



Press Release

November 13, 2006

NIH and Santhera Announce Positive Results of Study with SNT-MC17/idebenone in Friedreich's Ataxia (FRDA)

Data Presented at the 3rd International Scientific Friedreich's Ataxia Conference

Bethesda, Maryland, USA, and Liestal, Switzerland – The US National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) presented results of their recently completed clinical trial with SNT-MC17/idebenone in Friedreich's Ataxia (FRDA). Data were presented by Dr. Nicholas Di Prospero at the 3rd International Scientific Friedreich's Ataxia Conference in Bethesda, MD, on November 10 to 12. This six month double-blind, placebo-controlled trial was carried out in collaboration with Santhera Pharmaceuticals, a Swiss specialty pharmaceutical company with a focus on neuromuscular diseases.

The trial enrolled 48 genetically-confirmed FRDA subjects between 9 and 18 years of age (mean age: approx 14 years). Subjects were randomized to placebo or one of three dose arms for SNT-MC17/idebenone given three times a day as fixed daily doses (see "Study Design and Dosing" below).

The trial supported the safety and favorable tolerability of SNT-MC17/idebenone in young patients with FRDA at all doses up to 2250 mg/day. There were no subject withdrawals in this study.

More importantly, the study demonstrated promising efficacy for SNT-MC17/idebenone in particular on the validated International Cooperative Ataxia Rating Scale (ICARS) as well as the Activity of Daily Living (ADL) scale. The study also showed a dose-response favoring the intermediate and high doses over the low dose of the study medication.

These new data support the investigator's and Santhera's belief that SNT-MC17/idebenone has the potential to provide a possible treatment for this devastating disease.

Dr. Nicholas Di Prospero, principal investigator of the study, said: "Our data from this trial support SNT-MC17/idebenone to be safe and well tolerated. The dose-dependent effects on neurological outcome measures in a period of just six months indicate that the intermediate and high doses as used in this study may be required for efficacy. On behalf of the study team I would like to thank the patients and their families for their support in this important clinical study."

Dr. Thomas Meier, Chief Scientific Officer of Santhera said: “The results of this trial are very promising. We have seen evidence of an improvement in neurological function, which is obviously encouraging for a patient group for whom there is currently no treatment. In addition, the positive effect of SNT-MC17/idebenone on activity of daily living parameters such as for example cutting food, dressing and personal hygiene is an important finding.”

Ron Bartek, President of the Friedreich’s Ataxia Research Alliance (FARA) added: “On behalf of Friedreich’s ataxia patients and families everywhere, FARA would like to express its gratitude for the public-private partnership that has pulled together the collaborative forces of an excellent and dedicated team at NIH/NINDS, our pharmaceutical industry partner Santhera, and our non-profit foundation. We see in this promising phase II clinical trial confirmation that the Friedreich’s ataxia community, by working hard together and collaborating broadly, has indeed entered the treatment era. We eagerly await further steps in the clinical development of SNT-MC17/idebenone and the prospects of achieving FDA approval of the first treatment for this devastating disease.”

Study Design and Dosing

The Phase II trial was a double blind, placebo-controlled study, which enrolled 48 genetically-confirmed FRDA subjects between 9 to 18 years of age (mean age: approx. 14 years). Eleven to thirteen subjects were randomized to placebo or one of three dose arms for SNT-MC17/idebenone: low dose (180 mg/d for patients <45 kg; 360 mg/d for patients >45 kg; equivalent to approx. 4 to 8 mg/kg/day), intermediate dose (450 mg/d for patients <45 kg; 900 mg/d for patients >45 kg; equivalent to approx. 10 to 20 mg/kg/day), or high dose (1350 mg/d for patients <45 kg; 2250 mg/d for patients >45 kg; equivalent to approx. 30 to 50 mg/kg/day). Patients were also stratified according to the GAA triplet repeats (>800 and <800 repeats on the shorter allele) to control for genetic factors. The total treatment time was six months.

Neurological Assessments and Activity of Daily Living Score

ICARS (International Cooperative Ataxia Rating Scale) consists of a one-hundred-point semi-quantitative scale based upon 19 simple testing maneuvers compartmentalized into postural and stance, limb, speech, and oculomotor components and has been previously applied to this patient population in clinical studies.

