Current Trials for Alternative Treatment of Phenylketonuria

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Clinical Trials To Be Discussed

- **Sapropterin Dihydrochloride (BH₄) Trials**
  - *Nutritional and Neurotransmitter Changes in PKU Subjects (Investigator Initiated)*

- **PKU-016 / ASCEND Assessment of Sapropterin Dihydrochloride Clinical Efficacy in Neuropsychiatric Disorders (Multisite BioMarin Initiated)**

- **Other Trials (Multisite BioMarin Initiated)**
  - PEG-PAL
  - Blood Phe Monitor
**Diversified Approach to PKU Treatment**

<table>
<thead>
<tr>
<th>PEG-PAL</th>
<th>Blood Phe monitor</th>
<th>Saproterin dihydrochloride</th>
</tr>
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<tbody>
<tr>
<td><em>investigational</em></td>
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</table>
Study’s Purpose

Sapropterin Dihydrochloride (BH₄) Trial

To evaluate change in body composition, nutritional, and neurotransmitter status in patients who initiate BH₄ therapy for the treatment of phenylketonuria (PKU)

This presentation will focus on our clinic’s unique classification system and the impact of BH₄ therapy
**Study’s Design**

- **Visit 1:** Baseline
- **Visit 2:** Determine preliminary responsiveness
- **Visit 3:**
- **Visit 4:**
- **Visit 5:** Exit

**All visits:**
- Height & weight
- 12 hour urine sample

**Additional at Baseline, Visit 5:**
- DEXA

This presentation will focus on preliminary data from these three study visits.
**Classification Paradigm**

- **Two sequentially applied criteria:**
  1. >15% decrease in plasma Phe concentration
  2. Dietary and Medical food adjustment
     - Ability to increase dietary Phe tolerance by at least 300 mg
     - Ability to decrease medical food need by at least 25%

**Diet Adjustment**
*(Criteria #2)*

**RESPONDER**
*Continue BH₄ therapy, evaluate necessity of MF*

- **YES**
  - Restricting intact protein (dietary Phe)?
  - Plasma Phe concentration ≤ 360 μmol/L?

  - **NO**
    - Consuming MF?
    - Progressively reduce dietary Phe intake

  - **YES**
    - Decrease dietary Phe by 350 mg per week until blood Phe < 360 μmol/L
    - Add 25% of original MF prescription

    - **NO**
      - Blood Phe concentrations < 360 μmol/L

- **NO**
  - Ensure protein needs are met; if not, adjust MF consumption accordingly
  - Decrease MF consumption by 25% per week until plasma Phe > 360 μmol/L

**DEFINITIVE RESPONDER**
*Pre-BH₄ dietary Phe tolerance increased by 300 mg/day AND Pre-BH₄ therapy MF needs decreased by at least 25%*

**PROVISIONAL RESPONDER**
*Only Blood Phe responder*

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Provisional Responders

• Initially meet change in plasma Phe concentration criteria but cannot significantly change dietary Phe tolerance
  – True response or artifact of our testing protocol?
    • Could be affected by incurrent illness and/or dietary non-compliance at baseline, subsequent changes over month 1
      – Two of the Provisional Responders were sick at baseline measurement, potentially inflating plasma Phe concentrations

Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
Provisional Responders

• Why patients in this group matter:
  – If they are a subclass of responders
    • May illuminate functionality of exogenous BH$_4$ or add to genotype-phenotype associations
    • Need to evaluate of blood Phe maintenance on BH$_4$ vs. on diet therapy alone
  – If they are an artifact of the protocol
    • May show that a one month protocol leads to false-positives

Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
Implementation of Classification Paradigm in a Clinical Population

BASELINE, (Study Visit 1)
58 patients
(34M, 24F)

MONTH 1 (Study Visit 2)
57 patients
(34M, 23F)

1 patient loss to follow-up

PRELIMINARY RESPONDERS
Blood PHE responders
32 patients
(21M, 11F)

1 patient loss to follow-up;
1 patient electively removed from BH₄
2 patients not classified due to protocol non-compliance

