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.
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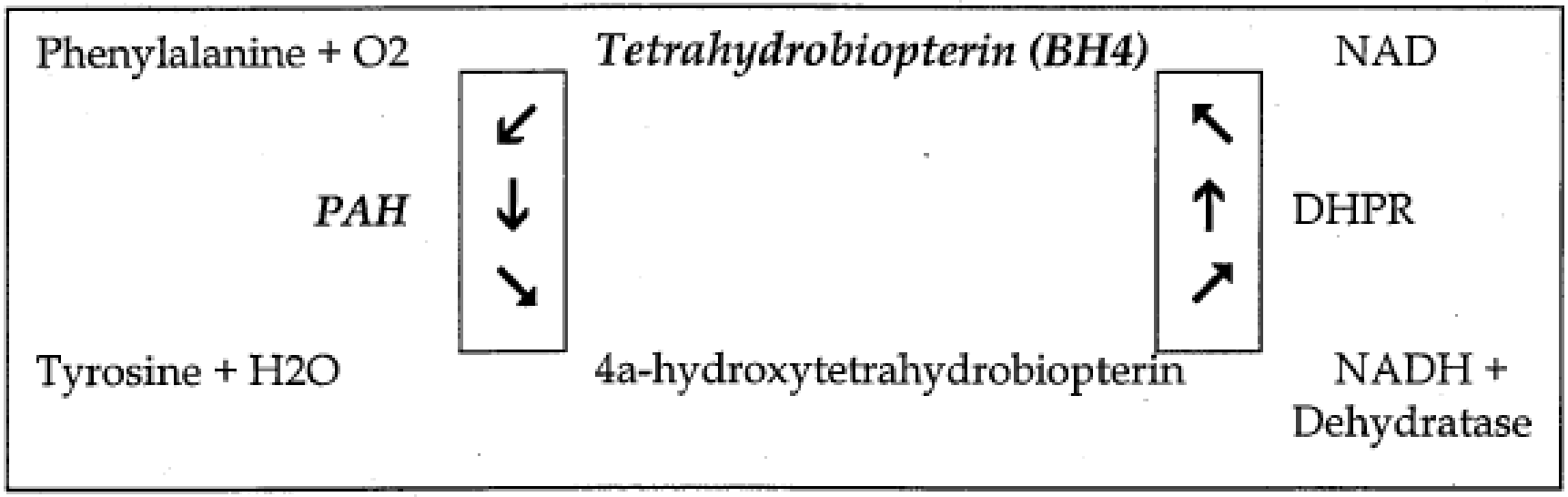
Objectives

- Review two rare diseases: Phenylketonuria and N-actetylglutamate 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

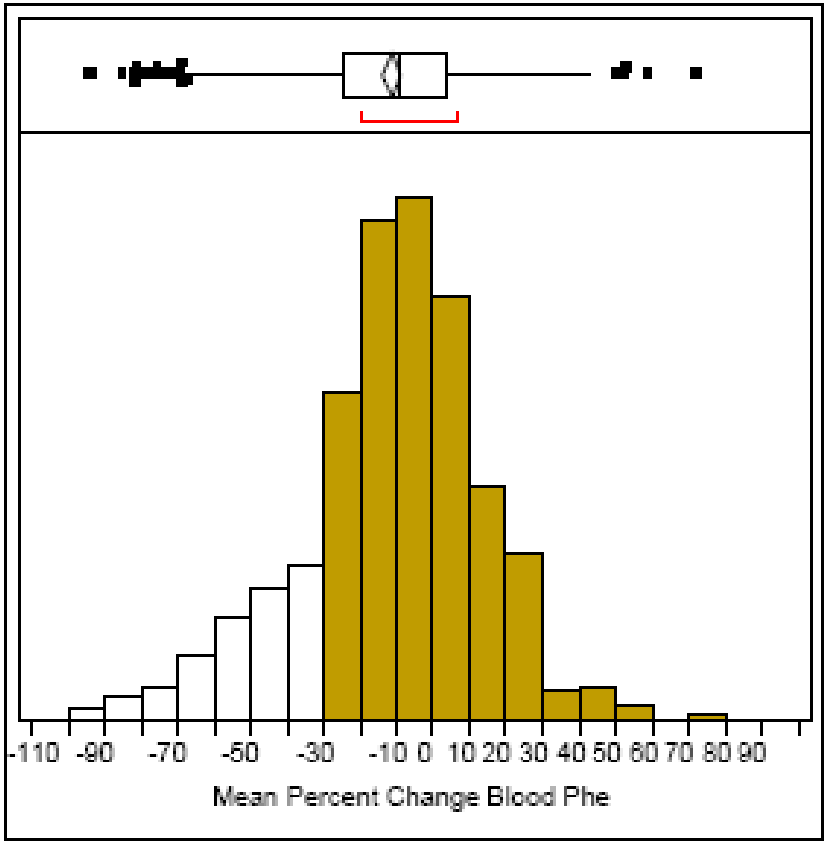
- Study 1: Open-label, uncontrolled "screening" study
  - Identify potential responders to Kuvan
- Study 2: Short-term, Randomized, double-blind, placebo-controlled study
- Study 3: Open-label, uncontrolled study in pediatric patients with well-controlled blood Phe

