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Potential of Pegvaliase Therapy in Normalizing Diets of Patients with Phenylketonuria: Analysis of Phase 3 PRISM Clinical Trials Data

Overview of phenylketonuria (PKU)

PKU is an autosomal recessive genetic disorder, affecting amino acid metabolism

PAH deficiency leads to the accumulation of Phe in the blood and brain

It is characterized by the deficiency of phenylalanine hydroxylase (PAH), which converts phenylalanine (Phe) to tyrosine

Elevated Phe levels in the brain affect cerebral myelin and protein synthesis and cause a deficiency of serotonin and dopamine neurotransmitters

Medical nutrition therapy (MNT) for the management of PKU

MNT refers to the consumption of PKU-specific medical foods and modified low-protein foods to meet dietary requirements while restricting the amount of intact (food-derived, natural) protein to limit Phe intake

Challenges in MNT therapy

- Long-term adherence to the restrictive diets of MNT
- Inability to achieve recommended Phe targets with increasing age
- Malnutrition due to dietary restrictions

Phe tolerance

- Disease severity, stage of growth, pregnancy, illness, and response to treatment are important factors affecting the consumption of dietary Phe
- Adults with PKU tolerate <500 mg/day of dietary Phe, corresponding to ~10 g of intact protein

International consensus on blood Phe levels

- United States of America (USA):
  - 120–360 µmol/L
- Europe:
  - Age <12 years: 120–360 µmol/L
  - Age >12 years: 120–600 µmol/L

Pharmacological therapeutics for PKU

Sapropterin dihydrochloride

- Developed and marketed as Kuvan by BioMarin Pharmaceutical Inc., Novato, California, USA
- First non-dietary pharmacological therapy approved for PKU
- Only 20–56% of patients with PKU are responsive to sapropterin and MNT is required to maintain recommended blood Phe levels

Pegvaliase

- Developed and marketed as Palynziq by BioMarin Pharmaceutical Inc.
- Injectable once daily, the formulation of pegylated phenylalanine ammonia lyase (PAL) converts Phe to ammonia and trans-cinnamic acid
- Approved as an enzyme substitution therapy for patients with PKU in the USA (adults), Europe, Australia, Taiwan, and Canada (>16 years of age), and Japan (when indicated)
- In May 2018, it was approved for commercial use in the USA at doses of up to 40 mg/day
- In 2020, the US Food and Drug Administration approved a maximum dose of up to 60 mg/day
- Efficacy and safety of pegvaliase was established in Phase 3 clinical trials

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Study design of the pegvaliase Phase 3 clinical trial

Consisted of 3 sequential studies:

- PRISM-1 (NCT01819727)
- PRISM-2 (NCT01889862)
- Study 165–304 (NCT03694353)

PRISM-1 study

- Adults with PKU and no history of pegvaliase therapy, >18 years of age (or >16 years of age prior to a protocol change in August 2014)
- Self-administration of pegvaliase subcutaneous injection following a protocol-defined induction, titration, and maintenance dosing schedule
- Titration and dose-fixation of pegvaliase:
  - Initial dose: 2.5 mg once weekly
  - Gradually increased to randomized maintenance dose of 20 mg/day or 40 mg/day

PRISM-2 study

- Participants who continued pegvaliase treatment after PRISM-1 were enrolled in PRISM-2
- PRISM-2, a four-part clinical trial, included a long-term open-label extension study with a maximum dose of 60 mg/day

Study 165–304 trial

- Participants from PRISM-2 receiving doses of pegvaliase >40 mg/day were enrolled

- Throughout the Phase 3 trials, participants were recommended to maintain a dietary protein intake of <10% of their baseline levels
- Hypophenylalaninemia (HypoPhe): Blood Phe level <30 µmol/L on two consecutive measurements
- Dietary modifications were considered for participants with protocol-defined HypoPhe and were based on the participants' current protein intake relative to the recommended dietary allowance (RDA)

