Evaluation of Multiple Dosing Regimens in Phase 2 Studies of rAvPAL-PEG (BMN 165, Pegvaliase) for Control of Blood Phenylalanine Levels in Adults with Phenylketonuria

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BACKGROUND

Phenylketonuria (PKU) is a metabolic disease in which phenylalanine (Phe) cannot be metabolized to tyrosine due to deficiency of the enzyme phenylalanine hydroxylase. This condition is characterized by accumulation of Phe leading to neurocognitive dysfunction, developmental delay, and intellectual impairment (arti, if untreated.

Clinical Need

- A treatment that will help individuals with PKU safely achieve Wolking, reliable control of blood Phe concentrations and improve functional outcomes.

PEGAylated recombinant Anabaena variabilis phenylalanaeamine lyase (rAvPAL-PEG, pegvaliase).

- Potential injectable enzyme substitution therapy for the treatment of PKU
- Due to its bacterial origin, no PAL in the clinical trials was related to immunogenicity-related blood clearance.

METHODS

Phase 2 PAL-002 and PAL-004 studies reflect an evolution in the design of dosing regimens.

- PAL-002 open-label, multidose, prospective study: Weekly dosing of pegvaliase for 16 weeks.
- PAL-004 open-label, multidose, prospective study: 5-week induction, 8-week titration (13 weeks) and 3-week titration.

RESULTS

Baseline demographics:

- PAL-002: 40 subjects
- PAL-004: 16 subjects

- Age at enrollment: 26.2 (6.35) years
- Male, n (%): 80 (50)
- Female, n (%): 10 (60.5)
- Blood Phe concentration (μmol/L): 1310.8 (335.86) µmol/L
- BM1, kg/m²: 29.3 (7.65)

Safety summary:

- Although AEs and HAEs occurred in all subjects, most were mild to moderate in severity.
- Two subjects in PAL-002 discontinued pegvaliase due to AE (grade 1 skin reaction and grade 1 arthralgia) and one subject in PAL-004 discontinued pegvaliase due to AE (grade 2 angioedema).
- Analysis of hypersensitivity AEs using NIAID/FAAN criteria to identify events consistent with anaphylaxis revealed 4 events in PAL-002 and 5 events in PAL-004. All of these events resolved and none led to early drug discontinuation.
- Similar to PAL-002, injection site reactions were common in PAL-004; however, the most common AE in PAL-004 was arthralgia in 69% of subjects.
- In both studies, all subjects developed anti-PAL antibodies and the majority of subjects developed anti-PEG antibodies.

Conclusions:

- Dose regimens in the early Phase 2 studies (PAL-002 (0.001 to 0.1 mg/kg/week) and PAL-004 (0.06 to 0.8 mg/kg/day), were not adequate to attain optimal blood Phe reduction.
- Dosing was generally well tolerated in PAL-002, but the higher starting doses in PAL-004 resulted in more frequent HAEs requiring dose reductions.
- The majority of subjects from both studies enrolled in the PAL-003 long-term extension study and later achieved substantial Phe reduction.
- Results from these studies contributed to the design of the late Phase 2 study 165-205 with a fixed induction, titration and maintenance schedule designed to improve efficacy while decreasing HAEs.

Acknowledgments:

- The authors thank the patients and physicians who participated in this study. BioMarin Pharmaceutical Inc. provided funding for the study.

Data analysis, writing, editing, and poster production.

A Randomized, Placebo-Controlled, Double-Blind Study of Sapropterin to Treat Symptoms of ADHD and Executive Dysfunction in Children and Adolescents with Phenylketonuria

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PURPOSE

A sub-analysis to determine the impact of sapropterin therapy on Attention Deficit Hyperactivity Disorder (ADHD) symptoms and Executive Function deficits in a pediatric PKU population.

