Effective Health Care Program

Comparative Effectiveness Review
Number 56

Adjuvant Treatment for Phenylketonuria (PKU)

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Adjuvant Treatment for Phenylketonuria (PKU)

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Ms. Allison Glasser assisted with managing the day-to-day work of the review and developing meeting materials, tables, and appendixes.

Ms. Sharana Jones helped with coordinating project workflow, developing and formatting tables, and coordinating meetings.

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Adjuvant Treatment for Phenylketonuria (PKU)

Structured Abstract

Objectives: We systematically reviewed evidence on adjuvant treatment of phenylketonuria (PKU) and evidence for a target phenylalanine (Phe) level to minimize cognitive impairment.

Data Sources: We searched MEDLINE, PsycINFO, Embase Drugs and Pharmacology, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), the National Agricultural Library (AGRICOLA), and the reference lists of included studies. We searched the unpublished literature for additional data.

Review Methods: We included studies published in English before August 2011. We excluded studies with fewer than 10 individuals; individual case reports; and studies lacking relevance to PKU treatment or Phe levels and measures of cognition (intelligence quotient [IQ] or core domains of executive function). We meta-analyzed studies addressing Phe level and IQ, and summarized studies of treatment in tabular form.

Results: We located 17 studies providing data regarding blood Phe levels and IQ changes, 10 studies addressing sapropterin dihydrochloride (BH4), and 3 addressing the use of large neutral amino acid formulations (LNAAs). Blood Phe level is positively correlated with the probability of having an IQ of less than 85. This predicted probability exceeds the population probability (approximately 15 percent) at 400 μmol/L and reaches a maximum of about 80 percent at 2000 μmol/L. Currently, findings on the association of Phe levels and measures of executive function are inconsistent, and too few studies have used the same outcome measures to combine data meaningfully. BH4 research to date includes two randomized controlled trials (RCTs) and three uncontrolled open-label trials. Phe levels were reduced by at least 30 percent in up to half of treated participants (32 to 50 percent). In the one RCT that compared the effect of placebo on likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group. Three very small studies (total number of participants, 47) assessed LNAAs and reported no evidence that Phe levels were reduced to clinically meaningful levels.

Conclusions: The strength of the evidence is moderate for a threshold effect of a Phe level of 400 μmol/L associated with IQ <85. Evidence on the association of Phe and measures of executive function is insufficient. The use of adjuvant therapy in PKU is novel; the strength of the evidence is currently moderate for short-term effects on reducing Phe in a subset of initially responsive individuals and low for longer term effects on cognition.

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Executive Summary

Background

Etiology

Phenylketonuria (PKU) is a metabolic disorder in which an inability to properly metabolize the amino acid phenylalanine (Phe) leads to a buildup of Phe in the blood, causing neurotoxicity and resulting in intellectual disability, delayed speech, seizures, and behavior abnormalities. Individuals with PKU are also susceptible to other adverse outcomes, including impaired executive function, reduced processing speed, attention problems, impaired fine motor skills, and mental health concerns (such as anxiety and depression symptoms).[1,2]

The most severe form of PKU, classic PKU, is typically characterized by blood Phe levels exceeding 1,200 µmol/L while on a normal diet. PKU is typically diagnosed at birth following abnormal newborn screening results. With adherence to a Phe-restricted diet, poor outcomes can be mitigated. Nonetheless, management of PKU can be difficult and onerous for the patient and the family, leading to interest in identifying new ways of managing this lifelong condition. Further, questions remain as to the empirical basis for the selection of specific blood Phe levels as targets to reflect good dietary control.

Treatment of PKU

The mainstay for treatment of PKU is a diet that restricts the intake of Phe to control the Phe concentration in the blood. The usual treatment goal is a blood Phe level of 120 to 360 µmol/L. However, there is some variation in the target Phe level among clinics and across countries.[3,4] In addition to the low-Phe diet, many patients take vitamins and minerals daily to replace the nutrients that are absent in their restricted diet.[4]

Historically, Phe levels were monitored closely only during the first 6 years of life (the "critical period") because elevated Phe after that age was not believed to be detrimental. However, based on accumulated evidence over the last few decades, it is now the standard of care to recommend strict adherence to a Phe-restricted diet and routine monitoring of Phe levels throughout life.[3,5]

In 2007 the U.S. Food and Drug Administration (FDA) approved sapropterin dihydrochloride (Kuvan®, formerly known as Phenoptin) for the treatment of PKU under the stipulation that studies regarding the drug's efficacy and long-term safety continue. Sapropterin dihydrochloride (hereafter, BH4) is presumed to work by enhancing residual enzyme activity present in some individuals with PKU.

In addition to a Phe-restricted diet and BH4, another potential treatment for PKU is large neutral amino acids (LNAAs). LNAAs are considered nutritional supplements and are not subject to FDA approval. In theory, LNAAs decrease the brain Phe concentration by competing with Phe for shared amino acid transporters to cross the blood-brain barrier.[6,7]

Maternal PKU and Maternal PKU Syndrome

Poorly treated PKU in pregnant women will result in a teratogenic syndrome in the offspring, even if the offspring do not have PKU. Known as maternal PKU syndrome,[8] it can cause microcephaly, congenital heart defects, low birth weight, craniofacial abnormalities, and

intellectual disability in the child. Management of PKU during pregnancy can be very difficult. Some individuals may have loosened stringent dietary restrictions during adolescence, and restarting a diet that strictly limits protein may be challenging.[9] Complicating factors such as morning sickness, balancing severe protein restriction with adequate energy intake, insurance coverage limitations for medical foods and modified low-protein foods, maturity of the expectant mother, and her food lifestyle before pregnancy contribute to the challenges.

Objectives

Population

We focused this review on adjuvant pharmacologic treatment and treatment with LNAAs for all individuals, including infants, children, adolescents, adults, and pregnant women with PKU. We also examined evidence for target Phe levels to minimize or avoid cognitive impairment in individuals with PKU.

Interventions

We examined the following interventions: BH4 and LNAAs. The report does not address dietary restriction as the sole treatment for PKU, as its effectiveness has been shown in numerous studies and it is the standard of care.[5,10]

Comparators

We examined the effectiveness of BH4 plus dietary intervention (Phe-restricted diet and medical foods) compared with diet alone and the effectiveness of LNAAs plus dietary intervention compared with diet alone.

Outcomes

Our outcomes of interest for Key Question 1 included Phe levels and cognitive impairment, defined as deficits in either intelligence quotient (IQ) or measures of executive function. For measures of executive function, we sought outcomes in the following categories: working memory, attention, cognitive flexibility, planning, and inhibitory control. For treatment-related questions, we sought outcomes that included the individual's ability to liberalize diet while maintaining appropriate blood Phe levels, nutritional outcomes, quality of life, and changes in cognition, including executive function and IQ. We also report intermediate outcomes (Phe level, Phe tolerance, and Phe variability).

Key Questions

Key Questions were:

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition

(including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 6. What are the harms, including adverse events, associated with the use of BH4 or LNAAs in individuals with PKU?

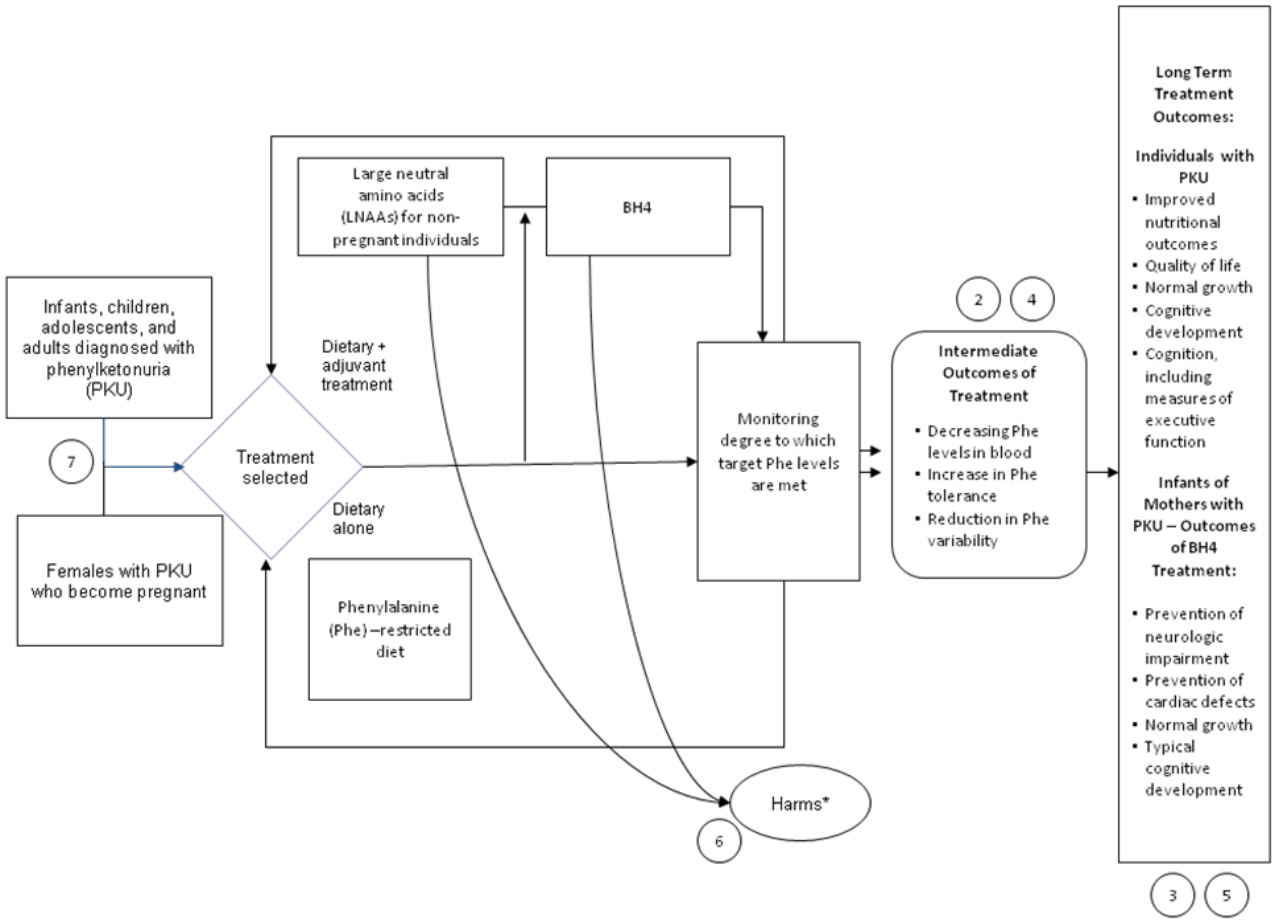
Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients?

Analytic Framework

The analytic framework (Figure A) summarizes the process by which treatment is chosen and modified for infants, children, adolescents, adults, or pregnant women with PKU. The treatment choice that is the basis of this review is whether to add pharmacologic therapy in the form of BH4 or LNAAs to dietary therapy. The primary target health outcome is maintenance of cognition; secondary outcomes include increasing the quality of life. Quantifying the levels of Phe provides an intermediate marker of treatment success because these levels are used to adjust the dietary intake of Phe.

