Efficacy and safety of pegvaliase in adolescents with phenylketonuria: Interim results from PEGASUS part 2

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Introduction

- Phenylketonuria (PKU) is an autosomal recessive condition characterized by elevated blood phenylalanine (Phe) levels that can lead to neurocognitive, behavioral, and psychiatric symptoms if left unmanaged[1]
- Blood Phe levels of ≤360 µmol/L are recommended for all individuals with PKU in the US; European guidelines recommend 120 to 600 µmol/L for adolescents aged 12 to 18 years[2,3]
- Pegvaliase, a subcutaneous enzyme substitution therapy, lowers blood Phe in adults with PKU[4,5]
- In PEGASUS (NCT05270837) part 1, the efficacy and safety of pegvaliase in adolescents with PKU (aged 12–17 years) were consistent with outcomes observed in adults, leading to the recent US Food and Drug Administration and European Medicines Agency approvals in this population[4,6,7]

Objective

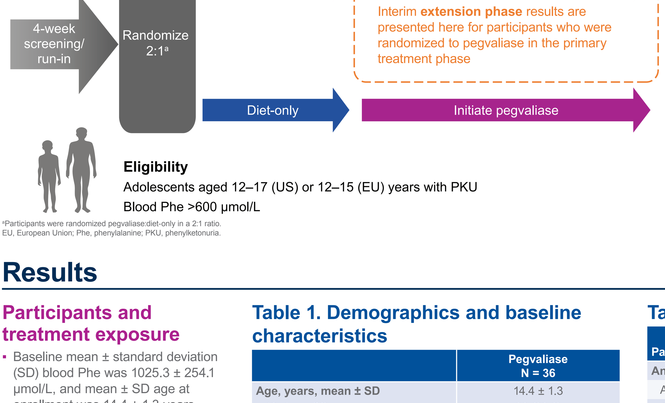
To evaluate long-term efficacy and safety data from adolescents with PKU randomized to pegvaliase based on an interim analysis of the extension phase (part 2) of PEGASUS

Methods

Study design

- PEGASUS is a 2-part, randomized (2:1), phase 3 study of efficacy and safety of pegvaliase vs diet-only in adolescents with a confirmed PKU diagnosis (**Figure 1**)
  - After 72 weeks (part 1), participants on diet-only transitioned to pegvaliase for the long-term extension (part 2)

Figure 1. PEGASUS study design



[a]Participants were randomized pegvaliase:diet-only in a 2:1 ratio.
EU, European Union; Phe, phenylalanine; PKU, phenylketonuria.

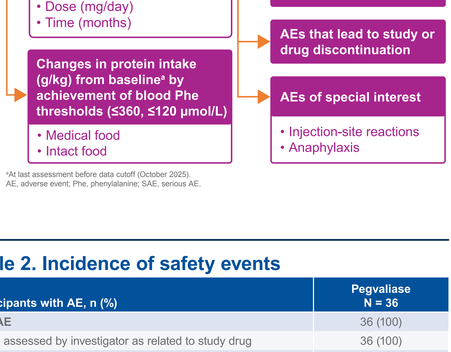
Analysis population

- Only participants initially randomized to pegvaliase in part 1 (N = 36) were included in this analysis

Endpoints

- We report interim part 2 summary efficacy and safety data from an October 2025 data cutoff date (**Figure 2**)

Figure 2. Analysis endpoints



[a]At last assessment before data cutoff (October 2025).
AE, adverse event; Phe, phenylalanine; SAE, serious AE.