METHODS

Randomized Blinded-Period Weeks 0-13

Open label Sapropterin Weeks 13-26

RESULTS

Baseline Characteristics

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

ADHD-RS Total Score

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

ADHD-RS Inattentive Score

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

ADHD-RS Hyperactivity Score

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

ADHD-RS Impulsivity Score

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

BRIEF Global Executive Function (GEC)

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

BRIEF Metacognition Index

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

BRIEF Behavioral Regulation Index

Mean Change Difference from Baseline to Week 13 and Baseline to Week 26

REFERENCES


ACKNOWLEDGMENTS

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NEUROPSYCHIATRIC COMORBIDITIES IN ADULTS WITH PHENYLKETONURIA: A RETROSPECTIVE COHORT STUDY

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Background

Adults with phenylketonuria (PKU) have been reported to experience neuropsychiatric symptoms, including anxiety, depression, and cognitive functioning problems. In contrast with the recent ACMG practice guidelines suggesting that phenylalanine hydroxylase (PAH) deficiency should be managed throughout life, only an estimated 30% of adults with PKU are currently followed in clinic [1,2]. Identifying medical and psychiatric comorbidities associated with PKU will inform the primary and specialty care management of adults with PKU.

Methods

- This nested, case-control study used ICD-9 codes from the MarketScan® insurance claims databases from 2006-2012.
- These databases provide healthcare claims data for US-based employer and government-sponsored health plans.
- Estimated prevalence of the neuropsychiatric comorbidity diagnoses for adults (≥20 years old in 2012) with PKU were compared with two comparison groups (diabetes and general population) matched by age, gender, geographic location, and insurance type.
- These groups were also stratified by age (20-29, 30-39, 40-49, 50-59, 60-69, 70-79) to examine comorbidity prevalence trends related to age.

