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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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ABSTRACT

Phenylketonuria (PKU) is a genetic disorder caused by deficiency of the enzyme phenylalanine hydroxylase (PAH), which results in phenylalanine (Phe) accumulation in the blood and brain, and requires lifelong treatment to keep blood Phe in a safe range. Pegvaliase is an enzyme-substitution therapy approved for individuals with PKU and uncontrolled blood Phe concentrations (>600 μmol/L) despite prior management. Aggregated results from the PRISM clinical trials demonstrated substantial and sustained reductions in blood Phe with a manageable safety profile, but also noted individual variation in time to and dose needed for a first response. This analysis reports longer-term aggregate findings and characterizes individual participant responses to pegvaliase using final data from the randomized trials PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862), and the open-label extension study 165–304 (NCT03694353). In 261 adult participants with a mean of 36.6 months of pegvaliase treatment, 71.3%, 65.1%, and 59.4% achieved clinically significant blood Phe levels of ≤600, ≤360, and ≤ 120 μmol/L, respectively. Some participants achieved blood Phe reductions with <20 mg/day pegvaliase, although most required higher doses. Based on Kaplan-Meier analysis, median (minimum, maximum) time to first achievement of a blood Phe threshold of ≤600, ≤360, or ≤ 120 μmol/L was 4.4 (0.0, 54.0), 8.0 (0.0, 57.0), and 11.6 (0.0, 66.0) months, respectively. Once achieved, blood Phe levels remained below clinical threshold in most participants. Sustained Phe response (SPR), a new method described within for measuring durability of blood Phe response, was achieved by 85.5%, 84.7%, and 78.1% of blood Phe responders at blood Phe thresholds of ≤600, ≤360, or ≤ 120 μmol/L, respectively. Longer-term safety data were consistent with previous reports, with the most common adverse events (AEs) being arthralgia, injection site reactions, headache, and injection

Abbreviations: AE, adverse event; AESI, adverse event of special interest; CTCAE, Common Terminology Criteria for Adverse Events; E(Phe_t), expected value of blood Phe at time *t*; HAE, hypersensitivity adverse event; FAAN, Food Allergy and Anaphylaxis Network; FDA, Food and Drug Administration; max, maximum; MedDRA, Medical Dictionary for Regulatory Activities; min, minimum; NIAID, National Institute of Allergy and Infectious Disease; PAH, phenylalanine hydroxylase; PAL, phenylalanine ammonia lyase; PD, pharmacodynamics; PEG, polyethylene glycol; Phe, phenylalanine; PK, pharmacokinetics; PKU, phenylketonuria; Q1, quartile 1 (25th percentile); Q3, quartile 3 (75th percentile); SAE, serious adverse event; SD, standard deviation; SMQ, standard MedDRA query; SpO_2, oxygen saturation; SPR, sustained Phe response; SPR_i, initial sustained Phe response; SPR_p, sustained Phe response proportion (proportion of follow-up time that the confidence band remained below the specified Phe threshold)..

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site erythema. The incidence of most AEs, including hypersensitivity AEs, was higher during the early treatment phase (≤6 months) than later during treatment. In conclusion, using data from three key pegvaliase clinical trials, participants treated with pegvaliase were able to reach clinically significant blood Phe reductions to clinical thresholds of ≤600, ≤360, or ≤ 120 μmol/L during early treatment, with safety profiles improving from early to sustained treatment. This study also supports the use of participant-level data and new ways of looking at durable blood Phe responses to better characterize patients' individual PKU treatment journeys.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of the enzyme phenylalanine hydroxylase (PAH), which results in phenylalanine (Phe) accumulation in the blood and brain [1]. Adults with PKU may experience impaired executive function and neuropsychiatric and neurological symptoms, with higher rates of inattention, hyperactivity, anxiety, and depression compared with the general population [2]. Lifelong treatment is required to control blood Phe levels for most patients with PKU [3,4]. In the US, a target blood Phe level of 120 to 360 μmol/L is recommended for all treated patients with PKU [3]. In Europe, this target range is recommended for those aged <12 years and a higher upper target of 600 μmol/L is recommended for patients aged ≥12 years [4]. In addition, patients with PKU are advised to follow a Phe-restricted diet, with sapropterin also recommended for sapropterin-responsive patients [3,4]. However, achievement of recommended blood Phe targets is suboptimal due to difficulty with dietary adherence [5,6], and only 20% to 56% of patients with PKU respond to sapropterin [7]. In a survey of 44 clinics and over 1500 actively managed adults with PKU in the US conducted prior to the commercial availability of pegvaliase, 62% of patients aged 18 to 29 years and 71% aged ≥30 years had blood Phe levels >360 μmol/L with higher blood Phe levels (>1200 μmol/L) seen in 15% and 20% of patients, respectively [6]. Moreover, an estimated 32% of all patients and 55% of adults aged ≥30 years were considered lost to follow-up and not being actively managed [6].

Pegvaliase is a pegylated phenylalanine ammonia lyase (PAL) enzyme, self-administered via subcutaneous injection, that converts Phe to ammonia and trans-cinnamic acid [8–10]. It is approved as an enzyme-substitution therapy for adults (US) or patients aged ≥16 years (Europe) with PKU and uncontrolled blood Phe concentrations >600 μmol/L on existing management [8,11]. Because pegvaliase is a bacterially derived protein, patients produce anti-drug antibodies to pegvaliase and immunologic adverse events (AEs) are expected [12]. Therefore, pegvaliase uses an induction, titration, and maintenance dosing schedule, allowing patients to achieve individualized efficacious doses of up to 60 mg once daily.

The efficacy and safety of pegvaliase induction, titration, and maintenance dosing for patients with PKU were characterized in the Phase 3 PRISM-1 and PRISM-2 clinical trials, using data collected up to September 2016 [12,13]. Pegvaliase led to mean blood Phe reductions that were clinically meaningful and statistically significant versus placebo [13] and sustained on a population level for up to 24 months [12]. In the randomized discontinuation trial of PRISM-2 (Part 2), Harding et al. showed that mean blood Phe reductions were maintained in participants receiving pegvaliase, but returned to baseline in participants who were switched to placebo, indicating a causal association between pegvaliase use and blood Phe lowering [13]. In the previous analysis by Thomas et al. [12], long-term blood Phe data were summarized at monthly intervals relative to baseline, which were averaged to provide the mean blood Phe for the entire PRISM-1 parent population over time. However, summaries of population-level data on time to first response, dose at first response, and mean blood Phe reduction do not necessarily reflect the experience of individual patients. Therefore, this analysis aimed to report the longer-term overall outcomes, as well as characterize individual participant responses to pegvaliase, using final data from PRISM-1, PRISM-2, and the open-label extension study 165–304.

2. Materials and methods

2.1. Study design

This is an analysis of participant-level data from the pegvaliase PRISM-1 (NCT01819727), PRISM-2 (NCT01889862), and 165–304 (NCT03694353) clinical trials; study designs have been described previously [12]. Informed consent was obtained from each study participant or their legal representative, study protocols were approved by the relevant institutional review board, and all studies were conducted in accordance with the Declaration of Helsinki.

Briefly, PRISM-1 was a randomized, open-label, parallel-group, Phase 3 study that enrolled pharmacologic treatment-naive adults with PKU [12]. Pegvaliase was administered with an induction, titration, and maintenance dosing schedule (Fig. 1 and **Supplementary Table 1**). During the titration phase, dose and frequency were increased to the randomized maintenance dose of 20 or 40 mg/day. There was customizability in the dose escalation speed, with duration of titration based on tolerability (median 10–11 weeks; range 9–33 weeks). Prior to the August 2014 protocol amendment, premedication to reduce severity of hypersensitivity adverse events (HAEs) was optional. However, after the protocol amendment, premedication with a histamine H_1-receptor antagonist, an H_2-receptor antagonist, and an antipyretic, if tolerated, was required to reduce severity of HAEs during the induction and titration periods. Investigators were also given greater flexibility to reduce or interrupt pegvaliase dosing due to mild AEs (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), an observer was required to be present for the first 16 weeks of pegvaliase administration, and education on HAE signs and symptoms was provided to participants.

