EFFICACY AND SAFETY OF THE RECOMMENDED PEGVALIASE DOSING REGIMEN IN ADULTS WITH PHENYLKETONURIA IN THE PHASE 3 PRISM STUDIES

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Disclosures

- Employee and stockholder of BioMarin Pharmaceutical Inc.

Phenylketonuria (PKU) and Uncontrolled Blood Phe

- 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 concentrations of Phe are neurotoxic with significant neurological, neurocognitive, neuropsychiatric, and psychosocial consequences in PKU patients of all ages
- Even with early treatment adults with PKU experience high rates of neuropsychological and neurological symptoms (**Figure 1**[1-8])

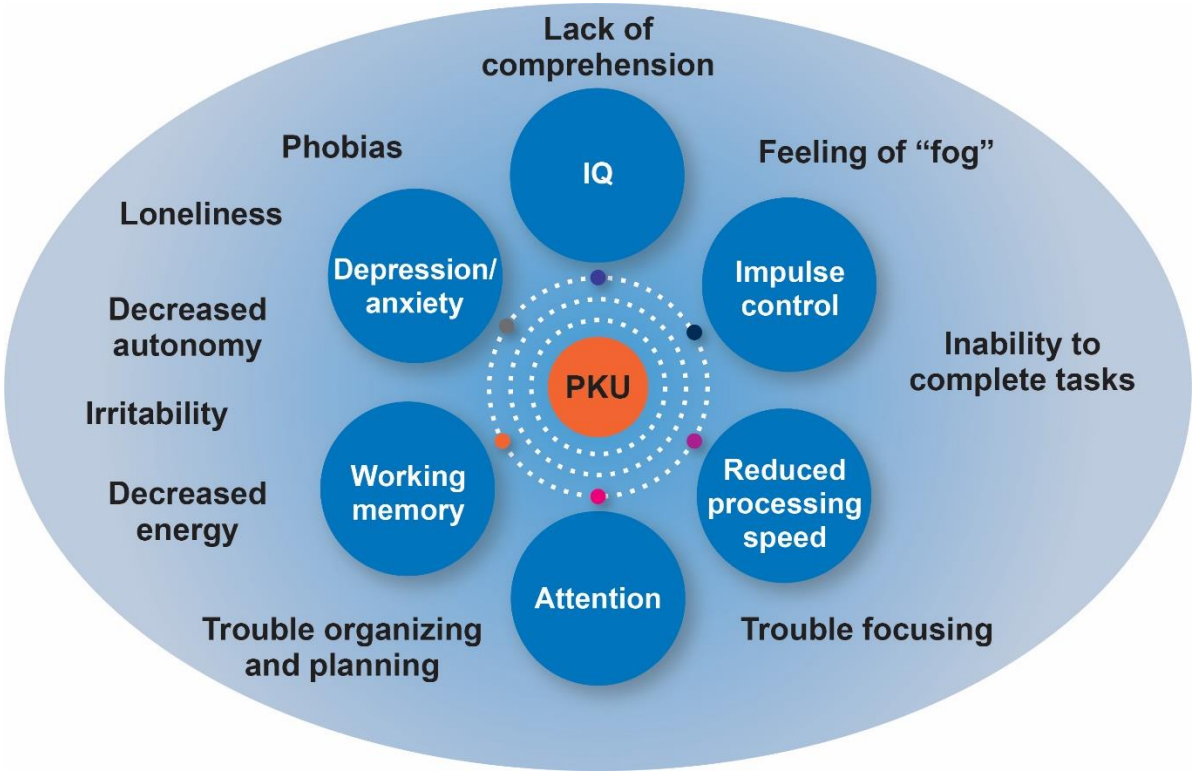


Figure 1

1. Moyle JJ, et al. *Neuropsychol Rev*. 2007;17(2):91-101.
2. Bilder DA, et al. *Dev Neuropsychol*. 2016;41(4):245-260.
3. Vockley J, et al. *Genet Med*. 2014;16(2):188-200.
4. Enns GM, et al. *Mol Genet Metab*. 2010;101:99-109.
5. Christ SE, et al. *Mol Genet Metab*. 2010;99(suppl 1):S22-S32.
6. Gentile JK, et al. *Mol Genet Metab*. 2010;99(suppl 1):S64-S67.
7. Bone A, et al. *Psychosomatics*. 2012;53(6):517-523.
8. Brumm VL, et al. *Mol Genet Metab*. 2010;99(suppl 1):S59-S63.

