

Long-term management strategies for pegvaliase use in phenylketonuria: Lessons learned from the Phase 3 PRISM open-label extension study

Harding CO, Whitehall KB, Lilienstein J, Sazova O, Lindstrom K, Levy DG, Burton BK. Genetics in Medicine. 2025;27:101459.

Long-term management strategies for pegvaliase use in phenylketonuria: Lessons learned from the Phase 3 PRISM open-label extension study

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Background

- Pegvaliase pharmacokinetics differ among individuals, causing variable times to reach target blood Phe levels
- This study aimed to model pegvaliase's impact on blood Phe levels in PKU and identify markers to guide diet and dose adjustments after immune tolerisation



PRISM study design

- Participant-level data were used from PRISM-1, PRISM-2 and 165-304 trials to develop a PK/PD model that explains individual-level blood Phe patterns as a function of pegvaliase clearance during the maintenance phase

Key findings



PK/PD modelling

In the post-I/T period, **consistently low blood Phe** should be seen as a sign that **immune tolerance** has likely been achieved



Example patient-level coding

Dose escalation induced immune tolerance and stable blood Phe control, **allowing down-dosing over time**



Down-dosing

Down-dosing was most successful when started at **very low blood Phe levels**



Safety profile

Highest AE rates occurred during I/T, when antibody titers were peaking



Conclusions

A staged approach to pegvaliase treatment includes achieving immune tolerance, liberalising diet, and gradually reducing dose

AE, adverse event; I/T, induction/titration; PD, pharmacodynamics; Phe, phenylalanine; PK, pharmacokinetics; PKU, phenylketonuria.

Treatments mentioned in this document may not be approved for use in your country. Please consult local licensing authorities for further information. In the EU/European Economic Area, PALYNZIQ® (pegvaliase) is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/L) despite prior management with available treatment options. Pegvaliase indications and prescribing information are listed at the end of this document. Some links in this document are "external links" to websites over which BioMarin has no control and for which BioMarin assumes no responsibility. This publication summary has been developed and funded by BioMarin. ©2026 BioMarin International Ltd. All Rights Reserved. For healthcare professionals only. COM-ET-1288. Date of preparation: March 2026.



Background



Pegvaliase is an enzyme substitution therapy that provides an alternative pathway to metabolise Phe¹



The Phase 3 PRISM clinical trials demonstrated pegvaliase as an efficacious treatment in reducing blood Phe^{2,3}

- However, PK variability among patients impacts the time to achieve target blood Phe levels, resulting in variable times to achieve blood Phe targets



This study aimed to model pegvaliase's impact on blood Phe levels in PKU and identify markers to guide diet and dose adjustments after immune tolerisation



Methods

Study design & population



- Data were analysed from **261 adults** with PKU who received pegvaliase in the PRISM-1 (induction of 2.5 mg/once weekly followed by 20 mg/day to 40 mg/day), **PRISM-2** (5 mg/day to 60 mg/day), and **165-304 trials** (>40 mg/day)
- Participants followed an **I/T/M** dosing regimen and were eligible to continue based on pegvaliase dose and response





Methods

PK/PD modelling

- PRISM-2 included a 2-part PK/PD sampling period completed by a subset of 57 participants
- Pegvaliase in human blood was measured using ELISA
- Blood Phe was collected throughout the study period, initially at monthly intervals, and at later time points at bimonthly intervals
- A PK model was used to estimate **immune-mediated drug clearance** using Michaelis–Menten kinetics
- A PD model was used to link pegvaliase exposure to **dietary Phe intake** and **blood Phe concentration**

SPR

- Initial SPR was defined as the time after treatment initiation at which the upper bound of the confidence band crosses and falls below clinical thresholds (≤ 600 , ≤ 360 , ≤ 120 $\mu\text{mol/L}$)





Methods

Down-dosing analysis:

- A total of 84 participants achieved SPR360 and were evaluated for **down-dosing success** based on timing and blood Phe levels
- Dose adjustments were classified as successful if **Phe control was maintained** without rebound or escalation

Assessments conducted

PK/PD

Blood Phe collected throughout the study period

3-day diet diaries, reviewed and analysed using nutrient analysis software

Self-reported injection logs
(dose, time, site)

Safety
Total and neutralizing antibodies to pegvaliase





PK/PD modelling shows pegvaliase dose and clearance affects blood Phe control



The model shows the relationship of blood pegvaliase concentration to pegvaliase exposure and the sensitivity of blood Phe to variations in pegvaliase clearance