PRISM-1 participants were eligible to continue to the four-part PRISM-2 study (Fig. 1) [12]. Participants could enter Part 4 directly from PRISM-1, or from PRISM-2 Part 1, Part 2, or Part 3 (after completion of Part 2). In Part 4, the pegvaliase dose could be adjusted to 5 to 60 mg/day, based on tolerability, to achieve individualized blood Phe goals. Before escalating to 60 mg/day dosing, participants were required to complete a total of ≥52 weeks of pegvaliase treatment (in this study or in previous studies) and a minimum of 8 weeks of treatment with 40 mg/day pegvaliase. Alternative dosing regimens were also permitted provided they were agreed to by the sponsor's medical monitor prior to initiation.

The safety and efficacy of pegvaliase at doses >40 mg/day were further evaluated in study 165–304 (NCT03694353), an open-label extension for participants who were treated at doses exceeding the labelled pegvaliase dose at the time of its first approval [8]. While 12 participants from the Phase 2 studies 165–205 (NCT01560286) and PAL-003 (NCT00924703) enrolled in PRISM-2, and seven participants from PAL-003 enrolled in study 165–304, our results are restricted to those who initiated pegvaliase in PRISM-1 (Fig. 1). The first participant enrolled in PRISM-1 in May 2013 and the last person enrolled in PRISM-2 Part 4 in February 2019. Participants enrolled in study 165–304 from September 2018 to February 2019, and the last participant completed the study in January 2021.

2.2. Study population

The study population consisted of all participants who initiated

treatment in PRISM-1 and includes all data through their last follow-up.

2.3. Outcome measures

2.3.1. Safety

AEs were coded in accordance with the Medical Dictionary for Regulatory Activities MedDRA, version 18.0 (https://www.meddra.org/) and clinical laboratory tests (hematology, chemistry, and urinalysis) were regularly recorded. The severity of AEs was assessed using the CTCAE (version 4.03 or 5.0). Anaphylaxis was a prespecified AE of special interest (AESI) and was defined using National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) criteria [14], and those events confirmed by an external expert were referred to as acute systemic hypersensitivity reactions. Other prespecified, sponsor-defined AESIs included HAEs, injection site reactions, injection site skin reactions lasting ≥14 days, generalized skin reactions lasting ≥14 days, arthralgia, and angioedema.

2.3.2. Blood Phe

Blood Phe was collected at least every 4 weeks throughout the study until participants reached Week 25 of PRISM-2 Part 4, after which assessments were conducted every 8 weeks. Participants were instructed to fast for approximately 2.5 to 5 h prior to blood Phe assessments and to have their samples collected at the same time of day.

2.3.3. Dose

The date, time, and volume of each administration of pegvaliase was recorded by the participant and sent to the investigational center monthly, along with used and unused study drug containers for record reconciliation.

2.3.4. Dietary Phe

Dietary Phe was self-reported by participants using 3-day diet diaries, preferably completed in the 3 consecutive days prior to their next scheduled study visit and was analyzed using the nutrient analysis software program, Metabolic Pro®' (Genetic *Metabolic* Dietitians International, Hillsborough, NC).

2.4. Statistical analysis

Safety endpoints included the incidence of AEs and exposure-adjusted AE rates. Kaplan-Meier analyses were used to estimate the proportion of participants who achieved clinically meaningful blood Phe reductions during at least one assessment over 48 months.

Efficacy endpoints included the proportion of participants who achieved clinically meaningful reductions in blood Phe concentrations to clinical thresholds of ≤600, ≤360, and ≤ 120 μmol/L at each time point; the time to reach a blood Phe concentration at clinical thresholds of ≤600, ≤360, or ≤ 120 μmol/L; the proportion of participants with a clinically meaningful blood Phe reduction who achieved a sustained Phe response (SPR), based on the point of initial SPR (SPR_i; at ≤600, ≤360, or ≤ 120 μmol/L); and the proportion of follow-up time spent in SPR (SPR_p; at ≤360 μmol/L).

By-visit data summaries at nominal study visits could not be produced for the long-term analysis of pegvaliase Phase 3 data due to the variable nature of study visits and the time each participant spent in PRISM-1, PRISM-2 Part-1 and Part-4, and 165–304. Aggregate blood Phe data were summarized at monthly intervals relative to baseline. To assess individual differences, plots for each enrolled participant were generated to summarize their blood Phe assessments, pegvaliase exposure, and dietary Phe intake from baseline to their last follow-up day (**Supplementary Fig. 1**). For each participant, a generalized additive model was used to smooth the blood Phe time series and capture the expected value of blood Phe at time *t*, $E(Phe_t)$, given adjacent or local blood Phe measures, and a 95% confidence band for the smoother estimate of $E(Phe_t)$ was calculated. The confidence band represents the range of plausible expected blood Phe values for any arbitrary point in time (interpolating over the time series), given locally retrospective and prospective information. SPR was considered to have been achieved when the upper bound of the confidence band was below each of the commonly used blood Phe concentration thresholds of ≤600, ≤360, or ≤ 120 μmol/L. SPR_i was defined as the time point at which the upper limit of the confidence band first crossed below each of these threshold criteria. SPR_p represents the proportion of follow-up time that the confidence band remained below each blood Phe threshold. SPR_i and SPR_p were estimated for individual participants, and summary estimates were estimated for groups.

Associations between the time on pegvaliase treatment at lower

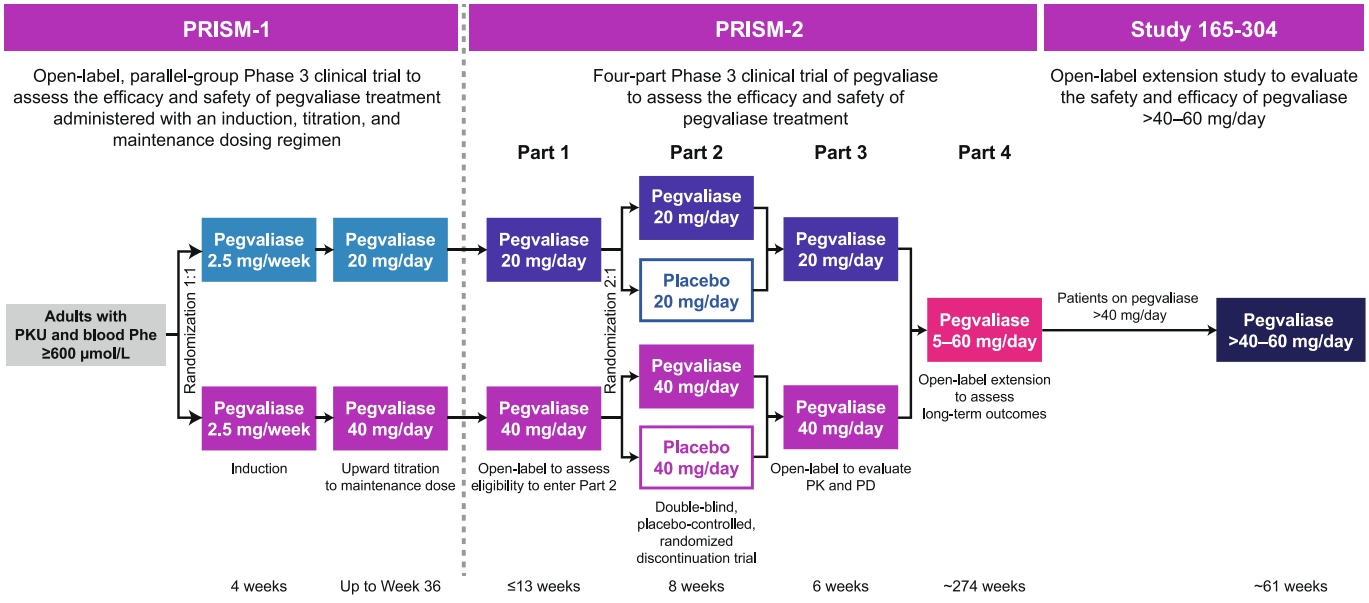


Fig. 1. Study designs for PRISM-1, PRISM-2, and study 165–304. Abbreviations: PD, pharmacodynamics; Phe, phenylalanine; PK, pharmacokinetics; PKU, phenylketonuria.

