Real-world safety and tolerability of pegvaliase: A non-interventional surveillance study in Japan

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Background

- Phenylketonuria (PKU) is a rare autosomal recessive genetic disorder caused by pathogenic variants in the phenylalanine hydroxylase (PAH) gene, leading to deficient PAH enzyme activity that results in elevated concentrations of phenylalanine (Phe) in the blood and brain[1]
- Pegvaliase is a phenylalanine ammonia lyase substitution therapy that was approved in Japan in 2023 for individuals with PKU ≥15 years old[2,3]
- Safety and efficacy of pegvaliase for the treatment of individuals with PKU in Japan was assessed in the 165-305 clinical trial[4,5]
- Here, we present the study design and interim data from an ongoing post-marketing surveillance study in Japan to assess the real-world safety and tolerability of pegvaliase

Summary

- The 165-601 study is a multi-center, single country, non-interventional surveillance study designed to assess the long-term safety and tolerability of pegvaliase in individuals with PKU treated in the real-world setting in Japan
- Interim data from the first 18 months of the study show no new safety concerns among participants receiving pegvaliase in the real-world setting; reported adverse events were generally manageable with standard of care
- It is anticipated that data from this ongoing study will provide important information on the real-world safety and effectiveness of pegvaliase for the treatment of individuals with PKU in Japan

Methods

Study design

- The 165-601 study is a multi-center, single country, non-interventional surveillance study designed to assess the long-term safety and tolerability of pegvaliase in individuals with PKU treated in the real-world setting in Japan
  - Data collected in the study are included in periodic safety reports to the Japanese health authorities
  - All individuals with a diagnosis of PKU and who are currently receiving pegvaliase are required to register

Data collection and analysis

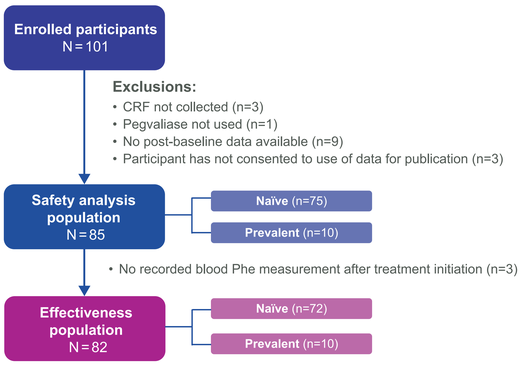
- Participant data are collected at the time of enrollment and at follow-up clinic visits, conducted according to standard of care, throughout the duration of the study
- Data to be captured in the study include: patient demographics, medical history, prior and concomitant medication use, pegvaliase prescribing regimen, safety outcomes (including all serious adverse events [SAEs] and adverse drug reactions [ADRs]), pregnancy status (including fetal outcomes), laboratory measures (including blood Phe), and diet information (total protein, intact protein, medical food protein, and Phe intake)
- For participants who discontinue pegvaliase treatment during the study, reason for discontinuation is collected and data collection will be continued for a period of one year after the date of discontinuation
- In this interim report, descriptive analyses of participant demographics and baseline characteristics, frequency of adverse events, and Phe levels over time are summarized

Results

Study participants

- As of 23 May 2025 (data cut off), a total of 101 participants from 41 sites had been enrolled
- Among enrolled participants, 85 were considered in the safety population (see **Figure 1** for inclusion/exclusion criteria)
  - 10 participants had received pegvaliase in clinical trials prior to enrollment (prevalent participants) and 75 participants initiated pegvaliase treatment after it became available commercially on 24 May 2023 (treatment naive participants)
  - 82 out of the 85 participants had available blood Phe measurements after initiation of pegvaliase treatment (effectiveness population)

Figure 1. Study participants



- Participant demographics and baseline characteristics are shown in **Table 1**: 44 (51.8%) were female; 75 (88.2%) were ≥18 years at enrollment, 10 (11.8%) were aged 15-17 years at enrollment (mean age at enrollment: 30.2 years)
  - The majority of patients (92.9%) were on dietary therapy prior to initiation of pegvaliase treatment

