Pegvaliase for the treatment of phenylketonuria: A pivotal, double-blind randomized discontinuation Phase 3 clinical trial

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ABSTRACT

Introduction: Pegvaliase is a recombinant Anabaena variabilis phenylalanine ammonia lyase (PAL) enzyme under investigation for treatment of adult phenylketonuria (PKU). This manuscript describes results of a randomized discontinuation trial (RDT) designed to evaluate the effects of pegvaliase treatment on blood phenylalanine (Phe) and neuropsychiatric outcomes in adults with PKU.

Methods: PRISM-2 is a 4-part, Phase 3 study that enrolled adults with PKU receiving pegvaliase treatment (initiated in a prior Phase 2 or Phase 3 study). The RDT, Part 2 of PRISM-2, was an 8-week trial that evaluated change in blood Phe concentrations, neuropsychiatric and neurocognitive measures, and safety outcomes in PRISM-2 participants who had achieved at least a 20% blood Phe reduction from pre-treatment baseline with pegvaliase treatment. Participants were randomized 2:1 to either continue pegvaliase (20 mg/day or 40 mg/day) or switch to matching placebo.

Results: The pooled pegvaliase group enrolled 66 participants and each placebo group enrolled 14 participants. The primary endpoint of change in blood Phe concentration from RDT entry to RDT Week 8 was met with clinically meaningful and statistically significant differences between the pegvaliase and placebo groups. Mean (SD) blood Phe at the beginning of the RDT when all participants were receiving pegvaliase was 563.9 μM (504.6) in the group assigned to the 20 mg/day placebo group ($n = 14$), 508.2 μM (363.7) in those assigned to the 40 mg/day placebo group ($n = 14$), and 503.9 μM (520.3) in those assigned to continue pegvaliase treatment ($n = 58$). At Week 8 of the RDT, the least squares mean change (95% confidence interval) in blood Phe was 949.8 μM (760.4 to 1139.1) for the 20 mg/day placebo group and 664.8 μM (465.5 to 864.1) for the 40 mg/day placebo group in comparison to 26.5 μM (−68.3 to 121.3) for the pooled (20 mg/day and 40 mg/day) pegvaliase group ($P < 0.0001$ for pooled pegvaliase group vs each placebo group). Adverse events (AEs) were usually lower in the pooled placebo group when compared to the pooled pegvaliase group. The most common AEs for the pooled pegvaliase and pooled placebo groups were arthralgia (13.6% and 10.3%, respectively), headache (12.1% and 24.1%), anxiety (10.6% and 6.9%), fatigue (10.6% and 10.3%), and upper respiratory tract infection (1.5% and 17.2%).

Conclusion: Mean blood Phe reduction was sustained in the pegvaliase group, while placebo groups had mean

blood Phe concentration increase toward pre-treatment baseline levels. Results from this study confirmed the efficacy of pegvaliase in maintaining reduced blood Phe concentrations with a manageable safety profile for most participants.

1. Introduction

Phenylketonuria (PKU; OMIM 261600), an autosomal recessive disorder caused by a deficiency in phenylalanine hydroxylase (PAH) enzyme activity, results in an accumulation of phenylalanine (Phe) in the blood and brain [1,2]. Elevated blood Phe concentration can cause neurologic, cognitive, developmental, psychiatric, and behavioral complications that decrease quality of life [3–5].

The lifelong goal of PKU treatment is to reduce and maintain blood Phe concentration in the range of 120 μmol/L to 360 μmol/L, as recommended by the American College of Medical Genetics and Genomics (ACMG) guidelines [2]. Under the guidance of metabolic specialists, individuals with PKU are counseled to severely restrict consumption of dietary Phe, an essential amino acid present in protein foods, and supplement their diets with low-Phe or Phe-free amino acid–fortified medical foods and special low-protein modified foods [2]. A pharmacologic therapy, sapropterin dihydrochloride (sapropterin, KUVAN®, BioMarin Pharmaceutical Inc., Novato, CA), a synthetic form of tetrahydrobiopterin, a cofactor for PAH, is also available and indicated for use in conjunction with dietary Phe restriction [2,6].

