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Biodistribution and Tolerability of HMI102, a Novel AAVHSC15 Encoding Human Phenylalanine Hydroxylase, in Cynomolgus Monkeys

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A six-month GLP study to assess the biodistribution and tolerability of HMI-102, a recombinant AAVHSC15 gene transfer vector encoding human phenylalanine hydroxylase (*PAH*), was conducted in cynomolgus monkeys. The AAVHSC15 capsid is a natural Clade F adeno-associated virus (AAV) variant that was isolated from CD34+ human peripheral blood stem cells from healthy adults. HMI-102 is an investigational AAV vector-based gene therapy under development for the treatment of patients with phenylketonuria (PKU), a rare disease caused by inherited mutations in the *PAH* gene that result in the absence or deficiency of PAH activity. PAH, which in humans is expressed in hepatocytes, is a critical enzyme for the formation of tyrosine (Tyr) from phenylalanine (Phe), an essential amino acid obtained exclusively from the diet. This study consisted of three groups, each with 2 male and 2 female cynomolgus monkeys, and each group received either vehicle or HMI-102 at a low or a high dose as a 30-minute intravenous (IV) infusion. The dose range was selected to approximate the expected clinical dose range. Animals were sacrificed at 3 months (low dose) and at 6 months (vehicle and high dose). A concurrent study with the same manufactured lot was conducted in the mouse model of disease, the Pah^{enu2} mouse, and timepoints were selected to allow for direct comparison. This also allowed comparison of the pharmacodynamic activity of HMI-102 in mice to the potential exaggerated pharmacology in nonhuman primates expressing supranormal levels of human PAH. A key endpoint was also to assess the allometric scaling of AAVHSC15 between mouse and cynomolgus monkey to allow for dose extrapolation to humans. Endpoints in this study included both safety and biodistribution. Safety was assessed by physical examinations, clinical observations, body weight, food consumption, ophthalmoscopic examinations, ECG's, immune response to capsid and transgene, clinical pathology and histopathology. Biodistribution (vector genome and human *PAH* mRNA levels) were assessed in liver biopsies taken at 1 month and 3 months post-dose, and comprehensive tissue collections at 3 months and 6 months post dose. HMI-102 was well tolerated at the doses tested for up to 6 months. Vector genome levels per cell in the liver were similar to the levels found in the livers of Pah^{enu2} mice receiving the same doses of HMI-102. The doses utilized resulted in normalized Phe levels

in Pah^{enu2} mice within one week, with concomitant increases in Tyr levels. In cynomolgus monkeys, treatment with HMI-102 did not alter blood Phe or Tyr concentrations, as expected given the known allosteric regulation of PAH. The results of this study support the planned Phase 1/2 gene therapy clinical trial of HMI-102.