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Oral Presentation

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3:30 p.m. ET

Long-Term Systemic Expression and Cross-Correction Ability of HMI-203, Investigational Gene Therapy Candidate for Mucopolysaccharidosis Type II (MPS II), or Hunter Syndrome

Patel K, Smith L, Gingras J, Tzianabos A, Schulman L, Zhivich V, Kivaa M, Faulkner D, Sengooba A, Behmoiras L, Seabrook T, Dollive S, Avila N, Zhao J, White Y, Newman J, Woodcock S, Smith S, Francone O and Seymour A

Homology Medicines, Inc.

Mucopolysaccharidosis type II (MPS II), or Hunter syndrome, is a rare X-linked lysosomal storage disorder caused by mutations in the iduronate-2-sulfatase (*IDS*) gene, resulting in loss of I2S activity leading to systemic (peripheral organs and central nervous system (CNS)) toxic lysosomal accumulation of glycosaminoglycans (GAGs). GAGs are large polysaccharides made of repeating disaccharide units responsible for providing structure and hydration to the cell. The disease results in skeletal dysplasia, joint stiffness, organomegaly, airway obstruction and, in severe cases, neurocognitive deficits. Hunter syndrome occurs in approximately 1 in 100,000 to 1 in 170,000 males, and causes significantly reduced lifespan, with the severe form leading to life expectancy of 10 to 20 years

The proposed therapeutic mechanism of gene therapy candidate HMI-203 is based on both intracellular expression and synthesis of active I2S, as well as high levels of expression and secretion of active I2S enzyme to support cross correction. Herein, we report preclinical data where a single intravenous dose of HMI-203 delivering human *IDS* via a rAAVHSC vector in the MPS II murine model resulted in dose-dependent and long-term transduction, *IDS* expression and I2S enzymatic activity in the evaluated tissues, e.g., liver, brain and serum through 52 weeks post-dose. A significant correlation was observed between liver and serum I2S activity, suggesting that the liver was likely the major contributor to the elevated levels of active I2S in the serum. The circulating I2S protein in the serum was functionally active (i.e., 90 kDa form) and cross-correction activity via a mannose-6-phosphate receptor dependent pathway was demonstrated using an *in vitro* competition assay. The robust and broad *IDS* tissue expression, along with demonstrated cross-correction significantly reduced GAG heparan sulfate (GAG-HS) to wild type (WT) levels in all evaluated organs associated with the disease, cerebrospinal fluid (CSF) and urine. In addition, lysosomal-associated membrane protein-1 (LAMP1) levels were significantly reduced to WT-like levels in the peripheral organs and CNS tissues. Of note, positive and significant correlations were observed between reduction in GAG-HS and LAMP1 levels in the CNS and brain and CSF GAG-HS levels, suggesting that CSF GAG-HS levels could be indicative of overall brain GAG and lysosomal burden levels in the clinic. Taken together, we have demonstrated that HMI-203 combines transduction and expression with the potential for cross-correction. These HMI-203 IND-enabling studies support HMI-203 as a gene therapy candidate for the treatment of MPS II.