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Pegvaliase for the treatment of phenylketonuria: Results of a long-term phase 3 clinical trial program (PRISM)

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ABSTRACT

Background: Phenylketonuria (PKU) is caused by phenylalanine hydroxylase (PAH) deficiency that results in phenylalanine (Phe) accumulation. Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), converts Phe to trans-cinnamic acid and ammonia, and is a potential enzyme substitution therapy to lower blood Phe in adults with PKU.

Methods: Two Phase 3 studies, PRISM-1 and PRISM-2, evaluated the efficacy and safety of pegvaliase treatment using an induction, titration, and maintenance dosing regimen in adults with PKU. In PRISM-1, pegvaliase-naïve participants with blood Phe > 600 μmol/L were randomized 1:1 to a maintenance dose of 20 mg/day or 40 mg/day of pegvaliase. Participants in PRISM-1 continued pegvaliase treatment in PRISM-2, a 4-part clinical trial that includes an ongoing, open-label, long-term extension study of pegvaliase doses of 5 mg/day to 60 mg/day.

Results: Of 261 participants who received pegvaliase treatment, 72.0% and 32.6% reached ≥12 months and ≥ 24 months of study treatment, respectively, and 65% are still actively receiving treatment. Mean (SD) blood Phe was 1232.7 (386.4) μmol/L at baseline, 564.5 (531.2) μmol/L at 12 months, and 311.4 (427) μmol/L at 24 months, a decrease from baseline of 51.1% and 68.7%, respectively. Within 24 months, 68.4% of participants achieved blood Phe ≤600 μmol/L, 60.7% of participants achieved blood Phe ≤360 μmol/L, below the upper limit recommended in the American College of Medical Genetics and Genomics PKU management guidelines, and 51.2% achieved blood Phe ≤120 μmol/L, below the upper limit of normal in the unaffected population. Improvements in neuropsychiatric outcomes were associated with reductions in blood Phe and were sustained with long-term pegvaliase treatment. Adverse events (AEs) were more frequent in the first 6 months of exposure (early treatment phase) than after 6 months of exposure (late treatment phase); 99% of AEs were mild or moderate in severity and 96% resolved without dose interruption or reduction. The most common AEs were

Abbreviations: ACMG, American College of Medical Genetics and Genomics; ADHD RS-IV IA, Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale; AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DMC, Data Monitoring Committee; HAE, hypersensitivity adverse event; Ig, immunoglobulin; ISR, injection-site reaction; ITT, intent-to-treat; MedDRA, Medical Dictionary for Regulatory Activities; NAb, neutralizing antibodies; NIAID/FAAN, National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network; PAH, phenylalanine hydroxylase; PAL, phenylalanine ammonia lyase; PEG, polyethylene glycol; Phe, phenylalanine; PKU, phenylketonuria; PKU-POMS, PKU-specific Profile of Mood States; POMS, Profile of Mood States; SD, standard deviation; RDT, randomized discontinuation trial; RDA, recommended dietary allowance; SAE, serious adverse event; TAb, total pegvaliase antibodies

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arthralgia (70.5%), injection-site reaction (62.1%), injection-site erythema (47.9%), and headache (47.1%). Acute systemic hypersensitivity events consistent with clinical National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network anaphylaxis criteria were observed in 12 participants (17 events); of these, 6 participants remained on treatment. Acute systemic hypersensitivity events including potential events of anaphylaxis were not associated with immunoglobulin E, and all events resolved without sequelae.

Conclusion: Results from the PRISM Phase 3 program support the efficacy of pegvaliase for the treatment of adults with PKU, with a manageable safety profile in most participants. The PRISM-2 extension study will continue to assess the long-term effects of pegvaliase treatment.

1. Introduction

Phenylketonuria (PKU; OMIM 261600), an autosomal recessive inborn error of metabolism, is characterized by deficiency of the enzyme phenylalanine hydroxylase (PAH), which metabolizes phenylalanine (Phe) [1]. PAH deficiency leads to elevated blood Phe concentrations, which are toxic to the brain; in adults with PKU, elevated blood Phe is associated with cognitive dysfunction, memory impairment, and behavior and psychiatric problems, such as depression and anxiety, all of which can reduce quality of life [2–4].

Because of the consequences of elevated blood Phe levels, guidelines from the American College of Medical Genetics and Genomics (ACMG) recommend lifelong treatment of PKU, with the primary goal of therapy to lower blood Phe to the range of 120 µmol/L to 360 µmol/L [1]. Treatment involves severe restriction of dietary Phe (found in natural protein foods), supplemented with Phe-free amino acid–modified medical foods and special low-protein foods, alone or with sapropterin dihydrochloride (sapropterin, KUVAN®, BioMarin Pharmaceutical Inc., Novato, CA) [1,5].

