Design of a phase 3 open-label randomized controlled multi-center study evaluating the safety and efficacy of pegvaliase in adolescents (ages 12–17) with phenylketonuria

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Learning Objectives

- Highlight the clinical impact of phenylketonuria (PKU) during adolescence and the need for novel therapies
- Describe the key study design elements of PEGASUS (NCT05270837), an ongoing trial on the safety and efficacy of pegvaliase in adolescents with PKU

Introduction

- Practice guidelines for PKU recommend life-long management and maintenance of metabolic control as essential to optimal functioning of individuals with PKU[1,2]
- Lifelong sustainment of Phe within recommended guidelines is important as elevated Phe can cause neurocognitive and psychiatric symptoms at any age
  - Elevated Phe is associated with executive dysfunction, depression, and a variety of behavioral and psychiatric problems[3-6]
- However, adolescents face many barriers to sustaining guideline recommended blood Phe levels with medical nutritional therapy (MNT) **(Table 1)**

Table 1. Barriers to sustaining target Phe levels in adolescents treated with MNT

Barriers
Uncontrolled Phe is associated with executive dysfunction making it more challenging to follow diet[7]
Distaste for formula and synthetic low protein foods[8]
Changes in palate making compliance to Phe-restricted diet more difficult[9]
Exposure to broader range of food[8]
Peer pressure[8]
Increased socialization[10]
Increased independence[10]
Lower parental oversight[11]

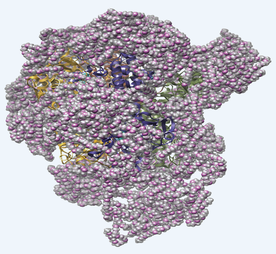
Rationale

- Pegvaliase is a genetically modified phenylalanine ammonia lyase (PAL) enzyme product of the cyanobacterium *Anabaena variabilis* **(Figure 1)**
- Unlike PAH, the PAL enzyme is active in plasma and, independently of cofactor BH4 which is required for PAH activity, catalyzes Phe to *trans*-cinnamic acid (*t*-CA) and ammonia, which are metabolized in the liver and excreted in the urine, respectively

Figure 1. Pegvaliase mode of action

Phenylalanine Ammonia Lyase (PAL)

- Converts Phe to *trans*-cinnamic acid and ammonia

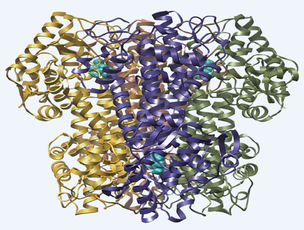


PEGylation

- Masks antibody-binding sites on PAL
- Decreases immune clearance
- Increases plasma half-life

Pegvaliase

- PEGylated (polyethylene glycol)
- Enzyme *substitution* therapy



- Pegvaliase (Palynziq®) received marketing authorization in the US, European Union (EU), Canada, and Australia in adult patients (US >18 years of age, EU/Canada/Australia >16 years of age) with PKU who have uncontrolled blood Phe ≥600 µmol/L on existing management after demonstrating substantial and sustained reductions in blood Phe with a manageable safety profile, despite identified risks
- PEGASUS is a Phase 3 Multi-Center Study to Evaluate the Safety and Efficacy of Subcutaneous Injections of Pegvaliase in Adolescent Subjects (Ages 12–17) With PKU featuring an Open-Label Randomized Two-Arm (Active vs Diet-Only Control) Design (NCT05270837)

Table 2. PEGASUS objectives

Primary Outcomes	Secondary Outcomes	Other Endpoints of Interest
Change in blood Phe concentration	Change in total dietary protein intake	Neurocognitive assessments
Incidence of treatment-emergent adverse events as assessed by CTCAE v5.0		Pegvaliase pharmacokinetics and pharmacodynamics

Study Design

- This two-part randomized controlled study **(Figure 2)** will enroll approximately 54 adolescents with Phe >600 µmol/L (ages 12–17 years (US), inclusive; 12–15 years (EU), inclusive)

