



Friedreich's Ataxia (FRDA)

FRDA is a rare but severe neuromuscular disease that results in the degeneration of an individual's nerve and muscle tissue. Disease symptoms may include any of the following:

- Muscle weakness and loss of coordination (ataxia) in the arms and legs;
- Vision impairment, hearing loss, and slurred speech;
- Aggressive scoliosis (curvature of the spine);
- Serious heart changes (enlarged heart – hypertrophic cardiomyopathy).

FRDA affects both Caucasian males and females equally. Based on published epidemiologic studies, an estimated 20,000 people suffer from the disease in Europe and North America. Average life expectancy for people with FRDA is limited to approximately 35 to 50 years.

Causes

FRDA is an inherited disease causing mutations in the gene encoding protein *frataxin*. This protein is essential for the proper functioning of the mitochondria (the energy production centers of a cell). Insufficient levels of *frataxin* negatively impact nerve and muscle tissues, as these cells are particularly energy demanding.

Diagnosis

Doctors usually diagnose FRDA by performing a careful clinical examination, which includes a medical history and a thorough physical examination. Tests that may be performed include an electromyogram (EMG), nerve conduction studies, an electrocardiogram (EKG), an echocardiogram as well as genetic testing to identify the affected gene. Genetic testing is carried out in certain specialized laboratories and can provide information to assist with clinical diagnosis and carrier status determination.

Signs and Symptoms

Symptoms usually begin between the ages of 5 and 15 years but can appear as early as 18 months or as late as 50 years of age on rare occasions. The first symptom to appear is usually difficulty in walking, or gait ataxia.

Prognosis

As the disease progresses, people suffer increasingly severe symptoms such as loss of motor coordination, fatigue, slurred speech, hearing and visual impairment; and spinal deformation. Generally, within 10 to 20 years after the appearance of the first symptoms, the person is confined to a

wheelchair, and in later stages patients become completely incapacitated. Life expectancy may be affected, particularly in patients who develop cardiomyopathy, a cardiac complication that is frequently associated with FRDA.

Treatment

Current treatments are focused on support therapies, such as walking aids, wheelchairs, physical and speech therapy, and corrective surgery, as well as psychological support. At present, there are no specifically developed and approved pharmacological therapies available for the treatment of FRDA in the US or Europe.

SNT-MC17 (INN: idebenone) Mode of Action

Santhera's lead compound SNT-MC17 is a small molecule optimized to improve the electron transport chain in mitochondria, the energy producing cells factories. Specifically, SNT-MC17 is believed to facilitate the transport of electrons within mitochondria, helping maintain correct electron balance, which is necessary for the production of cellular energy. Nerve and muscle cells, including heart muscle cells, are particularly energy-demanding and are, therefore, more prone to rapid cell damage or death due to mitochondrial dysfunction. Through preserving mitochondrial function and protecting cells from oxidative stress, it is believed that SNT-MC17 can prevent cell damage and increase the production of energy within impaired cells of people with FRDA.

Clinical Development of SNT-MC17 in FRDA

A recent clinical trial conducted in collaboration with the US National Institutes of Health (NIH) has shown improvement on neurological parameters and activities of daily living scores in FRDA patients after treatment with SNT-MC17 for six months at daily doses of 900 mg or 2250 mg for adult patients. The results of the study were presented at the 3rd International Friedreich's Ataxia Scientific Conference in Bethesda, Maryland/US, in November 2006.

Based on the positive data from this trial and under a new EU Guideline for development of drugs to treat diseases in small patient populations, Santhera intends to file the Marketing Authorization Approval (MAA) for SNT-MC17 in FRDA in Europe in summer 2007. If everything goes according to plan, chances are good that the product could be launched in Europe in the second half of 2008 by Santhera's marketing partner Takeda. The ongoing Phase III trial in Europe will be continued to collect additional safety and efficacy data particularly for the high dose in a wider population of FRDA patients.

In the US, Santhera has submitted these data to the Food and Drug Administration (FDA) and, as a result, will file a new protocol under its open IND (Investigational New Drug). At the same time, the Company will ask for Special Protocol Assessment (SPA) with the FDA. The protocol will reflect the major findings from the collaborative NIH trial regarding neurological endpoints and the effective doses. Patient recruitment is expected to start in summer 2007.

