Achievement of a sustained Phe response in adolescents receiving pegvaliase in an interim analysis of PEGASUS

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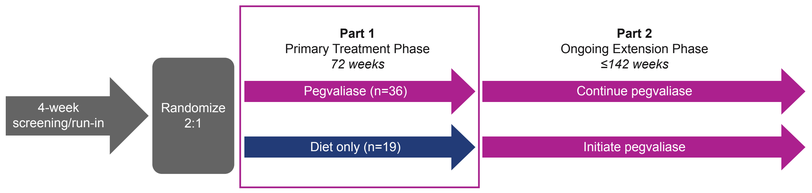
Background

- Phenylketonuria (PKU) is an autosomal recessive condition characterized by elevated blood Phe levels resulting from phenylalanine hydroxylase deficiency, which in the brain can lead to neurocognitive, behavioral, and psychiatric symptoms[1]
- Historically, PKU has been managed with medical nutrition therapy (MNT; including a Phe-restricted diet, medical food, and supplements)[1]
  - However, individuals are often unable to achieve and sustain guideline-recommended blood Phe concentrations of ≤360 µmol/L with MNT alone[2,3]
- Adolescents with PKU face challenges including an increased risk of mental health disorders, anxiety and depression (even with satisfactory metabolic control), and MNT-heightened food-related anxiety[4,5]
  - These challenges may be due to the burden of living with a chronic condition and developmental vulnerabilities (eg, social pressures and hormonal changes)[5]
  - Social pressures and increased responsibility for self-management and independence during adolescence can also contribute to worsening adherence to MNT and blood Phe targets[4,6]
- Pegvaliase is an enzyme substitution therapy approved for adults and adolescents who have uncontrolled blood Phe >600 µmol/L on existing management[7]
- In the phase 3 PRISM clinical development program, many pegvaliase-treated adults with PKU achieved a sustained Phe response (SPR)[8–10]
- PEGASUS is an ongoing, phase 3, open-label, randomized controlled trial evaluating the safety and efficacy of pegvaliase in adolescents aged 12–17 years with PKU and blood Phe concentration >600 µmol/L (NCT05270837) (**Figure 1**)
  - Interim data showed a statistically significant, clinically meaningful reduction in blood Phe concentrations with pegvaliase compared with diet only,[11] leading to the recent US approval of pegvaliase for individuals aged ≥12 years[7]
- We describe the efficacy and safety of participants who achieved an SPR of ≤360 µmol/L (SPR≤360) during the primary treatment phase (Part 1) of PEGASUS

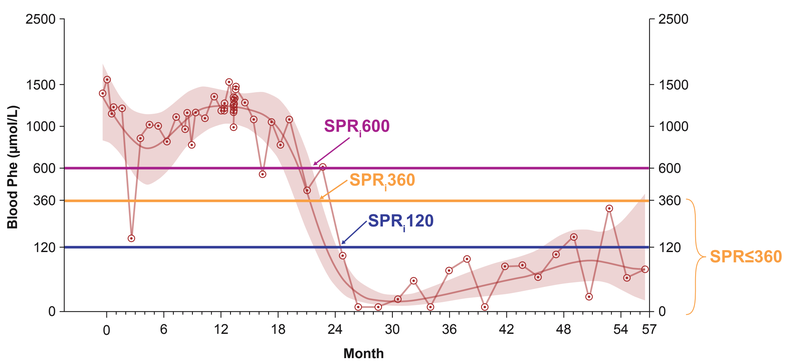
Methods

Figure 1. PEGASUS study design



- Proportions of participants achieving blood Phe ≤600, ≤360, and ≤120 µmol/L by the end of Part 1 were evaluated using interim data (January 2025 data cut-off)
- For each participant, an individual-level longitudinal pattern using all serial blood Phe measurements was described with a nonparametric smoothing function
- SPR was considered achieved when the upper bound of a 95% confidence band of blood Phe levels (representing the range of plausible expected values of blood Phe) was below each Phe threshold at a given point in time; initial achievement of SPR was defined as SPR_I (**Figure 2**)[10]
- Changes from baseline to week 72 in blood Phe, intact protein intake, and medical protein intake were evaluated in participants achieving SPR≤360
- Event rates of the most common adverse events (AEs) and AEs of special interest were analyzed