Several studies demonstrate that many adults with PKU have elevated blood Phe concentrations, indicating that blood Phe control for this population is a significant challenge and current treatment strategies are not efficacious for all patients [7–10]. An estimated 88% of adults with PKU are unable to adhere to Phe-restriction long term, and even in those reporting adherence, blood Phe concentrations above recommended ranges commonly occur [4,10–13]. Sapropterin is currently the only pharmacologic agent approved to treat adults with PKU, though it is only effective in patients with residual PAH activity; in clinical trials, only 20%–56% of patients with PKU responded to sapropterin, as measured by a reduction in blood Phe concentration [2,6,14,15]. There remains a significant unmet need for new treatments to help patients achieve guideline-recommended Phe levels and to optimize long-term patient outcomes [2].

Pegvaliase, produced through PEGylation of recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), is an investigational enzyme substitution therapy designed to reduce blood Phe concentration in adults with PKU [16]. The PAL enzyme converts Phe to ammonia and trans-cinnamic acid, which are metabolized by the liver and excreted in the urine. The addition of polyethylene glycol (PEG) decreases immunogenicity and improves drug stability [16,17]. A Phase 1 clinical study demonstrated a single dose of pegvaliase treatment reduced blood Phe concentrations [17]. Phase 2 clinical studies of pegvaliase demonstrated that treatment leads to meaningful and sustained reductions in blood Phe concentrations [18–20].

Thomas et al. recently reported on the overall Phase 3 clinical program for pegvaliase, which consisted of two studies, PRISM-1 and PRISM-2 [21]. The findings of the pivotal portion of PRISM-2, the randomized discontinuation trial, are reported here (NCT01889862).

The primary aim of the RDT was to evaluate blood Phe concentrations in participants who continued receiving a stable dose of pegvaliase compared to participants who were administered placebo treatment.

2. Methods

The RDT was an 8-week, randomized, double-blind, placebo-controlled trial in adults with PKU (Supplementary Fig. 1). The primary objective of the RDT was to determine change in blood Phe concentration as treatment was withdrawn in the placebo-treated groups compared to the pegvaliase-treated group; the secondary objectives were to compare the change in inattention and mood symptoms, and safety; and an exploratory substudy had the objective to compare change in executive function between the groups.

Consistent dietary intake of protein and Phe reported at baseline were to be maintained throughout the study. Participants recorded all dietary protein intake from medical food and natural food for 3 consecutive days prior to each clinic visit in diet diaries, which were analyzed by dietitians using MetabolicPro® (Genetic Metabolic Dietitians International, Decatur, Georgia, USA). All individuals consented to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

2.1. RDT participants

The RDT enrolled adults aged ≥ 18 years with PKU receiving 20 mg/day or 40 mg/day pegvaliase in Part 1 of PRISM-2. Because hypersensitivity adverse events associated with initiating pegvaliase are more common in the first 6 months of treatment and could lead to unblinding, the RDT enrolled participants who were already receiving treatment with pegvaliase. For participants receiving neuropsychiatric medications, the dose must have been stable. All participants must have been willing and able to maintain stable protein intake.

2.2. RDT randomization

In the RDT, participants were randomized 2:1 by an interactive web-response system to continue their current dose of pegvaliase (20 mg/day or 40 mg/day) or to receive matching placebo (20 mg/day or 40 mg/day of Dextran 40®), which contained 22% Dextran. Investigators, study staff, participants, and the sponsor were blinded to the RDT study drug assignment.

Randomization was stratified by blood Phe (≤ 600 μmol/L or > 600 μmol/L) using the last 2 consecutive measurements in Part 1 and Attention Deficit Hyperactivity Disorder Rating Scale IV (ADHD RS-IV) inattention (IA) subscale score (≤ 12 or > 12 or missing) using the treatment-naïve baseline measurements.