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

Figure 3: Mean Percent Change Blood Phe; AP (N=485)



Source: Original NDA review

- 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%

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

	Sapropterin (N=41)	Placebo (N=47)
Baseline Blood Phe Level[1] (µmol/L)		
Mean (±SD)	843 (±300)	888 (±323)
Percentiles (25th, 75th)	620, 990	618, 1141
Week 6 Blood Phe Level (µmol/L)		
Mean (±SD)	607 (±377)	891 (±348)
Percentiles (25th, 75th)	307, 812	619, 1143
Mean Change in Blood Phe From Baseline to Week 6 (µmol/L)		
Adjusted Mean (±SE)[2]	-239 (±38)	6 (±36)
Percentiles (25th, 75th)	-397, -92	-96, 93
Mean Percent Change in Blood Phe From Baseline to Week 6		
Mean (±SD)	- 29 (±32)	3 (±33)
Percentiles (25th, 75th)	-61, -11	-13, 12

→p<0.001 [ANCOVA]

Source: Current Kuvan label located on the "Drugs @ FDA" website.

Conclusions

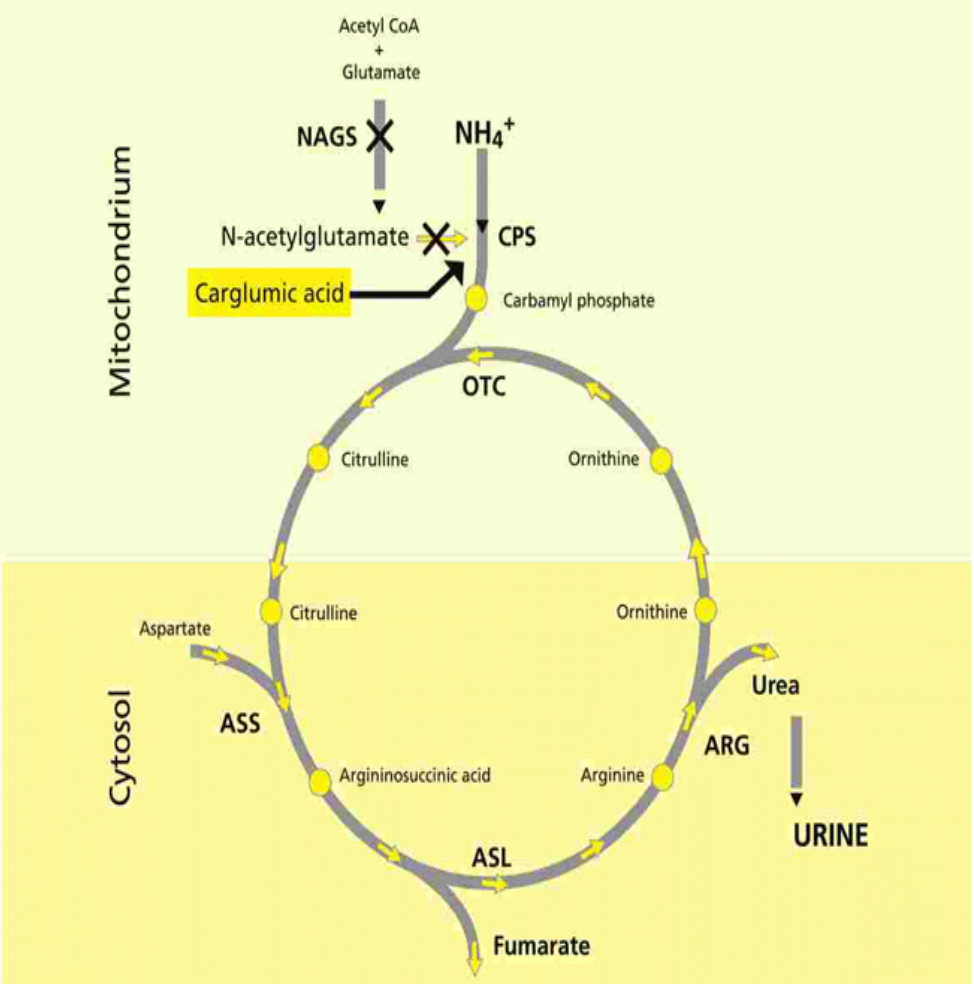
- Summary: Kuvan was approved for use in patients with BH4 responsive PKU
- Open-label study design used to identify potential responders to enroll into a subsequent enrichment study
- Since not all questions were answered prior to approval, post-marketing studies/assessments include:
  - Safety, efficacy, 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