PKU and Unmet Therapeutic Need

- Current European and US guidelines recommend treatment for life for PKU patients to achieve recommended levels of blood Phe[1,2]
- Even actively managed adults with PKU are unable to sustain guideline blood Phe levels **(Figure 2)**
- Adherence to medical nutritional therapy (MNT) worsens with age; most adults (78%) and adolescents with PKU are unable to adhere to the severe dietary restrictions needed to control blood Phe levels[3-5]
- Of the subset of patients who can adhere to MNT, many do not achieve adequate Phe control[6]

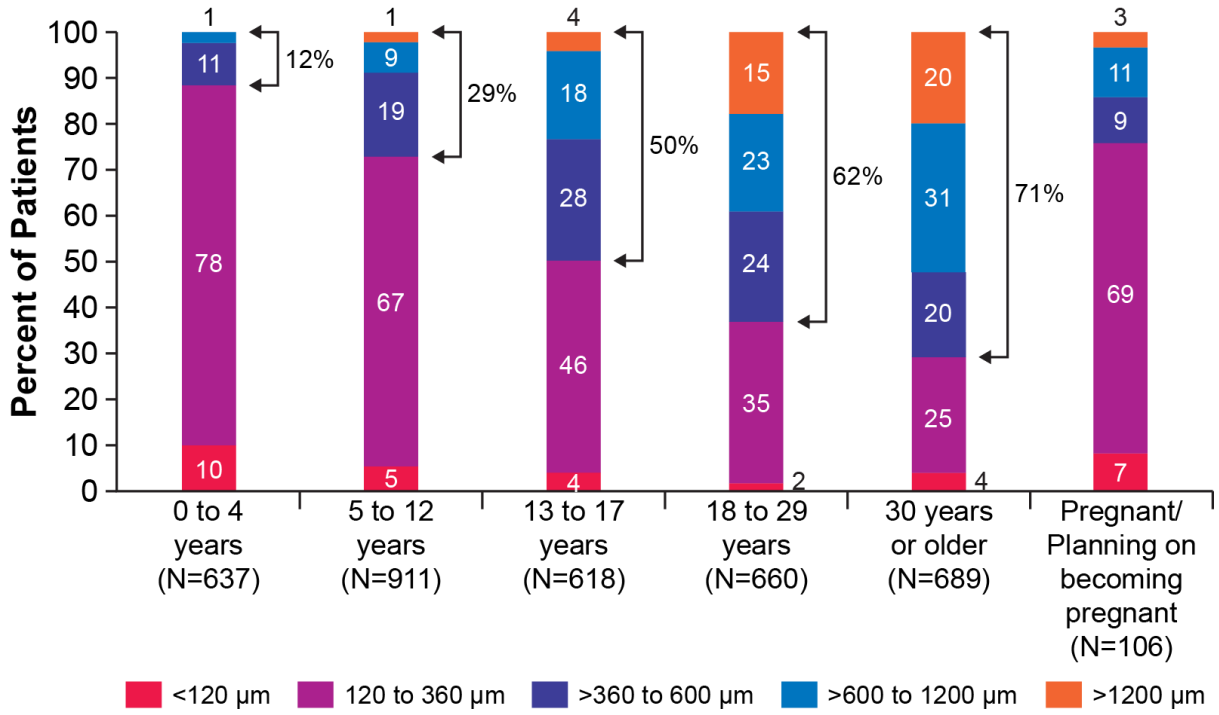


Figure 2

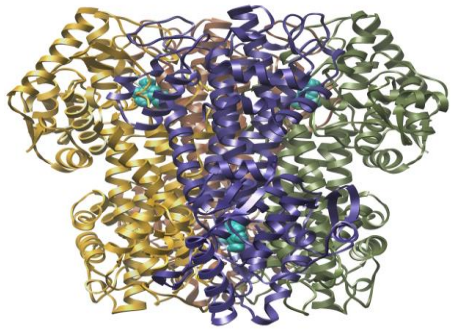
1. Vockley J, et al. *Genet Med.* 2014;16(2):188-200.
2. van Wegberg AMJ, et al. *Orphanet J Rare Dis.* 2017;12:162.
3. Jurecki ER, et al. *Mol Genet Metab*. 2017;120:190-197.
4. Berry SA, et al. *Genet Med.* 2013:15(8):591-599.
5. Waisbren SE, et al. *Mol Genet Metab*. 2007;92(1-2):63-70.
6. Enns GM, et al. *Mol Genet Metab*.2010;101:99-109.

