ACMG Annual Clinical Genetics Meeting
Poster Presentation
April 14, 2021

HMI-203: Gene Therapy Developmental Candidate for Mucopolysaccharidosis Type II (MPS II), or Hunter Syndrome

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Mucopolysaccharidosis Type II (MPS II), or Hunter syndrome, is a rare X-linked lysosomal storage disorder (LSD) which occurs in approximately 1 in 100,000 to 1 in 170,000 males. This disease is caused by various mutations in the iduronate-2-sulfatase IDS gene, resulting in loss of I2S enzyme and associated enzymatic activity, leading to subsequent systemic (peripheral organs and central nervous system (CNS)) accumulation of toxic lysosomal glycosaminoglycans (GAGs). The latter are large polysaccharides made of repeating disaccharide units responsible for providing structure and hydration to the cells. The disease results in debilitating skeletal dysplasia, joint stiffness, hepatosplenomegaly, airway obstruction and, in severe cases, neurocognitive deficits. These severe forms lead to life expectancy of 10 to 20 years in affected patients.

Herein, we report early preclinical gene therapy data where a single intravenous (I.V.) dose of an investigational gene therapy (HMI-203) delivering human IDS (hIDS) in the MPS II murine model resulted in a wide systemic (peripheral organs and CNS) transduction and corresponding detection of hIDS transcript expression. In serum, significant levels of functionally active, as demonstrated via an in vitro cross-correction assay, hI2S enzyme were observed within a week of dosing and found to be stable out to 28 weeks post dose (last time point evaluated). The robust hIDS transcript expression significantly reduced GAGs (i.e. heparan sulfate) and LAMP-1 (lysosome-associated membrane protein-1) levels in the brain, liver, heart, spleen, lung and kidney tissue, when compared to age-matched vehicle-treated MPS II mice. Lastly, sustained levels of HMI-203 driven hI2S expression demonstrated amelioration of phenotypic symptoms associated with joints and digits deformities in the MPS II mouse model. Based on these nonclinical data, HMI-203 IND-enabling studies are ongoing to support the development of HMI-203 as a gene therapy for the treatment of MPS II.