

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

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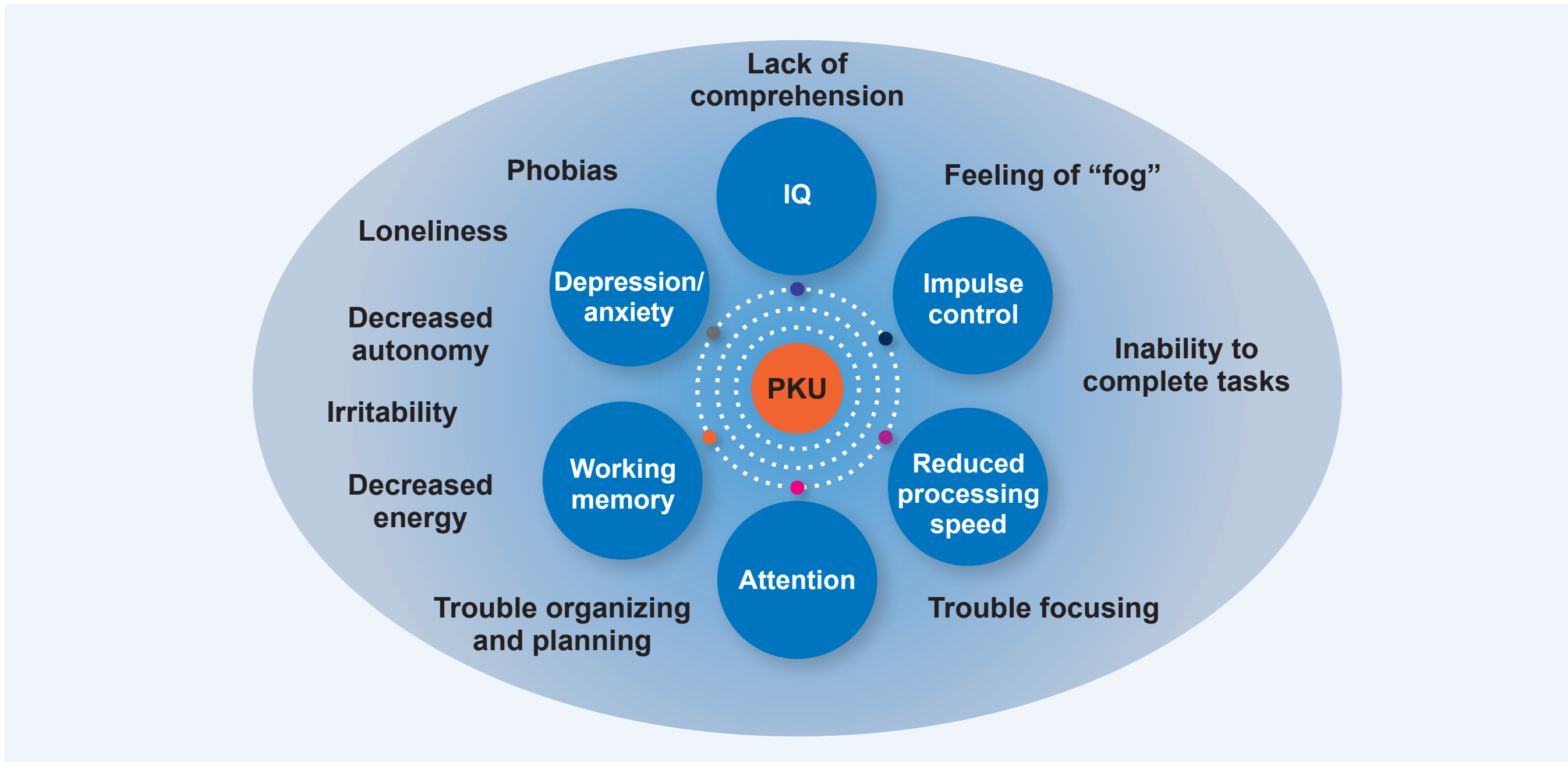
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Introduction