Figure 2. PEGASUS study design

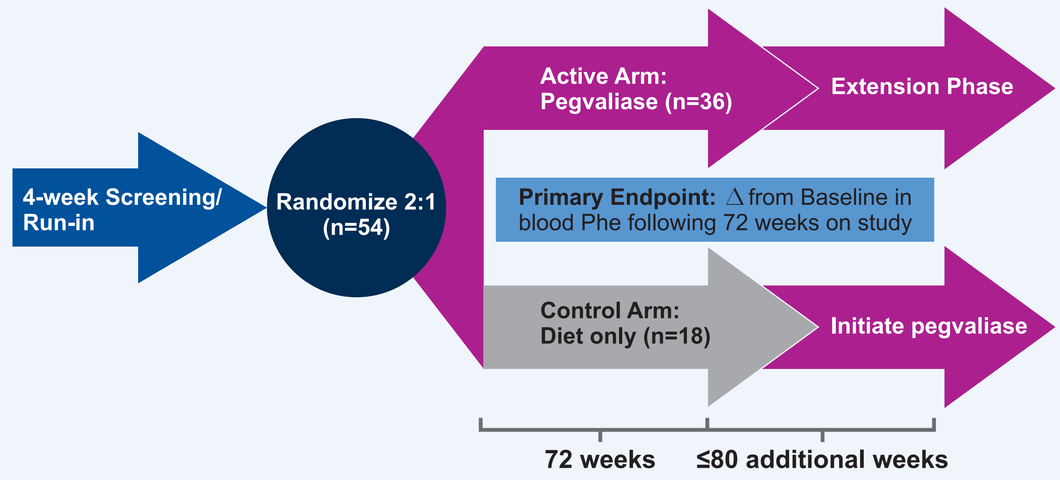


Table 3. PEGASUS key inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Is 12 to 17 years old (US), inclusive, or 12 to 15 years EU), inclusive, at the start of the Screening/Run-in Period (Day -28).	Previous treatment with pegvaliase.
Diagnosis of PKU and failure to maintain recommended blood Phe levels on existing management (sapropterin dihydrochloride and Phe-restricted diet) demonstrated by 2 blood Phe concentration measurements >600 µmol/L during the Screening/Run-in Period (7 to 10 days in between blood Phe assessments) and average blood Phe concentration >600 µmol/L over the past 12 months (per available data).	Use of any medication that is intended to treat PKU, including the use of large neutral amino acids, within 14 days prior to the administration of study drug on Day 1.
Willing and able to maintain and adjust dietary and medical protein food intake according to the study protocol under the supervision of a study dietician or adequately trained designee per investigator discretion during study participation.	Use or planned use of any injectable drugs containing polyethylene glycol (PEG; other than pegvaliase), including medroxyprogesterone injection, within 3 months prior to the start of Screening/Run-in and during study participation with the exception of COVID-19 vaccinations. A history of organ transplantation or on chronic immunosuppressive therapy.
If on medication for ADHD, depression, or other psychiatric disorder, stable dose of medication for ≥8 weeks prior to enrollment and willing to maintain stable dose unless a change is medically indicated.	Use of any investigational product or investigational medical device within 30 days prior to Screening/Run-in or requirement for any investigational agent prior to completion of all scheduled study assessments.
An adult (≥18 years of age) has been identified who is willing and competent to observe the participant during study drug administration and for a minimum of 1 hour following administration.	A positive test for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody.
Participants must be capable of giving signed informed consent.	Alanine aminotransferase (ALT) concentration > 2 × the upper limit of normal (ULN). Creatinine > 1.5 × ULN.
If sexually active, male or female participants must not plan to become pregnant (self or partner) and must use 2 acceptable methods of contraception while participating in the study beginning at Screening and for 4 weeks after discontinuing study drug.	Inability to identify and/or communicate to others that the participant is experiencing symptoms of potential anaphylaxis due to cognitive impairment or other reasons.

Study Locations

Figure 3. PEGASUS study locations

Summary

- Pegvaliase is an enzyme substitution therapy approved to treat adults with PKU who have blood Phe ≥600 µmol/L on existing management
- The results of this study will characterize the risks and benefits of pegvaliase compared to diet only in adolescents with PKU, for whom current treatment options leave a substantial unmet need

References

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Conflict of Interest

ACM has participated as a clinical trial investigator for BioMarin and has received consulting and speaker fees from BioMarin, PTC Therapeutics, and APR.

Find out more about the PEGASUS study at ClinicalTrials.gov

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