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HMI-202, Investigational Gene Therapy 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 adult. 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, which become toxic. This excess sulfatide leads to the destruction of myelin, a key protective layer of the nerve fibers, resulting in nerve damage. Herein, we are reporting preclinical gene therapy data in a murine model of MLD where a single intravenous dose of HMI-202 (AAVHSC15-hARSA) crossed the blood-nerve and blood-brain barriers and led to a dose-response relationship in vector genome copies, ARSA protein and ARSA enzymatic activity in the central nervous system (CNS). HMI-202 expression patterns and corresponding enzymatic activity were rapidly detected in key biologically relevant regions of the brain (brainstem, cortex, cerebellum and white matter tracks), spinal cord (gray matter and ascending white matter tracks of the posterior column) and peripheral nervous system (dorsal root ganglion and sciatic nerve) in lysosomes of both neuronal and glial cellular profiles. In summary, HMI-202 is a promising gene therapy in development for the treatment of MLD based on mouse data demonstrating its rapid onset of action and ability to achieve hARSA activity levels at or above the therapeutic threshold (10-15% of normal hARSA activity). Based on these preclinical data, IND-enabling studies of CNS gene therapy development candidate HMI-202 are ongoing.