Santhera Pharmaceuticals Holding AG
Hammerstrasse 49
CH-4410 Liestal / Switzerland
Phone +41 61 906 89 50
Fax +41 61 906 89 51
www.santhera.com

Santhera Reports New Data and Updates on Regulatory Filings for Raxone® (idebenone) in Duchenne Muscular Dystrophy (DMD)

Liestal, Switzerland, November 11, 2015 –Santhera Pharmaceuticals (SIX: SANN) announces that it has now completed comparative analyses of the respiratory outcomes for patients in its successful Phase III DELOS trial with data from a natural history DMD patient cohort collected by the Cooperative International Neuromuscular Research Group (CINRG). These and other supporting analyses previously discussed with regulatory authorities will be included in the regulatory filings in the US (NDA) and EU (MAA) expected for 1Q 2016. In order to expand the DMD population that is the subject of these initial filings, the Company also prepares to conduct a new trial in DMD patients using glucocorticoid steroids.

"We thank CINRG for their excellent work on a number of analyses which further support the robustness of the DELOS outcome, validate the DELOS primary endpoint as clinically relevant and demonstrate further the efficacy of Raxone on respiratory function in patients not using concomitant glucocorticoid steroids", commented **Thomas Meier**, PhD, CEO of Santhera. "Together with the recently completed patient and caregiver survey prepared by PPMD, which underlined the importance of treating pulmonary complications in patients with DMD, we have now all data we wanted to include in our regulatory filing dossiers according to our previous discussions with regulators. The expected shorter review timelines due to the fast track status allowing for priority review in the US and a filing as a Type II variation of the existing marketing authorization in the EU should lead to regulatory decisions next year. The new study we plan to start soon addresses a clear medical need for the treatment of respiratory function decline also in patients using glucocorticoid steroids and follows requests by physicians and the DMD community. If successful, we will seek to extend the label accordingly to include this substantial group of DMD patients."

"We are glad that we could support Santhera in their efforts to further strengthen the results and interpretation of their successful DELOS trial ", added **Craig McDonald**, MD, Professor and Chair of the Department of Physical Medicine & Rehabilitation at UC Davis (USA) and study chair of the CINRG natural history study. "This is the first time where data from the CINRG Duchenne Natural History Study was used to support an industry partner in the analysis of a completed study measuring impact of a drug on disease progression in DMD. These natural history data also were important for the planning of a new trial using respiratory function outcomes in patients with DMD using concomitant glucocorticoid steroids. This again demonstrates the tremendous value of the large natural history data set collected by CINRG with over 400 DMD patients currently included."

Additional data analyses completed in support of regulatory filings.
Following early discussions with the FDA, Santhera has now completed the following analyses and reports:

- Significant correlations between Peak Expiratory Flow (PEF), the primary endpoint of the DELOS trial, and Forced Vital Capacity, a well-validated marker of irreversible morbidity and mortality in DMD, and incidence of severe respiratory events , confirming the relevance of PEF as an intermediate clinical endpoint.
- Comprehensive demonstration of the robustness of the positive outcome of the DELOS trial by excluding the effect of potential imbalances in baseline demographics, previous glucocorticoid steroid use and dropouts on the overall outcome.
- Additional analyses of the DELOS trial outcome demonstrating effect of Raxone on bronchopulmonary events (including airway infections). The resulting hazard ratio for the number of patients reporting at least one bronchopulmonary event was 0.332 (95% CI: 0.131, 0.843; p = 0.020) and 0.271 (95% CI: 0.118, 0.623; p = 0.002) for the total cumulative number of events in favor of Raxone treatment. Similar analysis of systemic antibiotic use showed that patients treated with Raxone clearly used less antibiotics compared to patients receiving placebo
- While previous published results from the DELOS trial focused on expiratory muscle function in patients with DMD, new data demonstrate also positive effect of Raxone on inspiratory muscle function. Specifically, Raxone compared to placebo stabilized the maximum inspiratory flow based on the measurement of inspiratory flow reserve and inspiratory forced vital capacity over the 52-week study period.
- The first successful comparison of the outcomes for a clinical trial population (DELOS) with the outcomes for a natural history population (CINRG) matched patient-by-patient to the DELOS population. For this external validation of the DELOS study findings, CINRG compared the annual rate of change in PEF%p in its natural history population with that seen in DELOS. CINRG identified a matched patient for each DELOS patient by considering the baseline PEF%p value, previous use of glucocorticoids and the age of the patient. The matching and comparison was based on a prospective analysis plan prepared by CINRG in collaboration with Santhera and resulted in comparable baseline characteristics of the CINRG patients and the DELOS patients. The analysis of the longitudinal data met the pre-specified criterion of showing that the annual decline among the untreated CINRG natural history patients in PEF%p was at -6.3% (95% CI: -10.6% to -2.0%) closer to the decline of the placebo-treated DELOS patients at -8.5% (95% CI: -12.8% to -4.2%) than the change in those treated with Raxone -2.4% (95% CI: -6.5% to 1.7%).

The extended data sets now available are currently being compiled and integrated for use in regulatory filings. In the US, the FDA will be briefed on the extent of the new data sets in the coming weeks. Santhera expects to have a second pre-NDA meeting with the FDA in 1Q 2016 and following a supportive outcome would then submit the NDA. In the EU, these new data will be incorporated in the application for marketing authorization for DMD to be filed as Type II variation of the marketing authorization previously granted for the indication Leber's Hereditary Optic Neuropathy (LHON). The dossier is expected to be submitted also in 1Q 2016.

