



The long-term safety and efficacy of pegvaliase 60 mg/day in adults with phenylketonuria

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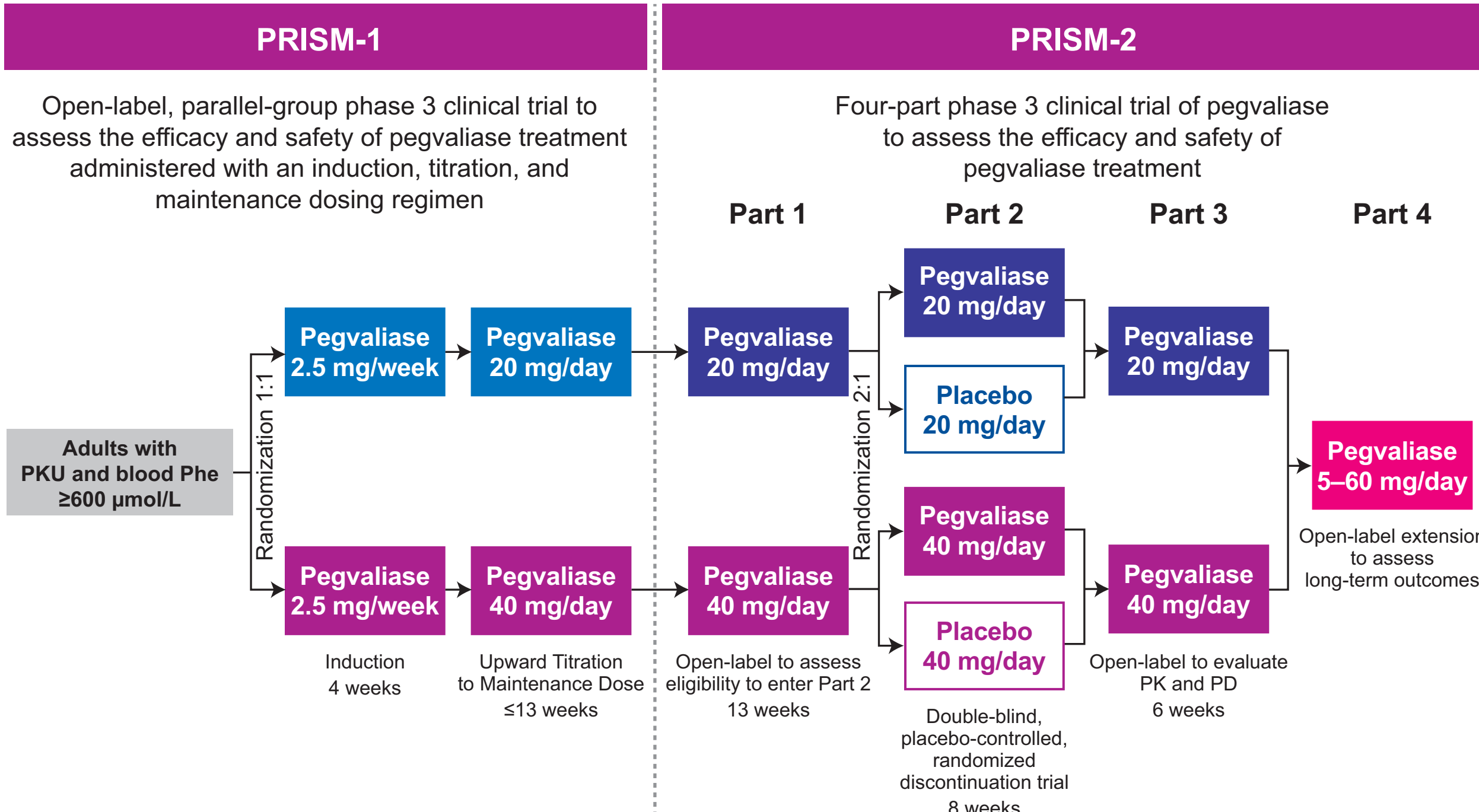
Background

- 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 brain¹
- 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 60 mg once daily⁶ and by the European Commission for patients ≥16 years at doses of up to 60 mg once daily⁷
- 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