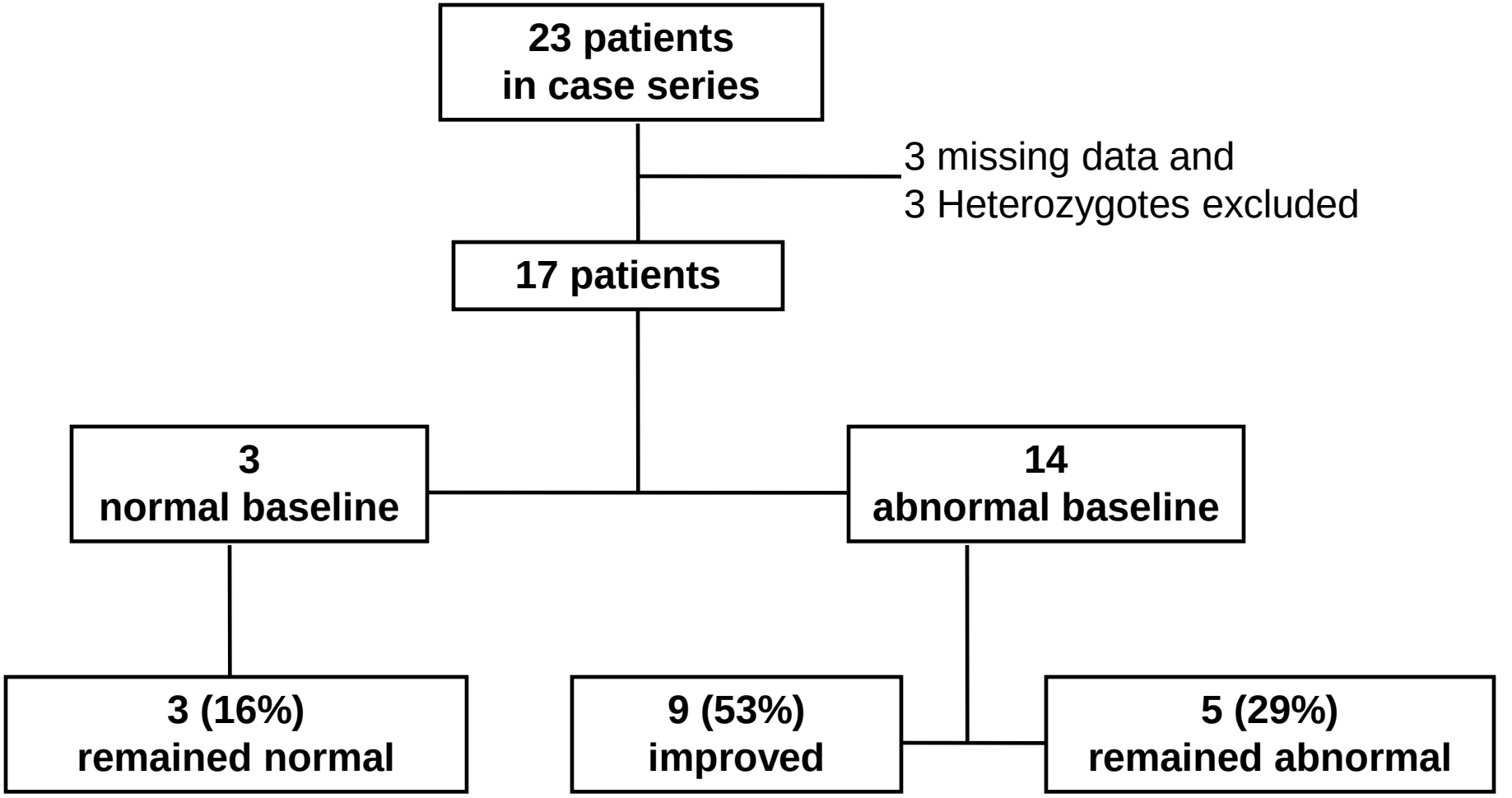
- Retrospective case series in 23 patients with NAGS deficiency treated over 16 years
  - 13 evaluable patients with "complete" documentation of ammonia levels and clinical course
  - 6 evaluable patients without concomitant ammonia lowering therapies or protein restriction
- Efficacy outcomes
  - Plasma ammonia, glutamine and citrulline levels in short and long term
  - Growth, neurological and psychomotor developmental outcomes
- No formal statistical analysis

