Can small, open-label trials be used to establish efficacy?  
A tale of two trials

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Disclaimer and Acknowledgements

• The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.

• I would like to acknowledge Ethan Hausman, M.D. for his contributions to the slides I will be presenting. He has previously given talks at this course on Kuvan.
Objectives

- Review two rare diseases: Phenylketonuria and N-acetylglutamate synthase (NAG-S) Deficiency
- Review the open-label clinical trials leading to the approval for products to treat these conditions
- Understand the differences in these clinical trials
- Review specific clinical development contexts that may allow for use of open-label trials to establish efficacy
Pertinent PKU Background

- Patients have reduced/altered function of an enzyme (PAH) that breaks down the amino acid phenylalanine (Phe).
  - 1/10,000 live births in the US, or about 28,000 US patients

- Phe builds up to toxic levels in the blood
  - **Unaffected**: Blood Phe < 1 mg/dL (60 uM)
  - **PKU**: Blood Phe from 6 to > 30 times normal.

- Elevated blood Phe leads to progressive neurocognitive impairment
  - **Goal**: all patients < 600 uM, children younger than 8 years old <480 uM; NIH Consensus Conference 2000

- High blood Phe in pregnant women can cause heart and brain damage in off-spring
  - **Goal**: <360 uM from 3 months prior to conception through delivery; NIH-CC 2000
PKU Background

PAH → phenylalanine hydroxylase
H2O → cellular/mitochondrial water
DHPR → dihydropteridine reductase
NAD(H) → nicotinamide adenine dinucleotide dehydratase (*arch.* dehydrogenase)
Treatment

• **Low dietary protein (low-Phe diet):**
  – Lowers blood Phe
  – Improves neurocognitive outcomes
  – Decreases risk to off-spring of affected women
  – Potential biomarker

• **Strict life-time adherence to a low-Phe diet is difficult to maintain.**

• **Therefore, a drug that helps reduce blood Phe that has a favorable risk profile might be a useful adjunct to low Phe diet.**
Pharmacologic Treatment

- Kuvan® 6-R-tetrahydrobiopterin (6R-BH4, sapropterin).
  - Postulated to work in the subset of patients with residual PAH activity

- The Sponsor and FDA therefore determined that a short-term study comparing blood Phe in drug- and placebo-treated patients was reasonable for establishing efficacy.

- Longer duration studies could be used to enhance the safety database
Planned Studies

• Study 1: Open-label, uncontrolled “screening” study
  – Identify potential responders to Kuvan

• Study 2: Short-term, Randomized, double-blind, placebo-controlled study

• Study 3: Open-label, uncontrolled study in pediatric patients with well-controlled blood Phe
Study 1

• Study 1: Screening study for potential responders.
  – Open-label, uncontrolled clinical trial of approximately 500 patients with PKU, ≥8 years old, baseline blood Phe levels ≥450 uM
  – Diet not necessarily controlled (e.g.: “usual” pre-study diet: +/- diet control). Patients instructed not to make changes in dietary Phe intake.
  – Dose: 10 mg/kg/day for 8 days
• For the purposes of this study, response was empirically defined as a ≥30% decrease in blood Phe from Baseline.
• At Day 8, 20% of patients responded.
Study 1: Mean blood Phe

- **Overall (N=485)**
  - Day 1=1004 uM
  - Day 8=906 uM
  - Mean % change = -11%

- **Responders (N=96)**
  - Day 1=806 uM
  - Day 8=414 uM
  - Mean % change =-50%

- **Non-Responders**
  - Day 1=1054 uM
  - Day 8=1027 uM
  - Mean % change=-2%

Source: Original NDA review
Study 2

• **Study 2: Confirmatory Study:**
  – Responders from Study 1 entered a 6-week randomized (1:1), double-blind, placebo-controlled study. Kuvan (10 mg/kg/day) or placebo for 6 weeks
  – Diet not necessarily controlled (e.g.: “usual” pre-study diet: +/- diet control). Patients again instructed not to make changes in dietary Phe intake.