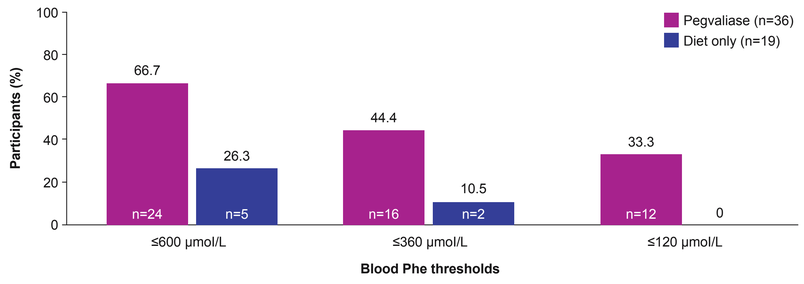
Figure 2. Example of achievement of SPR in an individual PRISM participant



Results

- Among the 36 pegvaliase-treated participants, 24 (66.7%) achieved ≥1 clinically relevant blood Phe threshold during Part 1
- Proportionally more participants receiving pegvaliase than those treated with diet only achieved ≥1 clinically relevant blood Phe concentration threshold during Part 1 (**Figure 3**)

Figure 3. Participants achieving blood Phe thresholds at any point[a]



[a]During Part 1 (intention-to-treat population).

- In the pegvaliase arm, 13 participants achieved SPR≤360 (**Table 1**)
  - No participants in the diet-only arm achieved SPR≤360
- Most (81.3%) pegvaliase-treated participants who achieved a single Phe level ≤360 µmol/L at any point went on to achieve SPR≤360
- Time to first achievement of SPR≤360 ranged from 2 to 16 months
- 8 (61.5%) participants achieved SPR≤360 on doses ≥40 mg/day, and 5 (38.5%) did so on doses of ≤20 mg/day
- Safety profiles were similar between participants achieving SPR≤360 and the overall pegvaliase-treated group, although AE rates were slightly lower in those achieving SPR≤360
- Among participants achieving SPR≤360, rates of common AEs decreased from induction/titration to maintenance:
  - Injection site reactions: 16.3 to 1.3/person-year
  - Arthralgia: 3.3 to 0.4/person-year
  - Hypersensitivity reactions (HSRs): 0.7 to 0.2/person-year
- No participants achieving SPR≤360 experienced anaphylaxis/acute systemic HSR
- In the SPR≤360 group, hypophenylalaninemia was experienced by 4 participants (0.5/person-year) during induction/titration and 8 participants (0.8/person-year) during maintenance

Table 1. Summary of participants who achieved SPR≤360 µmol/L

Participants in pegvaliase arm	n=36
Phe ≤360 µmol/L by database lock, n (%)	16 (44.4)
SPR≤360, n (%)[a]	13/16 (81.3)
Participants who achieved SPR≤360	**n=13**
Mean time to achievement of SPR≤360, months (range)	**10.2 (2, 16)**
Achievement of SPR≤360 by dose (mg/day), n (%)	
10	1 (7.7)
20	4 (30.8)
40	7 (53.8)
60	1 (7.7)
Blood Phe, µmol/L (range)	
Mean at baseline	860.7 (635.3, 1201.3)
Mean at end of Part 1[b]	165.2 (9.5, 473.5)
Mean change from baseline[b]	**−695.5 (−1132.8, −270.5)**
Percentage change	**−79.9%**
Intact protein, g/kg/day (range)	
Mean at baseline	0.21 (0.08, 0.47)
Mean at end of Part 1[b]	0.68 (0.09, 1.47)
Mean change from baseline[c]	**+0.47 (−0.03, 1.17)**
Percentage change	**+240.4%**
Medical protein, g/kg/day (range)	
Mean at baseline	0.87 (0.25, 1.49)
Mean at end of Part 1[b]	0.53 (0.0, 1.29)
Mean change from baseline[c]	**−0.34 (−1.27, 0.49)**
Percentage change	**−41.8%**

[a]Percentage based on the number of participants who achieved blood Phe ≤360 µmol/L by database lock (n=16). [b]Blood Phe at end of Part 1 was defined as the average of weeks 69 and 73 to reduce visit-level variability and provide a stable estimate of treatment effect. [c]Dietary changes were allowed in Part 1 for participants who experienced hypophenylalaninemia (blood Phe <30 µmol/L on 2 consecutive measurements), allowing protocol-directed adjustments in protein intake.