DEFINITIVE RESPONDERS
19 patients
(11M, 8F)

NON-RESPONDERS
25 patients
(13M, 12F)

PROVISIONAL RESPONDERS
Blood Phe responders
9 patients
(6M, 3F)

1 patient further assessed, but could not liberalize diet

Summary of Responsiveness

**Preliminary Classification (Month 1)**

- Preliminary Responders: 55.1% (n=32)
- Non-Responders: 43.1% (n=25)
- Preliminary Loss to Follow-Up: 1.7% (n=1)

**Definitive Classification (After Diet adjustment)**

- Definitive Responders: 32.7% (n=19)
- Provisional Responders: 15.5% (n=9)
- Non-Responders: 43.1% (n=25)
- Definitive Loss to Follow-Up, Unclassified: 8.6% (n=5)

Data adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
## Demographics at Baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All Participants (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>17.3 ± 11.0</td>
</tr>
<tr>
<td>Participants &lt;18yrs, n (%)</td>
<td>36 (62.1%)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>34 (58.6%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.3 ± 30.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>149.0 ± 23.0</td>
</tr>
<tr>
<td>Baseline plasma Phe (μmol/L)</td>
<td>693 ± 412</td>
</tr>
</tbody>
</table>

*Table adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).*
Metabolic Control

**BASELINE**
- 76% (n=44)
- 24% (n=14)

**MONTH 1**
- 50% (n=29)
- 2% (n=1)
- 48% (n=28)

**YEAR 1**
- 55% (n=32)
- 17% (n=10)
- 28% (n=16)

Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
Metabolic Control by Group

### Baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>Definitive Responders</th>
<th>Provisional Responders</th>
<th>Non-Responders</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>15</td>
<td>5</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>

### Month 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Definitive Responders</th>
<th>Provisional Responders</th>
<th>Non-Responders</th>
<th>Unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>2</td>
<td>17</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

### Year 1

<table>
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<tr>
<th>Group</th>
<th>Definitive Responders</th>
<th>Provisional Responders</th>
<th>Non-Responders</th>
<th>Unclassified</th>
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<tr>
<td>Participants</td>
<td>9</td>
<td>10</td>
<td>15</td>
<td>2</td>
</tr>
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</table>

- **<360 μmol/L**
- **>360 μmol/L**
- **Loss to Follow-Up**

Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
**Plasma Phe Over Time by Group**

**Plasma Phe Concentration (μmol/L)**

- **Non-Responders (n=18)**
- **Provisional Responders (n=8)**
- **Definitive Responders (n=19)**

*Note: All Definitive Responders and 7/8 Provisional Responders remained on BH₄ over the course of the year*

Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).
Changes in Diet Prescription

- **Dietary Phe Rx (mg/day)**
  - Definitive Responders slightly higher Phe diet at baseline
  - None of the Provisional Responders could double dietary Phe Rx

- **Protein Equivalents from medical food (g/day)**
  - All of the Provisional Responders stayed on 100% of their original MF Rx

*Concept adapted from manuscript in preparation: Singh RH and Quirk ME, (2011).*
Future Analyses of Data

• **Neurotransmitters**
  – Blood and urine samples currently being analyzed
    • Results expected by early fall 2011

• **Quality of Life**
  – Results expected by early fall 2011

• **Nutritional Status**
  – Trends over 12-month period (blood and reported dietary intake)

• **Body Composition**
  – DEXA results will be analyzed
• PKU patients, even if early and continuously treated, exhibit:
  – Neurocognitive features
  – Psychiatric symptoms
  – Deficits in executive function

• PKU-016 Study
  – BioMarin-Initiated
    • Evaluating effects of BH₄ on neuropsychiatric symptoms and cognitive features
  – Randomized, double-blind, placebo-controlled
  – Study is conducted in the United States and Canada and has recently started recruitment
    • Anticipated enrollment: 200 patients
“A Double-blind, Placebo-controlled, Randomized Study to Evaluate the Safety and Therapeutic Effects of Sapropterin Dihydrochloride on Neuropsychiatric Symptoms in Subjects with Phenylketonuria (PKU ASCEND)”