2.3. RDT study drug administration

Study product (pegvaliase or placebo) in the RDT was self-administered subcutaneously every day for 8 weeks, with rotation of injection sites between doses (ie, upper arm, thigh, buttocks, or abdomen) and with at least 1 in. separation between injection sites, in the cases of multiple injections (for example, two 20 mg injections given for a 40 mg dose). The date, time, volume, and injection location of each dose of pegvaliase was recorded in a workbook that was collected at scheduled clinic visits. The RDT study drug compliance rate was calculated for the pegvaliase groups as the total amount of study drug taken divided by the planned dose and for the placebo groups as the number of days dosed divided by the duration of RDT.

2.4. Mitigation of hypersensitivity adverse events

Participants were trained to recognize and respond to potential hypersensitivity adverse events (HAEs) and were given epinephrine injectors for use in the case of an acute systemic hypersensitivity event, including potential events of anaphylaxis. Investigators used clinical judgment to decide if a participant should have an observer present during study drug administration or use premedication prior to each

dose of study drug with a histamine H1 antagonist, H2 antagonist, and, if tolerated, an antipyretic.

2.5. Assessments

Assessments in the clinic were performed on Days 1, 28 (Week 4), and 56 (Week 8) of the RDT. Efficacy and safety endpoints were compared between those who continued pegvaliase and those who switched to placebo.

The primary efficacy endpoint was change in blood Phe concentration. A secondary efficacy endpoint was the change in Attention Deficit Hyperactivity Disorder Rating Scale IV (ADHD RS-IV IA) in-attention subscale score, for participants with a baseline ADHD RS-IV IA subscale score > 9. Additional secondary efficacy endpoints for the efficacy population were changes in ADHD RS-IV IA subscale score, Profile of Mood States (POMS) score, PKU-specific Profile of Mood States (PKU-POMS) score, and PKU-POMS confusion subscale score.

Neuropsychiatric assessments for inattention and mood were administered by experienced test raters trained on each instrument, previously validated for use in PKU [22,23]. The ADHD RS-IV instrument was administered by investigators and POMS was self-administered by study participants. The IA subscale score of the ADHD RS-IV is considered more relevant compared to the hyperactivity subscale of the ADHD RS-IV, as inattention symptoms are more prevalent in adults with PKU [23]. The IA subscale score ranges from 0 to 27, with higher scores indicating a greater degree of impairment and a score > 9 indicating the presence of inattention symptoms [23]. The POMS instrument consists of a 65-item questionnaire rated using a 5-point Likert scale, and the sum of the scores is reported; scores range from −32 to 200, with higher scores indicating greater mood symptoms [22].

The PKU-POMS includes a subset of the items in the POMS and was developed for the PRISM studies to specifically assess transient and variable mood states relevant to PKU [22]. It consists of a 20-item questionnaire and is rated using the same 5-point Likert scale used in the POMS, with a possible score range of −12 to 58. The confusion subscale scores, a 3-item subset questionnaire of the PKU-POMS, are also reported; scores range from 0 to 11 in this domain. PKU-POMS and the confusion subscale scores were derived from POMS results.

Additional neuropsychiatric assessments to evaluate executive function were performed in an exploratory substudy (NCT02468570) of RDT participants using 3 pre-defined tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) considered relevant for PKU [24]. CANTAB is a computerized and validated set of performance-based tasks designed for neuropsychological research that have demonstrated sensitivity in detecting executive function impairments [24]. Endpoints studied were stop signal task (SST) reaction time, rapid visual processing (RVP) mean response latency, and spatial working memory (SWM), with lower scores representing a better result [24]. Major executive function domains that were assessed by these endpoints include inhibitory control and cognitive flexibility (SST task), sustained attention (RVP task), and visuospatial working memory (SWM task).

Participants were evaluated for safety by assessing vital signs, physical examination, adverse events (AEs), and clinical laboratory tests (chemistry, hematology, and urinalysis). Safety endpoints were assessed by examining the incidence, exposure-adjusted AE rate, and severity grade for all AEs reported during the study period.

AEs were coded by preferred term in accordance with the Medical Dictionary for Regulatory Activities (MedDRA, version 18.0 [25]). Additional AEs of interest for assessments included acute systemic hypersensitivity events, hypersensitivity adverse events, injection-site reactions, injection-site skin reactions lasting ≥14 days, generalized skin reactions lasting ≥14 days, and arthralgia.

