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THE LONG-TERM SAFETY AND EFFICACY OF PEGVALIASE 60 MG/DAY IN ADULTS WITH PHENYLKETONURIA

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（BioMarin）

Phenylketonuria (PKU) and Uncontrolled Blood Phe

- PKU is caused by deficiency in the phenylalanine hydroxylase (PAH) enzyme, resulting in phenylalanine (Phe) accumulation in the blood and brain
- High concentrations of Phe are neurotoxic with significant neurological, neurocognitive, neuropsychiatric, and psychosocial consequences (**Figure 1**[1-8])
- Even actively managed adults with PKU are unable to sustain guideline-recommended blood Phe levels[9]

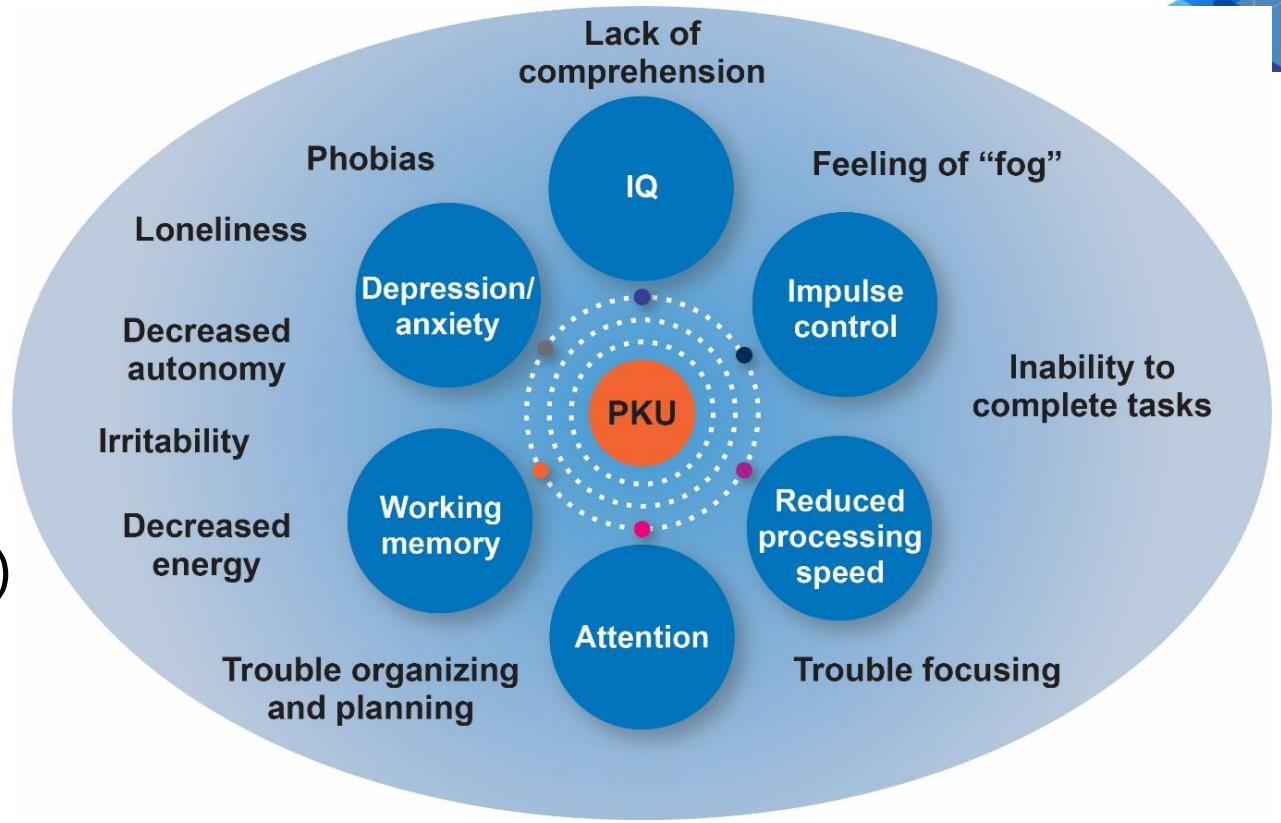

Figure 1

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. 9. Jurecki ER, et al. *Mol Genet Metab*. 2017;120:190-197.