Results

Participants and treatment exposure

- Baseline mean ± standard deviation (SD) blood Phe was 1025.3 ± 254.1 µmol/L, and mean ± SD age at enrollment was 14.4 ± 1.3 years (**Table 1**)
- At the October 2025 data cutoff, mean ± SD treatment duration was 27.6 ± 8.7 months

Safety

- Hypersensitivity was reported in 34 (94.4%) participants, injection-site reaction in 32 (88.9%), and arthralgia/arthritis in 28 (77.8%; **Table 2**)
- Three (8.3%) participants experienced anaphylaxis (National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria)
- AEs led to treatment and study discontinuation for 2 (5.6%) and 1 (2.8%) participants, respectively

Table 1. Demographics and baseline characteristics

	Pegvaliase N = 36
Age, years, mean ± SD	14.4 ± 1.3
12–15, n (%)	30 (83.3)
16–17, n (%)	6 (16.7)
Sex, n (%)	
Female	22 (61.1)
Male	14 (38.9)
Race, n (%)[a]	
White	30 (83.3)
Black or African American	2 (5.6)
Asian	1 (2.8)
Other[b]	0
Blood Phe concentration (µmol/L)	
Mean ± SD	1025.3 ± 254.1
Median (min, max)	996.0 (635.3, 1554.7)
Treatment duration, months	
Mean ± SD	27.6 ± 8.7
Median (Q1, Q3)	28.9 (26.8, 31.8)

[a]Not reported, n = 3.
[b]Other includes American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and Other.
Max, maximum; min, minimum; Phe, phenylalanine; Q, quartile; SD, standard deviation.

Table 2. Incidence of safety events

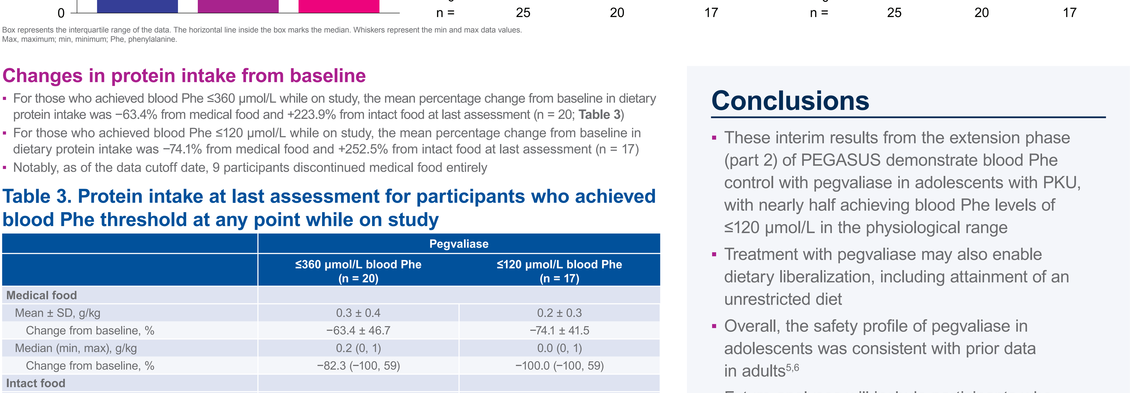
Participants with AE, n (%)	Pegvaliase N = 36
Any AE	36 (100)
AEs assessed by investigator as related to study drug	36 (100)
AEs leading to dose reduction	11 (30.6)
AEs leading to dose interruption	21 (58.3)
AEs leading to study drug discontinuation	2 (5.6)
AEs leading to study discontinuation	1 (2.8)
Any SAE	5 (13.9)
Most common (≥30%) AEs by preferred term	
Hypersensitivity	34 (94.4)
Injection-site reaction	32 (88.9)
Arthralgia/arthritis	28 (77.8)
Hypersensitivity reaction (US)	18 (50.0)
Injection-site skin reaction ≥14 days duration	17 (47.2)
Hypersensitivity reaction (EU)	16 (44.4)
Arthralgia (steroid treatment)	15 (41.7)
Neuropsychiatric disorder	15 (41.7)
Hypophenylalaninemia on a single measurement	14 (38.9)
Hypophenylalaninemia on 2 or more consecutive measurements	11 (30.6)

AE, adverse event; EU, European Union; SAE, serious AE.