In maternal PKU, treatment is intended to prevent impairment in the infant (who typically does *not* have PKU) caused by the teratogenic effects of excessively high Phe levels in the maternal bloodstream.

Figure A. Analytic framework for treatment questions



BH4 = sapropterin dihydrochloride; LNAAs = large neutral amino acids; Phe = phenylalanine; PKU = phenylketonuria
*Encompasses a full range of specific negative effects, including the narrower definition of adverse events. Can include costs, medical side effects, poor quality of life, etc.
Note: Numbers in circles indicate the positioning of Key Questions in the treatment process.

Methods

Input From Stakeholders

The topic was nominated in a public process. With Key Informant input, we drafted initial Key Questions, which the Agency for Healthcare Research and Quality (AHRQ) reviewed and posted to a public Web site for public comment. Using public input, we drafted final Key Questions, which AHRQ reviewed. We convened a Technical Expert Panel (TEP) to provide input during the project on issues such as setting inclusion/exclusion criteria and refining the analytic framework.

Data Sources and Selection

Data Sources

We searched five databases: MEDLINE® via the PubMed interface, PsycINFO (CSA Illumina interface; psychology and psychiatry literature), Embase Drugs and Pharmacology, the

Cumulative Index of Nursing and Allied Health Literature (CINAHL) database, and the National Agricultural Library (AGRICOLA) database. We hand-searched reference lists of included articles and recent reviews for additional studies and invited TEP members to provide additional citations.

We also searched Internet resources to identify regulatory information and current research; resources included the Web sites of regulatory agencies and clinical trials registries. Additionally, we searched commercial databases and a number of PKU-related Web sites specifically for any legal procedures related to the drug that might be a source of additional data. We also searched compilations of abstracts presented at major scientific meetings addressing PKU for treatment-related presentations given from 2006 (where possible) to 2011.

Inclusion and Exclusion Criteria

Table A summarizes the criteria we used to assess studies for inclusion in the review. As noted, this report focuses on the use of adjuvant treatments for PKU and does not address dietary restriction alone. The effectiveness of dietary restriction has been demonstrated in previous studies,[5,10] and it is well established as the cornerstone of PKU therapy.[3]

Table A. Inclusion and exclusion criteria

Overall Exclusion Criteria
• Did not include at least 10 individuals with PKU
• Did not address treatment of PKU or did not provide data to assess association between Phe levels and cognitive outcomes (IQ, measures of core domains of executive function)
• Did not address outcome measures of interest
• Were not published in English
Exclusion Criteria for Studies Addressing IQ and Phe Levels
• Did not meet overall criteria above
• Did not include early-treated individuals with PKU (as specified in study)
• Did not provide Phe level and IQ data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
• Did not provide a correlation between Phe level and IQ
Exclusion Criteria for Studies Addressing Measures of Executive Function and Phe Levels
• Did not meet overall criteria above
• Did not include early-treated individuals with PKU (as specified in study)
• Did not provide Phe data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
• Did not provide executive function data for each participant or mean/median data plus measure of variance (e.g., standard deviation)
• Did not provide a correlation between Phe level and a measure of executive function
• Did not include a control group of healthy individuals to provide a normative measure

Table A. Inclusion and exclusion criteria (continued)

Exclusion Criteria for Studies of Maternal PKU/Maternal PKU Syndrome and Phe Levels
• Did not meet overall criteria above
• Did not provide Phe level and IQ data for each participant or mean/median levels plus measure of variance (e.g., standard deviation)
• Did not provide a correlation between maternal Phe level and offspring IQ

IQ = intelligence quotient; Phe = phenylalanine; PKU = phenylketonuria

Screening of Studies

Two reviewers separately evaluated each abstract. If one reviewer concluded that the article could be eligible, we retained it. Two reviewers independently read the full text of each included article to determine eligibility, with disagreements resolved via third-party adjudication.

Data Extraction and Quality Assessment

Data Extraction

All team members entered information into the evidence tables. After initial data extraction, a second team member edited entries for accuracy, completeness, and consistency. In addition to outcomes for treatment effect, we extracted data on harms/adverse effects.

Quality Assessment

Two reviewers independently assessed quality, with differences resolved though discussion, review of the publications, and consensus with the team. We rated studies as good, fair, or poor quality and retained poor studies as part of the evidence base discussed in this review. More information about our quality assessment methods is in the full report.

Data Synthesis and Analysis

Evidence Synthesis

We meta-analyzed studies addressing the relationship between Phe level and IQ. We defined measurements of Phe reported in studies as concurrent (<6 weeks) with IQ testing or historical (taken more than 1 year prior), or both. We also considered measurements taken before age 6 to constitute the critical period. We estimated two models, one for each type of Phe measurement (concurrent and historical), using Bayesian hierarchical mixed-effects models estimated using Markov chain Monte Carlo methods.[11] In both analyses, we were interested in predicting the probability of an IQ below 85 at varying levels of blood Phe.

We used summary tables to synthesize studies addressing the treatment of PKU and summarized the results qualitatively.

Strength of Evidence

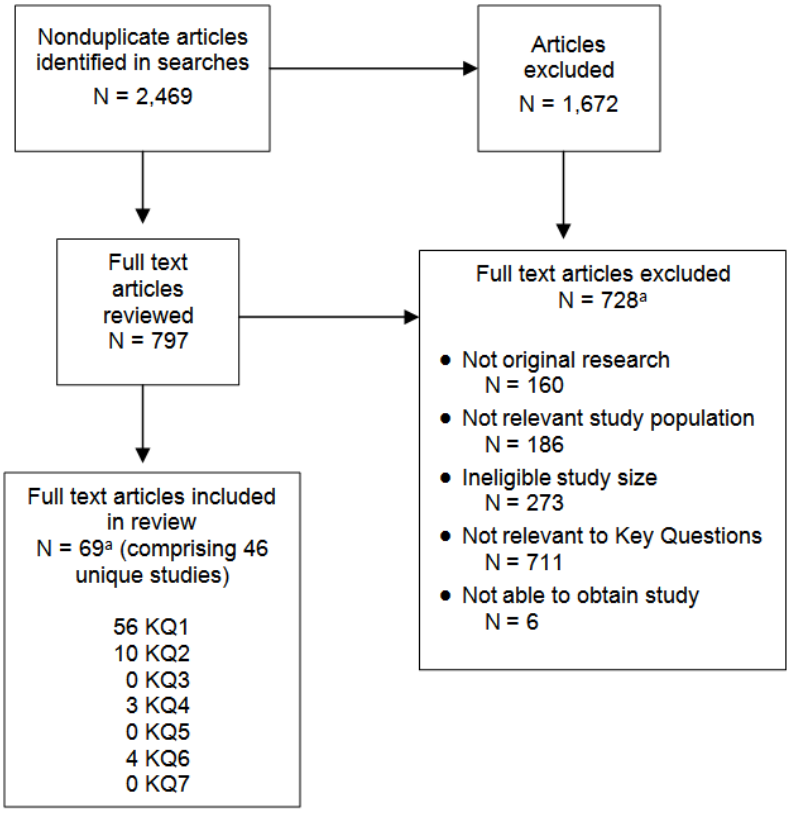
The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence. Strength of evidence can be regarded as insufficient, low, moderate, or high. We established methods for assessing the strength of evidence based on the Methods Guide for Effectiveness and Comparative Effectiveness Reviews,[12] developed by AHRQ's Evidence-based Practice Center Program. We assessed the strength of evidence for key

outcomes identified by the clinical investigators to be most clinically important: cognitive outcomes including IQ and executive function, nutritional outcomes, quality of life, and liberalization of diet. Secondary outcomes included changes in blood Phe levels, Phe variability, and Phe tolerance.

Results

Our searches retrieved 2,469 citations (Figure B). We reviewed the full text of 797 studies. Of the 797 full-text articles reviewed, we retained 69 articles (comprising 46 unique studies).

Figure B. Flow of studies identified for the review



KQ = Key Question; N = number
[a]The total number of (1) articles in the exclusion categories and (2) those addressing each Key Question exceed the (1) number of articles excluded and (2) total number included because most of the articles fit into multiple exclusion categories or addressed more than one Key Question.

Key Question 1a: Evidence for Optimal Phe Levels To Minimize Cognitive Impairment

Phe Levels and Impairments in IQ

Seventeen unique studies (reported in 21 publications) met our criteria and addressed the relationship between Phe levels and IQ.[13-33] We rated one study[20,21] as good quality and five

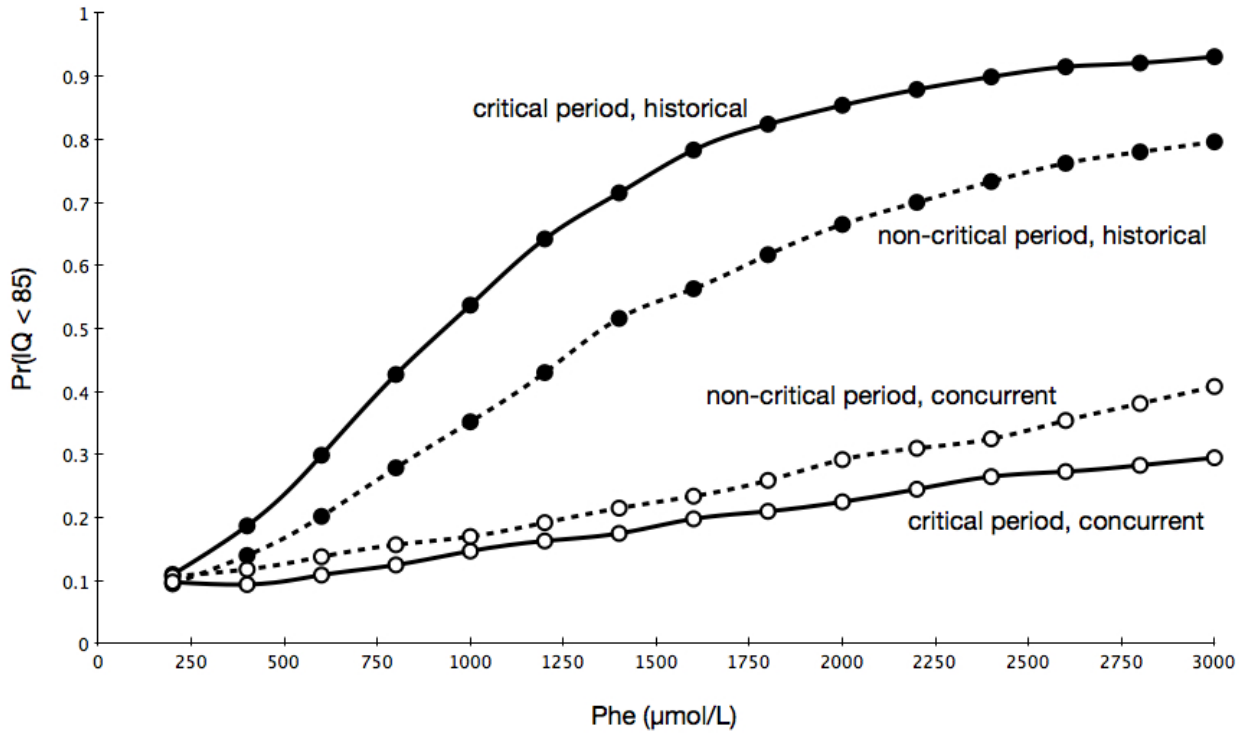
studies as fair quality.[16,18,24,27,32,33] The remaining studies[13-15,17,19,22,23,25,26,28-31] were rated as poor quality.

