BIOBUSINESS BRIEFS

TRIAL WATCH

Enzyme replacement success in Phase III trial for rare metabolic disorder

BioMarin Pharmaceuticals has recently announced positive results from the Phase III trial (MOR-004) of its enzyme replacement therapy (ERT) BMN-100 — recombinant human *N*-acetylgalactosamine-6-sulphatase (GALNS) — for the treatment of mucopolysaccharidosis type IVA (MPS-IVA; also known as Morquio A syndrome). The study met both its primary and secondary end points, and the company plans to apply for marketing authorization in the first quarter of 2013.

The mucopolysaccharidoses are a group of rare inherited lysosomal storage disorders (LSDs) caused by a deficiency in or absence of specific lysosomal enzymes, resulting in the accumulation of complex carbohydrates within the body. In MPS-IVA there is a deficiency in galactosamine-6-sulphatase, an enzyme that is responsible for degradation of the keratan sulphate that is normally found in the bone, cartilage and cornea. MPS-IVA is characterized by skeletal dysplasia, short stature and motor dysfunction, and is often associated with neurological and vision problems, restricted breathing, joint stiffness and heart disease.

"At present, conventional therapy for MPS-IVA is symptomatic and limited to palliative procedures, which have little impact upon mortality," says John Hopwood, Head of the Lysosomal Diseases Research Unit, South Australian Health Medical Research Institute, Adelaide, Australia. However, intravenous administration of a recombinant form of the deficient lysosomal enzyme has become established as a promising therapeutic option for disorders of this type. "ERT has been approved for the treatment of non-CNS-involved MPS-I and MPS-II patients and all MPS-VI patients, as well as other LSD types, including Gaucher's, Fabry's and Pompe's diseases," notes Hopwood.

The multicentre MOR-004 trial, which represents the largest Phase III ERT study to date, involved 137 patients aged 5 years or older who received weekly or bi-weekly infusions of 2 mg per kg of GALNS or placebo for 24 weeks. Patients treated weekly with GALNS met the primary end point of the study, exhibiting a mean increase of 22.5 metres in the 6-minute walk test at 24 weeks. These patients also met the secondary end points, displaying an increase in the 3-minute stair climb and a decrease in urinary keratan sulphate levels. In addition, there was a trend towards improvement in pulmonary function. Importantly, GALNS was generally well tolerated. An extension study, MOR-005, is ongoing and preliminary data indicate further improvements in endurance at 36 and 48 weeks.

The positive results also provide further encouragement for the ERT strategy in general, although some issues need to be addressed to maximize its potential. "ERT is in clinical development for at least five other LSD types, and successful ERT for MPS-IVA increases confidence that, in general, intravenous ERT represents a therapeutic option for all non-CNS-involved MPS and LSD types," says Hopwood. "However, there is a need for early disease detection and the development of accurate prognostics, as treating pre-symptomatic neonates has been shown to maximize the benefit of ERT. In addition, given that there are more than 60 LSD types, many with extremely low prevalence, there is a special need to improve the regulatory and clinical development processes needed to develop effective therapies for these ultra-rare disorders," he concludes.

Sarah Crunkhorn