Results

Prevalence and Relative Risks for Medical Diagnoses of All PKU Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>PKU Diabetes Controls</th>
<th>General Controls</th>
<th>PKU / Diabetes Relative Risk</th>
<th>PKU / General Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Disorders</td>
<td>64.51</td>
<td>64.98</td>
<td>0.99 (0.87,1.10)</td>
<td>1.44 (1.31,1.58)</td>
</tr>
<tr>
<td>Depression</td>
<td>19.17</td>
<td>19.75</td>
<td>0.99 (0.87,1.10)</td>
<td>1.60 (1.49,1.72)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>15.61</td>
<td>15.55</td>
<td>1.16 (1.08,1.24)</td>
<td>1.70 (1.57,1.85)</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>13.43</td>
<td>13.70</td>
<td>0.98 (0.91,1.05)</td>
<td>1.99 (1.82,2.16)</td>
</tr>
<tr>
<td>Migraines / Headache</td>
<td>8.42</td>
<td>8.12</td>
<td>1.04 (0.95,1.14)</td>
<td>1.64 (1.47,1.84)</td>
</tr>
<tr>
<td>Movement Disorders / Parkinson's / Tremors</td>
<td>7.36</td>
<td>6.30</td>
<td>1.17 (1.05,1.31)</td>
<td>2.34 (2.05,2.66)</td>
</tr>
<tr>
<td>Epilepsy / Convulsions</td>
<td>5.23</td>
<td>4.95</td>
<td>1.06 (0.93,1.21)</td>
<td>2.24 (1.92,2.62)</td>
</tr>
<tr>
<td>Intellectual Disabilities</td>
<td>4.64</td>
<td>4.85</td>
<td>0.96 (0.87,1.06)</td>
<td>0.93 (0.83,1.05)</td>
</tr>
<tr>
<td>Bipolar Disorders</td>
<td>4.27</td>
<td>5.61</td>
<td>0.73 (0.62,0.84)</td>
<td>1.39 (1.17,1.63)</td>
</tr>
<tr>
<td>Psychosis / Schizophrenia</td>
<td>3.63</td>
<td>3.40</td>
<td>1.07 (0.92,1.24)</td>
<td>1.80 (1.52,2.15)</td>
</tr>
<tr>
<td>Cognitive and/or Personality Changes</td>
<td>3.53</td>
<td>2.63</td>
<td>1.34 (1.14,1.59)</td>
<td>2.17 (1.79,2.61)</td>
</tr>
<tr>
<td>Secondary to GMC</td>
<td>3.34</td>
<td>1.94</td>
<td>0.85 (0.76,0.95)</td>
<td>0.70 (0.58,0.84)</td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>3.26</td>
<td>2.37</td>
<td>1.38 (1.16,1.63)</td>
<td>1.57 (1.31,1.89)</td>
</tr>
<tr>
<td>Dementia</td>
<td>2.85</td>
<td>2.37</td>
<td>1.20 (1.01,1.43)</td>
<td>1.79 (1.46,2.23)</td>
</tr>
<tr>
<td>ADD / ADHD</td>
<td>2.83</td>
<td>2.37</td>
<td>1.20 (1.01,1.43)</td>
<td>1.79 (1.46,2.23)</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>2.33</td>
<td>1.87</td>
<td>1.30 (1.12,1.51)</td>
<td>1.89 (1.60,2.20)</td>
</tr>
<tr>
<td>Behavioral Conduct</td>
<td>2.09</td>
<td>1.88</td>
<td>1.17 (1.07,1.28)</td>
<td>1.10 (0.98,1.23)</td>
</tr>
<tr>
<td>Alcohol Dependence</td>
<td>1.84</td>
<td>2.35</td>
<td>1.05 (0.89,1.24)</td>
<td>0.90 (0.71,1.14)</td>
</tr>
<tr>
<td>Personality Disorders</td>
<td>1.55</td>
<td>1.31</td>
<td>1.18 (0.98,1.41)</td>
<td>0.94 (0.76,1.16)</td>
</tr>
<tr>
<td>Fatigue / Malaise</td>
<td>1.40</td>
<td>1.09</td>
<td>0.57 (0.47,0.69)</td>
<td>0.76 (0.62,0.93)</td>
</tr>
<tr>
<td>Developmental Disorders</td>
<td>1.18</td>
<td>1.40</td>
<td>0.85 (0.73,0.99)</td>
<td>0.73 (0.61,0.87)</td>
</tr>
<tr>
<td>OCD</td>
<td>1.15</td>
<td>0.52</td>
<td>0.39 (0.21,0.51)</td>
<td>0.33 (0.15,0.67)</td>
</tr>
<tr>
<td>PDD (Autism Spectrum Disorders)</td>
<td>0.86</td>
<td>0.23</td>
<td>0.13 (0.06,0.26)</td>
<td>0.12 (0.06,0.23)</td>
</tr>
<tr>
<td>Phobias</td>
<td>0.66</td>
<td>0.78</td>
<td>0.81 (0.63,1.03)</td>
<td>0.89 (0.70,1.12)</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>0.42</td>
<td>0.63</td>
<td>0.67 (0.47,0.95)</td>
<td>1.27 (0.75,2.15)</td>
</tr>
<tr>
<td>Tourette's / Tic Disorders</td>
<td>0.22</td>
<td>0.05</td>
<td>0.65 (0.40,1.03)</td>
<td>2.56 (1.38,4.76)</td>
</tr>
</tbody>
</table>

Prevalence of Intellectual Disabilities

Females outnumbered males by 1.6x but this ratio was kept constant across the 3 populations

Adults with PKU demonstrated an increased relative risk of being diagnosed with anxiety, intellectual disability (ID), movement disorders, eating disorders, dementia, ADD/ADHD, behavioral conduct disorders, developmental disorders, OCD, PDD, and Tourette's/Tic disorders, as compared with both control groups

Compared with diabetes, adults with PKU had lower relative risk for medical diagnoses of substance abuse, alcohol dependency, bipolar disorders, and multiple sclerosis

Adults who may have been late-treated (≥50 years old) experienced a higher rate of ID than young adults, illustrating the success of newborn screening