The studies included a total of 432 individuals with PKU. A majority of studies included primarily participants under age 25 at intake,[13-16,18,20,23,24,27,28,31,33] with five studies including only participants under age 15 at intake.[13,16,24,28,31] Dietary control varied among the studies, with five studies reporting that all participants were adhering to a restricted diet,[13,14,16,25,31] seven reporting a mix of dietary control (some participants on and some off a restricted diet),[17-23,33] and three reporting that participants had discontinued a restricted diet.[15,24,26] Dietary status was not clearly reported in the remaining two studies.[27-30]

We developed two meta-analytic models (Figure C). The first represents the relationship of Phe and IQ when Phe was measured "historically" (more than 12 months before IQ measurement). In the second model, Phe and IQ were measured concurrently (within 6 weeks of each other). Note that the two lines corresponding to historical measures of Phe in Figure C (top two lines) both demonstrate increasing probability of low IQ at higher blood Phe levels, regardless of whether IQ was measured during childhood (solid line) or beyond (dashed line), with a stronger association seen between Phe measured in early childhood and later IQ.

The two lower lines in the figure describe probability of IQ <85 as a function of Phe when measured concurrently. There is a lack of strong association in measurements taken concurrently during the critical period, as noted by the relatively flat line.

Figure C. Probability of IQ <85 at varying blood Phe levels and Phe measurement times



IQ = intelligence quotient; Phe = phenylalanine; Pr = probability

Phe Levels and Impairments in Executive Function

Nineteen unique studies, reported in 26 papers,[20,21,23,25,28-31,34-51] provided data on Phe levels and on measures of executive function. After reviewing these as possible candidates for meta-analysis, clinical and statistical experts determined that a meta-analysis would not be appropriate

for any component of executive function, as not enough studies used the same type of neuropsychological measure to allow for combining of data. Further, these studies cannot be meaningfully aggregated since the measures of executive function relevant for individuals with PKU have not yet been established.

Overall, while Phe levels correlate with various assessments of executive function in some papers, the degree to which they are correlated and the correlation on individual measures are inconsistent.

Phe Levels and Impairments Related to Maternal PKU and Maternal PKU Syndrome

Data predominantly from one longitudinal study provide support for the increased risk observed of poor cognitive outcomes in the offspring of women with high maternal blood Phe concentrations. The Maternal PKU Collaborative Study was initiated in 1984 to study the implications of maternal PKU, and specifically to assess outcomes when Phe is controlled in pregnant women. The study reported that timing of maternal metabolic control, defined as the number of weeks gestation before plasma Phe levels remained consistently lower than 605 μmol/L, was associated with lower child cognitive scores at 4 and 7 years of age.

A model of the form of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood[52] confirmed that the relationship between maternal blood Phe and offspring cognitive outcomes was not linear, that a threshold of 360 μmol/L is the level at which cognitive impairment was significantly more common in offspring of mothers with PKU than in controls, and that a linear relationship between Phe levels and impaired cognitive outcomes occurred after this threshold. Importantly, while other factors, including maternal characteristics, severity of mutations, and offspring head circumference, contributed strongly to outcomes at 1 year of age, by age 2, maternal Phe strongly overtook other factors in predicting cognitive impairment.

Key Question 1b: Evidence for Optimal Phe Levels To Minimize Cognitive Impairment for Different Age Groups

We examined the potential effect of age in the meta-analysis of the relationship of Phe and IQ. Any influence of age was adequately represented by whether the Phe measurements were historical or concurrent and whether they were taken in the critical period.

Key Question 2: Effectiveness of BH4 in PKU

Ten studies evaluated the effects of BH4[53-62] in patients with PKU. These studies included two randomized controlled trials (RCTs) (one of good quality[54] and one of fair quality[55]), two uncontrolled open-label trials of good[53,58] and one of fair[60] quality, one poor-quality prospective cohort,[62] and four poor-quality case series.[56,57,59,61] No study included more than 80 participants in the treatment arm, and the total number of individuals treated in all studies was 284. Participants ranged in age from birth to 58 years, and most had demonstrated responsiveness to BH4 in a loading study. Of note, the definitions of positive response to BH4 differed and are described in the full report.

BH4 was studied in doses that ranged from 5 mg/kg/day to 26 mg/kg/day, over time periods of up to 22 weeks in trials and 9 years in one case series. The degree to which participants adhered to a restricted diet varied by study, and baseline Phe levels ranged from below 300 to over 1,300 μmol/L. All randomized and open-label trials and three case series evaluated the

short-term outcome of reduction in Phe levels. Five studies reported on Phe tolerance (amount of daily Phe intake at which blood Phe stays steady),[55,57-59,61] and two reported on Phe variability.[56,62] Only one study[59] assessed our primary outcomes of interest, including measures of cognition and nutritional status. No study evaluated quality-of-life outcomes.

Phe levels were reduced by at least 30 percent (the level used in studies submitted to the FDA to assess responsiveness) in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies. In the one RCT that compared the effect of placebo on the likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group.[54] Data from the uncontrolled open-label trial[53] following this RCT[54] suggested a sustained response for up to 22 weeks duration, with 46 percent achieving a 30-percent reduction in Phe levels.

In the second RCT,[55] similarly positive effects were reported at a dosage of 20 mg/kg/day in children on Phe-restricted diets. At week 3, those receiving BH4 had a greater reduction in Phe levels at their baseline dietary Phe intake. In the other uncontrolled open-label trial,[58] BH4 (7 to 20 mg/kg/day) was associated with reduced Phe levels among participants both on and off Phe-restricted diets. Overall, participants' responses to different dosages of BH4 varied, with individualized dose adjustments needed according to target plasma Phe and dietary intake. Response also varied by different baseline Phe levels, with those with the highest baseline levels having lower response rates.

These two studies[55,58] also examined the effect of BH4 use on Phe tolerance in individuals responsive to BH4, as did three case series.[57,59,61] In all five studies, Phe tolerance improved over time. Only the RCT,[55] however, provides comparative data with a placebo group. At a dosage of 20 mg/kg/day over 10 weeks, participants in the treatment group increased their Phe tolerance (daily medical foods tolerated) from 0 mg/kg at baseline to 20.9 mg/kg/day while maintaining blood Phe levels at <360 μmol/L, compared with an increase of 2.9 mg/kg/day in the placebo group. However, response varied substantially within the treatment group, with 33 percent tolerating an increase of between 31 and 50 mg/kg/day in supplement form but the rest of the participants tolerating lower levels of supplementary Phe. The degree to which this variability is associated with other factors possibly associated with Phe tolerance is unknown.

One small case series reported on IQ and nutritional outcomes for up to 1 year on 5 mg/kg/day BH4 treatment.[59] After 1 year of treatment, the 11 participants discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were similar to scores before treatment and development quotients were within normal limits.

Key Question 3: Effectiveness of BH4 in Pregnant Women With PKU

We did not identify any studies addressing this question.

Key Question 4: Effectiveness of LNAAs in PKU

Three studies addressed the effects of LNAAs,[7,63,64] including a fair-quality[63] and poor-quality[64] RCT and a poor-quality uncontrolled open-label trial.[7] The studies included a total of 47 participants. Participant numbers in the RCT treatment arms were 16[63] and 20[64] on LNAAs, while the uncontrolled open-label trial included 11.[7] Participants were between 11 and 45 years of age. The trials were short, with treatment between 1 and 8 weeks, and dosages ranged from 250 mg/kg/day to 1g/kg/day. Two of the three studies measured reductions in Phe levels,[7,64] and one assessed cognitive outcomes.[63]

This fair-quality study[63] reported a positive effect on executive functioning, specifically verbal generativity, cognitive flexibility, and self-monitoring. Overall, participants who were using a Phe-free medical food for their nutritional needs did not experience a decrease in Phe, although those not adhering to diet or not using their formula did. In all three studies, blood Phe decreased after 1 week of treatment but remained above clinically acceptable levels.

Key Question 5: Effectiveness of LNAAs in Pregnant Women With PKU

We did not identify any studies addressing this question.

Key Question 6: Harms of Adjuvant Treatment for PKU

Of the 10 studies examining the effectiveness of BH4 in participants with PKU, 4 studies[53-55,60] reported any type of harm related to the intervention drug. The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting, but harms were not significantly more common in the treatment arm than in the placebo. One trial of LNAAs[63] assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use.

Key Question 7: Effectiveness of BH4 and LNAAs for Subgroups of Individuals With PKU

We did not locate any studies addressing this question.

Discussion

Key Findings

Increased Phe is associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately15 percent) at Phe over 400 µmol/L and leveling off at about 80 percent at 2,000 µmol/L. This supports the typical target goal for Phe level in individuals with PKU (120 to 360 µmol/L).[3]

Notably, the negative association between Phe and IQ is strongest when Phe is measured at least 1 year prior to IQ testing. The Phe level obtained more than 1 year before IQ testing is likely to be a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship lends support to the principle that cognitive effects accumulate over a long time period, and thus concurrent measurements are poor predictors of a cognitive effect. The strongest associations are seen in the group for which historical measurements were taken during the critical period (<6 years old) and associated with later IQ, although historical measurements taken after the critical period are also associated with risk of low IQ. Hence, control of Phe levels during the critical period is particularly important, and there is no evidence that control can be relaxed after early childhood. Current clinical practice is to maintain Phe control even in adulthood, which is supported by this analysis.

Currently, findings on the association of Phe levels and any specific measure of executive function are inconsistent, and too few studies have used the same outcome measures to combine their data in any meaningful way. This is an important area for future research, with foundational research needed to validate specific outcomes for measuring executive function in individuals

with PKU. In maternal PKU, current evidence supports the need to achieve dietary control as early as possible in pregnancy, and ideally to maintain a Phe level of 120 to 360 μmol/L.