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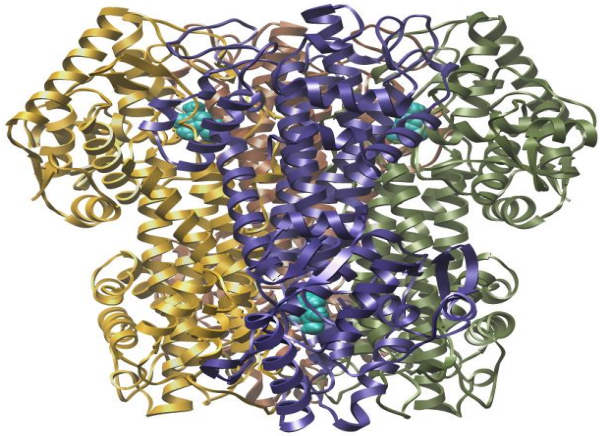
Pegvaliase is an Enzyme Substitution Therapy to Reduce Blood Phe in PKU Patients Independent of PAH Activity

Phenylalanine ammonia lyase (PAL)

- Converts Phe to *trans*-cinnamic acid and ammonia



PEGylation

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

Pegvaliase

- PEGylated (polyethylene glycol)
- Enzyme substitution therapy

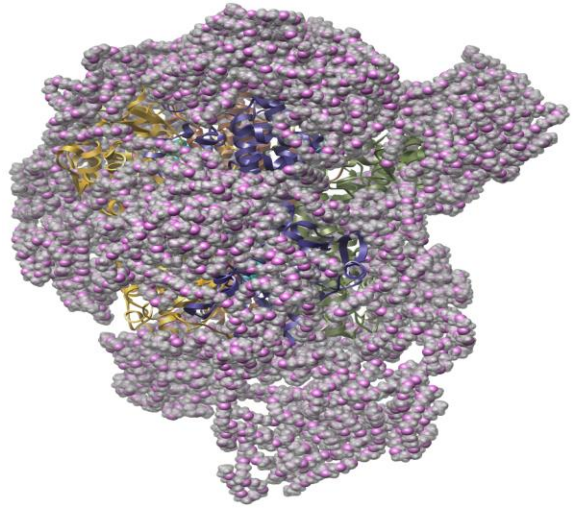


Figure 2

Sarkissian CN, Gámez A. *Mol Genet Metab*. 2005;86(Suppl 1):S22-S26.
Bell SM et al. *PLoS ONE*. 2017;12(3):e0173269.

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US Label Recommended Dosing Schedule

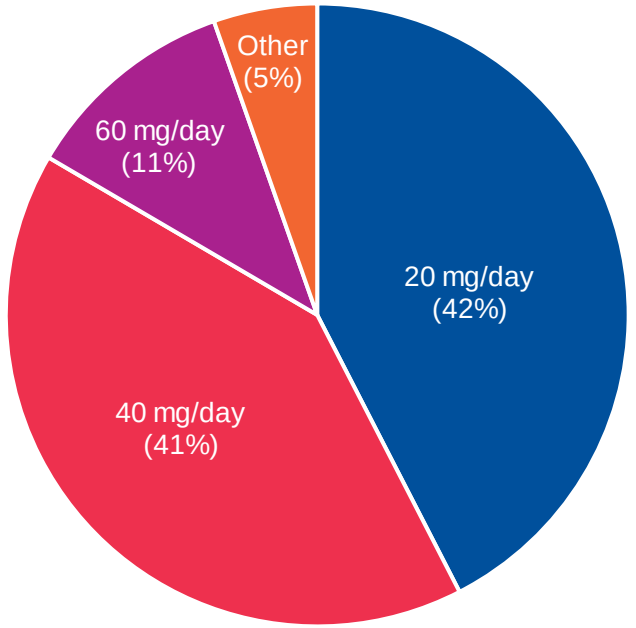
Dosing to 60 mg/day should be considered in patients who have not responded with 40 mg/day after 16 weeks

