Adeno-associated viruses (AAVs) have emerged as key viral-based delivery vehicles for gene therapy in the nervous system due to their stable transgene expression in post-mitotic cells, neuronal tropism, lower risk of insertional mutagenesis and diminished immune response. We have reported the identification of novel AAVs derived from human hematopoietic stem cells (AAVHSCs). These novel AAVHSCs map to AAV Clade F and have demonstrated to effectively cross the blood-brain-barrier (BBB) following intravenous (IV) delivery in non-human primates, thus creating the potential for therapeutic applications in treating human genetic diseases of the central nervous system (CNS). 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 in sulfatides leads to the destruction of myelin, a key protective layer of the nerve fibers. Herein, we are reporting preclinical gene therapy data in a murine model of MLD where a single intravenous dose of AAVHSC15 expressing human ARSA (hARSA) led to 30-115% of normal hARSA enzyme activity levels in the murine CNS, exceeding the established therapeutic target of 10-15%. Moreover, the AAVHSC15-hARSA expression patterns were detected in key biologically relevant regions of the brain (brainstem, cortex, cerebellum and white matter tracks) and spinal cord (gray matter and ascending white matter tracks of the posterior column) in both neuronal and glial cellular profiles. Based on these preclinical data, IND-enabling studies of CNS gene therapy development candidate HMI-202 have been initiated in MLD.