HAEs were identified using a modified version of the hypersensitivity standardized MedDRA query (SMQ) that included preferred terms of arthralgia, arthritis, eye inflammation, eye irritation, eye pain, joint stiffness, joint swelling, pyrexia, vision blurred and polyarthritis, and the broad algorithmic anaphylactic reaction SMQ.

Potential acute systemic hypersensitivity events were identified using the hypersensitivity SMQ, the anaphylactic reaction SMQ, and MedDRA preferred terms to identify all AEs that could potentially be component manifestations of acute systemic hypersensitivity events as well as all AEs reported as anaphylactic reactions by preferred term. All potential episodes of acute systemic hypersensitivity events were reviewed by an allergist/immunologist independent of the clinical site and sponsor to identify events consistent with clinical criteria of ana-phylaxis defined by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN [26]) and Brown's severe criteria [27] (ie, hypoxia, hypotension, or neuro-logic compromise).

Injection-site reactions were identified using the MedDRA high level term of injection-site reaction. Injection-site skin reactions were identified using a specified list of MedDRA preferred terms with a reported duration of ≥14 days. 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.

2.6. Statistical analysis

Descriptive summaries of continuous variables included number of participants (n), the mean, standard deviation (SD), median, minimum, maximum, and 95% confidence interval (CI; as appropriate) for the mean. Descriptive summaries of categorical variables included number of participants, frequency, and percent. The treatment-naïve baseline was defined as the value prior to the first dose of pegvaliase administered in any clinical study (ie, pegvaliase-naïve baseline). The RDT entry value for assessments was defined as the last available measurement prior to first administration of study drug in the RDT.

Analyses of the efficacy endpoints were performed using the modified intent-to-treat (mITT) population, which consisted of participants that had maintained their pegvaliase dose (determined per randomization in PRISM-1 or per randomization upon enrolling in Part 1) of 20 mg/day or 40 mg/day in Part 1 of PRISM-2 and that had a blood Phe reduction of ≥20% (from the mean of 2 consecutive blood Phe assessments) from treatment-naïve baseline at the time of RDT entry. A ≥20% reduction in blood Phe was considered a first signal of pharmacologic effect, and used to determine a population with which the effects of treatment withdrawal for placebo-treated subjects could be observed. In addition, a subgroup analysis was performed for those participants who scored > 9 on the ADHD RS-IV IA subscale at baseline. For safety analyses, all participants who received any study drug in the RDT were included.

The efficacy endpoint analyses were performed for the change from RDT entry to Week 8 using mixed model repeated measures (MMRM) method with treatment group (ie, pegvaliase, placebo), visit, and treatment-by-visit interaction as factors for adjusting for RDT entry blood Phe.

As RDTs can be affected by carryover effects of prior treatment, the difference in the potential carryover effect between the 2 placebo groups was tested (referred to hereafter as poolability). The change in blood Phe concentration from RDT entry to Week 8 was compared between the 20 mg/day placebo group vs the 40 mg/day placebo group using the MMRM method. The 20 mg/day and 40 mg/day placebo groups were not deemed poolable (ie, P value was ≤0.1), therefore the comparison for the primary outcome was MMRM analysis between the pooled pegvaliase group vs the 20 mg/day placebo group and between the pooled pegvaliase group vs the 40 mg/day placebo group. Based on the RDT study design, the pegvaliase-treated groups remained on their stable pegvaliase dose throughout the 8 weeks of the RDT. The data for the pegvaliase groups were pooled because no change on blood Phe concentration was expected at Week 8 of the RDT.

Statistical tests were 2-sided at the 0.05 significance level, and all CI were 2-sided, 95%. Enrollment target was 72 participants to provide 97% power to detect a statistically significant difference in the primary endpoint. For analysis of the primary efficacy endpoint in RDT, the Hochberg procedure was used for multiplicity adjustment [28]. Between the primary and secondary efficacy endpoints and within the secondary efficacy endpoints in RDT, the sequential hypothesis testing procedure was used for multiplicity adjustment.