Table 1. Recommended Dosing Schedule

Treatment	Duration (weeks)	Dosage*
Induction	4	2.5 mg once weekly
Titration	1	2.5 mg twice weekly
	1	10 mg once weekly
	1	10 mg twice weekly
	1	10 mg four times per week
	1	10 mg once daily
Maintenance†	24	20 mg once daily
	16	40 mg once daily
Maximum‡	16	60 mg once daily

*Additional time may be required prior to each dosage escalation based on patient tolerability. † Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to 40 mg once daily in patients who have not achieved a response with 20 mg once daily continuous treatment for at least 24 weeks. Consider increasing to a maximum of 60 mg once daily in patients who have not achieved a response with 40 mg once daily continuous treatment for at least 16 weeks. ‡ Discontinue pegvaliase in patients who have not achieved an adequate response after 16 weeks of continuous treatment at the maximum dosage of 60 mg once daily.

Figure 3. Maximum dose US commercial dispensing data[1]



1. Lah M, et al. *Mol Genet Metab Rep.* 2022;33:100918.

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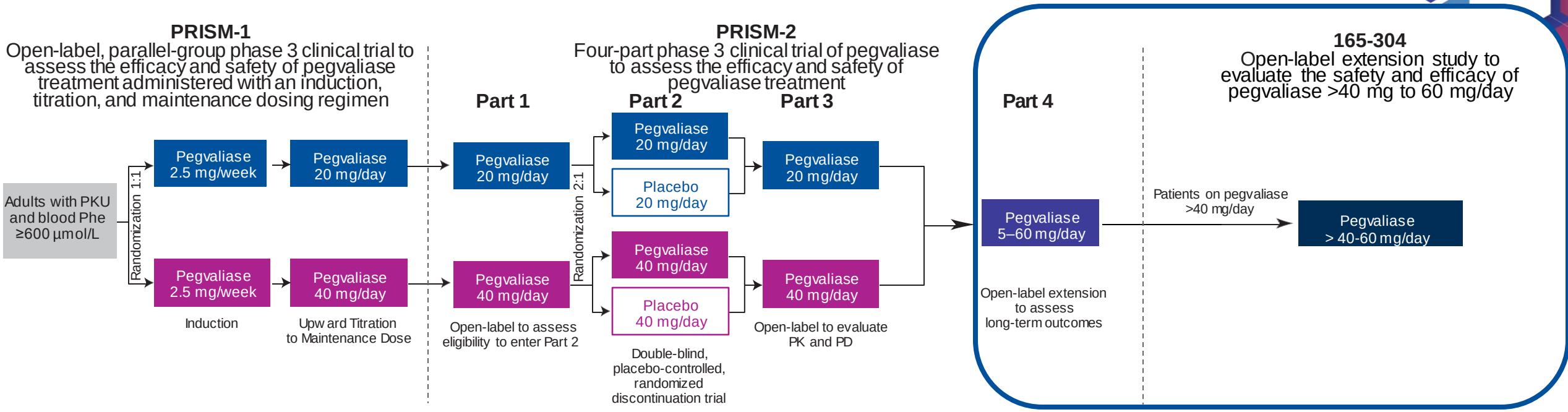
Use of Pegvaliase Up to 60 mg/day Dose Was Approved in US from the Results of the Phase 3 PRISM Trials

Figure 4. Study design for PRISM-1, PRISM-2, and 165-304



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Baseline Characteristics - Similarities and Key Differences

Baseline characteristics of 60 mg/day stable dose reflect the overall population; marginal differences observed in weight and % male

