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Poster Presentation
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Gene Therapy for Metachromatic Leukodystrophy (MLD) That Crosses the Blood-Nerve and Blood-Brain Barriers in Mice and Non-Human Primates

Gingras J, St-Martin T, Gall K, Seabrook TA, Lotterhand J, Avila N, Rivas JI, Mercaldi M, Newman J, Wright T, Krupa S, Francone O and Seymour A

Homology Medicines, Inc.

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 dose of HMI-202 (AAVHSC15-human ARSA (hARSA)) crosses the blood-nerve and blood-brain barriers (BNB and BBB) in juvenile non-human primates (NHPs) and in the ARSA knock out (KO) murine model of MLD. In the ARSA KO mice, hARSA expression patterns were nearly identical to that of murine ARSA (mARSA) distribution in the nervous system of wild type age-matched littermates, in both neuronal and glial cellular profiles. In adult ARSA KO mice, we show a dose-response relationship in hARSA activity, transcript and vector genome copies in the central nervous system (CNS) where normal levels of hARSA activity are detected as early as 1 week following administration (earliest time-point of collection) and levels at or above normal are sustained out to 52 weeks post-dose in the CNS (end of study). A similar CNS hARSA expression profile was detected 1 week post-dose in ARSA KO neonates and sustained out to 12 weeks (end of study). In addition, we demonstrate that HMI-202 can modulate key disease-associated biochemical markers including myelin and lymphocyte (MAL) transcript levels, lysosomal-associated membrane protein-1 (LAMP-1) accumulation and sulfatide levels in the CNS of treated MLD mice.

In summary, HMI-202 crosses the BNB and BBB in mice and NHPs. Moreover, it demonstrates the ability to achieve CNS enzymatic activity levels that are sustained at/or above normal human brain levels, rapid onset of expression, broad biodistribution

and a biological effect on sulfatide levels in this murine disease model⁷. 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.