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Santhera Announces Positive Results with Lonodelestat in Early Phase Cystic Fibrosis Trial

Pratteln, Switzerland, March 1, 2021 – Santhera Pharmaceuticals (SIX: SANN) announces positive results from its multiple ascending dose Phase 1b study with lonodelestat, a potent inhibitor of human neutrophil elastase (hNE), in patients with cystic fibrosis (CF).

Lonodelestat is a potent and selective peptide inhibitor of human neutrophil elastase (hNE), currently being developed in cystic fibrosis (CF). Neutrophil elastase is an enzyme associated with tissue inflammation, leading to degradation of the lung tissue in cystic fibrosis and several other pulmonary diseases. Data from previous Phase 1a studies demonstrated that single dose inhalation of lonodelestat can lead to high drug concentrations within sputum, resulting in effective hNE inhibition [1, 2].

The double-blind, placebo-controlled dose-escalation Phase 1b study in patients with CF assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of orally inhaled multiple daily doses of lonodelestat for up to four weeks (clinicaltrials.gov id: NCT03748199). In addition, the study investigated proof of mechanism of lonodelestat by measuring activity of hNE, an inflammatory biomarker for monitoring of disease progression in CF. Santhera acknowledges the support of the Cystic Fibrosis Foundation (CFF) by providing funding for the conduct of the Phase 1a and 1b safety trials with lonodelestat.

A total of 32 patients were randomized in four cohorts of eight patients each and received lonodelestat starting with 80 mg once daily (QD), 80 mg twice daily (BID), 160 mg QD, each administered for 15 days, followed by a last cohort with 40 mg QD administered for 28 days which was chosen after observing an effect on forced expiratory volume in 1 second (FEV1) in some patients treated with the highest doses (80 mg BID and 160 mg QD). In all four cohorts and over all treatment durations, lonodelestat demonstrated a good tolerability and no serious side effects (SAEs or AEs Grade 3 or higher) were reported by the patients. Results showed a linear dose-exposure relationship over the dose range from 40 mg to 160 mg, with no accumulation in plasma or sputum. In all cohorts, a transient, near complete inhibition of elastase activity was observed after inhalation. In addition, in some patients in the 40 mg QD cohort, a constant level of near complete inhibition gradually developed over the 28 days of drug inhalation. The results from the safety analyses and the confirmed effect on the hNE biomarker by lonodelestat are very encouraging for further development in CF and other inflammatory lung diseases and have established a safe dose regimen. The findings from this study will be taken into account in the design of future studies.

“This study provides promising data on the safety of lonodelestat and its potential to inhibit elastase in cystic fibrosis and maybe other chronic inflammatory conditions of the lung where neutrophils play a prominent role in the disease process,” said **Marcus Mall, MD, Professor and Head of Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine at the Charité-Universitätsmedizin Berlin**. “The landscape of treatment options for patients with cystic fibrosis has changed in the recent years with the approval of new drugs, but there is still a medical need for drugs like lonodelestat that counteract the chronic inflammation and degradation of lung tissue which

contributes to pulmonary exacerbations. Lonodelestat may add a new treatment modality for CF patients and I am very excited about the future development of lonodelestat and the next study."

"We are very much encouraged by the trial results which support the hypothesis that lonodelestat may possess properties to counteract underlying inflammatory processes and which indicate treatment was well tolerated in patients with CF. This demonstrates for the first time that complete inhibition of neutrophil elastase can be achieved over a prolonged treatment duration by local delivery through inhalation. We would like to thank the patients, the investigators and their study teams for their participation in this study," said **Dario Eklund, CEO of Santhera**. "After additional analyses of the results, we will be optimizing the further clinical development program to advance lonodelestat for the treatment of CF. In parallel, we are proactively pursuing collaborations with partners to assess and exploit the potential of lonodelestat in other pulmonary diseases"

References:
[1] Sellier Kessler O et al. Effect of POL6014, a potent and selective inhaled neutrophil elastase inhibitor, in a rat model of lung neutrophil activation. Am J Respir Crit Care Med 2018; 197: A2988
[2] Lagente V et al. A novel protein epitope mimetic (PEM) neutrophil elastase (NE) inhibitor, POL6014, inhibits human NE-Induced acute lung injury in mice. Am J Respir Crit Care Med 2009; 179: A5668
[3] Barth P et al. Single dose escalation studies with inhaled POL6014, a potent novel selective reversible inhibitor of human neutrophil elastase, in healthy volunteers and subjects with cystic fibrosis. J Cyst Fibros 2020; 19: 299-304

About lonodelestat

Lonodelestat (previously known as POL6014), a highly potent and selective peptide inhibitor of human neutrophil elastase (hNE), is in development for the treatment of cystic fibrosis. Santhera obtained the worldwide, exclusive rights from Polyphor AG to develop and commercialize lonodelestat in CF and other diseases. In preclinical studies lonodelestat was effective in animal models of neutrophil activation in lung tissue and of acute lung injury (ALI) [1, 2]. Currently available clinical data demonstrated that single and multiple doses (Phase 1b) of lonodelestat when administered by inhalation via an optimized eFlow® nebulizer (PARI Pharma GmbH) can lead to high drug concentrations within the lung, resulting in inhibition of hNE in sputum of patients, an enzyme associated with lung tissue inflammation [3]. The Phase 1b study further confirmed the tolerability of lonodelestat after treatment of up to four weeks in patients with CF. Lonodelestat may also show therapeutic benefit for a range of neutrophilic pulmonary diseases with high medical need such as non-CF bronchiectasis (NCFB), alpha-1 antitrypsin deficiency (AATD), chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS) or primary ciliary dyskinesia (PCD). Lonodelestat has EU orphan drug designations (ODD) for the treatment of CF as well as for AATD and PCD in both EU and US.

About cystic fibrosis

Cystic fibrosis (CF) is a rare, hereditary, life-threatening, progressive disease affecting approximately 70,000 patients in the U.S. and Europe and is characterized by persistent lung infection and chronic inflammation thereby limiting the ability to breathe over time. Activated or necrotic neutrophils liberate human neutrophil elastase (hNE) in the lung that causes damage to structural, cellular and soluble components of the pulmonary microenvironment. High levels of hNE play a central role in the pathophysiology of CF and correlate with disease severity as measured by functional lung parameters. Inhibition of hNE is expected to stop or slow the damage to lung tissue and may help to improve the overall quality of life for individuals with CF.

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, currently investigated in a pivotal study in patients 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 ex-North American rights to its first approved product, Raxone® (idebenone), 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.

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