

National Horizon Scanning Centre

Idebenone (SNT-MC17) for Friedreich's ataxia

September 2007



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Idebenone (SNT-MC17) for Friedreich's ataxia

Target group

- Friedreich's ataxia (FRDA)

Background

FRDA is a genetic neuromuscular disorder that causes progressive damage to both the central and peripheral nervous system. It is an autosomal recessive condition caused by a defect in the gene encoding the protein frataxin. Reduced levels of frataxin lead to mitochondrial iron accumulation that generates oxidative stress and results in tissue damage, and a reduction in mitochondrial ATP biosynthesis to 30% of normal levels due to defects in the electron transfer chain¹. Symptom onset is usually between the ages of 5-15, but can present as early as 18 months or as late as 30 years. Initial symptoms include gait disturbance, upper extremity ataxia, speech problems, loss of muscle control and muscle wasting.

Although FRDA is primarily a neurological disease, hypertrophic cardiomyopathy is a life threatening complication, with around 80% of patients having abnormal ECGs (echocardiography). Other complications include skeletal problems such as scoliosis and foot deformities; and diabetes which affects around 10-20% of patients². Prognosis is variable, with average life expectancy ranging from 25-50 years, although patients free of cardiac complications may survive beyond this.

Technology description

Idebenone (SNT-MC17, Sovrima) is an oral synthetic quinone analogue of the antioxidant coenzyme Q10 (Co Q10). Idebenone is a potent free radical scavenger, but unlike CoQ10, it does not switch function from an antioxidant to an auto-oxidant under hypoxic (low oxygen) conditions. Idebenone also acts as an enhancer of the flow of electrons in the electron transfer chain, thereby increasing the amount of ATP synthesis. Clinical studies suggest that idebenone protects heart muscle from iron-induced damage³, and may also prevent progression of neurodegeneration by acting as a free radical buffer.

Idebenone is administered at a starting dose of 900 mg per day rising to 2,250 mg per day for individuals with a bodyweight > 45 kg; and 450 mg per day rising to 1,350 mg per day for individuals with a bodyweight ≤ 45 kg, given over 3 doses. It is not clear if the drug will be suitable for all age ranges, or restricted to any particular subgroups of patients.

Low dose idebenone is marketed in Italy (Mnesis, Daruma) and Portugal (Cerestabon) for cognitive disorders. Mnesis has a temporary approval in Switzerland for the treatment of cardiomyopathy associated with Friedreich's Ataxia, and is available under compassionate use legislation in other EU countries.

Idebenone (Sovrima) is in Phase II clinical trials for Duchenne Muscular Dystrophy and Leber's Hereditary Optic Neuropathy.

Innovation and/or advantages

If successful in trials and licensing, idebenone will be the first specifically licensed therapy for FRDA.

Developer

Santhera Pharmaceuticals and Takeda.

Place of use

- | | | |
|--|---|--|
| <input type="checkbox"/> Home care e.g. home dialysis | <input type="checkbox"/> Community or residential care e.g. district nurses, physio | <input type="checkbox"/> Primary care e.g. used by GPs or practice nurses |
| <input checked="" type="checkbox"/> Secondary care e.g. general, non-specialist hospital | <input checked="" type="checkbox"/> Tertiary care e.g. highly specialist services or hospital | <input type="checkbox"/> Emergency care e.g. paramedic services, trauma care |
| <input type="checkbox"/> General public e.g. over the counter | <input type="checkbox"/> Other: | |

Availability, launch or marketing dates, and licensing plans:

A marketing authorisation application was filed in Europe in July 2007 (based on phase II data), with launch anticipated in the second half of 2008⁴. Idebenone has been granted orphan drug status in Europe and the US.

NHS or Government priority area:

This topic is relevant to:

- The Long-term (Neurological) Conditions National Service Framework (NSF).

Relevant guidance

- Ataxia UK. Management of Ataxia: Guidelines on Best Clinical Practice. March 2007⁵.