The FDA approved BH4 in 2007 as a potential adjuvant treatment with dietary control. Two RCTs and three uncontrolled open-label trials are currently available in the literature; there is substantial overlap in the participants across the studies. Phe levels were reduced by at least 30 percent (the usual research target) in up to half of treated participants (32 to 50 percent). In the one RCT that compared the effect of placebo on likelihood of a 30-percent reduction in Phe, only 9 percent of those on placebo achieved this effect after 6 weeks, compared with 44 percent of the treated group.[54] In a 2.6-year uncontrolled open-label trial of BH4, most of the 90 study completers were reported to have reached clinical targets in Phe levels. No studies have linked these results to longer term clinical or patient-reported outcomes. The strength of evidence for the effects of BH4 on lowering Phe levels in BH4-responsive individuals in the short term is moderate, as is the strength of evidence for a lack of harms of BH4. The strength of the evidence for the effects of BH4 on cognitive outcomes is low based on a combination of evidence from the RCTs on Phe and evidence from the meta-analysis of the relationship of Phe and IQ. The strength of the evidence is insufficient for all other outcomes (Phe tolerance and the ability to liberalize the diet, Phe variability, quality of life, and nutritional outcomes).

In theory, supplementation of a Phe-restricted diet with large neutral amino acids might have beneficial effect on cognition, as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However, there is insufficient evidence to suggest that LNAAs could be a viable treatment option for reducing Phe levels or increasing Phe tolerance. There have been only three very small studies (total number of participants, only 47), and there is no evidence that Phe levels were reduced to clinically meaningful levels in the short time they were studied.

Applicability of Evidence

The degree to which current research may not be applicable to the clinical population with PKU is a concern, given the small size and homogeneous populations in each of the studies. For example, the two RCTs of BH4[54,55] each focused on a distinctly different population--one on a slightly older population nonadherent to diet and one on a somewhat younger group with tight dietary control. Thus, it is unclear whether the results should be synthesized, or whether either study can confirm the results of the other. Nonetheless, individuals from both studied populations are likely to be seen in routine clinical care, and clinicians should find the results applicable to some of their patients. Of greater concern is the focus on intermediate outcomes; current evidence is lacking on clinically relevant and longer term outcomes, including ability to liberalize the diet, cognitive effects, and quality of life.

Future Research

The existing research gaps related to the use of adjuvant pharmacologic therapy in PKU are both substantive and methodologic. Research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for specific studies. Furthermore, in part because it affects so few people, funding for PKU research is limited, and to date, treatment research is almost exclusively supported by the pharmaceutical industry. Other rare conditions have benefited from an overall research agenda. Thus, we recommend a multicollaborator process that includes a public-private partnership that could create a powerful tool for the future of PKU research in the form of a longer term (perhaps 10-

year) research agenda. Furthermore, there is tremendous potential for development of a multicenter research consortium to comprehensively evaluate the complete system of care for individuals with PKU.

Funding from private or public entities should help establish a long-term prospective registry through which the consortium could collect comprehensive and detailed data on individuals with PKU. This could include additional support or linkage with the existing registry that is specific to use of Kuvan, the Phenylketonuria Demographic, Outcomes, and Safety (PKUDOS) registry. The expanded registry could include, but need not be limited to, data on short- and long-term outcomes of treatment, such as executive function, nutritional status, growth, and quality of life. Ideally, this registry would include a biorepository that would help identify any genotype-phenotype correlations and provide a multidimensional perspective on the effectiveness in practice of treatments, both in the short and long term.

One corollary might be a committee of experts and individuals with PKU to focus on harmonizing data collection; standardizing outcomes assessments; requiring specific and stringent standards for conducting double-blind placebo-controlled trials that adhere to the high standards required for synthesis and use in treatment guidelines; and selecting and implementing studies that clarify the short- and long-term outcomes of treatments and interventions for individuals with PKU, including psychological outcomes. For example, since dietary restriction is the essential cornerstone in the treatment of PKU, it would be helpful to study various methods that would improve adherence to dietary management and other intervention strategies in order to improve outcomes throughout the lifespan, especially for adolescents and adults with PKU. With the establishment of a multicenter consortium, registry, and biorepository, PKU could serve as a model for studying the short- and long-term outcomes of treated inborn metabolic diseases. The field already has a starting position, with the Maternal PKU Collaborative Study a case in point.

Future Research on the Relationship of Phe and Cognition

A significant limitation in the current body of research on the relationship between blood Phe level and cognitive outcomes is the lack of consistent methodologies using standardized tools and measures and consistent data collection across centers. The result is that many studies provide incomplete data that cannot be used in meta-analyses. In future research, details about familial IQ, socioeconomic status, maternal education, age at initial treatment, and concurrent medications should be fully described so they might be used in a more extensive meta-analysis of Phe-IQ associations.

One basic need is to better understand the degree to which the perceived association changes by age, with the practical implication of understanding the degree of dietary control necessary across age groups. Because tight control is important, an understanding is needed of the supports that might be helpful as individuals age. Related to this is the need for additional measures beyond Phe to assess adequate control. This requires an understanding of what outcomes are clinically important, and their relative value to patients and their families. For this to be possible, complete and accurate measurement of Phe and cognition over fairly long periods of time is necessary, perhaps through a long-term followup study or through the multisite collaboration suggested above. Finally, the effects of mild hyperphenylalaninemia as opposed to those of classic, mild, and moderate PKU should also be clarified.

Although research is being conducted on executive function outcomes for individuals with PKU, there is no consensus on which measures of executive function are most appropriate. This

highlights the need for fundamental research, because measures of executive function tend to be better reflections of success with day-to-day activities than targeted measures such as IQ. It is plausible that some measures of executive function may be more sensitive to changes in Phe than IQ. The sensitivity, validity, and acceptability of individual executive function measures in PKU have yet to be established or agreed upon, and current research reflects a reliance on a wide range of outcomes, making synthesis of relationships and pooling of results difficult.

Given the reported association between PKU and an increased incidence of inattention, anxiety, and depressive symptoms, additional studies on these and other psychological issues in PKU are also warranted.

Future Research on Pharmacologic and Other Adjuvant Treatment

BH4

Research on the use of BH4 as an adjuvant therapy in PKU management consists of small, tightly controlled multisite efficacy studies, two of which are RCTs. The greatest research need in this area is thus for larger studies. Given the known difficulty of accruing large numbers of participants, however, researchers should also use existing datasets and, as recommended, use a consortium and multisite approach to gathering data.

Ideally, studies will be conducted in both tightly controlled and nonadherent populations, and among different age groups, with appropriate design and power for subgroup analyses. Research should continue to include RCTs, but prospective cohort studies that may have the potential to provide additional effectiveness data (including data on treatment outside of a controlled clinical setting), adherence data, and longer term evidence would also be helpful to support understanding of the role of BH4 in clinical care. These studies should provide substantially more detail on the range of benefits and harms associated with treatment. For example, a better understanding is needed of the effects of BH4 in children less than 4 years of age and pregnant women, and while it may be challenging or inappropriate to conduct RCTs in these populations, observational cohorts or registry data are essential.

Data are not currently available to understand potential modifiers of treatment effectiveness in order to select the best populations for targeting further research and treatment. Moreover, the variability in responsiveness to BH4 is unexplained, and subpopulations that have a unique response to this medication have not been well characterized. Causes of variability may be multifactorial and likely include individual patient and genotype differences, drug dose, and individual patient behavior such as dietary adherence. It is unclear, in particular, why a high proportion of individuals who have an initial response in loading studies at screening do not have a durable response in efficacy trials, while those who do have a response demonstrate a significant effect. The degree to which this observed variation may be associated with suboptimal adherence should be assessed.

Another area of potential research is the use of adherence supports for both drug and diet to optimize potentially positive outcomes. It is assumed that support at familial, social, and system levels may be helpful, and this idea should be empirically addressed.

Long-term efficacy outcomes beyond 22 weeks and safety outcomes beyond 3 years are currently unavailable, as are measures of behavioral change, cognition, and patient-reported outcomes, including quality of life. The degree to which reductions in blood Phe are associated with measurable cognitive outcomes or even patient perception of increased mental clarity is

unknown. Furthermore, explicit assessment of the potential for liberalization of the diet and the subsequent nutritional effects has yet to be conducted.

Future research should comprise larger studies designed to allow subgroup analysis of the effectiveness of adjuvant pharmacologic therapy for PKU. Although the current literature does not provide evidence for effectiveness in all target patients, some benefit is seen in some patients. Whether these patients differ from the overall population in terms of genotype is an area of current research focus that has the potential to allow targeting of treatment.

A number of studies are reportedly underway to address gaps in the current literature. These include a long-term study of the effect of BH4 on neurocognitive function in young children, a study of the effect in adolescent patients with attention-deficit hyperactivity disorder, and a registry that includes pregnant women. However, we stress the importance of making data available and note that several commitment studies have been listed as completed but have yet to make findings available. These include studies on the cardiac effects of BH4. Another commitment study that is reported as fulfilled is an open-label study to study the safety and efficacy of BH4 for treating patients with hyperphenylalaninemia, yet no results have been made available. Finally, publicly funded studies to confirm and expand on reported efficacy and effectiveness data are needed.

LNAAs

The three very small studies of LNAAs cannot be considered as more than proof of concept at this time, and if further work is to occur in this area, it should be done in well-conducted RCTs of adequate size. The mechanism by which LNAAs may work should be clarified, as should the optimal target population and specific treatment goals. The current formulations that have been tested require taking many pills per day, so the formulations should be made more palatable.

Conclusion

The commonly used blood Phe target of 120 to 360 μmol/L is supported in our meta-analysis.[3] Notably, the negative association between Phe and IQ is strongest when Phe is measured at least 1 year prior to IQ testing. The Phe level obtained more than 1 year before IQ testing is likely a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship supports the principle that cognitive effects accumulate over a long time period, that concurrent measurements are poor predictors of a cognitive effect, and that control should be continued into adulthood. Review of the research on maternal PKU supports the need for dietary control as early as possible before pregnancy or in pregnancy and maintenance of Phe control to prevent poor cognitive outcomes in infants.

Dietary management remains the mainstay of treatment for PKU, and maintaining control over the lifetime is an appropriate goal. Nonetheless, there is potential to support patients in achieving their clinical goals and possibly liberalizing their diet with adjuvant therapy. BH4 has been shown in two RCTs and two open-label trials to reduce Phe levels in some patients, with significantly greater reductions seen in treated versus placebo groups.

We do not yet have the ability to predict which patients are most likely to be responders, as all participants in the trials were initially responsive in screening tests but not necessarily so in the efficacy studies. One RCT also demonstrated increased Phe tolerance using BH4 among children on restricted diets. Overall, harms associated with the drug were minor and did not occur more frequently in the treatment group than in placebo arms. To date, there are no data to directly establish the potential effects of BH4 on longer term clinically important outcomes,

including cognition, executive function, and quality of life. Significant gaps in the evidence include effectiveness of the drug in a range of patients outside of the clinical trial setting. Thus, while the strength of evidence is moderate for a large positive effect of BH4 on reducing Phe levels over the short term in some groups of patients showing initial responsiveness, evidence for the effect of BH4 on longer term clinical outcomes is low and is based on indirect associations, including our meta-analysis.

In theory, supplementation of a Phe-restricted diet with LNAAs might have a beneficial effect on cognition, as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However, there is insufficient evidence to suggest that LNAAs could be a viable treatment option for reducing Phe levels or increasing Phe tolerance.

