**HMI-103 Mechanism of Action**

**HMI-103** is an investigational gene editing vector designed to:

- Address underlying genetic cause of PKU
- Deliver functional copies of the PAH gene to hepatocytes
- Integrate into target PAH locus in the genome via non-nuclease-based AAV-mediated homologous recombination (HR), which is a high-fidelity natural DNA repair process for gene editing
- Treat adult and pediatric PKU with dual mechanism of action in transduced liver cells
- Maximize PAH expression through PAH and liver-specific promoter integration and episomal expression in transduced cells
- Restore Phe metabolism following a single intravenous (I.V.) infusion

**Preclinical Efficacy and Safety**

**Objectives:**
- Evaluate pre-clinical safety and efficacy of HMI-103, a nuclease-free gene editing candidate for humans, and its mouse surrogate vector in appropriate models
- Assess on-target and potential off-target integration

**Materials:**
- Vectors packaged in AAV/HSC15 (adeno-associated virus [AAV] serotype HSC15) capsid using Homology’s platform process
- Mouse surrogate vector evaluated in Pahnull mouse model of PKU and Wild Type (WT) mice
- HMI-103 tested in humanized-liver xenograft mouse model

**Introduction**

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 underlying defect of the disease - the presence of baltic pathogenic variants in the PAH gene.

This leaves a significant unmet medical need for patients with PKU due to PAH deficiency.

**Standard of care ➔ onerous low Phe diet has poor compliance**

**Pre-controlled diet not sufficient to reduce Phe levels to within American College of Medical Genetics and Genomics (ACMG) targets (120-360 μmol/L) or EU targets (120-600 μmol/L)**

**Approved therapeutics do not reconstitute normal biochemical pathways for ~95% of patients: all require chronic dosing vs. a potential one-time treatment**

**Physicians and patients seek new treatment options**

**HMI-103 Clinical Trial Design**

**Phase 1, open-label, dose-escalation trial evaluating the safety and efficacy of a one-time single i.v. dose of HMI-103 in participants with Classical PKU due to PAH deficiency**

**To decrease the potential for an immune response to HMI-103, pheEDIT uses a prophylactic immunosuppressive regimen with a corticosteroid and the T-cell inhibitor, tacrolimus.**

**pheEDIT and Long-term Extension Study Overview**

**Pretreatment Period**
- Up to 30 days

**Study Period**
- HMI-103 administration on Day 1
- No test article
- Safety monitoring
- Efficacy monitoring
- Plasma Phe monitoring
- Diet compliance

**Long-term Extension Study**
- 13 years

**Inclusion**
- Eligibility and baseline assessments
- At least one Phe level ≥ 400 μmol/L (10 mg/dL) during pretreatment period
- No evidence of germline transmission

**Exclusion**
- Participants with PKU that is not due to PAH deficiency
- Presence of anti-AAV/HSC15 neutralizing antibodies during screening
- Elevated Hemoglobin A1c or elevation of liver enzymes
- Abnormal hematology values
- Previously received gene therapy for the treatment of any condition

Based on IND-enabling studies demonstrating efficacy of HMI-103 studies in the mouse, HMI-103 received Fast Track designation by the United States (U.S.) Food and Drug Administration (FDA). The pheEDIT Phase 1 gene editing clinical trial (NCT05222178) has been initiated, and recruitment is ongoing.

Demonstration of positive safety and efficacy results in an adult population may allow for enrollment of younger participants in future studies.