Disclosure Slide

Financial Disclosure for:

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Phase 3 PRISM studies: Efficacy & safety of pegvaliase 60mg in adult patients with PKU

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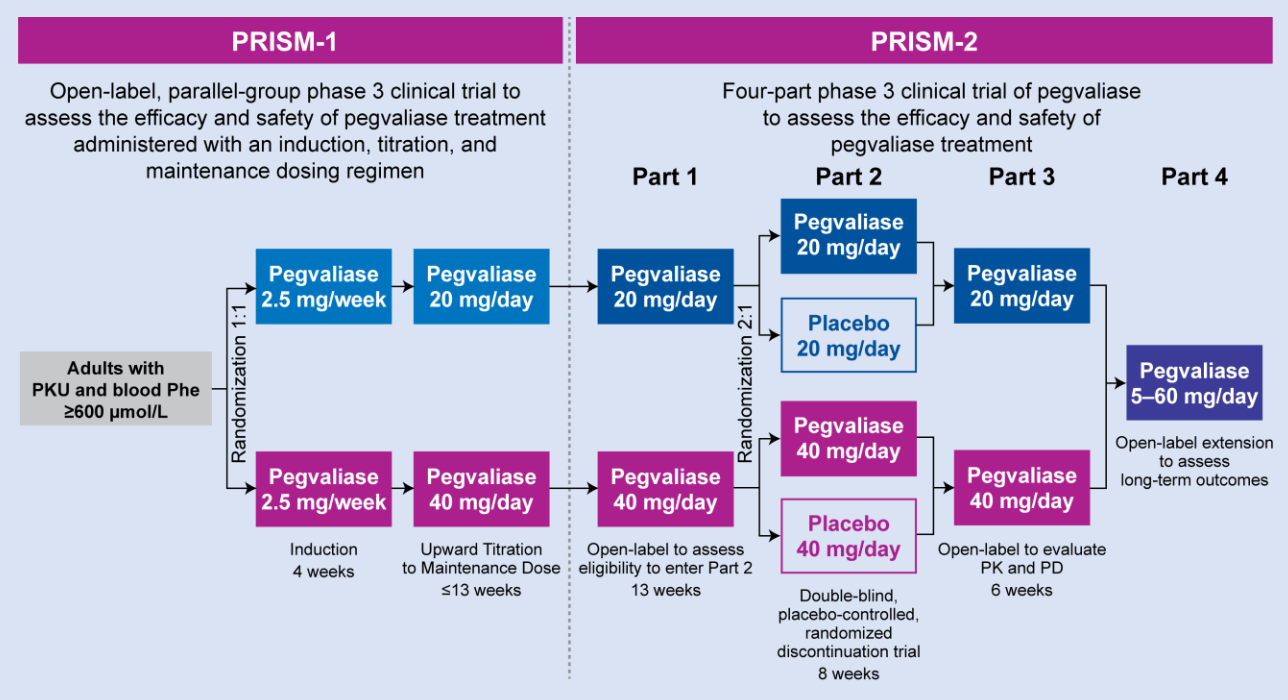
- Phenylketonuria (PKU) is caused by a deficiency in activity of the phenylalanine hydroxylase (PAH) enzyme resulting in elevated levels of phenylalanine (Phe) in the blood and tissues, which can be toxic to the brain[1]
- Current European and US guidelines[1,2] recommend treatment for life for patients with PKU:
  - 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
- Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase, is a subcutaneously administered enzyme substitution therapy that converts Phe to trans-cinnamic acid and ammonia[3–5]
- Pegvaliase (Palynziq®) is approved for PKU patients with uncontrolled blood Phe concentrations >600 µmol/L on existing management in the US for adults at doses of up to 40 mg once daily[6] and by the European Commission for patients ≥16 years at doses of up to 60 mg once daily[7]
- Herein we present the results of patients who received pegvaliase 60 mg during the long-term extension of the PRISM-2 study (NCT01889862)