Table 2. Baseline characteristics

	Stable 60 mg Dose Cohort	Other PRISM Participants
Number of subjects	51	222
Age (years), Mean ± SD	28.5 ± 9.3	28.0 ± 6.6
Female, n (%)	20 (39.2%)	119 (53.6%)
Weight (kg), Mean ± SD	86.7 ± 25.7	78.5 ± 19.8
Body Mass Index* (kg/m^2), Mean ± SD Underweight/Normal, n (%) Overweight, n (%) Obese, n (%)	29.6 ± 7.5 17 (33.3%) 11 (21.6%) 22 (43.1%)	28.1 ± 6.7 85 (38.3%) 61 (27.5%) 76 (34.2%)
Blood Phe (µmol/L), Mean ± SD	1304 ± 358	1213 ± 389

* BMI Categories defined by Weir CB & Jan A. (2019). BMI classification percentile and cut off points. Underweight/Normal (<25 kg/m^2), Overweight (<25 - <30 kg/m^2), Obese (≥30 kg/m^2)

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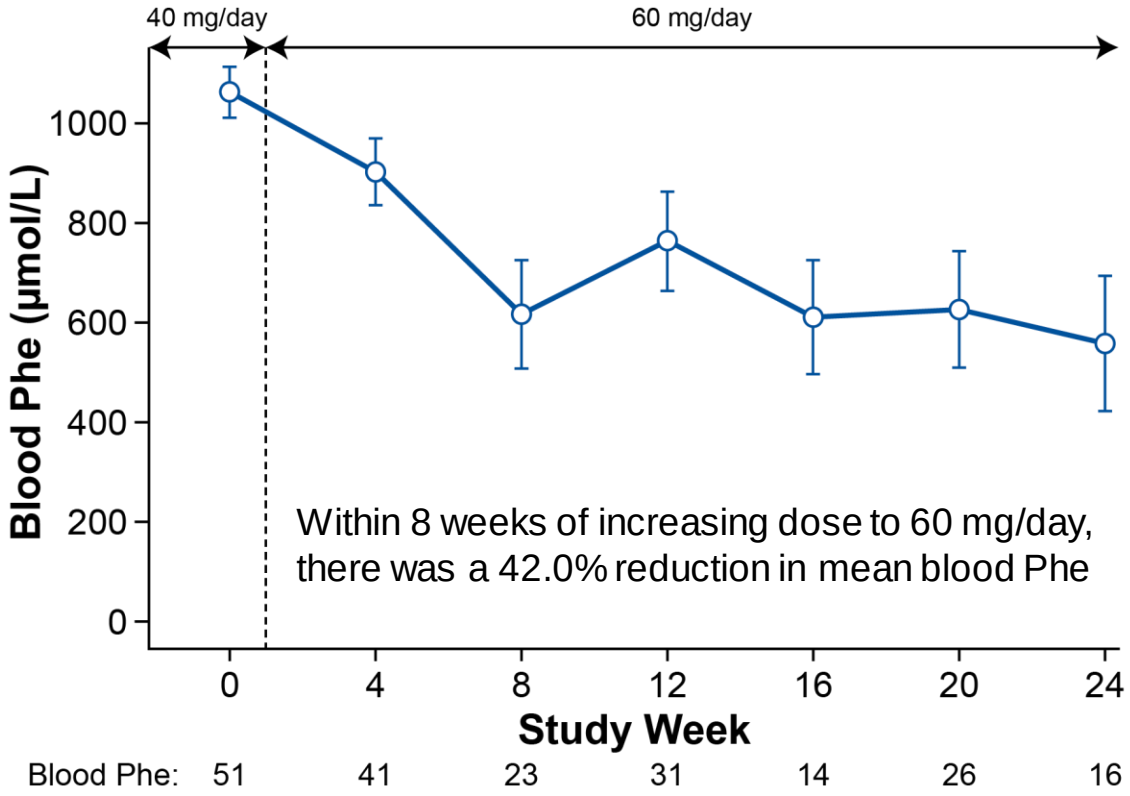
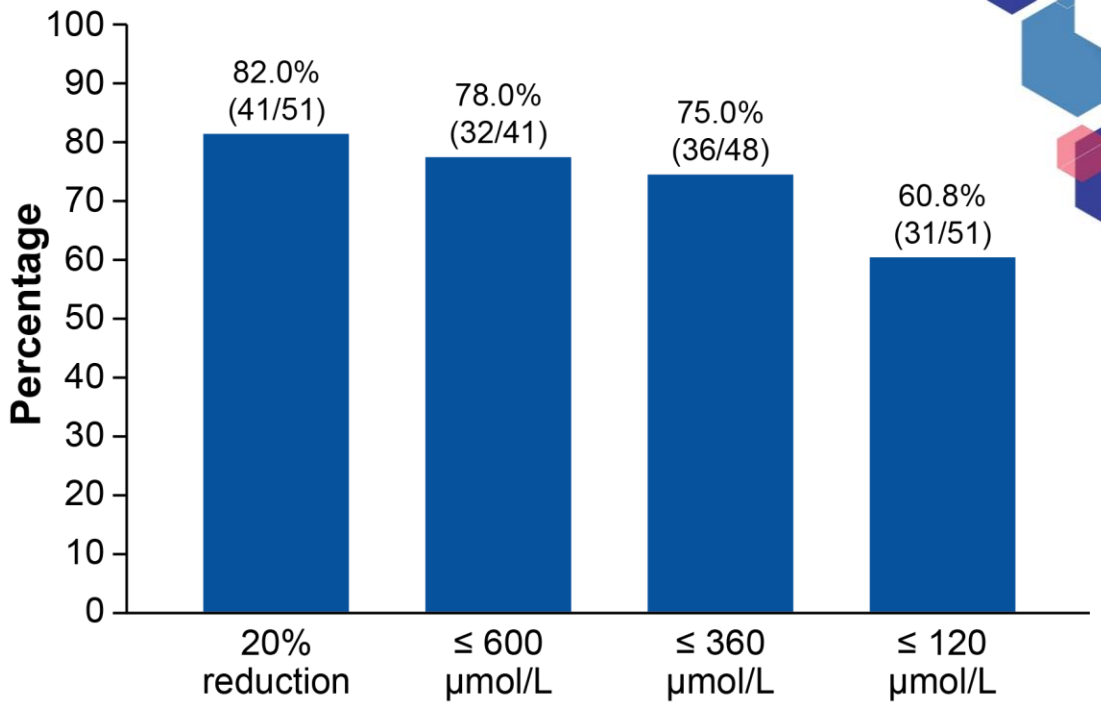
Blood Phe Reductions After Titration to 60 mg in the First 24 Weeks (Figure 5) and Through the End of Long-term Follow-up (Figure 6)