Inclusion criteria and dietary considerations

- Europe:
  - Blood Phe concentration of >600 µmol/L at baseline
  - Cessation of sapropterin 14 days prior to the first pegvaliase dose
- Supplemental tyrosine of 1,500 mg/day (three 500 mg tablets)
- Participants from PRISM-1 who had a baseline diet assessment were included

Assessments

Dietary protein intake

- Diet was recorded for three consecutive days immediately prior to each clinical visit for dietician review
- Protein intake and corresponding Phe levels were monitored using data from participants' 3-day diet diaries and analyzed using a nutrient analysis software
- Total protein measured comprised collective amounts of:
  - Medical protein: Protein from medical food
  - Intact protein: Dietary protein from food sources containing Phe

Laboratory assessments

- Blood samples were collected as per the schedule in each study protocol
- Plasma Phe and tyrosine were evaluated by ion-exchange chromatography
- Nutrition-related parameters such as levels of albumin, creatinine, and blood urea nitrogen (BUN) were assessed

Changes in weight and body mass index (BMI)

- Height, weight, and BMI data were collected as part of the pretreatment baseline medical history
- Weight and BMI were assessed at 6-month intervals as safety outcomes

Statistical analysis

- Outcomes were analyzed based on participants' baseline medical protein intake:
  - >75% of total protein intake from medical protein
  - Some protein intake from medical protein (>0% but <75% of total protein)
  - No intake of medical protein
- Evaluation of sustained Phe response (SPR) with pegvaliase: A longitudinal model utilizing data of individual participants across both PRISM studies and Study 165–304
- In addition, time-to-event models assessed associations between achieving SPR <360 µmol/L and baseline dietary patterns, Cox regression/accelerated failure time models were used for multivariable models, and logistic regression evaluated riks of developing low albumin, creatinine, and BUN levels due to HypoPhe

Results of the pegvaliase Phase 3 clinical trial

Demographic and baseline clinical characteristics

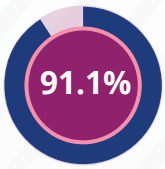
- Mean age: 29.1 (± 8.67) years
- Female: 49.2%
- Mean BMI: 28.4 (± 6.73) kg/m^2
- Mean blood Phe level: 1,237.0 (± 387.02) µmol/L
- No difference in attrition rates across groups
- Participants consuming >75% medical protein at baseline were relatively younger, with lower mean baseline Phe levels
- Decrease in the number of participants with available dietary assessments at yearly time points:
  - At baseline: 250
  - Month 12: 154
  - Month 24: 80
  - Month 36: 76
  - Month 48: 43

Efficacy

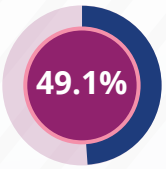
Protein intake over time

- Up to 48 months of the trial duration:
  - Total protein intake remained stable across the 3 baseline dietary groups
  - Increase in intact protein intake in all 3 baseline dietary groups
  - Decrease in medical protein intake in patients with PKU who consumed medical protein at baseline
- After month 48, the trial data was unclear and affected by a low number of participants

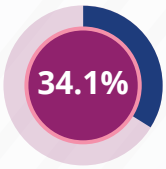
Reduced need for medical protein after treatment with pegvaliase in patients consuming:



No medical protein at baseline



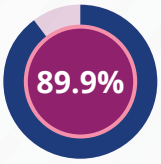
Some medical protein at baseline



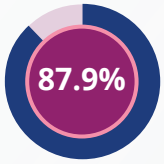
>75% medical protein at baseline → Did not need medical protein at the last assessment

Impact of pegvaliase on tyrosine levels

- Blood tyrosine levels at baseline:
  - Normal range for most participants
  - Lower for participants who consumed some or no medical protein
- No significant changes in blood tyrosine levels over time when analyzed by baseline dietary group
- Mean compliance with tyrosine supplementation per protocol: 78.7%
- Normal blood tyrosine levels were observed in:



Measurements assessed during the HypoPhe state



Measurements assessed during non-HypoPhe state

- No relationship between blood tyrosine levels and HypoPhe after adjusting for age, race, and sex

