Investigating the patient-relevance of achieving blood Phe thresholds in PKU: Results from an analysis of the OPAL study

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Background

- Phenylketonuria (PKU) is characterized by chronic elevations of blood phenylalanine (Phe). Untreated patients with PKU can have Phe levels >1200 µmol/L, while the normal physiologic upper limit is ~120 µmol/L
- The objective was to investigate the patient-relevance of blood Phe reductions by exploring the association between blood Phe and patient-reported outcomes (PRO) in PKU

Methods

OPAL Study and Analysis

- A secondary analysis was conducted using an interim data cut (March 2024) of OPAL, an ongoing phase 4, multicenter, observational study assessing the real-world safety and effectiveness of pegvaliase
- Pegvaliase is an enzyme substitution therapy approved for the management of uncontrolled blood Phe (> 600 µmol/L) in adults (≥18 years in the USA; ≥16 years in the European Union)
- Blood Phe monitoring was recommended monthly (collected per local standard of care), and PRO data were collected at four visits: baseline, 24-, 48-, and 96-weeks post-baseline
- The PKU Symptom Severity and Impacts Scale (PKU-SSIS; psychometric validation ongoing) is a PKU-specific PRO employing a 7-day recall period. PKU-SSIS total score ranges from 0 to 100; higher scores indicate greater severity
- Analysis employed a linear mixed model predicting the PKU-SSIS total score from the study visit, the number of visits at which blood Phe was ≤120 µmol/L (0/4, 1/4, or 2/4 visits), and the interaction between those two main effects
  - Windowing: All blood Phe within PRO recall period averaged, where multiple blood Phe measurements were available
  - Marginal mean estimates of change from baseline (CFBL) were used to help interpret the interaction effects
  - Sensitivity analyses examined the effect of missing data (complete case and last observation carried forward [LOCF])

Results

Sample characteristics

- The baseline sample size, average blood Phe in µmol/L, and average PKU-SSIS total score are presented for this OPAL data cut **(Table 1)**

Table 1. Baseline descriptives

Variable	Statistic
Number of participants	48
Blood Phe* in µmol/L, mean (SD)	1010 (366)
PKU-SSIS total score, mean (SD)	31.6 (15.9)

*Baseline is defined as the median of blood Phe concentrations taken on enrollment day 1 or up to 6 months prior.

- Participant sample sizes stratified on number of visits with blood Phe ≤120 µmol/L are presented in **Table 2**. Post-baseline reductions in sample size were primarily due to the fact the study is ongoing

Table 2. Participant sample size per OPAL visit stratifying on # of visits blood Phe ≤120 µmol/L over trial duration

OPAL Study Visit	Number and proportion of participants, N (%), contributing per OPAL visit		
	0/4	1/4	2/4
Baseline	29 (100%)	13* (100%)	6 (100%)
Week 24	27 (93%)	13 (100%)	5 (83%)
Week 48	23 (79%)	10 (77%)	6 (100%)
Week 96	18 (62%)	8 (62%)	5 (83%)

*As an example, this cell indicates that from patients who achieved ≤120 µmol/L once over the four visits, 13 had data available at baseline

Mixed model results

- The blood Phe ≤120 µmol/L by study visit interaction was significant ($p < 0.05$), indicating that those achieving blood Phe ≤120 µmol/L post-baseline experienced more improvement in PKU-SSIS total score compared to those who did not ($p < 0.05$)

Estimated PKU-SSIS scores given blood Phe achievement

- Large improvements in PKU-SSIS were estimated when patients achieved blood Phe ≤120 µmol/L thresholds **(Figure 1)**
- The marginal means and 95% confidence intervals estimated for changes from baseline to week 96 were –4 (–8.7, 0.69), –11 (–15.0, –6.5), and –18 (–26.0, –9.6) points for those experiencing 0, 1, or 2 visits of Phe ≤120 µmol/L
- Results were maintained with sensitivity analyses (complete case and LOCF)
- When investigating within patients who achieved two visits with blood Phe stratified on four thresholds (1200, 600, 360, and 120), the greatest improvement in PKU-SSIS scores were seen when blood Phe ≤120 µmol/L was achieved **(Figure 2)**

Figure 1. Estimated PKU-SSIS changes as visits with blood Phe ≤120 µmol/L increase

