**2021 European Society for Gene & Cell Therapy Virtual Conference (ESGCT)**
**Poster Presentation**
**October 19, 2021**

# HMI-103: An Investigational Gene Editing Vector for Phenylketonuria (PKU)

Benard L, Lamppu D, Prasad A, Wright J, Von Stetina JR, Thompson J, Wright T, Avila N, Francone O and Seymour A

Homology Medicines, Inc.

PKU is a rare autosomal recessive monogenic disorder. Greater than 98% of cases are due to mutations in the phenylalanine hydroxylase (*PAH)* gene, resulting in deficient activity of PAH, a hepatic enzyme that catalyzes the formation of tyrosine, a precursor to neurotransmitters, from phenylalanine (Phe). Untreated PKU results in progressive, irreversible neurological impairment during infancy and early childhood. Restricting protein and Phe intake is standard of care for most PKU patients.

HMI-103 is an investigational gene editing vector packaged in AAVHSC15 designed to deliver functional copies of human *PAH* to hepatocytes with the potential to restore PAH activity and normalize Phe metabolism. HMI-103 contains locus- and human-specific homology arms (HA) flanking the *PAH* sequence (cDNA), which are designed to guide the cDNA to the *PAH* locus and integrate through non-nuclease-based, AAV-mediated homologous recombination.

IND-enabling studies of HMI-103 showed integration into the *PAH* locus without introducing *de novo* single nucleotide variants, insertions or deletions in hepatocytes in humanized-liver xenograft mice. Fidelity of integration has been verified by long-read sequencing. No off-target integration was detected via molecular analysis.

A mouse surrogate gene editing vector was used in GLP toxicity studies in the *Pah*$^{enu2}$ PKU murine model and germline transmission studies in C57BL/6J mice. Blood Phe was normalized in *Pah*$^{enu2}$ mice at all doses tested and there were no test-article related findings. There was no evidence of germline transmission.

These data demonstrated integration, fidelity, and HA-specificity for the *PAH* locus and preclinical safety of HMI-103 and are supportive of clinical trial initiation.