P034

Reduction of blood phenylalanine in participants enrolled in OPAL, an observational study, mirror findings from the US-based PRISM population

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Introduction

- Phenylketonuria (PKU) is an inborn error of amino acid metabolism characterized by chronic elevations of blood phenylalanine (Phe). Elevated Phe is toxic to the brain and tissues[1]
- While dietary management is historically the standard of care[1], Adults with PKU (AwPKU) are often unable to achieve and sustain guideline recommended blood Phe levels with this approach[2], creating an unmet need for treatment options that can reduce blood Phe
- US guidelines[3] recommend an upper treatment target of 360 µmol/L for all ages while European (EU) guidelines[1] recommend maintenance of blood Phe levels between 120-600 µmol/L for individuals with PKU ≥ 12 years of age
- Pegvaliase is a blood Phe lowering enzyme substitution therapy approved for AwPKU (≥18y in US[4]; ≥16y in EU[5]) with Phe ≥600 µmol/L, and adults (≥15y) in Japan[6]
- The safety and efficacy of pegvaliase is well characterized from the clinical trial program[7-9], but further insight on the ability to lower blood Phe in a real-world setting is needed
- OPAL is a currently enrolling Phase 4 multicenter observational study recruiting in Germany, the US, and Italy, with planned enrollment of 100 participants
- Herein we compare blood Phe reduction from a Phase 3 PRISM study cohort which most closely followed the labeled dosing schedule, to an interim analysis of patients enrolled from Europe (EU) in OPAL in the real-world setting

Methods

- AwPKU who are either currently receiving (Prevalent) or have been recommended to receive pegvaliase (Incident) with blood Phe ≥600 µmol/L are eligible to enroll in OPAL
- The OPAL modified full analysis set (mFAS) includes individuals who had a baseline Phe at enrollment and who were on study for at least 24 weeks at the time of the interim analysis in December 2022
- The US label maintenance dosing subgroup (n=118, referred to as the PRISM 118 population) is defined as individuals enrolled in PRISM with a baseline blood Phe ≥600 µmol/L who were randomized to and received at least 1 dose of pegvaliase 20 mg once daily, before titrating to higher maintenance doses
- Blood Phe was collected monthly in PRISM and as per local standard of care in OPAL

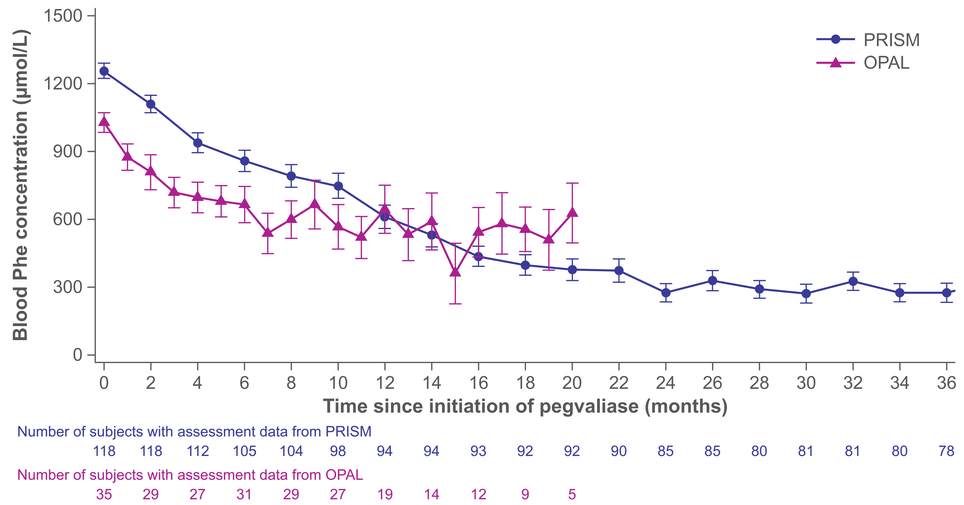
Results

- At the time of the interim data cut in December 2022, 26 Incident and 20 Prevalent patients had been enrolled in Germany with a mean ± SD age of 32.2 ± 10.6 and 27.8 ± 10.6 yrs respectively
- Baseline demographics of the OPAL mFAS and PRISM 118 population are reported in **Table 1**
- In the OPAL mFAS (n =35) mean ± SD Phe was 1055.9 ± 253.8 µmol/L at enrollment baseline. At 24 (n=31) and 52 (n=16) weeks of follow-up mean blood Phe was reduced to 665.5 ± 444.76 and 532.6 ± 456.81 µmol/L, respectively
- In comparison to the PRISM (n=118) population the mean blood Phe was 1269.8 ± 375.4 µmol/L at baseline and reduced to 886.8 ± 483 at 24 weeks of treatment (n=104) and 574.5 ± 539.7 at 52 weeks (n=86) in PRISM
- Mean Phe reduction of each population since initiation of pegvaliase is shown in **Figure 1**
- Duration of treatment and dosing information is reported in **Table 2**

Table 1. Baseline Demographics

	OPAL mFAS (n=35)	PRISM 118
Blood Phe, µmol/L (mean, SD)	1055.9 (253.8)	1269.8 (375.4)
Age at enrollment, years (mean, SD)	29.6 (10.5)	30.3 (8.8)
Sex (% female)	37.1%	47.5%
Race (% white)	97.1%	99.2%

Figure 1. Mean Phe Reduction PRISM 118 vs. OPAL mFAS



Study weeks in OPAL were converted to months to align with PRISM (divided by 4; 48 weeks = 12 months).

Table 2. OPAL Dosing information

		Overall (n=35)	Incident (n=17)	Prevalent (n=18)
Duration of treatment at IA-1, weeks	Mean (SD)	62.1 (42.4)	46.2 (25.9)	77.1 (49.7)
Dose (mg/day) at 24 weeks of follow-up	Mean (SD)	24.2 (8.8) (n=24)	24.2 (8.6) (n=12)	24.3 (9.3) (n= 12)
	Median	20.0	20.0	20.0
Dose (mg/day) at 52 weeks of follow-up	Mean (SD)	37.7 (13.8) (n=16)	38.3 (18.4) (n=6)	37.4 (11.42) (n=10)
	Median	40.0	35.0	40.0

Conclusions

- Early results from the first interim analysis of the OPAL mFAS demonstrate that pegvaliase produced substantial reductions in blood Phe levels. These effects in the real-world OPAL population are consistent with the US-based Phase 3 PRISM clinical trial program
- Future analyses are planned to explore the impact of blood Phe level on participant well-being and health related quality of life
- The results of OPAL will provide meaningful insight into the real-world use of pegvaliase

References

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Acknowledgements:

The authors would like to thank the OPAL & PRISM study sites and participants.

Disclosures:

MM, FR, and ACM have received consulting fees and travel support from BioMarin and are investigators on the OPAL study; ACM & FR have received speaker fees from BioMarin. OS, KG, SR, and MK are employees and stockholders of BioMarin.

Funding

The OPAL & PRISM studies and this poster were funded by BioMarin Pharmaceutical Inc.

Presented at the 2024 ACMG Annual Clinical Genetics Meeting: Mar 12–16, 2024, Toronto, ON, Canada

MMRC-PEG-P-00296