Ad hoc announcement pursuant to Art. 53 LR

Santhera and ReveraGen Announce Positive Topline Results with Vamorolone after Completion of the VISION-DMD Study

- **Vamorolone given throughout the study showed sustained efficacy across multiple endpoints over 48 weeks and the good safety and tolerability profile was confirmed**
- **Switching from *prednisone to vamorolone* after week 24 maintained efficacy and improved on multiple safety parameters including restoration of growth trajectory and reduction of behavioral changes up to week 48**
- **Switching from *placebo to vamorolone* after week 24 resulted in an improvement of multiple efficacy outcome parameters with no apparent increase in the rate of treatment-emergent adverse events (TEAE) up to week 48**
- **Study confirmed good safety and tolerability profile of vamorolone with 98% subjects completing the period from week 24 to week 48**

Pratteln, Switzerland, and Rockville, MD, USA, November 23, 2021 – Santhera Pharmaceuticals (SIX: SANN) and ReveraGen BioPharma, Inc (US: private) announce new topline results after completion of the VISION-DMD study at week 48. As previously reported, the FDA considered the safety and efficacy data of vamorolone at 24 weeks (period 1) sufficient for an NDA filing. Efficacy assessments at the now reported completion at week 48 (period 2) included Time to Stand (TTSTAND) velocity, 6-Minute Walk Test (6MWT), Time to Run/Walk 10 meters (TTRW) velocity, and North Star Ambulatory Assessment (NSAA). Vamorolone 6 mg/kg/day showed maintenance of efficacy across all parameters until end of study at week 48, and was statistically superior to 2 mg/kg/day for TTSTAND velocity and 6MWT but not for TTRW velocity or NSAA. For subjects who continued on the same dose of vamorolone throughout the study, the safety profile was consistent between periods with no increase in frequency or severity of adverse events being observed over time. Subjects switching from 24-week treatment with prednisone to vamorolone 6 mg/kg/day showed no loss of efficacy through to the end of the study. In addition, vamorolone treatment at both doses reversed the growth impairment seen during prednisone treatment and was associated with fewer adverse events, including those associated with corticosteroid use.

VISION-DMD was a pivotal double-blind Phase 2b study designed to demonstrate efficacy and safety of vamorolone compared to placebo and prednisone (active control) in the treatment of DMD [1, 2]. In the first 24-weeks (period 1), 121 ambulant boys aged 4 to <7 years were randomized to receive vamorolone (2 or 6 mg/kg/day) or prednisone (0.75 mg/kg/day) or placebo. 114 subjects continued for another 24 weeks (period 2), where those on vamorolone 2 and 6 mg/kg/day continued to end of study on these doses, and those on prednisone and placebo had been previously randomized to receive vamorolone 2 or 6 mg/kg/day after a 4-week tapering period. 112 subjects completed the study.

Efficacy of vamorolone established at 24 weeks was maintained over 48-week treatment period
Efficacy at week 48 was assessed for measures including TTSTAND velocity, 6MWT, TTRW velocity and NSAA. The size of effect (change from baseline) observed at the primary endpoint at week 24 for vamorolone 6 mg/kg/day was maintained at week 48 for TTSTAND velocity (0.052 vs 0.045 rises/s), NSAA (3.4 vs 3.5 points), TTRW velocity (0.29 vs 0.23 m/s) and improved for 6MWT (37 vs 48 meters).

Vamorolone 2 mg/kg/day showed clinically relevant and robust efficacy at week 24 for the pre-defined hierarchical endpoints of TTSTAND velocity and 6MWT, as well as NSAA which was an exploratory endpoint. At week 48, vamorolone 6mg/kg/day was statistically superior to vamorolone 2 mg/kg/day in TTSTAND velocity (p=0.010) and 6MWT (p=0.047) but not for TTRW velocity (p=0.37) and NSAA (p=0.60).

The efficacy benefit seen with prednisone in period 1 was maintained when subjects were switched to vamorolone 6 mg/kg/day during period 2: TTSTAND velocity (0.28 vs 0.27 rises/s), 6MWT distance (407 vs 408 meters), TTRW velocity (2.20 vs 2.20 m/s) and NSAA (25.6 vs 26.2 points), all absolute values.

Vamorolone at both doses was generally safe and well tolerated

Of the 114 subjects who entered into period 2, two subjects discontinued treatment (one adverse event, one withdrawn consent). Three serious adverse events thought to be unrelated to study drug were reported during vamorolone treatment.

For subjects who continued on the same dose of vamorolone throughout the study, the safety profile was consistent at week 48 compared to the results previously reported at week 24.

