Efficacy and safety of the recommended pegvaliase dosing regimen in adults with phenylketonuria in the phase 3 PRISM studies

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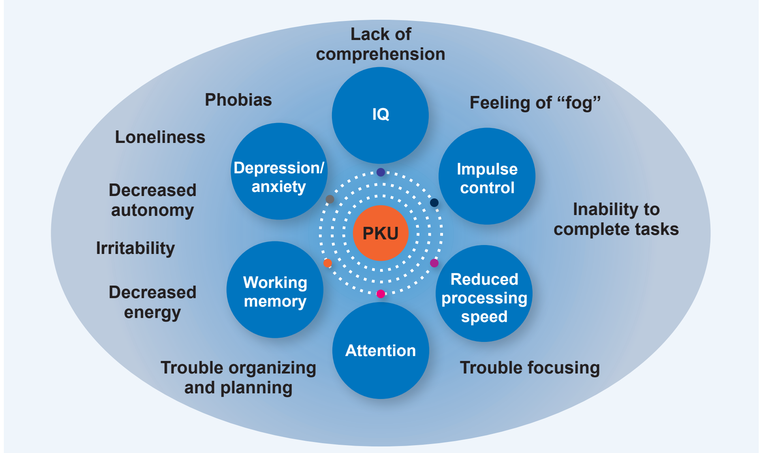
Introduction

- 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 impacting patient health and wellbeing (**Figure 1**)

Figure 1. PKU and uncontrolled blood Phe[1-8]

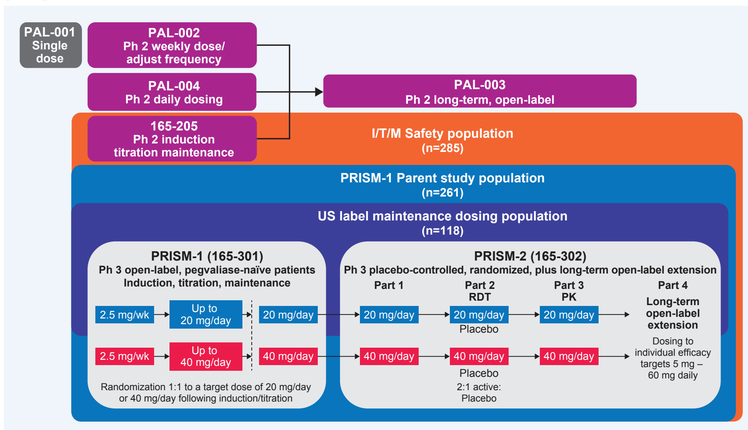


- Current European and US guidelines recommend treatment for life for patients with PKU to achieve recommended levels of blood Phe[1,9]
- Adherence to medical nutritional therapy (MNT) worsens with age; most adults and adolescents with PKU, even if actively managed, are unable to adhere to the severe dietary restrictions needed to control blood Phe levels[10-12]
- Of the subset of patients who can adhere to MNT, many do not achieve adequate Phe control[4]
- Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for the treatment of adults with PKU who have blood Phe >600 µmol/L[13-17]. In 2020 the US label was updated expanding the approved doses from up to 40 mg/day to up to 60 mg/day. Herein we present pegvaliase safety and efficacy including the updated label maintenance dosing population

Methods

- The safety and efficacy of pegvaliase has been studied in a clinical trial program spanning over a decade (**Figure 2**)
- The phase 2 trials examined several different dosing approaches and informed the induction/titration/maintenance (or I/T/M) dosing regimen used in the label enabling phase 3 PRISM-1 (165-301, NCT01819727) and PRISM-2 trials (165-302, NCT01889862)

Figure 2. Pegvaliase clinical trial program study populations



- Safety: includes all participants from the clinical program who underwent the I/T/M dosing regimen (N=285)
- Efficacy: the US label maintenance dosing population (n=118) was retrospectively defined as participants who were randomized to and received at least one dose of 20 mg in PRISM-1, and whose baseline blood Phe was >600 µmol/L, to mirror the US recommended dosing schedule. The primary efficacy endpoint (Part 2 RDT) and long-term outcomes for the PRISM-1 parent study population have been reported upon previously[18-19]

Results

Table 1. Baseline characteristics

	PRISM-1 parent study population (N=261)[18]	US label maintenance dosing population (n=118)
Blood Phe, µmol/L, Mean (SD)	1232.7 (386.4)	1269.8 (375.4)
Age at enrollment, years, Mean (SD)	29.2 (8.8)	30.3 (8.8)
Sex, female, n (%)	130 (49.8%)	56 (47.5%)
Race, white, n (%)	254 (97.3%)	117 (99.2%)
Body mass index, kg/m^2, Mean (SD)	28.4 (6.7)	29.3 (7.0)
Receiving protein from medical food, n (%)	149 (57.1%)	68 (57.6%)
>75% of protein intake from medical food, n (%)	41 (15.7%)	19 (16.1%)
Dietary Phe intake, mg/day, Mean (SD)	1700.2 (1194.4)	1766.6 (1171.1)