For the safety analyses, data on the incidence, exposure-adjusted event rate, Common Terminology Criteria for Adverse Events (CTCAE) severity grade (mild, moderate, severe, life-threatening, death) [29], and relationship to pegvaliase of all treatment-emergent AEs were reported. Safety was analyzed according to the study drug assignment.

For the endpoints in the CANTAB substudy, the change from RDT entry to Week 8 was compared for the pooled pegvaliase and pooled placebo groups with an analysis of covariance (ANCOVA) model using treatment group, RDT entry blood Phe concentration and efficacy measure as factors. Cohen's d method was used for measuring the effect size of CANTAB domains for difference between pooled pegvaliase and pooled placebo groups, calculated as the difference between means of two treatment groups divided by a pooled standard deviation [30].

3. Results

3.1. Participant disposition

A total of 86 participants enrolled in the RDT and met eligibility criteria for the efficacy analyses. This included 29 participants in each active treatment group (20 mg/day or 40 mg/day pegvaliase) and 14 participants in each matching placebo group (20 mg/day or 40 mg/day placebo). There were 9 additional participants that enrolled in the RDT and were randomized to a treatment arm, but as they did not meet criteria for the efficacy analyses, these 9 participants are only included in the safety analyses.

3.2. Participant characteristics

Participant characteristics are presented in Table 1. Mean blood Phe at RDT entry was 503.9 μmol/L in the pooled active group and 536.1 μmol/L in the pooled placebo group. A total of 5 participants were following a Phe-restricted diet, defined as having > 75% of their total protein intake from medical food.

3.3. Treatment compliance

The mean (SD) treatment drug compliance rate during the RDT for participants receiving 20 mg/day and 40 mg/day of pegvaliase was 95.9% (9.17%) and 96.7% (4.94%), respectively, of the total prescribed dose. The rate in participants receiving 20 mg/day or 40 mg/day of placebo was 98.3% (3.32%) and 96.8% (5.32%), respectively.

3.4. Efficacy

3.4.1. Blood Phe

From RDT entry to Week 8, mean blood Phe concentration for participants in the pegvaliase treatment group was stable, while participants who were switched to placebo showed mean blood Phe increases. The primary endpoint of the RDT was met with a least squares (LS) mean change (95% CI) from RDT entry to Week 8 of 949.8 μmol/L (760.4 to 1139.1) for the 20 mg/day placebo group and 664.8 μmol/L (465.5 to 864.1) for the 40 mg/day placebo group in comparison to 26.5 μmol/L (-68.3 to 121.3) for the pooled (20 mg/day and 40 mg/day) pegvaliase group ($P < 0.0001$ for pooled pegvaliase group vs each placebo group)(Fig. 1). Overall dietary protein intake did not change during RDT and analyses adjusting for dietary protein intake suggest it did not appreciably affect primary study results.

3.4.2. Neuropsychiatric measures

In participants with an ADHD RS-IV IA subscale treatment-naïve score > 9, the LS mean changes (95%) between the pooled pegvaliase group and the 20 mg/day or 40 mg/day placebo groups were 4.7 (-0.19, 9.5; $P = 0.06$) and 2.8 (-2.0, 7.5; $P = 0.24$), respectively, from start of RDT to RDT Week 8. For all participants in the efficacy population, the differences in LS mean change (95% CI) between the pooled pegvaliase group with the 20 mg/day or 40 mg/day placebo groups were 0.5 (-2.1, 3.1; $P = 0.70$) and 1.6 (-1.2, 4.5; $P = 0.25$), respectively. In the analysis of the secondary endpoints for neuropsychiatric and mood changes between RDT entry and Week 8, there were no significant differences observed between treatment groups (Table S1).

CANTAB testing results in 9 participants (6 in the pooled pegvaliase group, 3 in the pooled placebo group) who additionally participated in this substudy numerically favored pegvaliase treatment for all exploratory endpoints. Participants in the pooled pegvaliase group had an improvement in sustained attention, measured by RVP mean response latency at Week 8, compared with a worsening in the pooled placebo group. The pooled pegvaliase group also demonstrated improved visuospatial working memory with a decrease in the number of errors made on the SWM, compared with an increase in errors by the placebo group. The pooled placebo group had an increased score (greater worsening) in the SST task, measuring inhibitory control and cognitive flexibility, as compared to the pooled pegvaliase group (Table S2).

