Pipeline development

Pharming's R&D team is now continuing formal work on two major projects in Pompe disease and Fabry's disease, with two others in early stage development. In addition, the team is working on bringing new forms of RUCONEST® to clinical testing and approval, including new small IV (IV Lite), intramuscular and subcutaneous versions. An oral version is also being explored.

ALPHA-GLUCOSIDASE FOR THE TREATMENT OF POMPE DISEASE

Pompe disease (also known as Acid Maltase Deficiency or Glycogen Storage Disease type II) is an inherited muscular myopathy disorder caused by the build-up of a complex sugar called glycogen in the body's cells. It affects around 1 in 40,000 people in general, varying within different ethnic groups. Pompe disease is a rare multisystem genetic disorder that is characterised by absence or deficiency of the lysosomal enzyme alpha-glucosidase (GAA). This enzyme is required to breakdown (metabolise) the complex carbohydrate glycogen and convert it into the simple sugar glucose. Glycogen is a thick, sticky substance and failure to achieve proper breakdown results in massive accumulation of lysosomal glycogen in cells, particularly in cardiac, smooth, and skeletal muscle cells. Pompe disease is a single disease continuum with variable rates of disease progression and different ages of onset. The infantile form is characterised by severe muscle weakness and abnormally diminished muscle tone (hypotonia) without muscle wasting, and usually manifests within the first few months of life. Additional abnormalities may include enlargement of the heart (cardiomegaly), the liver (hepatomegaly), and/or the tongue (macroglossia). Without treatment, progressive cardiac failure usually causes life-threatening complications by the age of 12 to 18 months. Pompe disease can also present in childhood, adolescence or adulthood, collectively known as late-onset Pompe disease. The extent of organ involvement may vary among affected individuals, but skeletal muscle weakness is usually present with minimal cardiac involvement. Initial symptoms of late-onset Pompe disease may be subtle and may go unrecognised for years. Pompe disease is caused by mutations of the GAA gene and is inherited as an autosomal recessive trait. The only approved therapy to date is Enzyme Replacement Therapy (ERT) wherein recombinant human α-glucosidase, produced by Chinese Hamster Ovary (CHO) cells (Myozyme®/Lumizyme® from Genzyme – now Sanofi-Aventis), is administered intravenously (I.V.) every 2 weeks with a dosing of 20 mg/kg body weight. Patients receiving ERT need treatment during their entire life. The major drawbacks in ERT are immune responses which can be raised towards an impure recombinant protein and low efficacy due to limited ability of the protein to reach and bind to its specific receptors on target cells, which seems to be the main reason for the high dosing. Several alternatives to Myozyme® are under development, including α-glucosidase with a different glycosylation pattern (Oxyrane, Amicus Therapeutics) and a gene therapy approach by Duke University.

Human recombinant α-glucosidase has been produced in transgenic animals before. Until 2002, Genzyme together with Pharming generated transgenic rabbits producing α-glucosidase. Production levels were as high as 8 g/L (Bijvoet et al. 1998, 1999). The transgenic material was shown to be active in clinical trials. In 2002 all assets related to the α-glucosidase program (animals, constructs, notebooks, IP, etc.) were transferred to Genzyme under the Settlement Arrangements of 15 August 2002. Genzyme then stopped the program, preferring to continue with the better-understood CHO-cell program which became Myozyme®, but scaling issues forced it to develop a second almost identical cell-line version to achieve capacity, which became Lumizyme®. Pharming's new product is intended to have better immunogenicity, safety and efficacy profiles than Myozyme®/Lumizyme®. The product will not be considered a 'Biosimilar' by the authorities as it is produced on a totally different production platform. The approach by Pharming (if successful) may therefore result in a so-called 'Biobetter'. In 2015, sales of Myozyme®/Lumizyme® were €650 million, an increase of 12.4%.