doses and the achievement of blood Phe thresholds at higher doses were analyzed using logistic regression, with the achievement of blood Phe ≤360 or ≤ 120 μmol/L or SPR at one of these blood Phe thresholds as a binary outcome (yes/no), and the timing of pegvaliase dose escalation as a continuous covariate. Due to the complexity of the dataset, standard analytic approaches were found to be insufficient to describe the loss of blood Phe control after the achievement of SPR. Instead, individual participant data were coded by four independent clinical reviewers (BKB, COH, KL, and JL). Loss of blood Phe control was defined as a single blood Phe level > 600 μmol/L or as a cluster of elevated blood Phe levels, with the majority being >360 μmol/L.

3. Results

3.1. Demographic and baseline clinical characteristics

Of the 261 participants treated with pegvaliase in PRISM-1, 203 were treated in PRISM-2 and 30 were treated in study 165–304. The mean follow-up time for the 261 participants from initial enrollment through to the end of their last enrolled study was 36.6 months (range 0.5–89.3 months). In total, 101 participants discontinued (54 from PRISM-1, 46 from PRISM-2, one from study 165–304).

Overall, mean participant age was 29.1 years, 49.8% were female, and mean baseline Phe concentration was 1232.7 μmol/L (median 1221.0 μmol/L) (Table 1). There were no notable differences from the overall population in participants who continued to PRISM-2. However, in those who continued in study 165–304, the proportion of women was lower, and participants in this group also had slightly higher baseline mean age, body mass index, and blood Phe levels.

Of the 101 participants who discontinued, about half discontinued treatment within the first 6 months of treatment, and about one third within the first 3 months (Table 2). The most common reason for discontinuation was AEs (15.3% of all participants). Overall, 69.0% of the discontinuations due to AEs occurred within the first 6 months of treatment, and discontinuations were more common before than after the August 2014 protocol amendment, with 46.9% versus 28.8% of participants discontinuing, respectively.

3.2. Pegvaliase exposure

The mean duration of treatment with pegvaliase across all trials was 36.6 months (Table 3) and 63.6% of participants had ≥24 months of treatment. Treatment duration was longer in participants who continued in both PRISM-2 and study 165–304 compared with the overall participant population. The majority of participants from the PRISM-1 parent population (56.7%) and of those continuing to PRISM-2 (67.5%) received a maximum stable maintenance dose of ≥40 to <60 mg/day, whereas the majority of participants in study 165–304 (90%) received a maximum stable maintenance dose of ≥60 mg/day (see Table 3 for the definition of maximum stable maintenance dose).

3.3. Post-treatment blood Phe concentrations

Overall, there was a substantial reduction in blood Phe that was sustained on a population level through the end of follow up (**Supplementary Fig. 2).** Of all 261 participants, 71.3% ($n = 186$), 65.1% ($n = 170$), and 59.4% ($n = 155$) achieved a clinically significant blood Phe reduction to ≤600, ≤360, and ≤ 120 μmol/L, respectively. Of the 75 participants who did not achieve a blood Phe threshold of ≤600 μmol/L, 67 (89.3%) discontinued pegvaliase before reaching this threshold, with a mean follow-up time of 7.7 months. Two participants completed PRISM-1 only, with a mean follow-up time of 5.9 months. Six participants completed either PRISM-2 or study 165–304 without achieving a blood Phe threshold of ≤600 μmol/L, with a mean follow-up time of 56.1 months. Of the 14 participants who achieved a blood Phe threshold of ≤600 μmol/L but not ≤360 μmol/L, 10 discontinued before reaching this threshold, two completed PRISM-1 only with a mean follow-up time of 7.4 months, and two completed the study without achieving a clinically meaningful reduction (mean follow-up time of 62.2 months). Of the 16 participants who achieved a blood Phe threshold of ≤360 μmol/L but not ≤120 μmol/L, 11 discontinued before reaching ≤120 μmol/L, and five completed the last enrolled study with a mean follow-up time of 41.8 months.

The Kaplan-Meier cumulative probability of achieving a clinically significant blood Phe reduction of ≤600, ≤360, or ≤ 120 μmol/L at least once by 6 months was 42.8%, 30.1%, and 22.4%, respectively (Fig. 2). At 48 months, the cumulative probability of achieving a clinically significant blood Phe reduction of ≤600, ≤360, or ≤ 120 μmol/L at least once was 93.0%, 90.8%, and 86.2%, respectively. Most participants who achieved blood Phe ≤600 μmol/L also achieved lower blood Phe thresholds. The median (minimum, maximum) time to first achievement of a blood Phe threshold of ≤600, ≤360, or ≤ 120 μmol/L was 4.4 (0.0, 54.0), 8.0 (0.0, 57.0), and 11.6 (0.0, 66.0) months, respectively (Table 4 and Fig. 3**).** A small proportion of participants were able to achieve a

Table 1
Baseline demographics and characteristics of the PRISM-1 parent population.

Variable	Overall ($N = 261$)[a]	PRISM-2 ($N = 203$)	Study 165–304 ($N = 30$)
Age at enrollment, years			
Mean (SD)	29.1 (8.8)	29.3 (8.8)	30.2 (9.0)
Sex, n (%)			
Female	130 (49.8)	96 (47.3)	13 (43.3)
Race, n (%)			
White	254 (97.3)	199 (98.0)	30 (100.0)
thnicity, n (%)			
Not Hispanic or Latino	253 (96.9)	195 (96.1)	29 (96.7)
Blood Phe (μmol/L)			
Mean (SD)	1232.7 (386.4)	1228.8 (381.7)	1369.8 (288.6)
Median	1221.0	1201.0	1466.5
Body mass index (kg/m^2)			
n	260	202	30
Mean (SD)	28.4 (6.7)	28.1 (6.6)	31.5 (7.5)
Median	27.7	27.4	33.1
Total protein (g/day)			
n	250	196	28
Mean (SD)	64.8 (32.2)	66.3 (30.7)	62.5 (31.2)
Median	62.6	65.3	55.7
Protein intake from intact food (g/day)			
n	250	196	28
Mean (SD)	38.5 (27.7)	38.4 (28.0)	42.5 (28.4)
Median	29.9	29.1	36.5
Protein intake from medical food (g/day)			
n	250	196	28
Mean (SD)	26.3 (28.5)	27.9 (29.1)	20.0 (29.2)
Median	16.8	20.0	0.0
>75% of protein intake from medical food, n (%)	41 (15.7)	36 (17.7)	3 (10.0)
Dietary Phe intake (mg/day)			
n	250	196	28
Mean (SD)	1700.2 (1194.4)	1714.6 (1231.4)	1877.1 (1272.2)
Median	1357.0	1339.3	1480.5

Abbreviations: Phe, phenylalanine; SD, standard deviation.
[a] Participants from PRISM-1 (treatment-naïve).

