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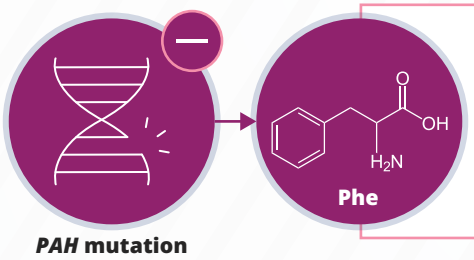
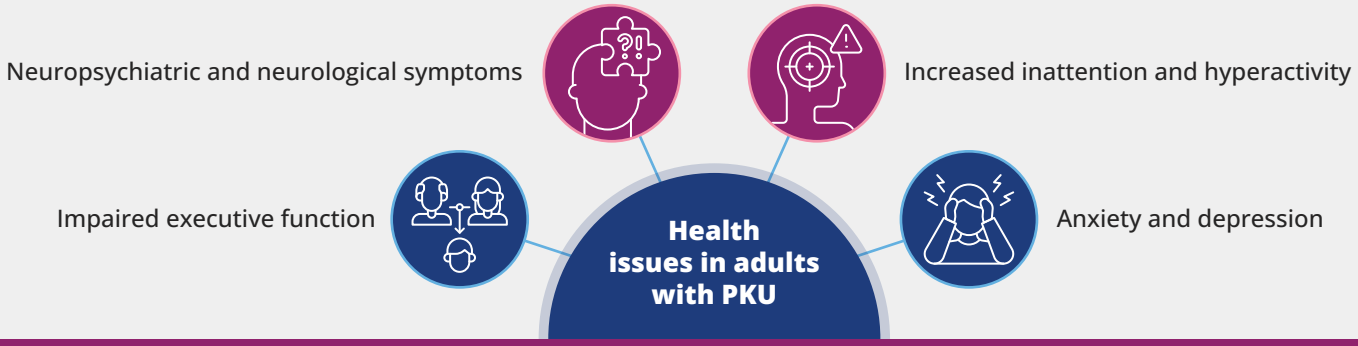
Validating the Sustained Efficacy and Safety of Pegvaliase in Treating Adults with Phenylketonuria: An Individual Participant Response Analysis of Cumulative Results from the PRISM Clinical Trials

Overview of phenylketonuria (PKU) and pegvaliase



PKU is a genetic disorder caused by the deficiency of the enzyme phenylalanine hydroxylase (PAH) leading to the accumulation of phenylalanine (Phe) in the blood and brain



PKU necessitates lifelong treatment to maintain blood Phe levels within a safe range

Target a safe range of blood Phe in treated individuals with PKU

United States

- 120 to 360 µmol/L

Europe

- 120 to 360 µmol/L for <12 years of age
- Not more than 600 µmol/L for >12 years of age

Recommended measures for managing blood Phe levels

- Phe-restricted diet (comprising low-protein alternatives at the expense of high-protein foods)
- Oral sapropterin, a cofactor for PAH

Barriers to achieving Phe safe range

- Only 20 to 56% of patients with PKU respond to sapropterin
- Difficulty with dietary adherence
- Lack of follow-up and active management

Pegvaliase

Developed by BioMarin Pharmaceutical Inc., pegvaliase is the first enzyme-substitution therapy approved for adults with PKU and uncontrolled blood Phe concentrations >600 µmol/L

What is known about pegvaliase?

Pegvaliase is the pegylated derivative of a Phe metabolizing enzyme, phenylalanine ammonia lyase (PAL), that converts Phe to ammonia and trans-cinnamic acid

- Self-administered via subcutaneous injection
- Bacterially derived protein that triggers anti-drug antibody production, resulting in immunologic adverse events (AEs)
- Induction, titration, and maintenance dosing to achieve individualized efficacious doses, up to 60 mg once daily

