New England Consortium of Metabolic Programs Annual Meeting
Oral Presentation
November 6, 2020

The pheNIX Trial: the First-In-Human Gene Therapy Trial for PKU due to Phenylalanine Hydroxylase (PAH) Deficiency

Bodamer O[1,2],

[1]Division of Genetics and Genomics, Boston Children's Hospital, [2]Broad Institute of Harvard University and MIT

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 in combination with approved therapies that reduce blood PHE concentrations. PKU treatment guidelines vary by region. The American College of Medical Genetics and Genomics (ACMG) recommends that treatment for PKU is lifelong with target PHE levels of 120–360 µmol/l for all patients of all ages" [1]. In contrast, European guidelines recommend target PHE levels of 120–600 µmol/ l [2]. AAVHSC15-mediated gene therapy is being developed for the long-term 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. Observations through Sept. 30, 2020 are reported.

Results: Six adult subjects with PKU have been administered HMI-102 in the dose-escalation phase; two in each dose cohort. Post-treatment follow-up varies by subject, and ranges from 10-52 weeks. There have been no treatment-related serious adverse events. As observed with other AAV-based gene therapies, glucocorticoid-responsive transaminitis was observed to varying degrees. 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: PHE reductions following treatment with a mid- or high-dose of HMI-102 were observed and dose selection for the expansion phase of the trial is pending.

Funding disclosure: pheNIX is sponsored by Homology Medicines, Inc.

[1]Vockley J et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline. Genetics in Medicine 2014;16: 188-200.

[2]van Spronsen FJ et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol 2017; 5: 743–56.