Continued studies that include adequate numbers of participants should be conducted in both tightly controlled and nonadherent populations, and among different age groups, for both types of adjuvant therapies. In addition, data on effectiveness in various groups of patients outside the clinical trial setting are needed, including data on those individuals with variability in adherence.

Registries have been established and will provide important data, as will ongoing studies that measure additional outcomes, including behavioral and psychiatric measures. Data are not currently available to understand potential modifiers of treatment effectiveness, including genotype. Moreover, the variability in responsiveness to BH4 is unexplained.

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Introduction

Phenylketonuria (PKU) is a metabolic disorder in which an inability to properly metabolize the amino acid phenylalanine (Phe) leads to a buildup of Phe in the blood and subsequent neurotoxicity that can cause intellectual disability, delayed speech, seizures, behavior abnormalities, and other medical and mental health problems if untreated. PKU is typically diagnosed soon after birth using biochemical tests that are performed after an abnormal newborn screening result. The most severe form of PKU, classic PKU, is typically characterized by blood Phe levels exceeding 1200 μmol/L while on a normal diet. With adherence to a Phe-restricted diet, poor outcomes can be mitigated. Nonetheless, management of PKU can be difficult and onerous for the patient and the family, leading to interest in identifying new ways of managing this lifelong condition. Further, questions remain as to the empirical basis for the selection of specific blood Phe levels as targets of good dietary control.

Etiology of PKU

The enzyme phenylalanine hydroxylase (PAH) converts phenylalanine to tyrosine in the liver. In PKU, individuals have defective PAH activity, leading to a toxic accumulation of phenylalanine in the blood and multiple tissues.[1] High blood levels of Phe in untreated PKU can result in multiple medical problems, including intellectual disability, delayed speech, seizures, and behavior abnormalities.[2-4] Individuals with PKU are also susceptible to other adverse outcomes, including impaired executive function, reduced processing speed, attention problems, impaired fine motor skills, and mental health concerns (such as anxiety and depression symptoms).[5, 6]

Every individual has two copies of the gene that encodes the PAH enzyme. If both copies of the gene have pathologic mutations, then the enzyme will be dysfunctional. However, there are more than 500 known mutations that can occur in this particular gene, and it is likely that particular mutations are related to the severity of PKU. Mutations resulting in little or no enzyme activity may cause classic PKU[7] while other mutations result in some residual PAH activity that may be associated with mild or moderate PKU. To date, precise genotype-phenotype relationships have not been consistently reported, and substantial work remains to be done on describing the possible relationship between specific mutations and their clinical implications.

Prevalence and Treatment

Approximately 1 in 13,500 to 19,000 infants in the United States is born with PKU.[7, 8] The incidence of PKU varies based on ethnicity, with a higher prevalence among Native American and Caucasian individuals.[7, 9] The established treatment for PKU is a special diet that restricts the intake of dietary Phe in order to maintain a safe level of Phe concentration in the blood. The diet for individuals with PKU involves restriction of intact protein tailored to the patients' individual tolerance. The diet consists mostly of vegetables, fruits, cereals, and fats to provide intact protein and nutrients. The remaining amount of protein and essential nutrients needed for body growth, development, and maintenance are provided by medical foods specifically designed for individuals with PKU. Medical foods are typically Phe-free and vary in their micronutrient and macronutrient composition. However, they serve as medically-necessary vehicles for providing adequate protein and calories in a form that is tolerated. Low protein foods provide energy and contribute an acceptable quantity and quality of food In addition to the low-Phe diet, many

individuals take vitamins and minerals daily to replace the nutrients that are absent in their restricted diet, but there is concern that individuals with PKU may suffer from various nutritional deficiencies.[10] Adherence to the diet can be difficult for individuals and their families because the medical foods/formula can be unpalatable and expensive, and are frequently not covered by third party payors.[2-4] Individuals with PKU may consume protein substitutes, but such substitutes also typically have a poor taste.[11]

Total Phe intake is the total amount of Phe that an individual ingests each day from food. Based on the severity of the disease, individuals with PKU can tolerate different quantities of total Phe intake. This is referred to as *Phe tolerance*. In infancy this prescribed amount of dietary Phe is based on body weight and growth. After early childhood it may be prescribed as a daily allowance. Phe levels are monitored frequently and appropriate modifications to the total Phe intake are recommended in order to determine the ideal Phe tolerance for the individual patient.

In a given individual, Phe tolerance changes with age and metabolic demand, such as during periods of accelerated growth, pregnancy, and chronic or acute illness. For example, infants with PKU have their Phe level monitored weekly to monthly. As they get older and depending how regularly they access care, Phe measurements may become less frequent, and healthy adults with well-controlled PKU may only get Phe level measurements a few times a year, despite the recommendation of the National Institutes of Health (NIH) that blood Phe be monitored monthly.[8] Historically, Phe levels were only monitored closely during the first six years of life (the "critical period") because elevated Phe after that age was not believed to be detrimental. However, based on accumulated evidence over the last few decades, it is now standard of care to recommend strict adherence to a Phe-restricted diet and routine monitoring of Phe levels throughout life.[8, 12]

The efficacy of the dietary restriction is monitored by measuring Phe levels in the patient's blood. In general, the treatment goal is a Phe level of 120 to 360 μmol/L. However, there is some variation in the target blood Phe level between clinics and across countries,[8, 10] and questions remain about the empirical basis for selecting a specific Phe level as a target. Furthermore, people with classic PKU require lifelong treatment, but some disagreement remains as to whether individuals with milder PKU can relax dietary restrictions at any point in their lives.[7, 13]

Role of Pharmacologic Therapy

In 2007 the United States Food and Drug Administration (FDA) approved sapropterin dihydrochloride (Kuvan®, formerly known as Phenoptin), the first pharmacologic treatment for PKU, under the stipulation that additional studies be conducted to assess further the drug's efficacy and long-term safety. The goal of treatment with sapropterin dihydrochloride (hereafter, BH4) is to control blood Phe concentrations. Although treatment with BH4 would potentially allow a relaxation of the low-Phe diet, it is not intended to serve as a complete substitute for dietary intervention.[14]

The mechanism of action of BH4 is as a cofactor of the phenylalanine hydroxylase enzyme, increasing the activity level of the enzyme and increasing the amount of Phe that can be converted to tyrosine. Hypothetically, it should be more effective in individuals with residual PAH activity than in individuals with negligible to no enzyme activity. However, because the genotype-phenotype relationships in PKU are not fully understood, various loading tests are done to identify potential candidates for treatment. In loading tests, a trial of BH4 is given to the patient to determine whether they demonstrate initial responsiveness at some predefined level (e.g., 30 percent reduction in blood Phe after one week). In the studies that have been completed,

individuals must show some responsiveness to BH4 in the short term (generally a week or up to 1 month) to participate in longer trials of the drug. Loading tests used in practice and in research vary in terms of target reduction and timeframe, and none has been established as optimal for identifying candidates for treatment.

Role of Large Neutral Amino Acids

In addition to a Phe-restricted diet and BH4, another potential adjuvant therapy is large neutral amino acids (LNAAs). Several theories may explain the potential impact of LNAAs on the pathophysiology of PKU.[11] LNAAs may primarily decrease the brain Phe concentration by competing with Phe for transport across the blood-brain barrier.[15, 16] Because LNAAs inhibit influx of elevated amounts of blood Phe into the brain, they may prevent neurologic damage.[17] In addition, LNAAs may lower blood Phe levels by competitively inhibiting the transport of Phe via the carrier protein in the gastrointestinal tract.

In the United States, LNAA products are available under the brand names Lanaflex (marketed by Nutricia/SHS International), PheBloc (marketed by Applied Nutrition), and PreKUnil and NeoPhe (both marketed by Solace Nutrition). LNAAs are considered nutritional supplements and thus are not subject to FDA approval. The products are typically available without a prescription. Dosing is calculated by an individual's medical professional and is based on the amount of natural protein (which provides the dietary Phe prescription) and Phe-free protein contained in the medical food. LNAAs may be covered by insurance, but reimbursement varies depending on specific policies.

Despite potential benefits, there is uncertainty about the efficacy and safety of long-term use of LNAAs and the target patient population, including the appropriateness of its use in pregnant women with PKU. When used in clinical practice, LNAAs generally are offered to individuals who are unable to maintain dietary adherence.

Maternal PKU and Maternal PKU Syndrome

Poorly treated PKU in pregnant women will result in a teratogenic syndrome in the offspring, even if the offspring do not have PKU. Known as maternal PKU syndrome,[18] it can cause microcephaly, congenital heart defects, low birth weight, craniofacial abnormalities, and intellectual disability in the child. The syndrome was first recognized in 1956 when Charles Dent observed that women with PKU may have children with intellectual disability even though the children did not have PKU.[19] A review of treated and untreated pregnancies by Lenke and Levy in 1980 showed that women may have a differential risk of damage to the offspring based on the concentration of Phe in the mother (and, therefore, in the fetus) during pregnancy.[20] However, the best management of women with PKU who were considering pregnancy or who were already pregnant was unknown.

Based on the work on Lenke and Levy, several subsequent longitudinal studies have attempted to determine the optimal management of pregnant women with PKU. The Maternal PKU Collaborative Study was the largest of these initiatives. This prospective study, conducted from 1984 to 1996, was designed to determine the effectiveness of a Phe-restricted diet (Phe goal <360 μmol/L) for preventing morbidity in offspring of American, Canadian, and German women with PKU.[21] Other studies also looked at the outcomes of pregnancy in women with PKU.[20, 22-32]

Consequently, the NIH Consensus Development Conference has written guidelines for the management of PKU in pregnant women.[8, 33] In addition to traditional approaches, the guidelines recommend frequent monitoring of blood Phe concentration levels and outreach programs for

pregnant woman and women who are of childbearing age to reinforce social support and positive attitudes about a controlled diet.[8] However, management of PKU during pregnancy can be very difficult. Some individuals may have discontinued the diet during adolescence, and restarting an unpalatable diet that strictly limits protein can be very challenging. Complicating factors such as morning sickness, balancing severe protein restriction with adequate energy intake, insurance coverage limitations for medical foods and modified low protein foods, maturity of the expectant mother, and her previous food lifestyle before pregnancy contribute to the challenges. Furthermore, women with milder forms of PKU may no longer be followed by healthcare professionals with expertise in PKU.[34] Therefore, it currently is recommended that girls and young women with PKU adhere to the Phe-restricted diet throughout their lifetime, especially during the childbearing years of adolescence and young adulthood.