Clinical insights

- Visualization of clinical data from individual participants achieving SPR≤360 provided insights into the range of responses to pegvaliase and how different dosing strategies achieved Phe control and dietary liberalization (**Figure 4; Supplemental Material**)

Figure 4A. An early response to pegvaliase, which was sustained when reduced to a maintenance dose of 10 mg/day; the participant achieved substantial dietary liberalization without losing Phe control, even with a reduced maintenance dose of pegvaliase

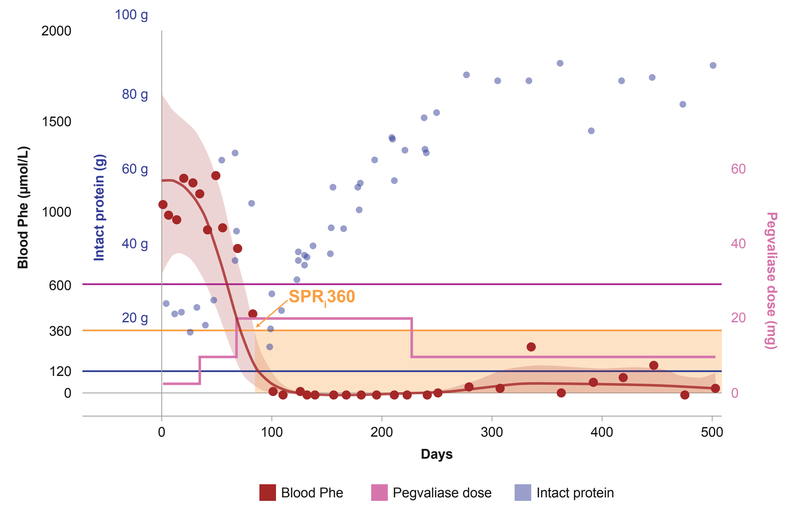
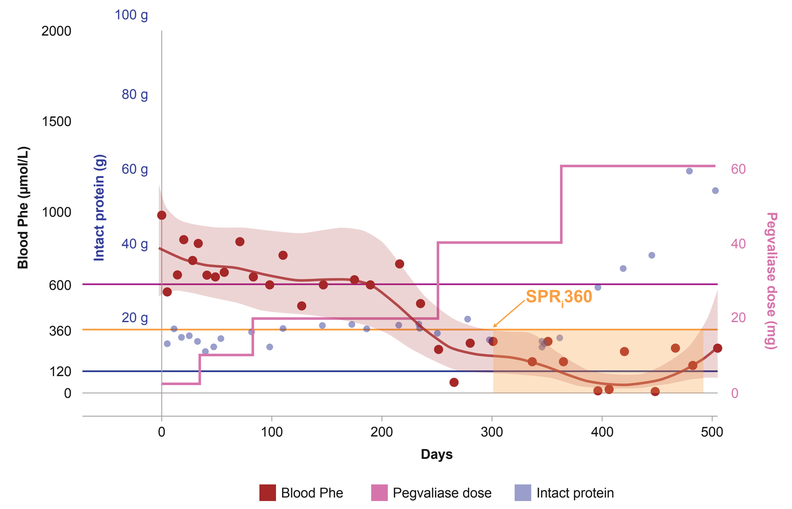


Figure 4B. A persistent treatment course and titration up to a dose of 60 mg/day may be required to achieve tolerization and reach target blood Phe levels; nevertheless, SPR and subsequent dietary liberalization were still achievable with continued adherence to pegvaliase treatment



Conclusions

- These interim results from PEGASUS identified adolescents who had clinically significant reductions in blood Phe concentration and achieved SPR≤360 with pegvaliase, and who were therefore able to increase their intact protein intake and decrease reliance on medical food
- Time to SPR≤360, dose levels, and safety profile were consistent with those in the adult PRISM trials[8–10]
- Although some participants had not yet responded to pegvaliase at the time of this interim analysis, these findings highlight the potential of pegvaliase to manage blood Phe in the adolescent population
- The ongoing extension phase of PEGASUS will further characterize the efficacy and safety of pegvaliase in adolescents with PKU

References

1. van Spronsen FJ, et al. *Nat Rev Dis Primers.* 2021;7(1):36. **2.** Burton BK, et al. *Mol Genet Metab.* 2024;141(1):108114. **3.** Rocha JC, et al. *Nutrients.* 2023;15(18):3940. **4.** Burton BK, et al. *Mol Genet Metab.* 2022;137(1-2):114–126. **5.** Pinto A, et al. *Nutrients.* 2025;17(21):3409. **6.** Jurecki ER, et al. *Mol Genet Metab.* 2017;120(3):190–197. **7.** PALYNZIQ (pegvaliase-pqpz). Prescribing information. BioMarin Pharmaceutical Inc.; 2026. **8.** Thomas J, et al. *Mol Genet Metab.* 2018;124(1):27–38. **9.** Harding CO, et al. *Mol Genet Metab.* 2018;124(1):20–26. **10.** Harding CO, et al. *Mol Genet Metab Rep.* 2024;39:101084. **11.** Sacharow S, et al. Oral presentation at ICIEM 2025; September 2–6, 2025.

