Occurrence of anaphylaxis in adult incident pegvaliase-treated PKU patients in a post-marketing safety analysis in the United States

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Background

- Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of the enzyme phenylalanine hydroxylase, which results in phenylalanine (Phe) accumulation in the blood and brain[1]
- High blood Phe in individuals with PKU is associated with neurocognitive deficits, impaired executive function, and reduced QOL[1]
- Pegvaliase is an enzyme substitution therapy indicated to reduce blood Phe concentrations in adults with PKU who have uncontrolled blood Phe concentrations >600 µmol/L on existing management[2]
- As a bacterially derived enzyme, pegvaliase elicits an immune response; immune-mediated adverse drug reactions including anaphylaxis were observed in clinical trials[3]
  - The incidence and exposure-adjusted event rates for anaphylaxis from the Induction/Titration/Maintenance (I/T/M) population (N=285) in the clinical studies were 10.2% and 0.05 episodes/person-year, respectively
  - All occurrences of anaphylaxis were managed successfully with the safe-use conditions implemented in the clinical studies
- As part of the approval of pegvaliase, the FDA required a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of pegvaliase outweigh the risk of anaphylaxis[2]
- The objective of this analysis was to estimate the real-world incidence of anaphylaxis in patients treated with pegvaliase in the US who were registered in the REMS program

Methods

- This was a retrospective observational cohort analysis of pegvaliase users between 24 May 2018 and 31 December 2022

Data source

- Record-linkage from three BioMarin data sources was performed to create one dataset for analysis:
  - **REMS database** is used to monitor all patients who are enrolled in REMS and has limited patient information (i.e., age and gender)
  - **Drug dispensing database** captures drug dispensing data from the REMS program and has data on date of pegvaliase dispense and the number of days' supply dispensed
  - **Pharmacovigilance database** is a repository for collecting information on adverse events (AEs), medication errors, and product complaints; reports on all AEs (including anaphylaxis) are captured in this database

Eligibility criteria

- **Incident users**
  - Patients with PKU enrolled in the REMS program
  - Had a REMS ID that can be linked with the Drug Dispensing Database, and
  - Had at least one drug dispensing record of pegvaliase recorded following FDA approval (on/after 24 May 2018)
  - Patients who had previously participated in a pegvaliase clinical trial were excluded
- **Prevalent users**
  - Patients with PKU enrolled in the REMS program
  - Had a REMS ID that is able to link with Drug Dispensing Database
  - Had at least one drug dispensing record of pegvaliase recorded following FDA approval (on/after 24 May 2018); and
  - Had a record of receiving pegvaliase in a clinical trial

Statistical analysis

- **Index date** for each cohort was defined as follows:
  - Incident users: start date of pegvalise treatment on/after 24 May 2018
  - Prevalent users: date of first pegvaliase prescription received after switching to commercial drug treatment on/after 24 May 2018
- **Anaphylaxis events** were defined as those reported as follows:
  - Anaphylactic/anaphylactoid reaction and/or
  - Had acute onset of symptoms with involvement of skin or mucosal tissue combined with respiratory compromise and/or reduced blood pressure, syncope (i.e., all cases where symptoms met National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network criteria) and/or
  - Were treated with adrenaline/epinephrine
- **Incidence proportion** was defined as the number of new patients reported with anaphylaxis in the given time period while receiving pegvaliase, divided by population at risk during that same time period
- **Exposure-adjusted incidence rate (EAIR)** was defined as the number of patients who experienced at least one anaphylaxis event, divided by the exposure time at risk of all patients who are at risk for the event
- **Exposure-adjusted event rate (EAER)** was defined as the number of anaphylaxis events experienced by patients at risk, divided by the total exposure time of all patients who are at risk for the event

Results

Study population

- As of 31 December 2022, 1986 patients had enrolled in the REMS program, and 1772 (89.2%) had at least one record of drug dispensed and were eligible for analysis (**Figure 1**)
  - Of these pegvaliase-treated patients, 1579 (89.1%) were incident users and 193 were prevalent users
- Among both incident users and prevalent users, the distribution of males vs females was approximately even (**Table 1**)
- Median age at index was 28 years for incident users and 34 years for prevalent users
  - The majority of incident users (94.4%) were adults aged ≥18; 5.6% were adolescents aged 12–17

Figure 1. Study population

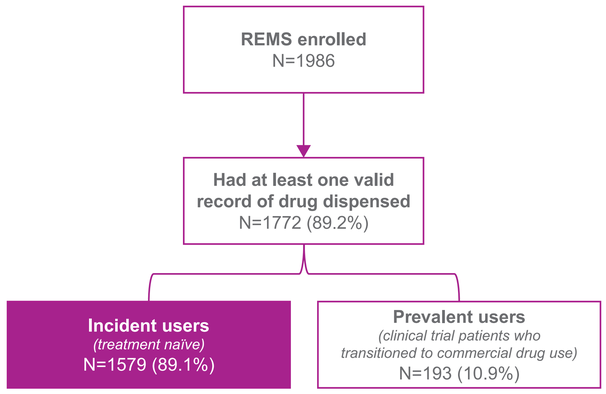


Table 1. Demographics

	Incident Users N=1579	Prevalent Users N=193
Sex, n (%)		
Male	730 (46.2)	94 (48.7)
Female	760 (48.1)	84 (43.5)
Missing	89 (5.6)	15 (7.8)
Age at index date (years)		
Mean (SD)	30.5 (11.4)	35.5 (9.1)
Median (IQR)	28 (20, 38)	34 (29, 42)
Range	10–79	20–62
Age at index date (years), n (%)		
<12	1 (0.1)	0 (0.0)
12–17	88 (5.6)	0 (0.0)
18-65	1486 (94.1)	193 (100)
>65	4 (0.3)	0 (0.0)