- 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 Phe¹⁻⁸

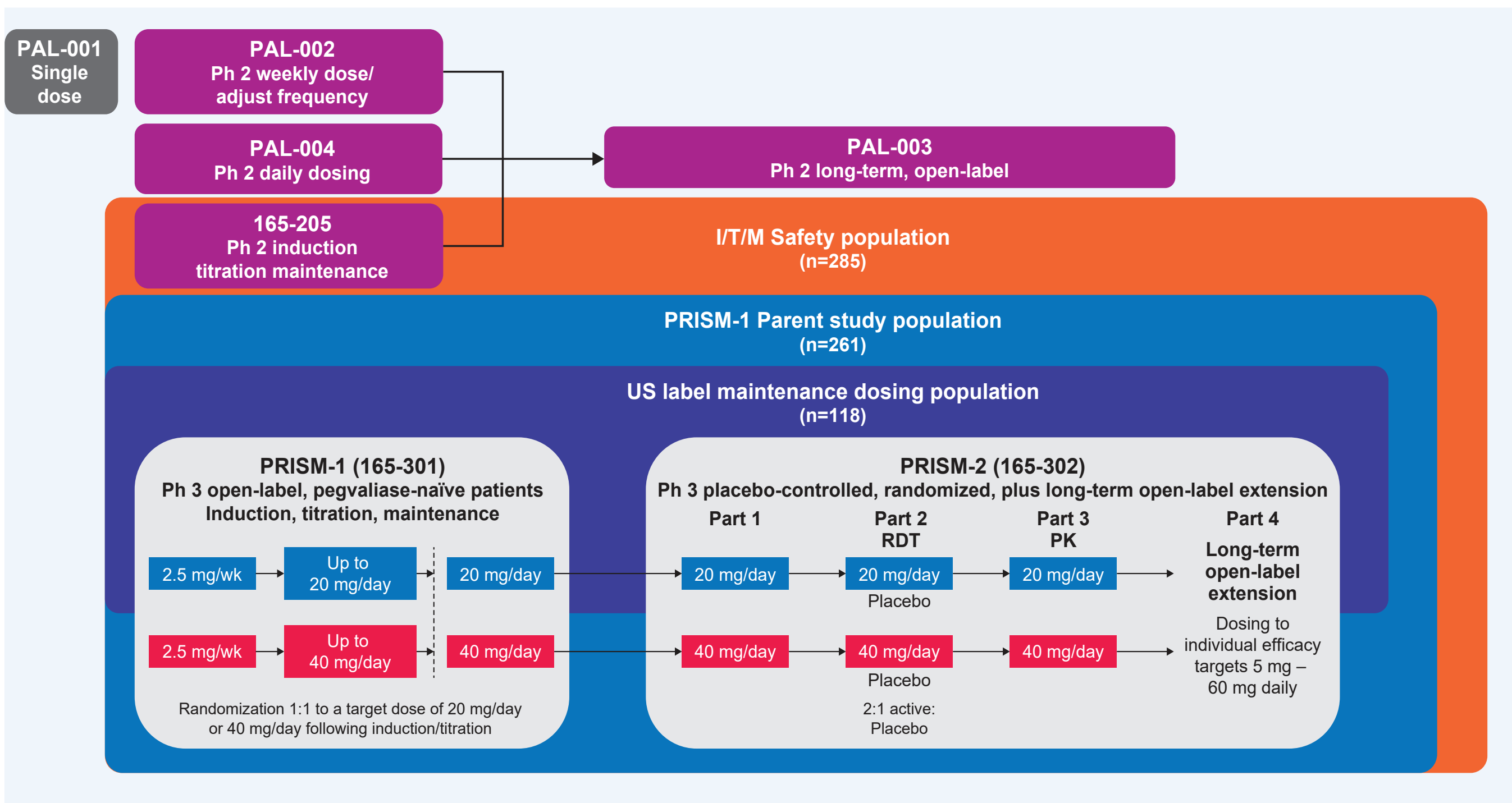


- Current European and US guidelines recommend treatment for life for patients with PKU to achieve recommended levels of blood Phe^{1,9}
- Adherence to medical nutritional therapy (MNT) worsens with age; most adults and adolescents with PKU, even if actively managed, are unable to adhere to the severe dietary restrictions needed to control blood Phe levels¹⁰⁻¹²
- Of the subset of patients who can adhere to MNT, many do not achieve adequate Phe control⁴
- Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for the treatment of adults with PKU who have blood Phe >600 µmol/L¹³⁻¹⁷. 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 previously¹⁸⁻¹⁹