Development and Commercialization Strategy for SNT-MC17 in FRDA

Santhera was granted orphan drug designations by the European Medicines Agency (EMA) and FDA in March 2004 for SNT-MC17 in the treatment of FRDA. Pending FDA approval, Santhera will market SNT-MC17 through its own specialty sales force in the US. Upon successful registration and marketing clearance in Europe for FRDA, SNT-MC17 will be sold by Santhera's marketing partner Takeda.

Market Opportunity

FRDA is a rare neuromuscular disease, affecting an almost exclusive Caucasian population which is distributed equally between Europe and North America. FRDA is a chronic disorder and requires life-long treatment. Based on the disease severity, prevalence, and the expected reimbursement level for pharmaceuticals that can reverse, or slow the progression of FRDA, Santhera estimates the market potential for such products to be approximately EUR 300 million in annual sales.

Duchenne Muscular Dystrophy (DMD)

DMD is the most common form of muscular degeneration, known as dystrophy, and results in rapidly progressive muscle weakness. Disease symptoms include:

- Muscle weakness, initially in the legs and pelvis and spreading to shoulders and neck muscles and followed by arm muscles;
- Muscle and skeletal deformities including spinal deformation;
- Respiratory failure and cardiac complications, both can be life threatening.

DMD is a serious genetic neuromuscular disease that affects 30,000 males of all ethnicities worldwide. The average age of onset is between 3 and 5 years of age with an average life expectancy of 30 to 35 years.

Causes

DMD is an X-linked recessive inherited disease, caused by mutations in the gene that encodes the protein *dystrophin*. *Dystrophin* function is best known for its role in muscle cells where it mechanically stabilizes the contracting elements in each muscle cell.

Diagnosis

Doctors usually diagnose DMD by carefully examining the posture and gait as the disease will have an effect on the way the affected boy stands, walks, runs, especially uphill or steps. There is usually a typical style of walking which can be recognized and which is often described as waddling. The diagnosis is usually confirmed by muscle biopsy and some doctors also recommend electromyography (EMG).

Signs and Symptoms

DMD is characterized by progressive muscle weakness and wasting throughout the body. Muscle wasting initially affects the legs and pelvis and then spreads to shoulders and neck muscles followed by the arm, respiratory and cardiac muscles

Prognosis

With disease progression, people with DMD suffer from severe medical conditions, and are often confined to a wheelchair during their teenage years. DMD results in muscle and skeletal deformities including spinal deformation and eventually leads to respiratory failure and cardiac complications that result in premature death.

Treatment

There is currently no effective treatment for DMD. Current treatments are focused on delaying or alleviating the disease's effects and include physical and occupational therapy and the use of

orthopaedic devices such as walking aids, wheelchairs and ventilator support to prevent respiratory failure in the advanced stages of the disease. Pharmacological treatment with corticosteroids may delay disease progression and prolong mobility, but the significant adverse effects of chronic steroid use have prevented the wide acceptance of this therapy.

Clinical Development of SNT-MC17 in DMD

A single center Phase IIa trial to establish the proof of concept for SNT-MC17 as a treatment of dilated cardiomyopathy and muscle weakness in DMD is ongoing in Europe. The trial is a 12 month double-blind, randomized, placebo-controlled trial which assesses the efficacy and tolerability of one dose level of SNT-MC17 compared to placebo in 8 to 16 year old boys with DMD and cardiac dysfunction. The primary endpoint of this trial is an assessment of the change in contractility of the heart muscle, which is an early predictor of cardiac failure in DMD. Secondary endpoints include the effects on muscle strength. A total of 21 patients have been enrolled into this study: 14 patients receive SNT-MC17 while 7 receive the placebo. Data from this trial are expected in the second half of 2007.

