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Poster Presentation
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Sustained Correction of Phenylketonuria by a Single Dose of AAVHSC Packaging a Human Phenylalanine Hydroxylase Transgene

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Adeno-associated viruses isolated from human CD34+ hematopoietic stem cells (AAVHSCs) have shown tropism for the liver in mice and non-human primates. To evaluate whether an AAVHSC could deliver a therapeutic gene and correct a disease phenotype in liver, AAVHSC15 was studied in PAH^{enu2} mice. These mice harbor a mutation (F263S) in the phenylalanine hydroxylase (*PAH*) gene resulting in < 1.0% of wild-type levels of PAH activity in liver, have 40-fold elevations in serum phenylalanine (Phe) on a normal chow diet, and are a model for severe phenylketonuria (PKU) in humans. AAVHSC15 packaging a human *PAH* transgene driven by a ubiquitously expressing promoter (AAVHSC15-PAH) was prepared. Mice received a single intravenous injection of vehicle +/- AAVHSC15-PAH. Serum levels of Phe and of tyrosine (Tyr) were analyzed weekly and livers were harvested for measurement of *PAH* vector genomes (VG) and *PAH* mRNA by ddPCR, and PAH bioactivity. One week post-dosing, serum levels of Phe were normalized to <150 μM, Tyr levels were increased, and *PAH* VG, *PAH* mRNA, and PAH bioactivity were increased in livers of treated animals. Durability of responses were dependent on dose of AAVHSC15-PAH administered. Neither changes in serum Phe nor hepatic PAH activity were observed in animals treated with vehicle alone. Vector sequences in AAVHSC15-PAH were optimized resulting in HMI-102. HMI-102 normalized serum Phe in PAH^{enu2} mice at ten-fold lower doses with durability in response seen out to >24 weeks. These data suggest that HMI-102 shows potential as a one-time, *PAH* gene replacement therapy for PKU in humans.