Exposure and disposition

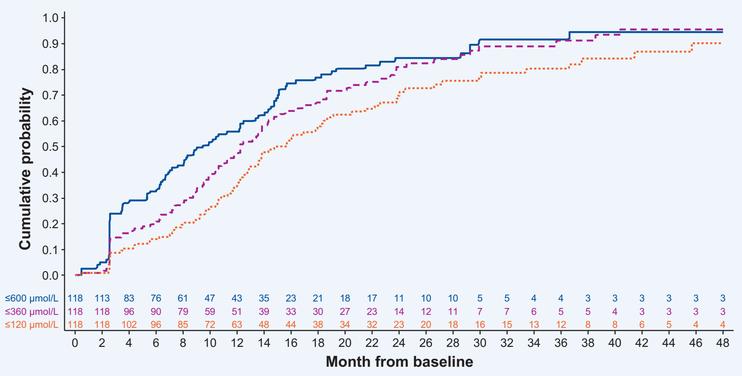
- Mean (SD) pegvaliase treatment duration for the total population was 32.1 (20.8) months

Table 2. Discontinuation summary

Discontinuations	PRISM-1 parent study population (N=261)[18]	US label maintenance dosing population (n=118)
Total discontinuations, % (n/N)	38.3% (100/261)	27.1% (32/118)
<6 months after enrollment	19.2% (50/261)	9.3% (11/118)
6–12 months after enrollment	7.3% (19/261)	5.1% (6/118)
12–18 months after enrollment	3.4% (9/261)	4.2% (5/118)
18–24 months after enrollment	5.0% (13/261)	5.1% (6/118)
>24 months after enrollment	3.4% (9/261)	3.4% (4/118)
Reasons for discontinuation, % (n/N)		
Adverse event	15.3% (40/261)	10.2% (12/118)
Subject withdrawal	11.1% (29/261)	9.3% (11/118)
Physician decision	3.8% (10/261)	1.7% (2/118)
Lost to follow-up, protocol deviation, pregnancy, or other reason	8.0% (21/261)	5.9% (7/118)

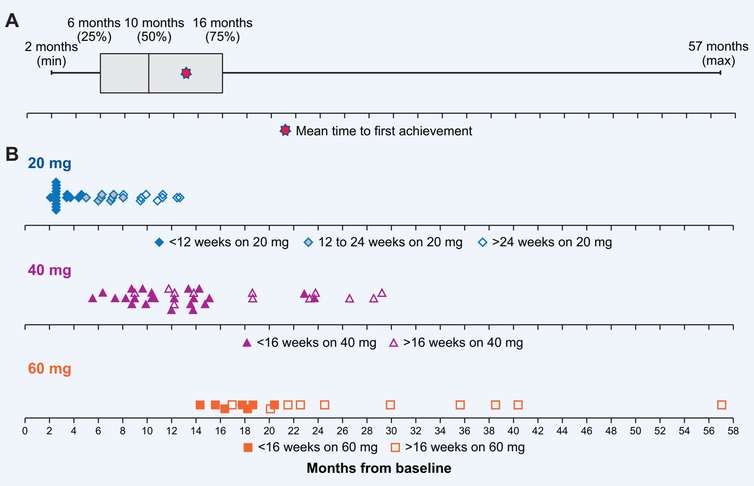
Note: The discontinuations in the n=118 population do not include those that occurred prior to receiving at least one 20 mg dose.

Figure 3. Kaplan-Meier analyses of time to blood Phe thresholds ≤600, ≤360, ≤120 µmol/L in US Label Maintenance Dosing Population (n=118)



- Out of 118 participants, 89 (75.4%) achieved blood Phe ≤360 µmol/L, 25 (21.2%) discontinued the study prior to achieving, and 4 (3.4%) completed the study without achieving

