

Santhera Provides Update on Filing for Conditional Marketing Authorization in Europe for Puldysa® (Idebenone) in Duchenne Muscular Dystrophy

Pratteln, Switzerland, March 28, 2019 – Santhera Pharmaceuticals (SIX: SANN) announces its intention to file an application for Conditional Marketing Authorization (CMA) for Puldysa® (idebenone) for the treatment of respiratory dysfunction in Duchenne muscular dystrophy (DMD) with the European Medicines Agency (EMA). Following scientific advice from EU regulatory authorities, completion and filing of the CMA for Puldysa in DMD is planned for the second quarter of 2019.

Santhera has expanded and substantiated its previous regulatory dossier with additional clinical data from patients treated with idebenone, new analyses of previously submitted data and new comprehensive natural history data, addressing requests from regulatory authorities. In its entirety, these new data demonstrate clinically relevant patient benefits and sustained therapeutic efficacy during treatment with idebenone for up to six years in patients with DMD. The new data package and filing strategy have been discussed in several pre-submission meetings with national regulatory authorities.

The initial indication intended for Puldysa is to treat respiratory dysfunction in patients with DMD who are not using glucocorticoids. The filing will be based on data from Santhera's Phase II (DELPHI) study, the long-term DELPHI-Extension study, the pivotal Phase III (DELOS) study [1-5] and the recently completed SYROS study, a collection of long-term data from patients who completed the DELOS study and continued to be treated with idebenone for up to six years [6].

Key data included in the forthcoming filing:

- *Clinical trial data demonstrate therapeutic potential for idebenone in the treatment of respiratory dysfunction in patients with DMD.* Pivotal data from the Phase III (DELOS) study, which met its primary endpoint, demonstrated clinically relevant treatment effects of idebenone compared to placebo on respiratory function outcomes [1-5]. Supportive evidence comes from the Phase II (DELPHI) study and its two-year open label extension study (DELPHI-E).
- *Idebenone has the potential to delay the time to clinically relevant milestones of disease progression.* Peak expiratory flow as percent predicted (PEF%p) is a sensitive and early marker of respiratory function decline in DMD. Analysis of natural history data showed that the treatment benefit observed with idebenone in the DELOS study on PEF%p could, when extrapolated, result in a delay in the initiation of assisted ventilation by three years with continued treatment, which is of high clinical relevance.
- *The beneficial treatment effects of idebenone are sustained year on year for up to six years.* The annualized decline in forced vital capacity percent predicted (FVC%p) and PEF%p remained consistently lower for a period of up to six years compared to data from a matched group of untreated patients enrolled in the CINRG natural history study. This long-term data from the SYROS study further support the potential for idebenone to modify the course of respiratory function decline and delay the time to clinically relevant milestones.

- *Idebenone has been shown to support preservation of respiratory function.* Treatment with idebenone also reduced the risk of important patient-relevant outcomes, including bronchopulmonary adverse events and hospitalizations due to respiratory causes as demonstrated in the pivotal study (DELOS) and maintained in the long-term data collection (SYROS).

“Our team has worked hard to assemble new data which substantially strengthen our regulatory dossier for Puldysa as a potential treatment for DMD,” said **Kristina Sjöblom Nygren, MD, Chief Medical Officer and Head of Development at Santhera**. “The continued dialogue with regulators and clinical experts in DMD has provided the necessary guidance which enabled us to close earlier data gaps by bridging clinical trial results to tangible and highly relevant patient benefits.”

“The choice for a conditional marketing authorization pathway was acknowledged by regulators and we are in final preparations to submit the filing dossier,” added **Thomas Meier, PhD, Chief Executive Officer of Santhera**. “The regulatory path of a conditional marketing authorization requires us to submit a full dossier with a new tradename, Puldysa®, to distinguish this product from Raxone® which was previously approved as treatment for patients with Leber's hereditary optic neuropathy.”

The European Medicines Agency (EMA) may grant a conditional marketing authorization for a new treatment to address unmet medical needs for patients. Medicines are eligible for conditional approval if they are aimed at treating seriously debilitating or life-threatening diseases. This includes orphan medicines. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should have a development plan in place to provide additional clinical data.

Idebenone has been granted orphan drug designation for the treatment of DMD by European, US, Swiss and Australian authorities.

References

- [1] Buyse et al. (2015), *The Lancet* 385:1748-1757
- [2] McDonald et al. (2016), *Neuromuscular Disorders* 26:473-480
- [3] Buyse et al. (2017), *Pediatric Pulmonology* 52:580-515
- [4] Mayer et al. (2017), *Journal of Neuromuscular Diseases* 4:189-198
- [5] Buyse et al. (2018), *Journal of Neuromuscular Diseases* 5: 419-430
- [6] To be presented at the 2019 MDA Clinical & Scientific Conference (April 13-17, 2019, in Orlando)

About Duchenne Muscular Dystrophy

DMD is one of the most common and devastating types of progressive muscle weakness and degeneration starting at an early age and leading to early morbidity and mortality due to respiratory failure. It is a genetic, degenerative disease that occurs almost exclusively in males with an incidence of up to 1 in 3,500 live male births 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. With age, progressive respiratory muscle weakness affecting thoracic accessory muscles and the diaphragm causes respiratory disease, impaired clearance of airway secretions, recurrent pulmonary infections due to ineffective cough, and eventually respiratory failure. There is currently no treatment approved for slowing loss of respiratory function in patients with DMD.

About Idebenone in Duchenne Muscular Dystrophy

Idebenone is a synthetic short-chain benzoquinone and a cofactor for the enzyme NAD(P)H:quinone oxidoreductase (NQO1) capable of stimulating mitochondrial electron transport, reducing and scavenging reactive oxygen species (ROS) and supplementing cellular energy levels.

DELOS was a Phase III, double-blind, placebo-controlled 52-week study which randomized 64 patients, not taking concomitant steroids, to receive either idebenone (900 mg/day) or matching placebo. The study met its primary endpoint, the change from baseline in peak expiratory flow (PEF) expressed as percent of predicted, which demonstrated that idebenone can slow the loss of respiratory function. Supportive data for idebenone were shown in the Phase II double-blind, placebo-controlled DELPHI study and its 2-year open-label extension study (DELPHI-E).

SYROS was a prospectively planned, retrospective collection of long-term respiratory function data from 18 patients who completed the DELOS study and subsequently received idebenone (900 mg/day) under Expanded Access Programs (EAPs). The SYROS study showed that the previously observed beneficial effect of idebenone in reducing the rate of respiratory function decline was maintained for up to six years during treatment.

About Santhera

Santhera Pharmaceuticals (SIX: SANN) is a Swiss specialty pharmaceutical company focused on the development and commercialization of innovative medicines for rare and other diseases with high unmet medical needs. The portfolio comprises clinical stage and marketed treatments for neuro-ophthalmologic, neuromuscular and pulmonary diseases. Santhera's Raxone® (idebenone) is authorized in the European Union, Norway, Iceland, Liechtenstein, Israel and Serbia for the treatment of Leber's hereditary optic neuropathy (LHON) and is currently commercialized in more than 20 countries. For further information, please visit www.santhera.com.

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