Pegvaliase Is an Enzyme Substitution Therapy Approved to Reduce Blood Phe in Adults with PKU[1]

Canadian Indication: Palynziq (pegvaliase injection) is indicated to reduce blood Phe concentrations in patients with PKU aged 16 years and older who have inadequate blood Phe control (blood Phe levels >600 µmol/L) despite dietary management.

Phenylalanine Ammonia Lyase (PAL)

- Converts Phe to *trans*-cinnamic acid and ammonia[2,3]



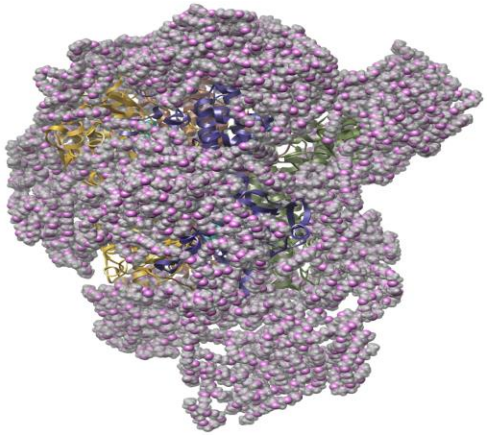
PEGylation

- Masks antibody-binding sites on PAL
- Decreases immune clearance
- Increases plasma half-life

Figure 3

Pegvaliase

- PEGylated (polyethylene glycol)
- Enzyme substitution therapy



[1]Palynziq Product Monograph, BioMarin Pharmaceutical (Canada) Inc., 2022
[2]Sarkissian CN, Gámez A. *Mol Genet Metab*. 2005;86(Suppl 1):S22-S26.
[3]Bell SM, et al. *PLoS ONE*. 2017;12(3):e0173269.

The Safety and Efficacy of Pegvaliase Have Been Studied in Clinical Trials Spanning Over a Decade