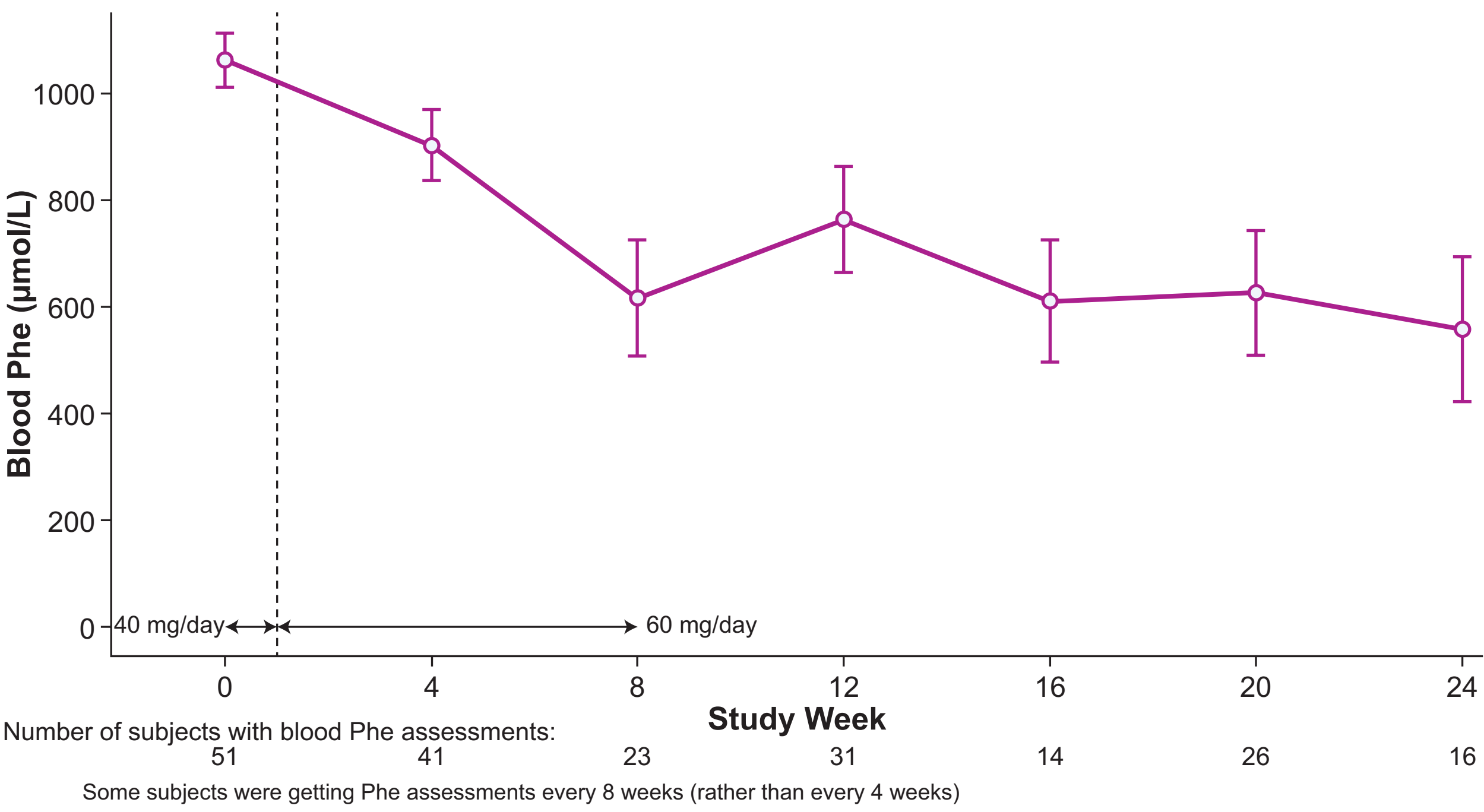
Table 1. Baseline and demographic characteristics

Characteristic	Stable 60 mg dose population	Overall Part 4 population (all doses)
Number of subjects	51	202
Age at enrollment 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

