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Evaluating trends in self-rated historic metabolic control and treatment history among PRISM participants

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Background

- Phenylketonuria (PKU) is caused by phenylalanine hydroxylase (PAH) enzyme deficiency resulting in elevated levels of phenylalanine (Phe) in the blood and tissues, which can be toxic to the brain[1]
- Current European and US guidelines[1,2] recommend lifelong maintenance of blood Phe levels within target range:
  - European guideline target range: 120–600 µmol/L for patients >12 years of age
  - American College of Medical Genetics (ACMG) guideline target range: 120–360 µmol/L for all patients
- The mainstay of PKU management is medical nutritional therapy (MNT), which severely restricts patients' natural protein intake to limit the consumption of dietary Phe, achieving total protein adequacy via addition of medical food rich in Phe-free protein
- Long-term metabolic control with MNT is difficult and worsens with age; most adults have Phe levels outside the recommended target range[3]
- Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase, is a subcutaneously administered enzyme substitution therapy approved to treat adults with PKU who have blood Phe >600 µmol/L on existing management[4,5]
- Pegvaliase works independently of PAH, and can lower Phe levels regardless of the amount of natural protein intake. This differs from the previously available pharmacologic therapy for PKU, sapropterin dihydrochloride, which relies on residual PAH activity and typically requires continuation of MNT for the 25-50% of PKU patients who are responders
- The objective of this exploratory analysis was to describe the self-reported PKU treatment history of participants in the phase 3 trials and their safety, efficacy, and disposition with long-term pegvaliase use

Methods

- Full methods of the phase 3 PRISM studies [PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862)] have been described previously.[6] In brief:
  - Pegvaliase-naïve participants with blood Phe >600 µmol/L were treated with pegvaliase for up to 274 weeks
  - Participants were required to maintain a consistent diet, with or without Phe-restriction, and to discontinue sapropterin
  - Blood Phe and dietary Phe were collected at the pre-pegvaliase baseline visit and at regular intervals; adverse events (AEs) were reported continuously throughout the study
  - The inattention subscale of the Attention Deficit Hyperactivity Disorder Rating Scale IV (ADHD RS-IV IA), a 9-item questionnaire with scores ranging from 0 to 27, was measured at baseline and throughout the study. Scores >9 were indicative of inattention
- As part of the phase 3 PRISM studies, the following data were collected to characterize the severity of the participant's PKU and degree of historical disease control:
  - Clinician-reported sapropterin responsiveness, defined as having a clinically significant decrease in blood Phe levels with >4 consecutive weeks of treatment with sapropterin (any dose) within 6 months of the PRISM-1 screening visit
  - Self-reported PKU history questions were developed by the sponsor based on input regarding clinical relevance to the patient population and included:
    - Highest lifetime blood Phe levels (highest level and age when this occurred)
    - How the participant categorized their overall lifetime metabolic control (excellent, good, poor, or none)
    - Age at which a low-Phe diet was discontinued (<6 years old, 6 to ≤12 years old, 13 to ≤19 years old, or 20 to 29 years old)
- In this analysis we report the descriptive summaries of the PKU history questionnaire. We also compare participants' self-reported PKU history to their outcomes in the phase 3 PRISM studies. Continuous variables are reported as mean and standard deviations; categorical variables include number of participants and percent. Tests for independence were conducted by T-test for continuous variables and Chi-square test for categorical variables

Results

- Of the 261 participants enrolled in the PRISM-1 trial, 241 completed at least one item on the PKU History Questionnaire and were included in this analysis
- Baseline mean blood Phe was higher in participants who reported worse historical metabolic control, discontinued diet at earlier ages, and met the definition of non-response to sapropterin compared to the overall population **(Table 1)**

Table 1. Baseline blood Phe by PKU Medical History Response

	n (%)	Baseline mean (SD) blood Phe, µmol/L
All PKU History Respondents	241 (100%)	1247.1 (384.8)
Lifetime metabolic control		
Excellent/Good	154 (64%)	1144.5 (348.8)
Poor/None	86 (36%)	1455.2 (370.9)
Highest lifetime blood Phe level, µmol/L		
<1200	52 (23%)	919.1 (252.8)
≥1200	176 (77%)	1346.7 (355.4)
Age of highest blood Phe, years		
<18	100 (44%)	1189.4 (369.8)
≥18	128 (56%)	1296.4 (384.7)
Discontinued low-Phe diet, if yes, age discontinued		
No, Never Discontinued Diet	107 (44%)	1079.3 (321.2)
Yes, Discontinued Diet	134 (56%)	1381.1 (379.9)
<6 years old*	12 (9%)	1545.8 (400.8)
6 to ≤12 years old	31 (23%)	1424.1 (433.1)
13 to ≤19 years old	67 (50%)	1370.9 (334.6)
20 to 29 years old	24 (18%)	1271.3 (402.7)
Sapropterin responder		
Yes	52 (27%)	1131.8 (363.7)
No	143 (73%)	1281.8 (375.9)

*Includes participants who were never on a Phe-restricted diet (n=2).