3.5. Safety

A total of 83.3% and 93.1% of participants in the pooled pegvaliase and pooled placebo groups, respectively, reported AEs during the RDT. In the pooled pegvaliase and placebo groups, the most commonly reported AEs (by preferred term) were arthralgia, headache, anxiety, fatigue, and upper respiratory tract infection. AEs with a ≥ 10% incidence difference between the pooled pegvaliase and placebo groups included headache and upper respiratory tract infection. (Table 2).

Participants in the pooled pegvaliase and placebo groups reported HAEs (39.4% and 13.8%, respectively), generalized skin reactions (10.6% and 0%, respectively) and injection-site skin reactions lasting ≥14 days (7.6% and 3.4%, respectively; Table 3).

The majority of participants experienced an AE that was mild or moderate in severity (53/66 [80.3%] in the pooled pegvaliase group; 27/29 [93.1%] in the pooled placebo group) and 97.5% of AEs did not lead to dose interruption or reduction. There were 2 serious AEs (SAEs), agitation and depression (n = 1 each) in the 40 mg/day pegvaliase group, both of which resolved and participants continued study drug administration. A single SAE occurred in the 20 mg/day placebo group of increased blood creatine phosphokinase that resolved. No participant

Table 1
Participant Characteristics at RDT Entry (mITT, *N* = 86).

	Pooled active (N = 58)	Pooled placebo (N = 28)
Age at enrollment,		
Mean (SD), years	30.6 (8.4)	31.2 (10.4)
Min, Max, years	18, 51	19, 51
Sex, n		
Female	31 (53.4%)	12 (42.9%)
Race, n		
White	58 (100.0%)	27 (96.4%)
Body mass index, kg/m²		N = 27
Mean (SD)	28.3 (6.6)	29.9 (7.0)
Min, Max	17.3, 48.2	19.9, 44.4
Blood Phe, μmol/L		
Mean (SD)	503.9 (520.3)	536.1 (432.5)
Min, Max	0, 1721.0	0, 1318.0

kg, kilogram; Max, maximum; Min, minimum; Phe, phenylalanine; SD, standard deviation. Sample size indicated if data was not available for all subjects.
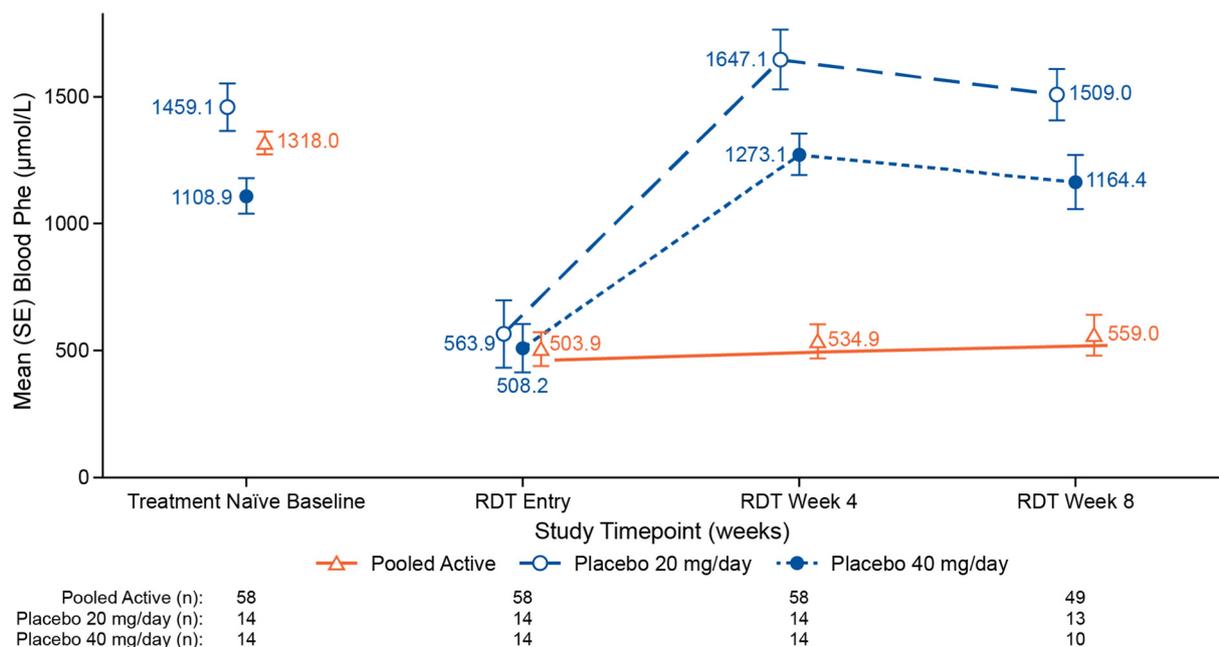
Fig. 1. Blood Phe concentration (mITT, N = 86). Treatment-naïve baseline was the blood Phe value prior to initiating pegvaliase treatment. mITT, modified intent-to-treat population; SE, standard error.

