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Santhera Starts Collaboration in Gene Therapy Research for Congenital Muscular Dystrophy with the Biozentrum, University of Basel, Co-Financed by Innosuisse

Pratteln, Switzerland, May 21, 2019 – Santhera Pharmaceuticals (SIX: SANN) announces its collaboration with the Biozentrum of the University of Basel to advance gene therapy research for the treatment of LAMA2-deficient congenital muscular dystrophy (LAMA2 MD or MDC1A). The program is supported by public funding for innovation in Switzerland through a grant from Innosuisse – the Suisse Innovation Agency. Innosuisse and Santhera will jointly invest CHF 1.2 million into this preclinical research collaboration.

Santhera has entered in a collaboration with Prof. Markus Rüegg from the Biozentrum, University of Basel, who pioneered a novel gene therapy approach for the treatment of LAMA2 MD. The simultaneous transgenic expression of specifically designed small protein domains, so-called linker proteins, helps to overcome structural and functional loss of muscle fibers in a mouse model for LAMA2 MD, demonstrating strong preclinical evidence for disease modifying potential. This novel gene therapy strategy developed by Prof. Rüegg and coworkers will use two linker proteins that are composed of domains derived from extracellular matrix proteins agrin, laminin and nidogen [1-4]. In animal models for LAMA2 MD this approach has led to restoration of muscle fiber basement membranes, recovery of muscle force and size, increased overall body weight and markedly prolonged survival [1]. The preclinical research collaboration between Santhera and the University of Basel will explore the feasibility of gene delivery by standard viral vectors as a basis for subsequent clinical work.

“LAMA2 MD is a severe form of congenital muscular dystrophy (CMD) which based on its molecular pathology offers the possibility for gene replacement,” said **Markus Rüegg, PhD, Professor for Neurobiology at the Biozentrum of the University of Basel**. “The approach we have optimized over the past years relies on the simultaneous expression of two linker proteins engineered from extracellular matrix proteins. We and others have shown that this approach has a profound beneficial effect in mouse models of the disease. I am looking forward to collaborating with Santhera as our translational research partner to advance our gene therapy approach towards clinical use.”

“Santhera is committed to advancing its neuromuscular pipeline and building on its leading expertise in drug development for neuromuscular diseases, including CMD,” added **Thomas Meier, PhD, CEO of Santhera**. “We are excited to collaborate with experts from the Biozentrum to advance this novel gene therapy approach to the clinic for the benefit of patients with this devastating disease. We build on our experience with *omigapil*, which we have recently studied in a Phase I clinical trial in patients with CMD in a collaboration with experts at the National Institutes of Health (USA). From our previous work we anticipate that this novel gene therapy approach and *omigapil* could act complementary. As before, we will continue working closely with clinical experts and the patient community to establish the best way forward.”

About LAMA2 MD (CMD Type 1A or MDC1A) and Emerging Therapy Approaches

Congenital muscular dystrophies (CMDs) are inherited neuromuscular diseases characterized by early-onset weakness and hypotonia alongside associated dystrophic findings in muscle biopsy. Progressive muscle weakness, joint contractures and respiratory insufficiency characterize most CMDs. Laminins are proteins of the extracellular matrix that help maintain muscle fiber stability by binding to other proteins. LAMA2-related muscular dystrophy (LAMA2 MD, also called MDC1A), is one of the most common forms of CMD. It is caused by mutations in the LAMA2 gene encoding the alpha2 subunit of laminin-211. Most LAMA2 MD patients show complete absence of laminin-alpha 2, are hypotonic (floppy) at birth, fail to ambulate, and succumb to respiratory complications.

Previous work has demonstrated that two linker proteins, engineered with domains derived of the extracellular matrix proteins agrin, laminin and nidogen, could compensate for the lack of laminin-alpha2 and restore the muscle basement membrane [1-4]. Through simultaneous expression of artificial linkers ("SEAL"), this gene therapy approach aims to overcome the genetic defect by substituting laminin-alpha2 deficiency with small linker proteins containing necessary binding domains to re-establish muscle fiber integrity. In a transgenic mouse model, the linker expression increased the lifespan of LAMA2-deficient mice 5-fold to a median of 81 weeks compared to 15.5 weeks in the disease model without the therapeutic linker expression [1]. Recently, it was demonstrated that such linker constructs could be applied by standard adeno-associated virus (AAV) vectors [5, 6].

Omigapil is a deprenyl-analog with anti-apoptotic properties. Previous work has demonstrated that *omigapil* provides benefit to LAMA2-deficient mice [7] and has additive effects to gene therapy using linker proteins [8]. Santhera obtained an exclusive license for *omigapil* from Novartis for the development in CMDs. As previously reported, Santhera has completed an ascending multiple dose cohort study (called CALLISTO) with *omigapil* in patients with two forms of CMD, including LAMA2 MD. CALLISTO met its primary objective to establish the pharmacokinetic profile of *omigapil*, applied as liquid formulation, and demonstrated that in this study the drug was safe and well tolerated in children and adolescents with CMD. Furthermore, this trial also demonstrated that it is feasible to run clinical studies in LAMA2 MD patients. *Omigapil* has orphan drug designations for CMD in the US and Europe and was granted fast track designation by the FDA.

References

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About Innosuisse – Suisse Innovation Agency

Innosuisse is the Swiss Innovation Promotion Agency. It is a federal entity under public law with a separate legal personality. Innosuisse's role is to promote science-based innovation in the interests of industry and society in Switzerland. Nowadays, the key to economic success is a combination of expertise, experience, research and development. Innosuisse especially promotes the partnership between academia and the market with innovation projects, networking, training and coaching, laying

the groundwork for successful Swiss start-ups, products and services. It provides considerable benefits for a prosperous and sustainable economy. Innosuisse provides support in accordance with the subsidiarity principle: it only supports projects if the innovation could not be implemented and market potential would not be tapped into without funding.

About the Biozentrum, University of Basel

The Biozentrum is the largest department at the University of Basel's Faculty of Science and one of the leading life sciences institutes in the world. The primary focus of this interdisciplinary institute is basic molecular and biomedical research and teaching. The Biozentrum holds a leading position nationally and internationally and closely networks with partners from the academic world and industry.

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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