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OPAL: A multicenter, observational study to evaluate the real-world outcomes of pegvaliase in adults with phenylketonuria

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Background

- Phenylketonuria (PKU) is an inherited disorder of amino acid metabolism caused by deficiency of phenylalanine hydroxylase which normally converts phenylalanine (Phe) to tyrosine, resulting in chronically elevated blood Phe levels[1]
- Phe is toxic to the brain and tissues; to prevent developmental delay a Phe-restricted diet supplemented with Phe-free medical food is initiated upon diagnosis. Treatment is recommended throughout life to achieve optimal outcomes
- EU guidelines[1] recommend blood Phe levels be maintained between 120-600 µmol/L for patients ≥12 years of age; US guidelines[2] recommend an upper limit of 360 µmol/L for all ages; however, many adults with PKU (AwPKU) are unable to achieve sustained Phe reduction with dietary management
- Pegvaliase is a blood Phe lowering enzyme substitution therapy approved for AwPKU with Phe >600 µmol/L[3] (>16 years in EU)[4]
- The safety and efficacy of pegvaliase was demonstrated in the Phase 3 PRISM program[5,6]; further insight on the real-world usage and associated patient outcomes is needed
- Herein we describe OPAL, a currently enrolling Phase 4 multicenter observational study evaluating outcomes in AwPKU on pegvaliase from routinely collected data and describe the participants enrolled to date

Methods/Study design

- OPAL is currently open to enrollment in Germany, with additional country activations pending in Italy and US and a planned enrollment of up to 100 participants
- The objectives of the study are to evaluate outcomes of pegvaliase use in a real-world clinical setting **(Table 1)**

Table 1. OPAL objectives

Primary Objective
To evaluate outcomes achieved with pegvaliase in a real-world setting as measured by blood Phe level over time
Secondary Objectives
To describe the dosing intervals and dosing of pegvaliase in each phase of treatment and the length of the titration phase
To describe the reported medical nutritional therapy (MNT) in each phase of treatment
To describe the relationship between changes in reported MNT and blood Phe level
To describe the co-medications of interest used in each phase of treatment, i.e., medications that prevent and control hypersensitivity reactions, medications that treat causes or symptoms of known comorbidities of PKU, psychiatric medications, and nutrient supplements
To describe the impact of blood Phe level on participants' wellbeing and health-related quality of life
To describe the impact of blood Phe level on socioeconomic parameters (partnership, employment, occupation)

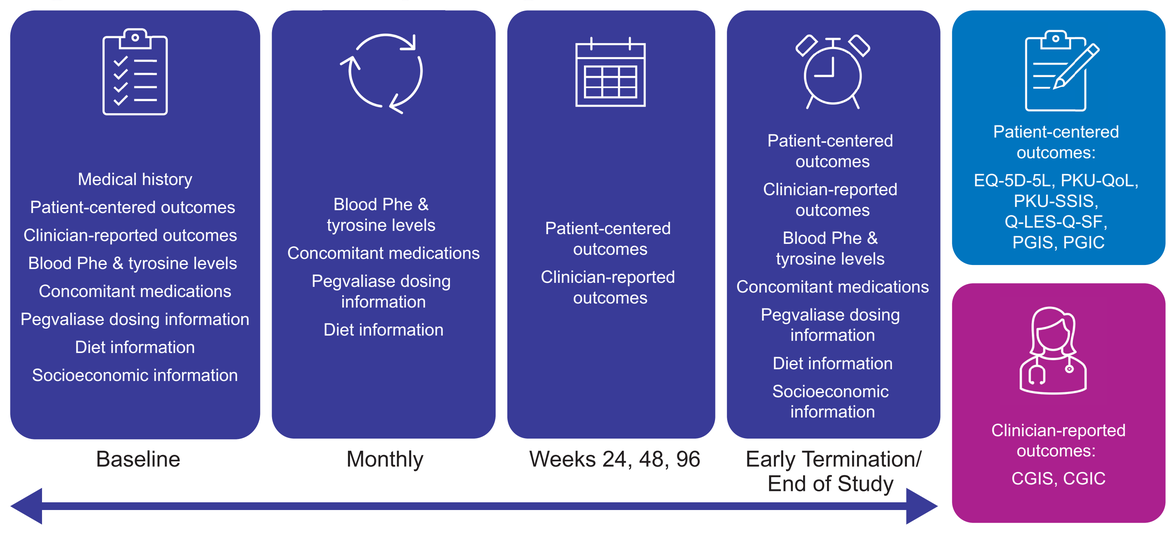
- Primary endpoints include: the distribution of blood Phe level at various timepoints; the mean change in Phe level from baseline over time, overall and stratified by baseline measures; the proportion of participants achieving blood Phe thresholds over time; the estimated value of blood Phe level at given timepoints, conditional on baseline blood Phe and other covariates
- Individuals with PKU are eligible to enroll if they are either currently receiving (Prevalent) or have been recommended to receive (Incident) pegvaliase with blood Phe >600 µmol/L **(Table 2)**