Development and Commercialization Strategy for SNT-MC17 in DMD

Subject to a positive outcome of the on-going Phase IIa trial, Santhera intends to seek protocol advice from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in order to prepare for a pivotal Phase III program. Santhera has received orphan drug designation for SNT-MC17 in DMD in both the EU and the US. Upon successful registration and marketing authorization for DMD, Santhera will market SNT-MC17 through its own specialty sales force in the US.

Market Opportunity

DMD is the most common and devastating type of muscular dystrophy affecting males of all ethnicities. DMD is a life-long disorder and requires treatment with pharmaceuticals for the duration of a patient's life. The market for pharmaceutical products that can treat DMD is estimated to be approximately EUR 400 million per annum, based on disease prevalence, severity and expected reimbursement levels.

Leber's Hereditary Optic Neuropathy (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a genetic disease that results in the degeneration of nerve cells in the retina, leading to the rapid loss of central vision and blindness. It affects predominantly young adult males.

Causes

LHON is caused by mutations of the genetic code within the mitochondria, the energy production centers in each cell, and is transmitted through the mother. The mutations ultimately lead to the reduction of cellular energy production resulting in cell damage and cell death, including those in the optic nerve.

Diagnosis

The diagnosis of LHON is extremely difficult and usually requires a neuro-ophthalmological evaluation and/or blood tests for DNA assessment (available in specialized laboratories only).

Sign and Symptoms

The symptomatic phase of LHON disease begins with the blurring of central vision. The effects are rapid and severe, with the damage to retina cells leading to blindness within a few months after the onset of symptoms.

Prognosis

After the initial symptoms appear, both eyes are usually affected within several months, leading to rapid loss of central vision and blindness. Within approximately 12 months of visual loss in one eye, over 97% of patients will experience vision loss in the second eye.

Treatment

At present there is no effective treatment for this disease.

Clinical Development of SNT-MC17 in LHON

Santhera is currently enrolling patient to its Phase IIa proof-of-concept trial in the UK and Germany. The study, which is a double-blind, randomized and placebo-controlled trial, is designed to assess the efficacy of SNT-MC17 on the progression of vision loss in symptomatic people with LHON. Up to 60 people with LHON will be recruited for the study and they will be treated for a period of nine months. A special statistical protocol allows for interim analysis after 12, 24, 36 and 48 patients have completed the trial.

Development and Commercialization Strategy for SNT-MC17 in LHON

Following this trial, and subject to positive results, Santhera plans to initiate Phase II/III trials in the EU and the US. Santhera has received orphan drug designation in both the EU and the US. Upon successful registration and marketing clearance for LHON, Santhera will market SNT-MC17 through its own specialty sales force in the US.

Market Opportunity

The prevalence of LHON was estimated in a recent study to be 3 per 100,000 individuals and is thus comparable in prevalence with inherited neuromuscular diseases such as Duchenne Muscular Dystrophy (DMD). As a genetic disease with well known family histories, there is a potential that not only LHON patients showing symptoms will be users of a treatment, but that carriers may also take a product on a preventative basis. The market for pharmaceutical products that can treat and ameliorate LHON is estimated by Santhera to be broadly comparable to that of DMD, based on estimated disease prevalence, severity and expected reimbursement levels.

Dyskinesia in Parkinson's Disease (DPD)

Parkinson's disease (PD) is the second most common neurodegenerative disease, and affects movement as well as disorders of mood, behavior, thinking, and sensation. Dyskinesia refers to an impairment of voluntary movement. In people with PD, dyskinesias are often the result of chronic levodopa therapy, the current standard treatment for PD. It is estimated that approximately 20% of all PD patients develop troublesome DPD within 5 years of initiating levodopa treatment.

Causes

The initial mechanisms responsible for levodopa induced dyskinesia are not clear, but these are related to widely varying blood levels of levodopa-derived L-dopa and possibly to storage and release of *dopamine* in brain areas where it should not normally occur. In PD, dopamine-producing neurons gradually die in an area in the middle of the brain called the substantia nigra, causing a shortage of dopamine. *Dopamine* helps to relay messages between areas of the brain that control body movement.

Diagnosis

Parkinson's disease can be difficult to diagnose accurately as there are currently no blood or laboratory tests that have been proven to help in diagnosing sporadic PD. Therefore the diagnosis is based on medical history and a neurological examination.