New trial planned in DMD patients using glucocorticoid steroids.
Santhera is currently preparing to start a new clinical trial to investigate whether Raxone treatment could also slow respiratory function loss in DMD patients treated with glucocorticoid steroids, a population previously not included in the successful DELOS trial. The new study was planned based on CINRG natural history data demonstrating that at a certain stage of disease progression patients on glucocorticoid steroids will experience the same rate of respiratory function loss as patients not using steroids, presenting an urgent medical need for treatment.

Patients who will be eligible to enroll will have already started to decline on respiratory function whilst on stable glucocorticoid steroid treatment. Study participants will receive either Raxone (900 mg/day) or placebo for the duration of 78 weeks. The trial targets to enroll approximately 260 DMD patients and will be conducted in Europe and the US. Further details of the inclusion and exclusion criteria will be announced at the time of patient enrolment expected to commence early 2016. Patients completing the trial will be offered enrolment into an open label extension study.

About Idebenone in Duchenne Muscular Dystrophy and the DELOS trial
DMD is one of the most common and devastating types of muscle degeneration and results in rapidly progressive muscle weakness. It is a genetic, degenerative disease that is inherited in an X-linked recessive mode with an incidence of up to 1 in 3,500 live born males worldwide. DMD is characterized by a loss of the protein dystrophin, leading to cell damage, impaired calcium homeostasis, elevated oxidative stress and reduced energy production in muscle cells. This results in progressive muscle weakness and wasting and early morbidity and mortality due to cardio-respiratory failure. Currently, glucocorticoid steroids are the only available medical treatment that can slow the decline in muscle strength and function irrespective of the disease-causing mutation. However, the effect is only partial and clinical use is limited by well-known side effects caused by glucocorticoid steroids. A recent study showed that ~42% of DMD patients 10 years and older had either never used glucocorticoid steroids or have discontinued their use.

The lack of the protein dystrophin leads to membrane instability and uncontrolled calcium influx and imbalance of intracellular calcium homeostasis in muscle cells. This results in reduced cellular energy production, increased reactive oxygen species (ROS) production and mitochondrial dysfunction, which contribute to muscle cell loss in DMD. Idebenone is a synthetic short-chain benzoquinone and a substrate for the enzyme NAD(P)H:quinone oxidoreductase (NQO1) capable of stimulating mitochondrial electron transport, supplementing cellular energy levels and inhibiting ROS production.

DELOS was a Phase III double-blind, placebo-controlled trial which randomized and treated 64 DMD patients not receiving concomitant glucocorticoid steroids. Patients 10-18 years of age received either Raxone tablets (900 mg/day) or matching placebo for 52 weeks. Data from the successful DELOS trial, which met its primary endpoint, were recently published in The Lancet (Buyse et al., (2015) Lancet. 385:1748-57).

Idebenone has been granted orphan drug designation for DMD in Europe and the US and has use patent protection until 2026 in Europe and 2027 in the US. The FDA recently granted Fast Track designation for Raxone (idebenone) for the treatment of DMD.

About CINRG

The Cooperative International Neuromuscular Research Group was founded in 1999 as the Clinical Research Arm of the Duchenne Muscular Dystrophy Research Center and the Research Center for Genetic Medicine at the Children's National Medical Center in Washington DC. It started, and remains, a multi-disciplinary and cross-institutional network of clinicians and scientists with the shared goal of wanting to positively impact the lives of neuromuscular disorder patients and their families. Today, CINRG is a global, state-of-the-art clinical research network, with over 20 sites, that has conducted many studies and has access to over 4,000 neuromuscular patients. The primary goal of CINRG is to study the cause(s), pathogenesis and clinical outcomes of neuromuscular disorders and to conduct well-controlled clinical studies that examine promising, therapeutic interventions that may improve quality of life or extend life for patients. The CINRG Coordinating Center is located at the Children's National Medical Center in Washington, DC. The CINRG Duchenne Natural History Study (DNHS), led by a team of investigators at the University of California, Davis and funded through a combination of US Federal and patient advocacy foundation grants is presently the largest and most comprehensive multi-institution study ever conducted in individuals with DMD. The study has regularly followed more than 400 patients in 10 nations for up to 9 years each, and has combined genetic information, clinical measures of strength and function, pulmonary function, medical treatment and outcome data, and patient and family reports of activities, participation and quality of life. The data is being used to create a contemporary picture of individuals with DMD that guides the development of and interpretation of clinical trials, improves care practices, and validates clinical, biomarker and patient-reported assessment tools.

About Santhera

Santhera Pharmaceuticals (SIX: SANN) is a Swiss specialty pharmaceutical company focused on the development and commercialization of innovative pharmaceutical products for the treatment of orphan mitochondrial and neuromuscular diseases. Santhera's lead product Raxone® is authorized in the European Union for the treatment of Leber's Hereditary Optic Neuropathy (LHON). Santhera develops Raxone®/Catena® in two additional indications, Duchenne Muscular Dystrophy (DMD) and primary progressive Multiple Sclerosis (ppMS), and omigapil for Congenital Muscular Dystrophy (CMD), all areas of high unmet medical need. For further information, please visit the Company's website www.santhera.com.

For further information, contact:

Thomas Meier, PhD, Chief Executive Officer
Phone +41 61 906 89 64
thomas.meier@santhera.com

Christoph Rentsch, Chief Financial Officer
Phone +41 61 906 89 65
christoph.rentsch@santhera.com

US investor contact:

Hans Vitzthum, LifeSci Advisors, LLC
Phone +1 212 915 2568
hans@lifesciadvisors.com

US Public Relations contact:

Deanne Eagle, Planet Communications
Phone +1 917 837 5866
deanne@planetcommunications.nyc

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