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HMI-202: Investigational Gene Therapy for Treatment of Metachromatic Leukodystrophy

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Metachromatic leukodystrophy (MLD) is an inherited autosomal recessive lysosomal storage disorder with a great unmet medical need. This fatal neurodegenerative disease occurs in the late infantile (prevalence of 1 in 40,000), juvenile, and adult forms. 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. Most commonly, MLD is caused by mutations in the *ARSA* gene and patients suffering from the disease are deficient in arylsulfatase-A (ARSA) enzyme. The disease is characterized by accumulation of supraphysiologic levels of lipids (sulfatides) in the brain, spinal cord and peripheral organs. This excess in sulfatide leads to toxicity and destruction of myelin resulting in severe nerve damage. Herein, we report preclinical gene therapy data where a single intravenous dose of HMI-202 (AAVHSC15-hARSA) crosses the blood-brain-barrier (BBB) and blood-nerve-barrier (BNB) in non-human primates and in a mouse model of MLD. In these mice, we show a dose-response relationship in hARSA enzymatic activity, transcript and vector genome copies in the central nervous system (CNS). HMI-202 hARSA enzymatic activity was detected within 1 week and sustained out to 12 weeks post-dose (end of study), in key diseased regions of the CNS, peripheral nervous system and organs. In addition, we demonstrate that HMI-202 can modulate MAL transcript, LAMP-1 protein and sulfatide levels in the CNS of treated MLD mice. In summary, HMI-202 is a promising gene therapy for the treatment of MLD based on data demonstrating its ability to achieve enzymatic activity levels at or above the targeted therapeutic threshold ($\geq$ 10-15% of normal human brain ARSA activity), rapid onset, sustainability, biodistribution and biological effect. Based on these preclinical data, IND-enabling studies of CNS gene therapy for the development of HMI-202 are ongoing.