Methods

- PRISM-2 Part 4 (see **Figure 1**) was comprised of an open-label extension, in which subjects could titrate up to 60 mg/day if they had a combined total of >52 weeks of pegvaliase and a minimum of 8 weeks at the 40 mg/day dosage in PRISM-2 and previous studies to achieve a blood Phe level <600 µmol/L
- Efficacy results are reported for the Stable 60 mg/day population, patients enrolled in PRISM-2 Part 4 who received 60 mg/day for ≥4 weeks with ≥80% adherence, and safety data are reported for all patients receiving at least one dose of 60 mg in PRISM-2 Part 4
- Final study results are reported from the last study visit on February 5, 2019

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



Results

Subject disposition

- The mean (SD) pegvaliase dose in the 202 subjects enrolled into Part 4 of PRISM-2 was 33 (13) mg/day, with total pegvaliase exposure of 572 person-years of which there were 96 person-years exposure on 60 mg/day
- 51 (25%) subjects comprised the Stable 60 mg dose population, having received 60 mg/day for ≥4 weeks with ≥80% adherence
- Baseline characteristics and demographics are shown in **Table 1**

Table 1. Baseline demographics and characteristics

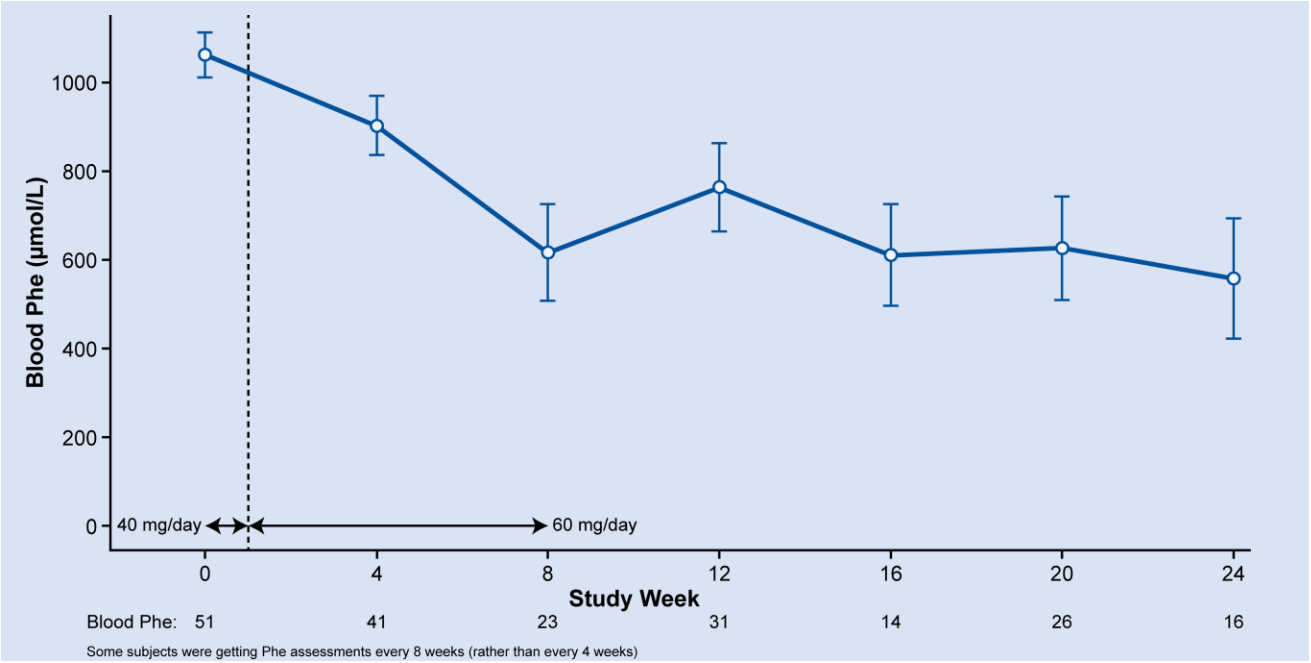
Characteristic	Stable 60mg Dose population	Overall PRISM 2 Part 4 Population
Number of subjects	51	202
Age at enrolment Mean (SD), years	28.49 (9.28)	29.36 (8.79)
Sex Female, n (%)	20 (39.2%)	99 (49%)
Body mass index Mean (SD), kg/m^2	29.62 (7.52)	28.14 (6.73)
Weight Mean (SD), kg Median (min, max), kg	86.67 (25.74) 46.40, 143	80.06 (21.37) 41.50, 143
Baseline blood Phe Mean (SD), µmol/L Median (min, max), µmol/L	1303.92 (358.08) 557, 2094	1234.16 (381.49) 285, 2229