Current treatments, however, are ineffective in many adults with PKU due to long-term adherence issues [4,6,7] or inadequate Phe-lowering effects [8–11]. Bik-Multanowski et al. [4] found in a study of 53 adults with PKU, only 10 were able to adhere to Phe restriction for 9 months. The majority of adults with PKU become lost to follow-up for various reasons, and likely have suboptimal metabolic control due to poor adherence to treatment in the absence of support from a metabolic clinic [6,12–14]. Yet even among patients who report dietary Phe restriction, many continue to experience blood Phe concentrations > 1000 µmol/L [9]. In PKU studies, only approximately 20% to 56% of patients in clinical trials of combination sapropterin with dietary Phe restriction responded to treatment [8,10,11], as sapropterin (a cofactor) is only effective in individuals who have residual PAH activity.

Recent publications further highlight the need for novel treatment approaches to help lower elevated blood Phe concentrations [1,14–16]. A 2015 survey of US metabolic clinics with > 1000 actively managed adults with PKU (ie, visited clinic within the last 3 years) estimated that 67% of their patients had blood Phe > 360 µmol/L, 45% had blood Phe > 600 µmol/L, and 18% had blood Phe > 1200 µmol/L [14]. Similar results were found in a patient self-reporting survey, with only 24% of adults with PKU reporting blood Phe ≤360 µmol/L within the past year, even though approximately 40% were receiving sapropterin treatment [15].

Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), is being developed as an enzyme substitution therapy to reduce blood Phe concentration in adults with PKU [17]. Pegvaliase converts Phe to ammonia and trans-cinnamic acid, which are metabolized by the liver and excreted in the urine, respectively [18,19]. PEGylation of the PAL enzyme is associated with a reduced immune response and improved pharmacodynamic stability, which is intended to reduce adverse events (AEs) and increase blood Phe–lowering activity, respectively [17]. Pegvaliase has been investigated in a single Phase 1 clinical trial (NCT00634660) [18], four Phase 2 clinical trials (NCT000924703, NCT01560286, NCT00925054, NCT01212744) [20–22], and two Phase 3 clinical trials, PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862). In PRISM-1, pegvaliase treatment was initiated using a dosing regimen based on the Phase 2 clinical trial experience. Participants in PRISM-1 then enrolled into PRISM-2 to continue pegvaliase treatment and long-term efficacy and safety assessments. Here, we report the combined results of the PRISM-1 and PRISM-2 Phase 3 clinical trials.

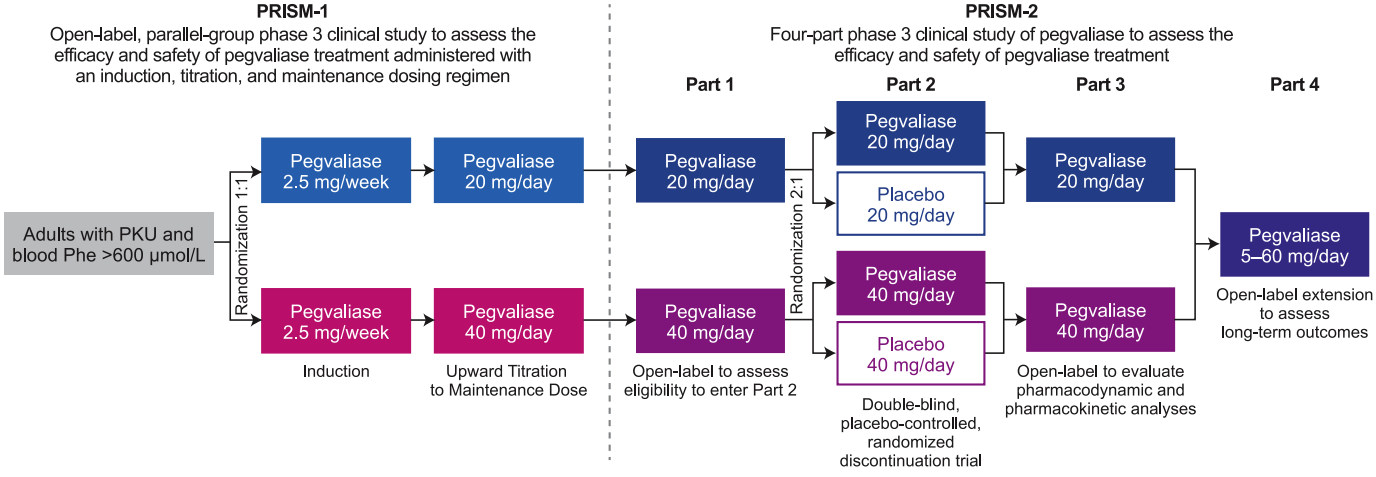

Fig. 1. Phase 3 PRISM Clinical Trial Program Study Design. In PRISM-1, pegvaliase was administered with an induction, titration, and maintenance dosing schedule, in participants randomized 1:1 to titrate to a maintenance dose of 20 mg/day or 40 mg/day. Participants continued pegvaliase treatment in PRISM-2, a subsequent 4-part clinical trial that enrolled participants who were previously exposed to pegvaliase. Part 1 of PRISM-2 identified eligible participants to enter Part 2, a double-blind, randomized discontinuation trial. Participants who completed Part 2 transitioned into Part 3, in which pharmacokinetic and pharmacodynamic assessments were conducted. Participants in PRISM-1 or Parts 1–3 of PRISM-2 ultimately transitioned into Part 4 of PRISM-2, an ongoing, open-label, long-term extension study.