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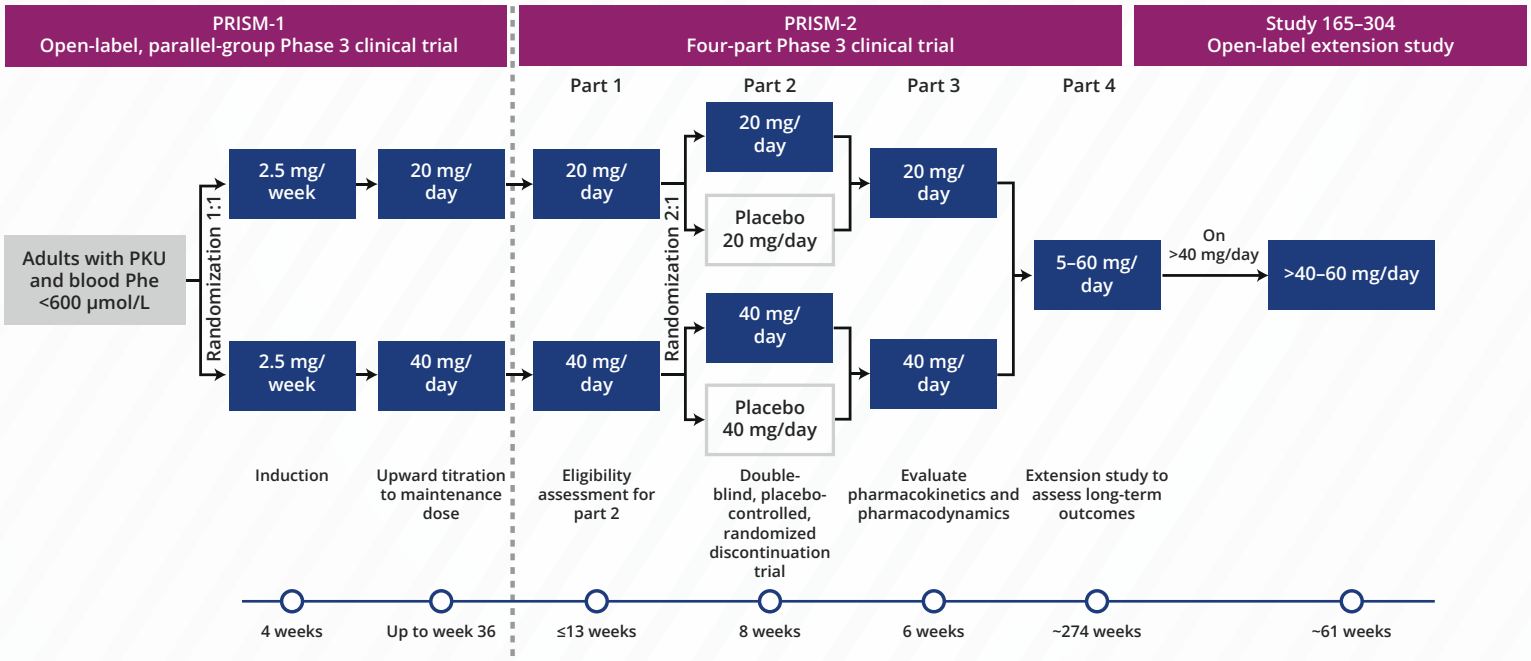
PRISM clinical trials

Phase 3 randomized PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862) clinical trials, along with the open-label extension study 165–304 (NCT03694353), characterized the efficacy and safety of pegvaliase



Study outcome assessments

Safety

AEs of specific interest
- Anaphylaxis
- Acute systemic hypersensitivity reactions

Sponsor-defined AEs of specific interest
- Hypersensitivity AEs (HAE)
- Injection site reactions
- Injection site skin reactions lasting ≥14 days
- Generalized skin reactions lasting ≥14 days
- Arthralgia
- Angioedema

Blood Phe levels

Assessed every 4 weeks at the study initiation and every 8 weeks after week 25 of PRISM-2 Part 4

Dietary Phe

Participant-reported 3-day diet diaries were analyzed using the nutrient analysis software program Metabolic Pro

Findings from PRISM clinical trials

Substantial and durable reductions in mean blood Phe

Long-term outcomes of pegvaliase treatment

Manageable safety profile

Continued use required to maintain reduced Phe levels

Limitations of the analysis

Population-level data do not reflect the experience of individual patients, especially in terms of:

- Time to the first response
- Dose at the first response
- Mean blood Phe reduction

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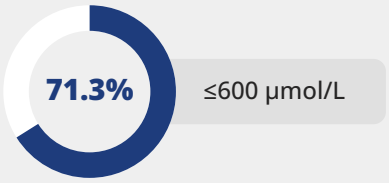
Long-term, individual participant response outcomes of pegvaliase treatment