Results

Efficacy

- Mean blood Phe for all subjects in Part 4 was reduced from treatment-naïve baseline levels (1226 µmol/L; n=215) to 392 (487) µmol/L (n=182) after 49 weeks of pegvaliase treatment at doses up to 60 mg/day
- For the Stable 60 mg/day dose population, mean (SD) blood Phe was 1063 (372) µmol/L (n=51) on the 40 mg/day dose. This decreased to 617 (528) µmol/L 8 weeks after increasing the dose to 60 mg/day (n=23). Reduction in blood Phe levels was sustained through 24 weeks (**Figure 2**)

Figure 2. Mean (SE) plot of blood Phe after dose titration from 40 mg/day to 60 mg/day in PRISM-2 Part 4 (60 mg/day Stable dose population; n=51)

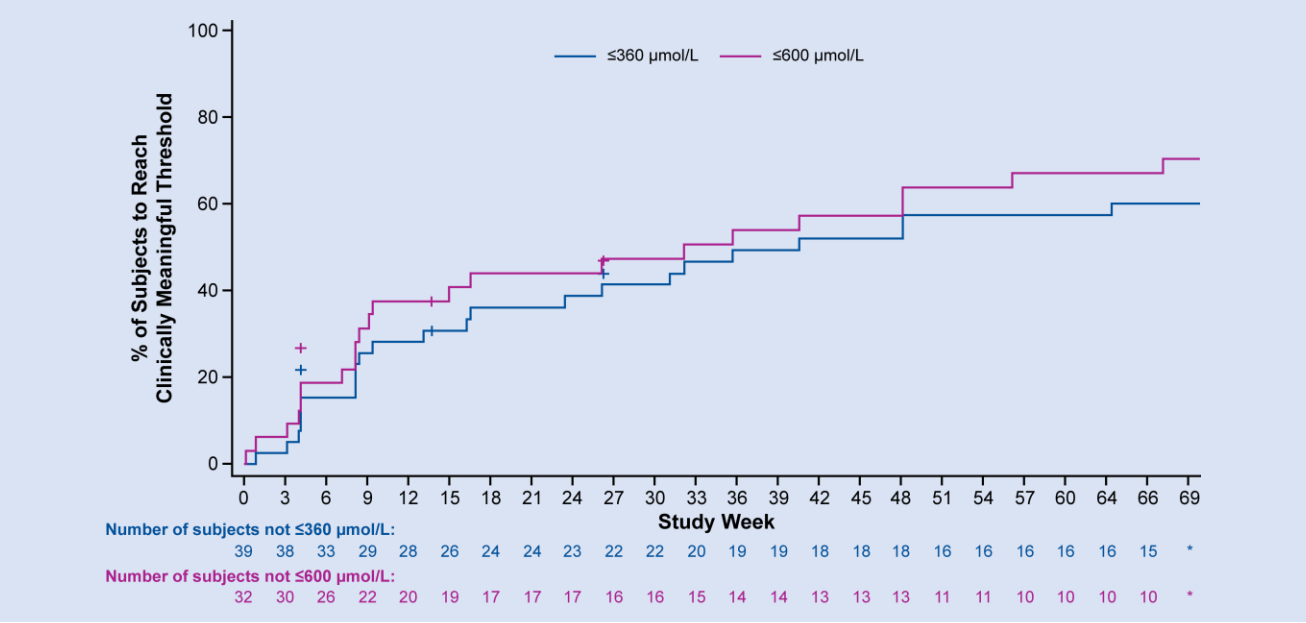


Results

Efficacy

- Following dose increase to 60 mg, an increase in the proportion of subjects reaching blood Phe thresholds was observed over time (**Figure 3**):
  - 38%, 44%, and 64% of subjects reached blood Phe levels ≤600 µmol/L by 12, 24, and 48 weeks on 60 mg/day dose, respectively
  - 28%, 39%, and 57% of subjects reached blood Phe levels ≤360 µmol/L by 12, 24, and 48 weeks on 60 mg/day dose, respectively