Signs and symptoms

Symptoms can occur at any age but in countries where PD is common, the average age at which symptoms begin is 55 to 60 years. Symptoms of PD are numerous and impair a patient's ability to move and function properly. Dyskinesias appear at the advanced stages of the PD.

Prognosis

Over time, movement disorders experienced by people with PD worsen. These are usually known as dyskinesias which include chaotic movements of limbs, face, tongue and the body. Dyskinesias are derived principally from long-term levodopa use. As a result, patients often require extended periods of hospitalization or placement in a full-time nursing environment.

Treatment

There is currently no pharmaceutical therapy specifically approved for the treatment of DPD. Although there is no cure for PD, some medication or surgery can provide relief from the symptoms. The current standard medical treatment is based on levodopa, which is converted into *dopamine* in certain brain cells, although *dopamine* agonists and certain other medications also play a significant role in disease management. These cells normally produce *dopamine*, a chemical that helps to relay messages between areas of the brain that control body movement.

JP-1730 (INN: fipamezole) Mode of Action

JP-1730 is an antagonist of the adrenergic alpha-2 receptors and offers a novel and unique mode of action to treat DPD. The rationale behind the development of JP-1730 is to increase noradrenergic turnover in certain areas of the brain, resulting in a rebalancing of the distorted brain network and alleviating the symptoms of advanced PD such as dyskinesias, motor fluctuations and cognitive impairment. In addition, JP-1730 is believed to extend the beneficial effects of commonly used levodopa and possibly dopamine agonists without the negative side effects associated with these treatments. Such therapy is expected to improve the quality of life of people with PD.

Clinical Development of JP-1730

In 2006, Santhera and Juvantia Pharma entered into a strategic cooperation to advance the development of Juvantia's compound JP-1730 for the treatment of people with DPD. Santhera intends to fund a Phase IIb double-blind, placebo-controlled trial with JP-1730 due to start in the US in 2007. The trial will further assess the compound's efficacy in the treatment of troublesome dyskinesias in a larger cohort of patients than the prior Phase IIa clinical trial conducted in the US by Juvantia. Based on the existing safety data for JP-1730, the intended trial will be a one-month efficacy trial taking advantage of Juvantia's open Investigative New Drug Application (IND) in the US.

The previous Phase IIa clinical trial was conducted by Juvantia in collaboration with the US National Institutes of Health (NIH). This trial which enrolled 21 patients was a placebo-controlled, double-blind study and tested three different doses of JP-1730. The study established clinical evidence that the compound has the potential to reduce DPD symptoms as well as prolongation of levodopa effects in PD patients.

Development and Commercialization Strategy for JP-1730

Santhera will be responsible for conducting and funding development work of the Phase IIb clinical trial with the assistance of Juvantia. Santhera has a call option to acquire all Juvantia shares at a later point in time. Santhera also plans to file for orphan drug designation in the EU and US covering the use of JP-1730 for the treatment of troublesome dyskinesia in a subset of people with PD. Upon successful registration and marketing clearance for DPD, Santhera will market JP-1730 through its own specialty sales force in the US.

