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Santhera Announces Positive Topline Results from LIONHEART Study with AGAMREE® (vamorolone) Demonstrating Unique Mineralocorticoid Receptor Antagonism

Pratteln, Switzerland, October 1, 2024 – Santhera Pharmaceuticals (SIX: SANN) announces the positive outcome of the LIONHEART study, confirming vamorolone's distinctive action also as a mineralocorticoid receptor antagonist, setting it apart from other corticosteroids.

The LIONHEART study, an open-label randomized, placebo- and eplerenone-controlled study involving 30 healthy adult male subjects, met its primary endpoint. It demonstrated a statistically significant increase in the urinary sodium/potassium ratio in the vamorolone arm compared to placebo ($p<0.0001$) following a fludrocortisone challenge. This increased ratio in urine provides clinical evidence for vamorolone's unique mode of action also as a mineralocorticoid receptor antagonist (MRA) in humans. Combined with its known properties as a dissociative glucocorticoid receptor agonist, these findings further differentiate vamorolone's pharmacological profile, distinguishing it from other corticosteroids.

Cardiac complications such as cardiomyopathy are a leading cause of morbidity and mortality in boys with Duchenne muscular dystrophy (DMD). While treatment with corticosteroids (and ACE inhibitors) has demonstrated a delay in the onset of cardiomyopathy, the addition of MRAs including eplerenone to standard of care has also shown an improvement in left ventricular systolic dysfunction, the benefit of which increases with earlier initiation [1-3].

"Mineralocorticoid receptor antagonists are strongly recommended but late when cardiac function is already reduced and tend to be used in the presence of myocardial fibrosis as detected in magnetic resonance imaging," explained **Prof Karim Wahbi, PhD, MD, Cardiologist at the APHP Hospital Cochin, Paris, France**. "What is intriguing about this mechanistic study is whether there is a synergistic benefit of the anti-inflammatory and MRA effects of vamorolone on the evolution of cardiac disease in children who started treatment early or if vamorolone could be of benefit to those who are already experiencing cardiac symptoms and wish to remain on a corticosteroid"

"The LIONHEART study is an important milestone to establish the proof of concept for a cardioprotective potential of vamorolone," stated **Shabir Hasham, MD, Chief Medical Officer of Santhera**. "We continue to collect data from patients who have been on vamorolone for up to seven years allowing us to better characterize long-term outcomes including any beneficial impact on cardiac complications in DMD."

About AGAMREE® (vamorolone)
AGAMREE is a novel drug with a mode of action based on binding to the same receptor as glucocorticoids but modifying its downstream activity. Moreover, it is not a substrate for the 11-β-hydroxysteroid dehydrogenase (11β-HSD) enzymes that may be responsible for local drug amplification and corticosteroid-associated toxicity in local tissues [4-7]. This mechanism has shown the potential to 'dissociate' efficacy from steroid safety concerns and therefore AGAMREE is positioned as a dissociative

anti-inflammatory drug and an alternative to existing corticosteroids, the current standard of care in children and adolescent patients with DMD [4-7].

In the pivotal VISION-DMD study, AGAMREE met the primary endpoint Time to Stand (TTSTAND) velocity versus placebo (p=0.002) at 24 weeks of treatment and showed a good safety and tolerability profile [4]. The most commonly reported side effects were cushingoid features, vomiting, weight increase and irritability. Side effects were generally of mild to moderate severity.

Currently available data show that AGAMREE, unlike corticosteroids, has been shown to be a dual mineralocorticoid antagonist and a dissociative glucocorticoid agonist based on animal experiments [7]. It has no restriction of growth [8] and no negative effects on bone metabolism as demonstrated by normal bone formation and bone resorption serum markers [9].

AGAMREE (vamorolone), an orphan medicinal product, is approved for use in the United States (Prescribing Information), the European Union (Summary of Product Characteristics) and the United Kingdom for the treatment of DMD.

About LIONHEART

The LIONHEART study (SNT-I-VAM-026) is an open label randomized, 3-arm, parallel-group, placebo and eplerenone controlled study to evaluate the mineralocorticoid receptor antagonism (MRA) effect of vamorolone in 30 healthy adult male subjects after challenge with fludrocortisone, a known mineralocorticoid receptor agonist. The primary endpoint was defined as the ratio of sodium to potassium (Na/K) and the corresponding logarithm of the ratio (log_{10}(10*Na/K) in urine at different time-points. Further analysis of the data is ongoing and will be presented at medical conferences.

References:

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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. Corticosteroids are the current standard of care for the treatment of DMD.

About Santhera

Santhera Pharmaceuticals (SIX: SANN) is a Swiss specialty pharmaceutical company focused on the development and commercialization of innovative medicines for rare neuromuscular diseases with high unmet medical need. The Company has an exclusive license from ReveraGen for all indications worldwide to AGAMREE® (vamorolone), a dissociative steroid with novel mode of action, which was investigated in a pivotal study in patients with Duchenne muscular dystrophy (DMD) as an alternative to standard corticosteroids. AGAMREE for the treatment of DMD is approved in the U.S. by the Food and Drug Administration (FDA), in the EU by the European Medicines Agency (EMA), and in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA). Santhera has out-licensed rights to AGAMREE for North America to Catalyst Pharmaceuticals and for China to Sperogenix Therapeutics. For further information, please visit www.santhera.com.

AGAMREE® is a trademark of Santhera Pharmaceuticals.

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