Table 2
Study discontinuations (intent-to-treat population).

Variable	Overall (*N* = 261)	Before protocol change (*N* = 143)	After protocol change (*N* = 118)
Total discontinuations after enrollment, % (n/N)	38.7 (101/261)	46.9 (67/143)	28.8 (34/118)
<6 months	19.2 (50/261)	23.8 (34/143)	13.6 (16/118)
0–3 months	11.9 (31/261)	14.7 (21/143)	8.5 (10/118)
3–6 months	7.3 (19/261)	9.1 (13/143)	5.1 (6/118)
6–12 months	7.3 (19/261)	9.1 (13/143)	5.1 (6/118)
12–18 months	3.4 (9/261)	5.6 (8/143)	0.8 (1/118)
18–24 months	5.0 (13/261)	4.9 (7/143)	5.1 (6/118)
24–30 months	2.3 (6/261)	0.7 (1/143)	4.2 (5/118)
30–36 months	1.2 (3/261)	2.1 (3/143)	0.0 (0/118)
>36 months	0.4 (1/261)	0.7 (1/143)	0.0 (0/118)
Reasons for discontinuation, % (n/N)			
Adverse event	15.3 (40/261)	20.9 (28/143)	10.2 (12/118)
Withdrawal	11.5 (30/261)	15.7 (21/143)	7.6 (9/118)
Physician decision	3.8 (10/261)	4.5 (6/143)	3.4 (4/118)
Lost to follow-up	3.4 (9/261)	4.5 (6/143)	2.5 (3/118)
Protocol deviation	1.2 (3/261)	2.2 (3/143)	0.0 (0/118)
Pregnancy	0.8 (2/261)	0.7 (1/143)	0.8 (1/118)
Other	2.7 (7/261)	1.5 (2/143)	4.2 (5/118)

Table 3
Pegvaliase exposure in the PRISM-1 parent population.

Variable	Overall (N = 261)[a]	PRISM-2 (N = 203)	Study 165–304 (N = 30)
Duration of treatment, months[b]			
Mean (SD)	36.6 (24.3)	44.5 (20.0)	75.7 (9.4)
Median (min, max)	38.6 (0.5, 89.3)	44.5 (3.6, 89.3)	78.8 (63.1, 89.3)
Duration of treatment, n (%)			
≥6 months	208 (79.9)	203 (99.0)	30 (100.0)
≥12 months	188 (72.0)	188 (92.6)	30 (100.0)
≥24 months	166 (63.6)	166 (81.8)	30 (100.0)
≥36 months	147 (56.3)	147 (72.4)	30 (100.0)
≥48 months	89 (34.1)	89 (43.8)	30 (100.0)
Treatment compliance rate,[c] %			
Mean (SD)	98.1 (6.10)	97.8 (6.15)	97.2 (6.63)
Median (min, max)	100 (54, 100)	100 (54, 100)	100 (76, 100)
Maximum stable maintenance dose,[d] n (%)			
Maintenance dose not achieved	38 (14.6)	0 (0.0)	0 (0.0)
≥20 to <40 mg/day	26 (10.0)	17 (8.4)	0 (0.0)
≥40 to <60 mg/day	148 (56.7)	137 (67.5)	3 (10.0)
≥60 mg/day	49 (18.8)	49 (18.8)	27 (90.0)
Last dose received,[e] n (%)			
<20 mg/day	63 (24.1)	33 (16.3)	0 (0.0)
≥20 to <40 mg/day	66 (25.3)	50 (24.6)	1 (3.3)
≥40 to <60 mg/day	103 (39.5)	91 (34.9)	11 (36.7)

Abbreviations: max, maximum; min, minimum; SD, standard deviation.
[a] All participants through last study enrolled.
[b] Time from the first dose to the last dose administered across all studies in which a participant was enrolled (PRISM-1, PRISM-2, Study 165–304). Intervals of missing doses that were > 28 days were excluded from the calculation of treatment.
[c] Calculated as 100 multiplied by (number of days in the dose category in the duration/number of days in the duration).
[d] Calculated as the maximum stable dose (defined achieving the randomized dose of 20 or 40 mg/day and maintaining that dose for at least 3 weeks; participants who had at least 4 consecutive weeks with 80% compliance with dosing at 60 mg/day were included).
[e] Last dose administered in the last study participant was enrolled.

clinically significant blood Phe reduction with <20 mg/day pegvaliase, but the majority of participants required 20 mg/day or higher to see a first response (Fig. 3). The median time to first clinically significant blood Phe reduction increased with the dose at which the reduction was achieved and was greatest in patients who responded at ≥60 mg/day dosing at all Phe thresholds (Fig. 3).

The majority of participants who achieved clinically meaningful blood Phe reductions also achieved SPR (Table 4). SPR at a blood Phe threshold of ≤600, ≤360, or ≤ 120 μmol/L was achieved by 85.5%, 84.7%, and 78.1% of blood Phe responders, respectively. For SPR ≤360 μmol/L, 28 participants achieved a blood Phe threshold of ≤360 μmol/L without achieving SPR ≤360 μmol/L. Of these, 15 discontinued early and, of the 13 participants who completed the study, eight achieved SPR <600 μmol/L and five did not. All participants who achieved SPR ≤360 μmol/L had at least one blood Phe level below 120 μmol/L.

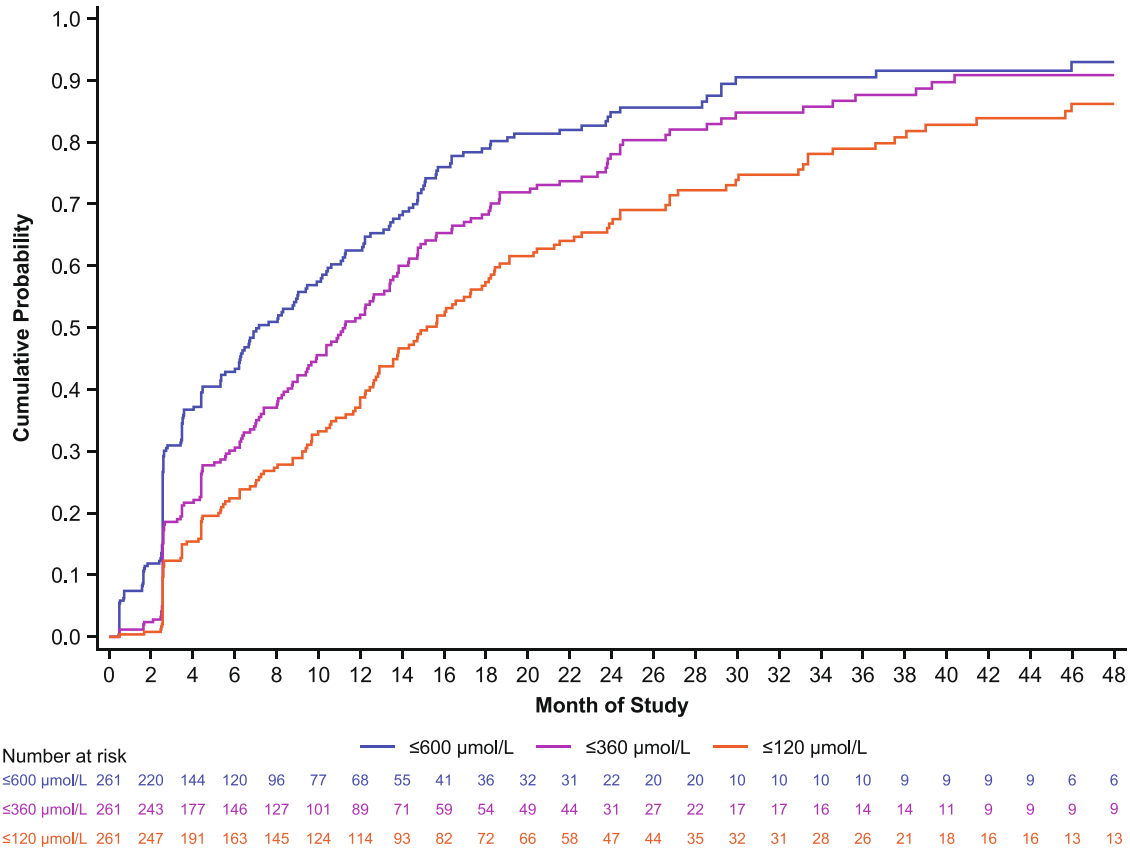
3.3.1. *Blood Phe control after SPR achievement*