Table 2

Adverse Events in RDT by Preferred Term With ≥10% Incidence Rate, Reported as the Percentage of Participants (safety population, N = 95).

	Pooled pegvaliase (N = 66)	Pooled placebo (N = 29)
Any AE, % (n)	83.3% (55)	93.1% (27)
Arthralgia	13.6% (9)	10.3% (3)
Headache	12.1% (8)	24.1% (7)
Anxiety	10.6% (7)	6.9% (2)
Fatigue	10.6% (7)	10.3% (3)
Upper respiratory tract infection	1.5% (1)	17.2% (5)
Injection site bruising	4.5% (3)	10.3% (3)
Alopecia	3.0% (2)	10.3% (3)
Irritability	3.0% (2)	10.3% (3)
Blood creatinine phosphokinase increased	1.5% (1)	10.3% (3)
Nasal congestion	1.5% (1)	10.3% (3)

AE, adverse event; RDT, randomized discontinuation trial.

discontinued the study drug or withdrew from the trial in RDT due to an AE (Table 3). No acute systemic hypersensitivity events including potential events of anaphylaxis were reported during the RDT.

4. Discussion

The results from the 8-week pivotal, placebo-controlled RDT show significant and clinically meaningful changes in blood Phe concentration with pegvaliase treatment in adults with PKU. A change in blood Phe concentration was demonstrated with a signficant difference between participants who continued pegvaliase and those who switched to matched placebo ($P < 0.0001$); mean blood Phe levels in the pegvaliase group were maintained, while those of the placebo-group increased toward treatment-naïve concentrations, meeting the primary outcome analysis in the RDT.

The blood Phe changes demonstrated with pegvaliase treatment from treatment-naïve baseline to RDT entry were substantial, with treatment groups achieving a mean blood Phe concentration < 600 μmol/L by the time of RDT entry (from treatment-naïve baseline values > 1100 μmol/L). The eligiblity criteria for the efficacy analyses was used to create a trial population in which the effects of

Table 3

Overview of Adverse Events in RDT, Reported as Event Rate per Person-Year and Total Number of Events (safety population, N = 95).

	Pooled pegvaliase (N = 66)	Pooled placebo (N = 29)
Total treatment exposure, person-years	9.8	4.4
Event rate, per person-year (total number of events)	42.7 (420)	29.1 (127)
AEs	83.3 (55)	93.1 (27)
AEs assessed by the investigator as drug related	66.7 (44)	55.2 (16)
AEs causing dose interruption or reduction	1.5 (1)	3.4 (1)
AEs causing study drug discontinuation	0	0
AEs causing study discontinuation	0	0
SAEs	3.0 (2)	3.4 (1)
SAEs assessed by the investigator as drug related	3.0 (2)	0
SAEs causing study drug discontinuation	0	0
SAEs causing study discontinuation	0	0
Acute systemic hypersensitivity event of anaphylaxis	0	0
Hypsersensitivity adverse event	39.4 (26)	13.8 (4)
Generalized skin reaction ≥14 days	10.6 (7)	0
Injection-site skin reaction ≥14 days	7.6 (5)	3.4 (1)
Arthralgia	13.6 (9)	10.3 (3)
Injection-site reaction	24.2 (16)	24.1 (7)

AE, adverse event; RDT, randomized discontinuation trial; SAE, serious adverse event. Event rate was calculated as total number of events divided by person-years of exposure.

pegvalise discontinuation could be readily observed. The RDT was not designed to measure the maximum effect of pegvaliase on efficacy endpoints, as dosing was based on randomization rather than a participant's response to pegvaliase, and the trial duration was relatively short.