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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)

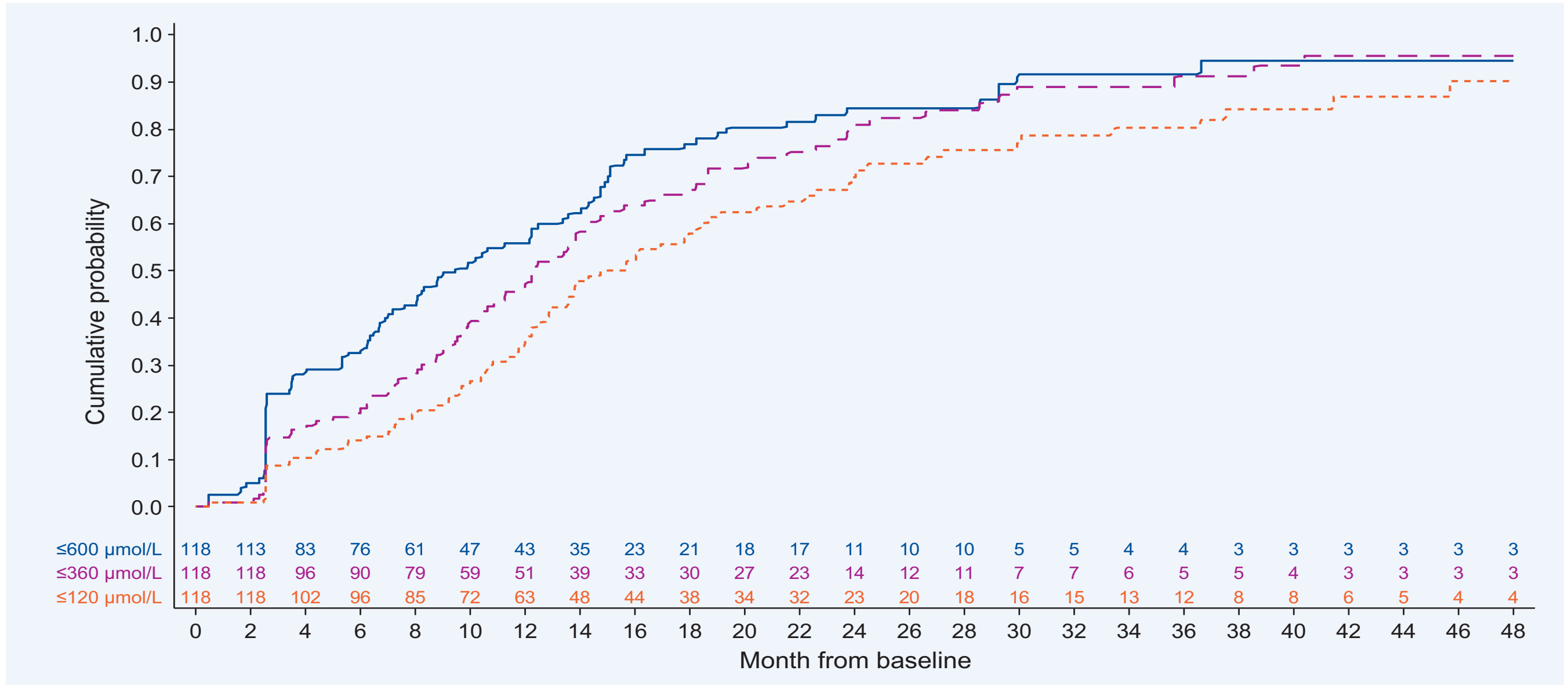
Exposure and disposition

- 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%)