- There were statistically significant differences in baseline characteristics of participants who self-reported a lifetime metabolic history of "Excellent/Good" vs "Poor/None" **(Table 2)**

Table 2. Comparison of baseline characteristics and PKU history for participants who self-reported metabolic control as "Excellent/Good" vs "Poor/None"

Population characteristics		Excellent/Good (n=154)	Poor/None (n=86)	X^2	p
Age at enrollment, years	Mean (SD)	27.6 (7.6)	32.7 (9.8)		<0.0001
Sex	Female	66 (43%)	48 (56%)	3.7	0.055
	Male	88 (57%)	38 (44%)		
Baseline BMI, kg/m^2	Mean (SD)	27.7 (6.2)	29.4 (7.1)		0.055
Baseline blood Phe, µmol/L	Mean (SD)	1136.3 (348.8)	1443.7 (370.9)		
	<1200	90 (58%)	23 (27%)	22.3	<0.0001
	≥1200	64 (42%)	63 (73%)		
Baseline dietary Phe, mg	Mean (SD)	1510.9 (1104.1)	2084.1 (1285.0)		0.0005
Participants on Restricted Diet (>75% medical food)	No	120 (81%)	72 (90%)	3.4	0.06
	Yes	29 (19%)	8 (10%)		
Any medical food baseline	No	42 (28%)	50 (63%)	25.9	<0.0001
	Yes	108 (72%)	30 (27%)		
Baseline ADHD RS-IV inattention subscale score*	Mean (SD)	8.5 (5.8)	11.7 (6.2)		
	≤9	94 (63%)	33 (39%)	12.3	0.0005
	>9	55 (37%)	51 (61%)		
PKU History					
Lifetime highest Phe category, µmol/L	<1200	47 (32%)	5 (6%)	19.1	<0.0001
	≥1200	101 (68%)	75 (94%)		
Discontinued diet ever	Discontinued diet				
	No, never	94 (61%)	12 (14%)	48.5	<0.0001
	Yes	60 (39.0%)	74 (86%)		
Of those discontinued, age of discontinuation	<6 years old**	2 (3%)	10 (14%)		
	6 to ≤12 years old	8 (13%)	23 (31%)	15.5	0.0015
	13 to ≤19 years old	33 (55%)	34 (46%)		
	20 to 29 years old	17 (28%)	7 (10%)		
Sapropterin responder	No	84 (69%)	58 (79%)	2.3	0.127
	Yes	37 (31%)	15 (21%)		

n's change between questionnaire items due to missing data. *ADHD RS-IV, Attention Deficit Hyperactivity Disorder Rating Scale IV. Higher scores indicate higher degree of impairment. Scores ≥9 indicate clinically significant impairment. **Includes participants who were never on a Phe-restricted diet (n=2).

Pegvaliase outcomes

- There were no statistically significant differences in total months of pegvaliase exposure or disposition between participants reporting an "Excellent/Good" history of metabolic control compared to those with "Poor/None" **(Table 3)**

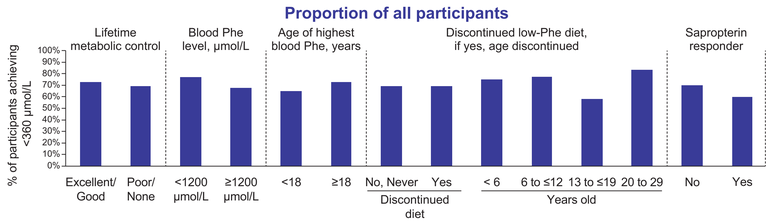
Table 3. Pegvaliase exposure and study disposition

Pegvaliase experience	Excellent/Good (n=154)	Poor/None (n=86)	X^2	p
Total pegvaliase exposure, months Mean (SD)	40.2 (22.9)	36.1 (25.0)		0.06
Disposition				
Completed PRISM-2	104 (68%)	50 (58%)	2.1	0.145
Discontinued early	50 (32%)	36 (42%)		
Reason for study drug discontinuation				
Adverse event	19 (38%)	13 (36%)		
Lost to follow-up	5 (10%)	4 (11%)		
Physician decision	4 (8%)	4 (11%)	4.4	0.349
Withdrawal by subject	12 (24%)	13 (36%)		
Other*	10 (20%)	2 (6%)		

*Other Includes: Pregnancy, protocol deviation, completion of PRISM-1 without entering PRISM-2.