Anxiety diagnoses were prevalent across the age cohorts

Conclusions

- Adults with PKU experience higher rates of intellectual disability, anxiety, autism, and other neuropsychiatric disorders, when compared to those with diabetes and the general population.
- In addition, adults with PKU have higher rates of depression, sleep disturbances, migraine, epilepsy/convulsions, bipolar disorders, phobias, personality disorders, psychoses/schizophrenia, fatigue/malaise, and phobias, as compared with the general population.
- These results support the need for continued monitoring of behavioral, psychiatric and neurocognitive functioning

References

[1] J. Vockley et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genetics in Medicine 2014; 16 (2) 188-200

Statistically above the control group
Statistically below the control group

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Phase 2 Studies Contribute to rAvPAL-PEG (BMN 165, pegvaliase) Phase 3 Trial Design

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Background

Phenylketonuria (PKU)
- Inherited metabolic disease in which phenylalanine (Phe) cannot be metabolized to tyrosine due to deficiency of the enzyme phenylalanine hydroxylase
- Characterized by accumulation of Phe leading to neurocognitive dysfunction

Clinical Need
- A treatment that will help individuals with PKU safely achieve lifelong, reliable control of blood Phe concentrations and improve functional outcomes

Pegvaliase
- (PEGylated recombinant Arubama vanillata phenylalanine ammonia lyase (rAv-PAL-PEG))
- Subcutaneous injectable enzyme substitution therapy to decrease Phe levels in patients with PKU
- Due to its bacterial origin, rAV-PAL is PEGylated to reduce immunogenicity

Phase 2 Experience

Dosing and Titration Explored in the Phase 2 Clinical Studies of Pegvaliase

**PAL-002 N=40**
- Weekly weight-based dosing with 8-week induction followed by 8-week dose titration
- Weekly low-dose induction followed by gradual dosage and frequency increases
- Well Tolerated Blood Phe reduction dependent on individual immune response
- Subjects in these 3 studies had option to continue in a long term safety and efficacy study, with further dose increases and continuation of long-term treatment

**PAL-004 N=16**
- 5 days/week dosing with faster titration for 13 weeks

**165-205 N=24**
- Weekly low-dose induction followed by titration to max. 375 mg/week dosed 5 days/week to blood Phe target ≤ 600 µmol/L for 24 weeks

**PAL-003 Extension Study (N=67)**
- Dosing 1 to 7 times/week with adjustments to achieve or maintain blood Phe 60 to 600 µmol/L

Dosing and Titration Conclusions from the Phase 2 Studies in Adults with PKU
- The majority of patients can be treated to meaningful blood Phe reductions with doses of 20 or 40 mg s.c. daily.
- Weekly, low-dose introduction of treatment, followed by gradual increases in dose and frequency, result in fewer hypersensitivity events.
- Blood Phe reduction appears to be dependent on dose and duration of treatment. The immune response to the compound is hypothesized to play a role in blood Phe reduction.
- Most Phase 2 subjects entered the long-term extension study, in which most achieved at least 2 consecutive blood Phe values ≤ 600 µmol/L in 25-40 weeks.

Phase 3 Study Design

Phase 3 Studies in Adults with PKU

**PRISM 301 Trial Design**
- Open-label, randomized study to assess safety and tolerability of induction, titration and maintenance dose regimen of subcutaneous pegvaliase, self-administered by adults with PKU naive to pegvaliase treatment

**PRISM 301 Baseline Characteristics**
- (as of 24 October 2014)
  - Total Subjects (n=159)
    - Age at enrollment (mean, SD): 28.8 (8.7) years
    - Subjects ≥ 18 years, n (%): 141 (88.7%)
    - Male, n (%): 141 (88.7%)
    - Female, n (%): 18 (11.3%)
    - Weight (kg), mean (SD): 81.08 (22.45)
    - Blood Phe concentration (µmol/L), mean (SD): 1202.8 (365.1)

**PRISM 302 Trial**
- Double-blind, placebo-controlled, four-arm randomized discontinuation study (RDT) to evaluate efficacy and safety of pegvaliase

Primary efficacy objective:
- To investigate blood Phe levels at the end of the 8-week RDT period

RDT design:
- Ensures a more homogeneous population on treatment entering the placebo-controlled phase
- Assessment of the Attention Deficit Hyperactivity Disorder (ADHD) Inattention subscale and the Profile of Mood States (POMS) scale.