Efficacy evaluation: Plasma Ammonia

	Baseline	Short-term (Day 1)	Short-term (Day 2)	Long-term
N	13	10	8	13
Mean (SD)	270.8 (358.8)	180.7 (357.7)	68.5 (78.0)	23.0 (6.89)
Median	**157.0**	**64.5**	**44.0**	**24.0**
Range	72.0-1428.0	25.0-1190.0	11.0-255.0	9.0-34.0

- 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



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)

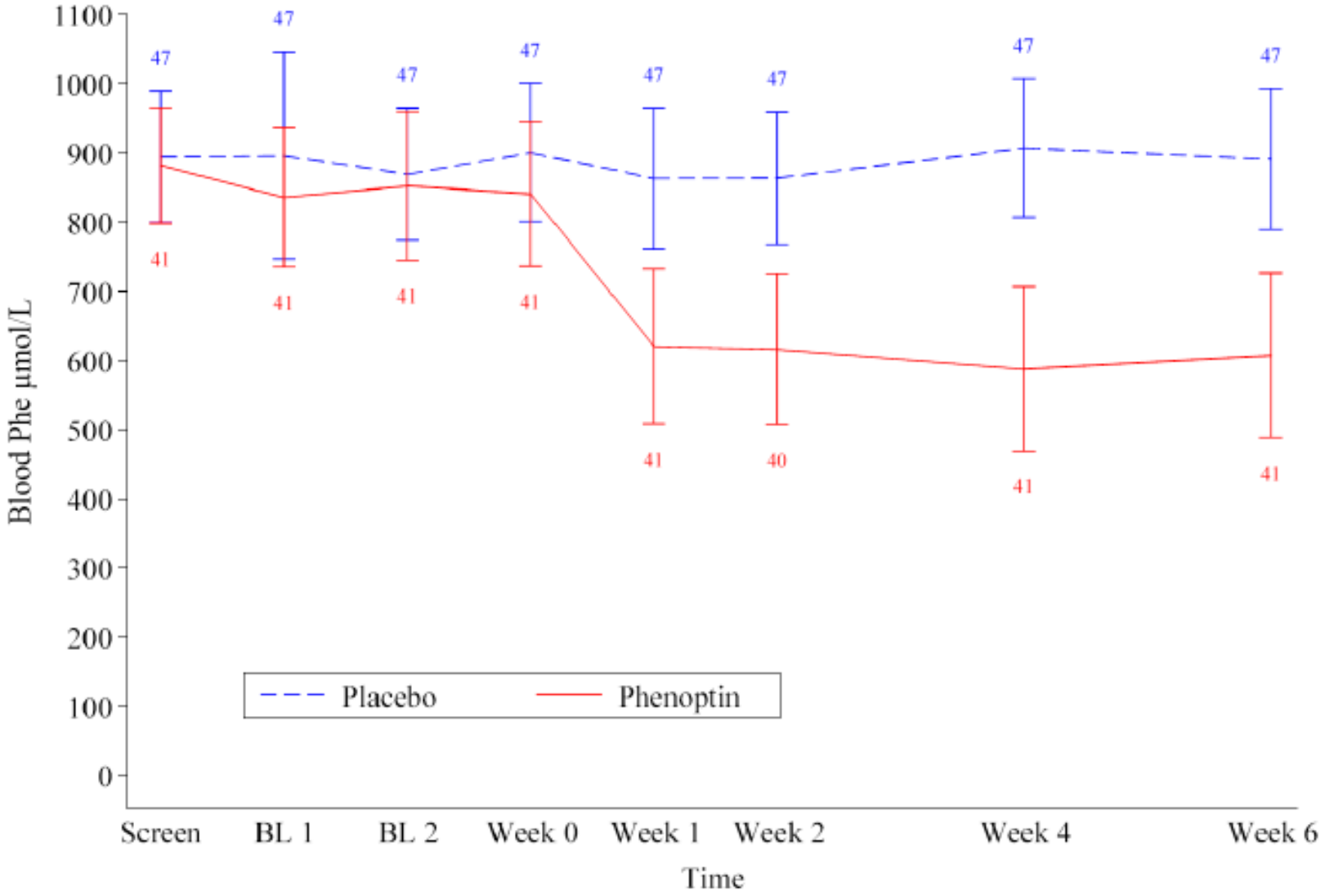
Study or subgroup	Low-phe diet N	Mean(SD)	High-phe diet N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 IQ at 4 years							
US/PKU Collaborative	58	94 (16)	53	91 (15)		100.0 %	3.00 [-2.77, 8.77]
Subtotal (95% CI)	**58**		**53**			**100.0 %**	**3.00 [-2.77, 8.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
2 IQ at 6 years							
US/PKU Collaborative	66	99 (16)	66	97 (15.7)		100.0 %	2.00 [-3.41, 7.41]
Subtotal (95% CI)	**66**		**66**			**100.0 %**	**2.00 [-3.41, 7.41]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.80), I^2 =0.0%							

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



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