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Patient-Focused Drug Development for a Single Intravenous Dose of HMI-203 Gene Therapy in Adult Mucopolysaccharidosis (MPS) II, or Hunter Syndrome, Patients.

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Introduction:
MPS II, a rare lysosomal storage disorder caused by mutations in the *IDS* gene, is comprised of two subtypes: one with progressive cognitive decline and survival into the teens (neuronopathic form) and the other without cognitive impact and survival into the third or fourth decade (non-neuronopathic form). Both subtypes have debilitating peripheral manifestations. HMI-203 is an investigational AAVHSC-mediated gene therapy that provides functional copies of the *IDS* gene. Preclinical data in the MPS II mouse model support its potential to address both the peripheral and CNS manifestations of MPS II. Ahead of its planned first-in-human clinical trial in adults with MPS II in 2021, Homology Medicines sought to better understand the burden of disease directly from patients to inform meaningful clinical outcomes and ensure a patient-focused drug development plan. Recent focus by other drug developers is on young neuronopathic patients, with the hope of preventing or reversing the cognitive delay that enzyme replacement therapy (ERT) cannot address. The disease burdens for all MPS II patients are significant, and in the adult population, the peripheral aspects of the disease are poorly understood, and therefore have gone unaddressed despite years of weekly ERT.

Methods:
We conducted 1:1 interviews with 7 MPS II adults using a standardized questionnaire to collect qualitative data to understand the most burdensome aspects of the disease and perceptions about current and future therapies.

Results:
Median age of patients was 26 (range 24-36) years. The most burdensome daily symptoms experienced by MPS II adults: limited mobility and range of motion 7/7; pain 6/7; hearing loss 6/7; difficulty walking or standing 3/7. The current therapies to manage MPS II symptoms: ERT 7/7; surgeries 7/7; supportive therapies (PT/OT, chiropractic) 6/7; hearing aids 4/7; cardiovascular 4/7. All patients received weekly ERT and cited it as their most beneficial therapy but noted its expense and the time and inconvenience required for weekly infusions. Patients wished that ERT more adequately addressed symptoms including pain, range of motion, hearing loss and chronic fatigue. All patients desired a potential one-time gene therapy that could alleviate the burden of weekly ERT and provide at least equal therapeutic benefit.

Conclusion:
MPS II patients are burdened by weekly ERT infusions and disease manifestations that ERT does not address. Based on the results of this study of MPS II patient experiences, Homology aims to incorporate patient-focused endpoints into its Phase 1/2 clinical evaluation of HMI-203 including the potential to discontinue ERT.