IQR, interquartile range; SD, standard deviation;

Pegvaliase exposure

- Pegvaliase exposure for incident and prevalent users is shown in **Table 2**
- Among incident users, the total pegvaliase exposure was 2764.2 person-years; and the median exposure was 1.6 years

Table 2. Pegvaliase exposure

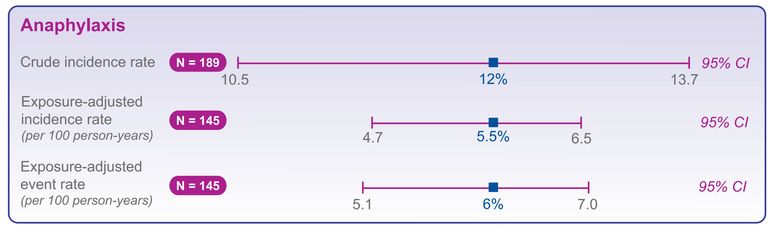
	Incident Users N=1579	Prevalent Users N=193
Duration of pegvaliase exposure (days)		
Mean (SD)	639.4 (452.3)	1152.7 (444)
Median (IQR)	592.0 (212.5, 1040.0)	1334.0 (783.0, 1494.0)
Range	3.0–1598.0	45.0–1641.0
Duration of pegvaliase exposure (years)		
Mean (SD)	1.8 (1.2)	3.2 (1.2)
Median (IQR)	1.6 (0.6, 2.8)	3.7 (2.1, 4.1)
Range	0.0–4.4	0.1–4.5

IQR, interquartile range; SD, standard deviation

Anaphylaxis rates

- Among incident users, the crude incidence proportion of anaphylaxis was 12%; the exposure-adjusted incidence rate of anaphylaxis was 5.5 per 100 person-years; and the exposure-adjusted event rate (EAER) was 6.0 per 100 person-years (**Figure 2**)

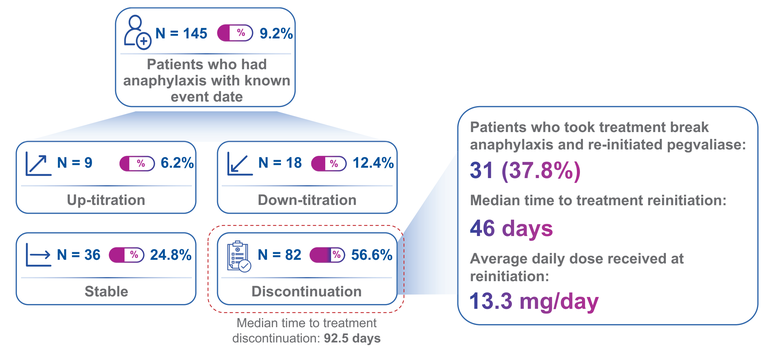
Figure 2. Anaphylaxis rates (incident users)



Treatment management following anaphylaxis

- To assess treatment management following the first anaphylaxis event (n=145 with known event date), the average daily dose for the prescription during the event was compared with the average daily dose in the subsequent prescription
- The most common response following an anaphylactic event was to discontinue treatment (56.6%), but many remained on therapy: 24.8% remained on a stable dose, 12.4% received a lower dose, and 6.2% received a higher dose (**Figure 3**)
- Of the 82 incident users who discontinued treatment after experiencing an anaphylaxis event, 37.8% re-initiated treatment within 46 days following the end of the last prescription prescribed at time of the event

Figure 3. Management of pegvalisase following first anaphylaxis event episode (incident users)



Up-titration: average daily dose for the prescription during which the AE occurred is lower than the average daily dose of the immediate subsequent prescription

Down-titration: average daily dose for the prescription during which the AE occurred is higher than the average daily dose of the immediate subsequent prescription

Stable: average daily dose for the prescription during which the AE occurred remains the same as the average daily dose of the immediate subsequent prescription

Discontinuation: no prescription for pegvaliase within the end date +14 days of the fill/prescription druing which the AE occurred

Conclusions

- In this real-world analysis of incident pegvaliase patients, the EAER for anaphylaxis was consistent with that observed in the 285 participants who received the I/T/M regimen in the pegvaliase clinical trial, at 6.0 vs. 5.29 events per 100 person-years, respectively
  - The clinical trial I/T/M dosing regimen most closely resembles the approved label dosing regimen
  - The incident user population in this study and the I/T/M population both had an approximately even distribution of male and female patients and the mean ages of the populations were similar (30.5 years in this study vs. 29 years in the I/T/M population)
- The total pegvaliase exposure among incident users in this analysis was approximately 5-times greater than that for the I/T/M population (2764 vs. 580 total person-years)
- Although the most common clinical response immediately following an anaphylaxis event was to discontinue treatment, one-third of these patients resumed treatment within 1.5 months; the majority of incident users persist with pegvaliase treatment despite experiencing an anaphylaxis event

References

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3. Thomas J et al. *Mol Genet Metab*. 2018;124(1):27–38.

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