The role of BH4 in pregnant women with PKU is still unclear, but given the benefits of the drug in other groups of individuals with PKU, this is a population of individuals that merit further study.[7]

Clinical Uncertainties

A Phe-restricted diet throughout life has been well-established as the cornerstone of treatment for PKU by studies such as the PKU Collaborative Study.[12] Yet PKU is a rare metabolic disease, and there are limited data on the best adjunct treatment in addition to diet for different ages. Although most clinics use a blood Phe level of 120 to 360 μmol/L as the goal treatment range, evidence is mixed on a specific optimal range for minimizing the clinical and cognitive effects of elevated blood Phe levels across different ages of individuals, including pregnant women. Furthermore, the efficacy, safety, and target populations for the concomitant use of BH4 or LNAAs with a Phe-restricted diet have not been established, and clinicians lack evidence-based support for when to prescribe BH4 or LNAAs and in which patients. The implications of liberalizing the diet in those patients who do achieve blood Phe levels below treatment goals are currently unknown in terms of their effect on short- and long-term clinical and cognitive effects. Finally, the safety and efficacy of the use of BH4 and LNAAs in pregnant women and in children, including infants, are unknown.[7, 35] Further complicating clinical decision making is the difficulty in studying such a rare disease. They range in age and severity of clinical disease and thus represent a very small yet highly heterogeneous population. Therefore, not only is research challenging logistically, but little federal funding is available to support such research. The availability and quality of research evidence is unlikely to reach the level of more common clinical conditions; nonetheless, we know with certainty that failure to treat this condition with a Phe-restricted diet with or without concomitant use of BH4 or LNAAs leads to very poor outcomes. Clinicians, patients, and their families must make the best decisions possible about what treatment avenues to pursue in the presence of uncertainty.

Goal of This Comparative Effectiveness Review (CER)

The overall goal of this CER is to inform clinician and patient decisions about adjuvant treatments for PKU in addition to dietary restriction. To this end, this CER summarizes evidence for the effectiveness of BH4 in individuals with PKU, including pregnant women. The review also summarizes the evidence for the effectiveness of LNAAs, including pregnant women, with PKU. We also address harms of BH4 and LNAAs reported in the PKU literature. “Harms” are defined by the Evidence-based Practice Center program as the totality of all possible adverse consequences of an intervention including, but not limited to, side effects of treatment.[36]

This review also seeks to examine the evidence for specific blood Phe levels to minimize cognitive impairment in individuals with PKU and whether specific levels may be applicable to specific age groups.

Scope and Key Questions

Scope of the Report

Evidence reviews of therapeutics seek to identify and systematically summarize objective information about the evidence related to factors including the:

- Effectiveness of specific, well-defined treatments
- Relative benefit of one treatment over another
- Common side effects and serious risks of a treatment.

We focused this review on pharmacologic treatment for infants, children, adolescents, adults, and pregnant women with phenylketonuria. The report does not address dietary restriction as the sole treatment for PKU as its effectiveness has been shown in numerous studies, and it is the standard of care.[12, 37]

Key Questions

We have synthesized evidence in the published literature to address these Key Questions:

Key Question 1a. What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 4. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13 to 21 years old with PKU
- Adults >21 years old with PKU

Key Question 5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

Key Question 6. What are the harms, including adverse events, associated with the use of BH4 or LNAAs in individuals with PKU?

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients? The following are examples of potential defining characteristics of subgroups:

- Demographic
- Clinical
- Genotypic
- Adherence

Organization of This Evidence Report

The Methods section describes our processes including search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and our method for extraction of data into evidence tables and compiling evidence. We also describe the approach to grading of the quality of the literature and to evaluating the strength of the body of evidence.

The Results section presents the findings of the evidence report, synthesizing them by Key Question and outcomes reported. We report the number and type of studies identified, and we differentiate between total numbers of publications and unique studies. In Key Question 1, we discuss the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment. In Key Questions 2 and 4, we emphasize the effect of BH4 and LNAAs on cognition, quality of life, and nutritional status in infants, children, adolescents, and adults with PKU. Key Questions 3 and 5 describe the evidence for effectiveness of BH4 and LNAAs in preventing neurological impairment, microcephaly, and cardiac defects in the offspring of women with PKU.

The final section of the report discusses key findings and expands on methodological considerations relevant to each Key Question. We also outline the current state of the literature and challenges for future research in PKU. The report also includes a number of appendixes to provide further detail on our methods and the studies assessed. The appendixes are as follows:

- Appendix A: Search Strategies
- Appendix B: Data Extraction Forms
- Appendix C: Evidence Tables
- Appendix D: Tools Used to Assess Quality of the Literature
- Appendix E: Quality of the Literature
- Appendix F: Meta Analysis Methods
- Appendix G: Excluded Studies
- Appendix H: Studies Addressing Executive Function
- Appendix I: Studies Addressing Maternal PKU
- Appendix J: Summary of New Drug Application Studies of Sapropterin
- Appendix K: Recent Conference Abstracts Addressing Adjuvant Treatment

We also include a list of abbreviations and acronyms at the end of the report.

Uses of This Report

This evidence report addresses the Key Questions (outlined in the previous section) by conducting a systematic review of published literature. We anticipate that the report will be of value to clinicians who treat individuals with PKU, including clinical geneticists, nurse

practitioners, dieticians, psychologists, and other healthcare professionals who have patients with PKU. In addition, current clinical guidelines lack information about when and in whom the use of BH4 may be an appropriate treatment approach. We anticipate that this report will provide some basis for updating current clinical guidance. The report itself is not a guideline. It is a review of evidence that other groups and individuals can use in developing guidelines or treatment decisions, but we assume that those decisions would be made with other considerations as well, including the severity of this disease, the certainty of poor outcomes in the absence of treatment with a Phe-restricted diet, and the challenges to conducting comparative effectiveness research given its status as a rare disease.

Methods

Topic Development and Refinement

The topic for this report was nominated in a public process. We drafted the initial Key Questions and analytic framework and refined them with input from key informants. These included individuals, such as geneticists, psychologists, metabolic dieticians, and nurse practitioners, who are the primary clinicians caring for individuals with phenylketonuria (PKU), as well as researchers in academia and the federal government. After review from the Agency for Healthcare Research and Quality (AHRQ), the questions and framework were posted to a public website. The public was invited to comment on these questions. After reviewing the public commentary, we drafted final Key Questions and submitted them to AHRQ for review. We identified clinical and research experts on the topic of PKU in the fields of genetics, nutrition, and psychology to provide assistance during the project. The Technical Expert Panel (TEP) contributed to the AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included eight members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and Key Questions at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria.

As noted, this report focuses on the use of adjuvant treatments for PKU and does not address dietary restriction alone. The effectiveness of dietary restriction has been demonstrated in previous studies,[12, 37] and it is well established as the cornerstone of PKU therapy.[8]

Role of the AHRQ Task Order Officer

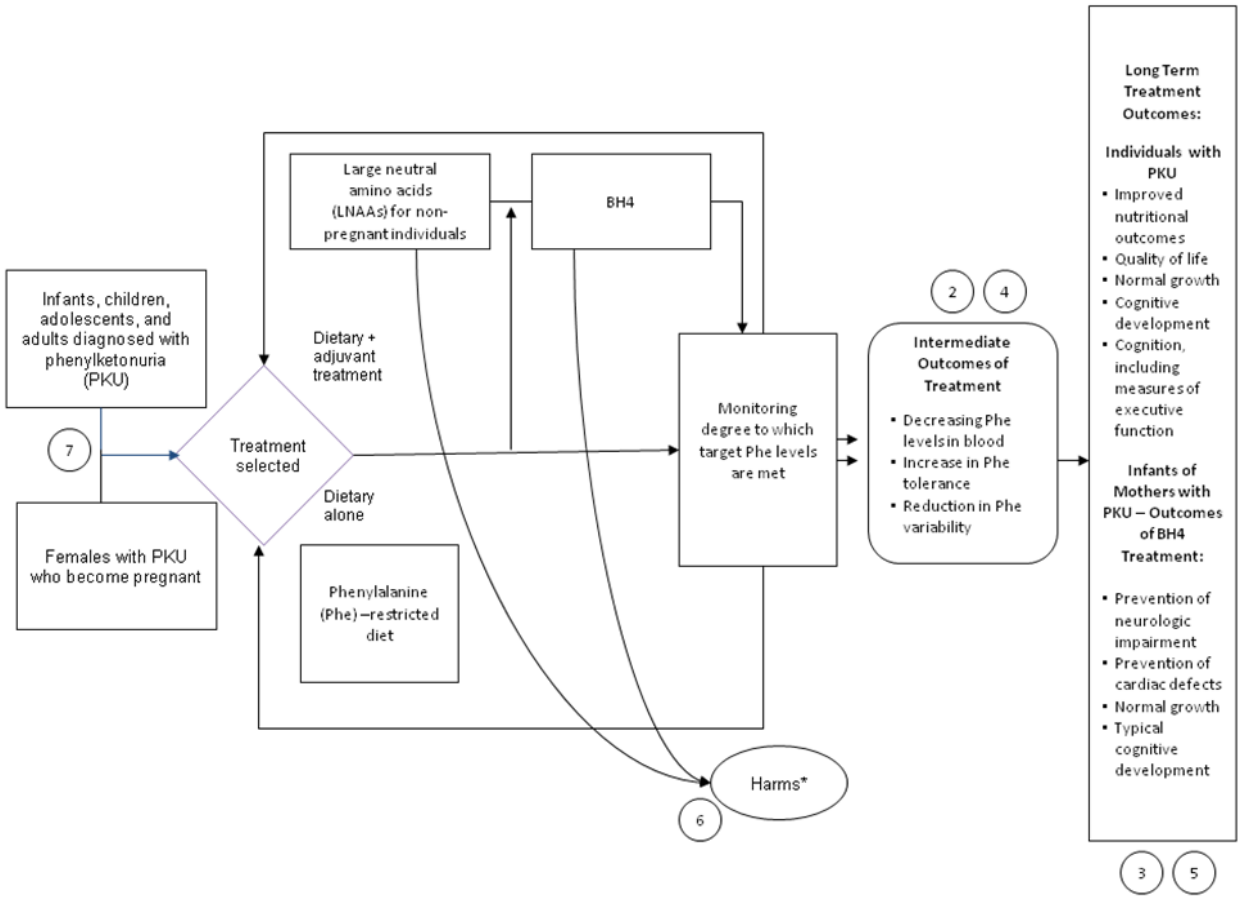
The Task Order Officer (TOO) was responsible for overseeing all aspects of this project. The TOO helped to develop a common understanding among all parties involved in the project, resolved questions and ambiguities, and addressed our queries regarding the scope and processes of the project. The TOO reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards.

Analytic Framework

We developed the analytic framework (Figure 1) based on clinical expertise and refined it with input from our key informants and TEP members. The framework summarizes the process by which treatment is chosen and modified for infants, children, adolescents, adults, or pregnant women with PKU. The treatment choice that is the basis of this review is whether to add adjuvant treatment in the form of sapropterin (BH4) or large neutral amino acids (LNAAs) to dietary therapy. The primary target health outcome is maintenance of cognition, with secondary outcomes including increasing quality of life. Monitoring blood phenylalanine (Phe) levels provides an intermediate marker of treatment success because these levels are used to adjust the dietary intake of Phe in an effort to mitigate the cognitive decline that can occur from elevated blood Phe levels.

In maternal PKU, treatment is intended to prevent neurologic impairment and cardiac defects in the infant (who typically does *not* have PKU) caused by the teratogenic effects of excessively high Phe levels in the maternal bloodstream. The Phe level of the mother is monitored throughout the pregnancy to guide modifications to the diet or other treatment approaches.