Table 2. OPAL key inclusion and exclusion criteria

Inclusion Criteria
Documented diagnosis of PKU per routine clinical practice
Planned to receive pegvaliase treatment as per the SmPC or currently receiving pegvaliase and has not reached controlled blood Phe levels (defined as blood Phe levels of >600 µmol/L, demonstrated by three recent consecutive blood Phe measurements), documented as part of their routine clinical care
Participant (or legally authorised representative for participants between 16 and 18 years of age) is willing and able to provide written informed consent after the nature of the study has been explained and prior to any data collection
Fluent in written and spoken local language
Exclusion Criteria
Legal incapacity or limited legal capacity without a legally authorised representative
Currently participating in an interventional study of any investigational product, device, or procedure

- After informed consent, the data elements of interest to be collected per local routine clinical practice include: PKU disease and treatment history; clinical outcome assessments, consisting of patient-centered outcomes and clinician-reported outcomes; laboratory assessments; dose and administration of concomitant medications and pegvaliase; and dietary data **(Figure 1)**. Descriptive statistics of the longitudinal repeated measures are planned

Figure 1. OPAL study design



CGIC, Clinical Global Impression of Change; CGIS, Clinical Global Impression of Status or Severity; EQ-5D-5L, 5 level EQ-5D; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Status or Severity; PKU, phenylketonuria; PKU-QoL, Phenylketonuria Impact and Treatment Quality of Life Questionnaire; PKU-SSIS, Phenylketonuria Symptom Severity and Impacts Scale; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form.

Results

- At the time of the interim data cut (December 2022), 26 Incident and 20 Prevalent participants had been enrolled in Germany. Baseline characteristics are shown **(Table 3)**

Table 3. Baseline characteristics

	Incident (n=26)	Prevalent (n=20)
Age (years), mean (SD)	32.2 (10.6)	27.8 (10.6)
Sex	38.5% Female	40.0% Female
Race	84.6% White	100.0% White
Blood Phe µmol/L, mean (SD)	1083 (287)	1027 (216)
PKU-QoL Overall Impact Score*, mean (SD) [n]	29.8 (19.5) [17]	26.4 (18.9) [14]

*PKU-QoL range 0-100, with higher scores indicating greater impact. Participants with available data prior to initiating treatment with pegvaliase were included.

Discussion/Conclusions

- Pegvaliase is an enzyme substitution therapy approved in EU for ages ≥16 and US for AwPKU who have blood Phe ≥600 µmol/L despite prior management with available treatment options
- The PKU-QoL measures aspects of disease burden and quality of life outcomes across domains relevant to PKU with higher domain scores indicating greater impact[7]
- The baseline average score for the PKU-QoL Overall Impact of PKU domain indicated moderate impact of PKU[8]
- The results of this ongoing study could provide meaningful insight into the real-world use of pegvaliase and help characterize patient outcomes associated with blood Phe reduction

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Conflicts of interest

FR and ACM have received consulting fees and travel support from BioMarin and are investigators on the OPAL study; ACM has received speaker fees from BioMarin. OS, SW, KG, and EK are employees and stockholders of BioMarin.

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