foetal tissues was demonstrated. The levels of radioactivity in fetal plasma and tissues at 2 and 6 hrs after administration were about 20% of the levels in maternal plasma. Idebenone and/or its metabolites were also excreted into milk in moderate amounts.

Metabolism

Idebenone is eliminated mainly via metabolism. A high first pass metabolism occurring in liver and intestinal mucosa results in that < 1% of idebenone reaches systemic circulation. The metabolism of idebenone includes oxidation and shortening of the side chain resulting in the metabolites QS-10, QS-8, QS-6 and QS-4. These metabolites including the parent compound is further modified by conjugation (glucuronidation or sulfatation) resulting in conjugated forms of the metabolites as well as the parent compound. The metabolism profile between species differ quantitively but not qualitatively.
The main metabolites in rats were sulfate conjugates of QS-4, QS-6 and QS-10. In dogs, the main metabolites in plasma were sulfate conjugate of idebenone and QS-4. The predominant metabolites in human plasma were identified as the sulphate conjugate of idebenone and the O-desmethylated glucuronic acid conjugate of QS-10 glucuronide. No human specific metabolite has been identified. Thus, the species chosen for toxicity studies are considered acceptable.

Excretion

At 72 h after oral or intravenous administration of [^{14}C]idebenone, elimination of radioactivity was almost complete. The main excretion route of idebenone and/or its metabolites was via urine in rats and dogs, which accounted for approximately 60 to 70 % of the dose. The main metabolites in urine of rats were sulfate conjugate of QS-4, QS-6 and QS-10. In dogs, the main metabolites were sulfate conjugate of idebenone and QS-4. In humans, approximately 80% of the dose was found to be excreted via urine, and major metabolites were the glucuronic acid and sulphate conjugates of QS-4.

PK drug interactions

The potential for inhibition of human Cytochrome P450 enzymes (CYP1A2, CYP2D6, CYP2E1, CYP2C9, CYP2C19, and CYP3A4) by idebenone was investigated in human liver microsomes *in vitro* (study 904600). The liver microsomes were supplied from several donors and frozen in -80 prior to the test procedure. A dose-related inhibition of at least 50% of CYP2C19 was detected at idebenone concentrations up to 1 µg/ml (IC_{50}=0.81 µg/ml). At least 50% inhibition of CYP1A2, CYP2D6, CYP2E1 and CYP3A4 activities was detected at idebenone concentrations between 1 to 5 µg/ml. CYP 2C9 was not inhibited at concentrations up 1000 µg/ml idebenone. No pharmacokinetic drug interaction studies with idebenone were performed *in vivo*.
Considering the human exposure at maximal therapeutic levels, the risk for inhibition of CYP2D6, CYP2E1 and CYP3A4 seemed low. A risk of inhibition of CYP1A2 and CYP2C19 could not be excluded and the risk for PK interactions was further evaluated in clinical pharmacokinetic studies (see "Pharmacokinetic interaction studies" in the Clinical Aspects section 3.4).

Toxicology

Single dose toxicity

Single dose toxicity was studied in mice and rats after oral, subcutaneous and intraperitoneal administration. The acute toxicity of idebenone was low in both species, where the LD_{50} was ≥ 10000 mg/kg after oral and subcutaneous administration. After intraperitoneal administration the average LD_{50} was above 700 mg/kg in mice and above 800 mg/kg in rats.
The acute toxicity of the main metabolite QS-4 was also studied, revealing lower LD_{50} than for the parent drug: values of 490 mg/kg and 1410 mg/kg were measured in mice after i.p. and oral administration respectively. In rats, the LD_{50} of the QS-4 metabolite was 420 mg/kg and 5490 mg/kg after i.p. and oral administration respectively.
The clinical signs of acute toxicity were essentially the same after administration of idebenone or QS-4; however, respiratory depression was seen in both rats and mice after administration of QS-4 but not after administration of idebenone.

Repeat dose toxicity (with toxicokinetics)

Idebenone was extensively tested in oral repeat-dose toxicity studies in mouse (3 months), rat (up to 12 months) and dog (up to 12 months). In studies ≥ 3 months, mice, rats and dogs were exposed to idebenone doses (oral / oral diet) up to 2000, 2500 and 500 mg/kg/day, respectively. Coloured urine due to coloured metabolites was observed in all three species. Coloured faeces were also seen in dogs occasionally.
In mice and rats, the main effect of idebenone was local changes in the forestomach mucosa. Yellow colouration and mucosal thickening of the forestomach, occasionally accompanied by forestom ach dilatation and appearance of red spots in the fore- and glandular stomach was observed at necroscopy. The histopathological findings comprised of dose-dependent increase in incidence/severity of submucosal inflammatory infiltrates, erosions and ulcerations of the forestomach, and hyperkeratosis and epithelial and basal cell hyperplasia, focal necrosis and oedema. In addition, degeneration and/or hyperplasia of the mucosal epithelium in the glandular stomach was observed in single rats. Oedema of the submucosa in the glandular stomach was also noted in single rats dose with 500 mg/kg/day for 26 weeks. In conclusion, in the mouse and rat subchronic and/or chronic studies the target organ was the forestomach, a rodent-specific organ with low clinical relevance for the human situation., the NOAEL (forestomach findings) was 640 mg/kg/day and approximately 20-160 mg/kg/day in mice and rats, respectively, giving exposure margins of 4-6 in mice and in the range of 1-30 in rats, compared to the highest recommended dose in man.
A high incidence of pituitary tumours/hyperplasia and mammary fibroadenomas/carcinomas was observed in female rats (oral diet) of the highest dose (160 mg/kg/day) in the 52-week study (C-14-434). Nevertheless, in the light of new historical data provided by the applicant, including incidences of pituitary and mammary tumours from the performing CRO Hazleton Laboratories around the time when the study was performed (circa 1984-1989), the reported findings were considered to be due more to a spurious finding than to a treatment related finding. Further reassurance was provided by data resulting from carcinogenicity experiments in rats and mice where no similar findings were reported.
In dogs, no systemic toxicity and therefore no target organ was identified. The only effects in this species were clinical signs, including gastrointestinal disturbances such as loose faces, diarrhoea and emesis, which limited the maximum repeatable dose to 500 mg/kg/day (NOAEL). The exposure margin was in the range of 8-200 compared to the highest recommended dose in man. Treatment of dogs with idebenone was associated with statistically significant changes in some haematology, clinical biochemistry and organ weight parameters but, since no clear patterns were evident and the observed deviations remained within the normal physiological limits, these changes were considered to be of no toxicological relevance.
Data from the more recent 28-day repeated dose toxicity studies corresponded well with the findings reported for the previous studies. There were only minor quantitative differences between the toxicity profiles of idebenone identified in the two sets of studies using materials from two different sources.
The toxicity of QS-4, the major metabolite of idebenone, was evaluated in a 5-week study in male rats, using intraperitoneal doses up to 45 mg/kg/day. No animal died, and no treatment-related abnormalities were observed at any dose tested. However, no conclusions could be made in comparison to idebenone-treated rats since the highest dose was too low in this study.

In conclusion, in the mouse and rat, the target organ was the forestomach, a rodent-specific organ, a finding considered to be of low clinical relevance. The exposure margins at NOAEL (forestomach findings) were 4-6 (mice, NOAEL 640 mg/kg/day) and 1-20 (rats, approximately 20-160 mg/kg/day) compared to the highest recommended dose in man. In dogs, no target organ could be identified; in this species soft faeces, diarrhoea, salivation and emesis appeared to be dose limiting at doses > 500 mg/kg/dose. The exposure margin at NOAEL (500 mg/kg/dose) was in the range of 8-200 compared to the highest recommended dose in man. Idebenone may be regarded as a relatively safe substance with no major or serious adverse effects. However, a high incidence of pituitary and mammary tumours was observed in rats in the 52-week study (C-14-434), and this was considered to be more a spurious finding rather than a treatment-related effect.

Repeated dosing in mice, rats and dogs showed overall no change in systemic exposure (AUC) of parent idebenone compared to single exposure. No gender difference in exposure with regard to parent idebenone was obvious. In general, a decrease in exposure in relation to dose was seen in rats at doses above 500 to 1000 mg/kg and earlier in dogs around 100 mg/kg. However, the high inter-individual variability in all dosed groups made interpretations of non-linearity uncertain.
The major metabolite QS-4 showed no change in systemic exposure, except for in the 13- and 26-week rat study where AUC increased more than 5-fold from the first to the last week of dosing. There was also a tendency of higher exposure of QS-4 in females compared to males, which was however not consistent through all studies.
The systemic exposure between studies at the same doses differed significantly both in rats and dogs (up to 19-fold). Various feeding strategies, formulation and analytical methods could explain partly these differences.

Genotoxicity

The genotoxicity of idebenone was extensively studied according to relevant guidelines *in vitro* and *in vivo*. Idebenone showed no genotoxic potential with respect to gene mutations in bacteria (Ames test, three studies) and DNA damage in the Rec assay. Idebenone gave an equivocal result in the Mouse lymphoma (TK locus) assay and produced positive results in the *in vitro* chromosomal aberration test (in two studies) using human peripheral lymphocytes. As the Applicant claims, the calstogenic effect could be considered to be linked to the cytotoxic effect at high concentrations *in vitro*, which are probably related to the redox properties of the substance. However, the effect could possible also depend on that whole blood cultures (containing lysed blood cells) were used in the *in vitro* chromosomal aberrations tests. In addition, no genotoxic effects were induced in the *in vivo* mouse micronucleus test (two studies with doses up to 5000 mg/kg and one study with doses up to up to 2000 mg/kg), *in vivo* chromosomal aberration test (rat, dosed up to 2500 mg/kg/day) and in the Unscheduled DNA Synthesis (UDS) test in rat liver (dosed up to 2500 mg/kg). For the *in vivo* studies the calculated exposure margins (parent idebenone) in mouse were 7-52 (Cmax) and 289 (AUC) and in rats 15 (Cmax) and 137 (AUC) compared to the highest recommended dose in man.
Taken together, the weight of evidence was sufficient to conclude that idebenone poses no genotoxic potential.

Carcinogenicity

In dietary carcinogenicity studies, mice and rats were treated with idebenone for 24 months at dose levels of 0, 640, 1280, 2000 mg/kg/day in mice, and 0, 500 and 1000 mg/kg/day in rats. The mice showed treatment-related non-neoplastic tissue changes in the forestomach (minimal non-specific histopathological signs of local irritation in the forestomach, mainly epithelial cell hyperplasia and hyperkeratosis) in all idebenone-treated groups (640-2000 mg/kg/day). The rats showed treatment-related non-neoplastic tissue changes in the forestomach (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) in both the idebenone-treated groups (500 and 1000 mg/kg/day).
No treatment-related tumour response was observed in male and female mice and in male rats after idebenone. A low incidence of squamous and basal cell tumours was seen only at the highest dose (1000 mg/kg/day, exposure margins of 108-133) in the forestomach of female rats. It was agreed that

these proliferative findings in the forestomach, a rodent-specific organ, were most likely a consequence of local irritation, and were considered to be of low clinical relevance.
Nevertheless, in a 52-week dietary toxicity study an increased incidence of pituitary tumours/hyperplasia and mammary fibroadenomas/carcinomas was observed in female rats receiving 160 mg/kg/day had when compared with controls. Further reassurance on the more likely spurious origin of these findings rather than treatment-related adverse effects was provided.
Based on parent idebenone PK data, the calculated exposure margins are 10.5 (C_{max}) and 136 (AUC) in mouse at NOAEL (2000 mg/kg/day) and 41-51 (AUC) in rats at NOAEL (500 mg/kg/day) compared to the highest recommended dose in man.

Reproduction Toxicity

In the rat fertility study with doses up to 500 mg/kg/day no effects on male or female fertility were observed but paternal toxicity was noted at the highest dose. In the rat embryo foetal development study with doses up to 1000 mg/kg/day, even at maternally toxic dose levels, no treatment-related changes at external, visceral or skeletal examination in the fetuses were observed.
In the rabbit embryo-foetal development study with doses up to 500 mg/kg/day, no treatment -related teratogenicity was found. Slight maternal toxicity was noted at 150 mg/kg/day such as chromaturia and decreased body weight gain.
In the pre- and postnatal developmental toxicity study in rats, treatment with idebenone had no effects on gestation or parturition. Maternal necropsy showed no treatment-related abnormalities. Maternal dosing had no adverse effects on pup growth and performance and on the offspring's reproductive performance.
In conclusion, idebenone seemed to have no effects on fertility and general reproductive performance, and there was no evidence of embryotoxic or teratogenic potential. The calculated exposure margins for 500 mg/kg (parent idebenone) in rats were 21-28 (AUC_{ss}) and for 150 mg/kg in rabbits were 2 (AUC_{ss}) to the average exposure for the highest recommended dose in men.

Local tolerance

No specific local tolerance studies were performed. The lack of such studies was considered acceptable as the local toxicity findings observed were limited to the forestomach in the rat (tissue species-specific), and no effects were reported in the dog.

Other toxicity studies

Immunotoxicity
Idebenone does not seem to be an immunotoxic compound neither in the repeat dose toxicity studies nor when idebenone was examined by means of the antibody production test in Ta:A/J mice and the active systemic anaphylactic (ASA) test in guinea-pigs.

Dependence
Due to the characteristics and intended use of Idebenone, concerns related to dependence potential are not expected.

Impurities
The total of all impurities (identified and unidentified) was set to a maximum of 1.0% and the specification limit for the mayor impurity of Idebenone - Impurity A - was set to 0.5%. The Applicant performed a package of qualification studies with levels of Impurity A as high as 0.68%, including an Ames test, a mouse micronucleus test and a 4-week toxicity study in rats. Taking into consideration data from these studies, where a increasing level of Impurity A neither increased the toxicity nor changed the toxicity profile of idebenone, Impurity A could be qualified to a specification limit of 0.5%.

Excipients
The excipients are well-known compounds. However, the inclusion of an azo-dye (Sunset Yellow) in a paedriatric population was considered not acceptable, as it is not desirable in formulations intended for a paediatric population, because of its sensitizing potential as well as its alleged role in children developing hyperactivity symptoms.

Photosafety
Idebenone does not absorb light at the wavelengths in the range of 290-700nm. Thus, there is no need for photosafety testing with idebenone.

Ecotoxicity/environmental risk assessment

The Applicant performed an Environmental Risk Assessment (ERA) for idebenone. A log Kow of > 2.99 did not exclude bioaccumulation potential. However, considering the ADME profile obtained in laboratory animals and humans, bioaccumulation was considered to be unlikely.
The applicant provided acceptable published data on the prevalence of the disease Friedreich`s ataxia in Europe. Based on these data the applicant calculated the concentration in surface water (PEC_{sw}) for Sovrima resulting in a value below the trigger value of 0.01µg/l for a phase II environmental fate and effect analysis. However, according to guideline EMEA/CHMP/SWP/4447/00, a calculation of PEC_{sw} has to be based on a market share of 100% for a given product. Thus, according to the guideline EMEA/CHMP/SWP/4447/00 the calculated value of PEC_{sw} exceeds the trigger for a Phase II environmental fate and effect assessment. The applicant's proposal to conduct a Phase II environmental fate and effect analysis for the active substance as a follow-up measure (FUM) was considered an acceptable approach if a positive opinion was to be granted.

2.3 Clinical aspects

Introduction

The clinical development programme for idebenone includes the following main studies:

1. A 6-month double-blind, placebo-controlled study of idebenone in Friedreich's ataxia (NICOSIA study).
2. Four Phase I studies in healthy volunteers.
3. The safety data set from the original Alzheimer programme.

An overview of the clinical studies with idebenone is provided in Table 1.

Table 1. Overview of clinical studies with idebenone.

Study reference	Short title	Study design	Patients entered	Daily dose, (regimen) and duration of treatment
Phase I/II studies in Friedreich's ataxia				
01-N-0167 (NIH)	Phase IA single-dose, dose-escalation pilot safety study	SD, O	79 patients: 27 children, 27 adolescents and 25 adults with Friedreich's ataxia mean age 9.3, 15.1 and 33.4 years respectively	single ascending doses of 2.5 mg/kg/day up to 75 mg/kg/day
04-N-0129 (NIH)	Phase IB multiple-dose pilot safety study	RD, O	15 patients (5 children, 5 adolescents and 5 adults) with Friedreich's ataxia mean age 10.6, 16.0 and 33.0 years respectively	60mg/kg/day for 30 days
NICOSIA study (NIH/Santhera)	Phase II dose-ranging, efficacy & safety study	R, PC, DB	48 patients aged 9-18 years with Friedreich's ataxia mean age ~14 years	t.i.d. dosage, depending on body weight ≤45 kg or >45 kg: Low dose, Group A: 180 or 360 mg/day Mid dose, Group B: 450 or 900 mg/day High dose, Group C: 1350 or 2250 mg/day; Placebo, Group D 6 months

SD: Single-dose; O: open-label; PC: placebo-controlled; DB: double-blind.

In addition to the data derived from the NICOSIA trial, data from a recent open label study with idebenone in FRDA patients performed in Spain (Pineda 2008) and from several published trials with idebenone in FRDA, one of which was double- blind, placebo controlled (Mariotti, 2003) were presented to support the present application of idebenone in FRDA.

At the time of the application the applicant was conducting a Phase III study in Europe (MICONOS trial), designed as a double-blind, parallel-group placebo-controlled study investigating the effects of three dose levels of idebenone versus placebo on neurological and cardiac function for 12 months in patients with Friedreich's ataxia. The study planned to recruit 204 patients in Germany, France, Belgium, the Netherlands and the UK. However, the recruitment rate was slow due to the disease prevalence in the Northern European countries, where the study was conducted, being lower than described in the literature. Additionally, many patients in Europe, particularly in Southern Europe, have access to idebenone through government-sponsored compassionate use programmes and are therefore not willing to join a placebo-controlled study. As of 15th May 2008 a total of 167 patients (137 of which were adults) had been recruited. The study was planned to deliver efficacy data on neurological (primary) and cardiac (secondary) endpoints in the adult population as well as safety data and, based on the current recruitment rate, the results from this trial were expected in late 2010 at the earliest.

In the US, a double-blind, parallel-group placebo-controlled study (US IONIA study) of two doses of idebenone versus placebo in FRDA patients under 18 years of age began in late 2007. This study was requested by the FDA to support the data obtained in the NICOSIA study. The study planned to analyze the effect of idebenone on the International Cooperative Ataxia Rating Scale (ICARS) as the neurological endpoint and to generate further data on neurological and ADL efficacy in paediatric patients. This trial planned to recruit 60 paediatric FRDA patients, and data were expected to be available by 2010.

There are no CHMP guidelines on the clinical development of medicines for the treatment of Friedreich's Ataxia.
Regulatory advice was obtained from the Dutch and Portuguese health authorities in 2004. Protocol assistance was given by CHMP (advice finalised during the plenary meeting held on 23-26 May 2005) concerning different aspects of the clinical development on the MICONOS phase III study with idebenone in FRDA patients with cardiomyopathy and neurological dysfunction that was ongoing at the time of the application (see above) but for which there were recruitment difficulties.

There was no paediatric development programme, but it was not required at the time of submission.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The clinical studies conducted by Santhera and Takeda were stated to be Good Clinical Practice principles compliant. Two Phase I studies conducted by the National Institutes of Health in patients with Friedreich's ataxia, originally not intended for regulatory use, were not fully GCP compliant.

Pharmacokinetics

The phase I clinical pharmacology program consists of 13 studies: 4 single- and multiple-dose studies (also investigating food effect), 4 interaction studies (amitriptyline, fluvoxamine, lithium and donepezil), 1 hepatic and 1 renal impairment study, 1 metabolism and disposition of ^{14}C-idebenone and 1 single- and 1 multiple-dose study in children, adolescents and adults with FRDA. Overall, at least 120 healthy subjects, 12 subjects with renal disease, 12 subjects with hepatic impairment and 94 FRDA patients were evaluated, and a total of 239 subjects reached study completion. No population analyses were performed.
Idebenone and subsequent metabolites were analysed with a HPLC-MS/MS method in plasma and urine. LC and coulometric/electrochemical detection were also used in some of the studies. In PK studies in special populations total idebenone (sum of unconjugated and conjugated idebenone) was analysed but there were no data on the pharmacologically active compound - unconjugated idebenone.
Pharmacokinetic parameters were calculated by using non-compartmental methods and standard statistical methods were applied.

In the phase I programme of the clinical development the 150 mg film-coated tablet intended for marketing was used, whereas a 60 mg film-coated tablet was used in the Phase II study and in the ongoing MICONOS study. Different batches were tested *in vitro* and showed no differences in their *in vitro* dissolution characteristics. Bioequivalence between the two formulations could not be assumed based on the *in vitro* dissolution profiles only (due to the different qualitative and quantitative tablet composition).

Absorption
After administration in fasting conditions, t_{max} of unconjugated and total idebenone was reached within a range of approximately 0.33-5 hours and 0.33-2.67 hours respectively. The absolute bioavailability of unconjugated idebenone was not determined, because no intravenous formulation was administered. The absolute bioavailability was however low, due to a high first pass effect. The absorbed amount was however extensive, although not necessarily in the form of unchanged idebenone, because of signs of gut flora metabolism from *in vitro* studies. No *in vitro* study was performed to evaluate permeability across Caco-2 cells and to determine if any transport protein was involved in the absorption.

After intake of high-fat food, AUC and C_{max} of unconjugated idebenone were increased approximately five to six-fold and four-fold respectively. An increased exposure was also seen after a continental breakfast. Administration with food is recommended in the proposed SPC (section 4.2), due to the very low absorption of unconjugated idebenone without food. The pivotal efficacy and safety study was performed in fed conditions.

Following repeated thrice daily dosing for three weeks with 750 mg (the highest dose), the mean (SD) values of C_{max} and AUC_{0-8} were 22.4 (13.5) ng/ml and 32.2 (19.2) ng x hr/ml, respectively.

Distribution
No determination of the volume of distribution was made since no intravenous formulation was administered. The plasma protein binding of unconjugated idebenone ranged from 93.0-99.7 %. A lower protein binding was observed at the lowest concentration tested; otherwise the protein binding was independent of concentrations. It was unclear what caused the deviation in protein binding at the lowest concentration tested of 1 ng/ml. The major binding protein was albumin (approximately 75 %). No confirmation of the degree of protein binding was made in healthy subjects or in subjects with renal or hepatic impairment.