Figure 1. Analytic framework for treatment questions



BH4 = sapropterin dihydrochloride; LNAAs = large neutral amino acids; Phe = phenylalanine; PKU = phenylketonuria
*Encompasses a full range of specific negative effects, including the narrower definition of adverse events. Can include costs, medical side effects, poor quality of life, etc.
Note: Numbers in circles indicate the positioning of Key Questions in the treatment process.

Literature Search Strategy

Databases

We employed systematic search strategies (Appendix A) to retrieve research on the treatment of PKU. Our primary literature search employed five databases: MEDLINE® via the PubMed interface, PsycINFO (CSA Illumina interface; psychology and psychiatry literature), Embase, the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database, and the National Agricultural Library (AGRICOLA) database. Our search strategies used a combination of subject heading terms appropriate for each database and key words relevant to PKU (e.g., phenylketonuria, pharmaceutical preparations, phenylalanine). We limited searches to the English language but did not set a date limit.

We also manually searched the reference lists of included studies and of recent narrative and systematic reviews and meta-analyses addressing PKU. We also invited TEP members to provide citations.

Search Terms

Controlled vocabulary terms served as the foundation of our search in each database, complemented by additional keyword phrases. We also employed indexing terms when possible within each of the databases to exclude undesired publication types (e.g., reviews, case reports, news), items from non-peer-reviewed journals, and items published in languages other than English.

Our searches for primary literature were executed between August 2010 and August 2011. Because we identified no literature on the pharmacologic treatment of pregnant women in our initial searches, we conducted an additional search to identify any case reports of pharmacologic management in pregnancy on February 4, 2011. Appendix A provides our search terms and the yield from each database.

Grey Literature

Grey Literature Search

We searched Internet resources to identify current research and regulatory information using topically relevant keywords (e.g., kuvan, sapropterin, phenylketonuria). All search results were limited to English language. Resources included the Web sites of regulatory agencies (U.S. Food and Drug Administration, Health Canada, European Medicines Agency, Japan's Pharmaceutical and Medical Devices Agency), and clinical trials registries (clinicaltrials.gov, International Clinical Trials Registry Platform, Current Controlled Trials, European Union Clinical Trials Register). We also searched compilations of abstracts presented at major scientific meetings addressing PKU (annual meetings of the National PKU Alliance, American College of Human Genetics, Society for Inherited Metabolic Disorders American Society of Medical Genetics, and the Society for the Study of Inborn Errors of Metabolism) for treatment-related presentations given from 2006 (where possible) to 2011. Abstracts for each conference for each year were not available electronically.

Additionally, we searched commercial databases such as LexisNexis and a number of PKU-related websites specifically for any legal procedures related to the drug that might be a source of additional data. Searches were executed between January and June 2011. Finally, per Evidence based Practice Center (EPC) protocol, the maker of Kuvan, Biomarin, as well as manufacturers of LNAAs (Applied Nutrition Corporation, Solace Nutrition, Nutricia North America), were invited to provide Scientific Information Packets, but none did so.

Review of Reviews

We searched for relevant systematic reviews that might provide information for this review. In particular, we found a body of review literature focused on the relationship between blood Phe and outcomes listed in the Key Questions. We assessed this literature systematically to determine whether it was specifically relevant to our research questions and of high quality.

We assessed relevance of the reviews by determining if the review (1) included studies of individuals with PKU, (2) assessed the relationship of Phe level and cognition, (3) included

studies with at least 10 participants, (4) included studies in English only, and (5) was conducted systematically. If a review met these criteria, then we assessed the quality of the review by considering elements assessing the rigor of a review's design and completeness of reporting.

Process for Individual Study Selection

For this review, the relevant populations for Key Question 2 and Key Question 4 were infants (<2 years), children (2 to 12 years), adolescents (13 to 21 years), and adults (≥21years) with PKU. The relevant population for Key Question 3 and Key Question 5 was pregnant women with PKU. All subgroups were relevant to Key Question 1, Key Question 6, and Key Question 7.

Inclusion and Exclusion Criteria

We developed criteria for inclusion and exclusion based on the patient populations, interventions, outcome measures, and types of evidence specified in the Key Questions and in consultation with the TEP. Table 1 summarizes criteria.

Table 1. Inclusion and exclusion criteria

Category	Criteria
Population	Humans only: • Infants with PKU* <2 years of age • Children with PKU* 2-12 years of age • Adolescents with PKU* 13-21 years of age • Pregnant women with PKU* • Adults with PKU* >21 years of age * As operationalized by study authors.
Interventions	BH4 LNAAs
Comparators	Dietary therapy alone (Phe-restricted diet and medical foods) or in conjunction with other intervention Placebo
Outcomes	Key Questions 1a, 1b Changes in cognition including executive function and IQ Key Questions 2-7 Intermediate Outcomes • Phe level • Phe tolerance • Phe variability • Harms Long term Outcomes • Cognitive outcomes • Liberalization of diet • Nutritional outcomes • Quality of life • Harms
Time period	All years

Table 1. Inclusion and exclusion criteria (continued)

Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs • Randomized controlled trials, uncontrolled open label trials, prospective and retrospective cohort studies with comparison groups, case series with no comparators, case control studies, and cross-sectional studies Sample size • N ≥ 10 individuals with PKU Other criteria • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results • Studies must include extractable data on relevant outcomes

BH4 = sapropterin dihydrochloride; LNAAs = large neutral amino acids; N = number; PKU = phenylketonuria

Study Population

Studies needed to provide adequate information to ensure that participants were in the target study population. We only included studies with human participants who had any form of PKU or hyperphenylalaninemia. We did not include studies with participants who had primary BH4 deficiency. We recognize that classification of the severity of PKU varies across countries and clinics.[8, 38-42] Therefore, we did not impose a specific classification of PKU types (e.g. classic versus moderate of mild); rather, we allowed the definitions of PKU as they were operationalized by study authors.

Language

We included only English language studies. Our technical experts concurred that very few studies on PKU are published in other languages, and those studies that are published in other languages are also typically published in English.

Time Period

No time limits were set in this review.

Sample Size

As an inclusion criterion, we set the cutoff level at a minimum of 10 participants. PKU is a rare condition; therefore, recruitment into larger research studies is slow and challenging. Most studies enroll fewer than 20 participants. We anticipated being unable to combine treatment studies analytically; thus it would not have been appropriate to include even smaller studies that would be unable to independently demonstrate effect. For the first Key Question on Phe and cognition, we intended to combine studies quantitatively; for those questions, using a minimum sample size of 10 provided ample data for analysis.

Study Design

We included randomized controlled trials (RCTs) and uncontrolled open label trials, prospective and retrospective cohort studies, and case series and case control studies addressing

the effectiveness of pharmacological treatment approaches (Key Questions 2 to 7). In addition to these designs, we included cross-sectional studies to address the question about identifying target blood Phe levels to optimize outcomes (Key Question 1).

Outcomes

Key Question 1 seeks to identify "specific Phe levels that are optimal for minimizing or avoiding cognitive impairment in individuals with PKU." We defined cognitive impairment as deficits in IQ or executive function. For measures of executive function, we sought outcomes in the following categories: working memory, attention, cognitive flexibility, planning, and inhibitory control. The specific measures for each of these outcomes used in studies meeting our criteria are presented in Table 2.

For treatment-related questions (Key Questions 2 to 7), we sought outcomes that included liberalization of diet, nutritional outcomes, quality of life, and changes in cognition, including executive function and IQ. We also report on intermediate outcomes (Phe level, Phe tolerance, and Phe variability).

Additional Criteria for Key Question 1

Phe Levels and IQ

Because the purpose of Key Question 1 was to identify a "specific" Phe level at which outcomes were observed, we required appropriate quantitative data to conduct the analysis for this question for both IQ and executive function. Papers needed to include either individual-level data on both Phe and the outcome or a mean/median and some measure of variance (usually standard deviation) for both.

For the purpose of the analysis of IQ in Key Question 1, while intellectual disability is defined as IQ score lower than 70 (i.e., two standard deviations below the population mean) and impairment in activities of daily living, IQ scores within the normal range could be considered impairment if they are lower than the expected value for the general population. Though necessarily subjective, we believe that a reasonable candidate for impairment is a threshold of one standard deviation below the population mean, or an IQ score of 85. It is expected that subjects below this threshold would exhibit at least some symptoms of cognitive impairment, such as poor language development, problem solving deficiencies, and memory deficits.

Phe Levels and Measures of Executive Function

To estimate a range of blood Phe levels associated with poor executive function outcomes, we sought to conduct a meta-analysis of papers that could provide data on this relationship. As such, we required that studies provide either individual data on blood Phe level and executive function measures or average Phe and executive function measures along with variance and correlation information. Studies also needed an appropriate control population (i.e., healthy individuals without PKU) for normative data.

Using input from clinical experts and published classifications of measures of executive function,[43] we grouped the measures employed in the studies meeting our criteria under core domains of executive function. These domains included working memory, cognitive flexibility, inhibitory control, attention, and planning (Table 2).

We then assessed whether the studies within each domain were suitable for meta-analysis by examining the number of studies using a given test. We required that a test be used in at least three studies to be considered for meta-analysis.

Table 2. Measures of executive function reported in studies assessed for this review

Domain	Measures
Attention	• Amsterdam Neuropsychological Tasks-Sustained Attention (Tempo, Bias) • California Verbal Learning Test-Auditory Attention Diagnostic Method • California Verbal Learning Test-Children's version • Color Word Interference Task • Continuous Performance Test-Omission Errors • Continuous Performance Test-Successfully recognized matches • D2-Aufmerksamkeits-Belastungs-Test • Sonneville Visual Attention Tasks-Calculation Exercise • Sonneville Visual Attention Tasks-Dot Pattern Exercise • Test of Everyday Attention for Children (Sky Search, Ode Transmission, Digital Distraction, Telephone Search, Sky Search Dual Task) • Videotracking • Wechsler Adult Intelligence Scale-Revised Digit Span Forward
Cognitive flexibility	• Contingency Naming Test • Delis-Kaplan Executive Functioning System Trail Making • Intradimensional/Extradimensional Set-Shifting Task • Trail Making Test A & B • Wisconsin Card Sorting Test (Categories, Perseverative Errors, Perseverative Responses) • Zahlen-Verbindungs-Test (Trail Making Test)
Inhibitory control	• Antisaccade • Behavior Rating Inventory of Executive Function Inhibit Scale • Continuous Performance Test-Commission Errors • Day-Night Stroop-like Test • Flanker/Eriksen and Schultz • Go/No Go • Stroop Color and Word • Stroop Word Reading Task
Planning	• Tower of Hanoi • Tower of London
Working memory	• Digit Span • Memory Search Task • n-Back • Self-Ordered Pointing • Spatial Working Memory • Wechsler Adult Intelligence Scale Third Edition-Working Memory Index • Wechsler Adult Intelligence Scale-Revised Digit Span Back • Wechsler Intelligence Scale for Children-III Digit Span • Working Memory Scale Third Edition

Screening of Studies

Once we identified articles through the electronic database searches, review articles, and bibliographies (discussed above), we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated each abstract for inclusion or exclusion, using an Abstract Review Form (Appendix B). If at least one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it for full text assessment.