Phe response

Figure 1. Proportion of all participants who achieved a blood Phe level <360 µmol/L by lifetime PKU History Response categories



Safety

- All participants experienced at least one AE while on pegvaliase. Most AEs were mild or moderate, and included hypersensitivity events, arthralgia, and injection site reactions. AE rates were similar across the spectrum of self-reported lifetime metabolic control **(Table 4)**

Table 4. Adverse events

Number of participants with event (%) Number of events (event rate per person-year)	Excellent/ Good (n=154)	Poor/ None (n=86)	All PKU History Respondents (N=241)
Total treatment exposure (person-years)*	456.6	223.1	680.0
AEs			
Any AE	154 (100.0%) 9926 (21.7)	86 (100.0%) 5610 (25.1)	241 (100.0%) 15583 (22.9)
AEs leading to study drug discontinuation	18 (11.7%) –	12 (14.0%) –	30 (12.4%) –
Any SAEs	32 (20.8%) 45 (0.10)	23 (26.7%) 35 (0.16)	55 (22.8%) 80 (0.12)
AEs of special interest/significance			
Hypersensitivity adverse event	149 (96.7%) 2192 (4.8)	83 (96.5%) 1335 (6.0)	233 (96.7%) 3539 (5.2)
Acute systemic hypersensitivity reaction	10 (6.5%) 16 (0.04)	4 (4.7%) 4 (0.02)	14 (5.8%) 20 (0.03)
Injection site reaction	146 (94.8%) 3134 (6.9)	81 (94.2%) 1382 (6.2)	228 (94.6%) 4541 (6.7)
Injection site skin reaction ≥14 days duration	76 (49.4%) 264 (0.6)	44 (51.2%) 124 (0.6)	120 (49.8%) 388 (0.6)
Arthralgia	131 (85.1%) 1142 (2.5)	77 (89.5%) 551 (2.5)	209 (86.7%) 1704 (2.5)

*Total treatment exposure was the aggregated duration of treatment across all participants (for each participant, time from the first dose to the last dose administered across all studies in which the participant was enrolled). Intervals of missing doses that were >28 consecutive days were excluded from the calculation of treatment duration

Conclusions

- Substantial reductions in mean blood Phe with pegvaliase were observed in participants regardless of prior metabolic control or age at MNT discontinuation
- AEs were observed in all participants at similar rates irrespective of PKU history and most were manageable with long-term pegvaliase use
- Disposition was consistent between groups regardless of historic metabolic control
- The majority of participants self-rated their pre-pegvaliase metabolic control as "Excellent/Good" despite having blood Phe levels above guideline-recommended ranges. Discontinuation of diet was the strongest predictor of whether they considered themselves as having "Excellent/Good" vs "Poor/None" metabolic control
- Participants who reported "Excellent/Good" lifetime metabolic control were significantly younger, reported consuming more medical food and less dietary Phe, had lower blood Phe levels, and had lower scores on the ADHD-RS inattentive subscale (indicating a lower degree of impairment) at baseline
- Participants who reported "Poor/None" lifetime metabolic control were also more likely to report a lifetime blood Phe of ≥1200 µmol/L and to have previously discontinued diet, doing so at younger age categories. These participants reported higher rates of ADHD inattentive symptoms at baseline, reaching a mean score >9 indicative of clinical significance. There was no significant difference in sapropterin response
- The self-reporting of "Excellent/Good" metabolic control with Phe levels >600 µmol/L at study entry represents a potential lack of insight into disease severity among some adults. This may indicate a need for additional dietary education as many self-report as being "on diet" despite dietary records indicating otherwise
- Confusion about what Phe levels are representative of "Excellent/Good" metabolic control may exist in part due to differing target Phe levels between published sets of guidelines (<360 vs <600 µmol/L) and due to changes in target Phe levels over time
- The self-reported age at discontinuation of MNT is in line with previously reported trends among the adolescent and adult PKU population[3], supporting the need for additional focus on adolescents to formally transition to adult care[7]

References

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