Phenom: A prospective clinical study on the clinical impact of phenylketonuria in adults (307-902)

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Background

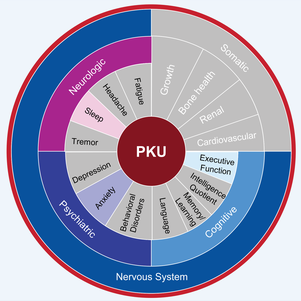
- Phenylketonuria (PKU) is an autosomal recessive disorder, characterized by deficiency in the activity of the liver enzyme, phenylalanine hydroxylase (PAH), which metabolizes phenylalanine (Phe) to tyrosine
- Deficient PAH activity leads to abnormally high levels of Phe in the blood and tissues, which are toxic to the brain[1,2]
- Current guidelines recommend life-long disease management to maintain blood Phe within a specific reduced range:

Guideline recommendations for blood Phe	
Normal	**Guideline recommendations**
30–120 µmol/L[3]	US, 120–360 µmol/L for all patients[1] EU, 120–600 µmol/L for patients >12 years of age[2]

Treatment options	
Phe-restricted diet	with or without the addition of sapropterin dihydrochloride (Kuvan®), which is only effective in the subset of patients who are BH4-responsive[4,5]
Pegvaliase (Palynziq®)	approved for the treatment of adults (≥18 years in the US and ≥16 years in the EU) with uncontrolled blood Phe levels (>600 µmol/L) on existing treatment[6,7]

- The majority of adolescent and adult patients with PKU managed with diet are unable to sustain guideline-recommended Phe levels[8] and currently available therapeutic options still have the burden of life-long treatment
- Though the impact of high Phe in adolescent/adults is not yet fully characterized, current evidence suggests that the clinical consequences are broad and while varied across patients, all have a considerable impact on patients' lives, including on psychiatric and neurocognitive domains (**Figure 1**)
- Further research is needed to better understand the clinical consequences of high Phe and how it can be best assessed to inform clinical monitoring and the development of future treatment options for patients with PKU
- A robust clinical program was developed to better understand the impact of high Phe levels on clinical symptoms in adolescent/adults and investigate the potential benefits following BMN 307, an investigational, single-administration, gene-transfer therapy designed to normalize Phe levels in patients with PKU[9]
- The BMN 307 clinical program includes two currently enrolling studies: Phenom (307-902, NCT04452513) and Phearless (307-201, NCT04480567), a two-part study evaluating the safety, efficacy, and tolerability of BMN 307 in patients with PKU and blood Phe >600 µmol/L at screening
- Herein we present preliminary data from Phenom patients who had at least 24 weeks of follow-up at the time of the interim analysis

Figure 1. Key clinical issues identified by PKU patients and clinicians



Methods

- Phenom is an ongoing, prospective, multicenter study measuring markers of disease and clinical outcomes for up to 96 weeks, with an enrollment target of 90 patients with PKU aged ≥14 years with blood Phe >600 µmol/L at screening who are not currently being treated for PKU with pharmacotherapy
- The study design has been previously described[9] and includes clinical measures in four areas: biomarkers and nutritional management, characteristics of PKU population, clinical outcomes, and mobile health assessments. In clinical outcome assessments (COAs), measuring symptoms from cognitive, psychiatric, and neurological domains include:
  - Inattention is being assessed by the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention (ADHD-RS IV IA)[10] subscale (0–27). Scores >9 indicate symptoms of inattention
  - Anxiety is being assessed by the Generalized Anxiety Disorder 7-Item (GAD-7)[11] scale (0–21). A score of 10 or higher is associated with symptoms of anxiety
  - Daytime sleepiness is being assessed by the Epworth Sleepiness Scale (ESS)[12] (0–24). Scores of 10 or higher are observed in obstructive sleep apnea patients
- Interim results are reported for the subpopulation with blood Phe and COAs assessed at baseline and at 24 weeks

Results

Patient disposition

- As of July 2020, 21 patients were enrolled in Phenom (including 4 adolescents), and 10 patients had completed 24 weeks of follow-up (including 2 adolescents); baseline demographics and characteristics are summarized in **Table 1**
- Of the 10 patients included in this analysis, 2 were <18 years old at baseline, with mean (SD) age of 16.8 (1.2) years, BMI 26.2 (4.2) kg/m^2, baseline blood Phe was 992.5 (5.0) µmol/L, and 1 (50%) female was on a Phe-restricted diet