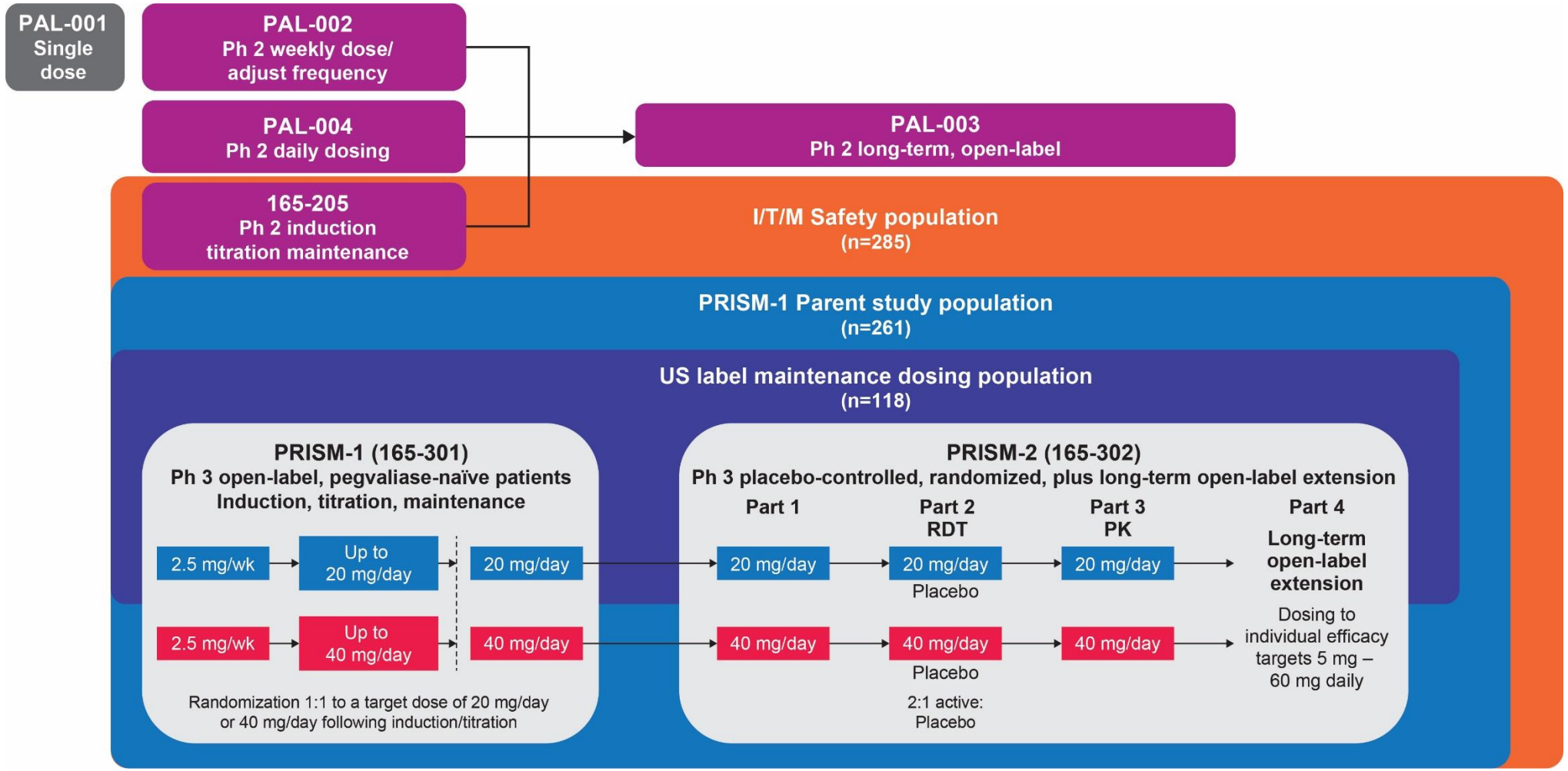


Figure 4

PRISM-1: Induction/Titration/Maintenance Dosing Regimen[1]

Study period	Duration (weeks)	Dose (mg)	Frequency of Admin/week	Total Weekly Dose (mg)
Induction	4	2.5[a]	1	2.5
Titration	Up to 30	2.5	2[b]	5
		10	1	10
		10	2[b]	20
		10	4	40
		10	7	70
		20	7	140
Maintenance	At least 2	20 or 40	7	140 or 280

[a]Self-administration of at least first 2 doses performed in clinic.
[b]Recommended to separate doses by at least 1 day.

Table 1

[1]Thomas J, et al. *Mol Genet Metab*. 2018;124(1):27-38.

PRISM Studies: Pre-Treatment Baseline for the US Label Maintenance Dosing Population (n=118) Was Consistent with the PRISM-1 Parent Population Overall[1] (N=261)

	PRISM-1 Parent Study Population (N=261)	US Label Maintenance Dosing Population (n=118)
Blood phenylalanine, 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)

Baseline was defined as the last measurement before the first dose of pegvaliase (i.e., treatment-naïve) in PRISM-1. Sample size may vary due to missing data. Dietary Phe and total protein intake (includes medical food and natural dietary protein intake) was calculated as the daily average intake over 3 days prior to the assessment point.

Table 2

Definition of n=118 population was subjects with a baseline blood Phe ≥600 µmol/L who were randomized to, and received, ≥1 dose of pegvaliase 20 mg once daily.

[1]Thomas J, et al. *Mol Genet Metab*. 2018;124(1):27-38.

Discontinuations were most frequent in the first 6 months of treatment, with adverse events cited as the most common reason

Discontinuations	PRISM-1 Parent Study Population (N=261)	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)