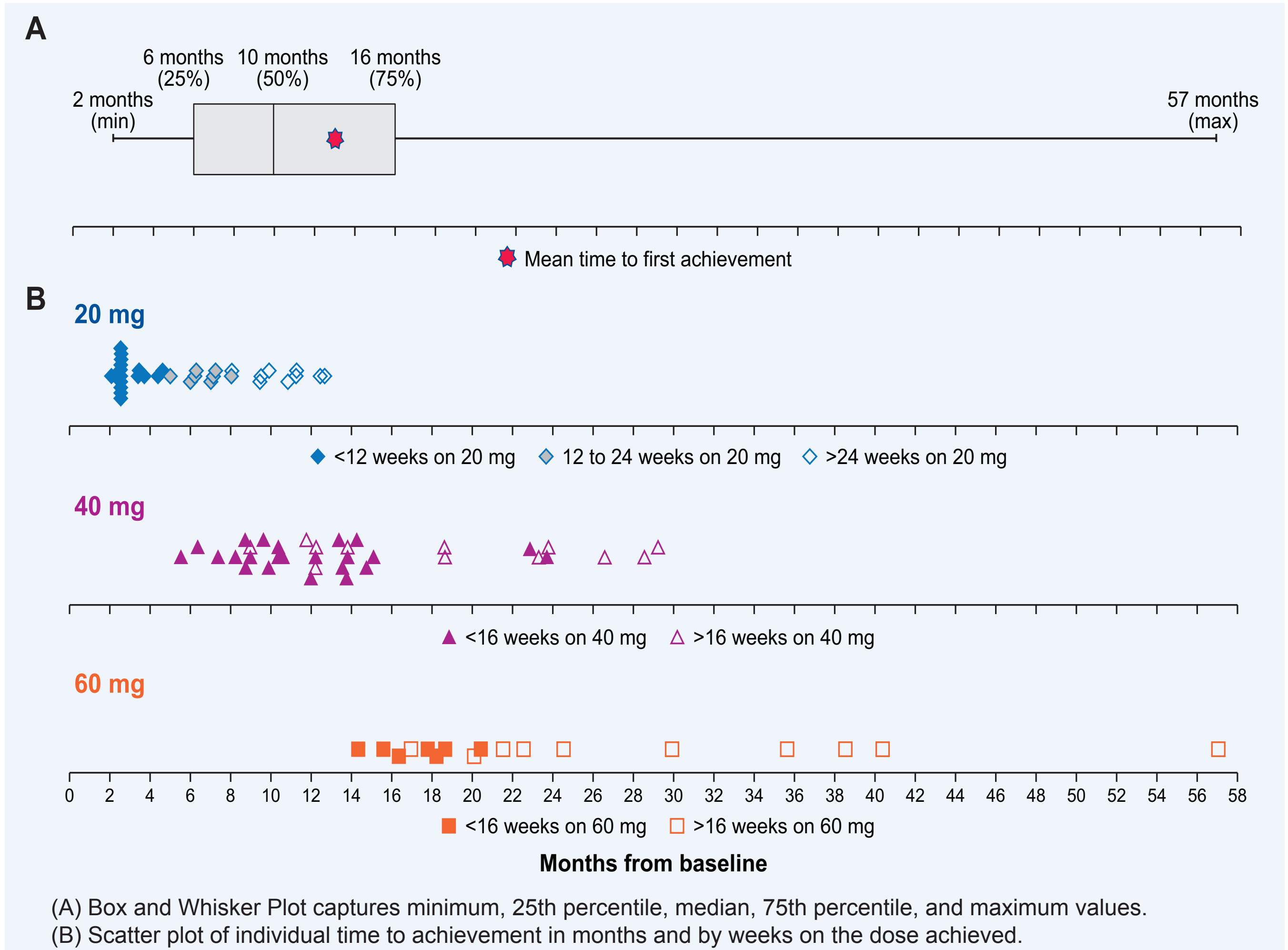