• **Efficacy (response):** Mean change in blood Phe at Wk 6.
  – Mean change in the Kuvan-treated group from Baseline minus mean change in the Placebo-treated group from Baseline.
### Study 2 Efficacy Table

<table>
<thead>
<tr>
<th></th>
<th>Sapropterin (N=41)</th>
<th>Placebo (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Blood Phe Level</strong> (μmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>843 (±300)</td>
<td>888 (±323)</td>
</tr>
<tr>
<td>Percentiles (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;)</td>
<td>620, 990</td>
<td>618, 1141</td>
</tr>
<tr>
<td><strong>Week 6 Blood Phe Level</strong> (μmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>607 (±377)</td>
<td>891 (±348)</td>
</tr>
<tr>
<td>Percentiles (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;)</td>
<td>307, 812</td>
<td>619, 1143</td>
</tr>
<tr>
<td><strong>Mean Change in Blood Phe From Baseline to Week 6</strong> (μmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted Mean (±SE)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-239 (±38)</td>
<td>6 (±36)</td>
</tr>
<tr>
<td>Percentiles (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;)</td>
<td>-397, -92</td>
<td>-96, 93</td>
</tr>
<tr>
<td><strong>Mean Percent Change in Blood Phe From Baseline to Week 6</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>-29 (±32)</td>
<td>3 (±33)</td>
</tr>
<tr>
<td>Percentiles (25&lt;sup&gt;th&lt;/sup&gt;, 75&lt;sup&gt;th&lt;/sup&gt;)</td>
<td>-61, -11</td>
<td>-13, 12</td>
</tr>
</tbody>
</table>

→ p<0.001 [ANCOVA]

Source: Current Kuvan label located on the “Drugs @ FDA” website.
Conclusions

- **Summary**: Kuvan was approved for use in patients with BH4 responsive PKU

- Open-label study design used to identify potential responders to enroll into a subsequent enrichment study

- Since not all questions were answered prior to approval, post-marketing studies/assessments include:
  - Safety, efficacy, and pharmacokinetic studies in patients < 4 years old at study entry
  - Long term growth, and neurocognitive studies in patients < 8 years old at study entry
  - Implementing a registry to last at least 15 years, and including assessments for effects on pregnancy/lactation
  - Gene analyses to characterize response based on specific mutations/polymorphisms
And now for something completely different... Carglumic acid for N-acetylglutamate synthase (NAGS) deficiency
N-acetyl glutamate synthase (NAGS) deficiency

- Rarest urea cycle defect
- Approximately 50 cases known worldwide
- High plasma ammonia
- Clinical symptoms are related to severe and/or prolonged hyperammonemia
Clinical “Studies” Information

• Retrospective case series in 23 patients with NAGS deficiency treated over 16 years
  – 13 evaluable patients with “complete” documentation of ammonia levels and clinical course
  – 6 evaluable patients without concomitant ammonia lowering therapies or protein restriction

• Efficacy outcomes
  – Plasma ammonia, glutamine and citrulline levels in short and long term
  – Growth, neurological and psychomotor developmental outcomes

• No formal statistical analysis
### Efficacy evaluation: Plasma Ammonia

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Short-term (Day 1)</th>
<th>Short-term (Day 2)</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>270.8 (358.8)</td>
<td>180.7 (357.7)</td>
<td>68.5 (78.0)</td>
<td>23.0 (6.89)</td>
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<tr>
<td>Median</td>
<td>157.0</td>
<td>64.5</td>
<td>44.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Range</td>
<td>72.0-1428.0</td>
<td>25.0-1190.0</td>
<td>11.0-255.0</td>
<td>9.0-34.0</td>
</tr>
</tbody>
</table>

- Long-term treatment: Median 5.8 years; range 1.3-16 years
- All patients demonstrated consistent and sustained lowering of plasma ammonia levels
- All were treated exclusively with Carbaglu in the long-term
- Some of these patients were treated initially with other ammonia lowering therapies
Efficacy evaluation: Neurologic outcome

23 patients in case series

3 missing data and 3 Heterozygotes excluded

17 patients

3 normal baseline

3 (16%) remained normal

14 abnormal baseline

9 (53%) improved

5 (29%) remained abnormal
Advisory Committee Meeting

- Do the clinical data included in the Carbaglu application for treatment of hyperammonemia in NAGS deficiency provide substantial evidence of efficacy?
  - Vote: 12 yes; 0 no

- Committee comments:
  - Underlying pathophysiology of the disease is well understood and the mechanism of action of the drug is clear
  - Despite the retrospective nature of the study presented, plasma ammonia decreased with Carbaglu treatment and remained decreased long-term
  - Elevated ammonia potentiates most of the neurologic problems with this disease and neurologic improvements were observed during treatment with Carbaglu

- The committee believed this application meets the legal and regulatory definition for substantial evidence.
Conclusions