Table 3

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

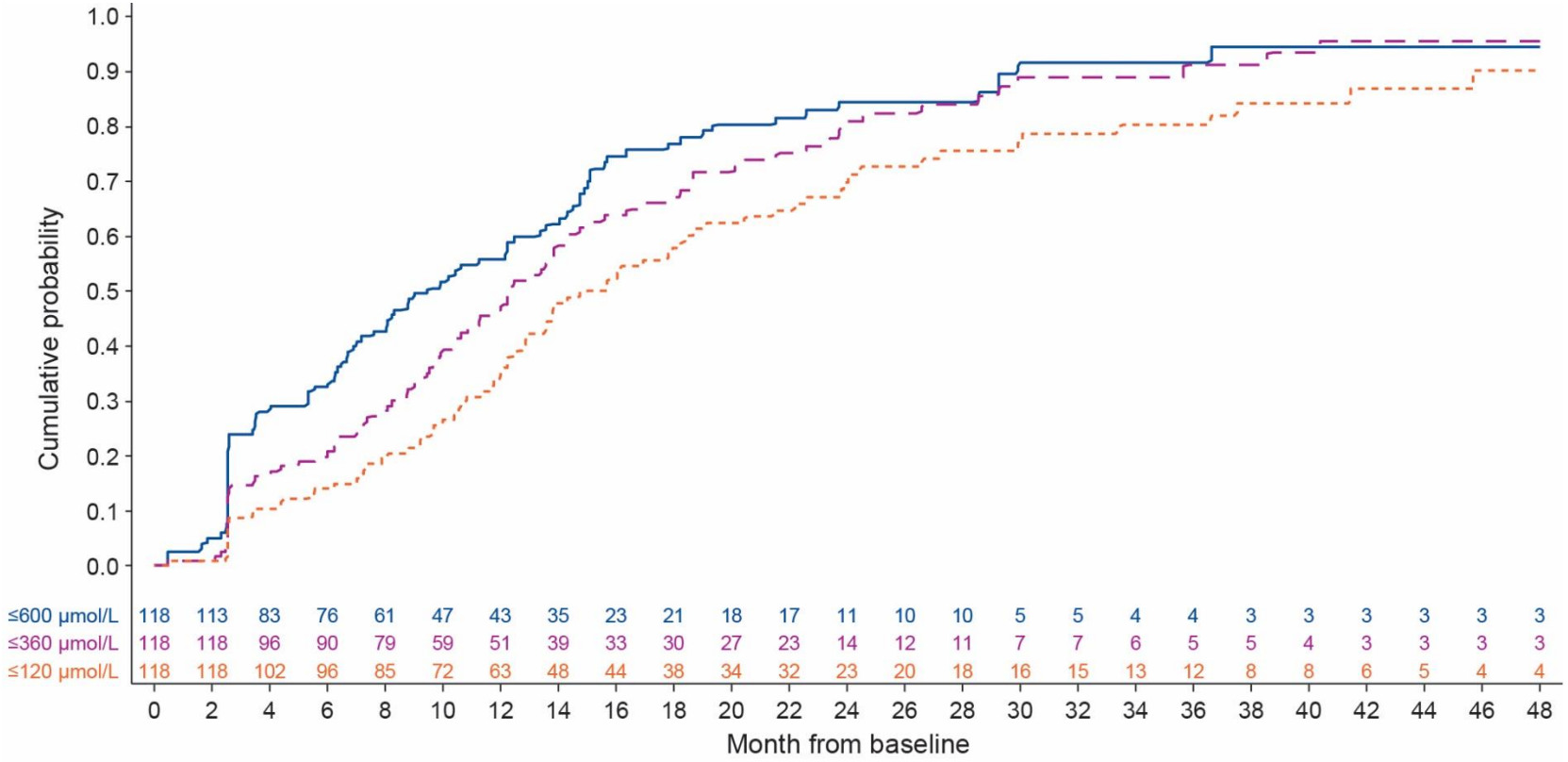


Figure 5

Distribution of time and dose at first achievement of ≤360 µmol/L for those who achieved (n=89/118)