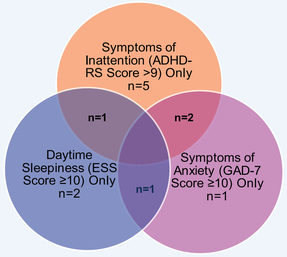
Table 1. Baseline characteristics

Characteristic	Patients with 24 weeks follow-up (n=10)	All patients (N=21)
Demographics		
Age at enrollment, mean (SD), years	33.1 (10.7)	32.7 (12.3)
<18 years at enrollment, n (%)	2 (20%)	4 (19%)
Sex, Female, n (%)	4 (40%)	10 (48%)
Race, White, n (%)	10 (100%)	21 (100%)
BMI, mean (SD), kg/m^2	33.3 (10.7)	30.6 (9.5)
Biomarkers and nutritional management		
Blood Phe, mean (SD), µmol/L	1144.1 (277.9)	1159.4 (301.6)
Blood tyrosine, mean (SD), µmol/L	58.9 (24.5)	51.8 (19.1)
On Phe-restricted diet[a], n (%)	1 (10%)	3 (14.3%)
Total protein intake, mean (SD), g	90.6 (39.6)	69.6 (39.4)
Protein intake from intact food, mean (SD), g	48.7 (25.0)	42.1 (26.0)
Clinical outcomes		
Symptoms of inattention[b], yes/total assessed (%)	3/8 (37.5%)	8/18 (44.4%)
Symptoms of anxiety[c], yes/total assessed (%)	2/8 (25%)	4/15 (26.7%)
Daytime sleepiness[d], yes/total assessed (%)	1/8 (12.5%)	4/16 (25.5%)

[a]Participants were considered on restricted diet if >75% of total protein intake was from medical food. [b]ADHD-RS IV IA raw score >9. [c]GAD-7 raw score ≥10. [d]ESS raw score ≥10.

- Of the 21 patients enrolled, clinically significant symptoms of inattention, sleepiness or anxiety reported at baseline occurred in 12 (57.1%) participants (**Figure 2**)

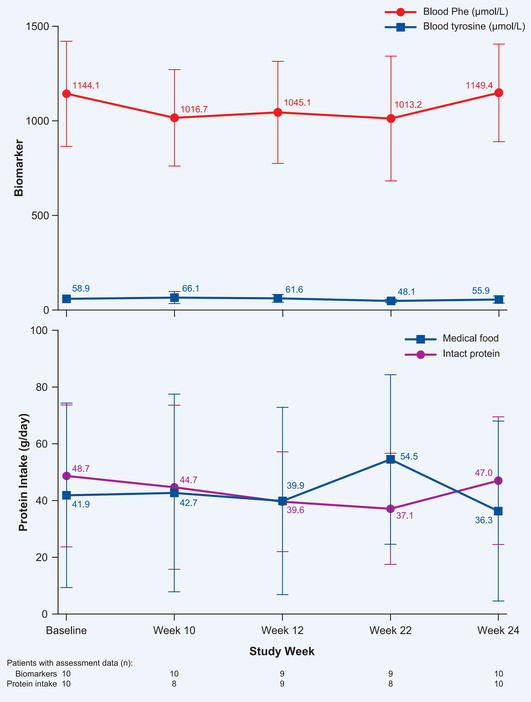
Figure 2. Venn diagram of the distribution of patients who reported clinically significant symptoms of inattention, anxiety or sleepiness at baseline



Biomarkers & nutritional management

- Mean (SD) blood Phe remained elevated and stable over time, with 1144 (278) µmol/L at baseline and 1149 (258) µmol/L at 24 weeks (**Figure 3**)

Figure 3. Biomarkers and nutritional management over time

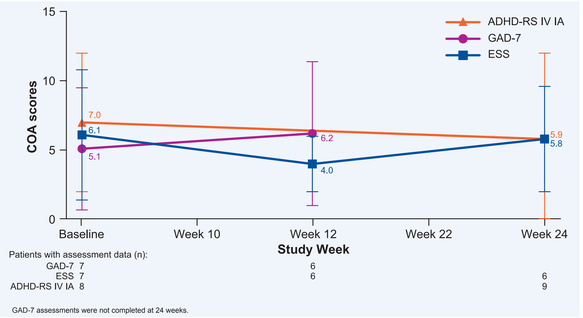


- Mean (SD) protein intake from intact food remained consistent over time, with 48.7 (25.0) g at baseline and 47.0 (22.5) g at 24 weeks (**Figure 3**)

Clinical outcome assessments

- Symptoms of inattention, anxiety, and daytime sleepiness were consistent over time (**Figure 4**)

Figure 4. Clinical assessments over time



GAD-7 assessments were not completed at 24 weeks.

Conclusions

- Baseline demographics appear to be in line with previous clinical programs designed to treat adults with PKU who are above guideline levels on dietary management
- Clinical outcome assessments show the heterogeneity of symptoms in patients with PKU with symptoms of inattention, generalized anxiety and daytime sleepiness observed in a proportion of patients at baseline, including several patients with multiple symptoms at baseline with individual scores varying over time
- In addition, the key endpoint (blood Phe) remains stable over time
- Results from this prospective study will provide robust insights into the clinical impact of uncontrolled Phe and the most appropriate tools to assess the symptoms or burden of PKU in adolescent and adult patients

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Acknowledgements

The authors would like to thank the study investigators, study coordinators, study site support staff, and study participants. Medical writing support was provided by Gillian Clague (BioMarin). Poster design was provided by Terry Manspeaker (Show Your Science, LLC).

Disclosures

COH has received grants and consulting fees from BioMarin. TG has received honorarium as a DSB member. HHW, AS, DN, RB, and KG are employees of BioMarin. DA has received speaker fees and research grants from BioMarin. AS-V has received consulting fees from and participated as a clinical trial investigator for BioMarin. JV declares no conflicts of interest.

Presented at the ACMG Annual Clinical Genetics Meeting: April 13–16, 2021