Table 1. Participant demographics and baseline characteristics

	Safety analysis population N=85
Sex, n (%)	
Male	41 (48.2)
Female	44 (51.8)
Age at enrollment (years)	
Mean (SE)	30.2 (1.1)
Median (range)	29 (15–57)
Age at enrollment, n (%)	
15 years	3 (3.5)
16 years	2 (2.4)
17 years	5 (5.9)
≥18 years	75 (88.2)
Height (cm)	*n=79*
Mean (SE)	162.7 (1.0)
Median (range)	163.5 (147.2–180.8)
Weight (kg)	*n=80*
Mean (SE)	64.8 (1.5)
Median (range)	62.9 (39.3–104.1)
Body mass index (kg/m²)	*n=79*
Mean (SE)	24.4 (0.6)
Median (range)	23.4 (15.3–39.8)
On dietary therapy prior to initiation of pegvaliase, n (%)	
Yes	79 (92.9%)
No	6 (7.1%)

SE, standard error

Safety

- Among the 85 participants included in the safety analysis population, the total pegvaliase exposure time was 89.1 person-years, as of the data cutoff
- Data on incidence of adverse events (AEs) among enrolled participants in the safety population are shown in **Table 2**
  - AEs are recorded as reported by the investigators and were not adjudicated for causal relationship with pegvaliase use
  - A total of 223 events were observed in 60 participants (71%)
  - Observed common AEs were consistent with those observed in pegvaliase clinical trials; the most common AEs were arthralgia, urticaria, and pyrexia
- Two participants discontinued pegvaliase after enrollment (one due to a safety event and one due to transfer to another clinic)

Table 2. Adverse events (safety population)

	Safety population (N=85)	
	Number (%) of participants with event	Number of events
Any AE	**60 (70.6)**	**223**
Most common AEs (occuring in ≥5 participants)		
Musculoskeletal and connective tissue disorders		
Arthralgia	16 (18.8)	23
Skin and subcutaneous tissue disorders		
Urticaria	11 (12.9)	31
Rash	8 (9.4)	9
General disorders and administration site conditions		
Pyrexia	10 (11.8)	11
Injection site erythema	8 (9.4)	20
Injection site reaction	6 (7.1)	7
Injection site pain	5 (5.9)	7
Injection site swelling	5 (5.9)	11
Malaise	5 (5.9)	7
Immune system disorders		
Anaphylactic reaction	9 (10.6)	14
Metabolism and nutrition disorders		
Hypophenylalaninemia	9 (10.6)	13
Nervous system disorders		
Headache	5 (5.9)	10

AE, adverse event
All AEs were coded using version 27.1 of the Medical Dictionary for Regulatory Activities (MedDRA)

Blood Phe

- Although the 165-601 study is primarily designed to assess long-term safety and tolerability of pegvaliase, data on Phe levels collected during the course of routine care will provide insight into the real-world effectiveness of pegvaliase
- Among treatment naïve participants (n=72), mean (median) blood Phe concentration at last measurement prior to treatment initiation was 1157.4 (1236.0) µmol/L; mean (95% CI) change from pre-treatment baseline at 12 months after treatment initiation (n=45) was –318.7 (–448.0, –189.3) µmol/L (**Table 3**)
- Median pegvaliase dose 12 months after treatment initiation was 140 mg/week (n=45)

Table 3. Blood Phe levels (effectiveness population, treatment naïve participants)

	Pre-treatment Baseline	Time from treatment initiation (months)			
		3	6	9	12
Treatment naïve participants (n=72)					
n	72	64	62	53	45
Blood Phe (µmol/L), mean (SE), median	1157.4 (44.9) 1236.0	918.3 (53.4) 1005.0	844.8 (62.3) 885.0	823.6 (63.4) 924.0	767.9 (69.1) 672.0
Change from baseline in blood Phe (µmol/L), mean (95% CI)	-	-227.8 (-317.4, -138.3)	-321.5 (-421.2, -221.8)	-328.1 (-459.9, -196.3)	-318.7 (-448.0, -189.3)
Pegvaliase dose (mg/week), mean (SE), median	-	78.6 (7.6) 70.0	113.7 (7.7) 140.0	126.5 (9.1) 140.0	166.2 (15.9) 140.0

CI, confidence interval; SE, standard error

References

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Disclosures

Mika Ishige reports travel support and lecture fees from BioMarin; Mahoko Furujo reports lecture fees from BioMarin; Nami Sugiyama is an employee of BioMarin Pharmaceutical Japan K.K. and holds stock or stock options in BioMarin Pharmaceutical Inc; Naomi Schwartz is an employee of and holds stock or stock options in BioMarin Pharmaceutical Inc; Takashi Hamazaki reports advisory fees and lecture fees from BioMarin.

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