After first achievement of SPR at a blood Phe threshold of ≤600, ≤360, or ≤ 120 μmol/L, the mean SPR_p (the proportion of follow-up time that the confidence band remained below each blood Phe threshold) for the corresponding blood Phe threshold was 76.0%, 73.0%, and 60.0%, respectively. Dose adjustments were common among participants in PRISM-2 Part 4 and study 165–304, and, although more restricted by the study design, dietary adjustments also occurred in many participants, as reported previously [12]. In those participants who lost SPR for any duration of time, participant-level coding was used to assess the relationship between loss of SPR and changes in pegvaliase dose and dietary intake (see **Supplementary Fig. 1** as an example). Excluding blood Phe excursions attributable to protocol-driven dose withdrawals in PRISM-2 Part 2 (randomized discontinuation trial) and Part 3 (pharmacokinetic/pharmacodynamic analyses), the majority of the occurrences of loss of SPR were associated with changes in dose (including reduction, irregularity, or withdrawal) as assessed by four independent clinical reviewers (range 55%–80%). Loss of SPR was rarely attributable to changes in intact protein intake (2%–6% of occurrences). In the remainder of cases, loss of SPR was not clearly attributable to changes in intact protein intake or pegvaliase dose. The regaining of SPR was frequently observed.

3.4. *Safety and tolerability measures*

The longer-term safety data were consistent with what was previously reported by Thomas et al. [12]. Although all participants reported ≥1 AE during the study (Table 5 and **Supplementary Table 2**), most were mild or moderate in severity. The most commonly reported AEs by preferred term (**Supplementary Table 2**) were still arthralgia (75.9%), injection site reaction (63.6%), headache (55.2%), and injection site erythema (49.0%), although in the earlier report, injection site erythema was more commonly experienced than headache [12]. The exposure-adjusted rates of 1.7, 2.6, 1.4, and 0.9 events per person-year, respectively (**Supplementary Table 2**), were lower than in the previous report [12].

A total of 91 serious AEs occurred in 63 patients (24.1%), with an



	Participants Achieving Threshold (%)[a]		
Month	Phe ≤600 µmol/L	Phe ≤360 µmol/L	Phe ≤120 µmol/L
6	42.8	30.1	22.4
12	62.5	52.1	38.7
24	84.8	78.1	66.8
36	90.5	87.6	78.9
48	93.0	90.8	86.2

Fig. 2. Kaplan-Meier estimation of proportion of participants achieving clinically significant Phe thresholds with long-term pegvaliase treatment. [a] Participants from PRISM-1 (treatment-naïve; $N = 261$). Abbreviation: Phe, phenylalanine.

overall exposure-adjusted event rate of 0.12 per person-year (Table 5). The exposure-adjusted rate of serious AEs was highest during the first year of treatment.

The incidence of most AESIs was higher during the early treatment phase (≤6 months' treatment) than later in treatment, with the incidence and exposure-adjusted event rates generally decreasing with longer treatment exposure (Table 5). HAEs, injection site reactions, and arthralgia were the most common AESIs (95.4%, 93.1%, and 85.1%, respectively). Approximately half of patients experienced an injection site skin reaction or generalized skin reaction that lasted at least 14 days. Severe acute systemic hypersensitivity reactions occurred in three (1.1%) patients, all within the first 6 months of treatment; anaphylaxis occurred in 26 (10%) patients, mostly within the first year of treatment.

4. Discussion

In this analysis, we characterized the long-term safety and efficacy of pegvaliase in participants with PKU using the data from three key pegvaliase clinical trials. In addition to investigating blood Phe responses and the probability of achieving blood Phe thresholds in the overall population, we used participant-level coding to better characterize individual participant blood Phe responses over time. Furthermore, we developed a novel measure of the durability of blood Phe reduction, the SPR, which may have clinical applicability in the assessment of pegvaliase therapeutic efficacy in individual patients.

Participants with PKU in this study received pegvaliase for approximately 3 years, on average. With this treatment duration, the majority of participants were able to reach clinically significant blood Phe reductions to the thresholds of ≤600 (71%), ≤360 (65%), and ≤ 120 µmol/L (59%). By 6 months, the cumulative probability of achieving a clinically significant reduction within these blood Phe thresholds at least once was 43%, 30%, and 22%, respectively. Most participants who remained on pegvaliase treatment achieved clinically significant blood Phe reductions at later time points, and most participants who achieved blood Phe ≤600 µmol/L also achieved lower blood Phe thresholds. By 48 months, 93%, 91%, and 86% of participants were able to reach at least one clinically significant blood Phe reduction to the thresholds of ≤600, ≤360, and ≤ 120 µmol/L, respectively. These findings support the long-term efficacy and durability of pegvaliase for the treatment of people with PKU.

The American College of Medical Genetics and Genomics' Therapeutics Committee recommends a target blood Phe level range of below 360 µmol/L for all patients with PKU in the US [3]. Pegvaliase was previously demonstrated to lead to clinically meaningful and statistically significant reductions in mean blood Phe levels versus placebo in the Phase 3 PRISM-1 and -2 trials [12,13]. In the longest published

Table 4
Proportion of participants achieving clinically significant Phe thresholds and sustained Phe responses.

Variable	Participants with sustained responses ($N = 261$)[a]		
	Phe ≤600 µmol/L	Phe ≤360 µmol/L	Phe ≤120 µmol/L
Time to first achievement of threshold, months			
n	186	170	155
Mean (SD)	8.1 (9.1)	10.7 (9.9)	14.1 (12.6)
Median (Q1, Q3)	4.4 (2.5, 12.1)	8.0 (2.6, 14.7)	11.6 (4.4, 18.4)
Min, max	0.0, 54.0	0.0, 57.0	0.0, 66.0
Achievement of SPR, %			
n	159	144	121
Proportion of total population	60.9	55.2	46.4
Proportion of Phe responders	85.5	84.7	78.1
SPR_p, %			
n	159	144	121
Mean (SD)	76.0 (26.6)	73.0 (28.1)	60.0 (33.3)
Median (Q1, Q3)	86.0 (59.9, 96.0)	82.0 (51.3, 96.7)	62.0 (30.6, 91.8)
Min, max	4.0, 133.0	9.0, 114.0	1.0, 139.0

Abbreviations: max, maximum; min, minimum; Phe, phenylalanine; Q1, quartile 1 (25th percentile); Q3, quartile 3 (75th percentile); SD, standard deviation; SPR, sustained Phe response; SPR_p, sustained Phe response proportion (proportion of follow-up time that the confidence band remained below the specified Phe threshold).
[a] Participants from PRISM-1 (treatment-naïve).

analysis of PRISM-1 and -2 data before this study, mean (SD) blood Phe levels in participants with PKU ($N = 261$) decreased from 1232.7 (386.4) µmol/L at baseline to 564.5 (531.2) µmol/L at 12 months and 311.4 (427) µmol/L at 24 months, representing decreases of 51.1% and 68.7%, respectively [12]. Similar to this long-term analysis of data up to 48 months, the cumulative probability of achieving blood Phe levels of ≤600, ≤360, and ≤ 120 µmol/L at 6 months in that study was 39.8%, 27.1% and 19.7%, respectively. Within 24 months, 68.4%, 60.7%, and 51.2% of participants achieved these blood Phe thresholds, respectively [12]. Separate analyses indicated that approximately 44% of participants had hypophenylalaninemia, defined as <30 µmol/L on two consecutive measurements, at least once during pegvaliase treatment [15]. Taken together, these data show that an increasing proportion of participants are able to reach stringent blood Phe thresholds with a longer duration of pegvaliase treatment. This is consistent with recommendations advising that time to response varies between individuals and may be >1 year [16].

