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A prospective clinical study on the clinical impact of phenylketonuria in adolecents and adults: Phenom study design

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Background

- Phenylketonuria (PKU) is an autosomal recessive disorder, characterized by a complete or profound 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]

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®)
- recently 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)[6,7] on existing treatment

- Even with currently available treatments, there is an unmet medical need, as all current therapeutic options have a burden of lifelong treatment
- As Phe is ubiquitous in natural foods, a Phe-restricted diet (with or without sapropterin) is onerous and has limited long-term efficacy
- The majority of adolescent and adult PKU patients managed with diet are unable to sustain guideline-recommended Phe levels[6]; notably, the upper limits of guideline-recommended Phe levels are 3–5 times the upper limit of normal physiology
- Although patients treated with pegvaliase have shown substantial and sustained reductions in Phe, it requires daily subcutaneous injections for the remainder of the patient's life
- Though not yet robustly characterized, current evidence suggests that the clinical consequences of dietary management and poor Phe control in adolescents and adults with PKU are broad and significant, including negative effects on neuropsychological outcomes, such as neurocognition, executive function, and quality of life (**Figure 1**)
  - A recent concept elicitation study with PKU patients and PKU-treating clinicians found that the key clinical issues reported by PKU patients are attention (67% of PKU patients), processing information (47%), and memory (50%)[8]
  - Similarly, PKU-treating clinicians reported attention (100% of clinicians), memory (88%), and organization and planning (75%) as key concepts impacting PKU patients[9]
- Further research is needed to better understand the clinical consequences of high Phe to inform clinical monitoring and the development of future treatment options for patients with PKU, such as BMN 307, an adeno-associated viral gene therapy
- Herein we report the design of Phenom (307-902), an observational study in adolescent and adult patients with PKU designed to measure markers of disease and clinical outcomes over a period of up to 96 weeks

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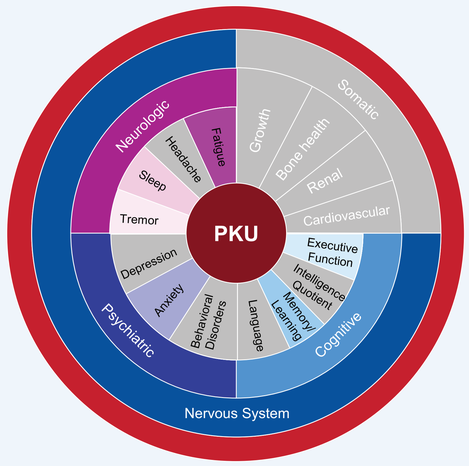
Figure 1. Key clinical issues identified by PKU patients and clinicians



Methods

Participants

- Phenom will enroll up to 90 participants ≥14 years of age who have been diagnosed with PKU
- Inclusion criteria include a screening plasma Phe level >600 µmol/L, and no current pharmacotherapy to treat PKU

Clinical Measures

- The clinical measures in Phenom were carefully selected in collaboration with PKU patients, providers, and advocates in the PKU community with the goal to robustly characterize clinical outcomes in adolescents and adults with PKU, while minimizing participant and site burden

Figure 2. Clinical measures

Biomarkers and Nutritional Management Assessments
- In line with standard PKU management and to build a robust database for comparison with existing or future PKU therapies, participants will have routine blood draws throughout the study to assess the following biomarkers:
  - Plasma Phe
  - Plasma Tyrosine
  - Blood nutritional markers, such as 25-hydroxy (OH) Vitamin D and methylmalonic acid (indicator of vitamin B-12 deficiency)
- Similarly, an established measurement tool will be used to assess participants' protein intake from natural sources and medical foods:
  - Diet Diary

Characterization of the PKU Population
- To inform the development of future gene therapies the following will be collected:
  - PAH genotype
  - Adeno-associated viral seroprevalence

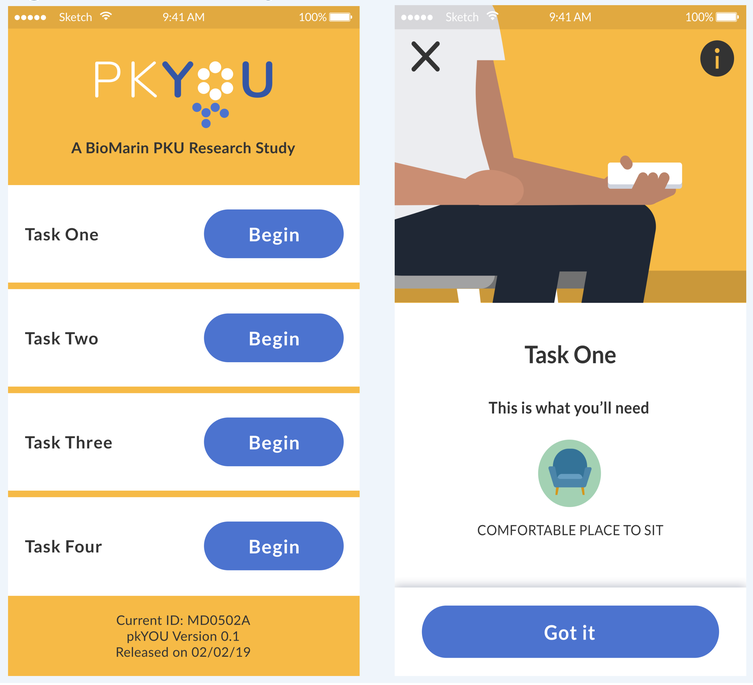
Clinical Outcomes
- Periodic in-clinic assessments will be conducted to measure the clinical outcomes that PKU patients, providers, and advocates identified as most significant to PKU patients, including:
  - Inattention
  - Difficulty processing information
  - Poor memory
  - Anxiety
  - Fatigue

Mobile health (mHealth)
- Using a mobile phone in combination with a wearable heart rate and actigraphy monitoring device, clinical outcomes will be assessed weekly in a real-world setting. Outcomes assessed will include:
  - Inattention
  - Processing information
  - Working memory
  - Tremor
  - Sleep

The mHealth platform

- Historically, measuring the impact of PKU in an adolescent or adult's life is challenging, as clinical symptoms are broad and heterogeneous across PKU patients and clinical symptoms can wax and wane over time
- In partnership with an app developer and PKU patients, mHealth (**Figure 3**) has been developed for Phenom to address this gap
- The platform was developed to make completing assessments easier for both the patient and the clinical site, and to allow for more frequent assessments in the real world to better characterize the fluctuation of symptoms over time

Figure 3. User-friendly interface of the mHealth platform



Conclusions

- This study will help to address the current gap in understanding the clinical impact of uncontrolled blood-Phe in adolescents and adults with PKU, the fluctuation in severity of symptoms over time, and explore the utility of novel technology and methods of measuring clinical outcomes in PKU patients
- Results from this 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
- As such, data collected in this study will be used in the development of future treatment options, as well as informing clinicians on effective ways to measure the status and progress of PKU patients over time

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