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A 5-Year Retrospective Study of Individuals with Phenylketonuria (PKU) Treated at Two Specialized Clinics

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PAH deficiency is an inborn error of metabolism due to mutations in the *PAH* gene, resulting in phenylketonuria (PKU). The mutations lead to absent or deficient PAH enzyme which converts phenylalanine (Phe) to tyrosine (Tyr), a precursor to multiple biologically important downstream neurotransmitters. Phenotypes range from mild HPA (Phe 120-360 μmol/L) to classical PKU (Phe over 1200 μmol/L). With the advent of newborn screening in 1963, managing the disease by low Phe diet in infants before clinical symptoms appear became the standard of care. However, maintaining a lifelong highly restrictive and onerous diet is challenging for many and that a prescribed diet alone is often insufficient for achieving Phe goals. Untreated PKU in children results in progressive irreversible neurological impairment. Current treatments do not address the underlying genetic defect.

HMI-100-001 is a retrospective chart review of patients with a diagnosis of PKU due to phenylalanine hydroxylase (PAH) deficiency using records spanning a 5-year period ending in November 2017 to capture real-world data associated with managing PKU under current standard of care.

The study was conducted at two U.S. clinics, and a total of 152 patients (10-40 years old) were enrolled (65.8% with classical PKU). Data were collected from electronic medical records from baseline to 5 years prior to baseline +/- 3 months, and characterized demographics, medical history, treatments and blood Phe. The number of patients with consecutive lab values decreased as the Phe threshold was lowered (Phe below 600, 360, 120 and 30 μmol/L). The data demonstrated decreased Phe control with age; mean Phe ± standard error for patients 10-18 and over 18-40 was 456.8 ± 27.0 and 694.7 ± 36.7 μmol/L respectively. 62.5% of patients were reported as having a history of at least one neuropsychiatric comorbidity, and adults were more likely than adolescents (69.5% vs. 54.3%). 90 of 98 PAH genotypes collected were distinct mutations; the 6 null-null genotypes were associated with classical PKU. Despite use of protein restriction, Phe concentrations over 360 μmol/L were observed, particularly in classical PKU patients. Overall the demographics and clinical data were consistent across both sites.

These real-world data show that Phe levels were elevated, even when patients were on a Phe-restricted diet, and mostly above 360 μmol/L (considered well-controlled based on current U.S. treatment guidelines). There remains an unmet need for therapies to control Phe concentrations without a Phe-restricted diet. As an autosomal recessive, monogenic defect, PKU due to PAH deficiency is a suitable condition for potential AAV-based gene therapy.