Clinical need and burden of disease

FRDA affects males and females equally with an estimated incidence of around 1 per 30,000 live births². Estimates of prevalence vary from around 1 per 100,000 to 1 per 50,000 population (between 520 to 1,050 patients in England and Wales)^{6,7}. Although rare, FRDA accounts for half of all hereditary ataxias.

FRDA impacts severely upon quality of life. Most young people diagnosed with FRDA require mobility aids such as a cane, walker or wheelchair by their teens or early 20s and many require surgery for scoliosis. Regular follow-up with annual ECGs, echocardiograms, urine and blood tests is necessary to monitor the development of cardiomyopathy and diabetes.

Existing comparators and treatments

There are currently no licensed products available for FRDA. Treatment is symptomatic and supportive. Diabetes and cardiac complications are treated pharmacologically. Amantadine may provide some limited improvement in ataxic symptoms, but is not recommended in patients with cardiac abnormalities. Orthopaedic conditions, such as foot deformities and scoliosis, are treated surgically or with braces, while physical therapy can prolong the use of the arms and legs.

Efficacy and safety

There are several published placebo-controlled, uncontrolled and/or open label trials of low dose (5 mg/kg) idebenone in Friedreich's ataxia. Santhera are also using safety results from trials in Alzheimer's dementia in their regulatory submission.

Trial name or code	Idebenone vs placebo. Phase II ⁸	MICONOS trial (SNT-III-001 ⁹) ^a	IONIA trial (SNT-III-002) ¹⁰
Sponsor	Santhera Pharmaceuticals; US National Institute of Neurological Disorders and Stroke (NINDS)	Santhera Pharmaceuticals.	Santhera Pharmaceuticals.
Status	Press release. Publication in press ¹¹ .	Ongoing.	Ongoing.
Location	USA	UK, Germany, Netherlands, Belgium, France.	USA
Design	Randomised, double-blind, placebo-controlled.	Randomised, double-blind, placebo-controlled.	Randomised, double-blind, placebo-controlled.
Participants in trial	n=48; 9-18 years; randomised to placebo or idebenone. Patients weighing \leq 45 kg: low dose 180 mg; mid dose 450 mg; high dose 1,350 mg. Patients weighing $>$ 45 kg: Low dose 360 mg; mid dose 900 mg; high dose 2,250 mg.	n=204; $>$ 8 years of age; randomised to idebenone or placebo. Patients weighing \leq 45 kg: low dose 180 mg; mid dose 450 mg; high dose 1,350 mg. Patients weighing $>$ 45 kg: low dose 360 mg; mid dose 900 mg; high dose 2,250 mg.	Details of the study not disclosed.
Follow-up	6 months	12 months	-
Primary outcome	Reduction in oxidative stress measured by surrogate marker 8-hydroxy-2-deoxyguanosine in urine.	Neurological parameters (ICARS scale), left ventricular mass, activities of daily living.	-
Secondary outcomes	International Cooperative Ataxia Rating Scale (ICARS ^b), Friedreich's Ataxia Rating Scale (FARS ^c), cardiac function, activities of daily living.	-	-
Key results	No change in primary endpoint between groups. Dose-related improvement of ICARS: placebo +0.1 points vs +4.0 points idebenone; and activities of daily living at intermediate and high doses. Subgroup analysis (excluding severely and mildly affected patients) ICARS: -2.0, +0.6, +4.3 and +5.8 for placebo, low, mid and high doses (p=0.01). FARS changed by 2.5, 1.8, 4.7 and 5.9 points for placebo, low, mid and high doses.	-	-
Expected reporting date	-	Study commenced Dec 2005, recruitment slow due to small patient population.	Due to commence Autumn 2007.

^a Despite filing a marketing authorisation application based on phase II data, Santhera intends to continue its ongoing phase III trial in Europe. The protocol has been amended to focus on the neurological aspects of FRDA, with cardiomyopathy being dropped as an inclusion criterion. This also now applies to the US phase III study.

^b International Cooperative Ataxia Rating Scale (ICARS) assesses sensory and motor skills.