FARS (Friedreich’s Ataxia Rating Scale) consists of a 25 maneuver exam along with 3 quantitative performance measures. The exam covers bulbar function, upper limb coordination, lower limb coordination, peripheral nervous system function, deep tendon reflexes, stability and gait. The performance measures include a timed 25-foot walk for ambulation, a 9-hole peg test for upper limb coordination and function, and a quantitative measure of speech performance. The use of FARS has been recently validated as a neurological scale for this population.

The Activity of Daily Living (ADL) score consists of 9 tests adding up to a 36-point scale with emphasis of basic tasks such as cutting food, dressing and personal hygiene.

Summary of the Statistical Analysis

Data were collected at baseline and after six months of treatment and presented as raw means. Differences between all treatment groups were analyzed using a standard ANCOVA model. The hypothesis for dose-effects was tested using the Jonckheere statistical method. In addition Santhera conducted an analysis using the least square means of each data set, allowing for pairwise comparisons between SNT-MC17/idebenone dose groups and placebo.

The Study Results in Detail

The primary endpoint of this study was to determine changes in an exploratory surrogate marker, 8-hydroxy-2-deoxyguanosine, measured in urine of patients. There was no significant change in this biochemical marker across treatment groups.

The study examined as secondary endpoints the potential efficacy of SNT-MC17/idebenone on neurological findings and activity of daily living in patients with FRDA. The key findings were:

- FRDA patients showed an indication of improvement on the ICARS (International Cooperative Ataxia Rating Scale) scale at intermediate and high doses of SNT-MC17/idebenone after six months of treatment.

Specifically, the placebo arm performed on average 0.1 point better on the ICARS than at the beginning of the study while, both the intermediate and high dose arms improved by ≥ 4.0 points on the total scale. Patients on the low dose improved by 0.3 point on average resulting in a p-value of 0.14 using the ANCOVA analysis including all treatment groups and a p-value of 0.03 for the hypothesis that there is a dose-dependent effect (Jonckheere test). Combining the intermediate and high dose arms in an exploratory analysis by Santhera resulted in an improvement on the ICARS for the combined doses which was different from placebo as determined in a pairwise comparison with a p-value of < 0.05 .

A subgroup analysis as predefined in the statistical analysis plan was performed by excluding mildly affected FRDA patients with < 10 ICARS points at baseline as well as more severely affected patients that were dependent on a wheelchair most of the time with > 54 points ICARS at baseline. This analysis revealed a stronger dose-response relation of the effect. Patients receiving placebo declined on the ICARS by 2.0 points while patients on the low dose improved by 0.6 point, patients on the intermediate dose improved by 4.3 points and patients on the high dose improved by 5.8 points resulting in a p-value of 0.01 using the ANCOVA analysis including all treatment groups and a p-value of 0.002 for the hypothesis that there is a dose-dependent effect (Jonckheere test).

- When analyzed for the total Friedreich's Ataxia Rating Scale (FARS), patients on placebo changed by 2.5 points indicating a possible placebo effect or greater variability on this scale. While there was an improvement of 1.8 points on FARS for patients treated with the low dose of SNT-MC17/idebenone, treatment with the intermediate dose improved by 4.7 points and patients on the high dose improved by 5.9 points, although these did not reach statistical significance. A subgroup analysis excluding mildly and severely effected patients revealed that patients on placebo improved by 0.2 point on FARS while patients on the intermediate and high dose improved by 5.2 points

respectively and patients on the low dose improved by 0.8 point ($p=0.04$ for the hypothesis that there is a dose-dependent effect; Jonckheere test).

- There was a positive indication of difference in the activities of daily living (ADL) scale between patients receiving placebo and patients receiving the intermediate and high dose of SNT-MC17/idebenone. Specifically, patients on placebo performed worse by 1.0 point on ADL over the 6 months treatment period, while patients receiving the intermediate dose improved by 1.2 points ($p=0.035$ for pairwise comparison according to Santhera's additional analysis). Patients on the high dose improved by 0.8 point on ADL and patients on the low dose improved by 0.3 point, respectively.

After excluding mildly and severely affected patients the Jonckheere analysis revealed a clear dose-response relation of the effect. Under these conditions patients receiving placebo worsened by 0.8 point on ADL while patients on the low dose remained unchanged. In contrast, patients on the intermediate dose improved by 1.3 points on ADL and patients on the high dose improved by 1.4 points resulting in a p -value of 0.05 for the hypothesis that there is a dose-dependent effect.