While this analysis supports sustained blood Phe reductions with pegvaliase for up to 48 months, interpretation of treatment response is complicated, owing to different participant- and protocol-related factors that can lead to variations in individual blood Phe measurements over time. The use of conventional metrics for blood Phe measurement at different time points can also have problematic statistical operating characteristics. For example, means can obscure underlying sample variability, and standard deviations assume normal distributions. From the PRISM studies, we have observed that each participant's longitudinal pattern of repeated blood Phe measurements is, understandably, variable. Therefore, a single blood Phe measurement at an arbitrary time point, or data averaged for a study population, has poor reliability as an indicator of an individual's specific blood Phe response. In addition, the mean and median blood Phe values in participants enrolled in the PRISM studies have been observed to diverge over time, with mean values being skewed more towards higher blood Phe levels at later time points, which would underestimate the size of any blood Phe decrease in response to treatment (unpublished data). Therefore, we also used individual

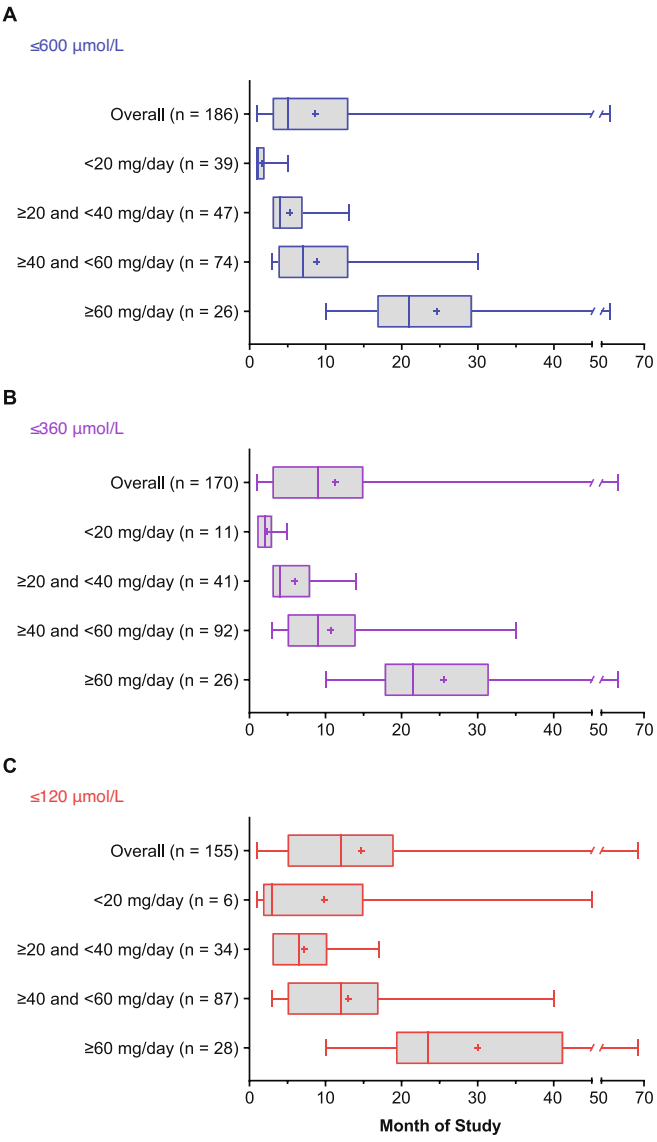


Fig. 3. Time to first achievement of clinically significant Phe thresholds by dose at response. Boxplots show the median (vertical line within each box), mean (cross within box), interquartile range (box), and minimum and maximum (error bars). Abbreviation: Phe, phenylalanine.

participant data and participant-level coding to model each participant's blood Phe response over time, to better reflect individual treatment journeys. The recommended dosing schedules in the US and European pegvaliase labels both indicate that dosing adjustments can be made based on 'adequate response' [8,11]. There is currently no definition for 'adequate response', although the pegvaliase label defines Phe control as blood Phe ≤600 µmol/L [8,11]. However, as these definitions may not be sufficient to reach guideline-recommended target blood Phe levels [3], we investigated sustained blood Phe responses at ≤600, ≤360, and ≤ 120 µmol/L for our participant-level analyses.

Using participant-level data, 86%, 85%, and 78% of participants who achieved a blood Phe threshold of ≤600, ≤360, or ≤ 120 µmol/L (61%, 55%, and 46% of the total study population), respectively, went on to achieve a sustained response at that threshold. Participants sustained their blood Phe response at ≤600, ≤360, or ≤ 120 µmol/L for 76%, 73%, and 60% of their observation period, respectively. All participants who achieved a sustained blood Phe response at ≤360 µmol/L also had at least one blood Phe level below 120 µmol/L. Participant-level coding allowed us to investigate the reasons behind loss of blood Phe control on

Table 5
Adverse event overview by treatment phase, reported as event rate (events/person-years) and total number of events: final analysis (N = 261).

