Improvements in blood phenylalanine and health-related quality of life outcomes among adults with PKU receiving pegvaliase in the OPAL study

McNutt M[1], Sazova O[2], Karimi M[2], Schwartz NRM[3], Rutsch F[4], Muntau AC[5]

[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]BioMarin Europe Ltd., London, UK; [3]BioMarin Pharmaceutical Inc., Novato, CA; [4]Department of General Pediatrics, Muenster University Children's Hospital, Muenster, Germany; [5]University Medical Center Hamburg-Eppendorf (corporation under public law), Hamburg, Germany

Background

- Phenylketonuria (PKU) is a rare, autosomal recessive disorder of amino acid metabolism characterized by chronic elevations of blood phenylalanine (Phe) that can lead to neuropsychological and cognitive impairment in adults[1,2]
- Despite medical nutritional therapy involving severe dietary restrictions, many patients with PKU struggle to maintain recommended blood Phe levels, impacting their quality of life[1,3]
- Pegvaliase is a blood Phe-lowering enzyme substitution therapy approved for adults (US) or patients aged ≥16 years (Europe) with PKU and Phe >600 µmol/L[1,3–5]
- OPAL is an ongoing, Phase 4, multicenter, observational study designed to assess the real-world safety and efficacy of pegvaliase in adults with PKU enrolled from sites in the US, Germany, and Italy
- Here, we present results from a second interim analysis of the OPAL study, and assess the real-world impact of pegvaliase treatment on blood Phe levels and health-related quality of life (HRQoL)

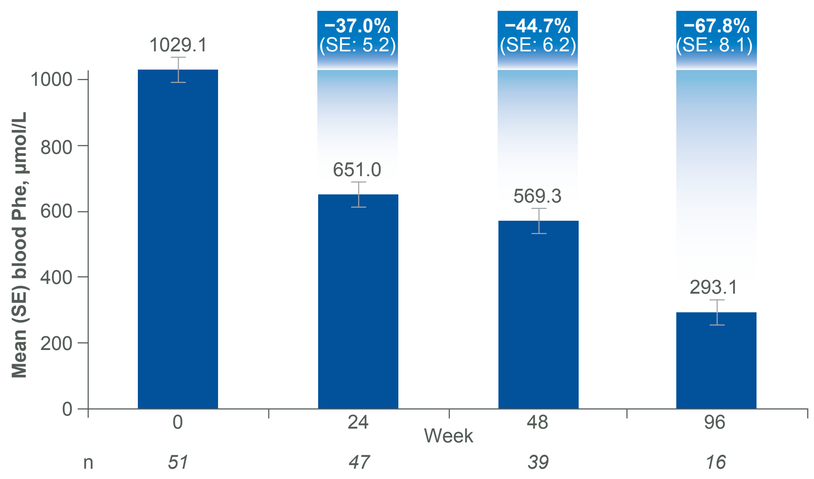
Methods

- Adults with PKU (aged ≥16 years) were eligible for inclusion in OPAL if they had blood Phe levels >600 µmol/L and were either currently receiving pegvaliase (prevalent population) or initiating pegvaliase at study enrollment (incident population)
- Blood Phe was collected at baseline and as part of routine clinical practice at each site (recommended once per month)
- The adult PKU Quality of Life (PKU-QoL) Questionnaire and PKU Symptom Severity and Impacts Scale (PKU-SSIS) were assessed at baseline and Weeks 24, 48, and 96
  - The PKU-QoL "Overall Impact of PKU" domain represents the emotional, practical, and social impact of PKU and was selected as the best representation of the impact of treatment on participants' HRQoL[6]
  - The PKU-SSIS is a content-validated, 22-item questionnaire comprising 6 domains; psychometric validation of the PKU-SSIS is ongoing[7]
- The OPAL modified full analysis set included participants who had a baseline Phe and screening/pre-study HRQoL assessments at enrollment and completed ≥24 weeks of the study at the time of the data cut (March 31, 2024)