Pegvaliase exposure is influenced by dose, dosing frequency and half-life



As the proportion of Phe metabolism achieved by pegvaliase increases, the impact of baseline Phe on the relationship between blood Phe and dietary Phe is reduced

Pegvaliase allows dietary Phe intake to be increased substantially with minimal blood Phe increases





Dose escalation led to immune tolerisation and stable blood Phe control, allowing successful down-dosing over time



Blood Phe stayed high for >1 year on 20 mg/day; increasing to 40 mg and then 60 mg caused fluctuations, followed by a rapid drop to <30 $\mu\text{mol/L}$



Changes in blood Phe signal the onset of immune tolerisation, and intact protein intake could be increased per protocol without losing blood Phe control

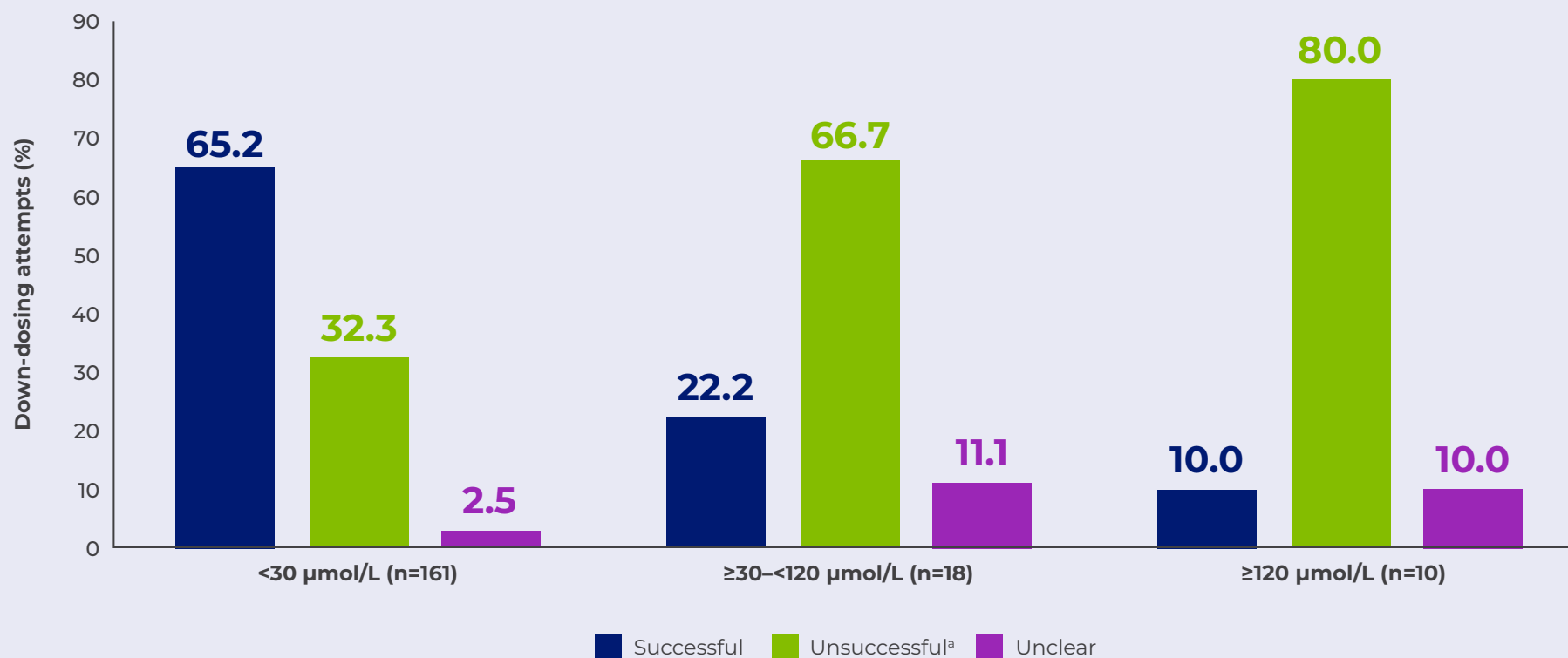


Over time, down-dosing to 40 mg/day and then 20 mg/day became possible without loss of blood Phe control





Down-dosing was most successful when started at very low blood Phe levels



^aDown-dosing was considered to be unsuccessful if SPR360 was lost or there was a spike in blood Phe leading to an immediate dose increase irrespective of loss of SPR360.

n represents number of down-dosing attempts. Down-dosing was attempted in 84 individuals a total of 189 times; 27/84 had one down-dosing attempt, whereas 57/84 had 2–6 down-dosing attempts. Phe, phenylalanine; SPR360, Sustained Phe Response ≤360 µmol/L.