Elimination
Unconjugated idebenone is metabolised by CYP450 enzymes (mostly CYP1A2, CYP2C19 and CYP3A4) and by conjugation (glucuronidation and sulfatation). CYP450 catalyses shortening of the carbon side chain resulting in QS10, 8, 6, 4 and corresponding conjugates.
In vivo metabolite profiling was performed up to 168 hours. The major metabolites identified in plasma were the sulphate conjugate of idebenone and the O-desmethylated glucuronic acid conjugate of QS-10. In urine, the major metabolites observed were the glucuronide and sulphate conjugates of QS-4. In faeces, there was a low excretion of approximately 7 % of the dose in humans and the metabolites could not be identified. The fraction of total idebenone and total QS10 excreted in urine after oral administration was lower than or just above 1% respectively. Approximately 87 % of the radioactive dose was recovered in urine and faeces. Repeated or a higher dose (up to 750 mg t.i.d.) did not seem to change significantly the metabolite profile pattern.
Since the major portion of the metabolites in plasma constitutes conjugated versions of idebenone, the risk of interactions affecting the CYP metabolism of idebenone was considered to be low.
No true clearance values were available since no intravenous formulation was administered. The mean terminal half-life was approximately 10.8 hours, ≈5 hours, ≈5 hours and 4.4 hours after single oral administration for total idebenone, total QS10, total QS6 and total QS4 respectively. No terminal half-life of unconjugated idebenone could be determined with the sampling schedule applied.
According to the applicant QS10 stands for 10-30 % of the activity of unconjugated idebenone and reassurance that the majority of the activity likely resides with unconjugated idebenone was provided.
The consequences of possible genetic polymorphism were not evaluated.

Variability
A very high variability with respect to both AUC and C_{max} of unconjugated idebenone was found, with CV% up to approximately 100 %. The CV% of total idebenone was lower, approximately 40-50%. No data on intra-individual variability was presented.

Dose proportionality and time dependencies
The pharmacokinetics of idebenone and its related metabolites in healthy volunteers was shown to be dose- and time-proportional for doses between 150 mg t.i.d. and 750 mg t.i.d. (study SNT-I-003). A prolonged half-life after multiple dose administration of total idebenone and total QS4 was observed, however the cause of this deviation could not be explained by an increased volume of distribution or by changes in oral clearance over time.

Target population
Idebenone was administered on a mg/kg basis in the target population studies, and a comparison to the exposure in healthy volunteers could not be made by direct comparison of the data. Dose linearity could be roughly concluded up to doses of 55 mg/kg in children and adults. In adolescents, linearity was concluded up to a dose of 75 mg/kg.

A weight-based posology could not be supported with the available PK data. Since only data for conjugated idebenone were available, the PK data could not be used to evaluate the impact of body weight on the PK of unconjugated idebenone. It was highly doubtful if the PK of conjugated idebenone reflected unconjugated idebenone. In addition, the weight-based posology was based on

very sparse data (n=14). Thus, additional PK data or efficacy data are required to clearly show that the weight-based posology is appropriate (for both groups of the weight adjusted dose).

In the ongoing MICONOS and IONIA studies limited sampling for population PK analysis is included. These samples will be analysed for both conjugated and unconjugated idebenone, allowing further exploration of the relationship between body weight and exposure because in both studies the same 45kg cut off is being used. Depending on the distribution of weights in the ongoing studies, it could be possible in future to conclude or exclude a correlation between body weight and clearance of unconjugated idebenone and possibly also to include a better justified weight cut-off. As a result, it was considered necessary to wait for the results of the MICONOS and IONIA studies that were still ongoing at the time of the opinion.

Special populations
Since unconjugated idebenone was not measured, only limited conclusions on the safety of the product could be drawn from the renal and hepatic impairment studies.
In patients with severe renal impairment the total idebenone exposure (conjugated and unconjugated) increased approximately 1.5-fold. Up to 3-fold increased exposure was observed in some individuals. For total QS10 (unconjugated and conjugated QS10) the exposure increase was approximately 1.9-fold. Up to 3-fold increased exposure was observed also for QS10 in some individuals. QS4 was not measured but it was expected to increase in patients with renal impairment because approximately 50 % of the dose is excreted as QS4 in the urine.
In patients with mild and moderate hepatic impairment the total idebenone exposure (conjugated and unconjugated idebenone) increased approximately 2-fold. Up to 3-fold increased exposure was observed in some individuals. For total QS10 (conjugated and unconjugated QS10), the exposure increase was approximately 3-fold. Up to 6-fold increased exposure was observed for total QS10 in some individuals.

The applicant's proposal to perform an additional study in patients with renal impairment was considered not meaningful, since satisfactory toxicokinetic data for QS4 to compare with were not available and there were very low levels of unconjugated idebenone in the urine.
Warnings in patients with renal impairment were included in the proposed SPC (section 4.4), together with a statement that QS4 is likely increased. In addition, in the event of a positive opinion, because of the unknown increase of unconjugated idebenone and the low dose applied in the hepatic impairment study, a contraindication in patients with moderate and severe hepatic impairment was to be recommended in section 4.3 of the SPC.

The applicant was requested to discuss the influence of age, gender and race on the PK of idebenone and related metabolites. Only data on total idebenone were provided, which highly limited the evaluation. No sufficient data were made available to evaluate the influence of age (upper age limits 71 years), although it was acknowledged that FRDA patients rarely reach these ages. Nevertheless, a statement on caution for elderly subjects treated with Sovrima was included in the proposed section 4.2. Likewise, it was not possible to evaluate the influence of gender on PK, since no data on unconjugated idebenone were available. With respect to race, the PK in non-Caucasians was considered not relevant for the intended indication, since FRDA is a Caucasian disease.

Pharmacokinetic interaction studies
An *in vitro* inhibition study was performed in order to evaluate the inhibition potential of unconjugated idebenone on CYP1A2, 2D6, 2E1, 2C9, 2C19 and 3A4. A dose-dependent inhibition was found for CYP2C19 and CYP1A2. Additional inhibition studies with idebenone were performed in order to evaluate the inhibition potential on CYP2B6 and CYP2C8. No significant inhibition was found. There was no information regarding the possibility of idebenone or its metabolites being a p-gp substrate and/or inhibitor. No *in vitro* induction studies were performed. The metabolites QS4, QS6 and QS10 (and their conjugated versions) and conjugated idebenone were not investigated with respect to CYP inhibition or induction.
Lower doses than those suggested in the actual application were used in the lithium, amitriptylin and fluvoxamine interaction studies. These three studies did not evaluate the effect of the concomitant medication on the pharmacokinetics of idebenone and QS10 or on unconjugated idebenone. The study

with donepezil employed a higher dose of idebenone and evaluated the effect of each medication on each other's pharmacokinetics. The pharmacokinetics of lithium was not affected by idebenone. The study with amitriptylin revealed that idebenone may affect CYP2C19 substrates to a limited extent (approximately 30 % increased concentrations). No effects were seen on the pharmacokinetics of donepezil. Since donepezil is metabolised via CYP3A4 and to a smaller extent via CYP2D6, the results were in agreement with the *in vitro* findings that idebenone does not inhibit CYP3A4 or CYP2D6. It is not known what caused the exposure increase of unconjugated idebenone in the donepezil interaction study.
The major elimination pathway appeared to be conjugation. Thus, no further pharmacokinetic interaction studies were requested, given that there was a low risk of a clinically significant effect on the pharmacokinetics of unconjugated idebenone by other CYP inhibitors and inducers. Also, the risk of clinically significant interactions by idebenone was considered low, since the therapeutic concentrations of idebenone are low in comparison to IC_{50} values and because of the high degree of protein binding of idebenone.

Pharmacodynamics

Mechanism of action

The mechanism of action for idebenone in the treatment of Friedreich's ataxia is not known, but there is some evidence that mitochondria respiratory chain dysfunction and oxidative damage may play a role in the mechanism behind the disease. Given that idebenone interacts with the mitochondrial ETC acting as an electron carrier and facilitating the generation of ATP (Sugiyama *et al.* 1985 a & b), its action in Friedreich's ataxia may be relevant, since a deficiency in mitochondrial ATP production has been reported in Friedreich's ataxia patient tissue (Lodi *et al.* 1999).

Primary and Secondary pharmacology

The indirect signs obtained from the clinical development conducted in FRDA patients did not provide additional support. When plasma and urinary levels of 8-hydroxy-2'-deoxyguanosine (8OH2'dG, a byoproduct of oxidative DNA damage) were measured along a 6-month treatment with idebenone no changes occurred. Unexpectedly, patients did not show the previously reported high plasma levels of 8OH2'dG at baseline. Besides, the reduction in response to oxidant treatment was not observed. These findings raised doubts about the claimed effect of idebenone on the oxidative stress reduction.

No specific pharmacodynamic drug interaction studies were performed. Even though this issue was considered not a major objection, it was still raised as a concern during the evaluation. Due to the lack of information from clinical studies, additional data were considered necessary in order to better characterise the primary and secondary endpoints of the product. The applicant was recommended to perform specific interaction studies to confirm that there were no pharmacodynamic interactions with commonly prescribed medicinal products (i.e. propranolol and glibenclamide) in FRDA patients. In these studies, in addition to pharmacokinetic parameters, pharmacodynamic parameters such as blood pressure and blood glucose were to be determined to exclude PD interactions with these co-medications.
Otherwise the potential for pharmacodynamic interactions appeared to be limited, given the mechanism of action of idebenone.

Clinical efficacy

The efficacy documentation provided for Sovrima in Friedrich's ataxia was primarily based on two sources:
- the phase II NICOSIA study;
- results from several published studies investigating the effect of idebenone on cardiac hypertrophy and neurological function in FRDA patients.

Dose response studies
No formal dose-response studies were performed as, according to the applicant, the Sovrima doses selected in the pivotal study were based on previous clinical experience with idebenone at the National Institute of Health and with other published clinical studies.

Main study
The pivotal study was a phase II study (NICOSIA study) designed as a 6-month double-blind, parallel group, placebo-controlled clinical study to determine the safety and efficacy of Sovrima administered to 48 patients with Friedreich's ataxia (FRDA).

METHODS

Study Participants
The pivotal study was a single-site study conducted at the NINDS Neurogenetics Branch in Bethesda, USA.
The **inclusion criteria** included a diagnosis of FRDA with confirmed FRDA mutations, age from 9-18 years at baseline, and weight between 30 to 80 kilograms. The patients had to be ambulatory (assistance devices permitted), neurologically symptomatic, and with no exposure to idebenone, coenzyme Q10 or other dietary supplements for a period of at least 1 month prior enrolment.
Exclusion criteria were: history of a hypersensitivity reaction to idebenone or coenzyme Q10; pregnant or lactating women; platelet count, white blood cell count or hemoglobin below the lower normal limit; alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT) or serum glutamic pyruvic transaminase (SGPT) greater than 1.5 × the upper normal limit. Bilirubin greater than 1.5 g/dL and clinically significant medical disease that, in the judgment of the investigators, would expose the subjects to undue risk of harm or prevent them from completing the study were other exclusion criteria.

Treatments
A total of 48 subjects were enrolled in the study and were randomized 1:1:1:1 in 1 of the 4 treatment arms: low Sovrima dose (≈ 5 mg/kg), 12 subjects; intermediate/mid dose Sovrima (≈ 15 mg/kg), 13 subjects; high dose Sovrima (≈ 40 mg/kg), 12 subjects; and placebo, 11 subjects. All 48 subjects received study treatment (37 subjects received Sovrima and 11 subjects received placebo).
All of the 48 subjects received at least 171 days of dosing. The median duration of treatment was 181 days for all groups except the intermediate Sovrima dose, which had a median dosing period of 182 days. The range of duration of dosing was 171 to 192 days for the combined Sovrima group and 176 to 197 for the placebo group. No subject discontinued study drug or withdrew from the study. Although all subjects attended the baseline and 6-month visits, one subject was unable to undertake efficacy evaluations at Month 6 due to a heavy cold.

After the first visit, Sovrima (60 or 150 mg tablets) or placebo were to be administered orally t.i.d. with food continuing for 6 months. Subjects were randomized to receive identical placebo tablets or one of the doses outlined in Table 2, based upon their weight. Patients were randomised into one of four treatment groups, the dose being adjusted depending on whether body weight was above or below 45kg.

Table 2. Treatment doses of Sovrima in the Nicosia trial.

Patient Body Weight	Sovrima Low Dose:	Sovrima Mid Dose:	Sovrima High Dose:	Placebo
≤45 kg	180 mg/day	450 mg/day	1350 mg/day	Placebo
>45 kg	360mg/day	900 mg/day	2250 mg/day	Placebo

Doses administered in three divided doses (eg, 450 mg = 150 mg t.i.d.)

According to the study protocol, patients were further stratified according to the length of the GAA repeat, to insure a balance between the groups in the proportion of patients with repeat lengths above 800 and below 800, respectively. There were 11 to 13 patients randomised in each of the dose arms.

Objectives

The primary objective of the study was to determine the effect of varying doses of Sovrima on oxidative stress as reflected by the change from baseline in the level of the oxidative stress marker 8-hydroxy-2' deoxyguanosine.

The secondary objectives were to evaluate the safety and tolerability of Sovrima, to explore the effects of Sovrima on neurological function, to explore the effects of Sovrima on cardiac parameters, to assess the effects of SOvrima on patients' quality of life, to explore the effects of Sovrima on functional capacity and to evaluate metabolic alterations, gene expression changes and markers of mitochondrial DNA damage.

Outcomes/endpoints

The **primary efficacy variable** was change in plasma 8-hydroxy-2'-deoxyguanosine (8OH2'dG) level from baseline to Month 6. 8OH2'dG, a by-product of oxidative damage to DNA, is regarded as a marker for oxidative stress. Elevated levels of 8OH2'dG and plasma malondialdehyde (MDA, a by-product of lipid peroxidation) have been reported in FRDA patients.

Secondary efficacy variables:

1. Neurological testing

Secondary assessments were the mean changes from the beginning to the end of the 6-month trial period in the following scales:

The International Cooperative Ataxia Rating Scale (ICARS), developed by a special ad hoc Committee of the World Federation of Neurology as an instrument which could be used in trials of new therapeutic agents in patients with different types of ataxia. The scale allows a detailed neurological examination of areas relevant to ataxia and is based on 19 testing manoeuvres compartmentalised into posture and stance disorders, limb ataxia, dysarthria and oculomotor disorders. The total sum of the 19 testing items is 100 points, 0 being no impairment and 100 the highest possible degree of impairment (negative numbers indicate an improvement).

The Friedreich's Ataxia Rating Scale (FARS) is a 25 manoeuvre exam which covers bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system function, deep tendon reflexes, stability and gait. The scale also includes 3 quantitative performance measures. Negative numbers indicate an improvement on the FARS.

*Activities of daily living (ADL***)** were assessed with a questionnaire adapted for the patient population. The scale consisted of 9 items relevant to daily living function in FRDA patients. The items include speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position and bladder function. Each item was scored from 0 to 4, 0 being normal, 4 being unable to conduct the activity, whereby a negative change corresponded to an improvement on the ADL scale.

2. Assessment of cardiac function

The cardiac data were to be analysed in the following populations:

- The full randomised population
- Patients with hypertrophic cardiomyopathy as indicated by:
  a) Maximum LV wall thickness, on echocardiographic or MRI assessment, greater than or equal to 13 mm - or greater than the upper normal limit corrected for age and body surface area calculated using the formulae by Henry (Henry et al, 1980)
  b) Patients with cardiomyopathy indicated by Relative Wall Thickness on echocardiography of >0.42 (Plehn J, as presented at 3rd International Friedreich's Ataxia Scientific Conference in Bethesda, Maryland, 2006).

Measures to be analysed included left ventricular mass (by cMRI), left ventricular mass/volume ratio, left ventricular mass index (by cMRI), maximal wall thickness (by cMRI), interventricular septal thickness (by echocardiography), relative wall thickness (by echocardiography), tissue doppler lateral E', CSA (critical surface area, by echocardiography), left ventricular ejection fraction (by cMRI). Other echocardiographic and cMRI measures were examined in an exploratory manner.

3. Quality of Life Survey (SF-10™)

A brief 10-question survey was administered by the principal or an associate investigator to the parent(s) or guardian(s) to examine the subject's health-related quality of life. This survey was developed as a valid health status assessment for the paediatric population (children ages 5 and over). The measure was not validated for FRDA patients and was not previously used in this population.

4. Other clinical assessments

- *Force Control Assessment*

The force control task used in this protocol involved submaximal isometric testing of the dominant knee extensors at 25% and 50% of the maximal voluntary contraction.

- *Gait Assessment*

Ataxic gait associated with cerebellar disorders is characterised by decreased gait speed, prolonged stance phase, and increased double-support time. Temporal aspects of gait were measured in this protocol using the so called "Stride Analyzer", which provides a measure of customary gait speed over a straight 10 m walkway. The measure was not validated for FRDA patients and was not previously used in this population.

- *Aerobic Testing*

Exercise testing outcome measures were 1) VO2 Peak, 2) Ventilatory Anaerobic Threshold (VAT), 3) oxygen uptake –work rate relationship (VO2-WR), and 4) Stroke Volume (SV) measured by TEB.

- *Visual Motor Testing Methods*

The Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test was utilized in order to assess visual-motor control through 5 separate tests: visual scanning, number sequencing, letter sequencing, number-letter switching, and motor speed. The measure was not validated for FRDA patients and was not previously used in this population.

Sample size

The sample size of 48 subjects (12 per arm) was chosen as an estimate of the smallest sample set that could provide a sufficient number of completing subjects within each arm to provide 90 % power to detect differences in the specified pattern for a test with α level of 0.05. Previous available data (Schulz *et al.*, 2000) was used as a basis for both estimated changes (an average percent decline of 20%) and variance (standard deviation of 0.18). Recruitment continued until 48 subjects were enrolled in the study. To allow for approximately 20% screening failures, the accrual ceiling was set at 60 subjects.

Randomisation

Subjects were randomized (1:1:1:1 to 1 of 3 active treatment groups or placebo) by block stratification using 2 strata defined by GAA repeat length of the shorter allele (<800 and >800) at the beginning of Day 2, after ensuring that all study criteria had been met. Because repeat length is directly correlated with disease onset and severity, subjects were randomized so as to ensure that all arms were balanced with regard to patient phenotype.

Blinding (masking)

The active and placebo medications were of identical appearance. Each patient was assigned a unique identification number and was randomized to a treatment group. The randomization code was not provided to the study personnel; sealed individual emergency envelopes were provided to the investigator, who was allowed to open them only in the event of a serious adverse event in which he deemed the information necessary.

Pharmacokinetic measurements were made only at the end of the study after completion of the clinical assessments.

Statistical methods

Analyses of the primary, secondary and other efficacy endpoints described above were to be based on all randomized subjects (intent-to-treat population [ITT]). Subjects in this population were analyzed according to the treatment to which they were randomly assigned. No other populations were defined.

The analysis of the mean change in the 8-hydroxy-2'-deoxyguanosine plasma level for the evaluation of the primary endpoint was to be performed using an analysis of variance (ANOVA) model that extracted the effects due to treatment and the stratification factor (allele length <800, ≥800). For subjects who did not have month 6 values, the last available post-randomization value was to be used to calculate change from baseline. Based on this ANOVA model, a step-down method, starting from the highest dose, was to be used in the treatment comparisons between active group and placebo in order to account for multiple comparisons.
If the comparison between Sovrima high dose and placebo was significant (at alpha = 0.05), then the next comparison was to be between Sovrima intermediate dose and placebo. If this comparison was significant (at alpha = 0.05), then the last comparison between Sovrima low dose and placebo was to be performed (at alpha = 0.05). The primary endpoint was also described for the pooled Sovrima group versus placebo. In addition, a subpopulation of mildly affected FRDA patients (as defined by an ICAR score of >10 and <54 at baseline) was also assessed for neurological function and activities of daily living parameters. Descriptive statistics for the primary variable were to be provided for the following subgroups: gender and ethnic origin (whites, other races). For each subgroup, the 95% confidence intervals were to be provided for treatment effects (individual Sovrima groups versus placebo as well as pooled Sovrima versus placebo). An exploratory analysis of the efficacy and safety endpoints was to be conducted on a more sensitive population that excluded subjects who had a baseline ICARS score of more than 54 or less than 10. An analysis was also to be conducted that excluded patients who had poor compliance (<80% on pill count and/or diary data).

The mean change in the other efficacy endpoints from baseline to month 6 was to be analyzed using an ANOVA model that extracted the effects due to treatment and stratification factor (allele length <800, ≥800). Other efficacy endpoints were meant to be supportive of the primary endpoints, and hence no adjustment for multiplicity was to be made. Percent change from baseline was also to be computed and described by treatment groups for the primary, secondary and other efficacy variables.
The cardiac data were to be analysed in the following populations:

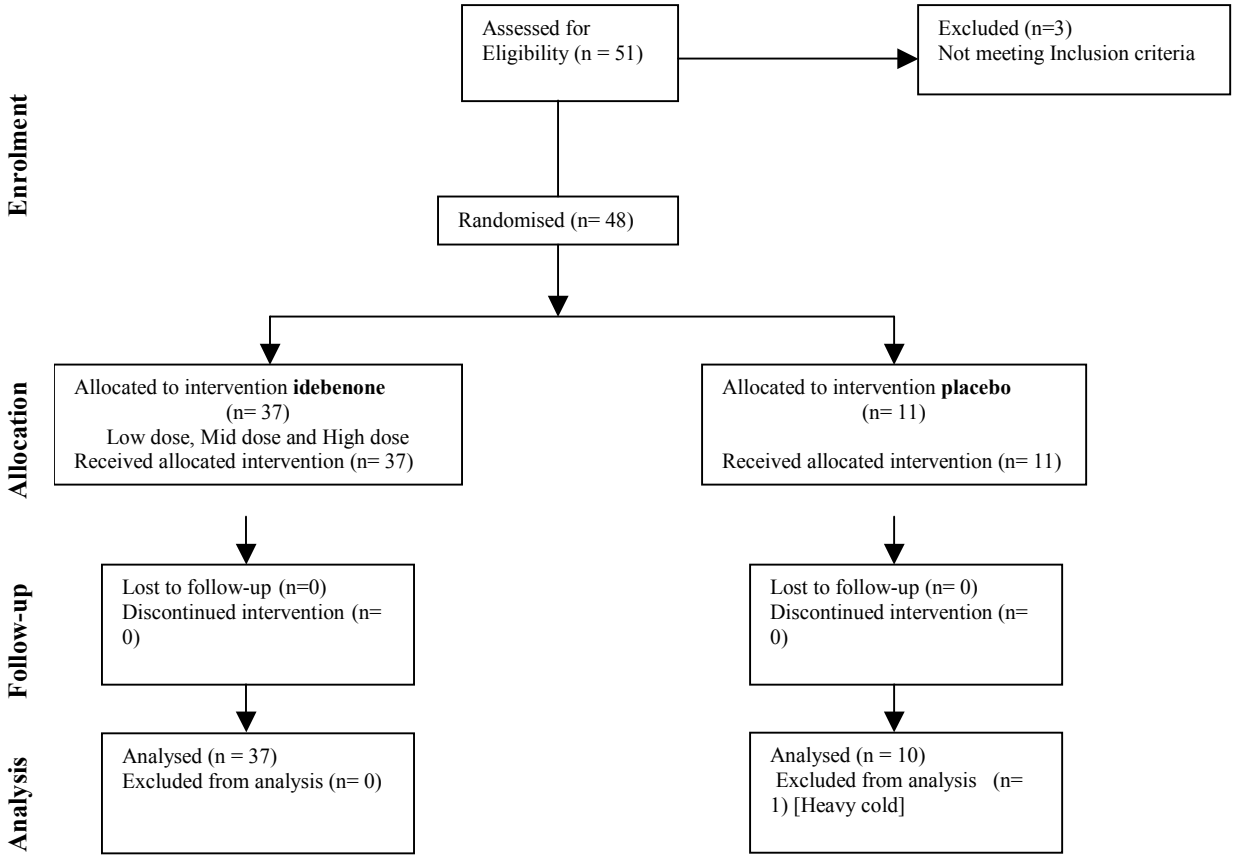
- The all randomised population;
- Patients with Hypertrophic cardiomyopathy as indicated by:
  - Maximum LV wall thickness, on echocardiographic or MRI assessment, ≥ to 13 mm - or greater than the upper normal limit corrected for age and body surface area calculated using the formulae by Henry (Henry et al, 1980);
  - Relative Wall Thickness on echocardiography of >0.42.

