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Clinical trial design for HMI-203 investigational gene therapy for Mucopolysaccharidosis (MPS II) informed by cross-correction potential and KOL Input

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MPS II is a rare lysosomal storage disorder (LSD) caused by mutations in the iduronate-2-sulfatase gene (*IDS*) and results in an accumulation of glycosaminoglycans (GAGs). HMI-203 is an investigational gene therapy being developed by Homology Medicines for the treatment of MPSII. HMI-203 is designed to restore iduronate-2-sulfatase enzyme (I2S) function through direct cell transduction and cross-correction, whereby functional enzyme is produced and secreted by transduced cells and is taken-up by neighboring or distant cells/tissues. Ahead of its first-in-human clinical trial for HMI-203 Homology is leveraging this biological mechanism along with expert key opinion leader (KOL) input on clinical trial design, including the safe discontinuation of enzyme replacement therapy (ERT) following a single intravenous administration of HMI-203. Here we describe data from a murine MPS II model demonstrating effective gene transduction by HMI-203, leading to successful secretion of active I2S. HMI-203 led to sustained systemic expression of IDS, as assessed by vector genome, transcript, and active I2S detected out to 52 weeks post-administration. Resulting systemic effects included decreased GAG levels, enhanced lysosomal integrity, and improvement in disease-associated skeletal and joint abnormalities. Serum from treated MPS II mice was shown to contain active I2S, which bound via mannose-6-phosphate receptors and translocated to the lysosome in cultured *IDS*-KO cells, supporting the cross-correction potential of HMI-203. Collectively, these gene therapy data strongly support the additional potential for cross-correction in patients with MPS II treated with HMI-203. Encouraged by these data, Homology conducted 1:1 interviews with 6 KOLs in an effort to gain input on clinical endpoints and define criteria which may predict safe discontinuation from ERT following HMI-203 administration. KOLs agreed that plasma I2S activity, urinary GAG levels, and the 6-minute walk test (6MWT) are meaningful parameters informing an ERT-discontinuation protocol for consideration in the HMI-203 gene therapy clinical trial.