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The pheNIX Trial: First-in-Human Gene Therapy Trial for PKU Due to Phenylalanine Hydroxylase (PAH) Deficiency

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Introduction: PKU due to PAH deficiency results from biallelic pathogenic variants in the PAH gene, which causes dietary phenylalanine (PHE) intolerance, and is associated with significant disease burden. Treatment includes life-long dietary protein restriction, medical foods, and approved therapies that reduce blood PHE concentrations. PKU treatment guidelines vary by region. The American College of Medical Genetics and Genomics (ACMG) recommends that “any combination of therapies that facilitate improvement in blood PHE levels for a given individual is appropriate,” and that treatment for PAH deficiency “be lifelong for patients with untreated PHE levels >360 µmol/l” and that “a treated PHE level of 120–360 µmol/l is recommended for all patients of all ages” (Vockley et al., 2014). European guidelines recommend that in PKU patients “aged 12 years or older, the target phenylalanine concentrations should be 120–600 µmol/L” (van Spronsen et al., 2017). AAVHSC15-mediated gene therapy is being developed for the treatment of PAH deficiency. The pheNIX trial (NCT03952156) is an open-label, concurrently controlled, multicenter, Phase 1/2 dose-escalation and dose-expansion gene therapy trial designed to evaluate the safety and efficacy of a single I.V. infusion of investigational gene therapy HMI-102 in PAH-deficient adults.

Methods: The pheNIX trial includes a dose-escalation phase and a dose-expansion phase, which is concurrently controlled. The dose-escalation phase of the pheNIX trial consists of sequential, ascending dose cohorts. An independent data monitoring committee convenes periodically to provide recommendations on trial conduct, dose-escalation, and dose-expansion.

Results: Six subjects have been administered HMI-102 in the dose-escalation phase; two subjects in each dose cohort (2E+13 vg/kg; 6E+13 vg/kg; 1E+14 vg/kg). Post-treatment follow-up varies by subject and extends up to 52 weeks (end of study). There have been no treatment-related serious adverse events. As observed with other AAV-based gene therapies, glucocorticoid-responsive transaminitis was observed. Decreases in PHE and/or increases in tyrosine (TYR) were observed, suggesting PAH biologic activity in both the mid- and high-dose cohorts, with some patients achieving PHE levels < 360 µmol/l by 12 weeks post-treatment.

Conclusions: The safety and efficacy observed following treatment with a mid- or high-dose of HMI-102 support dose selection of 6E+13 vg/kg and 8E+13 vg/kg for the dose-expansion phase of the trial. Recruitment for 15-20 subjects for the dose-expansion phase of the study is ongoing.