Figure 5. Mean (SE) plot of blood Phe in the first 24 weeks after dose titration from 40 to 60 mg/day



Participants were getting Phe assessments every 8 weeks (rather than every 4 weeks).

Figure 6. Percentage of participants achieving a meaningful blood Phe reduction after titration to 60 mg/day through the end of long-term follow-up*



*The percent of participants for each blood Phe milestone is calculated as percent of participants with Phe at each milestone on 60 mg/day amongst the participants who did not have Phe milestone using last Phe on or prior to reaching 60 mg/day dose.

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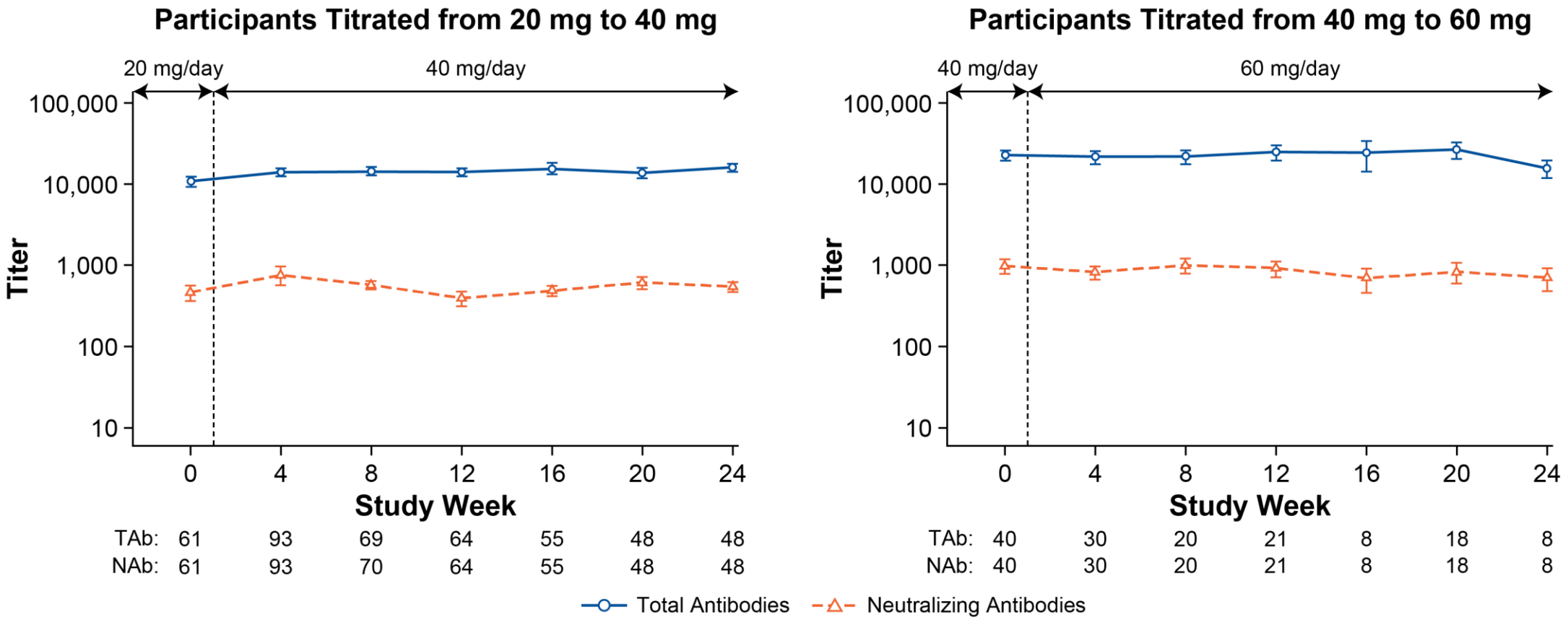
Impact of Dose Titration on Antibody Titers

- Antibody titers **remained stable** and did not increase over long-term treatment or after dose increases

Figure 7. Antibody titers in participants titrated from 20 to 40 mg/day and 40 to 60 mg/day