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Disclosures

SS, TAB, ML, ACM, HN, SO, CP, EV, NW, and JV have participated as investigators for BioMarin Pharmaceutical Inc. clinical trials. SS, ACM, and EV have received consulting payments, speaker fees, and travel costs from BioMarin Pharmaceutical Inc. SS has also received research grants from BioMarin Pharmaceutical Inc. ML has received consulting payments and travel costs from BioMarin Pharmaceutical Inc. NW has received consulting fees from BioMarin Pharmaceutical Inc. DB, K-MC, DL, KL, and NRMS are employees and shareholders of BioMarin Pharmaceutical Inc. JFR was an employee of BioMarin Pharmaceutical Inc. at the time of the analysis.

Abbreviations

AE, adverse event; **HSR**, hypersensitivity reactions; **MNT**, medical nutrition therapy; **Phe**, phenylalanine; **PKU**, phenylketonuria; **SPR**, sustained Phe response; **SPR_I**, initial achievement of sustained Phe response.

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Supplemental Information

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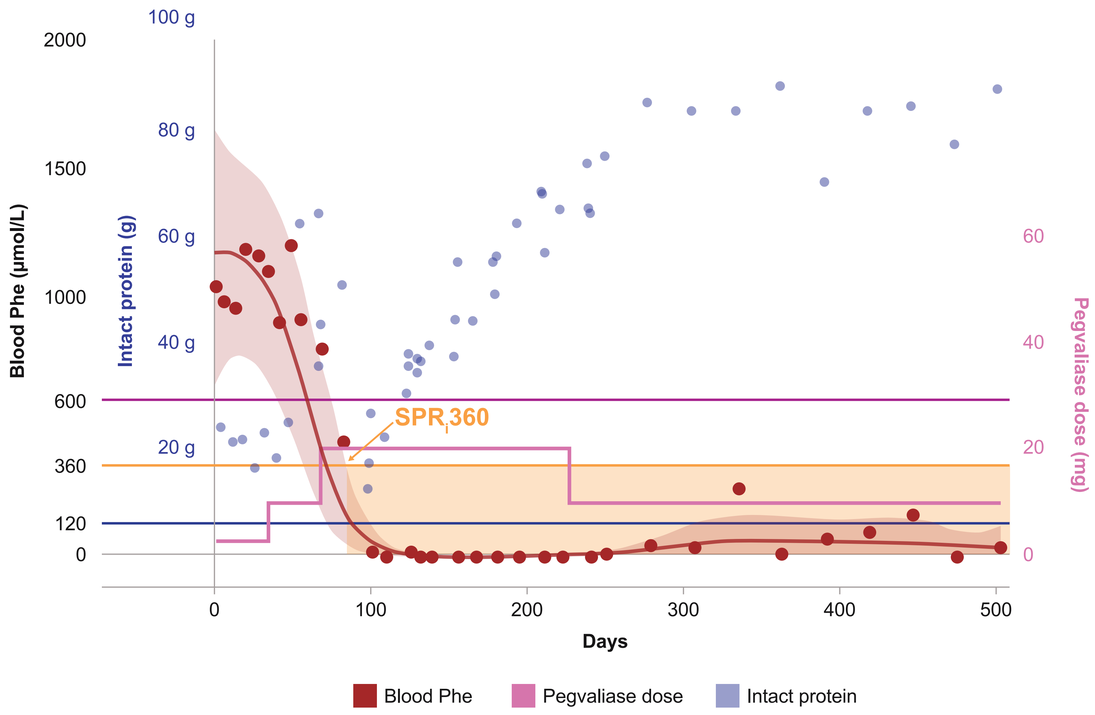