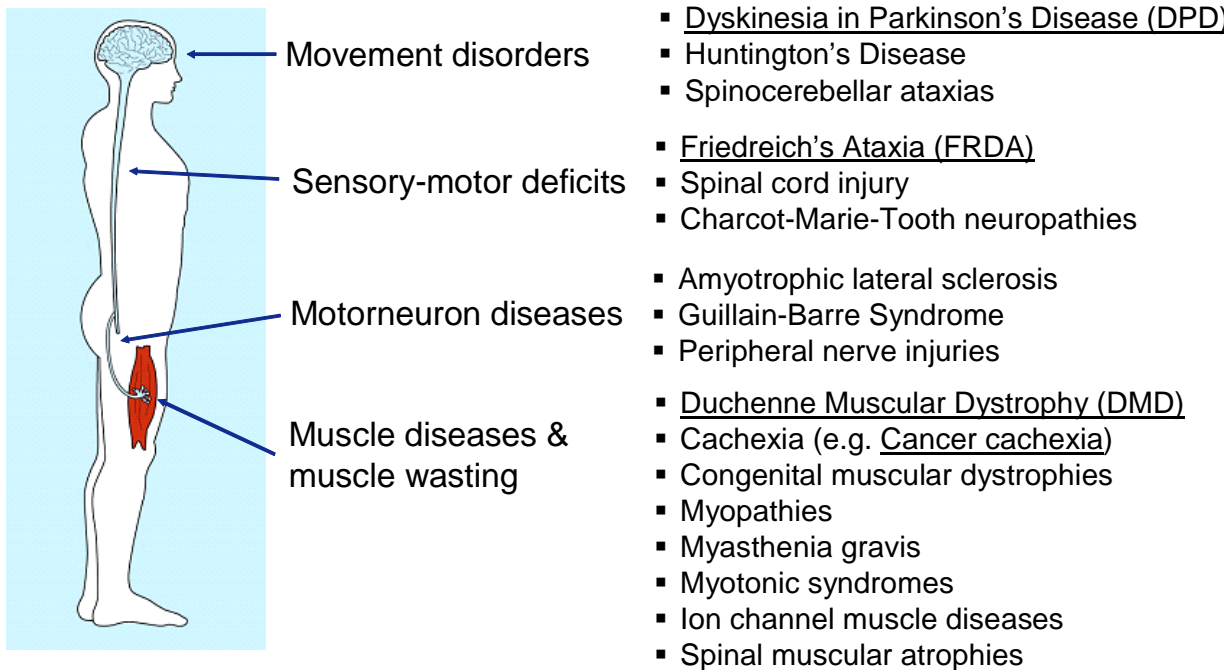
Market Opportunity

It is estimated that approximately 20% of all people with PD develop dyskinesia within five years of initiating levodopa treatment. This represents approximately 200,000 DPD sufferers worldwide. The market for pharmaceutical products that can treat DPD is estimated to be approximately EUR 500 million per annum, based on disease prevalence, severity and expected reimbursement levels.

Neuromuscular Diseases (NMD)

NMDs are characterized by high unmet medical need and usually affect relatively small patient populations, ranging from tens of thousands to only a few hundred patients worldwide. Over 200 distinct NMDs and movement disorders are known today, often characterized by devastating disabilities and leading to premature death. NMDs are mostly inherited, genetically determined disorders. People diagnosed with an NMD frequently suffer from significant and progressive loss of muscle tissue, resulting in impaired movement control, loss of mobility and respiratory capacity as well as heart malfunction.

People suffering from neuromuscular diseases are often members of well-organized patient groups and managed by specialty physicians, who act as central reference points for patients. NMDs usually qualify as orphan diseases which means that some of Santhera's drug candidates can benefit from orphan drug status.



Selected examples, areas underlined reflect Santhera's current areas of focus

Orphan drug legislation

Orphan drug legislation exists in both the US and the EU and is designed to encourage biotechnology and pharmaceutical companies to develop treatments intended for a rare diseases or conditions. These legislations provide for periods of market opportunities for orphan products, and other incentives.

Orphan drug designation under the US regulations:

- A rare disease or condition is defined as affecting less than 200,000 individuals;
- Seven year marketing exclusivity following the date of marketing approval by the Food and Drug Administration (FDA);
- Products receive other incentives such as tax credits, a fee waivers for regulatory submissions etc.

Orphan medical product under the EU regulation:

- A rare disease or condition is defined by affecting no more than 5 in 10,000 individuals in the EU;
- 10 year marketing exclusivity in the EU following the date of marketing approval by the European Medicines Agency (EMA);
- Products receive other incentives such as tax credits, a fee waivers for regulatory submissions etc.

Santhera was granted orphan drug designation in the US and in the EU for SNT-MC17 in Friedreich's Ataxia (FRDA) and Duchenne Muscular Dystrophy (DMD). Additionally, orphan drug designation has been granted in the EU for SNT-MC17 in Leber's Hereditary Optic Neuropathy (LHON) while a similar application has been filed in the US. The application is also planned for JP-1730 in DPD.