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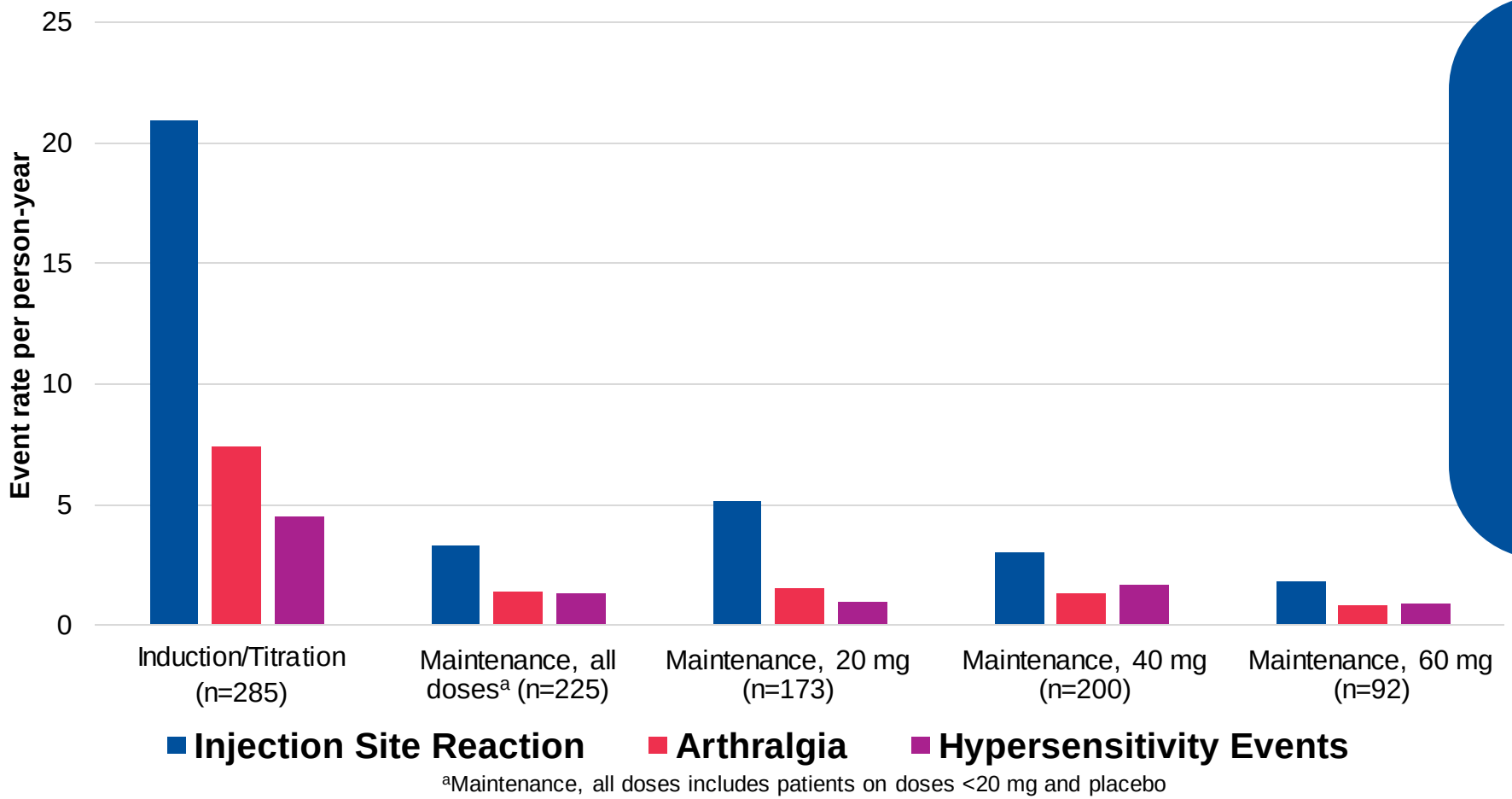
Rates of the 3 Most Common Adverse Events in ≥60 mg Cohort Mirrors Lower Maintenance Doses

Figure 8. Rates of 3 Most Common Adverse Events in ≥60 mg Cohort



[a]Maintenance, all doses includes patients on doses <20 mg and placebo

- Maintenance is defined as when participants reached stable dose for 8 weeks
- Hypersensitivity events includes anaphylaxis (anaphylaxis event rate per person-year: 0.25 Induction/Titration; 0.05 for Maintenance, all doses)

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

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Conclusions

- The unique immune response to pegvaliase requires dose individualization
  - Demographics of ≥60 mg dose cohort are similar to the larger phase 3 population
- Participants requiring exposure to higher doses achieved guideline-recommended thresholds
  - The maximum labeled dose of pegvaliase presents an opportunity for successful disease management to both EU, US, and Japanese targets
  - Long term, dose reductions were possible after efficacy achievement
- There were no new safety signals in the 60 mg stable dosing cohort
  - AE rates mirror that of lower maintenance doses
  - Total and Nab were stable when escalating between maintenance doses
- The 60 mg/day dose provides an opportunity for meaningful Phe reduction while maintaining an acceptable safety profile

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