• An advisory committee agrees that despite the absence of a prospective, well-controlled trial, the evidence was sufficient because:
  – Endpoints were objective and outcomes were robust and sustained
  – The population studied included most of the known patients
Overall Conclusions

• Understanding Rare Disease Natural History
  – Endpoints
  – Study Design

• Open-label studies are possible but not under all circumstances
  – One size does NOT fit all
  – Context of the situation is unique for all rare diseases
  – Evidentiary standards are NOT different for rare diseases

• Early and frequent communication with FDA
Challenge Questions

• What was the purpose of the open-label, uncontrolled Kuvan study?
  A. Identify responders to be enrolled in a R, DB, PC controlled trial
  B. Establish substantial evidence of efficacy as a single trial
  C. To confuse FDA

• Under very specific circumstances, can a small, open-label, uncontrolled clinical trial be used to support substantial evidence of efficacy of a product?

• Name 2 conditions in the Carbaglu clinical trial that allowed for this trial to support substantial evidence of the efficacy in the treatment of NAG-S deficiency.
Back up slides
**Review:** Dietary interventions for phenylketonuria

**Comparison:** 3 PKU participants at diagnosis: Low-phenylalanine diet versus moderate phenylalanine diet

**Outcome:** 3 Intelligence Quotient (IQ)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Low-phe diet</th>
<th>High-phe diet</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
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<tr>
<td>1 IQ at 4 years</td>
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<tr>
<td>US/PKU Collaborative</td>
<td>58</td>
<td>94 (16)</td>
<td>53</td>
<td>91 (15)</td>
<td>100.0 %</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>58</strong></td>
<td><strong>94 (16)</strong></td>
<td><strong>53</strong></td>
<td><strong>91 (15)</strong></td>
<td><strong>100.0 %</strong></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect: Z = 1.02 (P = 0.31)</td>
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<tr>
<td>2 IQ at 6 years</td>
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<tr>
<td>US/PKU Collaborative</td>
<td>66</td>
<td>99 (16)</td>
<td>66</td>
<td>97 (15.7)</td>
<td>100.0 %</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>66</strong></td>
<td><strong>99 (16)</strong></td>
<td><strong>66</strong></td>
<td><strong>97 (15.7)</strong></td>
<td><strong>100.0 %</strong></td>
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<td>Heterogeneity: not applicable</td>
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<td>Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0.0%</td>
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</tbody>
</table>

**Poustie VJ, Wildgoose J. Dietary Interventions for PKU.**

**Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001304.**
Why no diet control

• **Postulates**
  
  – Mean change in blood Phe if Kuvan has no effect should be zero
  
  – Under study conditions of no particular diet control other than instructions to maintain diet, patients are just as likely to increase as decrease their dietary Phe. Therefore, in the short-term, mean change in blood Phe should be zero.

• **Since Study 1 did not control for diet, a >30% decrease in blood Phe was empirically chosen to define a decrease that was more likely to be associated with Kuvan treatment than undocumented changes in diet.**

• **Reasonable approach if preliminary findings were confirmed in a subsequent placebo-controlled study.**
Blood Phe Profiles

- **Placebo**
- **Phenoptin**

<table>
<thead>
<tr>
<th>Time</th>
<th>Screen</th>
<th>BL 1</th>
<th>BL 2</th>
<th>Week 0</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
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<tbody>
<tr>
<td></td>
<td>41</td>
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</table>

Blood Phe μmol/L
Study 3

- **Study 3 (2 part study)**
  - Part 1: **Open-label, uncontrolled** study of 90 patients with PKU, 4 to 8 years old, baseline blood Phe ≤480 uM
  - **Phe restricted diet.** Instructed not to make changes in their diet during the study.
  - Dose: Kuvan 20 mg/kg/day for 8 days
  - Part 2: Dietary protein and drug dose adjustable based on blood Phe.

- **Part 1:** At Day 8, 56% of patients were identified as responders (≥30% decrease in blood Phe from Baseline)
  - Conclusion Part 1 → Likelihood of response may increase with higher dose (20 vs. 10 mg/kg/day) OR lack of diet control in Study 1 may have partially masked response

- **Part 2:** Study design issues [modifiable drug and diet] and efficacy outcome data precluded use in labeling.
Objectives

• Understand the challenges in designing adequate and well controlled trials to study NAGS deficiency

• Review a unique clinical development plan for an ultra-rare disease

• Understand the importance of identifying clinically important objective endpoint measurements in clinical “study” design