Study subjects

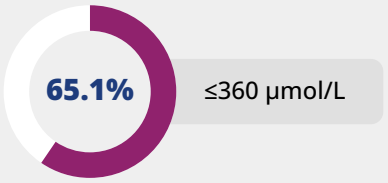
261 participants with PKU who initiated pegvaliase treatment in PRISM-1, with data available through their last follow-up

- Mean age: 29.1 years
- Females: 49.8%
- Mean baseline blood Phe: 1,221 µmol/L
- Mean follow-up time: 36.6 months

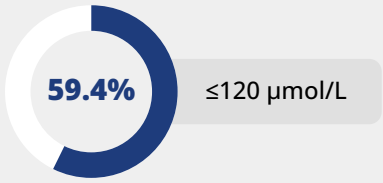
Significant proportion of participants with PKU achieved lower blood Phe thresholds in PRISM-1



≤600 µmol/L



≤360 µmol/L



≤120 µmol/L

Time to first achieve a blood Phe clinical threshold

Blood Phe threshold	Median (minimum, maximum)
≤600 µmol/L	4.4 (0.0, 54.0) months
≤360 µmol/L	8.0 (0.0, 57.0) months
≤120 µmol/L	11.6 (0.0, 66.0) months

Dose of pegvaliase needed

Most patients with PKU required higher doses of pegvaliase >20 mg/day to observe the first response of blood Phe lowering

Sustained Phe response (SPR)

New method of measuring the durability of treatment response

- SPR_i: Point of initial SPR at ≤600, ≤360, or ≤120 µmol/L, when the blood Phe levels first fall below the clinical thresholds
- SPR_p: Proportion of follow-up time spent in SPR at ≤360 µmol/L

Majority of blood Phe responders achieve SPR

Blood Phe threshold	Achieving SPR (%)	Mean SPR_p (%)
≤600 µmol/L	85.5	85.4
≤360 µmol/L	84.7	81.0
≤120 µmol/L	78.1	68.4

Loss of SPR is associated with changes in: • Pegvaliase dose (55%–80%) • Intact protein intake (2%–6%)

Upon treatment continuation, individuals frequently regain SPR

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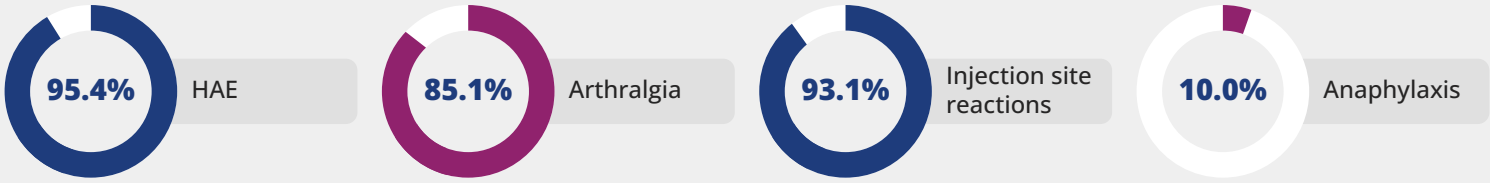
Manageable safety profile of pegvaliase

- Longer-term safety data is consistent with previous reports
- Blood Phe can drop below 30 µmol/L with pegvaliase treatment in the absence of allosteric feedback regulation of PAL in response to changing blood Phe concentrations. PAL does not need a cofactor for Phe conversion
- 15.3% of participants discontinued treatment due to AEs
- Higher incidence of AEs during the early treatment phase (≤6 months)
- Adding premedication to mitigate the severity of HAEs greatly decreased the frequency of treatment discontinuations resulting from AEs

Overall incidence of common AEs of specific interest



Majority of AEs following pegvaliase treatment were mild or moderate in severity and resolved without dose interruption or reduction

Key messages

- **Cumulative data from three key pegvaliase clinical trials validate the durability of treatment responses, with an increasing proportion of participants achieving blood Phe thresholds over a longer treatment duration**
- **The participants' safety profile improved with longer exposure to pegvaliase, supporting the long-term efficacy and safety of pegvaliase for the treatment of adults with PKU**
- **This study highlights the advantages of participant-level data analysis and a new way of reporting SPR to better characterize patients' individual PKU treatment experience**

Sponsor

BioMarin Pharmaceutical Inc. funded this study and was involved in the study design, data collection, data analysis, and preparation of the manuscript and this infographic, as well as the decision to submit the manuscript for publication.

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Pegvaliase for the treatment of phenylketonuria: Final results of a long-term phase 3 clinical trial program

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