Down-dosing: Key insights



Down-dosing was most likely to succeed when the preceding blood Phe was $<30 \mu\text{mol/L}$



Higher pre-down-dosing Phe levels were linked to a higher failure rate



Gradual, stepwise reduction was recommended until desired blood Phe levels were established

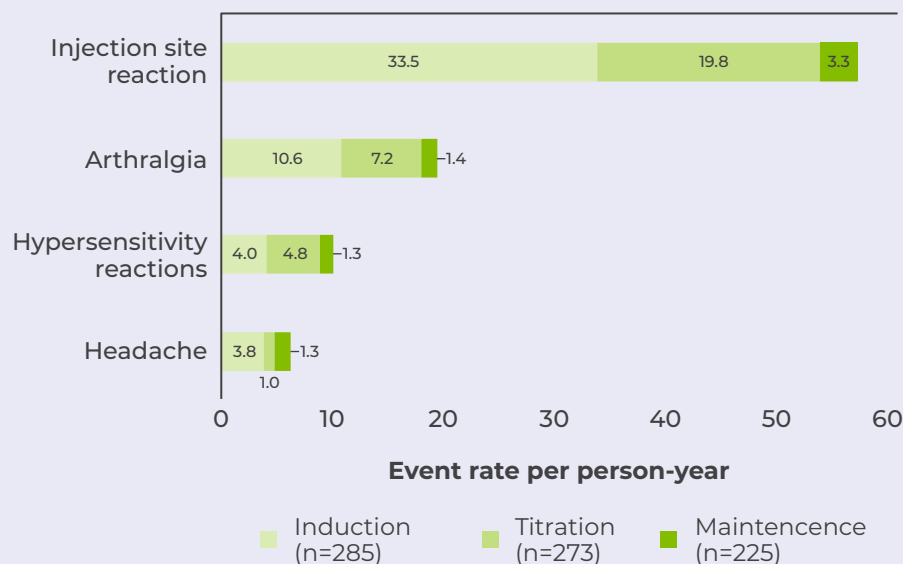




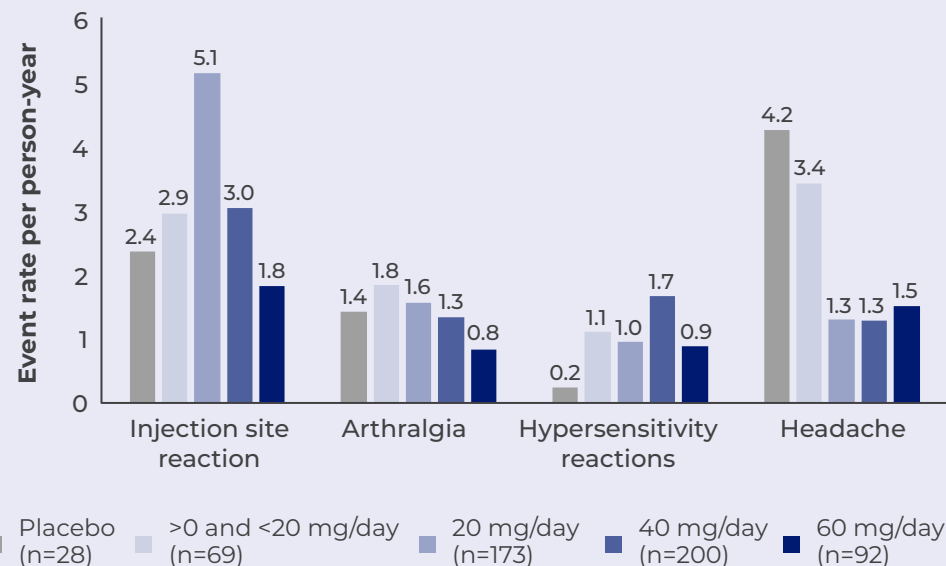
Safety results

AE rate per person per year

By treatment phase



By maintenance dose



AE rate is highest during induction and declined during maintenance, with AE rate remaining low across all maintenance doses



Figures adapted from BioMarin data on file.
AEs of special interest with data available by treatment phase and maintenance dose were presented.
AE, adverse event.