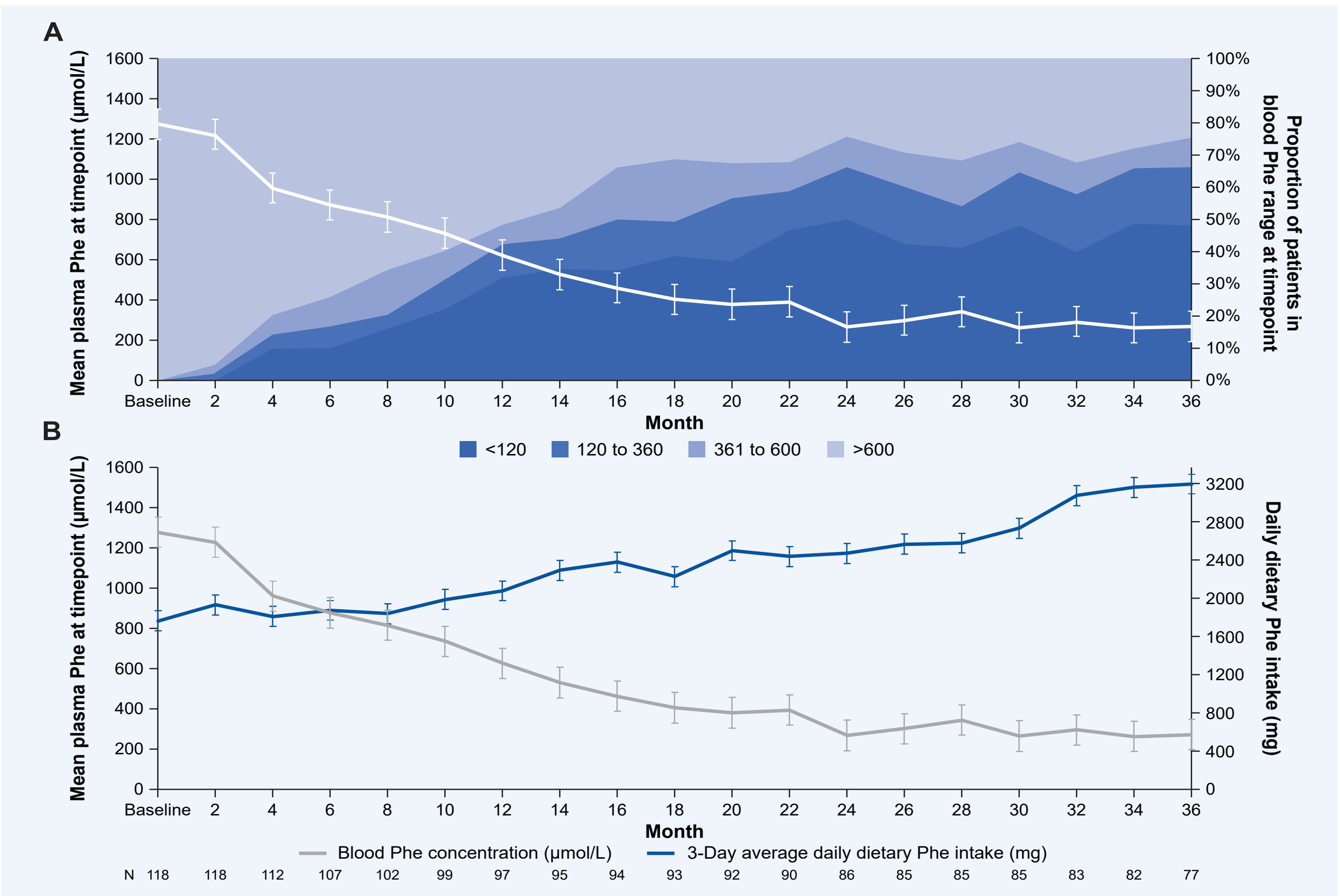


