juMPStart: Phase 1, Open-Label, Dose-Escalation Safety and Efficacy Gene Therapy Study Evaluating HMI-203 in Adults with MPS II

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Introduction

Mucopolysaccharidosis type II (MPS II) is a rare X-linked lysosomal storage disorder affecting primarily males. The disease is caused by mutations in the iduronate 2-sulfatase (*IDS*) gene resulting in the loss of iduronate 2-sulfatase (I2S) enzyme activity and subsequent systemic accumulation of glycosaminoglycans (GAGs).

Life Expectancy
- Onset of Symptoms between 1 and 3 years of age
- Early mortality in severe form
- Variable and shortened life-span for attenuated patients

Disease Manifestations
- Debilitating skeletal dysplasia, hepatosplenomegaly and airway obstruction
- Neuronopathic form of MPS II –progressive neurocognitive effects due to GAG accumulation in the central nervous system (CNS)

Standard of Care
- Weekly ERT (idursulfase) administration does not cross the blood-brain barrier, therefore does not impact CNS disease manifestations
- Therapeutic burden due to the frequency and duration of infusions, limited ability to travel, repeated needle sticks and sporadic infusion-related reactions

Current standard of care does not address the full spectrum of clinical manifestations experienced by patients with MPS II.

This leaves high unmet medical need for MPS II treatment that addresses both the peripheral and cognitive aspects.

HMI-203 has the potential to effectively treat the features of MPS II with a single dose delivered via peripheral infusion.

HMI-203

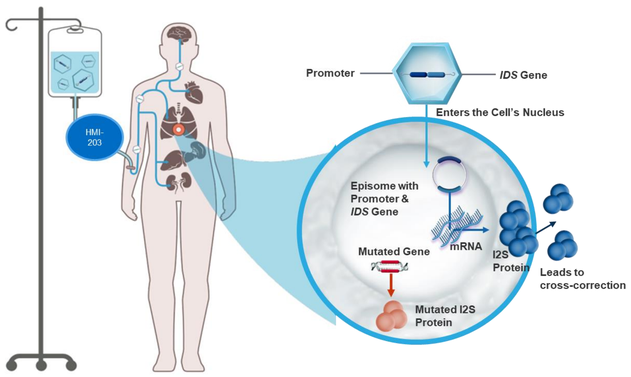
HMI-203 is a Gene Therapy delivered as a one-time I.V. administration

- Systemic Delivery and Expression of the *IDS* Gene to Peripheral Tissues and the CNS
- Resulting I2S Enzyme Activity at Levels Sufficient to Metabolize Excess GAGs
- Cross-Correction with Ability to Provide Functional I2S To Non-Transduced Cells

Potential for Elimination of the Need for Weekly ERT Infusions

HMI-203 Mechanism of Action

HMI-203 had been designed to deliver functional copies of the *IDS* gene and restore I2S enzyme function through both direct cell transduction and cross-correction.



Preclinical Safety and Efficacy

Objectives:
- Evaluate safety of HMI-203 in wild-type mouse (WT; C57BL/6J)
- Evaluate preclinical efficacy of HMI-203 in an MPS II mouse model (Muenzer murine model: B6J.Cg.*Ids*^{tm1Muen})[1]

No safety findings were identified associated with HMI-203 in GLP studies in WT mice.

- The potential of germline transmission of HMI-203 is considered a low risk, based on the results of a germline transmission study conducted in WT mice with the same rAAVHSC (recombinant adeno-associated virus [AAV]) capsid.

Single I.V. Dose of HMI-203 Led to Widespread Transduction and Expression in Peripheral Organs and CNS with Long-term Durability in the MPS II Mouse Model

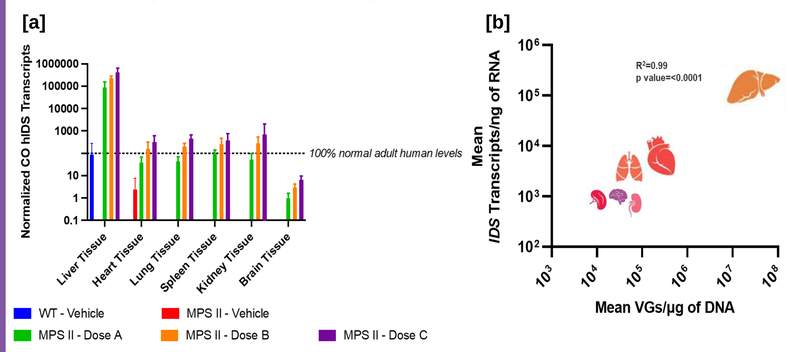


Figure 1: a) HMI-203 transcripts compared to human levels. The average number of CO-hIDS mRNA transcripts for each mouse was normalized to average normal adult human levels of IDS transcripts in corresponding tissues and expressed as a percentage (ie, normal=100%). Dotted line denotes 100% average normal adult human IDS mRNA transcript levels. Colors differentiate each group. Error bars denote standard deviation (SD) between individual mice (n=5 mice per group). Dose A through Dose C are increasing doses. b) HMI-203 vector genomes (VGs; determined by ddPCR) and are plotted with CO-hIDS mRNA transcripts (determined by qPCR). Timepoint is 52 weeks post dose and represents a single dose level (high dose) (n=4-5 mice per group).