Diet and Phe response to pegvaliase therapy

- Duration for 50% of the entire cohort to achieve blood Phe targets:
  - 8 months: Blood Phe <600 µmol/L
  - 11 months: Blood Phe <360 µmol/L
  - 15 months: Blood Phe <120 µmol/L
- In unadjusted analysis, participants consuming medical protein had significantly higher chances of achieving SPR <600 µmol/L compared to those consuming no medical protein
- No significant differences in probability for achieving SPR <360 or SPR <120 µmol/L across the 3 baseline dietary groups

Changes in weight and BMI

- Consistency in weight and BMI over the trial period, with minor increases in participants consuming no medical protein
- Significantly higher baseline BMI in participants consuming no medical protein compared to other baseline dietary groups in both unadjusted analyses and after adjustment for age and sex
- In participants with at least one HypoPhe event, the changes in weight and BMI were not significant across the 3 baseline dietary groups

Exploratory assessments

Alopecia

- Number of participants who reported alopecia: 49
- Total number of episodes of alopecia: 76
- Characteristics of participants with alopecia:
  - Longer durations of pegvaliase therapy
  - Easily achieve HypoPhe state
  - Longer duration in HypoPhe state
- Participants with alopecia:
  - Females: 83.7%
  - Overweight: 40.8%
- 87.8% of participants had a marked drop in Phe levels before the first episode of alopecia and ~2.5 months after the drop in alopecia occurred

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Markers of malnutrition in participants with HypoPhe

- In measurements made during the HypoPhe state in participants who experienced HypoPhe:
  - 98.5% had a normal range of albumin levels
  - 98.8% had a normal range of BUN levels
  - 97.1% had a normal range of creatinine levels
- No participant who experienced HypoPhe had a low albumin or BUN level
- Low creatinine measurements drawn during the HypoPhe state: 1.2%

Insights from the pegvaliase Phase 3 clinical trial

- At baseline:
  - ~40% of participants did not consume any medical protein
  - ~43% of participants consumed some medical protein
  - ~16% of participants needed >75% of their total protein from medical protein
- By the last assessment:
  - >90% of participants remained in the "no medical protein" dietary group
  - Drastic reduction in the number of participants consuming some medical protein and >75% of their total protein from medical protein

Treatment with pegvaliase:
- Reduced reliance on medical protein
- Allowed participants to increase both intact protein and total protein intake
- Lowered blood Phe to normal levels

Patients with PKU consuming medical protein have significantly higher chances of achieving blood Phe <600 µmol/L compared to those consuming no medical protein in unadjusted analyses

Normal serum albumin, BUN, and creatinine levels during HypoPhe state among participants who experienced HypoPhe suggest that HypoPhe does not increase the risk of protein malnutrition in adult patients with PKU receiving pegvaliase therapy

Lowering the dose of pegvaliase is recommended if blood Phe is <30 µmol/L and the individual is consuming the recommended daily intake of protein

Alopecia was the only adverse event that occurred during pegvaliase Phase 3 studies and was reported more frequently in participants with HypoPhe

Participants who developed alopecia may have experienced telogen effluvium condition, triggered by a rapid decrease in blood Phe levels

Limitations and future aspects

Analysis of alopecia was affected by the lack of complete records for some episodes and the retrospective nature of patient-level coding of events

The impact of 'normalized' diets lacking medical protein following therapy with pegvaliase needs to be evaluated in future research studies, focusing on longer-term outcomes, neurocognition, nutritional status, and tyrosine levels

Key messages

Pegvaliase is an effective pharmacological drug that enables patients with PKU to manage their blood Phe levels without the need for medical proteins and Phe-restricted diet

Most individuals with PKU who received pegvaliase were able to achieve and maintain clinically recommended blood Phe levels while consuming a normal diet

Protein malnutrition was not detected based on available data, and alopecia was the only adverse event that occurred during pegvaliase Phase 3 studies

Sponsor

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Evaluating change in diet with pegvaliase treatment in adults with phenylketonuria: Analysis of Phase 3 clinical trial data

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