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Phase 3 PRISM studies: Update of efficacy and safety of pegvaliase for the treatment of adults with phenylketonuria

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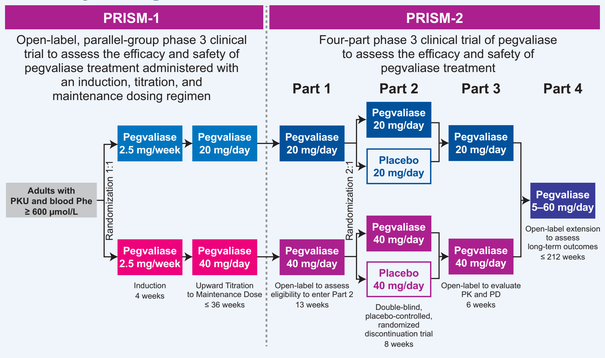
Background

- Phenylketonuria (PKU) is caused by deficiency in activity of the liver enzyme, phenylalanine hydroxylase (PAH), resulting in phenylalanine (Phe) accumulation in the blood and brain. High Phe levels are associated with neuropsychological deficits[1-5]
- Current European and US guidelines recommend treatment for life for patients with PKU to achieve recommended levels of blood Phe
  - US guidelines: 120–360 µmol/L for patients of all ages
  - European guidelines: 120–360 µmol/L for patients ≤12 years of age and 120–600 µmol/L for patients >12 years of age
- Most adults (78%) and adolescents with PKU are unable to adhere to the severe dietary restrictions needed to control blood Phe levels[6]
- Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), converts Phe to trans-cinnamic acid and ammonia[7-9]
- Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for PKU patients with uncontrolled blood Phe concentrations >600 µmol/L on existing management in the US in May 2018 for adults at doses of up to 40 mg once daily and by the European Commission in May 2019 for patients aged ≥16 years at doses of up to 60 mg once daily[10,11]

Methods

- Phase 3 PRISM studies evaluated the ability of subcutaneous pegvaliase to lower blood Phe in adults with PKU (**Figure 1**)
- Efficacy endpoints included observed blood Phe levels, inattention subscale score of the Attention Deficit Hyperactivity Disorder Rating Scale IV (ADHD RS-IV IA), and PKU-POMS confusion subscale score
- Safety endpoints included incidence of adverse events (AEs) and exposure-adjusted event rates of AEs
- Results reported here are as of end of study February 5, 2019

Figure 1. Study design of PRISM-1 and PRISM-2



Results

Table 1. Baseline demographics and characteristics

Characteristic	All Participants (ITT, N=261, unless otherwise indicated)
Age at enrollment Mean (SD), years	 29.1 (8.7)
Sex Female, n (%)	 130 (49.8%)
Race White, n (%)	 254 (97.3%)
Body mass index, n=260 Mean (SD), kg/m^2 Min, max	 28.4 (6.7) 17.1, 47.3
Dietary Phe intake, n=250 Mean (SD), mg/d Median, mg/d	 1700.2 (1194.4) 1357.0
Receiving protein from medical food, n (%)	149 (57.1%)
>75% of protein intake from medical food, n (%)	41 (15.7%)
Blood Phe Mean (SD), µmol/L [mg/dL] Median, µmol/L [mg/dL] Min, max	 1232.7 (386.4) [20.5] 1221.0 [20.35] 285.0, 2330.0

Exposure

- A total of 261 subjects were enrolled; mean pegvaliase treatment duration for the total population was 32.1 (20.8) months
- 79.7% of subjects had ≥6 months of pegvaliase treatment (72.0% had ≥12 months, 62.5% had ≥24 months, 54.9% had ≥36 months, and 26.8% had ≥48 months of pegvaliase treatment)

Disposition

Table 2. Discontinuation summary

Discontinuations	All Participants (ITT, N=261)
Total discontinuations, % (n/N)	38.3% (100/261)
<6 months after enrollment	19.2% (50/261)
6–12 months after enrollment	7.3% (19/261)
12–18 months after enrollment	3.4% (9/261)
18–24 months after enrollment	5.0% (13/261)
>24 months after enrollment	3.4% (9/261)
Reasons for discontinuation, % (n/N)	
Adverse event	15.3% (40/261)
Subject withdrawal	11.1% (29/261)
Physician decision	3.8% (10/261)
Lost to follow-up	3.4% (9/261)
Other reason	2.7% (7/261)
Protocol deviation	1.1% (3/261)
Pregnancy	0.8% (2/261)

Most common AEs leading to discontinuation: Anaphylactic reaction, arthralgia, injection-site reaction, rash generalized