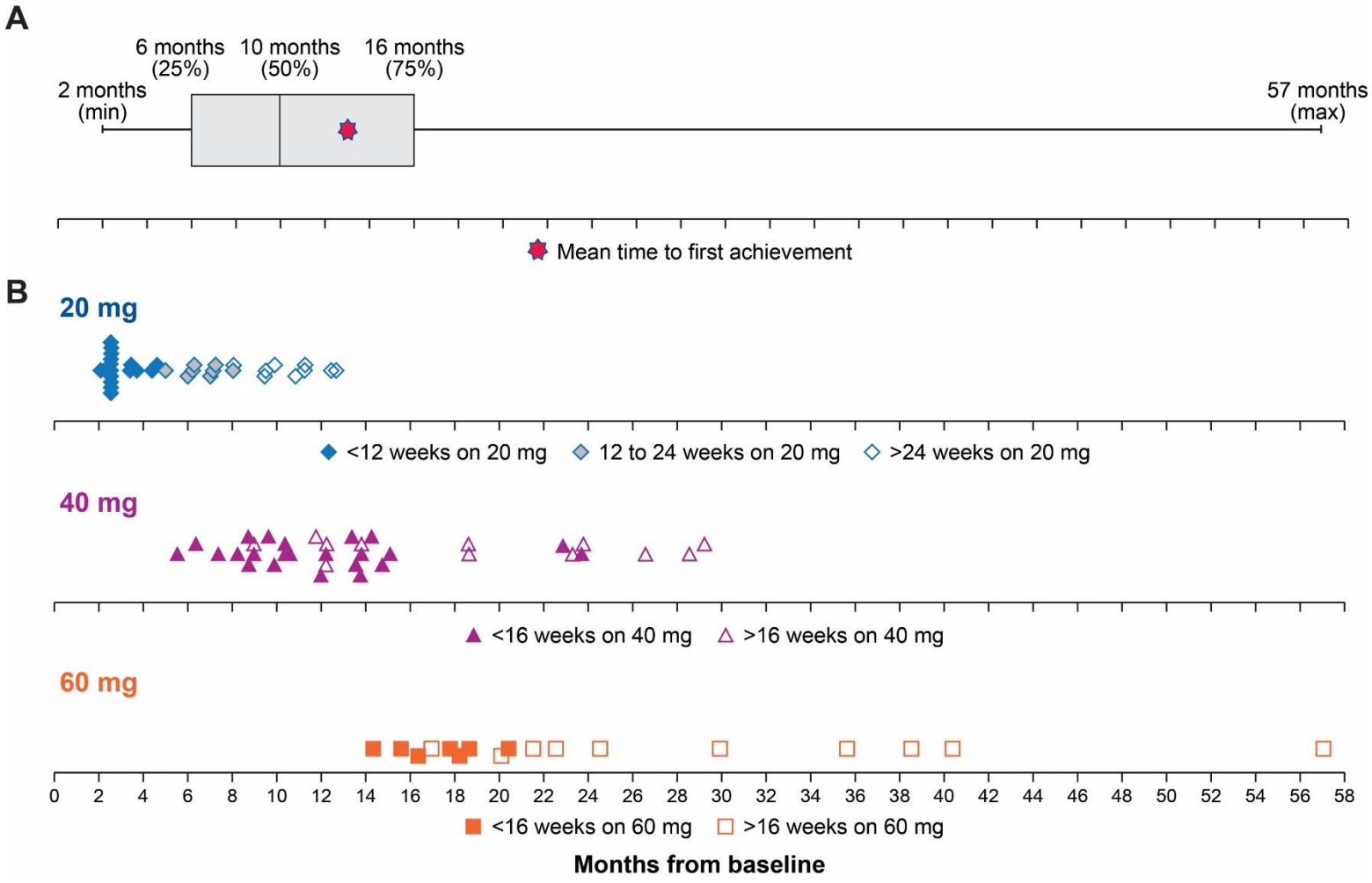


Figure 6

Mean blood Phe levels and A. proportion of patients within each blood Phe category and B. daily dietary Phe intake over time (N=118)