		Late treatment phase (>6 months)					
Participants with event, n (%) Events, n [rate per person-year]	Early treatment phase (≤6 months) (N = 261)	>6 months to ≤1 year (N = 210)	>1 to ≤2 years (*N* = 188)	>2 to ≤3 years (*N* = 165)	>3 years (*N* = 147)	Total (*N* = 210)	Overall (N = 261)
Total treatment exposure, person-years[a]	115.6	96.8	174.3	153.4	211.1	635.9	751.7
Any AE	261 (100%) 6784 [58.67]	201 (95.7%) 2310 [23.87]	182 (96.8%) 3300 [18.93]	159 (96.4%) 2089 [13.62]	125 (85.0%) 2380 [11.28]	208 (99.0%) 10,079 [15.85]	261 (100%) 16,863 [22.43]
Any SAE	23 (8.8%) 26 [0.22]	15 (7.1%) 20 [0.21]	14 (7.4%) 18 [0.10]	7 (4.2%) 8 [0.05]	12 (8.2%) 19 [0.09]	42 (20.0%) 65 [0.10]	63 (24.1%) 91 [0.12]
HAE[b]	234 (89.7%) 1805 [15.61]	123 (58.6%) 415 [4.29]	128 (68.1%) 775 [4.45]	84 (50.9%) 362 [2.36]	75 (51.0%) 393 [1.86]	176 (83.8%) 1945 [3.06]	249 (95.4%) 3750 [4.99]
Acute systemic hypersensitivity reaction[c]	7 (2.7%) 8 [0.07]	5 (2.4%) 9 [0.09]	2 (1.1%) 2 [0.01]	1 (0.6%) 1 [0.01]	1 (0.7%) 1 [<0.01]	8 (3.8%) 13 [0.02]	15 (5.7%) 21 [0.03]
Severe acute systemic hypersensitivity reaction[c]	3 (1.1%) 3 [0.03]	0 0	0 0	0 0	0 0	0 0	3 (1.1%) 3 [<0.01]
Anaphylaxis (per FDA criteria)[d]	14 (5.4%) 15 [0.13]	6 (2.9%) 11 [0.11]	2 (1.1%) 3 [0.02]	3 (1.8%) 3 [0.02]	3 (2.0%) 3 [0.01]	12 (5.7%) 20 [0.03]	26 (10.0%) 35 [0.05]
Injection site reaction[e]	232 (88.9%) 2957 [25.57]	115 (54.8%) 602 [6.22]	94 (50.0%) 630 [3.61]	53 (32.1%) 339 [2.21]	45 (30.6%) 329 [1.56]	156 (74.3%) 1900 [2.99]	243 (93.1%) 4857 [6.46]
Injection site skin reaction[f] ≥14 days duration	72 (27.6%) 153 [1.32]	39 (18.6%) 72 [0.74]	40 (21.3%) 111 [0.64]	27 (16.4%) 48 [0.31]	20 (13.6%) 53 [0.25]	90 (42.9%) 284 [0.45]	129 (49.4%) 437 [0.58]
Generalized skin reaction[g] ≥14 days duration	63 (24.1%) 93 [0.80]	22 (10.5%) 31 [0.32]	42 (22.3%) 58 [0.33]	22 (13.3%) 29 [0.19]	22 (15.0%) 48 [0.23]	82 (39.0%) 166 [0.26]	123 (47.1%) 259 [0.34]
Arthralgia (sponsor-defined)[h]	194 (74.3%) 1022 [8.84]	72 (34.3%) 214 [2.21]	82 (43.6%) 222 [1.27]	55 (33.3%) 185 [1.21]	63 (42.9%) 149 [0.71]	138 (65.7%) 770 [1.21]	222 (85.1%) 1792 [2.38]
Angioedema (sponsor-defined)[i]	11 (4.2%) 20 [0.17]	4 (1.9%) 5 [0.05]	2 (1.1%) 2 [0.01]	0 0	0 0	6 (2.9%) 7 [0.01]	17 (6.5%) 27 [0.04]
Angioedema (per FDA criteria)[j]	11 (4.2%) 24 [0.21]	5 (2.4%) 6 [0.06]	3 (1.6%) 3 [0.02]	0 0	0 0	7 (3.3%) 9 [0.01]	18 (6.9%) 33 [0.04]

Abbreviations: AE, adverse event; FAAN, Food Allergy and Anaphylaxis Network; FDA, Food and Drug Administration; HAE, hypersensitivity adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NIAID, National Institute of Allergy and Infectious Disease; SAE, serious adverse event; SMQ, standard MedDRA query; SpO_2, oxygen saturation.

For each treatment phase and time interval, only AEs with onset within that phase or interval were included. Event rate was calculated as total number of events divided by person-years of exposure.

[a] Total treatment exposure was the aggregated duration of treatment across all participants (for each participant, time from the first dose to 30 days after the last dose administered across all studies in which the participant was enrolled). Intervals of missing doses that were > 28 consecutive days were excluded from the calculation of treatment duration.

[b] HAEs were identified using a modified hypersensitivity SMQ, which included the additional preferred term AEs of arthralgia, arthritis, eye inflammation, eye irritation, eye pain, joint stiffness, joint swelling, pyrexia, blurred vision and polyarthritis, and the broad algorithmic anaphylactic reaction SMQ.

[c] Acute systemic hypersensitivity reactions represent those episodes adjudicated as anaphylaxis by the external expert. Manifestations of acute systemic hypersensitivity reactions (type III) in this study were consistent with the symptoms included in the product labels in the European Union, Australia, and Taiwan, ie., a combination of the following acute signs and symptoms: syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, and tongue), flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, and diarrhea). Acute systemic hypersensitivity reactions were considered severe by the external expert based on the presence of cyanosis or $SpO_2 \leq 92\%$, hypotension (systolic blood pressure below 90 mmHg in adults) or syncope.

[d] Anaphylaxis events were defined based on FDA criteria (meets NIAID/FAAN criterion #1 [14], or is reported as anaphylaxis or a synonym, or the patient was treated with epinephrine irrespective of symptoms), and the symptoms of the episodes were consistent with those listed in the US prescribing information, namely signs & symptoms: syncope, hypotension, hypoxia, dyspnea, wheezing, chest discomfort/chest tightness, tachycardia, angioedema (swelling of face, lips, eyes, tongue), throat tightness, skin flushing, rash, urticaria, pruritus, and gastrointestinal symptoms (vomiting, nausea, diarrhea).

[e] Injection site reactions were identified using the MedDRA high-level term of injection site reaction.

[f] Injection site skin reactions were identified using a specified list of MedDRA preferred terms with a reported duration of ≥14 days.

[g] Generalized skin reactions were identified using a specified list of MedDRA preferred terms and any events identified by the MedDRA broad vasculitis SMQ, with a reported duration lasting ≥14 days.

[h] Events related to arthralgia were identified using the MedDRA preferred term of arthralgia. In addition, the sponsor selected the additional preferred terms of back pain, musculoskeletal pain, pain in extremity, and neck pain, which are considered synonyms of arthralgia.

[i] In addition to using the MedDRA broad angioedema SMQ to identify angioedema events, the sponsor performed an assessment and adjudication of selected preferred terms in the angioedema high-level term MedDRA query.

[j] Symptoms of angioedema included pharyngeal edema, swollen tongue, lip swelling, mouth swelling, eyelid edema, and face edema.

a case-by-case basis. The majority of the cases in which participants lost SPR ≤600 μmol/L could be attributed to dose reductions, irregularities, or withdrawal, and only rarely as a result of changes to diet. This suggests that pegvaliase doses can be titrated to optimize the durability of efficacy without a Phe-restricted diet. However, a proportion of cases of SPR loss could not be attributed to either dose or diet. One possibility is that loss of response may be related to the development of scar tissue and/or poor absorption at frequently used injection sites, although this could not be assessed in this study.

The variability in time to blood Phe thresholds was due to participant- and protocol-related factors, including individual variations in time and dose needed to respond to treatment, individual immune responses, and protocol-defined dosing requirements. There was no association between time on treatment at lower pegvaliase doses and the probability of achieving the Phe thresholds at higher doses. Participants required different pegvaliase doses to reach Phe thresholds; however, given adequate time and dosing, nearly all participants achieved clinically meaningful blood Phe levels. Overall, these results suggest that in

patients who are tolerating treatment but who have not yet achieved blood Phe targets, there is no reason to escalate pegvaliase dosing more slowly than the recommended dosing schedule.

In the safety analyses, the AEs following pegvaliase treatment were mostly mild or moderate in severity, and the majority resolved without dose interruption or reduction. No deaths, sequelae, or AEs leading to prolonged hospital admission were reported over the course of the study. The most commonly reported AEs were arthralgia, injection site reactions, headache, and injection site erythema. The primary determinant of AE rates was time on treatment, as the rates of the most common AEs noticeably decreased from the induction and titration phases to the maintenance phase, irrespective of dose. This trend also was evident when comparing the exposure-adjusted AE rates reported herein with those of the previous analysis by Thomas et al. at a point when only 23 participants had been treated for >3 years [12]. As described by Thomas et al., discontinuations were most common during early treatment and less common after the protocol amendment that required premedication to reduce severity of HAEs during the induction and titration periods [12]. Similarly, the incidence and severity of AESIs were also lower following the protocol amendment [12]. Moreover, it is important to note that many of the signs and symptoms of HAEs overlap with those of separately defined AESIs, including anaphylaxis, angioedema, and arthralgia; therefore, it is possible that some individual cases of AESIs were counted more than once. Total and neutralizing antibody titers remained stable as participants were titrated from pegvaliase 20 to 40 mg/day and from 40 to 60 mg/day. Overall, these safety results were consistent with, and extend, the previously published 24-month analysis of PRISM-1 and -2 data [12].

