ESTEVE announces the start of a natural history study in patients with Sanfilippo Syndrome Type A (MPSIIIA)

- **Data collection from medical records of patients will help to better understand the progression of this rare disease and interpret the results of the treatment currently being developed by ESTEVE and the Autonomous University of Barcelona**
- **Sanfilippo Syndrome is a devastating neurodegenerative disease, classified as rare, that affects almost 1 for every 100,000 children, who hardly survive beyond their adolescence**
- **The Spanish Medicines Agency supports the project in terms of efficacy and preclinical safety, and the company expects to start the Phase I/II trial with patients in the third quarter of 2015**

Barcelona, 31 July 2014.- The main purpose of the natural history study is to evaluate the course of disease progression by collecting data from the medical records of patients who only have to meet the criterion of definitive diagnosis of this disease. The study will be performed in all the Spanish centers where patients with Sanfilippo Syndrome Type A are being, or have been, treated. This information will be critical for the correct interpretation of the results of the gene therapy clinical trial currently being developed by ESTEVE for the treatment of MPSIIIA.

The study was approved by the IRB/IEC of the Sant Joan de Déu Hospital of Barcelona and by relevant authorities in accordance with applicable laws. The study will be started this September, and the participation of 23 Spanish centers is expected so far. These centers will provide data from the medical records of 40 patients affected by Sanfilippo Syndrome Type A. For best possible study robustness, the purpose is to include all the patients diagnosed in Spain.

Gene therapy and innovative administration route

As anticipated by ESTEVE in a press release issued last March, the gene therapy in development consists of a viral vector that contains an optimized version of the human sulfamidase gene —a missing enzyme in these patients— that improves this gene's expression.

Preclinical results in an animal model of MPSIIIA suggest that, once the levels of enzyme activity are increased in the brain and the rest of the body, the accumulation of glycosaminoglycans (the substances metabolized by the sulfamidase) in the cells is significantly reduced, the neuroinflammation and dysfunction in the brain and other affected organs is controlled, the animal's behavior improves considerably, and life expectancy is clearly extended and reaches near-normal values.

One important innovation of this gene therapy is its administration route —one single intracranial puncture with administration into the cerebrospinal fluid—, which is similar to the procedure used to treat hydrocephalus in children (a frequent procedure in pediatric neurosurgery). This administration route ensures uniform distribution of the medicinal product throughout the brain—the main organ affected by the disease. Also, based on the

anatomical and functional characteristics of the brain, the possible immunogenic effects of gene therapy are minimized.

Regulatory (Spain, Europe and USA)

From the beginning, the project has been developed in close communication with regulatory authorities, and has qualified for orphan designation issued by both European and USA authorities. In addition, the project has been subject to two Scientific Advices by the Spanish Medicines Agency (2011 y 2014) and the EMA (2012), and has an approved Paediatric Investigation Plan by the EMA (2014).

The study is in an advanced Preclinical Phase, and the medicine to be used in preclinical safety studies —leading to the Phase I/II clinical trial scheduled for the third quarter of 2015— is now being manufactured.

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 ESTEVE

ESTEVE 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.

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Study-related info: Adelaida Morte, M.D., ESTEVE, email: amorte@esteve.es, Tel. 93 446 60 00 Extension nr. 66581. Dr. Morte will address questions by pediatricians treating these patients.

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