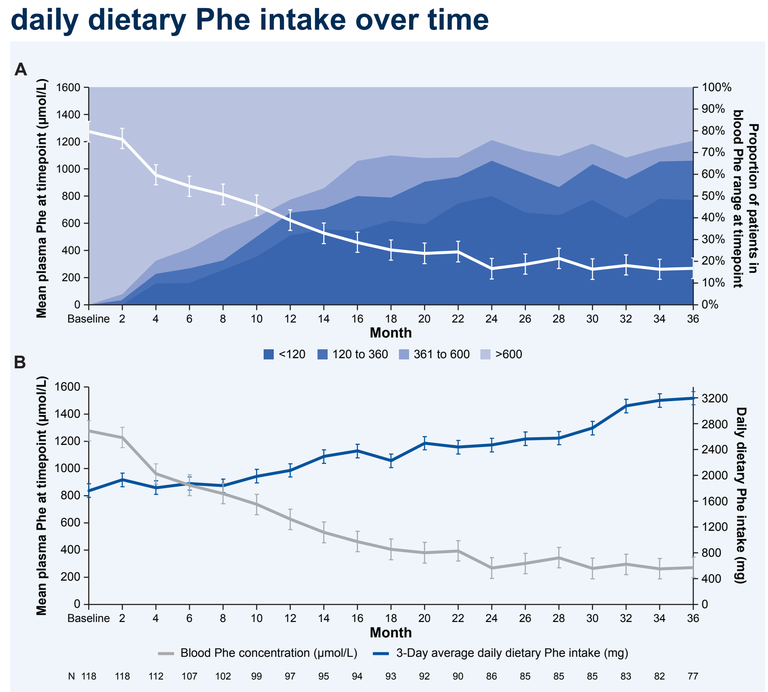
Figure 4. Distribution of time (months) to first achievement of blood Phe ≤360, (A) all participants who achieved (n=89, 75.4%) and (B) by weeks on dose each achieved: 20 mg (n=38, 42.7%), 40 mg (n=34, 38.2%), 60 mg (n=17, 19.1%)



(**A**) Box and Whisker Plot captures minimum, 25th percentile, median, 75th percentile, and maximum values.

(**B**) Scatter plot of individual time to achievement in months and by weeks on the dose achieved.

Figure 5. Mean blood Phe levels and (A) proportion of patients within each blood Phe category and (B) daily dietary Phe intake over time



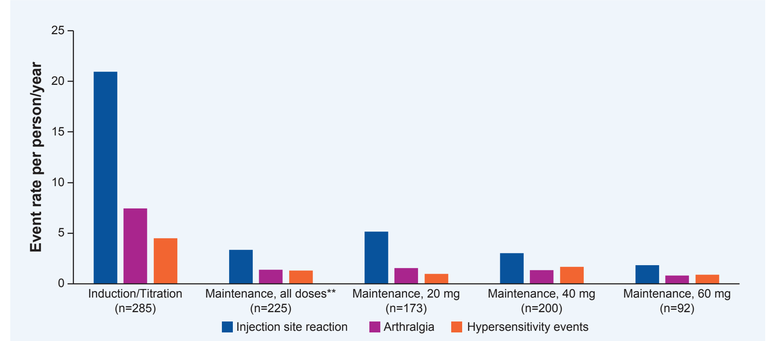
Safety

Table 3. Exposure-adjusted event rates and subject incidence of AEs over time I/T/M Safety population (N=285)

Number of patients with event (%) Number of events (Event per person-year*)	Early (≤6 months) (N=285)	Late (>6 months)					Overall (N=285)
		>6 months to ≤1 year (N=230)	>1 year to ≤2 years (N=208)	>2 years to ≤3 years (N=183)	>3 years (N=165)	Total (N=231)	
Total treatment exposure (person-years)	126.9	106.3	192.6	170.2	197.0	666.6	793.7
AE	284 (99.6%) 7387 (58.21)	219 (95.2%) 2627 (24.71)	202 (97.1%) 3708 (19.25)	176 (96.2%) 2274 (13.36)	138 (83.6%) 2157 (10.95)	229 (99.1%) 10766 (16.15)	285 (100.0%) 18153 (22.87)
Serious AE	24 (8.4%) 27 (0.21)	16 (7.0%) 21 (0.20)	17 (8.2%) 22 (0.11)	8 (4.4%) 9 (0.05)	8 (4.8%) 14 (0.07)	43 (18.6%) 66 (0.10)	65 (22.8%) 93 (0.12)

*The event rate per person-year, exposure-adjusted rate, represents the number of episodes of an adverse reaction seen in a population of patients receiving treatment, over the time period it was received.

Figure 6. Exposure-adjusted event rates for 3 most common AEs by treatment phase I/T/M Safety population (N=285)



*Maintenance per label is defined as when subjects reached stable dose for 8 weeks.
**Maintenance, all doses includes patients on doses <20 mg and placebo.

Hypersensitivity events includes anaphylaxis (anaphylaxis event rate per person-year 0.25 Induction/Titration; 0.05 for Maintenance, all doses)

Conclusions

- In clinical trials, pegvaliase demonstrated substantial and sustained Phe reduction related to treatment duration and dose; long-term pegvaliase treatment had a manageable safety profile for most patients
- There was an increase in proportion of participants achieving blood Phe efficacy due to:
  - Increased time on treatment
  - Ability to adjust treatment dose
- Exposure-adjusted AE rate decreased over time
  - Arthralgia and injection site reactions were most common AEs
- The n=118 US label maintenance dosing population, whose clinical course approximates the commercially recommended maintenance dosing regimen, provides insight on the dose and time to first clinically meaningful Phe response

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