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# HMI-102, an Investigational Gene Therapy for Phenylketonuria (PKU)

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HMI-102 is an investigational gene therapy for phenylketonuria (PKU) due to phenylalanine hydroxylase (PAH) deficiency. The PAH enzyme converts phenylalanine (Phe) into tyrosine (Tyr). PAH deficiency is due to mutations in the *PAH* gene, resulting in excess Phe. It is inherited as an autosomal recessive, monogenic defect, making it suitable for potential AAV-based gene therapy.

PAH deficiency has a continuum of clinical phenotypes characterized by elevated blood Phe, ranging from mild hyperphenylalaninemia (HPA) (Phe 120-360 µmol/L) to classical PKU (Phe over 1200 µmol/L). Current U.S. treatment guidelines indicate treatment is not required for mild HPA. Untreated PKU in children results in severe neurological impairment. Adults treated with Phe-restricted diets as children also present with higher rates of neuropsychiatric comorbidities. HMI-102 delivers the human *PAH* gene to the liver using AAVHSC15, a Clade F AAV vector isolated from human hematopoietic stem cells. The gene is transcribed and translated into active PAH. HMI-102 was tested in $Pah^{enu2}$ mice, a murine model of PKU with several features consistent with the human classical PKU phenotype, including blood Phe over 1200 mM. HMI-102 normalized blood Phe within one week of administration in mice on a normal chow diet. Phe reduction was sustained for 48 weeks (lifespan of the mouse model).

HMI-102 also normalized blood Tyr, 5-HIAA in the brain, and darkened the mouse coat color, demonstrating restoration of Phe metabolism.

In GLP studies in non-human primates and mice, there were no adverse test-article related findings. Durable vector genomes (vg) and mRNA expression were present in the livers; vg levels were comparable in both species at given weight-based doses. Dose modeling simulations for baseline Phe up to 2400 mmol/L were done using $Pah^{enu2}$ efficacy data to select doses for the first-in-human (FIH) study. The modeling predicted a robust response for the starting dose.

In tandem, a retrospective chart review was conducted to characterize blood Phe control in 152 patients with PKU. The data showed high Phe levels despite dietary restriction, demonstrating an unmet need for therapies to control blood Phe. The data also confirmed the FIH study design eligibility criteria and endpoints.

Collectively, the nonclinical data and retrospective study supported initiation of the FIH study, which is assessing the safety, tolerability and efficacy of HMI-102 in adults with classical PKU.