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

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Phenylalanine hydroxylase (PAH) deficiency is an inborn error of metabolism due to mutations in the *PAH* gene, which results in phenylketonuria (PKU). The mutations result in the absence or deficiency of PAH, an enzyme that catalyzes the formation of tyrosine (Tyr) from dietary phenylalanine (Phe), leading to excess Phe. PAH deficiency is an autosomal recessive, monogenic defect, making it a suitable condition for potential AAV-based gene therapy.

PAH deficiency manifests as a continuum of hyperphenylalaninemia (HPA) phenotypes characterized by elevated blood Phe concentrations. Diagnostic sub-categories of PKU range from mild HPA (Phe levels 120-360 µmol/L) to the most common and severe form, "classic PKU," defined as Phe over 1200 µmol/L. Current U.S. treatment guidelines indicate that treatment is not required for mild HPA. With the advent of newborn screening in 1963, managing the disease by dietary restriction of Phe in infants before clinical symptoms appear became the standard of care. Untreated PKU in children results in progressive irreversible neurological impairment; however, even early-treated PKU adults present with higher rates of neuropsychiatric comorbidities. Maintaining the life-long diet requires the use of unpalatable protein substitutes, has side effects, and is difficult to adhere to, especially for adolescents and adults. There are no current treatments that address the underlying genetic defect.

HMI-100-001 is a retrospective study conducted at two specialized U.S. clinics that describes two cohorts of patients with HPA over a 5-year period ending in November 2017. A total of 152 patients (10-40 years old) were enrolled in this study. The primary objective was to describe blood Phe control in these patients over a five-year period. The results showed that most patients were diagnosed with classic PKU (64.3% in the 10 to 18 age group and 67.1% in the over 18 to 40 age group). The number of patients with consecutive lab values decreased as the Phe threshold was lowered (Phe levels below 600 µmol/L, 360 µmol/L, 120 µmol/L, and 30 µmol/L). The data confirmed prior research demonstrating a relationship between increased age and decreasing control of Phe concentrations, where mean Phe was 456.8 ± 27.0 µmol/L (mean + standard error) for patients 10 to 18 compared to 694.7 ± 36.7 µmol/L for patients over 18 to 40. Patients with classic PKU had higher mean Phe relative to the remaining diagnostic sub-categories of mild HPA, mild PKU, and moderate PKU. 62.5% of patients were reported as having a history of at least one neuropsychiatric condition, and 44.1% of patients were recorded as having more than one. 98 PAH genotypes were collected, with approximately 90 distinct mutations; the 6 null-null mutations were all found in the Classic PKU population. Despite use of protein restriction, Phe concentrations over 360 mmol/L were observed, particularly in classic PKU patients. Among the classic PKU patients, 73.3% in the 10 to 18 age group and 92.7% in the over 18 to 40 age group had a 5-year mean Phe over 360 µmol/L. Overall the demographics and clinical data were consistent across both sites.

Collectively, these real-world data show that Phe levels were elevated, even when a patient was on a Phe-restricted diet, and above the threshold (360 µmol/L) considered well-controlled based on current treatment guidelines. There remains an unmet need for therapies to control Phe concentrations without a Phe-restricted diet, particularly in patients diagnosed with classic PKU and those over 18 years of age.