Results

- 76 participants (48 incident, 28 prevalent) were enrolled at the time of the interim data cut, of whom 51 participants (29 incident, 22 prevalent) were included in the modified full analysis set (median duration of treatment [weeks]: 87.1 incident, 109.0 prevalent)
- Detailed safety information was not collected; 9 (11.8%) participants discontinued pegvaliase (treatment stopped, n=4; physician decision, n=1; withdrawal by participant, n=4)
- Mean age at study entry was 29.3 years, over half of study participants were male (58.8%), and most were White (92.2%); participants in the prevalent population had a numerically lower mean (SD) baseline blood Phe (994.3 µmol/L [240.2]) versus participants in the incident population (1055.6 µmol/L [274.4]) (**Table 1**)
- Blood Phe levels declined throughout the study; at Week 96, mean blood Phe in the overall population was reduced by nearly 70% compared with baseline (**Figure 1**)
- By Week 104, 70.6%, 58.8%, and 35.3% of the overall population (n=17) achieved blood Phe thresholds of ≤600, ≤360, and ≤120 µmol/L, respectively (**Figure 2**)
- HRQoL improved over follow-up, with reductions from baseline to Week 96 of –12.4 and –11.8 in PKU-QoL overall impact and PKU-SSIS total scores, respectively (**Figures 3,4**)

Figure 1. Overall mean blood Phe and percent change from baseline over time



SE, standard error.

Figure 2. Overall proportion of participants achieving clinically significant blood Phe thresholds

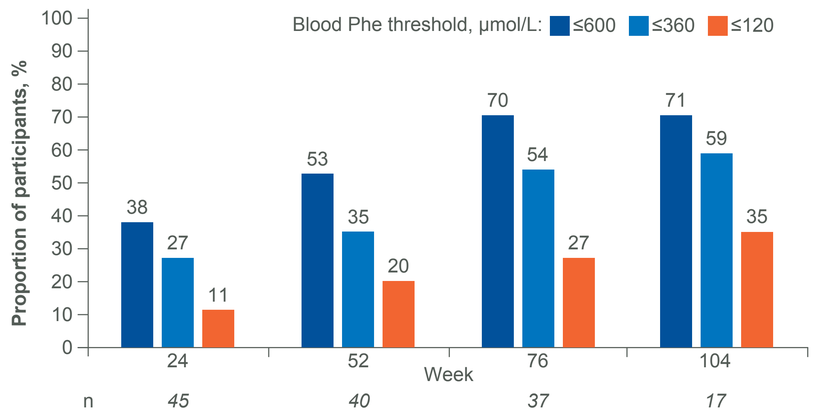
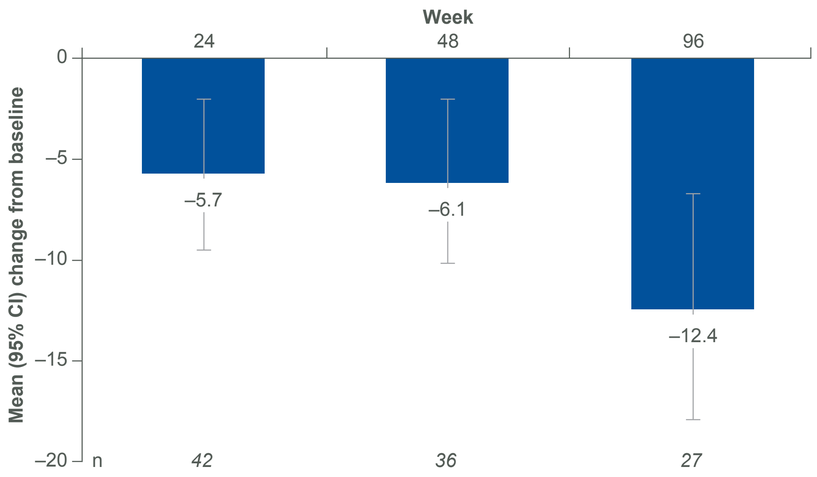
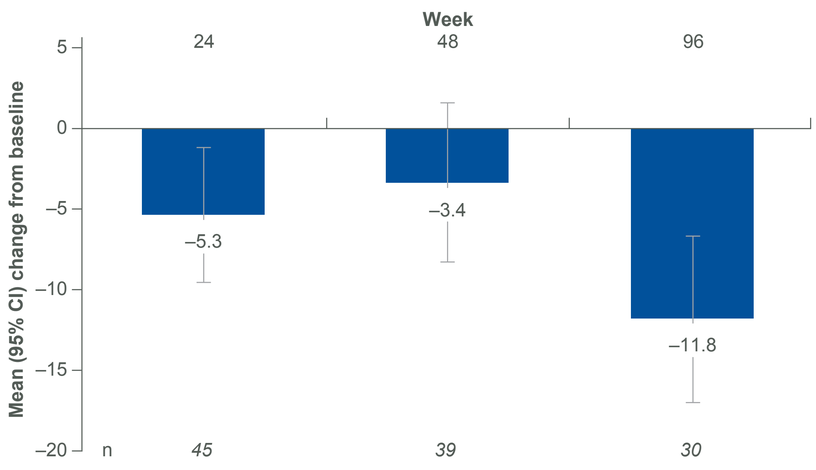