All variables were to be analysed as the change from baseline. No formal testing of significance was to be carried out, although p-values were to be calculated for comparisons between each dose of Sovrima and placebo as well as for pooled Sovrima groups versus placebo, in order to aid in the interpretation of any differences observed.

RESULTS

Participant flow

The following diagram describes the flow of the progress of study participants through all the phases of the trial.



Recruitment

The protocol was advertised on the NIH website and through support groups such as the Friedreich's ataxia Research Alliance (FARA). Active recruitment also included responding to inquiries made during the NINDS phase 1 trials. Inquiries were responded to by a letter briefly describing the study and requesting genetic confirmation for FRDA and medical records were mailed or faxed to the protocol research contact. Upon receipt of the records and genetic confirmation, the subjects were contacted to confirm the receipt of the requested information and were entered into the active protocol database. Using the active protocol database, the subjects were requested to participate in the study on a rolling basis and interested parties were scheduled for outpatient admission to the clinical centre.

Subjects who signed informed consent and assent forms but who were excluded on the second day of testing based on screening laboratory findings were defined as screen failures and counted towards patient accrual. The subject's case report form reflected the reason(s) for exclusion and their record were maintained in the study files.

Conduct of the study

Following informed consent and assent, the subjects underwent an initial medical history and physical exam followed by specific neurological, functional and cardiac testing over a 2-day outpatient visit. The subjects provided blood and urine samples for safety laboratory and biochemical analysis. Each eligible subject was then randomized to 1 of the 4 treatment arms and was provided with a 6-month supply of study drug or placebo to be administered t.i.d. The subjects were to have 2 scheduled visits at the National Institutes of Health Clinical Research Center (NIH CRC) at baseline and at month 6 for testing and laboratory monitoring over a 2-day outpatient visit. Follow-up laboratory monitoring was to be conducted monthly and at the end of the study (6 months). Additionally, the subjects were also to

have an ECG, vital signs (including orthostatics), a physical examination and medical history performed after 1 and 3 months by their primary care physician. The subjects were to have monthly follow-up telephone contact except at month 6, when the follow-up was to be part of the 2-day outpatient visit.

Baseline data
The basal demographic characteristics of the study population are shown in Table 3 (below).

Table 3. Basal demographics of the Nicosia study.

Parameter:		Placebo	Low dose	Mid Dose	High Dose
Age (years)	Mean	13.6	14.7	13.9	13.7
	Range	10.8 – 18.0	11.0 – 17.1	9.1 – 17.4	10.8 – 17.8
Gender	% Male	54.5	41.7	46.2	66.7
	% Female	45.5	58.3	53.8	33.3
Weight (kg)	Mean	50.9	52.5	44.6	45.3
	SD	14.9	16.5	11.2	9.3
Height (cm)	Mean	158.2	155.3	151.3	153.9
	SD	12.8	11.2	14.0	10.2

The mean age of onset of FRDA was similar for the low and high Sovrima dose groups and the placebo group (8.0, 8.2, and 8.2 years, respectively), but slightly lower in the intermediate Sovrima dose group (6.6 years). The minimum age in the range for age of onset of FRDA was lower for the low and intermediate Sovrima dose groups (1.5 years and 1 year, respectively) than for the high dose group and placebo (4.5 and 3 years, respectively). The mean ages (±standard deviation) of FRDA diagnosis for the low, intermediate, and high Sovrima dose groups were similar at 10.3 (±1.9) years, 9.7 (±2.4) years, and 9.8 (±2.3) years, respectively.
Patients were well matched at baseline across groups for age, sex, weight and height. The expected predominance of white subjects was observed (97.3% in the combined Sovrima group and 100% in the placebo group).
A total of 34 of the 48 subjects in the population of all randomized subjects had hypertrophy at baseline as assessed by predefined criteria of either
— a maximal left ventricular wall thickness of 13 mm or greater or
— a maximal left ventricular wall thickness greater than the upper limit of normal for maximal left ventricular wall thickness.
All patients received previously treatment for FDRA and other concomitant conditions. Antioxidant treatments for FRDA were withdrawn at least 1 month before the recruitment. A total of 38 out of 48 patients (7 in the low dose group, 11 in the mid dose group, 8 in the high dose group and 9 in the placebo group) had been treated with idebenone and/or coenzyme Q10.

Outcomes and estimation
Primary efficacy variable
Levels of the oxidative stress marker 8OH2'dG were determined using carbon column-based liquid chromatography with electrochemical detection in two batches of samples (48 samples collected at baseline and 48 samples collected at end of treatment). The baseline level of 8OH2'dG was in the same range as in healthy controls, which is in contrast to a previous publication (Schulz *at al.* 2000). The concentration for urinary 8OH2'dG normalised to creatinine was 4.77 (placebo), 4.79 (low dose), 4.15 (mid dose) and 5.50 (high dose) ng/mg creatinine – comparable to the range of 8OH2'dG levels seen in healthy controls (3.7-4.6 ng/mg creatinine). After 6 months of treatment, the mean levels of 8OH2'dG measured in the urine were reduced in all study groups (range: -1.35 to -2.27 ng/mg creatinine) with no statistical difference among treatment arms (Table 4).

Table 4. Change in plasma and urinary levels of 8-Hydroxy-2'-Deoxyguanosine from baseline to month 6.

8OH2'dG (all randomized subjects)			Idebenone		
Parameter		Placebo N=10	Low N=12	Mid N=13	High N=12
Plasma (ng/mL)	Baseline[1]	0.0287	0.0238	0.0215	0.0227
	Change EOT[1]	-0.0050	-0.0046	0.0004	0.0012
	SEM[2]	0.003	0.002	0.002	0.002
	P-value[3]	-	0.915	0.143	0.098
Urinary (ng/mL)	Baseline[1]	6.33	6.03	6.00	7.93
	Change EOT[1]	-1.63	-3.12	-1.81	-1.44
	SEM[2]	1.17	0.74	0.82	1.26
	P-value[3]	-	0.314	0.903	0.896
Urinary-ratio (ng/mg creatinine)	Baseline[1]	4.77	4.79	4.15	5.50
	Change EOT[1]	-1.52	-1.95	-1.35	-2.27
	SEM[2]	0.20	0.24	0.27	0.56
	P-value[3]	-	0.401	0.729	0.142

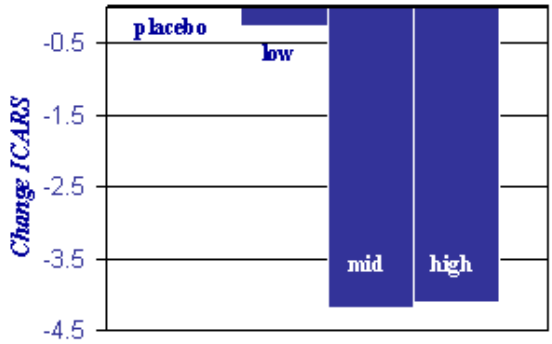
1: least square means based on model containing effects for Treatment and Allele; 2: raw means;
3: pairwise comparison to placebo; EOT: end of treatment

Secondary efficacy variable

International Cooperative Rating Scale (ICARS)

The total range of the ICARS is 0 to 100. Patients on the low dose Sovrima improved slightly (0.26 ICARS points) while patients on placebo deteriorated slightly by 0.08 ICARS points when compared to baseline. Patients treated for 6 months with Sovrima at the mid and high dose improved by ~4 points (corresponding to ≥10% improvement compared to baseline values) on the ICARS. The p-value for the overall ANOVA model to detect differences between treatment groups was 0.345. Using a pair wise comparison for each dose group vs. placebo indicated a trend to improvement favouring the mid (p=0.080) and high (p=0.086) doses of Sovrima versus placebo.

Fig. 1. Change from baseline to 6 months of the ICARS by treatment group (all patients randomised). The total range of ICARS is 0 to 100. The figure shows the interval 0 to 4.5.



ICARS	placebo	low	mid	high
baseline[1]	34.26	45.21	39.59	41.25
change[1]	0.08	- 0.26	- 4.19	- 4.12
SEM[2]	1.73	1.72	1.60	1.65
P-value[3]		0.891	0.080	0.086
N	11	11	13	12

1: least square means; 2: raw means; 3: pairwise comparison to placebo

The ICARS scores at baseline were not identical in all treatment groups, and the influence of the baseline ICARS as a confounding factor to the analysis was therefore tested. Only small differences in the outcome of the analysis were observed when including baseline scores as a covariate in the ANOVA model, indicating that the differences observed were not related to baseline differences.

An analysis pre-specified in the statistical analysis plan was conducted in which patients with very mild impairment (ICARS baseline score less than 10 points) and patients with more severe impairment (corresponding to an ICARS baseline score of greater than 54 points) were excluded. Only one patient had a score below 10 whereas 13 patients in total had ICARS scores over 54. Using this analysis, patients on the high and mid dose of Sovrima improved by 5.8 and 4.3 points respectively on the ICARS. Patients on low dose Sovrima only slightly improved, by 0.48 ICARS points, while patients receiving placebo deteriorated by ~2 points. Pair wise comparisons to placebo showed that the effects of mid and high dose Sovrima was statistically significant with p-values of 0.009 and 0.002, respectively. When the mid and high dose groups were pooled, there was a statistically significant improvement on the ICARS.

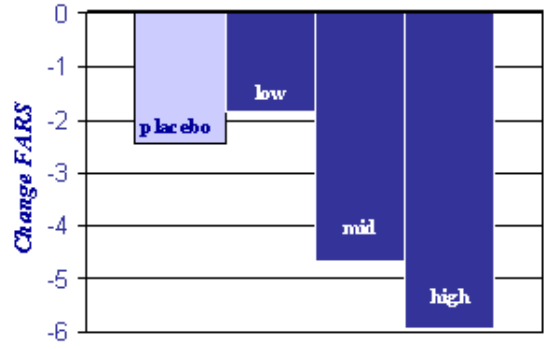
Thus, the results for ICARS in all patients randomised showed a trend for improvement for the mid and high doses vs. placebo, but the differences for the individual doses of Sovrima were not statistically significant. There was no clear trend for dose-response between the mid and high doses. In the Day 80AR the applicant was asked to clarify what should be regarded as a clinically relevant change in ICARS for an individual and then present the percentage of patients who fulfilled these criteria in each treatment group. The applicant performed a responder analysis where a clinically relevant change in the ICARS was defined as an effect with a magnitude equivalent, in absolute terms, to the natural rate of decline observed over a one year period in an untreated population. The results show a trend for an increase of responders in the mid and high dose groups of Sovrima.

<u>The Friedreich's Ataxia Rating Scale (FARS)</u>

The main component of the FARS is a detailed neurological examination consisting of 25 manoeuvres along with three quantitative performance measures. The examination covered the following areas: bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system function, deep tendon reflexes, stability and gait (maximum deficit = 117). A reduction in the FARS score was indicative of an improved neurological performance.

A mean improvement with 2.43 FARS points was observed for the placebo group. The low dose Sovrima group improved less than the placebo group, mean 1.83 FARS points. The mid dose improved with 4.6 FARS points and the high dose 5.9 FARS point. The differences did not reach statistical significance.

Fig. 2. Change from baseline for total FARS (all patients randomised).



FARS	placebo	low	mid	high
baseline[1]	47.13	56.53	49.80	51.42
change[1]	- 2.43	- 1.83	- 4.64	- 5.92
SEM[2]	2.22	2.20	2.04	2.10
P-value[3]		0.850	0.472	0.261
N	11	11	13	12

1: least square means; 2: raw means; 3: pairwise comparison to placebo

In response to the Day 120 LoQ the applicant presented the changes in the FARS subscores for the individual subjects in the NICOSIA study. There was a trend for improvement for the mid and high dose groups compared to placebo and low dose groups with the exception of the high dose bulbar score and the score for posture

FARS functional scores

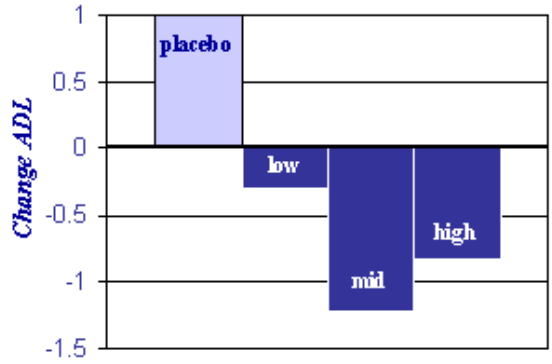
Performance measures conducted with the FARS included the following items: a timed 25-foot walk for ambulation, a 9-hole peg board test for upper limb coordination and function and a quantitative measure of speech performance, the PATA test.

There were no consistent or dose-dependent differences between the Sovrima and placebo and the results of the functional tests were highly variable.

Activities of daily living

Patients treated for 6 months with Sovrima generally improved on the ADL scale, with a stronger effect seen for the mid and high dose groups (mean improvement by 1.2 and 0.8 ADL points for the mid and high doses respectively). Patients on placebo deteriorated on the ADL scale by a mean of 1 point. Applying pair wise comparison to placebo indicated that patients on the mid dose improved (p=0.035) while patients on the high dose showed a trend towards improvement (p=0.083).

Fig 3. Changes from baseline for ADL scores. All patients randomised. The range of the scale is from 0 to 36. The figure shows the interval +1 to -1.5.



ADL	placebo	low	mid	high
baseline[1]	12.10	15.04	14.57	12.63
change[1]	1.0	- 0.30	- 1.23	- 0.83
SEM[2]	0.75	0.74	0.69	0.71
P-value[3]		0.226	0.035	0.083
N	11	11	13	12

1: least square means; 2: raw means; 3: pairwise comparison to placebo

Clinical Global Impression of Change (CGIC)

The Clinical Global Impression of Change was determined using a scale based on an interview with the patients and caregiver. The level of overall change from baseline was assessed on a 7-point scale.

There were no significant differences between active groups and placebo in the proportion of patients showing improvement on the CGIC. With regard to the fatigue scale, no differences between treatment groups on improvement of worsening of fatigue were observed.

Quality of Life
A quality of life scale (SF-10) was included in the efficacy assessments. There were no differences observed between the groups. In response to the Day 120 LoQ, the applicant has presented the results of the SF-10 physical and SF-10 psychological subscores. No consistent statistically significant differences between placebo and the Sovrima groups were observed.

Aerobic Exercise test
Aerobic exercise tests were conducted using a bicycle ergometer. No significant changes for any of the dose groups versus placebo were observed in exercise parameters such as peak workload and peak oxygen consumption.

Gait assessment
There were no significant differences between the groups.

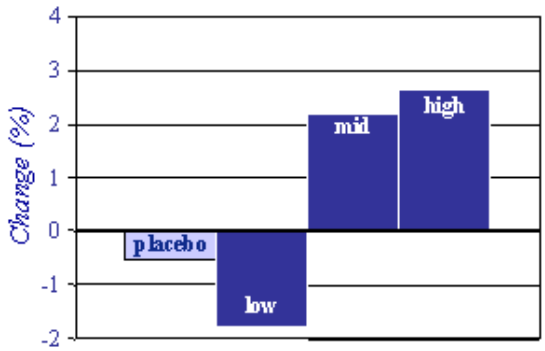
Visual Motor Testing Methods
There were no significant differences between the groups.

Cardiac results
Changes in cardiac anatomy and function were determined by cMRI and echocardiography.
34 of the 48 subjects in the population of all randomized subjects had hypertrophy at baseline as assessed by predefined criteria of either

- a maximal left ventricular wall thickness of 13 mm or greater or
- a maximal left ventricular wall thickness greater than the upper limit of normal for maximal left ventricular wall thickness (as defined by Henry, 1980).

With the responses to the D 120 LoQ the Applicant submitted an Addendum to the Final Clinical Study Report of the Nicosia trial which was stated to contain a final analysis of the study data for multiple cardiac parameters derived by cMRI and echocardiography. Data were presented on changes in left ventricular mass index (LVMI) and Left Ventricular Ejection Fraction (LVEF) derived by cMRI. The changes in LVMI presented in the D120 response document differed from the results presented in the original application, showing a more pronounced deterioration of the placebo group (from previously 1.01 g/ m^2 to now 1.78 g/m^2) and more improvement in the mid dose Sovrima group (from previously -3.24 to now -4.16 g/m^2) when compared with the results presented in the original dossier. With the revised analysis, the results for the mid dose of Sovrima became statistically significant. The results for LVEF presented in the response to D120 Questions also differed markedly from the results presented in the original dossier (see Fig 4 and Fig. 5) and the effect of the mid dose of Sovrima shown in the new data was more pronounced and reached statistical significance vs. placebo.

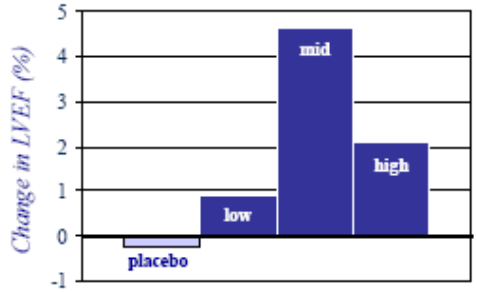
Fig.4. Change in LVEF from baseline by treatment group (all patients randomised) as presented in the original dossier (derived by echocardiography).



LVEF	placebo	low	mid	high
baseline[1]	72.41	72.12	71.04	67.27
change[1]	-0.51	- 1.74	2.20	2.64
± SEM[2]	2.29	2.63	2.12	2.23
P-value[3]		0.727	0.432	0.364
N	9	10	12	11

1: least square means; 2: from raw means; 3: pairwise comparison to placebo

Fig. 5. Change in LVEF from baseline by treatment group (all patients randomised) as presented in the response to the D120 LoQ (derived by MRI).



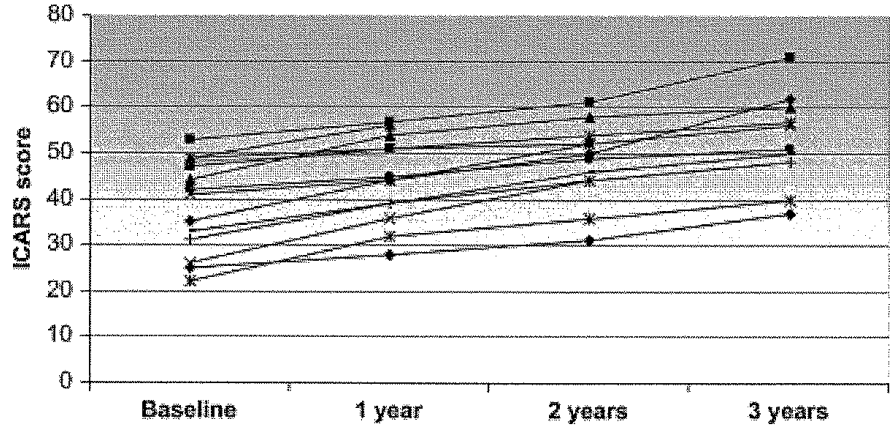
LVEF	placebo	low	mid	high
baseline[1]	63.77	59.58	58.70	58.07
change[2]	-0.24	0.90	4.62	2.08
± SEM[1]	2.24	1.22	1.30	1.66
P-value[3]		0.62	0.04	0.33
N	10	12	12	11

1: from raw means; 2: least square means; 3 pairwise comparison to placebo

According to the applicant the data presented in Fig. 5 were derived from cardiac MRI (cMRI) whereas the data presented in Fig. 4 were derived from echocardiography. However, in the initial application (Final Clinical Study Report-Nicosia trial) the data in Fig 4 were also reported as being derived by cMRI. This issue was confusing, as was also the different numbers of patients included in the treatment groups in the initial application and in the D120 response.
The applicant clarified the analyses of cardiac parameters by stating that in the preparation of the original study report the LVEF data derived from echocardiography assessments were erroneously interpreted as being MRI-derived data. The applicant also clarified the different number of patients included in the treatment groups in the original submission and in the final analysis provided with the D120 response, which related to the fact that the number of patients for which MRI data were available differed from the number of patients for which echocardiography data were obtained. In addition, Subject 001 (placebo, no LVEF data at baseline by echocardiography) was erroneously omitted from the other cardiac analyses and was then included in the final analysis. It remained, however, that the results obtained for LVEF with MRI in the final analysis differed very much from the results for LVEF obtained with echocardiography in the first analysis. The result for the mid dose of Sovrima was considerably more positive in the final MRI analysis (increase from 2.20 to 4.62), and the results for the low dose have changed from -1.74 to + 0.90 (see Fig. 1 and 2 above). The applicant did not provide an explanation for the great differences in results for LVEF depending on whether echocardiographic or MRI assessments were used.

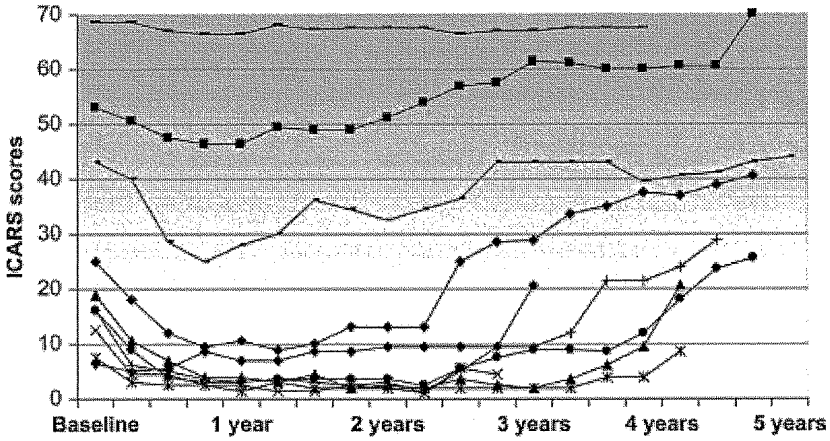
One additional study by Pineda *et al.* (Eur J Paediatr Neurol 2008 *in press*) was included in the responses to the day 120 LoQ. This was a small open-label prospective study in 14 adults (age range 18-46 years) and 10 paediatric patients (age range 8-18 years) with genetic diagnosis of Friedreich's ataxia. The duration of the study was 3-5 years. The adult patients started with Sovrima 5 mg/kg/day 1 year, then Sovrima 10 mg/kg/day for 1 year, and 20 mg/kg/day in the last year. The paediatric group started with 5 mg/kg/day of Sovrima for 18 months, then 10 mg/kg/day during the last 3 years and 6 months of study. Neurological evaluation was performed with ICARS, a score with a range from 0 to 100. Cardiological outcomes were studied by echocardiography once per year.
The results for ICARS for the adult population revealed a progression of the disease with increasing ICARS scores (indicating worsening of the disease) for all patients despite continuous Sovrima treatment (Figure 6).

