

European Society of Gene & Cell Therapy Annual Congress
Poster Session 2
October 18, 2018
12:40 p.m. CEST
Garden Floor

Durable Correction of Phenylketonuria *In Vivo* Following a Single Intravenous Dose of AAVHSC15 Packaging a Human Phenylalanine Hydroxylase Transgene

Seemin S. Ahmed, Jeff L. Ellsworth, Omar L. Francone, Deiby Faulkner, Arnold Sengooba, Hillard Rubin, Serena Dollive, Diana Lamppu, Teresa Wright, Deb Kinch, Albert Seymour

Homology Medicines, Inc., Bedford, MA

Novel Clade F adeno-associated viruses isolated from human CD34+ hematopoietic stem cells (AAVHSCs) show high liver tropism and potential for hepatic gene therapy. Phenylketonuria (PKU) is a rare metabolic disease arising from mutations in the *PAH* gene. Current treatments do not address the underlying genetic defect. PAH^{enu2} mice, a model of severe PKU, harbor a missense mutation (F263S) in the *PAH* gene reducing enzyme activity by 99% that causes a 40-fold elevation in serum phenylalanine (Phe) on normal chow diet. The human *PAH* transgene driven by a ubiquitous promoter packaged in AAVHSC15 (HMI-101) was administered as a single intravenous injection in PAH^{enu2} mice. Serum levels of Phe and tyrosine [metabolic substrate end product] 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 2000 μ M to <150 μ M ($p < 0.0001$). Dose-dependent increases in PAH vector genomes, mRNA, and enzymatic activity were observed. To maximize potency, vector sequences in AAVHSC15-PAH were optimized by addition of a liver-specific promoter to generate a vector HMI 102 that decreased serum Phe and increased serum Tyr in PAH^{enu2} mice even at ten-fold lower doses from the initial research vector with durable response seen out to 48 weeks in mice on normal chow. These data demonstrate that a single dose of HMI-102 resulted in long-term correction of PKU in PAH^{enu2} mice while on normal chow.