– Ends –

About Friedreich's Ataxia

Friedreich's Ataxia (FRDA) is a rare but severe genetic neuromuscular disorder that results in the degeneration of an individual's nerve and muscle tissue. This disorder causes loss of muscle control, uncoordinated movements, muscle wasting and thickening of heart walls which frequently leads to a shortened life span. FRDA affects both Caucasian males and females equally and it is estimated that about 20,000 patients suffer from the disease in both North America and Europe. Average life expectancy for FRDA patients is limited to approximately 35 to 50 years.

The disorder results from a genetic defect in the gene encoding for *frataxin*. Reduced levels of this protein ultimately result in impaired energy production in mitochondria, the cells' energy production centers, and elevated oxidative stress. Tissues that have the highest need for energy, in particular nerve and cardiac tissues, are primarily affected by *frataxin* deficiency resulting in pathological changes in heart muscle anatomy and function and loss of nerve cells. SNT-MC17/idebenone is believed to improve the balance and flow of electrons within the mitochondria, therefore increasing the energy production within nerve and muscle cells of FRDA patients, protecting these cells from cell death. A number of clinical trials have provided strong evidence that SNT-MC17/idebenone may offer an effective treatment option for FRDA associated heart wall thickening (cardiomyopathy). In addition, data from this collaborative NIH clinical trial suggest positive effects on neurological function.

About the US National Institute of Neurological Disorders and Stroke (NINDS)

The NINDS, a component of the National Institutes of Health in Bethesda, MD, is the leading agency for research on the brain and nervous system in the United States. More information about the NINDS is available at its website, www.ninds.nih.gov.

The National Institutes of Health (NIH) – The Nation’s Medical Research Agency – includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical and translational medical research, and it investigates the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov.

About Santhera

Santhera Pharmaceuticals is a Swiss specialty pharmaceutical company focusing on the discovery, development and marketing of small molecule pharmaceutical products for the treatment of severe neuromuscular diseases. Santhera’s vision is to become a leading specialty pharmaceutical company offering therapies for a number of indications in this area of high unmet medical need which includes many orphan indications with no current therapy.

Santhera currently has four clinical-stage development programs, three of which are investigating its lead compound, SNT-MC17/idebenone, in the treatment of Friedreich’s Ataxia (FRDA), Duchenne Muscular Dystrophy (DMD) and Leber’s Hereditary Optic Neuropathy (LHON). The fourth clinical program is investigating JP-1730/fipamezole for the treatment of Dyskinesia in Parkinson’s Disease (DPD) in cooperation with Juvantia, the compound’s owner. The most advanced program, SNT-MC17/idebenone in FRDA, has entered pivotal Phase III clinical development; the other clinical programs are in Phase II. Santhera’s drug pipeline comprises another three preclinical programs in cancer cachexia, DMD and type 2 diabetes (out licensed to Biovitrum). For further information on Santhera, please visit www.santhera.com.

About Friedreich’s Ataxia Research Alliance (FARA)

The Friedreich’s Ataxia Research Alliance (FARA) is a national, public, 501(c)(3), non-profit, tax-exempt organization dedicated to the pursuit of scientific research leading to treatments and a cure for Friedreich’s ataxia. FARA’s mission is to slow, stop, and reverse the damage caused by this disorder. For further information on FARA, please visit www.faresearchalliance.org.

For Further Information, Contact:

US National Institute of Neurological Disorders and Stroke

Dr. Kenneth H. Fischbeck, Chief of the Neurogenetics Branch

phone +1 301 435 9318, fischbek@ninds.nih.gov

Dr. Nicholas Di Prospero, principal investigator of the study

phone +1 301 435 9287, diprospern@ninds.nih.gov

Santhera Pharmaceuticals

Dr. Thomas Meier, Chief Scientific Officer

phone +41 61 906 89 87, thomas.meier@santhera.com

Thomas Staffelbach, VP Public & Investor Relations

phone +41 61 906 89 47, thomas.staffelbach@santhera.com

Media contact: Citigate

David Dible, phone +44 207 638 9571, david.dible@citigatedr.co.uk

Chris Gardner, phone +44 207 638 9571, chris.gardner@citigatedr.co.uk