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Oral Presentation

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Gene Therapy Candidate for Metachromatic Leukodystrophy (MLD): Summary of Preclinical *In Vivo* Data Following an Intravenous Delivery of HMI-202

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Metachromatic leukodystrophy (MLD) is an inherited autosomal recessive lysosomal storage disorder (LSD) with a great unmet medical need. This fatal neurodegenerative LSD occurs in three forms: late infantile (prevalence of 1 in 40,000), juvenile, and adult. The late infantile and juvenile forms represent the majority of the MLD patients where mortality at 5 years is estimated at 75% and 30%, respectively. MLD is most commonly caused by mutations in the *ARSA* gene and patients suffering from the disease are deficient in arylsulfatase-A (*ARSA*) enzyme activity. The disease is characterized by accumulation of sulfatides to supraphysiologic and toxic levels in the peripheral organs and nervous system. In the brain, excess sulfatides lead to the destruction of myelin, a key protective layer of the nerve fibers that enhances propagation of action potentials.

Herein, we report preclinical gene therapy data where a single intravenous (IV) dose of HMI-202 (AAVHSC15-human-*ARSA* (h*ARSA*)) crosses the blood-nerve- and blood-brain-barriers (BNB and BBB) in juvenile non-human primates (NHP) and in the *Arsa* KO murine model of MLD. In the HMI-202-treated adult *Arsa* KO mice, h*ARSA* expression patterns are nearly identical to that of murine *Arsa* (m*Arsa*) distribution in the nervous system of wild type age-matched littermates, in both neuronal and glial cellular profiles. In HMI-202-treated adult *Arsa* KO mice, we show a dose-response relationship in h*ARSA* enzyme activity, transcript, and vector genomes in the central nervous system (CNS). As early as 1 week following administration (earliest time-point of collection), near-normal human adult levels of h*ARSA* activity are detected in the CNS of HMI-202-treated adult *Arsa* KO mice, and levels are sustained at or above normal adult human brain levels throughout the study (52 weeks post-dose). Similarly, h*ARSA* enzyme activity is detected 1 week post-dose in the CNS of *Arsa* KO neonates and is sustained out to 12 weeks post-dose (end of study). Furthermore, we demonstrate modulation of key biochemical markers in the CNS, including murine neuronal sulfatides, myelin and lymphocyte (MAL) transcript, lysosomal-associated membrane protein-1 (LAMP-1), and glial fibrillary acidic protein (GFAP) levels in HMI-202-treated *Arsa* KO mice. Lastly, using the rotarod assay, we demonstrate a functional motor benefit in HMI-202-treated *Arsa* KO mice dosed prior to the detectable accumulation of CNS neuronal sulfatides (~2 months of age).

In summary, a single-IV dose of HMI-202 crossed the BNB and BBB in lower (mice) and higher (NHP) species. In addition, the ability to achieve h*ARSA* enzyme activity levels at or above normal human adult brain levels, rapid onset of expression, durability, broad biodistribution, modulation of key biomarkers, and functional motor benefit in a murine MLD disease model was demonstrated. These preclinical data from IND-enabling studies continue to support the further optimization and development of HMI-202 as a gene therapy for the treatment of MLD.