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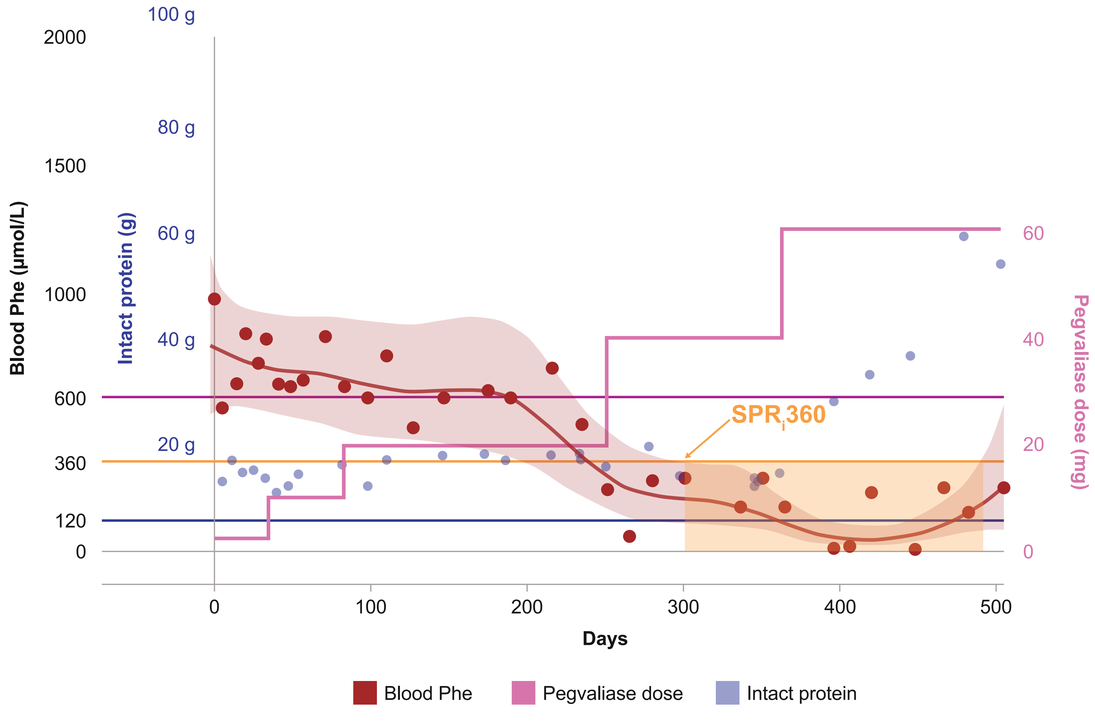

Figure 4C. After achieving SPR≤360, a dose increase allowed for sufficient pegvaliase exposure to liberalize dietary intake while maintaining SPR

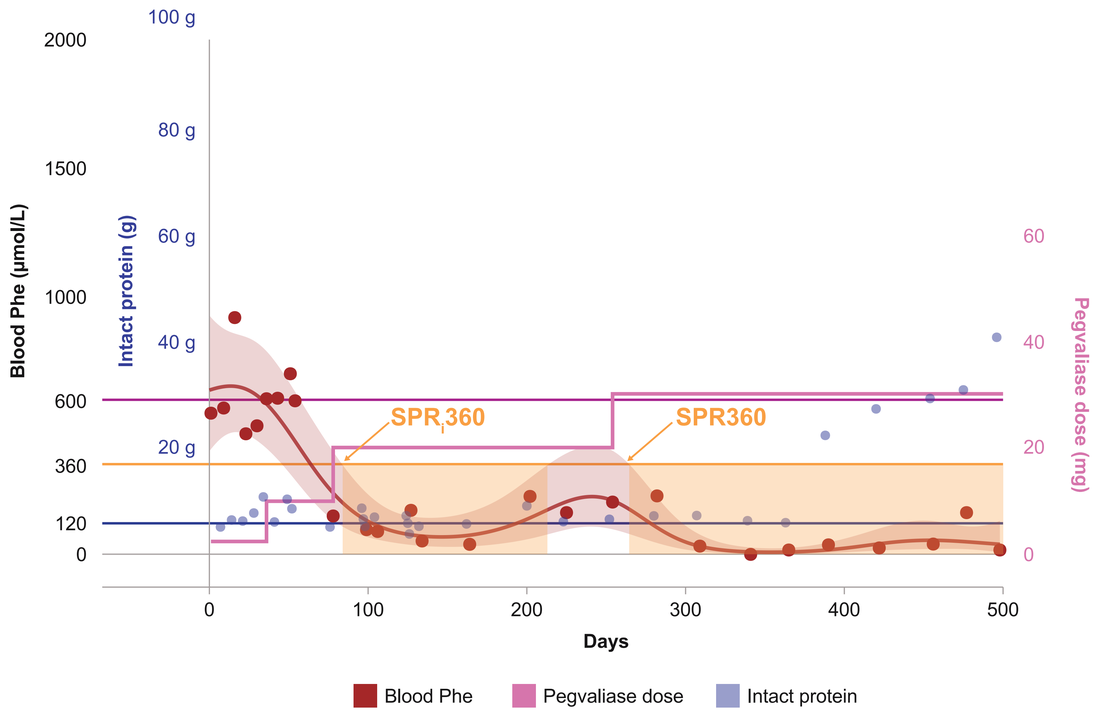

Figure 4D. Fluctuations in blood Phe can occur on the path to tolerization; an initial drop in Phe to ≤360 µmol/L may not be sustained, and higher doses may be needed to achieve SPR