Figure 3. Mean change from baseline in PKU-QoL overall impact domain scores over time[a]



[a]Decrease in PKU-QoL overall impact scores indicates improvement.
CI, confidence interval.

Figure 4. Mean change from baseline in PKU-SSIS total scores over time[a]



[a]Decrease in PKU-SSIS scores indicates improvement.
CI, confidence interval.

Table 1. Baseline characteristics

	Overall (N=51)	Incident population (N=29)	Prevalent population (N=22)
Age at enrollment, years, mean (SD)	29.3 (11.0)	30.5 (11.9)	27.8 (9.7)
Female sex, n (%)[a]	21 (41.2)	12 (41.4)	9 (40.9)
Race, n (%)			
Asian	1 (2.0)	1 (3.4)	0
White	47 (92.2)	26 (89.7)	21 (95.5)
Other	1 (2.0)	1 (3.4)	0
Not reported	2 (3.9)	1 (3.4)	1 (4.5)
Blood Phe[b], µmol/L			
Mean (SD)	1029.1 (259.5)	1055.6 (274.4)	994.3 (240.2)
Median	1023.1	1071.0	976.1
PKU-QoL overall impact score[c], mean (SD)	29.0 (16.7)	27.9 (16.6)	30.7 (17.1)
PKU-SSIS total score[c,d], mean (SD)	31.8 (16.4)	32.5 (17.3)	31.0 (15.4)

[a]Binary response; "male" or "female." [b]Baseline is defined as the median of blood Phe concentrations taken on enrollment Day 1 or up to 6 months prior. [c]Scored from 0–100 higher scores indicate greater impact. [d]Validation work is ongoing and total scores are subject to change.
CI, confidence interval; SD, standard deviation; SE, standard error.

Conclusions

- Blood Phe reductions among participants treated with pegvaliase in the OPAL study were consistent with the Phase 3 PRISM clinical trial program results,[8] indicating translation of the Phe-lowering benefits of pegvaliase in real-world clinical practice
- These data provide novel evidence showing a positive real-world impact of pegvaliase treatment beyond blood Phe reduction, demonstrated by improvements in HRQoL (PKU-QoL and PKU-SSIS scores)
- Final results from the OPAL study will further advance the understanding of the impact of pegvaliase treatment in routine clinical practice

References

1. van Wegberg AMJ, et al. *Orphanet J Rare Dis.* 2017;12:162. **2**. Yin S, et al. *Mol Ther.* 2025;33(1):119–132. **3**. Smith WE, et al. *Genet Med.* 2025;27(1):101289. **4**. Palynziq (pegvaliase) [EU Product Information]. Shanbally, Ireland: BioMarin International Ltd. 2019. **5**. Palynziq [package insert]. Novato, CA: BioMarin Pharmaceutical Inc. 2020. **6**. Regnault A, et al. *Orphanet J Rare Dis.* 2015;10:59. **7**. Karimi M, et al. Poster #P029: Presented at ACMG 2025. **8**. Thomas J, et al. *Mol Genet Metab.* 2018;124(1):27–38.

Acknowledgments

The authors would like to thank the staff and investigators at each OPAL study site, as well as the participants in the study. Medical writing support for this poster was provided by Samuel Devereux, MPharm, of Adelphi Communications (Macclesfield, Cheshire, UK).

Disclosures

MM, FR, and ACM have received consulting fees and travel support from BioMarin and are investigators on the OPAL study. ACM and FR have received speaker fees from BioMarin. MK and NS are employees and stockholders of BioMarin. OS is a former employee and stockholder of BioMarin.

Funding

The OPAL study and the development of this poster were funded by BioMarin Pharmaceutical Inc.

Presented at the 39th ESPKU Meeting, Hamburg, Germany, September 25–28, 2025.