Randomized Treatment Period
13 weeks

Placebo

Sapropterin Dihydrochloride
20 mg/kg/day

Week 13
Primary endpoint

Open-Label Period
13 weeks

Sapropterin Dihydrochloride
20 mg/kg/day

BH₄ treated subjects Week 13 compared to Week 26
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Rater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS) / Adult ADHD Self-Report Scale (ASRS)</td>
<td>Patient Reported Outcome. ADHD-RS completed by parent/Guardian. ASRS completed by patient</td>
</tr>
<tr>
<td>Hamilton Anxiety Rating Scale (HAM-A)</td>
<td>Psychiatrist or Psychologist</td>
</tr>
<tr>
<td>Hamilton Depression Rating Scale (HAM-D)</td>
<td>Psychiatrist or Psychologist</td>
</tr>
<tr>
<td>Clinical Global Impression (CGI)</td>
<td>PI or Health Care provider regularly seeing patient</td>
</tr>
<tr>
<td>Behavior Rating Inventory of Executive Function (BRIEF)</td>
<td>Completed by parent/Guardian for patients under 18, and completed by patient if over 18</td>
</tr>
</tbody>
</table>
• The **Primary Objective** of this study:
  – To evaluate the therapeutic effects of sapropterin dihydrochloride in subjects PKU who have a blood Phe level reduction ≥ 20% after their first 4 weeks of treatment
    • Symptoms of ADHD
    • Global function of subjects

• **Primary Efficacy** Variable for Symptoms of ADHD:
  – ADHD RS (for subjects 12 - 17 years of age)
  – ASRS (for subjects ≥18 years of age) scores

• **Primary Efficacy** Variable for Global Function:
  – CGI-Improvement (CGI-I)
**PEG-PAL:**

*Potential to Address the Entire Spectrum of PKU*

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### Sapropterin dihydrochloride

- Oral, small molecule (6R-BH4) cofactor for PAH
- For BH4-responsive patients (~15,000–25,000 individuals)
- FDA Approval December 2007

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### PEG-PAL

*(phenylalanine ammonia lyase) Investigational*

- Enzyme substitution therapy
- For patients who do not respond adequately to BH$_4$ or wish to reduce blood Phe levels beyond what is possible with BH$_4$
- Potential to bring blood Phe levels down to near normal with complete diet-liberalization

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~50,000 pts.

*in the developed world*
PEG-PAL Phase 1 Study: Substantial Phe reductions correlate with plasma concentration of PEG-PAL

Cohort 5 Mean Plasma Profiles with SD Error Bars

Mean (±SD) Plasma rAvPAL-PEG (ng/mL)

Mean (±SD) Plasma Phe (M)

Investigational drug

Courtesy BioMarin Pharmaceutical Inc.
• Phase 2 is an open-label, multi-center study in a series of dose escalating cohorts.

• Eight once weekly injections at a fixed dose is followed by dose and frequency optimization and an extension period where doses can be increased up to 2 mg/kg/week

• Study is ongoing and being conducted in the United States

• Study to date has enrolled 33 patients

• Phase 3 pivotal trial – Initiation expected in first half 2012

Investigational drug
Blood Phe Monitor (BPM): Upcoming Clinical Trials for Validation

- BPM System is a simple, easy to use, portable, handheld device for use at home

- Proposed Device Includes:
  - Meter: Detect signal, calculate value, display on user interface, store data
  - Test Sensors: Electrochemical reaction, disposable one-time use
  - Control solution, calibration device, instructions for use, data cable
  - Intended for all PKU patients; measures Phe 120-1999 µM (2-33 mg/dL)
Conclusion

This is an exciting time in the evolution of therapy for PKU!
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Special Thanks to: Drs. Marian Evatt, Thomas Ziegler, Paul Fernhoff & Muhammad Pervaiz

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Thank you for your attention

Questions?