Conclusions
- Data from multiple early-phase clinical studies have informed the design of the Phase 3 trials for pegvaliase.
- The design of the Phase 3 trials was based on information from Phase 2 studies using various dosage regimens, which demonstrated the relationships between dosage, duration of treatment, hypersensitivity reactions, and reduction of blood Phe concentrations.

Acknowledgments
BioMarin Pharmaceutical Inc. provided funding for the study, data analysis, writing, editing, and poster production.
**Methods**

**PAL-003 Phase 2 Extension Study**

Open-label, multi-site, prospective study evaluating long-term efficacy, safety, and tolerability of multiple subcutaneous doses of pegvaliase in adults with PKU

*Patients entered PAL-003 from one of three Phase 2 parent studies with various dosing regimens and with previous exposure to pegvaliase (range: 11 to 24 weeks; mean: 17 weeks).*

- **PAL-002**
  - Number of subjects: N=40
- **PAL-004**
  - Number of subjects: N=16
- **165-205**
  - Number of subjects: N=24

**PAL-003**

- Dose adjustments for safety and to achieve or maintain blood Phe 60 to 600 µmol/L
- Dosing 1 to 7 times/week
- Mean weekly dose: 186 ± 157 mg/week
- Study is ongoing: all results reflect interim data cut off April 24, 2014
- Up to approximately 4 years treatment data available

**Patient Disposition**

- **Enrolled** N=67
- **Treated** N=67
- **Discontinued** N=14
  - Adverse Event: 2 (3.0%)
  - Withdrawal of consent: 4 (6.0%)
  - Lost to Follow-up: 1 (1.5%)
  - Investigator Decision: 3 (4.5%)
  - Other: 4 (6.0%)

**Results**

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Total Subjects (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at enrollment (years), mean (SD)</strong></td>
</tr>
<tr>
<td>Subjects ≥ 18 years, n (%)</td>
</tr>
<tr>
<td>Subjects &lt; 18 years, n (%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Weight (kg, mean (SD))</td>
</tr>
<tr>
<td>Blood Phe concentration (µmol/L), mean (SD)</td>
</tr>
</tbody>
</table>

**Adverse Events Summary**

- Total Subjects (n=67)
- **Adverse event (AE):** 67 (100%)
  - Mild: 20 (30%)
  - Moderate: 41 (61%)
  - Severe: 6 (9%)
- **Serious AE (SAE):** 9 (13%)
- **Discontinued treatment due to SAE (1 arthralgia and peripheral neuropathy, 1 anaphylaxis):** 2 (3%)
- **AE requiring dose interruption:** 17 (25%)
- **AE requiring dose reduction:** 6 (9%)
- **AE leading to withdraw from study drug treatment:** 4 (6%)
- **Hypersensitivity AE:** 62 (93%)
- **Anaphylaxis (NIAID/FAAN criteria):** 4 (6%)
- **Death:** 0

**Adverse Events Related to Study Drug in ≥15% of Subjects**

- **Injection site:**
  - N=67
  - Percent of Patients: 90%
  - Related per investigator (not sponsor) assessment
- **Skin:**
  - N=67
  - Percent of Patients: 85%
  - Related per investigator (not sponsor) assessment

**Time to Blood Phe ≤ 600 µmol/L**

- **Subjects with at least 2 consecutive blood Phe levels < 600 µmol/L during PAL-003 study, n (%):** 54 (81%)
- **Time to blood Phe < 600 µmol/L, mean (SD):** 19.5 (20.4) weeks
- **Time to at least 2 consecutive blood Phe levels < 600 µmol/L, mean (SD):** 25.7 (21.7) weeks
- **Time to at least 4 consecutive blood Phe levels < 600 µmol/L, mean (SD):** 30.8 (23.8) weeks

**Acknowledgments**

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