Efficacy

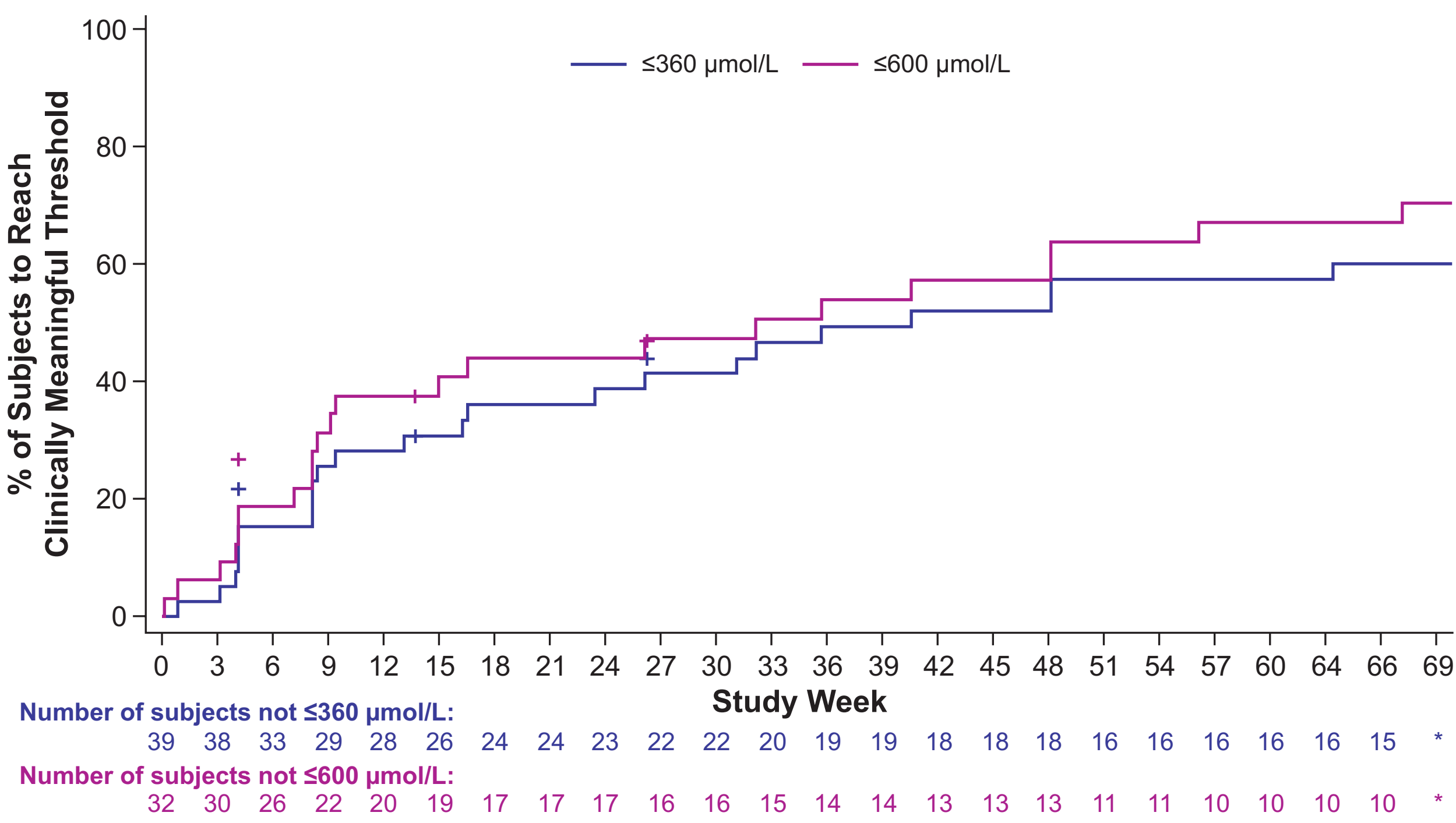
- Mean blood Phe for all subjects in Part 4 was reduced from treatment-naïve baseline levels (1226 µmol/L; n=215) to 392 (487) µmol/L (n=182) after 49 weeks of pegvaliase treatment at doses up to 60 mg/day
- For the Stable 60 mg/day dose population, mean (SD) blood Phe was 1063 (372) µmol/L (n=51) on 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)



- 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)



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
- 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**)
- 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)

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

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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