Figure 5. Mean blood Phe levels and (A) proportion of patients within each blood Phe category and (B) daily dietary Phe intake over time

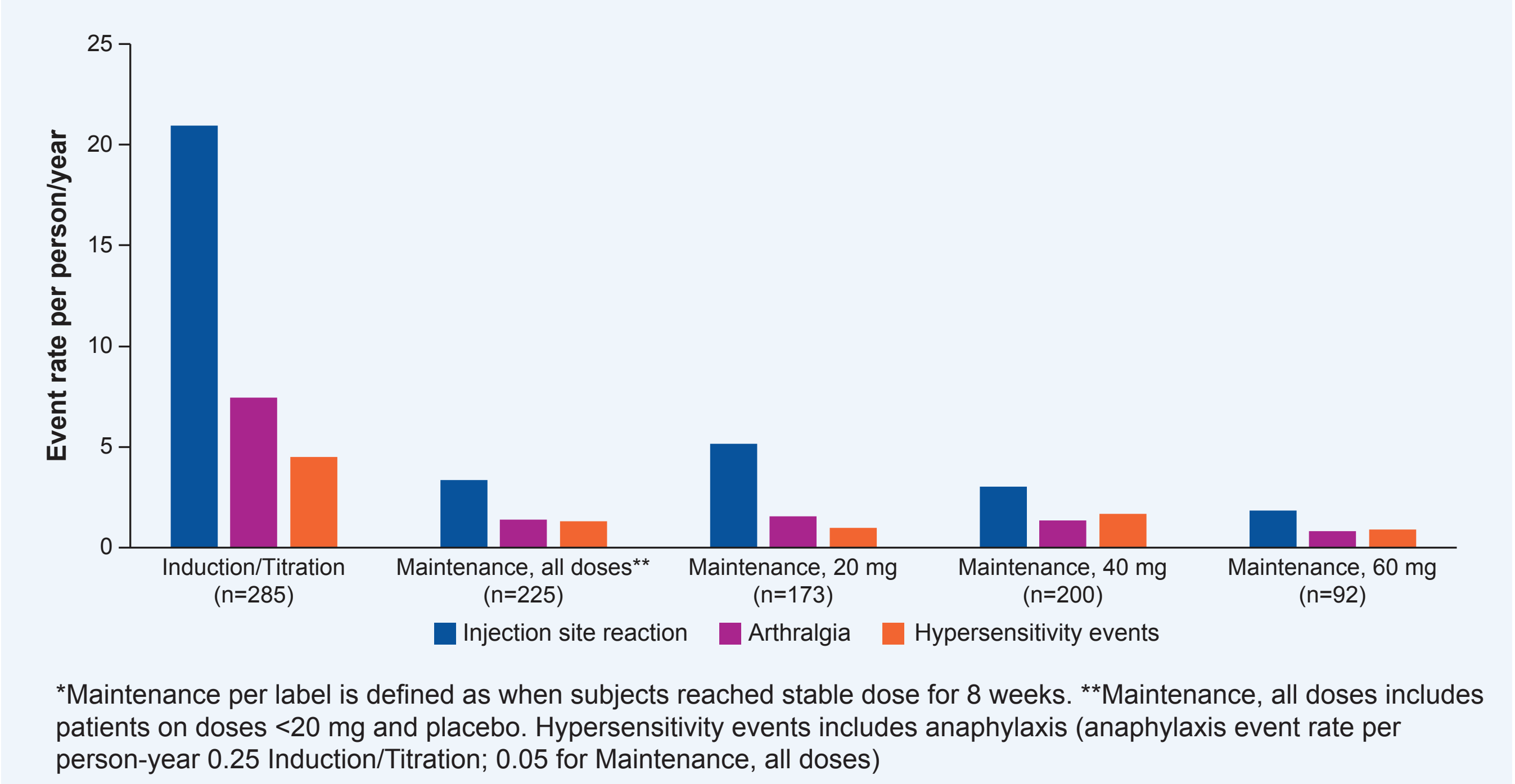


Safety

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%)	219 (95.2%)	202 (97.1%)	176 (96.2%)	138 (83.6%)	229 (99.1%)	285 (100.0%)
		7387 (58.21)	2627 (24.71)	3708 (19.25)	2274 (13.36)	2157 (10.95)	10766 (16.15)	18153 (22.87)
Serious AE		24 (8.4%)	16 (7.0%)	17 (8.2%)	8 (4.4%)	8 (4.8%)	43 (18.6%)	65 (22.8%)
		27 (0.21)	21 (0.20)	22 (0.11)	9 (0.05)	14 (0.07)	66 (0.10)	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