Figure 3. Kaplan-Meier curve of time to blood Phe ≤360 µmol/L and ≤600 µmol/L after dose titration from 40 mg/day to 60 mg/day in PRISM-2 Part 4 (60 mg/day Stable dose population; n=51)



Results

Safety

- Of the 202 subjects enrolled in PRISM-2 Part 4, 201 (99.5%) reported at least 1 AE
  - Overall, the highest severity AE was CTCAE Grade 1 for 5% of subjects, CTCAE Grade 2 for 79%, CTCAE Grade 3 for 15%, and CTCAE Grade 4 for 1.5% of subjects
  - Seven (3.5%) subjects experienced 11 episodes of acute systemic hypersensitivity reactions, none of which were severe; all resolved without clinical sequelae, and there were no intubations or deaths

Results

- As AEs are more common in the first 6 months of treatment, when patients are on lower doses, AEs occurring at or after 1 year of treatment were assessed by dose level
- During this period, subjects who received at least one 60 mg dose of pegvaliase (n=98, 94.7 person-years of exposure) had comparable or lower exposure adjusted event rates for AEs, serious AEs (SAEs), hypersensitivity AEs (HAEs), injection site reactions, and arthralgia compared with subjects receiving lower doses (**Table 2**)

Table 2. Overview of adverse events at or after one year of treatment by dose on or prior to adverse event onset (PRISM-2Part 4 population; N=202)

Number of subjects with event (%) Number of events (event rate per person-year)	Dosage on or prior to time of onset				
	<20 mg/day (n=202)	20 – <40 mg/day (n=202)	40 – <60 mg/day (n=193)	≥60 mg/day (n=98)	Any dose level (N=202)
Total treatment exposure (person-years)[b]	67.8	99.9	238.6	94.7	501.8
AEs					
Any AE	55 (27.2%) 1343 (19.80)	89 (44.1%) 1884 (18.87)	164 (85.0%) 4106 (17.21)	58 (59.2%) 1413 (14.92)	199 (98.5%) 8762 (17.46)
AEs leading to study drug discontinuation	0	1 (0.5%) -	5 (2.6%) -	1 (1.0%) -	7 (3.5%) -
Any SAE	7 (3.5%) 8 (0.12)	5 (2.5%) 10 (0.10)	16 (8.3%) 25 (0.10)	6 (6.1%) 6 (0.06)	32(15.8%) 49 (0.10)
AEs of special interest					
Acute systemic hypersensitivity reactions	0	1 (0.5%) -	3 (1.6%) -	0	4 (2.0%) -
Injection site reactions	9 (4.5%) 199 (2.93)	36 (17.8%) 279 (2.79)	90 (46.6%) 609 (2.55)	31 (31.6%) 216 (2.28)	127 (62.9%) 1304 (2.60)
Injection site skin reactions lasting ≥14 days	6 (3.0%) 57 (0.84)	14 (6.9%) 20 (0.20)	47 (24.4%) 88 (0.37)	17 (17.3%) 40 (0.42)	71 (35.1%) 205 (0.41)
Arthralgia	26 (12.9%) 136 (2.01)	39 (19.3%) 119 (1.19)	79 (40.9%) 294 (1.23)	32 (32.7%) 84 (0.89)	127 (62.9%) 633 (1.26)

Results

Safety

- No subjects experienced episodes of acute systemic hypersensitivity reactions after receiving 60 mg pegvaliase dose in Part 4, which had a maximum 274 weeks of follow-up
- Antibody titers in the Stable 60 mg dose population followed a similar pattern as observed in subjects at all other dose levels; titers remained stable or declined over time (data not shown)

Conclusions

- 25% of subjects in Part 4 of PRISM-2 received stable doses of 60 mg/day
- Substantial blood Phe reduction was observed after dose increase to 60 mg/day, which was sustained over time
- Safety profile of 60 mg/day dose was consistent with the lower maintenance doses

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