15th Annual WORLD*Symposium*
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Single Intravenous Dose of AAVHSC15 Packaging a Human Phenylalanine Hydroxylase Transgene Results in Durable Correction of Phenylketonuria *In Vivo*

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Novel recombinant Clade F adeno-associated viruses, originally isolated from normal human CD34+ hematopoietic stem cells (AAVHSCs), show high liver tropism and potential for liver-based gene therapy. Phenylketonuria (PKU) is a rare metabolic disease, resulting from mutations in the hepatic phenylalanine hydroxylase (*PAH*) gene. PKU is a suitable candidate for rAAV-based gene therapy as it is an autosomal recessive, monogenic defect. There are no current treatments that address the underlying genetic defect in PKU. In PAH^{enu2} mice, a missense mutation (F263S) in the *Pah* gene greatly reduces enzyme, causing a 40-fold elevation in serum phenylalanine (Phe) on a normal chow diet (containing 1% Phe), making the mice an appropriate animal model for severe PKU. The human *PAH* transgene, packaged in AAVHSC15 and driven by a ubiquitous promoter (AAVHSC15-PAH), was administered as a single intravenous injection in PAH^{enu2} mice. Mice were fed normal chow throughout the study. Serum levels of Phe and tyrosine (Tyr) [byproduct of Phe metabolism required for production of neurotransmitters] were measured weekly. Livers were harvested and processed to measure vector genomes, mRNA, and PAH enzyme activity. One week post-dose, Phe levels decreased from 2000μM to <150μM ($p<0.0001$) and were sustained out to >28 weeks post-dosing ($p<0.0001$) even as mice had a dietary intake of 1% Phe. Dose-dependent increases in PAH vector genomes, mRNA, and enzymatic activity were observed. Modifying the transgene to include a liver-specific promoter demonstrated decreased serum Phe and increased serum Tyr in PAH^{enu2} mice at ten-fold lower doses compared to the initial research vector. Sustained correction was seen out to 48 weeks in mice on normal chow. These data demonstrated that a single dose of AAVHSC15-PAH, designated HMI-102, resulted in long-term correction of PKU in PAH^{enu2} mice.