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Blood-Brain-Barrier Crossing Leads to Long-Term Efficacy in the CNS of HMI-203: Gene Therapy Development Candidate for Mucopolysaccharidosis Type II (MPS II), or Hunter Syndrome

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

Homology Medicines, Inc.

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 enzyme activity. This loss leads to subsequent systemic (including the central nervous system, or CNS) lysosomal accumulation of glycosaminoglycans (GAGs). Currently approved intravenously (IV) administered enzyme replacement therapies cannot efficiently cross the blood-brain barrier (BBB) and therefore do not improve neurocognitive deficits in MPS II patients. Herein, we summarize our CNS preclinical data for HMI-203, a gene therapy development candidate utilizing AAVHSC to deliver *IDS* in the MPS II murine model. Following a single IV dose of HMI-203, successful crossing of the BBB was observed, accompanied by widespread distribution and a dose-response in vector genomes, transcripts, I2S activity, and GAG reduction in brain tissue. At highest doses examined, I2S activity levels were comparable to wild-type (WT) mice and normal adult human brain tissue. Two highly correlated disease-relevant biomarkers, GAG-heparan sulfate and lysosomal-associated membrane protein, were reduced in a dose- and time-dependent fashion throughout the CNS. Lastly, HMI-203 prevented loss of cerebellar Purkinje neurons and progression of vacuolization in the brain. Long term and robust IDS expression observed in peripheral organs reduced tissue and urine GAGs down to WT levels with functionally active I2S protein sustained in the serum out to 52 weeks (end of study). These preclinical studies demonstrated BBB crossing with a single IV injection and support HMI-203 as an investigational gene therapy for the treatment of MPS II with potential to address CNS-related manifestations.