Conclusion



In the post-I/T period, consistently low blood Phe should be seen as a sign that immune tolerance has likely been achieved



Diet liberalisation is most likely to be successful if low blood Phe levels are observed and should proceed prior to attempts at down-dosing



Down-dosing should be slow and stepwise until the desired blood Phe levels have been established



A staged approach to pegvaliase treatment includes achieving immune tolerance, liberalising diet, and gradually reducing dose



References

1. PALYNZIQ[®] Prescribing information. BioMarin Pharmaceutical Inc.
<https://www.palynziq.com/prescribinginformation.pdf> (Accessed January 2026)
2. Harding CO, et al. Mol Genet Metab. 2018;124:20–26
3. Thomas J, et al. Mol Genet Metab. 2018;124:27–38

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Indications and prescribing information per region

Australia: PALYNZIQ® is indicated for the treatment of patients with PKU aged 16 years and older who have inadequate blood Phe control despite prior management with available treatment options. The Australian product information can be found [here](#).

Europe: PALYNZIQ® (pegvaliase) is indicated for the treatment of patients with PKU aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 µmol/L) despite prior management with available treatment options. The latest SmPC can be found on the PKU.expert website or click [here](#) for the SmPC.

Canada: 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 greater than 600 µmol/L) despite dietary management. The product monograph can be found [here](#).

Japan: PALYNZIQ® (pegvaliase) is indicated for the treatment of adult patients with PKU. The prescribing information can be found [here](#).

Brazil: PALYNZIQ® is indicated for the treatment of patients with PKU from 16 years of age with inadequate control of phenylalanine in the blood (phenylalanine levels in the blood greater than 600 µmol/L [10.0 mg/dL]) with existing treatment. The prescribing information can be found [here](#).

Scan for prescribing information

Australia



Europe



Canada



Japan



Brazil



Implementation guide

For internal use only

Implementation guide

Communications objectives:

- To facilitate clinical decision making when using PALYNZIQ® using a PK/PD model
- Describe how PK/PD modelling of PALYNZIQ® clearance informs understanding of immune tolerisation and its impact on dose, blood Phe, and diet during maintenance therapy

Main messages:

- Consistently low blood Phe after I/T with PALYNZIQ® indicates immune tolerance has been achieved
- Diet liberalisation should follow achievement of stable low blood Phe
- Down-dosing is most effective after very low blood Phe levels ($<30 \mu\text{mol/L}$) are achieved with PALYNZIQ®; these data suggest that when appropriate, it should be gradual and individualised to maintain control
- These data support a staged approach to PALYNZIQ® therapy: 1) immune tolerance, 2) diet liberalisation, and 3) gradual reduction of dose

Implementation guide

Which messages under the PKU Global Promotional Platform does this publication support?

1

Thriving With PKU

For people with PKU, the challenges of high Phe remain, with serious impacts to neurocognitive function

A rapid drop in blood Phe to $<30 \mu\text{mol/L}$ may indicate that immune tolerisation has been achieved therefore, intact protein intake could be increased per protocol without losing control of blood Phe levels. Over time, down-dosing to 40 mg/day and then 20 mg/day became possible whilst still maintaining target blood Phe levels.

2

PALYNZIQ® Foundations:

Study Design,
Efficacy Profile,
Safety Profile,
Admin, and
More

PALYNZIQ® has a manageable safety profile, established over years of clinical and real-world experience¹⁻⁴

Adverse event rates were highest during induction and declined substantially during maintenance, remaining low across all maintenance doses. The results suggest that PALYNZIQ® is an effective and a titratable tool for the management of blood Phe.

3

The PALYNZIQ® Impact

PALYNZIQ® may offer patients significant and sustained impact on the effects of PKU¹ – regardless of diet

A staged approach to PALYNZIQ® treatment includes achieving immune tolerance, liberalising diet, and cautiously reducing dose.

Phe, phenylalanine; PKU, phenylketonuria.

1. PALYNZIQ® Prescribing information. BioMarin Pharmaceutical Inc. <https://www.palynziq.com/prescribinginformation.pdf> (Accessed January 2026); 2. Harding CO, et al. Mol Genet Metab. 2018;124:20–26; 3. Thomas J, et al. Mol Genet Metab. 2018;124:27–38; 4. Harding CO, et al. Mol Genet Metab Rep. 2024;39:101084.