Fig. 6. Effect of long-term Sovrima treatment on the ICARS of adult FRDA patients.



The figure above shows a progression of the disease with increasing ICARS scores, indicating worsening of the disease, for all patients despite continuous Sovrima treatment. Hypertrophic cardiomyopathy (SP, PW and LVMI values) was not modified during the follow-up of adult cases (8 cases presented cardiomyopathy at the beginning and the end of the study, while the other 6 cases remained within the reference range).
In the paediatric population there was an initial improvement (reduction of ICARS scores), followed by an apparent stabilization and thereafter a continuous progression, as shown in Fig. 7.

Fig. 7. Effect of long-term Sorima treatment on the ICARS of paediatric FRDA patients.



In paediatric patients no significant differences were observed in any of the echocardiographic measurements when comparing baseline conditions and the end of the study. These results were considered of interest but not convincing with regard to the efficacy of Sovrima in FRDA.

Overall, no clear effect has been observed in this study, where heart function was within normal or almost normal range. This is seen by the authors as a signal of prevention of cardiomyopathy progression in this population. Nevertheless, the percentage of patients who would have developed cardiomyopathy if they had not been treated is unknown and, therefore, if the progression of the disease is or not prevented is uncertain. The low number of patients, the unpredictable risk of developing a cardiomyopathy and the lack of a control untreated group did not allow any firm conclusions.

Ancillary analyses
Analysis performed across trials (pooled analyses and meta-analysis)
Not applicable.

Clinical studies in special populations
Refer to above description for studies in paediatric patients.

Supportive study(ies)
9 published studies investigating the effect of idebenone (5 mg/kg/day, equivalent to the low dose of the pivotal study) on cardiac hypertrophy and neurological function in FRDA patients were provided by the applicant as supportive studies. One of these was a double-blind, placebo-controlled trial (Mariotti, 2003).

Table 5. Efficacy of idebenone in Friedreich's ataxia. Overview of academic clinical studies 1999-2007.

Reference	No. of patients	Duration of treatment (months)	Dose mg/kg/d	Type	Clinical Endpoint	Effect
Rustin 1999 Rustin 2004	3: (2 children 1 adult)	4-9 (5-year follow up)	5	OT	LVMI	improvement: 20% to 32 %
Schulz 2000	8	2	5	OT	Urinary marker 8OH2'dG#	significant decrease up to –20% (p<0.05)
Schöls 2001	9 (19-54 y)	1.5	360 mg/d	DB	LVMI IVS, PWT	no improvement no improvement
Artuch 2002	9 (11-19 y)	12	5	OT	ST PWT ICARS	no progression * no progression * improved (p=0.007)
Hausse 2002	38 (4-22 y)	6	5 1 pt: 10	OT	LVMI	>20% reduction in half of patients (p<0.001), stabilisation in rest of patients
Mariotti 2003	29 (1 patient on placebo died)	12	5	DB PC	LVMI treated LVMI control VS treated IVS control ARS	5.6 % ? 10.7 % ?, (p=0.01) 4.6 % ? 5.4 % ?, (p=0.004) no improvement
Buyse 2003	8 (8.6-27 y, mean 15 y)	12	5	OT	LVMI ejection fraction, cardiac strain, strain rate CAGRS	significant reduction improvement improvement improvement no improvement
Arnold 2006	20	several (up to 3.5y)	5, 10	OT	dysarthria hand dexterity fatigue total ICARS	improvement improvement improvement no change (10 patients)
Ribai 2007¶	88 (32±11 y at first visit)	6 months – 7 years	5	OT	ICARS treated ICARS non treated LVMI treated	1.93 ± 0.25 ? p.a.$ 4.43 ± 1.56 ? p.a. 4.1 ± 1.5 g/m² ? p.a.

ARS: ataxia rating scales; CAGRS: Cooperative Ataxia Group Rating Scale; DB: double blind; ICARS: International Cooperative Ataxia Rating Scale; IVS: interventricular septal thickness;
(L)VMI: (left) ventricular mass index; OT: open trial; PC: placebo controlled; PWT: posterior wall thickness;
*most patients had no or only mild changes at start of study; # 8-hydroxy-2'-deoxyguanosine;
$ data is mean ± St.dev.; evolution was determined with a linear mixed-effect model taking into account several variables incl. GAA repeat length, age of disease onset, etc.
¶natural history study; not focussed on idebenone effects.

1. Effect of idebenone on hypertrophic cardiomyopathy

Rustin 1999, 2004
Three patients (age 11, 19 and 21 years) with Friedreich's ataxia were treated openly with idebenone 5 mg/kg for 4-9 months. Evaluation of LVMI showed a reduction between 21 and 32 % after treatment. For one of these patients a further decrease of heart hypertrophy at follow-up after 5 years of idebenone administration (5 mg/kg bw) was reported.

Schulz et al. 2000
This study measured concentration of 8OH2'dG, a marker of oxidative DNA damage, and DHBA, a marker of hydroxyl radical attack, in the plasma of 33 patients with FRDA. However, no clinical evaluation of the patients was performed in this study.

Schöls 2001
This was a placebo-controlled crossover trial in nine ambulant patients with FRDA, performed in order to investigate the effect of idebenone on respiratory function using ^{31}P- magnetic resonance spectroscopy (^{31}P-MRS). The prolonged phosphocreatine recovery after exercise was analyzed as a direct measure of oxidative phosphorylation. The nine FRDA patients (five female, four male) had a mean age of 34 ± 11 years (range 19-54 years) and onset of symptoms varied from 12 to 36 years of age. Idebenone was given at a dosage of 360 mg/d. The duration was 6 weeks. Neurological deficits were assessed using the ICAR scale (the same scale that was used in the NICOSIA study). In addition, complex hand movements were analysed. Cardiologic monitoring included 12-channel ECG recordings, echocardiographic evaluation of the left ventricle and heart muscle enzymes.
(^{31}P-MRS) demonstrated mitochondrial impairment *in vivo* in skeletal muscle of all FRDA patients, but no recovery with idebenone. No effects were seen in clinical scores. Echocardiography showed no improvement of cardiomyopathy.

Artuch, 2002
This was an open-label trial performed in nine FRDA patients (age range 11-19 years) treated with idebenone 5 mg/kg/day. Patients were evaluated before the start of the study and throughout one year of treatment by ICARS scores, neurophysiological measurements and echocardiographic measurements.
Significant reduction was observed comparing the ICARS scores prior and after 3, 6 and 12 months of therapy. No differences were observed in echocardiographic measurements and neurophysiological investigations prior and 12 months after the start of the therapy.

Hausse et al. 2002
This was a prospective, open trial in 38 patients with FRDA aged 4-22 years (20 males, 18 females). Asymmetrical hypertrophic cardiomyopathy was observed in 10 patients and concentric hypertrophy in the others. No patient had dilated cardiomyopathy. The patients were given idebenone 5 mg/kg/day for 6 months. Cardiac ultrasound indices were recorded immediately before and after six months of oral idebenone. Shortening fraction, septal thickness and left ventricular posterior wall thickness were measured. After six months of idebenone treatment, a reduction in left ventricular mass of more than 20 % was observed in half of the patients. Cardiac hypertrophy stabilised in most of the remaining patients. The change in left ventricular mass index was not correlated with the number of GGA repeats of the small allele in the frataxin gene, or the stage of cardiac disease based on the initial ultrasound findings.

Mariotti et al. 2003
This was a 1-year randomised placebo-controlled trial of idebenone in 29 FRDA patients (6 women and 23 men). The mean age at enrolment was 26 years. 29 patients were randomised to placebo (15 patients) or idebenone (14 patients). The mean daily dose of idebenone was 324 mg (range 240-250 mg). Heart ultrasound variables were measured and neurological assessment was performed using the ICARS. After 6 months of treatment, an average reduction of 4.3 % was observed in the IVS in the idebenone group versus a 3.2 % mean increase in the placebo group (p=0.05). At 12 months, IVS thickness showed a 4.6 % reduction the idebenone group vs. a 5.5 % increase in the placebo group (p=0.004). Statistically significant reductions were also found for LVM, but there was no improvement in other ultrasound measures (left ventricular posterior wall thickness, or ejection fraction). The analysis of the ICARS total scores and sub scores did not reveal significant differences between the two patient groups.

Buyse et al, 2003
The authors reported a 1-year prospective open-label trial with idebenone on eight FRDA patients, aged between 8.6 and 27.1 years and with hypertrophic cardiomyopathy. All patients received oral idebenone 5 mg/kg in three doses, maximum 300 mg/day for 1 year. Patients were evaluated at

baseline and at 4, 8 and 12 months of treatment for ataxia, cardiac structure and function, biochemical markers and adverse effects.
The Cooperative Ataxia Group Raring Scale for Drug Trial for FRDA was used to assess neurological evolution at baseline and during therapy. The results of the neurological evaluation showed a progressive increase in total ataxia scores despite idebenone use. Cardiac evaluation showed a reduction of Left Ventricular Mass Index (LVMI) from 130 27 to 109 28 g/cm, p=0.03. These changes were not linear over time, appearing only toward the end of therapy. For the interventricular septum and the posterior wall there was a non-significant reduction after therapy.

Arnold et al. 2006
In this open-label study, clinical, electrophysiological and biochemical data were provided from 20 genetically confirmed FRDA patients. Neurological function and ataxia were investigated with ICARS after treatment with idebenone 5 mg/kg/day. 15 of 19 treated patients reported improvement on idebenone treatment in terms of dysarthria, hand dexterity or handwriting and fatigue. This improvement appeared gradually on treatment (within 6 weeks in 3 patients and within 6 months in the other 12). Follow-up (1.6 – 3.5 years, mean 2.9) with ICARS was available for 10 patients. The mean score did not change during follow-up. Analysis of a biomarker for oxidative stress, malondialdehyde (MDA), showed an unexpected increase in blood MDA levels in patients on idebenone.

Ribat et al. 2007
This was an open-label prospective study where 104 FRDA patients were examined every 6 months during a median period of 5 years. Neurological status was evaluated with the ICARS and a quantitative writing test. Cardiological evaluation included echocardiography, electrocardiography, and Holter monitoring. 88 of the patients accepted treatment with idebenone 5 mg/kg/day whereas 16 preferred not to be treated. The total ICARS score worsened during follow-up, whether or not the patients were treated with idebenone (1.93 ± 0.25 and 4.43 ± 1.56 points per year, respectively). Neurological progression was underestimated by the ICARS scores, which reached a plateau in patients with long disease durations. Cardiac hypertrophy decreased under treatment but cardiac function did not improve.

2. Effect of idebenone on neurological symptoms

The studies by Buyse *et al.* (2003) and Mariotti *et al.* (2003) discussed above did not show any effect on neurological symptoms. In the study by Artuch (2002), also briefly described above, a significant reduction was observed comparing the ICARS scores prior and after 3, 6 and 12 months of therapy with idebenone 5 mg/kg/day. In the study by Arnold *et al.* (2006) improvement was observed on some parts of the ICARS, whereas the study by Ribai *et al.* (2007) did not show any effect idebenone on neurological progression.

Discussion on clinical efficacy
In conclusion, the applicant submitted a single single-site phase II study in patients with Friedreich's ataxia. The mid and high doses of Sovrima that were used in this trial were higher than the doses previously used in published studies. The number of patients was limited, only 48.
No effect was seen on the primary endpoint, change in a surrogate marker for oxidative stress from baseline to month 6. The analyses of 8OH2'dG showed in fact similar results in all groups including the placebo group. These findings were not in agreement with the hypothesis that treatment with Sovrima decreases the levels of 8OH2'dG, a proposed surrogate marker for oxidative stress. Overall, the average 8OH2'dG level of FRDA patients was in the range of healthy controls and not abnormally high as previously reported. Differences in patients' age (patients were younger in the current study) and technical sampling handling were proposed as possible causes of this unexpected behaviour. Looking at the primary outcome results, the lack of an 8OH2'dG cut-off value at inclusion could be considered a drawback of the study. However, the role of 8OH2'dG levels in FRDA patients was still unclear and it was doubtful whether this biomarker could be considered as a valid surrogate endpoint of this disease.
Secondary endpoints included clinical scales for assessment of ataxia (ICARS, FARS), ADL, and parameters for evaluation of cardiac hypertrophy. The effect on the secondary endpoints ICARS and FARS was more pronounced for the mid and high doses of Sovrima than for the low dose, but the

differences did not reach statistical significance, and no clear dose-response was shown between the mid and high doses. In response to the Day 120 List of Questions, the applicant presented a responder analysis where a clinically relevant change in the ICARS was defined as an effect with a magnitude equivalent, in absolute terms, to the natural rate of decline observed over a one year period in an untreated population. The results of the responder analysis showed a trend for an increase of responders in the mid and high dose groups of Sovrima. There were no statistically significant effects of Sovrima on Clinical Global Impression of Change (CGIC), a Quality of Life scale (SF-10), Gait Assessment, Visual Motor Testing methods, or Aerobic Exercise test.

For the cardiac parameters, the applicant submitted a revised analysis with the responses to the Day 120 List of Questions. In the initial application, there was a trend to improvement for a measure of cardiac hypertrophy, the Left Ventricular Mass Index (LVMI), in the two highest dose groups, but the differences were not statistically significant. In the revised analysis, the mid dose of Sovrima resulted in a statistically significant improvement of LVMI as well as in a statistically significant improvement of a cardiac functional outcome parameter, Left Ventricular Ejection Fraction (LVEF). An unresolved issue remained as the applicant did not provide an explanation for the great differences in results for LVEF depending on whether echocardiographic or MRI assessments were used.

From the efficacy point of view, it would be expected that neurological and cardiac endpoints provided clinically meaningful information. Given that Freidreich's Ataxia is an inherited and progressive neurodegenerative condition, a large clinical effect of idebenone was not expected in the short term. However, it was considered necessary to show at least a delay in the progression of the disease for any potential treatment] In conclusion, although the submitted data for the mid and high doses of Sorima potentially suggested a modest beneficial effect of Sovrima on neurological and cardiac symptoms in FRDA, the submitted efficacy documentation was not considered sufficient for an approval of Sovrima for the treatment of Friedreich's ataxia. In addition, the effect of Sovrima in adult patients with Friedreich's Ataxia could not be considered demonstrated with the data provided. It was concluded that the results of the Nicosia trial needed to be confirmed with results from a large randomised trial. Overall, it was deemed necessary to wait for the results of the two ongoing phase III (EU MICONOS and US IONIA) trials, which were expected to be available by 2010.

An additional concern remained in that the PK data provided were very sparse and unconjugated idebenone was not measured; overall, the PK data provided did not support a weight-based posology. The applicant was requested to provide additional PK data on unconjugated idebenone or clinical data in support of the weight-based posology, showing effect in patients weighing above and below 45 kg, respectively. The applicant's approach to perform sparse sampling for population PK analysis in the ongoing MICONOS and IONIA studies was welcomed. Depending on the nature of the data (e.g. a satisfactory range of distribution of weights) there may be a possibility to either exclude or conclude a correlation between body weight and clearance of unconjugated idebenone and possibly also to include a better justified weight based posology and cut-off. Thus, also for this reason the results of the MICONOS and IONIA studies were deemed necessary.

Clinical safety

The Applicant put together a pooled safety database of the six phase III studies from the clinical development for Alzheimer's disease.

Evaluation of idebenone in Friedreich's ataxia (FRDA) began in the late 1990s.

The following four sets of clinical data were available to assess the safety of idebenone:
- The NIH / Santhera pivotal Phase II (NICOSIA) study in Friedreich's ataxia;
- The Takeda safety data from Phase III studies in Alzheimer's disease (AD);
- The four Santhera Phase I studies in healthy volunteers;
- The National Institutes of Health (NIH) Phase I studies in Friedreich's ataxia patients.

Patient exposure
Friedreich's ataxia studies

Data were available on 142 patients with Friedreich's ataxia who participated in the Phase I/II studies. Of these, 78 patients received single ascending doses of idebenone 2.5 mg/kg up to 75 mg/kg, and 15 patients received 60mg/kg/day for 30 days.
In the NICOSIA study, 48 patients received higher doses of Sovrima, ranging from 180 or 360 mg/day to 1350 or 2250 mg/day, depending on body weight, for 6 months. This equates to a dose range from approximately 4 mg/kg/day up to approximately 50 mg/kg/day.
An overview of the clinical studies in FRDA patients evaluated for safety is shown in Table 6.

Table 6. Phase I/II studies in Friedreich's ataxia

Study reference	Short title	Study design	Patients entered	Daily dose, (regimen) and duration of treatment
01-N-0167 (NIH)	Phase IA single-dose, dose-escalation pilot safety study	SD, O	79 patients: 27 children, 27 adolescents and 25 adults with Friedreich's ataxia mean age 9.3, 15.1 and 33.4 years respectively	single ascending doses of 2.5 mg/kg/day up to 75 mg/kg/day
04-N-0129 (NIH)	Phase IB multiple-dose pilot safety study	RD, O	15 patients (5 children, 5 adolescents and 5 adults) with Friedreich's ataxia mean age 10.6, 16.0 and 33.0 years respectively	60mg/kg/day for 30 days
NICOSIA study (NIH/Santhera)	Phase II dose-ranging, efficacy & safety study	R, PC, DB	48 patients aged 9-18 years with Friedreich's ataxia mean age ~14 years	tid dosage, depending on body weight ≤45 kg or >45 kg: Low dose, Group A: 180 or 360 mg/day Mid dose, Group B: 450 or 900 mg/day High dose, Group C: 1350 or 2250 mg/day; Placebo, Group D 6 months

SD: single-dose; O: open-label; RD: repeat dose; R: randomised; PC: placebo-controlled; DB: double-blind.

Alzheimer's disease studies
An overview of the Takeda Phase III studies in Alzheimer's disease patients to be evaluated for safety is given in Table 7.

Table 7.- Phase III efficacy and safety studies in Alzheimer's disease

Study reference	Short title	Study design	Patients entered	Daily dose, (regimen) and duration of treatment
PNFP-001	Safety & efficacy study of idebenone 120, 240 & 360 mg tid	R, DB, PC, PG	536 patients with mild to moderate probable AD. idebenone: 407 patients mean age 75.1 years; placebo: 129 patients mean age 74.5 years	idebenone 360 mg/day; idebenone 720 mg/day; idebenone 1080 mg/day; placebo 12 months
PNFP-002	Safety & efficacy extension study of idebenone 120, 240 & 360 mg tid	R, DB, PG	320 patients who had completed 12 months of treatment in study PNFP-001.	Idebenone 360 mg/day; idebenone 720 mg/day; idebenone 1080 mg/day; 12 months Patients continued their existing dosage of idebenone; those previously receiving placebo were transferred to the highest dose of idebenone
PNFP-004	Safety & efficacy study of idebenone 240 & 360 mg tid	R, DB, PC, PG	377 patients with mild to moderate probable AD. idebenone: 251 patients mean age 75.4 years; placebo: 126 patients mean age 76.0 years	idebenone 720 mg/day; idebenone 1080 mg/day; placebo (tid) 12 months
PNFP-005	Safety & efficacy study of idebenone 360 mg tid	R, DB, PC, PG	331 patients with mild to moderate probable AD. idebenone: 221 patients mean age 75.8 years; placebo: 110 patients mean age 75.3 years	idebenone 1080 mg/day; placebo 12 months
CV-2619/ PNFP-007	Safety & efficacy study of idebenone 360 mg tid or placebo added to treatment with donepezil	R, DB, PC, PG	402 patients with mild to moderate probable AD. P+D: 207 patients mean age 75.1 years; I+D: 213 patients mean age 76.5 years	idebenone 1080 mg/day + donepezil 10 mg qd; placebo (tid) + donepezil 10 mg qd 12 months
PNFP-008	Safety & efficacy study of idebenone 360 mg tid or placebo added to treatment with donepezil	R, DB, PC, PG	389 patients with mild to moderate probable AD. P+D: 195 patients mean age 73.6 years; I+D: 194 patients mean age 74.7 years	idebenone 1080 mg/day + donepezil 10 mg qd; placebo (tid) + donepezil 10 mg qd 12 months

R: randomised; DB: double-blind; PC: placebo-controlled; PG: parallel group.

All patients who received study medication were included in the analysis of safety. A pooled database of the six Phase III Takeda studies from an earlier stage of clinical development for Alzheimer's disease was created and evaluated. Data were pooled as six different treatment groups, i.e. placebo, three doses of idebenone, placebo + donepezil and idebenone + donepezil.
Patients were well matched at baseline across groups for age (mean, median and range), sex, weight and race. In all treatment groups, approximately 80% of patients were aged above 70 years and there were more females than males (the greatest proportion of females being in the idebenone 240 mg t.i.d. group). Mean, median and age ranges were similar, although the range was slightly wider in the idebenone 360 mg t.i.d. treatment group. In all treatment groups, approximately 90% of patients were Caucasian.

Overall, 2048 patients were exposed to idebenone in these studies for periods of up to a maximum of 2 years. In all treatment groups, the majority of patients received study medication for > 6 months, although from 7 to 12 months the percentage of patients remaining on idebenone 360 mg t.i.d. was less than in the other monotherapy groups. For patients receiving donepezil with either placebo or idebenone 360 mg t.i.d., exposure was similar in both treatment groups over the duration of studies PNFP 007 and PNFP 008.

The doses used in the AD trials were 360 to 1080 mg/day. Only the highest dose for AD was similar to the doses planned to be used for the FRDA indication patients (> 45 kg b.w.). Thus, the Alzheimer studies did not evaluate the maximum dose proposed in this application. The Alzheimer studies also involved a different age group; as a result, the safety data derived from these studies were considered of limited use.

Adverse events

Friedreich's ataxia studies

Data are presented separately for each of the Friedreich's ataxia studies since the study designs and dosages differed. In the NIH Phase I studies, adverse events were generally recorded only if they were considered to be possibly related to the study medication. Averse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 9.1, and toxicities were graded for severity according to the National Cancer Institute Common Toxicity Criteria (NCI CTC).

- NIH study 01-N-0167

In this single-dose study all cohorts completed dose-escalation to the maximum dose level allowed under the protocol (75 mg/kg) with no dose-limiting toxicity observed. Five AEs were reported in four of the children, and three of the five were in the highest dose group (75 mg/kg). Three AEs occurred in two of the adolescent patients, all receiving the 75 mg/kg dose. Fourteen AEs were reported in nine adult patients. Nausea was the most commonly reported AE in adults, occurring in seven patients, although only one was in the two highest doses. No adults in the two lowest dose groups experienced adverse events.

All the AEs were mild (NCI-CTC Grade 1), except one transient episode of hyperglycaemia reported as Grade 3. This occurred at the 5 mg/kg dose level in a diabetic patient with a history of poor glycaemic control and was deemed not related to study medication.

