ESTEVE AND U.A.B. ADVANCES IN THEIR PROGRAM TO DEVELOP A CURE FOR SANFILIPPO A SYNDROME

- **This gene therapy program is being developed in a public-private partnership between ESTEVE and the research team of Dr. Fàtima Bosch at the Center for Biotechnology and Gene Therapy of the Universitat Autònoma de Barcelona (UAB)**

- **ESTEVE announce the signing of agreements with REGENX and GÉNÉTHON which will allow it to initiate its phase I/II clinical trial in 2015**

- **Sanfilippo A is a rare and devastating neurodegenerative disease that affects approximately 1 in every 100.000 children that rarely survive past adolescence**

ESTEVE has announced the signing of two agreements that will enable it to progress the development of its gene therapeutic for the treatment of Mucopolysaccharidosis type IIIA (MPSIIIA or Sanfilippo A Syndrome) and begin a phase I/II clinical trial in 2015. The agreements are with the North American biotechnology company REGENX Biosciences, LLC (REGENX) and with the French non for profit organization GÉNÉTHON.

The license agreement with REGENX grants ESTEVE the right to use the adeno-associated viral vector, NAV rAAV9, in the development and commercialization of its investigational gene therapy for the treatment of Sanfilippo A Syndrome. The vector NAV rAAV9 is an integral part of the investigational therapeutic and enables the gene for the enzyme Sulfamidase, missing or defective in patients with Sanfilippo A Syndrome, to be delivered to and enter cells such as neurons and hepatocytes. Once inside the cells the gene expresses the Sulfamidase enzyme stably, compensating for its absence hence addressing the cause of the disease.

The agreement with GÉNÉTHON is for the development of the manufacturing process of the investigational gene therapeutic and its production for clinical trial use. The process to be developed will allow the production of the therapeutic for preclinical toxicology studies, the clinical trial and eventually for commercial use.

Public-private partnership ESTEVE-UAB

The Sanfilippo project was initiated by the research team of Dr. Fàtima Bosch at the Center for Biotechnology and Gene Therapy (CBATEG) of UAB and since 2009 is being developed within the framework of a public-private partnership between ESTEVE and the University, aimed at developing gene therapies for the treatment of this syndrome and related diseases

called mucopolysaccharidoses. This research project was initiated at the CBATEG due to the petition of the Asociación MPS-Fabry España.

In this partnership, ESTEVE leads all activities associated with the management and protection of intellectual property, regulatory activities, the coordination and supervision of GMP manufacturing, the preclinical toxicology studies as well as all clinical development. The CBATEG research team at the UAB brings to the partnership their scientific know-how and expertise in gene therapy including viral vector design and the development of preclinical disease models.

The **investigational gene therapeutic** consists of the viral NAV rAAV9, licensed from REGENX, which contains a version of the gene that codes for Sulfamidase that has been optimized to improve its expression levels. Experimentation using preclinical disease models performed by the CBATEG have validated the potential efficacy of this therapeutic approach. The treatment consists in the administration of gene therapy in the cerebrospinal fluid, the fluid that bathes the brain and spinal cord. The viral vector NAV rAAV9 has the advantage of its high affinity for the brain (main organ affected in this disease) than many of the other adeno-associated viral vectors, is harmless, not being known to cause any disease in humans. For its part, once the gene for the Sulfamidase enzyme reaches the cytoplasm of the neuron, it begins the production of the enzyme. Thus, it is produced enzyme which is secreted into spinal fluid, allowing its distribution throughout the brain and spinal cord and also reaching those neurons in which does not incorporate any viral vector. Furthermore, a small proportion of the gene therapeutic passes from the CSF into the peripheral circulatory system, thereby reaching organs such as the liver where it can enter hepatocytes and subsequently produce and secrete the Sulfamidase enzyme which then distributes throughout the body with the aid of the bloodstream.

In the preclinical disease model studied, after administering the gene therapeutic, the levels of Sulfamidase activity significantly increase both in the brain and the rest of the body, the accumulated glycosaminoglycans (substances that build up as a consequence of the disease) are eliminated from within cells, and signs of neuroinflammation disappear. Finally, and most importantly, the behavior is restored and the lifespan is prolonged close to normal.

The research team led by Dr. Bosch has further demonstrated in preclinical models, in that the gene therapeutic can be administered into the CSF through one intracerebroventricular administration, using a similar approach as the standard neurosurgical procedure employed for the treatment of patients with Hydrocephalus. This administration method represents a significant advantage over other potential approaches since it is based on an intervention that is considered standard practice in pediatric neurosurgery, and furthermore, it assures an even dosing of the therapeutic across all parts of the brain.

At this time the project, which has been granted **orphan status** by the European Medicines Agency (EMA) and the US Food and Drug Agency (FDA), is in the preclinical development phase, with the manufacturing of early batches expected to begin shortly to support the required preclinical toxicology studies, which, once completed, will allow us to initiate the phase I/II clinical trial in 2015.

This project has received financial support from the Spanish Ministry of Health, Social Policy and Equality, and from the Spanish Ministry of Economy and Competitiveness.

About MPS III A (Sanfilippo syndrome Type A)

Sanfilippo Syndrome Type A is a devastating disease that leads to progressive and significant deterioration in mental status of children who rarely live beyond their adolescence. Sanfilippo Syndrome, a lysosomal storage disease caused by the loss of the activity of the enzyme Sulfamidase, affects approximately 1 in 100,000 births and is often diagnosed once the symptoms have begun to appear.

About CBATEG of the Universidad Autónoma de Barcelona

The research team led by Dr. Fátima Bosch at the Center for Biotechnology and Gene Therapy (CBATEG) of UAB, investigates the pathophysiological causes of diabetes mellitus using transgenic animal models and develop gene therapy approaches for this disease based on genetic engineering of tissues with viral and non-viral vectors. In recent years, the group has applied its expertise to the development of gene therapies for inherited metabolic diseases such as Mucopolysaccharidosis.

About ESTEVE

ESTEVE (www.esteve.com) is a leading pharmaceutical chemical group based in Barcelona, Spain. Since it was founded in 1929, ESTEVE has been firmly committed to excellence in healthcare, dedicating efforts to innovative R&D of new medicines for unmet medical needs with high social impact, and focusing on high science and evidence-based research. ESTEVE has a strong partnership approach to drug discovery, development and commercialization. The company works both independently and in collaboration to bring new, differentiated best-in-class treatments to patients who need them. The company currently employs 2,300 professionals and has subsidiaries and production facilities in several European countries, USA, China and Mexico.