Growth velocity was preserved at both vamorolone doses. Body mass index (BMI) was stable for subjects continuing on vamorolone 2 and 6 mg/kg/day between assessments at week 24 and week 48 (mean z-score 1.15 vs 1.25 for 6 mg/kg/day; 0.76 vs 0.91 for 2 mg/kg/day where a z-score of 0 would represent the median value of an age-matched general population).

Safety and tolerability of switching from prednisone to vamorolone

Comparison of the safety outcome parameters of prednisone at week 24, following cross-over to vamorolone 2 or 6 mg/kg/day, showed an improved safety profile. In subjects, who were switched from prednisone to vamorolone 6 mg/kg/day, the number of total adverse events was reduced by 37% (70 vs 44) and the number of adverse events typically associated with corticosteroids was reduced by 60% (40 vs 16). Of particular interest, the number of adverse events reported as behavioral changes decreased by 60% (15 vs 6).

Stunting of growth observed with prednisone was reversed during treatment with vamorolone 6 mg/kg/day in period 2 (mean z-score -0.38 vs -0.12 where a z-score of 0 would represent a normal growth trajectory). An increase of BMI was observed with prednisone in period 1 (mean z-score from 0.94 to 1.40) but stabilized in period 2 with vamorolone 6 mg/kg/day (mean z-score 1.32).

Similar effects for safety and tolerability were observed with the switch from prednisone to vamorolone 2 mg/kg/day.

“Back in June, we announced the pivotal 24-week data from the VISION-DMD study which the FDA recently considered sufficient for our planned NDA filing. Now, we are very pleased to announce the completion of the VISION-DMD study, providing longer term data which both confirm earlier findings but importantly also support the potential benefits of vamorolone in overcoming some of the challenges these young children and families face in tolerating long term use of corticosteroids,” said **Dario Eklund, Chief Executive Officer of Santhera**. “We look forward to commencing the NDA submission with our partner ReveraGen and working with regulators to making vamorolone available as soon as possible.”

"We are delighted about the positive outcome of the pivotal VISION-DMD study as it brings to fruition over a decade of scientific research to design and develop a corticosteroid that has the potential to address very clear unmet medical needs that burden patients and families," said **Eric Hoffman, PhD, President and CEO at ReveraGen BioPharma.** "We extend our gratitude to all VISION-DMD participants, their families and caregivers, as well as investigators and study personnel, for their dedicated efforts in advancing this ground-breaking program for the benefit of patients with DMD."

"Short stature, behavioral changes and weight gain are some of the important concerns families and patients experience with corticosteroids, often limiting their use or even leading to treatment discontinuation. Based on data from the VISION-DMD study, promising data on restoration of normal growth, fewer side effects impacting behavior and encouraging data on body mass index (BMI) seen with vamorolone, this novel, first-in-class steroid has the potential to emerge as a valuable alternative to the current standard of care for DMD," said **Paula Clemens, MD, study Co-Chair, and Vice Chair of VA Affairs and Professor of Neurology, University of Pittsburgh School of Medicine**.

Regulatory submissions in the US and Europe in preparation

On November 17, Santhera and ReveraGen announced the successful completion of a first pre-NDA meeting with the U.S. Food and Drug Administration (FDA) for vamorolone for the treatment of DMD [3]. Based on the data presented to date, the FDA considered both the proposed clinical efficacy and safety data sufficient for an NDA filing. Acceptance of the NDA will be subject to FDA`s review of the complete filing. Based on the Fast Track Designation for vamorolone, the FDA deemed the plan to pursue a rolling NDA review acceptable. The NDA submission is to commence in Q1-2022. In the EU, the submission of the full Marketing Authorization Application is planned by the end of Q2 2022.

Upon approval, Santhera intends to commercialize vamorolone for the treatment of DMD through its own organization in the United States and main markets in Europe, and is seeking collaborations outside those regions for DMD and for additional indications worldwide. Santhera estimates the peak sales potential for vamorolone in the indication DMD alone to be in excess of USD 500 million in the US and the largest five European countries combined.

Vamorolone was discovered by US-based ReveraGen BioPharma, Inc. and is being developed in collaboration with Santhera who owns worldwide rights to the drug candidate for all indications.

References:

[1] ClinicalTrials.gov Identifier: NCT03439670, link

[2] Press release "Santhera and ReveraGen Announce Positive and Statistically Highly Significant Topline Results with Vamorolone in Pivotal VISION-DMD Study", June 1, 2021, link

[3] Press release "Santhera and ReveraGen Announce Successful FDA Pre-NDA Meeting for Vamorolone in Duchenne Muscular Dystrophy", November 17, 2021, link

[4] Heier CR at al. (2013). EMBO Mol Med 5: 1569–1585.

[5] Reeves EKM, et al (2013). Bioorg Med Chem 21(8):2241-2249.

