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HMI-202: Gene Therapy Development Candidate for Metachromatic Leukodystrophy (MLD)

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Metachromatic leukodystrophy, commonly known as MLD, is an inherited autosomal recessive lysosomal storage disorder with a great unmet medical need. This fatal neurodegenerative disease occurs in three forms: late infantile (prevalence of 1 in 40,000), juvenile and adult¹. The late infantile and juvenile forms represent the majority of the MLD patients and 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 activity². The disease is characterized by accumulation of supraphysiologic levels of lipids (sulfatides) to toxic levels in the nervous system and peripheral organs. These excess sulfatides lead to the destruction of myelin, a key protective layer of the nerve fibers also involved in conduction velocity of action potential propagation^{3,4,5,6}.

Herein, we report preclinical gene therapy data where a single intravenous (I.V.) dose of HMI-202 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 MLD⁷. In the HMI-202-treated *Arsa* KO mice, human *ARSA* (h*ARSA*) expression was nearly identical to that of murine *Arsa* distribution in wild type controls, in both neuronal and glial cells. At one-week post-dose, near normal human adult levels of h*ARSA* activity were detected and levels were sustained at or above normal adult human brain levels through 52 weeks in the CNS of *Arsa* KO mice. A dose-response relationship in h*ARSA* activity, transcript and vector genome copies in the CNS was observed in treated *Arsa* KO mice. In addition, we demonstrated HMI-202 modulation of key biochemical markers in the CNS, including LAMP-1 and GFAP, MAL transcript and neuronal sulfatide levels.

In summary, a single I.V. dose of HMI-202 crossed the BNB and BBB in lower (mice) and higher (NHP) species. In addition, the ability to achieve h*ARSA* enzymatic activity levels at or above normal human adult brain levels, rapid onset of expression, durability, broad biodistribution, and modulation of biomarkers in a murine disease model were demonstrated. Based on these preclinical data, IND-enabling studies of HMI-202 are ongoing to support the development of HMI-202 as a gene therapy for the treatment of MLD.

1. Gomez-Ospina et al., 2017; 2. Gieselmann, 2008; 3. Wolfe and Pietra, 1964; 4. Köhler et al., 2018; 5. Gieselmann et al., 1991; 6. Yavuz et Yükksekaya, 2011; 7. Hess et al., 1996