HMI-203 Demonstrated Long-term I2S Activity in Liver Tissue, Early and Sustained Secretion in Serum where Active I2S is Capable of Cross-Correction through M6P Pathway in the MPS II Mouse Model

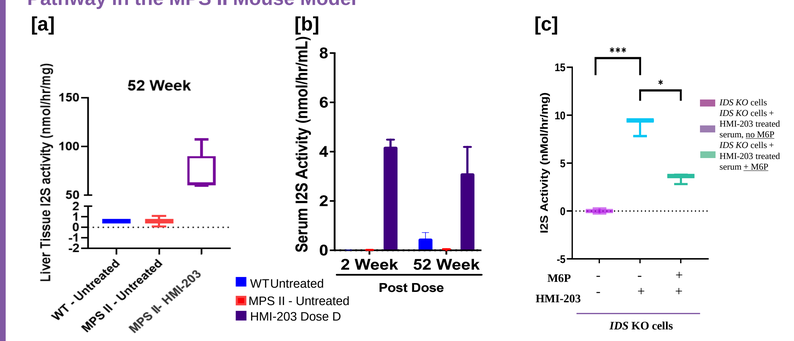


Figure 2: I2S enzymatic activity was determined by a two-step fluorometric enzyme assay. I2S activity in HMI-203-treated liver and serum samples were plotted following subtraction of the averaged background signal from MPS II vehicle-dosed mice (n=3-5 per dose group). Error bars denote standard deviation (SD). Dose D is the high dose. a) I2S activity in liver tissue 52 weeks post HMI-203 administration. b) I2S activity in serum at 2-and 52 weeks post HMI-203 administration. c) Mannose-6-phosphate (M6P) mediated I2S cross-correction in cultured *IDS*-KO HeLa cells with serum collected from HMI-203 treated mice 8 days post-dose. Statistical analysis was performed using a t-test. *p<0.05, *** p<0.001

HMI-203 Resulted in Sustained Reduction of the MPS II Biomarker Heparan Sulfate in Tissues and Urine in the MPS II Mouse Model

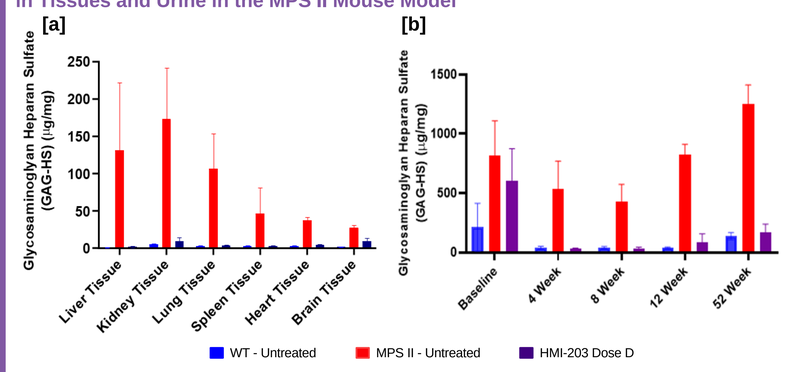


Figure 3: a) Tissue specific GAG-HS levels were determined by RapidFire mass spectrometry (MS) using a Heparan Sulfate (HS) standard curve and normalized to total protein. Timepoint shown is 52 weeks post HMI-203 administration. b) Urine GAG-HS levels were determined using RapidFire MS and normalized to creatinine levels in each urine sample. For a) and b), each group shows the average GAG-HS levels and standard deviation (SD) for each dose cohort. Colors differentiate each cohort (n=3-5 mice per group). Dose D is the high dose.

HMI-203 Significantly Reduced GAG-HS Levels in Cerebrospinal fluid (CSF) and Lysosomal Burden was Similar to WT levels in CNS Tissues of the MPS II Mouse Model

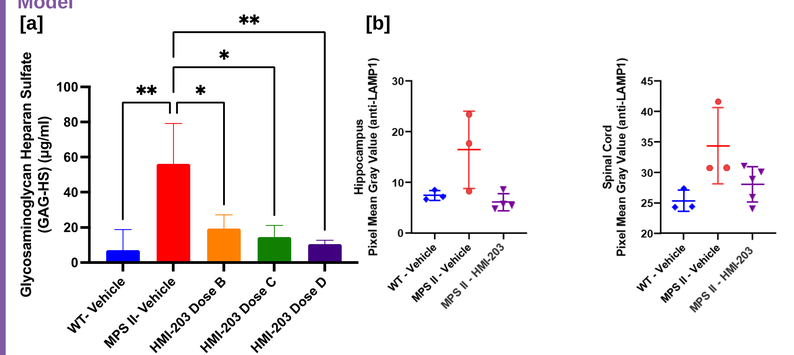


Figure 4: a) GAG-HS levels in Brain tissue. Statistical analysis was performed using a two-way analysis of variance (ANOVA). *p<0.05,, ** p<0.01, and **** p<0.0001. (n=3-15 mice per group). b) Lysosomal burden was evaluated in the hippocampus and spinal cord by calculating the anti- lysosomal-associated membrane protein-1 (LAMP1) protein expression levels via immunohistochemistry (ICH). Equal sized regions of interest from grayscale representative images for each mouse were analyzed. Color and symbols denote each cohort (n=3-5 mice per group). The HMI-203 dose was Dose D (high dose) and timepoint is 52 weeks post HMI-203 administration. Error bars denote standard deviation (SD). Statistical analysis was performed using a 1-way analysis of variance (ANOVA) test.