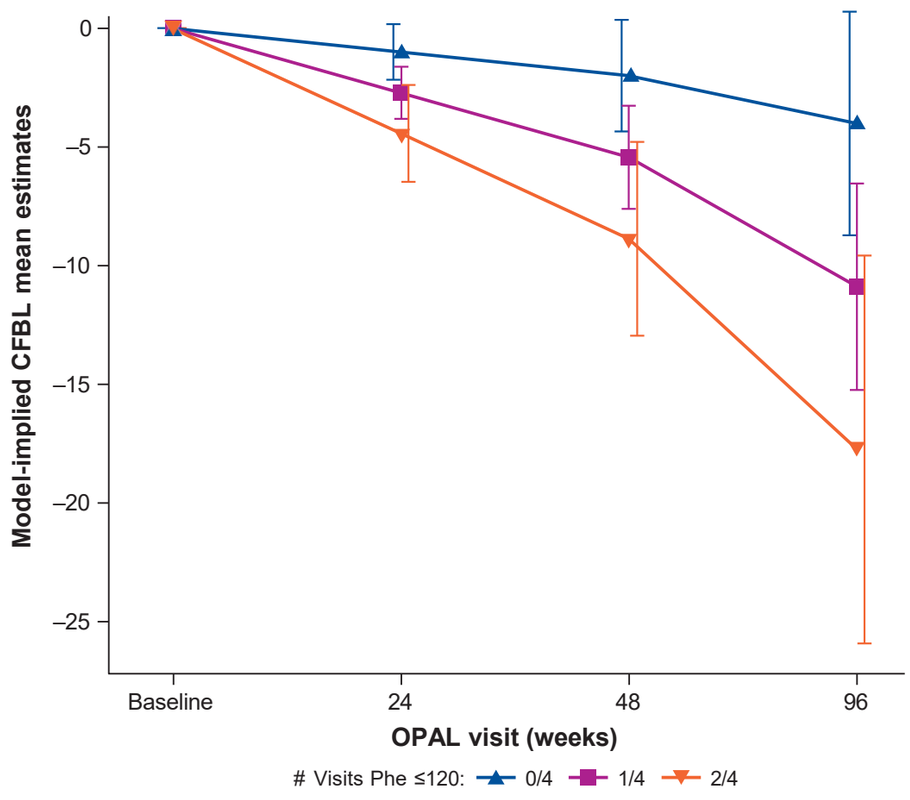
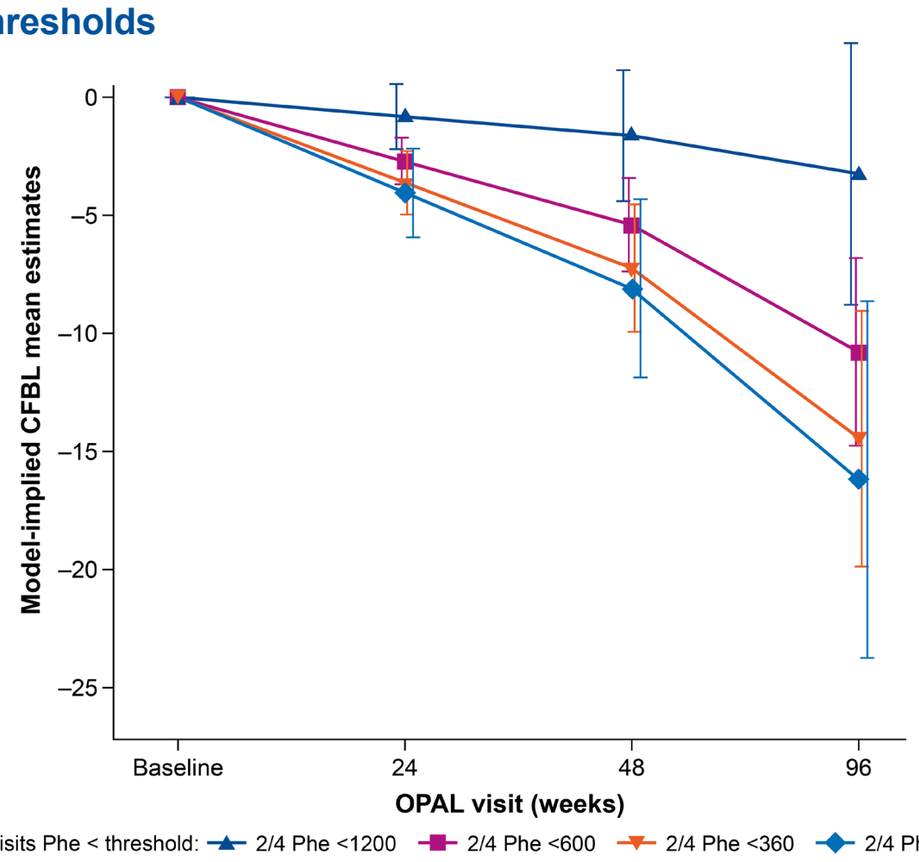


Figure 2. Estimated PKU-SSIS improvement across blood Phe thresholds



Conclusions

- This analysis demonstrates that pegvaliase-induced achievement of normal physiological blood Phe levels (Phe ≤120 µmol/L) results in significant improvements in patient-reported PKU symptoms and impacts

Disclosures

MK, DB, and PO are employees and shareholders of BioMarin Pharmaceutical Inc.; DS is founder of The Psychometrics Team which received funding for this research from BioMarin.

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