- NIH study 04-N-0129

In this study patients in all age groups received a daily dose of 60 mg/kg/day for 1 month. Fourteen of the fifteen patients completed the study. One child experienced Grade 1 nausea and diarrhoea on Day 2. Idebenone was stopped, the patient was re-challenged and the symptoms recurred, leading to withdrawal from the study. The four other children and the five adults completed the study without experiencing any AEs. Mild dyspepsia occurred in one adolescent, but it resolved and did not recur.

- NICOSIA study

A total of 260 adverse events were reported in the study, of which 82 were reported on the low dose, 72 on the middle dose, 48 on the high dose and 58 on placebo. Adverse events generally occurred at similar frequency with active medication and placebo. All reported adverse events were mild or moderate in severity, with the exception of two classified as serious adverse events as it is described in the "*Serious adverse event/deaths/other significant events*" section.

Table 8: Overview of the treatment-emergent adverse events occurring in more than one patient in the NICOSIA study, by treatment arm.

	Placebo Number of patients (%)	**Low dose** Number of patients (%)	**Mid dose** Number of patients (%)	**High dose** Number of patients (%)
	N = 11	**N = 12**	**N = 13**	**N = 12**
Preferred Term				
Upper respiratory tract infection	4 (36.4)	7 (58.3)	6 (46.2)	5 (41.7)
Headache	4 (36.4)	5 (42.7)	5 (38.5)	6 (50.0)
Myalgia	2 (18.2)	4 (33.3)	4 (30.8)	2 (16.7)
Gastroenteritis	1 (9.1)	3 (25.0)	5 (38.5)	2 (16.7)
Nausea	3 (27.3)	3 (25.0)	4 (30.8)	1 (8.3)
White blood cell count decreased	3 (27.3)	2 (16.7)	0	2 (16.7)
Diarrhoea	0	2 (16.7)	4 (30.8)	0
Dyspepsia	1 (9.1)	2 (16.7)	2 (15.4)	1 (8.3)

	Placebo Number of patients (%)	**Low dose** Number of patients (%)	**Mid dose** Number of patients (%)	**High dose** Number of patients (%)
	N = 11	**N = 12**	**N = 13**	**N = 12**
Fall	0	2 (16.7)	1 (7.7)	1 (8.3)
Influenza	1 (9.1)	1 (8.3)	1 (7.7)	1 (8.3)
Pharyngitis	1 (9.1)	1 (8.3)	2 (15.4)	0
Tachycardia	2 (18.2)	1 (8.3)	0	1 (8.3)
Vomiting	1 (9.1)	1 (8.3)	2 (15.4)	0
Anxiety	0	1 (8.3)	2 (15.4)	0
Epistaxis	3 (27.3)	0	0	0
Fatigue	0	1 (8.3)	0	2 (16.7)
Pyrexia	0	3 (25.0)	0	0
Toothache	0	1 (8.3)	1 (7.7)	1 (8.3)
Angina pectoris	1 (9.1)	0	0	1 (8.3)
Chest pain	1 (9.1)	0	1 (7.7)	0
Constipation	0	1 (8.3)	1 (7.7)	0
Depression	0	2 (16.7)	0	0
Dizziness	0	2 (16.7)	0	0
Dyspnoea	1 (9.1)	0	1 (7.7)	0
Hypersensitivity	0	1 (8.3)	0	1 (8.3)
Musculoskeletal chest pain	0	1 (8.3)	1 (7.7)	0
Urinary tract infection	0	1 (8.3)	1 (7.7)	0

The most common adverse events associated with Sovrima were gastrointestinal disorders (diarrhoea, nausea, vomiting and dyspepsia), although there did not appear to be a clear relationship between the Sovrima dose and the overall incidence of adverse events. The reported adverse events were mild or moderate, and did not lead to discontinuation of study medication, except for two adverse events (chest pain on placebo, nausea and vomiting 3 weeks after the end of treatment) which were classed as serious as they resulted in hospitalisation (please see section "*Serious adverse event/deaths/other significant events*").

Table 9: Treatment-emergent related adverse events in the NICOSIA study.

	Number (%) of Patients				
	Low Dose (n = 12)	**Mid Dose (n = 13)**	**High Dose (n = 12)**	**All Active Treatment Groups Combined (n = 37)**	**Placebo (n = 11)**
Any Body System	9 (75.0)	10 (76.9)	4 (33.3)	23 (62.2)	5 (45.5)
Cardiac Disorders	0	0	1 (8.3)	1 (2.7)	1 (9.1)
Angina pectoris	0	0	1 (8.3)	1 (2.7)	1 (9.1)
Gastrointestinal Disorders	6 (50.0)	8 (61.5)	1 (8.3)	15 (40.5)	4 (36.4)
Abdominal pain upper	0	1 (7.7)	0	1 (2.7)	0
Constipation	1 (8.3)	0	0	1 (2.7)	0
Diarrhoea	2 (16.7)	4 (30.8)	0	6 (16.2)	0
Dyspepsia	2 (16.7)	2 (15.4)	0	4 (10.8)	1 (9.1)

	Number (%) of Patients				
	Low Dose (n = 12)	**Mid Dose (n = 13)**	**High Dose (n = 12)**	**All Active Treatment Groups Combined (n = 37)**	**Placebo (n = 11)**
Nausea	2 (16.7)	3 (23.1)	1 (8.3)	6 (16.2)	3 (27.3)
Reflux oesophagitis	0	1 (7.7)	0	1 (2.7)	0
Vomiting	1 (8.3)	1 (7.7)	0	2 (5.4)	1 (9.1)
Infections and Infestations	1 (8.3)	0	0	1 (2.7)	1 (9.1)
Gastroenteritis	1 (8.3)	0	0	1 (2.7)	0
Influenza	0	0	0	0	1 (9.1)
Investigations	0	0	1 (8.3)	1 (2.7)	0
White blood cell count decreased	0	0	1 (8.3)	1 (2.7)	0
Musculoskeletal and Connective Tissue Disorders	0	2 (15.4)	0	2 (5.4)	0
Musculoskeletal chest pain	0	1 (7.7)	0	1 (2.7)	0
Myalgia	0	1 (7.7)	0	1 (2.7)	0
Nervous System Disorders	4 (33.3)	3 (23.1)	4 (33.3)	11 (29.7)	1 (9.1)
Disturbance in attention	0	1 (7.7)	0	1 (2.7)	0
Headache	3 (25.0)	2 (15.4)	4 (33.3)	9 (24.3)	1 (9.1)
Syncope	1 (8.3)	0	0	1 (2.7)	0
Psychiatric Disorders	1 (8.3)	0	0	1 (2.7)	0
Insomnia	1 (8.3)	0	0	1 (2.7)	0
Renal and Urinary Disorders	0	1 (7.7)	0	1 (2.7)	0
Chromaturia	0	1 (7.7)	0	1 (2.7)	0
Respiratory, Thoracic and Mediastinal Disorders	0	0	0	0	1 (9.1)
Dyspnoea	0	0	0	0	1 (9.1)

In the NICOSIA study there was no relation between AEs and dose and Sovrima appeared to have a good safety profile. The maximum doses employed in the NICOSIA study were lower than in Study 01-N-0167 (50 mg/kg/day vs 75 mg/kg/day), where most AEs were seen in the 75 mg/kg/day group.

Alzheimer's disease studies

The number of patients with any adverse events was similar in all treatment groups, being 76% to 80% in all except the group receiving the lowest dose of idebenone (120 mg t.i.d.) where it was slightly higher at 86%. The incidence of serious adverse events, severe adverse events and adverse events leading to withdrawal was similar in all treatment groups, including placebo. No clear dose relationship could be observed and there appeared to be no difference between monotherapy or combination therapy.

The most common adverse events overall were psychiatric disorders, which occurred with a higher frequency in the idebenone groups than in the placebo groups. The percentage of patients with psychiatric disorders were 10.2 % in the placebo group compared with 15.2 %, 18.1 % and 15.0 % in the idebenone groups 360 mg/day, 720 mg/day and 1080 mg/day, respectively. Agitation and confusion were most common among the psychiatric disorders.

The other most common adverse events were gastrointestinal disorders, especially diarrhoea and accidental injury. Several of these events occurred more frequently on active than on placebo treatment, especially the followings: diarrhoea, nausea, vomiting, abdominal pain, upper respiratory tract infections and somnolence. There was, however, no clear dose relationship apparent for any of these events.

An overview of treatment-emergent adverse events from the pooled database of studies in Alzheimer's disease is presented in the table below.

Table 10. Overview of treatment-emergent adverse events (Alzheimer's disease patients; safety population).

	Number (%) of patients per treatment group (t.i.d. dose)					
	Placebo	**Idebenone 120 mg**	**Idebenone 240 mg**	**Idebenone 360 mg**	**Placebo+ donepezil**	**Idebenone 360 mg+ donepezil**
	N = 362	**N = 217**	**N = 348**	**N = 633**	**N = 401**	**N = 407**
Number (%) of patients with:						
Any AE	278 (76.8)	186 (85.7)	277 (79.6)	504 (79.6)	317 (79.1)	314 (77.1)
Any treatment-related AE	113 (31.2)	107 (49.3)	154 (44.3)	239 (37.8)	139 (34.7)	147 (36.1)
Any severe AE	40 (11.0)	28 (12.9)	35 (10.1)	66 (10.4)	35 (8.7)	42 (10.3)
Any SAE*	50 (13.8)	33 (15.2)	40 (11.5)	75 (11.8)	47 (11.7)	57 (14.0)
AE that led to withdrawal	27 (7.5)	18 (8.3)	28 (8.0)	57 (9.0)	31 (7.7)	31 (7.6)

Source: Tables 5.1, 7, 8, 9, 10, Module 5.3.5.3.1

Percentages are based on the number of subjects in the safety population for each treatment group.

* Specific data on deaths were not collected on the Case Record Form (CRF) or included in the study databases, but are available from patient narratives in the individual study reports.

The safety profile of idebenone as demonstrated by the number of patients with adverse events, was comparable to placebo (or comparable to placebo added to donepezil 10 mg qd in studies PNFP-007 and -008]. Many of the most common adverse events were known to be commonly associated with Alzheimer’s disease (psychiatric disorders: agitation/depression/confusion) or related to the advanced age of these patients (urinary tract infection/incontinence; cardiovascular disorders: hypertension). However, the gastro-intestinal disorders, especially diarrhoea, nausea and vomiting were less likely to be age- or disease- dependent.

The most common adverse events (i.e. those which occurred in ≥ 5 % of patients in any one treatment group) and reported as being related to study medication are presented in Table 15, by descending frequency within body system.

Table 11: Treatment-emergent related adverse events experienced by ≥ 5% of patients in any treatment group (Alzheimer's disease patients; safety population).

	Number (%) of patients per treatment group (tid dose)					
	Placebo	Idebenone 120 mg	Idebenone 240 mg	Idebenone 360 mg	Placebo+ donepezil	Idebenone 360 mg+ donepezil
	N = 362	N = 217	N = 348	N = 633	N = 401	N = 407
Any treatment-related adverse event	113 (31.2)	107 (49.3)	154 (44.3)	239 (37.8)	139 (34.7)	147 (36.1)
Psychiatric Disorders – Any related event	37 (10.2)	33 (15.2)	63 (18.1)	95 (15.0)	48 (12.0)	53 (13.0)
Agitation	9 (2.5)	13 (6.0)	16 (4.6)	15 (2.4)	13 (3.2)	11 (2.7)
Confusion	5 (1.4)	4 (1.8)	16 (4.6)	11 (1.7)	1 (0.2)	4 (1.0)
Gastro-Intestinal System Disorders – Any related event	37 (10.2)	34 (15.7)	49 (14.1)	69 (10.9)	53 (13.2)	63 (15.5)
Diarrhoea	11 (3.0)	17 (7.8)	12 (3.4)	19 (3.0)	20 (5.0)	26 (6.4)
Nausea	6 (1.7)	9 (4.1)	14 (4.0)	15 (2.4)	21 (5.2)	21 (5.2)
Central & Peripheral Nervous System – Any related event	28 (7.7)	33 (15.2)	38 (10.9)	56 (8.8)	31 (7.7)	29 (7.1)
Dizziness	13 (3.6)	12 (5.5)	20 (5.7)	26 (4.1)	14 (3.5)	10 (2.5)
Headache	13 (3.6)	17 (7.8)	15 (4.3)	18 (2.8)	5 (1.2)	9 (2.2)

Source: Table 7, Module 5.3.5.3.1

Serious adverse event/deaths/other significant events

Phase I/II studies in Friedreich's ataxia

There were no deaths in any of the three Friedreich's ataxia studies. No serious adverse events were reported in the NIH Phase I studies. In the NICOSIA study, two adverse events were classified as serious since they led to hospitalisation. One patient receiving placebo, with a history of cardiomyopathy, was hospitalised for investigation of chest pain. Investigations were negative, including an ECG recorded during the pain episode. Another patient receiving low-dose idebenone was hospitalised due to nausea and vomiting for one day, 3 weeks after completing the study. The symptoms had occurred intermittently both before and during the study. The event was considered unrelated to study medication.

Phase III studies in Alzheimer's disease

Nineteen deaths occurred in this elderly population while on study medication or within 14 days of last dose. With one exception (in study PNFP-008, ventricular dysrhythmia in an 89-year-old was reported as possibly related according to the investigator, and assessed as not related according to the sponsor) none of the deaths were deemed by the investigators to be related to study medication.

Serious adverse events occurred most frequently in the respiratory, gastrointestinal and psychiatric body systems. The most common individual serious adverse events, although infrequent, were accidental injury (range 0.5% with idebenone 360 mg t.i.d. + donepezil to 2.3% with idebenone 120 mg t.i.d.; 1.9% with placebo) and agitation, where the highest incidence (1.7%) occurred with placebo treatment. The incidence of all other severe individual events was less than 1.0%, with the exception of myocardial infarction in the idebenone 120 mg t.i.d. group, which was slightly higher (1.4%). Most serious adverse events were considered by the investigators to be unrelated to study drug. The number of patients with any serious adverse events was similar across all treatment groups, including placebo. There was no trend for dose-related increase. Severe gastrointestinal adverse events were relatively uncommon (range 0.7 % with placebo + donepezil to 2.3 % with idebenone 120 mg t.i.d.), with no individual event being severe in more than 0.9% of cases.

The most common adverse events overall leading to discontinuation were psychiatric disorders (e.g. agitation, confusion and somnolence), gastrointestinal disorders (e.g. diarrhoea, abdominal pain, nausea and dyspepsia) fatigue, dizziness, accidental injury, rash and cerebrovascular disorder. The incidence of these adverse events was relatively evenly distributed between the placebo group and the active groups with no clear dose-response.

Laboratory findings

Haematological findings

In the NIH Phase I Friedreich's ataxia studies, there were no significant changes in the haematology or clinical chemistry parameters. In the NICOSIA study, low white cell counts were no more common with active medication compared with placebo. However, one child in the NICOSIA study (receiving high-dose Sovrima) was noted to have a low white cell count (2.2 x 10^9/L) at the final (month 6) visit. Sovrima was withdrawn according to plan, this being the final scheduled visit. Redraw on the same day showed a value of 2.7, while the following day the value was 2.0 x 10^9/L. Five days later the value had risen to 3.8 x 10^9/L. No other explanation for the observed leucopenia was found by either the investigator or the consulting haematologist, and the relationship to study medication was considered probable by the investigator.

In the WHO International Drug Monitoring Database, there were one report of aplastic anaemia and one report of agranulocytosis. Both reports were confounded by comedications and this made it difficult to determine the possible role of idebenone.

Hepatobiliary findings

No hepatobiliary disorders were reported during the NIH Friedreich's ataxia studies. In the Takeda drug interaction study PNFP-003, one subject discontinued due to significantly elevated liver enzymes (alkaline phosphatase, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) starting on Day 6, in Phase I of the study. These were recorded during per-protocol laboratory sampling and were not reported as adverse events. Abnormal values returned to within normal limits by the end of the study, with the exception of a clinically non-significant elevated lactate dehydrogenase (LDH; 285 u/L) at the final visit. Clinically significant elevated liver enzymes returned to baseline values within 4 weeks.

Safety in special populations

Renal impairment: A study in patients with severely impaired renal function was performed by Takeda. In these patients plasma exposure of total idebenone and QS10 increased 1.5-fold and 2-fold respectively, however larger increases were also observed. One patient had a serious adverse event (cerebral haemorrhage occurring 16 days after dosing), which was considered unrelated to study medication. No firm safety conclusion could be drawn from this single dose study on 120 mg and no multiple dose study was made available.

Hepatic impairment: An hepatic impairment study was performed by Takeda. One death, which was considered unrelated to study medication, occurred in a patient after surgery related to an episode of pancreatitis. In patients with impaired hepatic function (liver cirrhosis), there was no information on the increased exposure of the pharmacologically active compound (unconjugated idebenone). Given these uncertainties, a contraindication in patients with moderate and severe hepatic impairment was considered necessary.

Safety related to drug-drug interactions and other interactions

In healthy volunteers, no significant interactions between idebenone and lithium, amitriptyline, fluvoxamine or donepezil were observed. No other drug-drug interaction studies with idebenone were performed and no case reports of drug interactions were provided.

Post marketing experience

Haematological events

Postmarketing, there were 23 patients listed with blood cell abnormalities. Among these were 20 events (in 17 patients) involving reduced cell counts, as follows:

- Agranulocytosis: five events
- Granulocytopenia: three events
- Aplastic anaemia: one event, which ended fatally
- Leukopenia: four events
- Red blood cell count reduced: three events
- Thrombocytopenia: four events.

Hepatobiliary events
Postmarketing, hepatic laboratory abnormalities were reported as serious in nine patients.

Discussion on clinical safety
In conclusion, the submitted safety documentation comprised data from the trials for Friedreich's ataxia, the trials in the program for Alzheimer's disease in US, and postmarketing experience. For the applied indication higher doses of idebenone (450-2250 mg/day) were recommended than those used previously, and the documentation for these high doses was limited. In the NICOSIA study on FRDA patients the most common adverse events associated with idebenone were gastrointestinal disorders (diarrhoea, nausea and vomiting). There was no clear relation between the dose and the overall incidence of adverse events. One child in the NICOSIA study (receiving high-dose idebenone) was reported to have a low white cell count (2.2×10^9/L) probably related to idebenone.
The experience from the Alzheimer trials was considered to be of limited value since the doses were in general lower, and the AD patients were older and had more concomitant medications. The highest dose group in the Alzheimer trials was 1080 mg/day and with this dose the most common adverse events were gastrointestinal side effects (nausea, vomiting, and diarrhoea), somnolence, anxiety and rash.
There is a vast post-marketing experience with idebenone, particularly in Japan, which includes rare reports on serious blood adverse drug reactions and reports on serious hepatic laboratory abnormalities. However, the doses used for treatment of cerebrovascular disease were low, only 90 mg/day. The proposed dose recommendation for FRDA in the present application is much higher, from 900 mg to 2250 mg/day for patients weighing over 45 kg. As a result, the value of the post-marketing data for the safety assessment in the new indication was considered very limited.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP consider that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way and there are no major unresolved quality issues which could have a negative impact on the benefit/risk balance.,The inclusion of the azo-dye in the tablets composition remained an unresolved issue at the time of the opinion that could be solved post-authorisation in the event of a positive opinion.

Non-clinical pharmacology and toxicology

From the pre-clinical data provided, it appeared that idebenone is without any major adverse effect and is of low oral acute toxicity in animals. The only adverse effects observed were in the forestomach of mice and rats. The forestomach is a rodent-specific organ and the finding is considered to be of low clinical relevance. Idebenone is extensively metabolized, resulting in numerous metabolites which are found in plasma in significantly higher concentrations than parent idebenone. It is not known to what

extent the metabolites contribute to the observed pharmacodynamic effects and the toxicity. However, in view of the low observed toxicity it was considered that these uncertainties were acceptable especially in relation to the intended indication. The applicant was requested to conduct a Phase II environmental fate and effect analysis according to guideline EMEA/CHMP/SWP/4447/00.

Efficacy

The Applicant submitted the results of one 6-month phase II study in patients with Friedreich's ataxia with Sovrima doses higher than those previously used in published studies. The number of patients in the study was limited (n= 48). No effect was seen on the primary endpoint: change in a proposed surrogate marker for oxidative stress from baseline to month 6. For the secondary endpoints neurological assessment with the ICARS and FARS scales, there were trends for a more favourable outcome with the mid and high doses of Sovrima but the differences vs. placebo were not statistically significant. For measures of cardiac hypertrophy, the Applicant has submitted a revised analysis in the Day120 response document. The final analysis shows a statistically significant effect of the mid dose of Sovrima on a measure of cardiac hypertrophy, LVMI, and on a cardiac functional outcome parameter, Left Ventricular Ejection Fraction (LVEF). With the responses to the Day150 LoOI, the Applicant has provided some additional support for the claimed indication in terms of published data. Furthermore, the Applicant has informed the CHMP of two on-going phase III trials; the MICONOS study and the IONIA study.
Currently there is neither sufficient PK nor efficacy data to support the weight-based posology. The current PK data does not support a weight based posology. Sampling for population PK analysis is performed in the ongoing studies MICONOS and IONIA. Depending on the distribution of weights in the ongoing studies, it may be possible in future to conclude or exclude a correlation between body weight and clearance of unconjugated idebenone and possibly also to include a better justified weight cut-off.
To conclude, the efficacy documentation for Sovrima in the treatment of FRDA is primarily based on one pivotal 6-month phase II study which included 48 patients. There was no effect on the primary efficacy endpoint (the change from baseline to month 6 in the plasma level of 8-hydroxy-2'-deoxyguanosine (8OH2'dG), a surrogate marker for oxidative stress). A trend for positive effects of the mid and high doses of Sovrima was observed on scales for neurological assessment included as secondary efficacy endpoints. With regard to cardiac parameters, there was a statistically significant effect of the mid dose of Sovrima on measures of cardiac hypertrophy and cardiac function in the Applicant's revised analysis. For other secondary parameters, including SF-10 and Clinical Global Impression of Change, there were no statistically significant effects. Therefore the CHMP considered that efficacy of Sovrima for the treatment of FRDA has not been convincingly demonstrated. Even if the submitted data suggest that there might be a modest beneficial effect of the mid and high doses of Sovrima on neurological and cardiac symptoms in FRDA, the results need to be confirmed for a sufficient number of patients. The results of the ongoing phase III trials MICONOS and IONIA should be awaited.

The CHMP considered the possibility of approving the product under "Exceptional Circumstances"; however, this is not applicable given that phase III studies are currently recruiting and their results will give additional information on the efficacy of the compound. Likewise, "Conditional approval", with ongoing studies being part of the conditions, was also considered not applicable. Such approval requires that a positive B/R is established which cannot be said in this case given the limited and inconclusive efficacy documentation.

Safety

The overall possibility to assess the pharmacokinetics in patients with renal and hepatic impairment is hampered by the fact that there are no data on unconjugated idebenone. However, given the applicant's suggestion to contraindicate the product in patients with severe hepatic impairment, and the fact that the renal excretion of unconjugated idebenone is very low, a recommendation of caution in the product information was considered to be sufficient in case a positive opinion was to be granted.