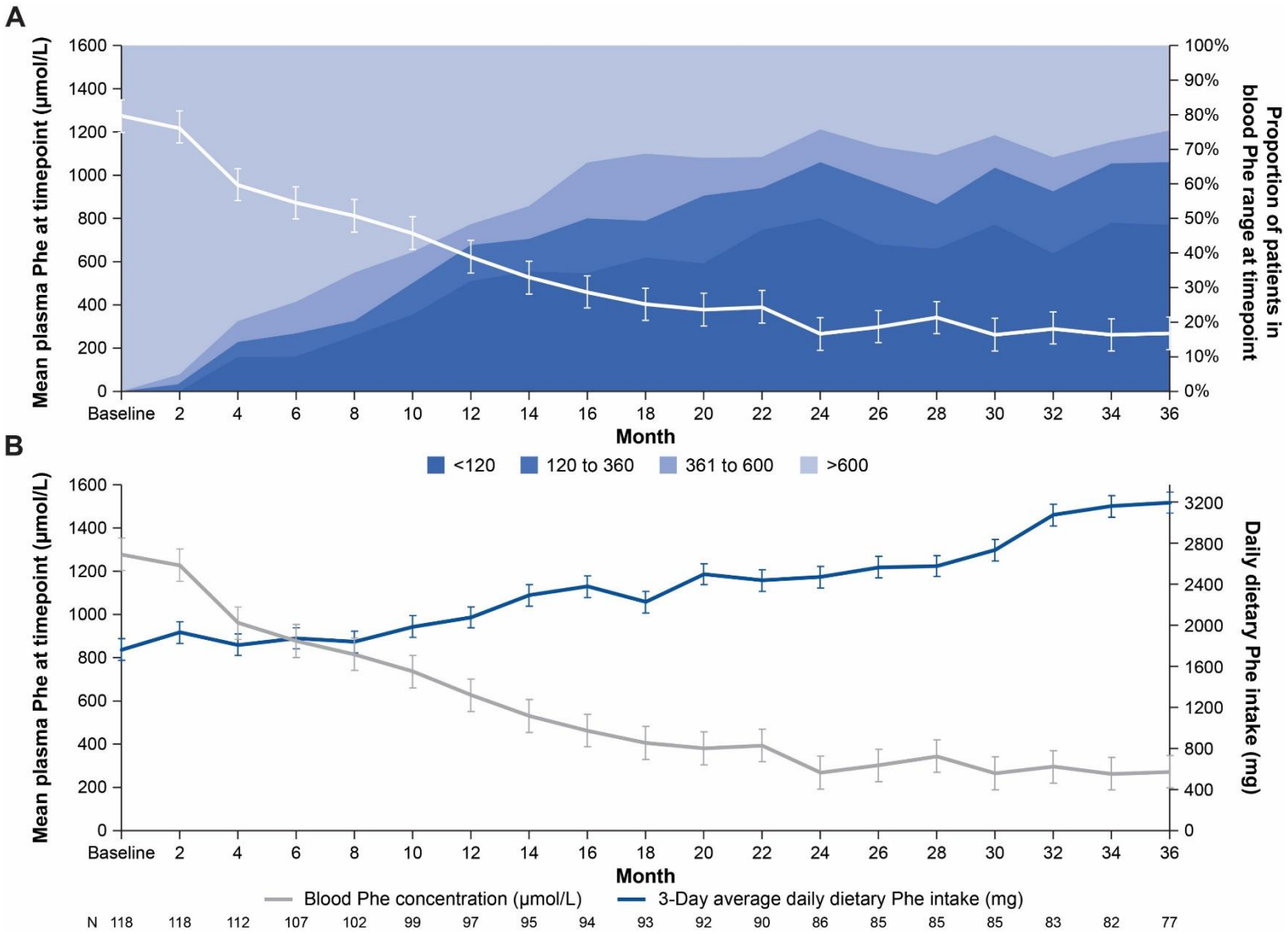


Figure 7

Safety Results: Overall Adverse Event Rate Decreased with Continued Exposure and Most AEs Were Mild or Moderate (N=285)

	Early (≤6 Months)	Late (>6 Months)					Overall
		>6 Months to ≤1 Year	>1Year to ≤2 Years	>2 Years to ≤3 Years	>3 Years	Total	
Participants, N	285	230	208	183	165	231	285
Total treatment exposure (person-years)	126.9	106.3	192.6	170.2	197.0	666.6	793.7
Event per Person-Year[1] (Number of Events)							
Adverse Event (AE)	58.21 (7387)	24.71 (2627)	19.25 (3708)	13.36 (2274)	10.95 (2157)	16.15 (10766)	22.87 (18153)
Serious Adverse Event (SAE)	0.21 (27)	0.20 (21)	0.11 (22)	0.05 (9)	0.07 (14)	(0.10) 66	0.12 (93)

[1]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.

Table 4

Acute Systemic Hypersensitivity (Anaphylaxis) Reactions Were Not IgE Mediated[1]

- 16 (5.6%) of 285 subjects experienced a total of 25 episodes of acute systemic hypersensitivity (anaphylactic) reactions, of whom 4 patients (1%, 4/285) experienced a reaction that was considered severe
  - 10/16 were re-challenged
    - 4/10 had at least one recurrence
    - No events occurred at time of next dose
    - 7/16 discontinued treatment
- No intubations or vasopressor therapy were required for any events
- No events associated with drug-specific immunoglobulin E at or near the time of the event
  - Immunogenicity studies suggest Type III, immune complex-mediated hypersensitivity
- All events resolved without sequelae

