

**American Society for Human Genetics (ASHG)**  
**Poster Session**  
**Oct 25, 2022**

A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of HMI-103, a One-Time Gene-Editing Vector in Adult Participants with Classical PKU Due to PAH Deficiency

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Phenylketonuria (PKU) is a rare autosomal-recessive inborn error of metabolism. If left untreated, phenylalanine hydroxylase (PAH) deficiency may result in progressive, irreversible neurological impairment. Neither a phenylalanine (Phe)-restricted diet nor currently available therapeutic treatments address the core biological defect of the disease—the presence of biallelic pathogenic variants in the *PAH* gene. This leaves a significant unmet medical need for patients with PKU due to PAH deficiency.

HMI-103 is an investigational gene-editing vector designed to: 1) deliver normal copies of the *PAH* gene to hepatocytes, 2) integrate into target *PAH* locus in the genome via non-nuclease-based AAV-mediated homologous recombination, 3) produce the PAH enzyme (via the dual mechanism of integration via homologous recombination and episomal expression), and 4) restore Phe metabolism. This approach is supported by studies in the *Pah<sup>enu2</sup>* mouse model in which blood Phe was reduced and maintained in juvenile and adult mice and in partially hepatectomized mice regrown with human hepatocytes. No clinical pathology, necropsy findings, or evidence of germline transmission were observed. The data demonstrated efficacy, integration, specificity for the target locus, and preclinical safety of HMI-103 and support initiation of a clinical trial.

This Phase 1, open-label, sequential, dose-escalation study (pheEDIT) will evaluate the safety and efficacy of a one-time, intravenous administration of HMI-103 in adult participants aged 18–55 years with classical PKU due to PAH deficiency who have uncontrolled disease despite standard of care or marketed treatments. Three dose levels of HMI-103 will be investigated, with up to 3 participants for each dose cohort. A maximum of 9 participants will be enrolled in the study. Enrollment will be staggered between participants in a given cohort.

To decrease potential for immune-response, pheEDIT will use a prophylactic immunosuppressive regimen consisting of a corticosteroid administered in combination with the T-cell inhibitor tacrolimus.

The primary study endpoints include incidence and severity of treatment-emergent adverse events (TEAEs) and AEs of special interest, and the mean percent change from Baseline in plasma Phe concentrations within each dose cohort post administration of HMI-103. These will be assessed through Week 104 plus long-term follow-up. Once positive safety and efficacy results are demonstrated in the adult population, Homology plans to enroll younger participants into future studies.