[6] Liu X, et al. (2020). Proc Natl Acad Sci USA 117:24285-24293.

About VISION-DMD

VISION-DMD is a Phase 2b study comprising a (1) pivotal 24-week period to demonstrate efficacy and safety of vamorolone (2 and 6 mg/kg/day) versus prednisone (0.75 mg/kg/day) and placebo, followed by a (2) 24-week period to evaluate the maintenance of efficacy and collect additional longer-term safety and tolerability data. 121 ambulant boys aged 4 to <7 years with Duchenne muscular dystrophy (DMD) were included in the study. The primary endpoint of the study was TTSTAND velocity at 24 weeks comparing the 6 mg/kg/day dose of vamorolone to placebo. TTSTAND velocity measures the speed at which subjects are able to stand up from lying in a supine position and is a strong and recognized marker for muscle function. Secondary efficacy outcome measures include TTSTAND velocity for vamorolone at the lower dose of 2 mg/kg/day, Six-Minute Walk (6MWT) and Time to Run/Walk 10 meters (TTRW) tests at 24 weeks. During the second 24-week period of this 48-week study, all participants received vamorolone. Participants from the placebo and prednisone arms had been randomized to receive either the 2 or 6 mg/kg/day dose of vamorolone and the vamorolone arms continued on their existing dose. In addition to efficacy, the study aimed to confirm the favorable tolerability profile of vamorolone with the potential to offer an alternative to current standard of care. Although glucocorticoids are part of the current care recommendations for DMD, their adverse effect profile limits their use.

In clinical studies to date, vamorolone was generally safe and well tolerated. The most commonly reported adverse events versus placebo from the 24-week VISION-DMD study were cushingoid features, vomiting and vitamin D deficiency. Adverse events were generally of mild to moderate severity.

About Vamorolone

Vamorolone is a first-in-class drug candidate that binds to the same receptor as corticosteroids but modifies its downstream activity and as such is a dissociative agonist [4-6]. This mechanism has the potential to 'dissociate' efficacy from typical steroid safety concerns and therefore vamorolone could emerge as a promising alternative to existing corticosteroids, the current standard of care in children and adolescent subjects with DMD. Start of US NDA rolling submission for DMD is anticipated in Q1-2022. Vamorolone has been granted Orphan Drug status in the US and in Europe for DMD, and has received Fast Track and Rare Pediatric Disease designations by the US FDA and Promising Innovative Medicine (PIM) status from the UK MHRA for DMD. Vamorolone is an investigational medicine and is currently not approved for use by any health authority.

About Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is a rare inherited X-chromosome-linked disease, which almost exclusively affects males. DMD is characterized by inflammation which is present at birth or shortly thereafter. Inflammation leads to fibrosis of muscle and is clinically manifested by progressive muscle degeneration and weakness. Major milestones in the disease are the loss of ambulation, the loss of self-feeding, the start of assisted ventilation, and the development of cardiomyopathy. DMD reduces life expectancy to before the fourth decade due to respiratory and/or cardiac failure.

About Santhera

Santhera Pharmaceuticals (SIX: SANN) is a Swiss specialty pharmaceutical company focused on the development and commercialization of innovative medicines for rare neuromuscular and pulmonary diseases with high unmet medical need. Santhera has an exclusive license for all indications worldwide to vamorolone, a first-in-class dissociative steroid with novel mode of action, which was investigated in a pivotal study in subjects with DMD as an alternative to standard corticosteroids. The clinical stage

pipeline also includes lonodelestat (POL6014) to treat cystic fibrosis (CF) and other neutrophilic pulmonary diseases as well as an exploratory gene therapy approach targeting congenital muscular dystrophies. Santhera out-licensed rights to its first approved product, Raxone® (idebenone), outside North America and France for the treatment of Leber's hereditary optic neuropathy (LHON) to Chiesi Group. For further information, please visit www.santhera.com.

Raxone® is a trademark of Santhera Pharmaceuticals.

About ReveraGen BioPharma

ReveraGen was founded in 2008 to develop first-in-class dissociative steroidal drugs for Duchenne muscular dystrophy and other chronic inflammatory disorders. The development of ReveraGen's lead compound, vamorolone, has been supported through partnerships with foundations worldwide, including Muscular Dystrophy Association USA, Parent Project Muscular Dystrophy, Foundation to Eradicate Duchenne, Save Our Sons, JoiningJack, Action Duchenne, CureDuchenne, Ryan's Quest, Alex's Wish, DuchenneUK, Pietro's Fight, Michael's Cause, Duchenne Research Fund, and Jesse's Journey. ReveraGen has also received generous support from the US Department of Defense CDMRP, National Institutes of Health (NCATS, NINDS, NIAMS), and European Commission (Horizons 2020). www.reveragen.com

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