[1]Palynziq Product Monograph, BioMarin Pharmaceutical (Canada) Inc., 2022

Safety Results: Rates of the 3 Most Common Adverse Reactions Decrease from Induction/Titration to Maintenance*, Irrespective of Dose[1]

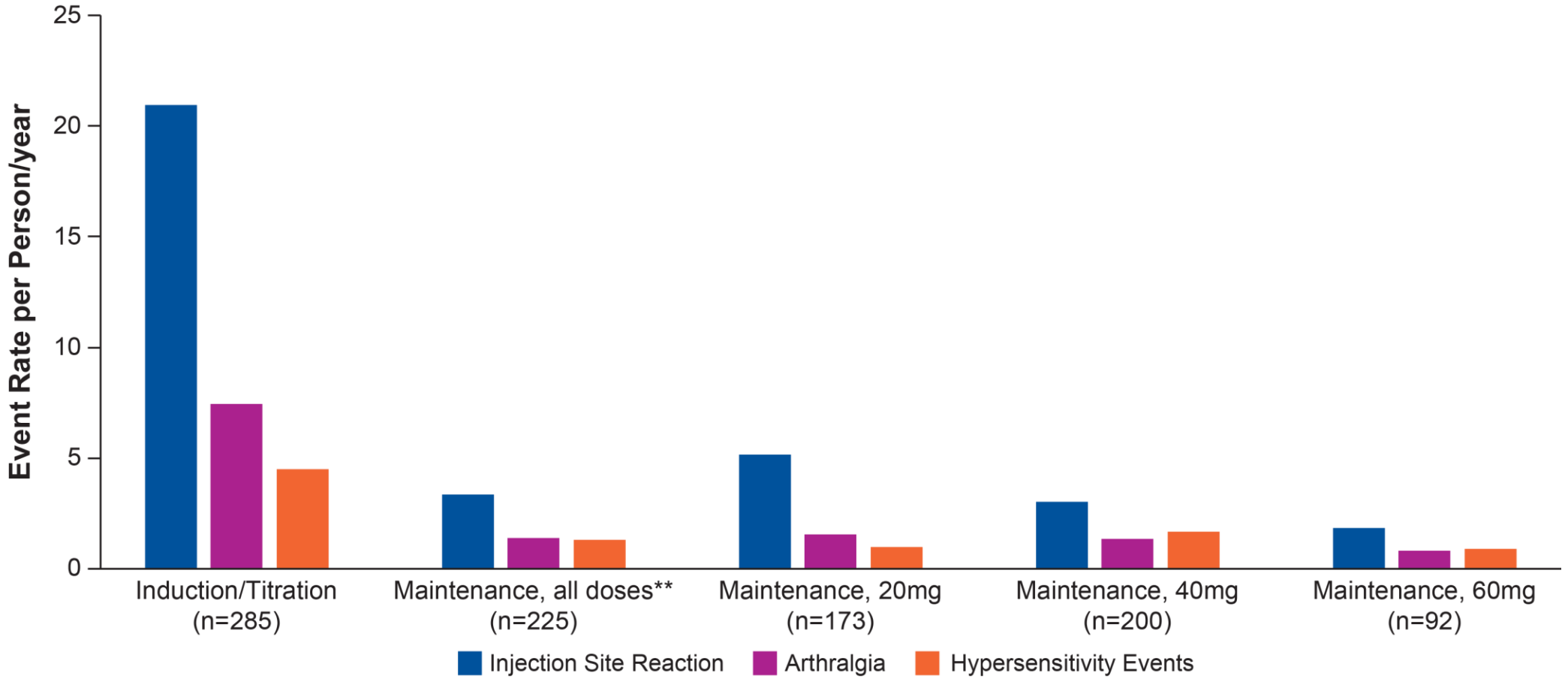


Figure 8

*Maintenance per US label is defined as w hen subjects reached stable dose for 8 w eeks. Definition of "Maintenance" for safety data varies by country. **Maintenance, all doses includes patients on doses <20mg and placebo Hypersensitivity events includes anaphylaxis (anaphylaxis event rate per person-year 0.25 Induction/Titration; 0.05 for maintenance, all doses)

[1]PALYNZIQ [package insert]. Novato, CA: BioMarin Pharmaceutical Inc.; November 2020.

Conclusions

- In clinical trials, pegvaliase demonstrated sustained and substantial 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