Blood Phe

- Substantial and sustained reduction in blood Phe was achieved despite a gradual increase in dietary Phe intake over time (**Figure 2**)
- Mean (SD) blood Phe decreased from pre-treatment baseline levels of 1233 (386) µmol/L (20.37 mg/dL) to 565 (531) µmol/L (9.33 mg/dL) at month 12 (n=164) and 333 (441) µmol/L (5.50 mg/dL) at month 24 (n=89)
  - Blood Phe reduction was stable through month 48, with a mean (SD) blood Phe of 412 (447) µmol/L (6.81 mg/dL)
- By month 24, 70% of subjects achieved blood Phe ≤600 µmol/L, 62% of subjects achieved blood Phe ≤360 µmol/L, and 52% of subjects achieved blood Phe ≤120 µmol/L
  - By month 48 these Phe thresholds were reached by 73%, 68%, and 61% of subjects, respectively
- Blood Phe reductions were associated with improvements in inattention and mood scores (**Figure 3**)

Figure 2. Reductions in blood Phe levels over time (A) compared with dietary Phe intake and (B) achievement of clinically relevant thresholds of blood Phe

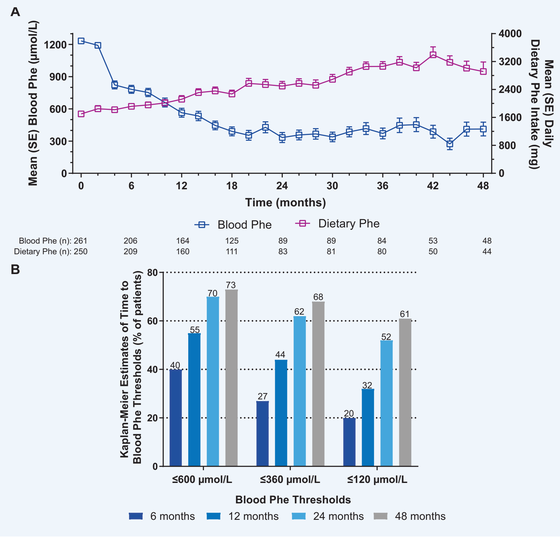
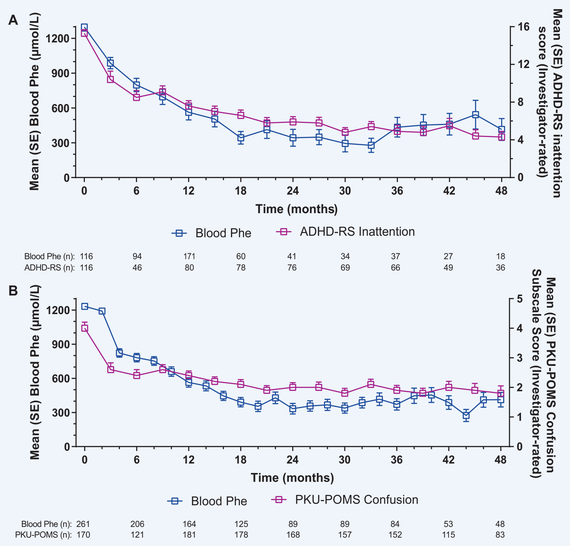


Figure 3. Reductions in blood Phe levels over time is associated with (A) reduction in ADHD-RS inattention score (in patients with baseline scores ≥9) and (B) reduction in PKU-POMS confusion subscale scores



Safety

- Most AEs were mild or moderate (99%), and most (96%) resolved without dose interruption or reduction
- The most common AEs were:
  - Arthralgia (76%)
  - Injection site reaction (64%)
  - Headache (55%)
  - Injection site erythema (49%)
- Event rate per person-year decreased from 58.7 in the first 6 months to 17.6 after the first 6 months
- Acute systemic hypersensitivity events: 15 (5.7%) of 261 subjects had 21 acute systemic hypersensitivity events confirmed by an independent allergist/immunologist to be consistent with clinical anaphylaxis criteria defined by National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network
  - the exposure-adjusted rate of events decreased from 0.08 to 0.03 before and after the first 6 months of pegvaliase treatment
  - 6 subjects discontinued after an acute systemic hypersensitivity event
  - 3 of 9 subjects remaining on study had subsequent events but none of these events occurred at time of next dose. One of these subjects discontinued after the recurrent event
  - Drug-specific IgE was not detected at or near the time of any acute systemic hypersensitivity event, suggestive of a Type III IC-mediated mechanism of hypersensitivity
  - No acute systemic hypersensitivity event required vasopressors or intubation, and all resolved without sequelae

Conclusions

- Pegvaliase treatment was associated with:
  - Substantial and sustained blood Phe reduction observed with increased dietary Phe intake
  - Improved mood and inattention scores temporally associated with reduction in blood Phe
- Manageable safety profile for most subjects who continued long-term treatment
- Exposure-adjusted AE rate decreased over time
  - Arthralgia and injection site reactions were most common AEs
  - Acute systemic hypersensitivity events were not IgE mediated and all resolved without sequelae

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