The Applicant has conducted no non-clinical or clinical pharmacodynamic drug interaction studies. In order to conclude that there are no pharmacodynamic interactions with commonly co-prescribed medicinal products in patients with FRDA it was considered necessary to perform the proposed interaction studies (propranolol and glibenclamide). Otherwise the potential for pharmacodynamic interactions seem limited, given the mechanism of action of idebenone.

The safety documentation in the clinical studies includes data from the trials for Friedreich's ataxia, the trials in the program for Alzheimer's disease in US, and postmarketing experience. For the applied indication higher doses of idebenone (450-2250 mg/day) are recommended than the doses previously used. The experience from the Alzheimer trials is of limited value since the doses were in general lower, and the AD patients are older and have more concomitant medications. The highest dose group was 1080 mg/day and with this dose, the most common adverse events were gastrointestinal side effects (nausea, vomiting, and diarrhoea), somnolence, anxiety, and rash. There is a considerable post-marketing experience with idebenone, but again the value of this experience is limited since in general low doses have been administered.

The post-marketing experience with idebenone includes rare reports of serious blood adverse drug reactions, and reports on serious hepatic laboratory abnormalities. During the procedure, the Applicant submitted a Risk Management Plan that does not fulfil the CHMP requirements. The plans for additional pharmacovigilance activities, extended follow-up and an observational multicentre cohort study would have been endorsed if the efficacy of Sovrima was convincingly demonstrated. However, the Applicant should describe the design, implementation and feasibility of the respective pharmacovigilance studies in adequate detail. More elaborate protocols should therefore be submitted in a revised RMP that should also include a summary of the proposed EU RMP revised in accordance with the template EMEA/192632/2006.

Risk-benefit assessment

In conclusion, the CHMP considered that, following review of the data provided, there are concerns with respect to the risk-benefit of Sovrima for use in the treatment of Friedreich's Ataxia in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years and in adult Friedreich's Ataxia patients with cardiomyopathy, for the following grounds:

- The efficacy of Sovrima for the treatment of Friedreich's ataxia has not been demonstrated. The efficacy documentation is based on primarily one study, evaluating a total of 48 Friedreich's ataxia patients. No statistically significant effect was observed for the primary endpoint.

- The reliability of the results of the secondary endpoints is questioned. There were many secondary endpoints of which only a subset showed statistical significance and only for one of the three dose levels. Given the multiplicity issues in considering multiple endpoints and multiple dose levels the level of statistical evidence is not considered compelling.

- There is no clear rationale for the dose-response pattern with the mid dose (450 mg/day for patients ≤ 45 kg body weight and 900 mg/day for patients >45 kg body weight) of Sovrima apparently performing better than the high dose (1350 mg/day for patients ≤ 45 kg body weight and 2250 mg/day for patients >45 kg body weight).

- The supportive evidence from published studies is insufficient. Most of the published studies were open-label and the results were not consistent across endpoints important to establish clinical benefit.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Sovrima in the treatment of Friedreich's Ataxia in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years and in adult

Friedreich's Ataxia patients with cardiomyopathy was unfavourable and therefore did not recommend the granting of the marketing authorisation.

3 RE-EXAMINATION OF THE CHMP OPINION

At the July 2008 CHMP meeting the CHMP concluded that the benefit-risk balance of Sovrima in the treatment of Friedreich's ataxia (FRDA) in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years and in adult Friedreich's Ataxia patients with cardiomyopathy was unfavourable and therefore did not recommend the granting of the market authorisation.

The applicant submitted the written notice requesting the re-examination on 7 August 2008 on 19 September 2008, and the detailed grounds for the re-examination of the grounds for refusal as outlined in the CHMP assessment report were submitted on 19 September 2008.
The meeting of SAG-CVS was held on 5 November 2008.

3.1 Grounds for re-examination

Ground for refusal 1: The efficacy of Sovrima for the treatment of Friedreich's ataxia has not been demonstrated. The efficacy documentation is based on primarily one study, evaluating a total of 48 Friedreich's ataxia patients. No statistically significant effect was observed for the primary endpoint.

> Applicant's position: In the view of the applicant the observed clinical efficacy of SOVRIMA (idebenone) for the treatment of FRDA has been demonstrated. Whilst the CHMP has acknowledged that clinical benefit has been shown, the CHMP has concluded that this is a modest effect. The applicant believes, however, that the relevance of this clinical benefit has been underestimated. The applicant presents testimony from experts experienced in the management of FRDA patients who report that the benefit demonstrated is clinically relevant and consistent with their experience with idebenone in daily practice.
>
> In view of the good safety profile of idebenone, and in combination with this clinical benefit, the applicant believes that the benefit/risk balance is positive at this point for paediatric FRDA patients.
>
> The applicant presents arguments demonstrating that the lack of a statistically significant effect for the primary endpoint, a non validated biomarker, is not relevant for the conclusions on clinical benefit/risk balance.

Ground for refusal 2: The reliability of the results of the secondary endpoints is questioned. There were many secondary endpoints of which only a subset showed statistical significance and only for one of the three dose levels. Given the multiplicity issues in considering multiple endpoints and multiple dose levels the level of statistical evidence is not considered compelling.

> Applicant's position: The applicant presents arguments that the clinical benefit was concluded from efficacy seen with validated secondary endpoints which showed a positive effect, whereas other exploratory endpoints were inconclusive. It is highlighted that the use of multiple endpoints is desirable in clinical studies in orphan diseases, where there is very limited clinical experience and where it can only be expected that several of these endpoints may be found to be inconclusive. In light of the small population available for clinical testing, the results should be interpreted based on clinical judgment, as presented in the experts' reports provided, rather than on statistical considerations alone.

Ground for refusal 3: There is no clear rationale for the dose-response pattern with the mid dose (450 mg/day for patients ≤ 45 kg body weight and 900 mg/day for patients >45 kg body weight) of Sovrima apparently performing better than the high dose (1350 mg/day for patients ≤ 45 kg body weight and 2250 mg/day for patients >45 kg body weight).

> Applicant's position: The applicant provides arguments that the mid and high dose of SOVRIMA performed comparably for all parameters in which efficacy has been shown,

which is consistent with a standard pharmacological dose response. Whilst the mid and high doses consistently performed better than the low dose and placebo, the applicant proposes the use of the mid (900 mg/day) dose at the present time in paediatric FRDA patients.

Ground for refusal 4: The supportive evidence from published studies is weak. Most of the published studies were open-label and the results were not consistent across endpoints important to establish clinical benefit.

Applicant's position: The applicant maintains the position that although the majority of studies were open label, with the notable exception of the double blind study by Mariotti, these still demonstrated consistent efficacy in FRDA, particularly in younger patients.

The applicant believes that the presented grounds justify reexamination of the negative opinion and proposes that SOVRIMA is approved for the treatment of paediatric FRDA patients at a dose of 900 mg/day conditional upon the results of the IONIA study in paediatric patients. The results of the ongoing MICONOS study in adult FRDA patients will be submitted at a later time in support of a variation for an adult indication.

Detailed positions

Ground for refusal 1

Applicant's position: The clinical relevance and importance of the observed effects with idebenone in paediatric FRDA patients in the NICOSIA study as well as in the published literature has not been acknowledged adequately during the review process. Particularly in the light of the good safety profile of idebenone the available efficacy data currently provide a positive benefit/risk balance in paediatric patients. This view is supported by experts in the field as presented in expert reports:

- Professor Schulz (University of Göttingen, DE) on the efficacy of idebenone with respect to improvement in neurological function and its clinical relevance
- Professor Rademakers, (University of Leuven, BE) with a supporting statement by Professor Erne (University Hospital of Luzern, CH) commenting on the efficacy of idebenone on FRDA-associated cardiomyopathy

While all experts welcome the ongoing clinical studies (IONIA & MICONOS) which are collecting additional efficacy data, particularly in adult FRDA patients (MICONOS), they also conclude their report with a recommendation that idebenone is made available to young FRDA patients immediately so that potentially avoidable decline in their condition is prevented.

The applicant agrees with the experts' opinion that the observed effects with idebenone are clinically meaningful and not "modest" as stated in the assessment report. The background supporting the clinical meaningfulness of the results observed is discussed in detail in the expert reports. For example, concerning the importance of the neurological effect observed, the average improvement on the ICARS scale in the NICOSIA trial is 4 points, in contrast to the 5 point decline seen in untreated FRDA patients over one year (Fahey, 2007) .

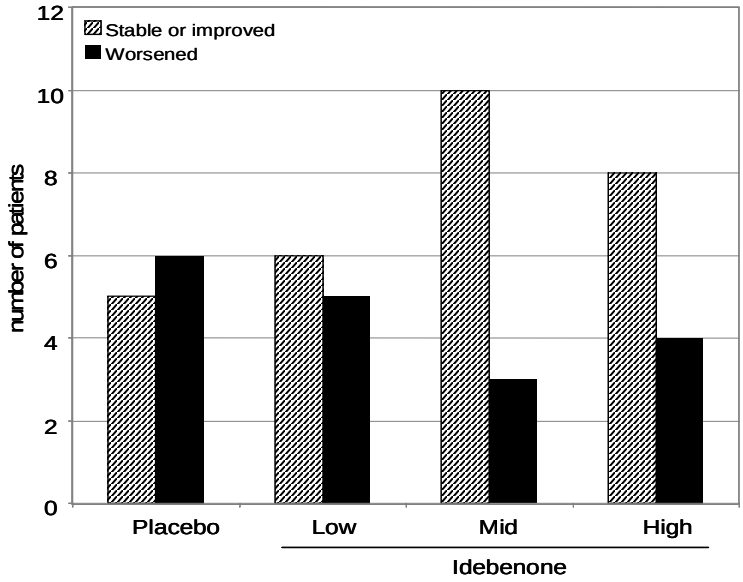
As explained in the Day 120 and Day 180 responses the proportion of patients showing such a clinically relevant response was increased in the mid and high dose groups as shown below:

Responder analysis for the ICARS scale as presented in D120 responses

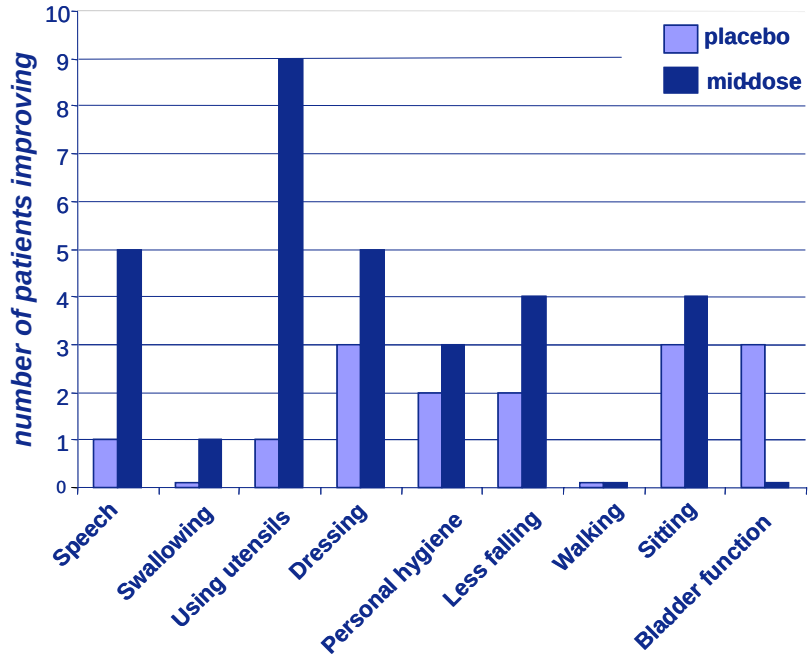
		Idebenone Dose		
	Placebo N=11	**Low** N=12	**Mid** N=13	**High** N=12
Patients with response on ICARS of > 5 points	1 (9.1%)	2 (17%)	5 (39%)	5 (42%)

The clinical effect seen in neurological function is further emphasized by the efficacy of idebenone on activities of daily living (ADL). The average improvement on the ADL scale with idebenone is 1 point compared to an average decline of 1 point (representing loss of key functional activities). Since a 1-point change in this scale is clinically meaningful, the 2-point difference in mean changes strongly supports the clinical importance of the effects observed.
When the data are presented as a responder analysis showing the number of patients that worsened compared to the number that improved / stabilized, a clear treatment effect on the mid and high dose is seen. This graph was presented in the Day 180 answers.

Number of patients stabilised/ improved or worsened on the ADL scale compared to baseline

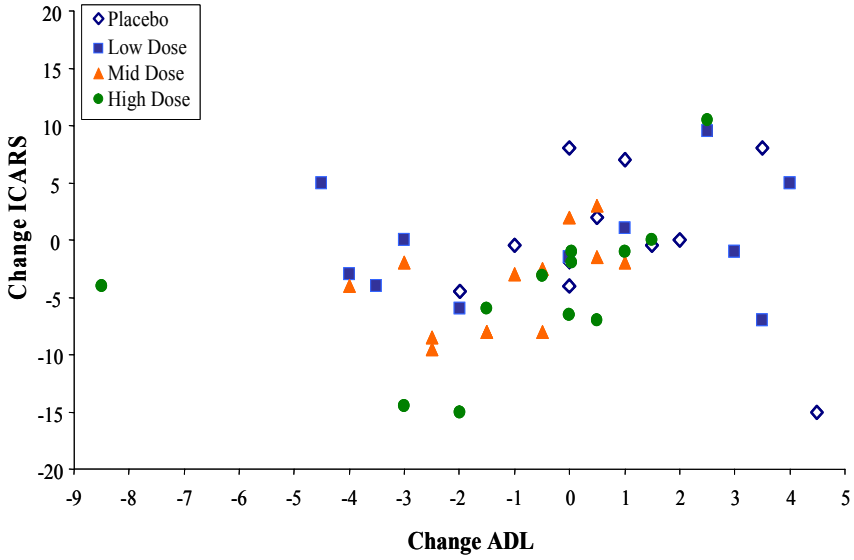


Further analysis of the efficacy in ADL subscores clearly demonstrates that a higher number of patients on mid dose idebenone improved compared to placebo in scale items addressing fine motor skills, such as speech, using utensils & cutting food, dressing and personal hygiene.
Number of patients improving on the ADL subscales (mid dose idebenone vs placebo):



In a progressive debilitating disease such as FRDA, which affects fine motor skills in young patients, preservation of activities of daily living is particularly important – but this does not seem to have been acknowledged in the current negative assessment.
The statistically significant correlation between the changes observed on ICARS and ADL scales, both of which are validated instruments, supports the conclusion of clinical meaningfulness of the neurological changes as shown in the scatter plot from the NICOSIA clinical study report.
Correlation of changes on ICARS and ADL for all treatment groups (graph taken from study report)

Pearson correlation coefficient: 0.308; p=0.035



The statement "*The efficacy documentation is based on primarily one study, evaluating a total of 48 Friedreich's ataxia patients*" in the major objection does not take into account the substantial body of evidence from independent studies which have reported a meaningful effect and good safety of idebenone (see Table below). This has led to the compound's approval under a temporary license in Switzerland (see expert comment, Professor Erne) for treating cardiomyopathy associated with FRDA and to the initiation of compassionate use programs in several countries throughout Europe. Whilst this availability has provided clear benefit to FRDA patients, it has made the conduct of placebo controlled studies very problematic.
Data concerning neurological efficacy in adults are limited to a few open-label studies using primarily low doses of idebenone which show inconsistent results. Clinically important neurological efficacy in children has however been reported by Pineda et al. (2008) who escalated doses up to the mid dose of the NICOSIA trial, and as in the NICOSIA study, observed symptomatic effects and the stabilization of neurological function (as discussed in the expert report by Professor Schulz).
The body of literature on cardiac effects was reported in the original submission but in the view of the Applicant was not considered appropriately by the assessors in reaching their conclusions. In short, the results of these studies consistently show improvement in cardiac hypertrophy and function in children and adults, where the treatment was of at least 4 months duration.

Overview of Published Clinical Studies with Idebenone in FRDA (period 1999-2008; in chronological order, full papers only)

Reference	**No. of patients** (age in y)§	**Duration treatmt.** (mo/y)	**Idebenone Dose‡**	**Type**	**Clinical Endpoints**	**Effect**
Rustin 1999	3 (11, 19, 21)	4-9 mo	5 mg/kg/d	OL	Cardiac: SWT, PWT, LVMI	↓SWT 31-36%, PWT 8-20%, LVMI 21-32%.
Rustin 2004	1 pts	5 y				↓ cardiac hypertrophy after 5 y.

Schulz 2000	8	2 mo	5 mg/kg/d	OL	Biomarker: Urinary 8OH2'dG[#]	↓ 20% ($p < 0.05$)
Schöls 2001	9 (19-54)	1.5 mo	360 mg/d (not weight adjusted)	RCT	Cardiac: SWT, PWT, LVMI, SF Biomarker: PCr recovery by ^{31}P-MRS	No improvement compared to placebo; treatment duration likely too short to allow conclusion Overall little changes in PCr, ↑ in ATP in aerobic exercise in 3 of 9 patients
Artuch 2002	9 (11-19)	12 mo	5 mg/kg/d	OL	Cardiac: SWT, PWT Neurological: ICARS	No change from baseline* ↓ 49% from baseline ($p=0.007$)
Hausse 2002	38 (4-22)	6 mo	5 mg/kg/d 1 pt: 10 mg/kg/d	OL	Cardiac: SWT, LVMI, SF	LVMI: >20% ↓ in half of patients ($p < 0.001$), stabilization in rest of patients SF: improvement in 5 of 6 pts with abnormal SF at BL
Mariotti 2003	29 (21-32)	12 mo	5 mg/kg/d (max: 450 mg/d)	RCT	Cardiac: LVM, SWT, PWT Neurological: ICARS	LVM: Ide: 5.6 % ↓; P: 10.7 % ↑, ($p=0.01$) SWT: Ide: 4.6 % ↓; P: 5.5 % ↑, ($p=0.004$) PWT: Ide: 8.6 % ↓; P: 2.4 % ↓, ($p=0.18$) No difference Ide *vs* P
Buyse 2003	8 (9-27)	12 mo	5 mg/kg/d (max: 300 mg/d)	OL	Cardiac: LVMI, SWT, PWT, Strain & strain rate (longitudinal & radial dimensions) Neurological: CAGRS	LVMI: 16.2% ↓; $p=0.03$ EOT *vs* BL. SWT & PWT: non-significant ↓ during study period. Strain / strain rate: significant improvement in regional myocardial function No improvement
Arnold 2006	20 (adults)	several mo (up to 3.5 y)	5-10 mg/kg/d	OL	Neurological: ICARS Biomarker: blood MDA	Improvement in dysarthria (63% of pts.), hand dexterity (58%), fatigue (47%) Total ICARS: no change during treatment for 2.9 y (10 pts). ↑ in MDA levels after Ide treatment (5 pts)
Di Prospero 2007	48 (9-17)	6 mo	L:180/360, M: 450/900, H: 1350/2250 mg/d[♦]	RCT	Neurological: ICARS, FARS, ADL Biomarker: urinary 8OH2'dG[#]	ICARS: dose-dependent ↓ in ITT population ($p=0.03$[•]); ambulatory patients[¥]: ↓on mid and high dose Ide (difference mid dose *vs* P: 6.24, $p=0.03$; high dose *vs* P: 7.67, $p=0.01$)[♣]. FARS: dose-dependent ↓ ($p=0.14$[•] for ITT, $p=0.04$[•] ambulatory pts) ADL: dose-dependent ↓ ($p=0.16$[•] for ITT, $p=0.05$[•] for ambulatory pts.) Values normal at BL; no change on Ide
Ribai 2007[¶]	104 pts (88 on Ide) (13-74)	6 mo – 7 y	5 mg/kg/d	OL	Neurological: ICARS Cardiac: LVMI, SWT, PWT, EF	Ide: 1.93 ± 0.25 ↑ p.a.[$]; P: 4.43 ± 1.56 ↑ p.a. LVMI: Ide: 4.1 ± 1.5 g/m^2 ↓ p.a.; SWT: Ide: 0.11 mm ±0.07 p.a. ↓ PWT: Ide: 0.40 mm ±0.08 p.a. ↓ EF: ↓

Pineda 2008	10 children (8-18) 14 adults (18-46)	up to 5 y	children: 5-10 mg/kg/d (max: 650 mg/d) adults: 5-20 mg/kg/d (max: 1400 mg/d)	OL	Neurological: ICARS Cardiac: LVMI, PWT, SWT, FS, EF	Children: initially improvement on ICARS, stabilize for prolonged period and return to baseline ICARS after 5 years. Adults: worsening on ICARS Stabilization on measures of cardiomyopathy in children and adults

ADL: Activities of daily living scale (note: a decrease on the ADL indicates improvement); BL: baseline; CAGRS: Cooperative Ataxia Group Rating Scale; EF: ejection fraction; EOT: end of treatment; FARS: Freidreich Ataxia Rating Scale (note: a decrease on the FARS indicates improvement); ICARS: International Cooperative Ataxia Rating Scale (note: a decrease on the ICARS indicates improvement); Ide: Idebenone; ITT: intent to treat; (L)VMI: (left) ventricular mass index; MDA: malondialdehyde; OL: open label trial; p.a.: per annum; P: Placebo; PCr: phosphocreatine; pts: patients; PWT: (left ventricular) posterior wall thickness; ^{31}P-MRS: ^{31}P magnetic resonance spectroscopy; RCT: randomized, placebo controlled trial; SF: shortening fraction; SWT: (interventricular) septal wall thickness;

‡ where available, max. daily dose provided in brackets
↑ increase
↓ decrease
§ age at baseline of study; rounded numbers
# 8-hydroxy-2-deoxyguanosine normalized to creatinine
* most patients had no or only mild cardiac hypertrophy at start of study (average SWT: 9.96 mm; PWT: 10.6 mm)
¶ natural history study; not focused on idebenone effects
$ data is mean ± SD; evolution was determined with a linear mixed-effect model taking into account several variables incl. GAA repeat length and age of disease onset.
♦ daily dose adapted to body weight. Low dose group (L): 180 mg/d for pts ≤ 45 kg body weight; 360 mg/d for patients > 45 kg body weight; Mid dose group (M): 450 mg/d for pts ≤ 45 kg, 900 mg/d for pts > 45 kg; High dose group (H): 1350 mg/d for pts ≤ 45 kg; 2250 mg/d for pts > 45 kg.
• Jonckheere trend test for dose-response
¥ defined as ICARS score at baseline of 10-54 (prespecified in statistical analysis plan)
♣ ANCOVA with Bonferroni correction for multiple comparisons

The applicant has emphasized the consistency of the results obtained in the NICOSIA study with those reported in the body of published supportive evidence. In the view of the experts this consistency is in line with their own clinical experience and should not be disregarded, (see reports of Professors Schulz, Rademakers and Erne).

When comparing the results of neurological and activities of daily living scales and cardiac imaging it becomes evident that in the NICOSIA trial a consistent improvement on mid and high doses versus placebo and low dose is observed. Therefore the conclusion was drawn that the independent reproduction of the same dose response pattern with multiple independent methods is a strong argument in favor of the pharmacological effect of idebenone in FRDA. This critical point is discussed in detail below.