The observation that the AE profile improved with the duration of treatment is supported by previous immunogenicity data from the pegvaliase clinical development program. The earlier 24-month analysis reported that the immune response was immature during early treatment, and participants had increasing levels of anti-polyethylene glycol (PEG) immunoglobulin (Ig)M and IgG antibodies, with decreasing levels of complement C3 and C4 [12]. During late treatment, anti-PEG IgM and IgG antibody responses decreased and complement C3 and C4 levels increased, while anti-PAL IgG levels remained high. It was concluded that anti-PAL IgG antibodies are less able to form complement-fixing immune complexes than anti-PEG antibodies due to PAL epitope masking by pegvaliase PEGylation, and that pegvaliase likely led to type III immune complex–mediated hypersensitivity [12]. The predominantly anti-PAL IgG response during late treatment also included pegvaliase-specific IgG4 antibodies [17]. This was consistent with the observed reduction in complement activation, because IgG4 antibodies do not activate complement and are associated with mature immune responses to prolonged protein administration. However, while increased IgG4 responses may suggest a state of clinical tolerance due to constant antigen exposure, there is currently no evidence that IgG4 is associated with the development of tolerance in type III hypersensitivity reactions [18]. An additional analysis of five open-label pegvaliase trials, including PRISM-1 and -2, reported that immunogenicity affected pegvaliase pharmacokinetics, but primarily during early treatment [19]. Immune responses to pegvaliase varied substantially between participants and were inversely related to drug concentrations, resulting in high variability in trough concentrations with the 20 and 40 mg/day doses. Again, anti-PEG IgG/IgM and anti-PAL IgM antibody responses peaked during early treatment; as immune responses matured (>6 months after initiation), higher pegvaliase doses and slower clearance contributed to higher plasma pegvaliase concentrations. The frequency of HAEs decreased with decreasing circulating immune complex concentrations, and pegvaliase concentrations increased with higher doses, indicating that HAEs were temporally associated with an immune response rather than high pegvaliase plasma levels.

The use of open-label data, the reliance on participants to record details of their pegvaliase administration, and the use of participant self-reported dietary Phe data may have introduced some biases into the study results. Patient-level coding was implemented to manage the high degree of complexity and inter-patient variability of the dataset. While this was performed independently and then adjudicated, the number of independent raters was small. In addition, bias may have been introduced as this post hoc analysis was conducted years after trial completion and reflects the context and experience gleaned from real-world use. However, this study included a large number of participants who were generally representative of the adult PKU population, investigated efficacy and safety for up to 4 years, and, to our knowledge, is the first study to characterize long-term individual blood Phe responses at the participant level.

In conclusion, using data from three key pegvaliase clinical trials, participants treated with pegvaliase were observed to reach clinically significant blood Phe reductions to the thresholds of ≤600, ≤360, or ≤ 120 μmol/L during early treatment. According to the study investigators, for some participants, this may have represented the first time since childhood that their blood Phe levels were brought into the therapeutic range. Treatment responses were durable, as the proportion of participants able to achieve blood Phe thresholds increased with longer treatment duration, and a majority of participants achieved and sustained blood Phe responses to the ≤600, ≤360, and ≤ 120 μmol/L thresholds. Pegvaliase safety data were as expected, with participants' safety profiles improving from early to late treatment. Overall, this analysis is consistent with earlier pegvaliase studies and further supports the long-term efficacy and safety of pegvaliase for the treatment of adults with PKU. This study also supports the use of participant-level data and new ways of evaluating sustained blood Phe responses to better characterize patients' individual PKU treatment journeys.

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Role of the sponsor

BioMarin Pharmaceutical Inc. was involved in the study design, data collection, data analysis, and preparation of the manuscript.

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Cary O. Harding: Writing – review & editing. **Nicola Longo:** Writing – review & editing, Methodology, Investigation. **Hope Northrup:** Writing – review & editing. **Stephanie Sacharow:** Writing – review & editing, Investigation. **Rani Singh:** Writing – review & editing. **Janet A. Thomas:** Writing – review & editing, Investigation. **Jerry Vockley:** Writing – review & editing. **Roberto T. Zori:** Writing – review & editing. **Kaleigh Bulloch Whitehall:** Writing – review & editing, Writing – original draft, Formal analysis. **Joshua Lilienstein:** Writing – review & editing, Formal analysis. **Kristin Lindstrom:** Writing – review & editing, Formal analysis. **Drew G. Levy:** Writing – review & editing, Formal analysis. **Shaun Jones:** Writing – review & editing. **Barbara K. Burton:** Writing – review & editing, Investigation.

Declaration of competing interest

COH has received consulting and speaker fees from BioMarin and has participated as a clinical trial investigator for BioMarin.

NL has received consulting fees from BioMarin, PTC Therapeutics, Moderna, and Nestlé; speaker fees from Recordati; travel support from BioMarin and Sanofi; and has participated as a clinical trial investigator for BioMarin, PTC Therapeutics, Moderna, Nestlé, and Homology Medicines.

HN has participated as a clinical trial investigator for BioMarin, Synlogic, Jnana Therapeutics, Sanofi, and PTC Therapeutics; has received consulting fees from BioMarin, Synlogic, Jnana Therapeutics, and PTC Therapeutics; and has received speaker's fees from BioMarin.

SS has participated as a clinical trial investigator for BioMarin, Synlogic, and PTC Therapeutics and received funding for investigator-initiated research from BioMarin. SS also reports participation in advisory boards for BioMarin (without personal compensation since 2018) and paid speaker engagement.

RS has participated as a clinical trial investigator, received grant funding, and funding for investigator-initiated research from BioMarin.

JT has participated as a clinical trial investigator and advisory board member for BioMarin.

JV has received consulting fees from BioMarin, LogicBio Therapeutics, Sangamo Therapeutics, Orphan Lab, Synlogic, Sanofi, Axcella Health, Agios Pharmaceuticals, and Applied Therapeutics, and has received travel grants from BioMarin and LogicBio Therapeutics.

RTZ is a consultant for BioMarin and is a principal investigator for Synlogic and PTC Therapeutics.

KBW, JL, KL, and DGL are employees of BioMarin Pharmaceutical Inc.

SJ is an employee of BioMarin UK.

BKB has received consulting fees and/or honoraria from Agios Pharmaceuticals, Aro, BioMarin, Chiesi, Horizon Therapeutics, JCR Pharmaceuticals, Maze Therapeutics, Moderna, Orchard Therapeutics, Passage Bio, Sanofi, Takeda, Travere Therapeutics, and Ultragenyx, and has conducted clinical trials funded by BioMarin, Denali Therapeutics, Homology Medicines, JCR Pharmaceuticals, Sangamo Therapeutics, Takeda, and Ultragenyx.

Data availability

The de-identified individual participant data that underlie the results reported in this article (including text, tables, figures, and appendices) will be made available together with the research protocol and data dictionaries, for noncommercial, academic purposes. Additional supporting documents may be available upon request. Investigators will be able to request access to these data and supporting documents via a website (www.BioMarin.com) beginning 6 months and ending 2 years after publication. Data associated with any ongoing development program will be made available within 6 months after approval of relevant product. Requests must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Research proposals will be evaluated relative to publicly available criteria available at www.BioMarin.com to determine if access will be given, contingent upon execution of a data access agreement with BioMarin Pharmaceutical Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101084.

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