Though the treatment effect on blood Phe associated with pegvaliase treatment withdrawal was demonstrated within 8 weeks in the RDT, a deterioration in neuropsychiatric or neurocognitive symptoms was not observed, perhaps because the trial duration or tools used were not adequate. The study did not require participants to report neuropsychiatric or neurocognitive symptoms at baseline, which may have

further limited ability to observe a difference. The nature of the ADHD RS-IV IA subscale and POMS tools, which largely depend on self-reporting of symptoms, used in a population known to have self-awareness issues affected by metabolic Phe control, may have further confounded results [31,32]. Performance-based measures, such as the CANTAB, may be more suitable than self-reporting symptom instruments. Exploratory results from the RDT suggest that improvements in executive function may be associated with pegvaliase treatment and may be observed within a shorter period of time; larger studies with performance-based tools are needed to explore the effect of treatment on executive function in adults with PKU.

Pegvaliase exhibited a manageable safety profile in most subjects in RDT with similar rates of AEs between the pooled pegvaliase and pooled placebo groups. Differences in the event rate of HAEs, generalized skin reactions lasting > 14 days, and injection-site skin reactions lasting > 14 days were observed with values higher in the pooled pegvaliase group than in the pooled placebo group. Overall most participants had events limited to mild or moderate severity and did not require dose changes or reductions in the RDT. This report of the RDT is of a selected proportion of patients participating in the randomized double-blind portion of the PRISM studies during a relatively short exposure period. More information applicable to pegvaliase treatment for chronic use has been reported by Thomas et al. [21].

Suboptimal outcomes are reported in adults with PKU, often associated with the burden of life-long Phe-restriction or inadequate efficacy of oral treatments to lower blood Phe. Pegvaliase is an investigational agent that may provide a daily injectable therapy for adults with PKU. Pegvaliase has a different mode of action than currently available PKU treatments and may potentially provide a pharmacological option for all adults with PKU, particularly those that have not demonstrated an adequate response to sapropterin or dietary approaches. The potential efficacy of pegvaliase to lower blood Phe to normal, unaffected population blood Phe levels (60–120 μmol/L) may also provide significant benefit, though more studies are needed. As with all therapies, risks and benefits of a treatment need to be considered by clinicians in determining the appropriate treatment approach for their patient.

5. Conclusions

A statistically significant difference in blood Phe concentration change in participants receiving pegvaliase compared to placebo treatment was observed, confirming the blood Phe efficacy of pegvaliase.

Contributions

MM was the medical monitor. ZG performed the statistical analysis. All authors interpreted the results, reviewed and contributed to the manuscript and were fully responsible for the content and editorial decisions related to this manuscript.

Conflicts of interest statements

CH, SA, JV, MS, BB, NL, and JP are investigators of BioMarin Pharmaceutical Inc. clinical trials. CH is a part of the trial steering committee, and has received research support and consulting fees (BioMarin). JV has received research support (BioMarin). MS was a primary investigator for the study, received funding for research travel and consulting, and partipated in advisory boards (BioMarin). BB has participated in advisory boards (BioMarin, ReGenXBio), received research support (Shire), consulting fees (Alexion, Shire, BioMarin), and participated as trial investigator (BioMarin, Shire, Ultragenyx, Alexion Armagen, Cytonet). NL has received funding for research, consulting and travel (BioMarin). JP has received consulting fees (BioMarin). HL is an advisory board member (BioMarin). ZG, HHW, MM, and JJ are BioMarin Pharmaceutical Inc. employees and stockholders.

Appendix A. Investigators and study sites

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2018.03.003.

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