^c FARS consists of a manoeuvre exam along with three quantitative performance measures.

Adverse effects	Well tolerated with no patient withdrawals.	-	-
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Estimated cost and cost impact

The cost of idebenone for the treatment of FRDA has yet to be determined. Any costs would be in addition to currently used symptomatic and supportive measures, but if idebenone was able to slow the progression of FRDA, it could delay the need for rehabilitation services and equipment, medical procedures and surgeries as well as concomitant medications.

The cost to the patient for Mnesis (idebenone, 45 mg tablet) temporarily registered for the treatment of cardiomyopathy in FRDA in Switzerland by Swiss Medic is €3.21 per tablet. At the sponsor's recommended dosing scheme for FRDA the estimated annual treatment costs would be:

	Starting dose	Higher dose
Patients weighing ≤45 kg	€1,700 (£8,315 ^d)	€5,100 (£24,945)
Patients weighing >45 kg	€23,400 (£16,630)	€8,400 (£41,504)

Potential or intended impact – speculative

Patients

- | | | |
|---|--|---|
| <input checked="" type="checkbox"/> Reduced morbidity | <input type="checkbox"/> Reduced mortality or increased survival | <input checked="" type="checkbox"/> Improved quality of life for patients and/or carers |
| <input type="checkbox"/> Quicker, earlier or more accurate diagnosis or identification of disease | <input type="checkbox"/> Other: | <input type="checkbox"/> Non identified |

Services

- | | | |
|--|--|---|
| <input type="checkbox"/> Increased use | <input type="checkbox"/> Service reorganisation required | <input type="checkbox"/> Staff or training required |
| <input type="checkbox"/> Decreased use | <input type="checkbox"/> Other: | <input checked="" type="checkbox"/> Non identified |

Costs

- | | | |
|--|--|---|
| <input type="checkbox"/> Increased unit cost compared to alternative | <input type="checkbox"/> Increased costs: more patients coming for treatment | <input type="checkbox"/> Increased costs: capital investment needed |
| <input type="checkbox"/> New costs: | <input checked="" type="checkbox"/> Savings: If it prevents the progression of the disease | <input type="checkbox"/> Other: |

References

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- ³ Rustin P, Von Kleist-Retzow JC, Chantel-Groussard K *et al.* Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. *Lancet.* 1999; 354: 477-479.
- ⁴ Santhera Pharmaceuticals Press release 31st January 2007. Santhera intends Early filing in Europe for SNT-MC17/idebenone in Friedreich's ataxia. Accessed 8th August 2007
- ⁵ Management of Ataxia: Guidelines on Best Clinical Practice. Ataxia UK. March 2007. Available online at http://www.ataxia.org.uk/publications_and_pictures/guidelines.pdf . Accessed 8th August 2007

^d Exchange rate £1.00 = €1.407 – on 6th September 2007

- ⁶ Winter RM, Harding AE, Baraitser M *et al.* Intrafamilial correlation in Friedreich's ataxia. *Clinical Genetics*, 1981, 20: 419 – 427.
- ⁷ Dürr A, Cossee M, Agid Y *et al.* Clinical and genetic abnormalities in patients with Friedreich's ataxia. *New Engl J Med*. 1996; 335 (16):1169-1175.
- ⁸ Santhera Pharmaceuticals Press Release 13th November 2006. NIH and Santhera Announce positive results of study with SNT-MC17/idebenone in Friedreich's Ataxia (FRDA). Accessed 4th September 2007.
- ⁹ Santhera Pharmaceuticals Press release 15th December 2005. Santhera starts European Phase III study with its lead compound SNT-MC17 (idebenone) in Friedreich's ataxia. Accessed 8th August 2007.
- ¹⁰ Santhera Pharmaceuticals Press release. Santhera reports successful 2006. Accessed 8th August 2007.
- ¹¹ DiProspero N, Baker A, Jeffries N *et al.* Neurological effects of high-dose idebenone in patients with Friedreich's Ataxia: a randomised, placebo-controlled trial. 2007; *Lancet Neurology* (in press)

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