Finally in assessing the benefit/risk balance of idebenone it should be taken into consideration that idebenone is very well tolerated and has an excellent historical safety profile. For example, the recommended dose of 900 mg/day would be supported by the large Alzheimer disease database which will significantly contribute to the safety information since in this program > 1000 patients were treated at a dose of 1080 mg/day. In this program idebenone was also shown to be safe and well tolerated, even in the frail elderly population involved. Indeed the overall AE profile was very similar to that observed in the FRDA population.

Overall the applicant is of the opinion that clinical benefit in the paediatric population has been demonstrated and that the benefit/risk balance in this population is positive.

The Applicant agrees that no statistically significant effect was observed for the primary endpoint. However, the clinical efficacy of SOVRIMA for the treatment of FRDA has been demonstrated by a number of secondary endpoints that showed that patients on an effective dose of idebenone improved on neurological function, activities of daily living and cardiac anatomy and function.

The selection of change in 8OH2'dG, a biomarker for oxidative stress, as primary endpoint was based on one single publication which suggested that 8OH2'dG is elevated in FRDA patients and that a reduction of this biomarker could offer a possibility to demonstrate the pharmacological action of idebenone in FRDA patients in a 6 months study. However, 8OH2'dG is not a validated biomarker for disease progression in FRDA and was an exploratory endpoint. Retrospectively, the selection of 8OH2'dG as primary endpoint for this study was not appropriate, as in the NICOSIA study 8OH2'dG

was not abnormal in FRDA patients at baseline and there was no change during the progression of the disease.
Early clinical work investigated the feasibility of 8OH2'dG as a biochemical marker for FRDA (Schulz 2000). This work has shown that 8OH2'dG is elevated in FRDA patients and can be reduced by idebenone treatment. When the NICOSIA study was designed, the investigators at the NIH proposed the change of 8OH2'dG as primary endpoint and to power the study based on the effect size observed in the Schulz study. The resulting sample size of 48 FRDA patients was compatible with the number that appeared feasible to be recruited by one study center from the paediatric patient population. The more clinically relevant parameters such as neurological (ICARS, FARS) and activities of daily living (ADL) scores as well as cardiac assessments (LVMI, LVEF) were declared secondary endpoints based on concerns that the expected effects would not be detectable in a small population.
However, the 8OH2'dG marker had not been validated in a controlled study and, most importantly, had never been tested in a paediatric FRDA population. The results of the NICOSIA study are in line with the available pharmacological data which indicate that oxidative stress is not an appropriate measure to monitor changes in disease state in FRDA considering the importance of mitochondrial dysfunction and resulting reduction in energy production for the pathology of this disease. These data rather indicate that idebenone acted by improving electron flow and increasing mitochondrial ATP biosynthesis.
More recent clinical work is consistent with the findings of the NICOSIA study in showing that the clinical efficacy of idebenone is not necessarily accompanied by a reduction in oxidative stress. The study of Arnold (2006) for example showed that another oxidative stress marker (malondialdehyde, MDA) was lower in FRDA patients compared to controls and increased to normal levels when patients were treated with idebenone. At the same time, however, improvements in fine motor skills and dysarthria were reported, again showing that markers for oxidative stress may not change in accordance with clinical improvements.
In summary**,** the lack of a biochemical effect of idebenone on a marker of oxidative stress can be explained by the fact that baseline values for 8OH2'dG were not abnormal, which is in contrast to a previous publication that was conducted with FRDA patients of a different age profile. The NICOSIA data are in line with current pharmacological models indicating that frataxin deficiency leads to a reduction in ATP biosynthesis as an important component of the disease rather than oxidative stress and suggests that idebenone acts by increasing ATP production rather than as an anti-oxidant.
A lack of appropriately validated endpoints is a hindering factor to conduct clinical trials in orphan diseases in general. This should be taken into consideration when evaluating the clinically meaningful changes in secondary endpoints as observed with idebenone in the NICOSIA study.

CHMP Position:

Results of one 6-month phase II study in patients (n=48) with Friedreich's ataxia with Sovrima doses higher than those previously used in published studies have been submitted. No effect was established on the primary endpoint: change in a proposed surrogate marker for oxidative stress from baseline to month 6.
For the secondary endpoints neurological assessment with the ICARS and FARS scales, there were trends for a more favourable outcome with the mid and high doses of Sovrima, however, the differences vs. placebo has not been statistically significant.
It still has to be determined whether a 4-point improvement in the ICARS can be considered clinically relevant.
Fahey et al (2007) had compared the FARS with others scales: ICARS, Functional Independence Measure (FIM) and Modified Barthel Index (MBI). Results showed that FARS is the best to use in clinical trials of FRAD. This is based on effect size, and power calculations that show that fewer participants are required to demonstrate the same effect of an intervention. Nevertheless, the exact change in any measure that is clinically important in FRAD is unknown at present (Lynch et al, 2005).It has to be noted that results on FARS were not significant.
It should be determined if a 4 point improvement in the ICARS scale (the total range of the ICARS is 0 to 100)or an improvement of 10% as compared to baseline value could be considered as clinically relevant.

For measures of cardiac hypertrophy the final analysis shows a statistically significant effect of the mid dose of Sovrima on a measure of cardiac hypertrophy, LVMI, and on a cardiac functional outcome parameter, Left Ventricular Ejection Fraction (LVEF).
For other secondary parameters, including SF-10 and Clinical Global Impression of Change, there were no statistically significant effects. The applicant focuses on the improvement seen on the ADL scale, which may be a hint for a clinically relevant improvement.
However, in summary this trial must be considered as a failed clinical trial based on the prespecified endpoints and outcome criteria.

The presented supportive evidence from other published clinical studies can be considered only as highly inconclusive and is of limited value as supportive evidence. The majority of the studies has been open-label, in most of them no statistically significant improvements on neurological or cardiac outcome has been established. However, trends for improvement on neurological and cardiac outcome can be considered after treatment with idebenone.

In a more detailed view only three studies were randomized and placebo-controlled. The 6-weeks idebenone treatment (Schöls et al, 2001) at 360 mg/day (a low dose) had not demonstrated any change in clinical neurologic rating score or the motor performance test neither in comparison to baseline nor in comparison to placebo. Echocardiography could not detect relevant changes.

Mariotti et al (2002) study (idebenone treatment during 12 months) had showed persistent moderate effects on echography indexes of heart hypertrophy. Analysis of ICARS total score and subscores did not reveal significant differences between the two groups of patients.

The third randomized-controlled study (Di Prospero et al, 2007) is the publication of results of NICOSIA study. To be noted that the authors concluded that the study results suggests that idebenone used at higher doses that previously tested may offer neurological benefit but have to be validated by Phase III clinical trials.

In the open-label study (Pineda et al, 2007) mentioned by the MAA, paediatric(5-10 mg/kg/day, maximum 650 mg/day) and adults patients (5-20mg/kg/day, maximum 1400 mg/day) were treated for 3-5 years . In paediatric patients, no significant differences were observed in total ICARS score when comparing baseline status and the end of the study. In all adults patients studied, ICARS scores increased. No significant differences were observed in any of the echocardiographic measurements in children, hypertrophic cardiomyopathy was not modified during the follow-up of adults cases. In conclusion, in children population no deterioration was observed, however, the natural history of the disease is unknown.
However, it should be discussed with the experts whether the hint that the age of the patient "at the initiation of treatment may be an important factor in the effectiveness" of the idebenone therapy can be concluded.

Overall the argumentation of the applicant can be followed and benefit-risk assessment based on clinical outcomes is clearly preferred over surrogate parameters with limited validation.
However, the results on the clinical outcomes measured as secondary endpoints are considered inconsistent and of questionable clinical relevance (see ground for refusal III.2).

Ground for refusal 2

Applicant's position: This ground for refusal does not take into account the difficulty of performing clinical trials in orphan indications. For clinical research in such indications it is extremely difficult if not impossible to validate properly endpoints for clinical trials due to the lack of clinical experience and of patients available for studies. As a consequence of this it is unavoidable and indeed desirable (as stated in the Guideline for Clinical Trials in Small Populations) to include multiple exploratory endpoints in clinical trials and therefore it is also unavoidable that many of these will not be met. Failure to demonstrate statistical significance in multiple endpoints in this situation reflects an inherent difficulty in the design of studies in orphan drugs and cannot be interpreted as failure of the drug to show efficacy.
Although the key secondary endpoints that were included in the NICOSIA study were adequately validated (eg ICARS, ADL, LVMI, LVEF), a number of exploratory endpoints were also included.

The following table lists the endpoints tested, their level of clinical validation as well as the results obtained:

Efficacy profile of idebenone across validated and exploratory endpoints

Category	End point	Clinically validated	Exploratory
Function	Activities of Daily Living	p=0.035	
Neurological	ICARS	p=0.080 (ITT) p=0.047 (ITT pooled)	
Cardiac	LVMI	p=0.036	
Cardiac	LVEF	p=0.040	
Cardiac	LVM	p=0.017	
Cardiac	Maximal wall thickness	p=0.058	
Neurological	FARS	Pattern consistent with ICARS	
Cardiac	Diastolic function	inconclusive	
Biochemical	8OH2 'dG (primary)		inconclusive
Cardiac	Cross sectional area		inconclusive
Force / exercise	Force control assessment		inconclusive
Force / exercise	Trail making test		inconclusive
Force / exercise	Exercise		inconclusive
Force / exercise	Gait analysis		inconclusive
Quality of Life	CGIC		inconclusive
Quality of Life	SF-10		inconclusive

The first eight endpoints in the table are endpoints that have been clinically validated to a certain extent in FRDA patients:

- The activities of daily living (ADL) scale has been validated in FRDA patients (Subramony 2005; Lynch 2006)
- ICARS total score, a widely used outcome measure in ataxia research, has been shown to be valid and has high inter-rater reliability in FRDA patients (Cano 2005; Storey 2004). This instrument was accepted as a suitable primary endpoint for the ongoing MICONOS study as part of the Scientific Advice provided by the EMEA prior to its initiation. Likewise, the FDA also accepted changes in the ICARS as an approvable endpoint for the IONIA study during their Special Protocol Assessment.
- Cardiac endpoints (LVMI, LVEF, LVM) have been validated in several clinical trials in FRDA (summarized by Meyer 2007).
- The FARS scale is a neurological instrument under development in the US (Subramony 2005; Lynch 2006), specifically designed for FRDA. In the NICOSIA trial, the first therapeutic trial in which the scale had been used, a similar dose response pattern compared to ICARS was observed. Although the FARS did not show a statistical significant response, its efficacy pattern was consistent with the ICARS. It should be noted however that this instrument takes at least twice as long to administer compared to the ICARS, which could have contributed to increased variability due to patient fatigue.

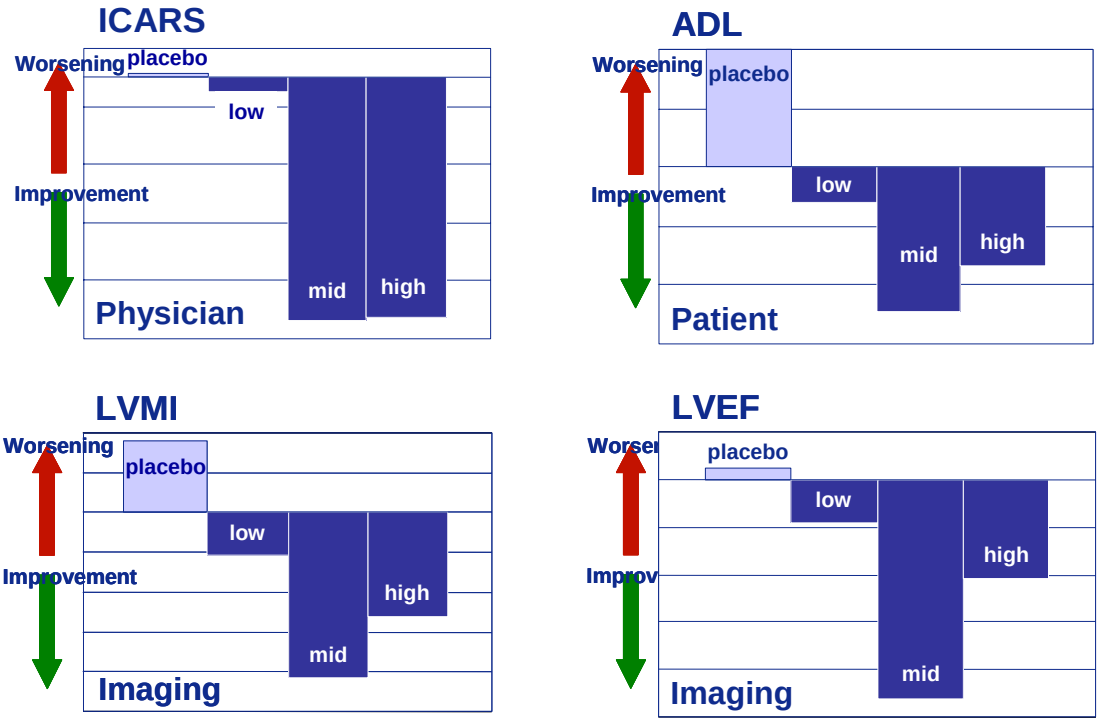
Several other endpoints such as force control and gait analysis showing high variability and inconclusive results were experimental in nature and had not been used previously in clinical trials in FRDA. Similarly, exercise testing proved very difficult for this ataxic population in spite of the use of a special ergometer. Lack of compliance in performing the exercise test resulted in very high data variability rendering efficacy assessments difficult.

The difficulty in prospectively selecting appropriate endpoints for a clinical trial in a rare disease is acknowledged in the Guideline for Clinical Trials in Small Populations. Even though this guideline was not applied by the CHMP in their review of the MAA, the difficulty remains.

Based on these arguments, the Applicant defends the selection of multiple secondary endpoints, including a number of non-validated and exploratory endpoints, to ensure the collection of valuable clinical data in a rare disease such as FRDA. Lack of efficacy in such exploratory endpoints should not be used to undermine the clinically meaningful effects seen in more validated endpoints.

The applicant acknowledges that the multiplicity issue has not been taken into account in the statistical analysis of the NICOSIA results. The applicant is however of the opinion that correction for this is not appropriate given the difficulty of conducting studies in this small population. The evidence for a true, clinically meaningful effect is derived not only from statistical considerations but also from the consistent pattern of results in different tests observed across independent endpoints. This consistent pattern in the dose response relationship favoring the mid and high doses over the low dose and placebo groups was seen in the NICOSIA trial and presented in the following graph reproduced from the Day 180 responses. Such a pattern in independently assessed parameters is considered unlikely to occur by chance.

Comparison of efficacy response for the treatment groups in the NICOSIA study



This consistency is also considered by experts as strong evidence for an important effect (see expert reports Professors Schulz and Rademakers) but was not commented on or acknowledged in the current assessment report and therefore, in the view of the Applicant, should be considered during re-examination.

An issue considered unresolved in the final assessment report was the perceived inconsistency between results from LVEF measured by echocardiography and MRI. The Applicant disagrees with this assessment of inconsistency and is supported in this view by the opinion of experts in the field (see cardiac expert report by Prof. Rademakers). Specifically, it is well documented in the literature that cardiac MRI methods to assess cardiac dimensions are far more sensitive and accurate than echocardiography (Grothues 2002). This includes a recent study comparing the two methods in FRDA patients (Meyer 2007).
Indeed, experts have emphasized that echocardiographic measurements of left ventricular ejection fraction show greater variability than those obtained by cardiac MRI. According to Professor George

Sutherland (St George's Hospital, London): "*this difference is an inherent part of the acquisition methods used by each technique. Echocardiography is a real time technique and as such single heart beat measurements which may be influenced by changes in respiration show a greater variability than the cardiac MRI measurement which is a measurement averaged over a large number of consecutive beats. This averaging reduces cardiac MRI measurement variability and thus means that MRI measurements are theoretically less variable than echo measurements*".

In the NICOSIA study LVEF was measured both by cardiac MRI and echocardiography. The overall response pattern for the placebo (worsening) and mid and high dose idebenone (improvement) was comparable for both types of assessments, as were the magnitudes of the changes observed at these doses. The overall similarity of the results obtained by the two techniques was emphasized in the cardiac expert report by Professor Rademakers.

CHMP Position:

As outlined earlier the argumentation of the applicant can be followed and benefit-risk assessment based on clinical outcomes is clearly preferred over surrogate parameters with limited validation. The choice of the biomarker as primary outcome measure can now be considered as premature and not sufficiently justified.

The scales used to assess secondary endpoints could be considered as appropriate (ICARS, FARS, LVMI, and LVM). Nevertheless, as already pointed out, the change in any measure that is clinically relevant is not discussed by the MAA.

The effect on secondary efficacy endpoint ICARS and FARS was more pronounced for the mid and high doses of Sovrima than for the low dose, but the differences did not reach statistical significance, and no clear dose-response was shown between the mid and high doses. A responder analysis was performed where a clinically relevant change in the ICARS was defined as an effect with a magnitude equivalent, in absolute terms, to the natural rate of decline observed over a one year period in an untreated population (Fahey, 2007). The results of the responder analysis showed a trend for an increase of responders in the mid and high dose groups of Sovrima. There were no statistically significant effects of Sovrima on other neurological secondary endpoints. However, the clinical relevance on the effect observed on ICARS should be discussed.

For the cardiac parameters, in the initial application, there was a trend for improvement for the measure of cardiac hypertrophy by MRI as well as by echocardiography) for the Left Ventricular Mass Index (LVMI), in the two highest dose groups, but the differences were not statistically significant. In the post-hoc analysis, taking into account MRI results only the mid dose of Sovrima resulted in a statistically significant improvement of LVMI as well as in a statistically significant improvement of a cardiac functional outcome parameter, Left Ventricular Ejection Fraction (LVEF). Taking into account that LVEF values at baseline were normal or slightly decreased these variations could be considered as consistent for the two methods (MRI and echocardiography). However, as for the neurological changes, the clinical relevance of the cardiac observed effects needs further discussion at the Scientific Advisory Group meeting.

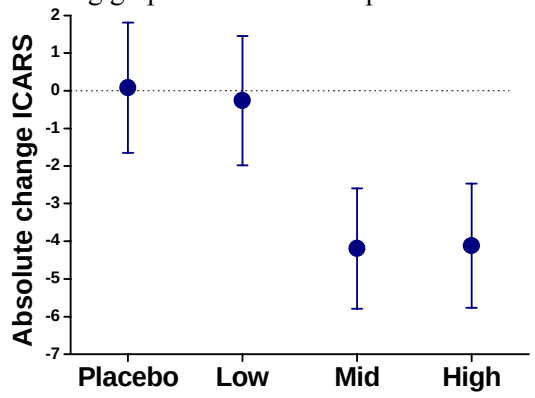
Ground for refusal 3

Applicant's position:
In the NICOSIA study report the dose response pattern for multiple parameters were presented, including both cardiac and neurological parameters. As presented by the applicant in the submission, the dose response curves of these different parameters all demonstrated a very similar pattern.

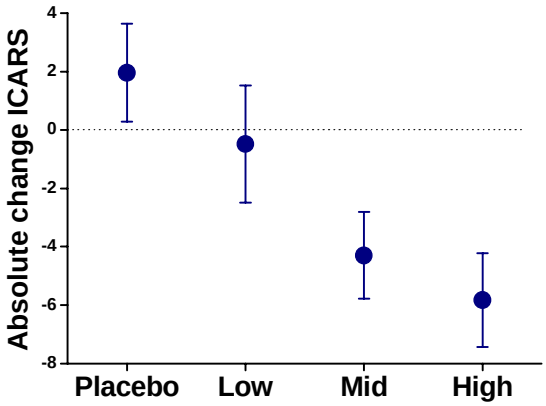
The concern was raised however that the dose response is better for the mid dose (450 mg/day for patients ≤ 45 kg body weight and 900 mg/day for patients >45 kg body weight) than for the high dose (1350 mg/day for patients ≤ 45 kg body weight and 2250 mg/day for patients >45 kg body weight) which cannot be explained.

The applicant does not agree with this conclusion for the following reasons:

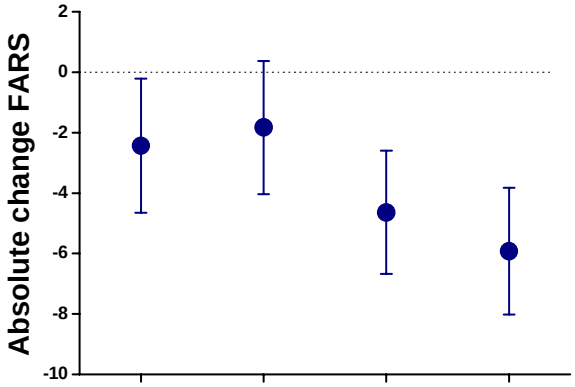
The rating scales used (ICARS, ADL, FARS) showed a consistent dose response pattern as shown in the following graphs when data are plotted as mean ± standard errors:



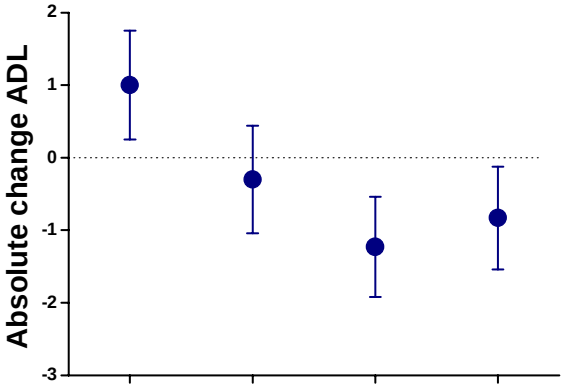
ICARS (ITT population)



ICARS (10<ICARS<54)



FARS (ITT population)



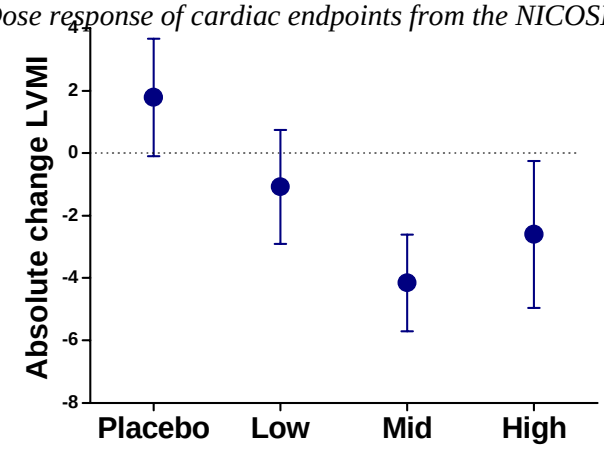
ADL (ITT population)

Dose response of neurological endpoints from the NICOSIA trial (mean ± SEM)

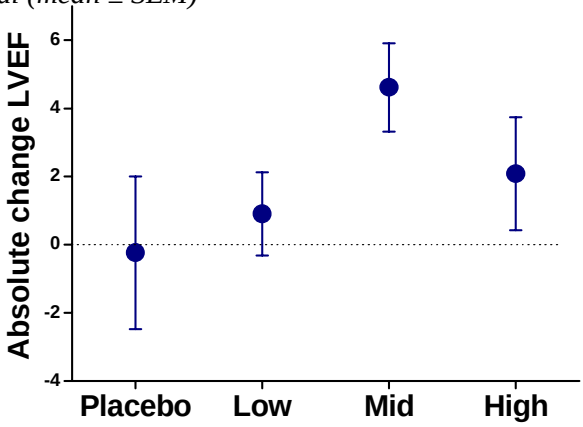
For all rating scales the low dose always gave the lowest response in patients on active treatment for all study populations analysed, whilst the mid and high dose groups consistently showed a better response. Considering the overlapping standard errors it cannot be concluded that the high dose was different from the mid dose and the applicant concludes that the mid dose reached or approached the maximum efficacious dose.