Blood Phe ≤600, ≤360, and ≤120 µmol/L threshold achievement

- Blood Phe ≤600, ≤360, and ≤120 µmol/L was achieved by 25 (69.4%), 20 (55.6%), and 17 (47.2%) participants, respectively
- The median (quartile 1 [Q1], quartile 3 [Q3]) time to ≤600, ≤360, and ≤120 µmol/L threshold achievement was 1.2 (1.0, 11.1), 10.0 (6.7, 14.7), and 13.8 (10.1, 20.1) months, respectively (**Figure 3**)
  - The median (Q1, Q3) dose to reach ≤600 µmol/L blood Phe was 15.0 (2.5, 40.0) mg/day, and the median (Q1, Q3) dose to reach both the ≤360 and ≤120 µmol/L thresholds was 40.0 (20.0, 40.0) mg/day

Figure 3. A) Proportion of participants, B) median time, and C) median dose to achieve blood Phe thresholds



Box represents the interquartile range of the data. The horizontal line inside the box marks the median. Whiskers represent the min and max data values.
Max, maximum; min, minimum; Phe, phenylalanine.

Changes in protein intake from baseline

- For those who achieved blood Phe ≤360 µmol/L while on study, the mean percentage change from baseline in dietary protein intake was −63.4% from medical food and +223.9% from intact food at last assessment (n = 20; **Table 3**)
- For those who achieved blood Phe ≤120 µmol/L while on study, the mean percentage change from baseline in dietary protein intake was −74.1% from medical food and +252.5% from intact food at last assessment (n = 17)
- Notably, as of the data cutoff date, 9 participants discontinued medical food entirely

Table 3. Protein intake at last assessment for participants who achieved blood Phe threshold at any point while on study

	Pegvaliase	
	≤360 µmol/L blood Phe (n = 20)	≤120 µmol/L blood Phe (n = 17)
Medical food		
Mean ± SD, g/kg	0.3 ± 0.4	0.2 ± 0.3
Change from baseline, %	−63.4 ± 46.7	−74.1 ± 41.5
Median (min, max), g/kg	0.2 (0, 1)	0.0 (0, 1)
Change from baseline, %	−82.3 (−100, 59)	−100.0 (−100, 59)
Intact food		
Mean ± SD, g/kg	0.7 ± 0.4	0.8 ± 0.4
Change from baseline, %	223.9 ± 189.9	252.5 ± 191.1
Median (min, max), g/kg	0.6 (0, 2)	0.7 (0, 2)
Change from baseline, %	184.8 (3, 684)	234.3 (3, 684)

Max, maximum; min, minimum; Phe, phenylalanine; SD, standard deviation.

Conclusions

- These interim results from the extension phase (part 2) of PEGASUS demonstrate blood Phe control with pegvaliase in adolescents with PKU, with nearly half achieving blood Phe levels of ≤120 µmol/L in the physiological range
- Treatment with pegvaliase may also enable dietary liberalization, including attainment of an unrestricted diet
- Overall, the safety profile of pegvaliase in adolescents was consistent with prior data in adults[5,6]
- Future analyses will include participants who switched from diet-only to pegvaliase at the start of the extension phase

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Disclosures

KL is an employees and stockholder of BioMarin Pharmaceutical Inc. **AS-V** has received consulting fees from Acer Therapeutics, Applied Therapeutics, BioMarin Pharmaceutical Inc., Horizon, and Ultragenyx and has participated as a clinical trial investigator for Acadia, Alexion, Amicus, BioMarin Pharmaceutical Inc., Cerecor, Genzyme, Homology Medicines, Horizon, Kaleido Biosciences, Mallinckrodt, and Ultragenyx. **AA** has participated in advisory boards for BioMarin Pharmaceutical Inc. **JBH** has received travel support and/or honoraria from Amicus, Chiesi, Immedica, Sanofi, and Takeda. **JK** and **YAZ** have no declarations. **DB** and **NRMS** are employees and stockholders of BioMarin Pharmaceutical Inc. **K-MC** is an employee and potential stockholder of BioMarin (UK) Ltd. **JAT** has participated as a clinical trial investigator for BioMarin Pharmaceutical Inc., Homology Medicines, Sanofi, and Synlogic and as an advisory board member for BioMarin Pharmaceutical Inc.

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