HMI-203 Prevented Progression of Craniofacial and Hindlimb Abnormalities in MPS II Mouse Model Compared to Vehicle MPS II Mouse Model Controls

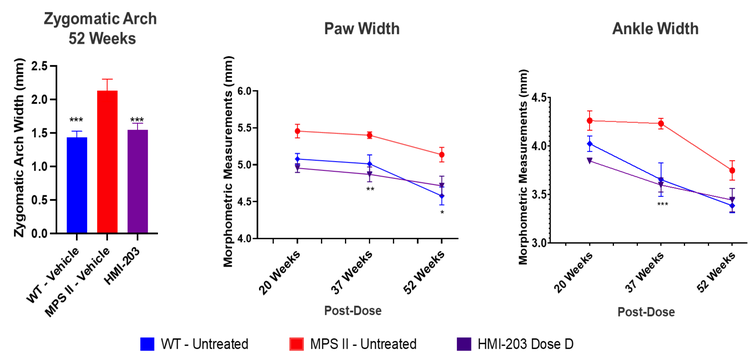
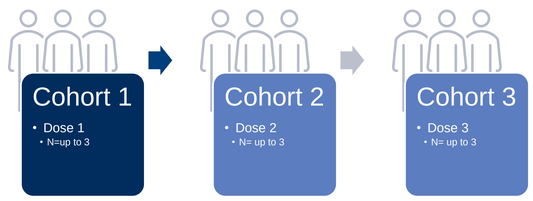


Figure 5: Zygomatic arch base, paw and ankle morphometric measurements were (n=3-5 mice per group) at 52 weeks post HMI-203 administration. Statistical analysis was performed using a two-way analysis of variance (ANOVA). * p- value <0.05, **p- value <0.01 and *** p-value <0.001.

juMPStart Clinical Trial Design

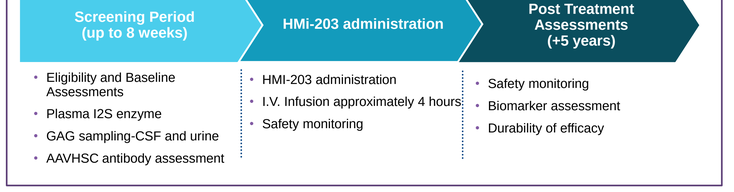
juMPStart is A Phase 1, Open-Label, Dose Escalation Study to Evaluate the Safety and Efficacy of HMI-203 in ERT-Treated Adults with MPS II



- All doses are expected to impact disease biomarkers
  - ✓ Urine GAG
  - ✓ Plasma I2S activity
- Biochemical criteria are specified for consideration of safe discontinuation of ERT

To decrease the potential for an immune response to HMI-203, juMPStart uses a prophylactic immunosuppressive regimen with a corticosteroid and the T-cell inhibitor, tacrolimus.

juMPStart Overview



Primary study endpoints include:
- Incidence and severity of treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESI; hepatic assessments)
- Mean percent change from Baseline in urine GAG levels and I2S activity through Week 52 following HMI-203 administration.

juMPStart Key Eligibility Criteria

Inclusion
- Adult males 18 to 45 years of age
- Compliant with regular treatments of idursulfase *and* clinically stable for at least 12 months prior to enrollment
- Participant has capacity to understand the purpose and risks of the study; is willing, able, and committed to comply with all study procedures for the duration of the trial (a total of 5 years after gene therapy administration)
- No contraindications to immunosuppressive regimen or study assessments
- Negative for neutralizing AAVHSC antibodies

Exclusion
- Multiple sulfatase disorder (MDS) determined by abnormal activity of another lysosomal sulfatase
- History of bone marrow transplant, stem cell transplantation or gene therapy
- Positive test result for human immunodeficiency virus (HIV), history of or current therapy for hepatitis C virus (HCV) or hepatitis B virus (HBV)
- Elevated liver enzyme levels or INR
- Known history of or identification of any inherited or acquired hypercoagulable condition or susceptibility to thrombotic microangiopathy (TMA)

Based on studies demonstrating efficacy of HMI-203 studies in the MPS II mouse model, the juMPStart Phase 1 gene therapy clinical trial (NCT05238324) has been initiated, and recruitment is ongoing in the United States and Canada.

Demonstration of positive safety and efficacy results in the adult population may allow for enrollment of younger and more severely affected participants in future studies.

References

[1] D'Avanzo F et al. Int J Mol Sci. 2020

ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT05238324