In agreement with the neurological data, both for the LVMI and LVEF, two independent cardiac parameters derived from MRI imaging, the same dose response was observed with the mid dose numerically being better than the high dose and the mid dose being statistically different from placebo. Because this result was obtained independently for two parameters these results are considered to reliably reflect a real change and benefit at the mid dose. Moreover the individual data demonstrate a similar response in individuals on mid and high dose.

Dose response of cardiac endpoints from the NICOSIA trial (mean ± SEM)



LVMI (ITT population)



LVEF (ITT population)

Considering the standard errors as presented in the graphs above, there is no apparent difference between the mid and high doses for any of the neurological or cardiac endpoints. Direct comparison between the mid and high doses vs placebo provided stronger p-values for the mid dose.
A responder analysis of the NICOSIA study further supports the view that there is no clinically meaningful difference in the efficacy of the mid and high doses of idebenone. The number of patients showing a clinically relevant response on ICARS defined as 5 or more points, a magnitude confirmed by experts (see expert report by Prof. Schulz), was similar between the mid and high doses (i.e. 39% and 42%, respectively). Likewise, a similar proportion of patients showed clinically relevant improvement on LVMI defined as 10% reduction as supported by experts (see report by Prof. Rademakers) on the mid and high doses (i.e. 31% and 25%, respectively).

In summary, the applicant interprets the dose-response data as a standard S-shaped curve with the mid and high dose showing comparable efficacy invalidating this argument of the refusal.

CHMP Position:

The weight based posology is based on very limited data and overall there was no clear difference in effects after treatment with the mid or high dosage of idebenone. However, in case that improvement seen with the mid dose could be considered as clinically meaningful this could be seen as the recommended dose.

Ground for refusal 4

Applicant's position:

The applicant agrees that most of the published studies are open label trials – with the notable exception of the double-blind, placebo-controlled study of Mariotti (2003) (see overview table on published clinical data with idebenone in FRDA above). However, the applicant does not agree that the results are inconsistent, particularly for the efficacy of idebenone on cardiomyopathy which has been investigated in the majority of published data so far.
It was described in the previously submitted documents that the cardiac effects observed in the NICOSIA study are consistently reproduced in all studies that had a minimum treatment period of 4 months, including the double-blind placebo controlled study of Mariotti (2003). The following table summarises the outcomes of the published literature with respect to cardiac efficacy (details are shown in the overview table on published clinical data with idebenone in FRDA above).

Author/Source	# Pts.	Months	Cardiac efficacy
Pineda (2008)	24	60	Yes (stabilization)
Mariotti (2003)	29	12	Yes (improvement)
Buyse (2003)	8	12	Yes (improvement)
Hausse (2002)	38	6	Yes (improvement)
Rustin (1999)	3	>4	Yes (improvement)
Schöls (2001)	9	1.5	No change

The lack of an effect reported by Schöls (2001) does not detract from the overall picture of efficacy since in that study the treatment duration (6 weeks) apparently was too short to induce a change in cardiomyopathy (reported as LVMI). This interpretation is in line with the study by Buyse (2003) who showed that changes in cardiac anatomy and function upon idebenone treatment develop over time and need several months before they can be measured.

The applicant therefore disagrees with the statement that the published literature is not consistent. In fact the NICOSIA data are strongly supported by studies reported in the published literature, including one double-blind placebo controlled study. The sum of clinical efficacy data available today in combination with the good safety profile of idebenone results in a positive benefit/risk balance, particularly for paediatric patients and should be the grounds for approval of SOVRIMA for FRDA in this age group. This interpretation is clearly supported by clinical experts experienced with the management of FRDA patients (see attached reports).

CHMP Position:

Efficacy clinical data in the published literature comes mostly from open-label studies and are not consistent.
Data from the randomized placebo-controlled studies show that 6-weeks idebenone treatment (Schöls et al, 2001) did not demonstrate any change in clinical neurologic rating score or the motor performance test neither in comparison to baseline nor in comparison to placebo. Echocardiography could not detect relevant changes.
Idebenone treatment during 12 months (Mariotti et al, 2002) had showed persistent moderate effects on echography indexes of heart hypertrophy, analysis of ICARS total score and subscores did not reveal significant differences between the two groups of patients.
The third randomized placebo-controlled study (Di Prospero et al, 2007) is the publication of results of NICOSIA study. To be noted that the authors concluded that the study results suggests that idebenone used at higher doses that previously tested may offer neurological benefit but have to be validated by Phase III clinical trials.
In conclusion, published data can not confirm at the present time the efficacy of idebenone in the treatment of neurologic and cardiac lesions of FRDA. Idebenone did not halt the progression of ataxia but may have an effect on the progression of cardiomyophathy, nevertheless the natural history of cardiac lesions in FRDA is not known and left ventricular diameter and mass may change spontaneously during the course of the disease in both directions (increased or decreased) (Meyer et al 2007).

Additional supporting information provided by the Applicant

In order to support the claim of clinical relevance of the available data, the Applicant herewith provides three expert reports, one focusing on the neurological effects of idebenone, and two on the cardiac effects. The reports are written by specialists in the field with clinical experience in the management of FRDA patients.
Key conclusions from these reports are as follows:
Neurological Expert Report (Prof. Schulz)

- The effects observed in the NICOSIA trials are clinically meaningful.
- The effect size is similar to a year of decline and therefore clinically meaningful.

- The effects on daily living function are remarkable and correlated with neurological change.
- The effects described in the NICOSIA trial are in agreement with clinical observations in children.

Cardiological Expert Report (Prof. Rademakers supported by Prof. Erne)

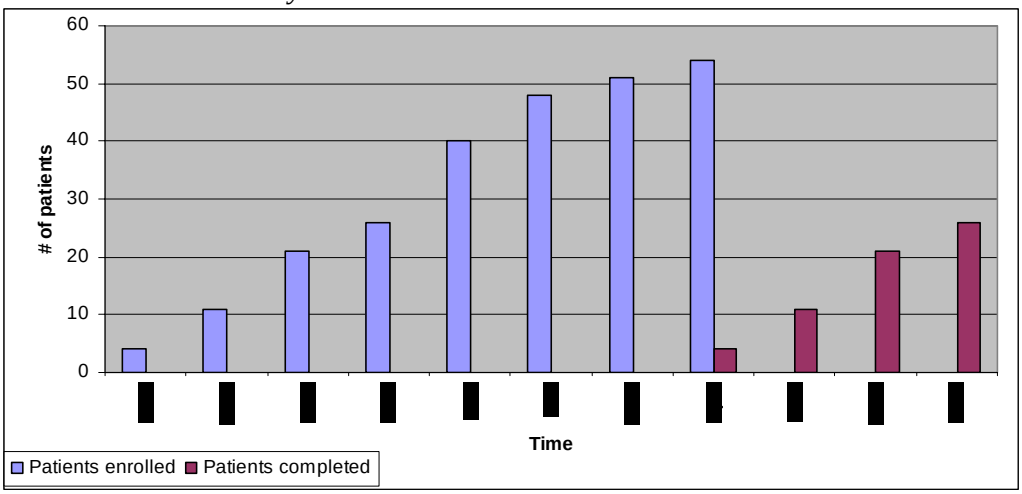
- The changes for LV mass and LVEF follow opposite directions when idebenone and placebo groups are compared, suggesting an effect on disease progression.
- The opposite direction of change on active drug and placebo observed in the NICOSIA study confirms the previous report of the double-blind, placebo controlled study of Mariotti.
- The potential effect on disease progression suggests possible prolongation of life expectancy as observed in an animal model of FRDA cardiomyopathy.

On-going studies: Two studies are currently ongoing with idebenone in FRDA.

The MICONOS trial (in EU) study is a double-blind, placebo-controlled, parallel group design study with 3 active doses of idebenone and placebo. The idebenone doses tested for 12 months are identical to those tested in the NICOSIA trial. The change on the ICARS between baseline and 12 months is the primary endpoint, while cardiac parameters assessed by echocardiography and MRI are secondary endpoints.
The study plans to enrol a total of 204 patients, of which 193 have been enrolled by today. It is anticipated that the last patient will be enrolled by the end of 2008 / early 2009 and data from this 12 months study will be available by the middle of 2010.
It is important to note that as of today more than 85% of the patients in the study are adult FRDA patients. Therefore, the MICONOS study will provide efficacy data for adult FRDA patients and the applicant will submit data from this study in support of a variation for an adult indication.

The IONIA trial (in the US) is a double-blind, placebo-controlled, parallel group design study, comparing 2 active doses of idebenone and placebo. The doses tested are the mid and high doses, which were previously tested in the NICOSIA study. The number of patients to be recruited in this 6 month study is 65 – 70 (depending on how many patients can be identified). The study is a paediatric trial recruiting FRDA patients with ages 8 – 18 years. The following graph shows the number of patients recruited by September 2008.

Recruitment chart IONIA study



It is anticipated that the last patient will be enrolled by the end of 2008 and it is expected that data become available by Q3 2009. A submission of a new MAA based on the IONIA data could be made by the end of 2009.

CHMP position:

The presented evidence from the NICOSIA trial and the other published clinical studies is still considered as inconclusive. It is acknowledged that trends for improvement on neurological and cardiac outcome are seen after treatment with idebenone, however the relevance of the effects should be discussed with the experts in the SAG. The statements of the three experts can be discussed there within broader terms.
Overall the CHMP considers it is worth waiting for the results of the ongoing clinical trials (IONIA; MICONOS) for a definite benefit risk assessment. At this stage the results of the NICOSIA trial and the additional evidence are too inconclusive even for a conditional approval.

Revised proposed indication

This MAA application is primarily based on the results obtained in the NICOSIA trial demonstrating efficacy of idebenone on neurological function and cardiomyopathy. Recognizing that this efficacy was demonstrated in young FRDA patients in the NICOSIA study, Santhera is accepting a restricted label for the patient group that would benefit most from an immediate approval of SOVRIMA, the children up to the age of 18 years. Therefore, the following revised label is proposed:

"Treatment of cardiac and neurological symptoms in paediatric patients with Friedreich's Ataxia"

This claim is fully supported by reports about the efficacy of idebenone in the published literature.

Taken into consideration the recommendation on the PK data and their interpretation for the posology provided by the CHMP in the assessment reports, a daily dose of 900 mg (i.e. 2 tablets 3 times a day) should be the recommended posology. This dose is equivalent to the mid dose in the NICOSIA trial and is supported by an appropriate safety data base in children, adolescents and adults.

The ongoing US IONIA trial is conducted in paediatric patients and results from this trial are expected by end of 2009. A complete new re-filing based on the IONIA data and considering the time for review would lead to an access to the drug for patients only in Q1 2011. As outlined above, due to the devastating and progressive nature of FRDA, paediatric patients across all EU countries should be given the chance to benefit immediately from idebenone at an effective dose. The applicant commits to provide data from the IONIA trial, which could constitute a condition for the approval in paediatric FRDA patients.
Data from the ongoing European MICONOS trial in adult FRDA patients will be filed at a later time in support of a variation for an adult indication.

In summary, the Applicant proposed a Conditional Approval for the treatment of cardiac and neurological symptoms in peadiatric patients with Friedreich's Ataxia at a dose of 900 mg per day (2 tablets 3 times a day) with data from the IONIA trial as a condition to be fulfilled by the end of 2009.

CHMP position:

"Conditional approval", with ongoing studies being part of the conditions, is considered not applicable. Such approval requires all of the requirements (a)-(d) are met:

1. That the B/R is positive, as defined in Article 1 (28a) of Directive 2001/83/EC
2. It is likely that comprehensive data can provided
3. Unmet medical needs will be fulfilled (no satisfactory methods or major therapeutic advantage)
4. Benefits of immediate availability outweigh risks due to additional data to be provided.

Point (1) is not fulfilled at present and point (4) cannot be considered fulfilled as compassionate use is already available.

Friedreich's ataxia (FRDA), the most common hereditary ataxia, is an autosomal recessive neurodegenerative disease with progressive gait and limb ataxia and cardiomyopathy as some of its clinical core features. The major cause of death is heart failure as a result of hypertrophic cardiomyopathy. No treatment other than supportive measures is available.

FRDA is caused by expansion of a GAA triplet located within the first intron of the frataxin gene on chromosome 9q13. There is a clear correlation between size of the expanded repeat and severity of the phenotype. Frataxin is a mitochondrial protein that plays a role in iron homeostasis. Deficiency of frataxin results in mitochondrial iron accumulation, defects in specific mitochondrial enzymes, enhanced sensitivity to oxidative stress, and eventually free-radical mediated cell death. Therefore FRDA is considered a nuclear encoded mitochondrial disease with decreased mitochondrial respiratory chain function and increased oxidative stress. Several medicinal products with the potential to improve mitochaondrial function (Coenzym Q10, selenium, N-acetyl-cysteine and idebenone) have been studied in Friedreich's Ataxia, however, proof that the improvements seen are clinically meaningful is missing. The following rationale is behind treatment of FRDA with idebenone: Idebenone [2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone] is a synthetic short chain analogue of ubiquinone (Coenzyme Q10), the vital cell membrane antioxidant and essential constituent of the cellular energy (ATP)-producing mitochondrial electron transport chain (ETC). Idebenone appears to act as an anti-oxidant that also enhances the flux of electrons along the ETC, thereby facilitating the generation of ATP. Based on these effects it has been postulated as a potential therapeutic agent for FRDA.

Results of one 6-month phase II study in patients (n=48) with Friedreich's ataxia with Sovrima doses higher than those previously used in published studies have been submitted (NICOSIA trial). No effect was established on the primary endpoint: change in a proposed surrogate marker for oxidative stress from baseline to month 6.
For the secondary endpoints neurological assessment with the ICARS and FARS scales, there were trends for a more favourable outcome with the mid and high doses of Sovrima, however, the differences vs. placebo have not been statistically significant. It still has to be determined whether a 4-point improvement in the ICARS and the proposed responder analyses could be considered clinically relevant.
For measures of cardiac hypertrophy the analysis shows a statistically significant effect of the mid dose of Sovrima on a measure of cardiac hypertrophy, LVMI, and on a cardiac functional outcome parameter, Left Ventricular Ejection Fraction (LVEF). Again, the clinical relevance of these results for the overall population of patients with FRDA is not sufficiently clear.
For other secondary parameters, including SF-10 and Clinical Global Impression of Change, there were no statistically significant effects. The applicant focuses on the improvement seen on the ADL scale, which may be a hint for a clinically relevant improvement.
However, in summary this trial is considered as a failed clinical trial based on the prespecified endpoints and outcome criteria.
The supportive evidence from other studies (mainly open-label) is still considered as weak. The results in favour of idebenone should be confirmed by further clinical trials, therefore the results of the ongoing studies (IONIA trial in paediatric patients; MICONOS trial in adults) are waited with high interest.

3.2 Overall conclusions from the Joint Assessment Report

With the grounds for re-examination the applicant has reiterated its position regarding the deficiencies identified in the CHMP assessment and provided further discussion of the points forming the ground of refusal by the CHMP. The applicant proposed a Conditional Approval for the treatment of cardiac and neurological symptoms in paediatric patients with Friedreich's Ataxia at a dose of 900 mg per day (2 tablets 3 times a day) with data from the IONIA trial as a condition to be fulfilled by the end of 2009.
However, both Rapporteurs conclude that even for this restricted indication the benefit-risk assessment of Sovrima is still negative as data are not consistent and robust enough. The major concerns pointed out in the CHMP grounds for refusal 1, 2, 3 and 4 are still valid and therefore do not allow accepting marketing authorization of Sovrima at that time. The results of the ongoing phase III trials (IONIA trial in paediatric patients; MICONOS trial in adults) should be awaited.

3.3 Questions addressed by the CHMP to the Clinical Neurosciences Scientific Advisory Group

For the evaluation of the grounds for re-examination, the CHMP also consulted the Advisory group of Experts who met the 5thof November 2008 to discuss the available evidence and answer to the following questions from the CHMP:

1. Which are the adequate measures to show a treatment effect in patients with Friedreich's Ataxia (FA) and what can be considered as clinically meaningful taking into consideration the natural course of the disease:

a. on neurological outcome?

b. on cardiac outcome?

2. In view of the methodological shortcomings of the NICOSIA trial, does the SAG consider as clinically meaningful the effects seen in this trial on neurological outcome with ICARS and on cardiac outcome after mid and high dosages of idebenone?"

3. Are the effects seen in paediatric patients more pronounced compared to adults?

The Applicant gave an oral explanation during the Experts meeting and had the opportunity to clarify their position in relation to the same questions.

Answers from the CNS SAG to the questions on Sovrima/Idebenone

1. Which are the adequate measures to show a treatment effect in patients with Friedreich's Ataxia (FA) and what can be considered as clinically meaningful taking into consideration the natural course of the disease:

c. on neurological outcome?

d. on cardiac outcome?

SAG answer: Friedreich's Ataxia (FRDA) is a true neurodegenerative disease with cardiac pathology that mostly contributes to the cause of death in these patients. However the clinical course of disease is variable, decline of neurologic functions is not linear (also depending on cardiac function) and the natural history of disease is still insufficiently characterised.

Point a): Multidimensional assessment tools (like FARS and ICARS) are considered valuable to capture the several symptoms of disease but their metric properties should be better documented. The most relevant neurological improvements to be taken into account are **walking and speech; dexterity** is also important for everyday life. ADL are very relevant and it is expected that clinically meaningful changes should be at least partly reflected on the global change.

As for other neurodegenerative diseases, is felt that the therapeutic benefit would mostly consist in slowing the progression of symptoms, and a 2-year observation period would be reasonable versus best standard of care. However FRDA being an orphan disease, ethical considerations push to identify the shortest useful observation duration. In this perspective it makes sense to wait for the results of the ongoing 1-year studies.

Point b): Short-term relevant cardiac parameters are to be considered for secondary endpoints in the treatment of FA. The SAG identified valuable cardiac surrogate endpoints: MRI, possibly gadolinium enhanced in order to quantify cardiac fibrosis; echocardiography for documenting both systolic and diastolic function; these endpoints should be evaluated over a period of 6-month or more adequately of 1-year.

Long-term data on cardiac morbid-mortality are still scarce in FA, and the SAG strongly recommend to collect data on these specific outcomes overtime in the general population of FDRA.

2. **In view of the methodological shortcomings of the NICOSIA trial, does the SAG consider as clinically meaningful the effects seen in this trial on neurological outcome with ICARS and on cardiac outcome after mid and high dosages of idebenone?"**

   SAG answer : The SAG considers the results of NICOSIA study suggestive of efficacy on the neurological outcomes; however they should be confirmed on larger numbers. The lack of improvement in **walking** is considered to limit the clinical meaningfulness of results, even if other relevant neurologic symptoms like speech or dexterity are improved. The observed 4-point change in ICARS is considered a relatively small effect.

   Observed cardiac outcomes are considered to affect only limited functional aspects and are inconsistent across the mid and high dose. The arguments brought by the Applicant during their presentation to the SAG, based on a parallel of FA cardiomyopathy with the hypertensive cardiomyopathy, cardiac hypertrophy as the key risk factor in FDRA, are not endorsed by the Experts cardiologists.

3. **Are the effects seen in paediatric patients more pronounced compared to adults?**

SAG answer: The SAG considered the objective elements in the dossier and presented by the Applicant during the meeting insufficient to document a more pronounced effect in the paediatric patients. Prevention of progression of the cardiac disease would be the more relevant aspect to document.

These views were shared by all the Experts.

The answers to the questions and more in details the position of the CNS-SAG was presented by the SAG Chairman at the CHMP during the November meeting. The Applicant presented their final position in an oral explanation at the same meeting.

3.4 Overall conclusions on grounds for re-examination

With the grounds for re-examination the applicant has reiterated its position regarding the deficiencies identified in the CHMP assessment and provided further discussion of the points forming the ground of refusal by the CHMP. The applicant proposed a Conditional Approval for the treatment of cardiac and neurological symptoms in paediatric patients with Friedreich's Ataxia at a dose of 900 mg per day (2 tablets 3 times a day) with data from the IONIA trial as a condition to be fulfilled by the end of 2009.

The CHMP, having considered the information submitted, considers that evidence of adequate, therapeutic efficacy is lacking, a favourable benefit/risk balance cannot be established and therefore recommends the refusal of the granting of the Marketing Authorisation for Sovrima.

The results of the ongoing phase III trials (IONIA trial in paediatric patients; MICONOS trial in adults) should be awaited.

The CNS SAG answers confirmed the scarcity of objective elements for a revised indication in the restricted paediatric population based on the NICOSIA trial. In particular the clinical relevance of the neurological and cardiac outcome measures estimated as secondary endpoints has been questioned.

3.5 Grounds for Refusal

In conclusion, the CHMP, based on review of the whole data provided and taking into account the answers from the CNS-SAG considered the following grounds for refusal are confirmed. Specifically:

There is still insufficient clinical documentation with respect to the benefit/risk balance of Sovrima in the revised indication proposed by the Applicant during the re-examination procedure:

"Treatment of cardiac and neurological symptoms in paediatric patients with Friedreich's Ataxia"

- The efficacy of Sovrima for the treatment of Friedreich's ataxia has not been demonstrated. The efficacy documentation is based on primarily one study, evaluating a total of 48 paediatric patients with Friedreich's ataxia. No statistically significant effect was observed for the primary endpoint.

- The reliability of the results of the secondary endpoints in the 48 paediatric patients is questioned. There were many secondary endpoints of which only a subset showed statistical significance and only for one of the three dose levels. Given the multiplicity issues in considering multiple endpoints and multiple dose levels the level of statistical evidence is not considered compelling.

- The supportive evidence from published studies is insufficient. Most of the published studies were open-label and the results were not consistent across endpoints important to establish clinical benefit.

- The objective elements in the dossier and presented by the Applicant during the meeting are insufficient to document robust and consistent effects in the paediatric patients studied in the NICOSIA trial. Further data from the ongoing studies are considered necessary.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the therapeutic efficacy is insufficiently substantiated and the benefit/risk balance of Sovrima in the treatment of Friedreich's Ataxia in paediatric and young adult patients, or in adult patients diagnosed within the last 5 years and in adult Friedreich's Ataxia patients with cardiomyopathy is unfavourable and therefore did not recommend the granting of the marketing authorisation.