Two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion/exclusion

criteria. Disagreements between reviewers were resolved by a third-party adjudicator. The group of abstract and full text reviewers included expert clinicians (TR, ML) and health services researchers (MM, SK, JF).

Data Extraction and Data Management

Evidence tables were used as data extraction tools and were jointly developed and tested by the team. All data were extracted by one team member and checked by a second. For Key Question 1, the data extraction process captured information on cognitive outcomes, as well as aspects of dietary treatment important to measuring Phe levels for Key Question 1. These included type of Phe measurement (lifetime, historical, concurrent, recent), treatment status (early, continuously), and disease type/classification. Evidence tables for the treatment questions collected this information as well as treatment details, key study design and comparator data. When possible to identify, analyses resulting from the same study were grouped into a single evidence table. The final evidence tables are presented in their entirety in Appendix C.

Individual Study Quality Assessment

We assessed quality using a domain-based approach, with separate tools as appropriate by study design. The detailed tools used to assess quality are in Appendix D. Studies for Key Question 1 were primarily cross-sectional, while treatment studies were largely RCTs or uncontrolled open label trials thus necessitating separate approaches. In addition, we used the McMaster harms tool[44] to assess harms in treatment studies.

Two reviewers independently assessed quality for each study, with final decisions made by third party adjudication and consensus of the team as needed. We describe the individual quality components below and report individual quality assessments for each study in Appendix E.

Determining Quality Levels

We used targeted sets of questions to assess randomized trials, case series, cohort, and case-control studies. Appendix D includes the individual questions used to assess each study type, and Appendix E lists scores for each question for each study. For all but the uncontrolled open label trials, we required that studies receive a positive score on all of the questions used to assess quality to receive a rating of "good." For uncontrolled open label trials, we scored studies with one negative score as fair quality and those with more than one negative score as poor quality.

Grading the Body of Evidence for Each Key Question

We evaluated the overall strength of the evidence for the primary outcomes. We used the approach to determining strength of evidence as described in the EPCs' Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[45] We assessed the strength of evidence for key outcomes identified by the clinical investigators to be most clinically important: cognitive outcomes including IQ and executive function, nutritional outcomes, quality of life, and liberalization of diet. Secondary outcomes included changes in blood Phe levels, Phe variability, and Phe tolerance.

We examined the following four major domains: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown or not applicable), directness (direct, indirect), and precision (precise, imprecise). We assigned each key outcome

for each comparison of interest an overall evidence grade based on the ratings for the individual domains.

The overall strength of evidence could be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); or "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect). When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

Data Synthesis

We used both qualitative and quantitative approaches to synthesizing the data. When possible in Key Question 1, we used meta-analytic approaches to identify threshold Phe levels.

Meta-analytic Methods

We provide a detailed description of the meta-analysis in Appendix F and summarize the methods here. We required that studies eligible for the meta-analysis include data in one of two forms:

- Individual level data: Measurements of both blood Phe and IQ for each non-control individual in the study (control individuals did not generally have Phe measurements taken), or
- Summarized data: Means/medians and standard deviations of Phe and IQ if individual level data were not available, provided that the study reported a correlation coefficient (Pearson's or Spearman's *r*) for these two measures, and data to allow for an associated measure of uncertainty for *r* to be computed.

We defined measurements of blood Phe reported in studies as concurrent (taken <6 weeks) with IQ testing, historical (taken more than one year prior), or both. No included studies reported Phe measurements taken more than 6 weeks but less than one year prior to IQ testing ("recent"). We also considered measurements taken before age 6 to comprise the critical period from the standpoint of cognitive development. To avoid pooling these disparate types of measurements, we estimated two models, one for concurrent Phe measurements and a second for historical Phe measurements. The model structure described below was replicated identically for concurrent and historical measurements of Phe to obtain separate estimates of their effects.

We meta-analyzed the association of blood Phe levels with IQ using a Bayesian hierarchical mixed effects model.[46] The advantages of using a Bayesian approach to meta-analysis were recognized over a decade ago,[47] and they have been applied extensively ever since.[48-55] It allows for straightforward probabilistic inference across studies, and can accommodate both fixed and random effects. In contrast to the more indirect measures of inference afforded by classical methods, all inference from Bayesian models is in the form of probability statements that

describe the uncertainty in the unknown quantities of interest (θ), given the information at hand (y):

$$\Pr(\theta|y) \propto \Pr(y|\theta)\Pr(\theta)$$

The left side of this equation is the posterior distribution of all unknown parameters in the model, while the right side shows that this posterior quantity is the product of a data likelihood and the prior distribution (i.e., before data are observed) of the model. While in principle the use of priors allows for the incorporation of extant information into the analysis, we used uninformative priors on all parameters, allowing the results from the included studies to completely inform the analysis.

Using random effects for meta-analysis permits us to abandon the tenuous assumption that the effects across studies are independent and identically distributed. Rather, we view them as *exchangeable* samples from a "population" of PKU studies. This conditional independence (i.e., conditional on population parameters) assumption avoids either having to combine studies in a single estimate (which assumes they are identical) or keeping them entirely separate (which assumes they are completely different), but rather, allows for some mixture of the two extremes. In contrast, fixed effects models force one of these unlikely extremes.

We specified random effects for the intercept and slope parameters of a linear relationship between blood Phe level and IQ. Importantly, this allowed each study to have its own parameters, each sampled from a notional population of parameters. Those with smaller sample sizes were automatically shrunk towards the population means for each parameter, with larger studies influencing the estimate of the population mean more than being influenced by it. In turn, the magnitude of the effect (i.e., slope) was specified partly as a function of a fixed effect for whether measurements of Phe were carried out during the critical period. Hence, the overall model was a hierarchical mixed effects model. Bayesian hierarchical models are very easily estimated using Markov chain Monte Carlo (MCMC) methods.[56]

As noted, all stochastic parameters were specified using diffuse prior distributions. For all linear model coefficients, a normal distribution with mean zero and precision (inverse-variance) 0.01 was used. For precision parameters, the standard deviation was modeled uniformly on the interval (0, 1000) and then transformed to inverse variance; this provides a better non-informative prior than modeling the precision directly.[57]

In order to evaluate the association of particular levels of Phe with the likelihood of cognitive impairment, we chose a threshold value of IQ to define impairment. For a standardized measure like IQ, a boundary of one standard deviation below the mean (IQ=85) is an appropriate choice. We used this threshold value to define indicator variables that were set to one if the value of the predicted IQ was below 85 during the current iteration of the MCMC sampler, and zero otherwise. Hence, for each combination of Phe level and critical period indicator, the total number of ones divided by the number of MCMC iterations represents a probability of observing IQ<85. To estimate the sensitivity of this probability to Phe, this probability was calculated for a range of blood Phe levels from 200 to 3000 μmol/L, in increments of 200. This was done for critical period and non-critical period Phe measurement, under both the historical and concurrent measurement models.

We coded the model in PyMC version 2.1[58] which implements several MCMC algorithms for fitting Bayesian hierarchical models. The model was run for one million iterations, with the first 900000 discarded as a burn-in interval. The remaining sample was thinned by a factor of ten to account for autocorrelation, yielding 10000 samples for inference. Posterior predictive checks[46]

were performed, which compare data simulated from the posterior distribution with the observed data. This exercise showed no substantial lack of fit for any of the studies included in the dataset.

Results

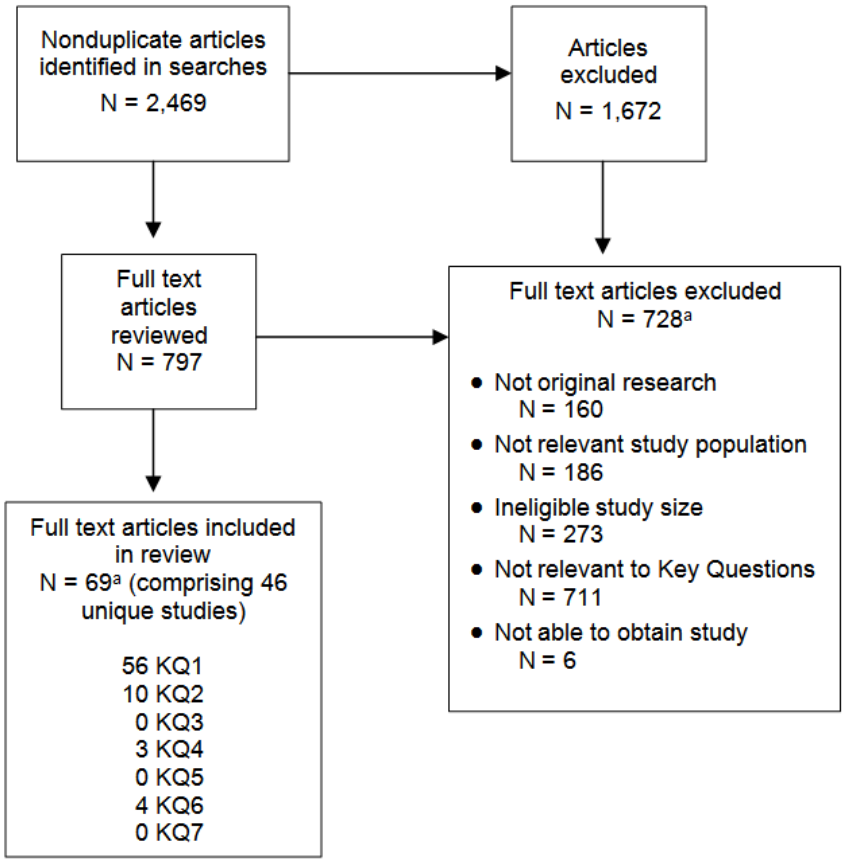
In this section we present findings for each Key Question, beginning with an overview of the content of the phenylketonuria (PKU) literature meeting our criteria, including the range of study designs used, approaches assessed and participants included. The detailed analysis of the literature provides further discussion and analysis.

Studies also are described in more detailed summary tables in the relevant section of text. For information on studies not included in the summary tables, please see the evidence tables in Appendix C; for information on quality scores for each study, see Appendix E.

Article Selection

We conducted a broad search to identify any titles or abstracts that might include relevant data for the review. Of the entire group of 2,469 titles and abstracts, we reviewed the full text of 797 because they either appeared to meet criteria or didn't provide enough information to determine definitively whether they should be in included (Figure 2). Of the 797 full text articles reviewed, 69 articles (comprising 46 unique studies) met our inclusion criteria. Reasons for article exclusion are listed in Appendix G.

Figure 2. Flow of studies identified for the review



KQ = Key Question; N = number

[a]The total number of (1) articles in the exclusion categories and (2) those addressing each Key Question exceed the (1) number of articles excluded and (2) total number included because most of the articles fit into multiple exclusion categories or addressed more than one Key Question.

Key Question 1a. What is the evidence that any specific phenylalanine (Phe) levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU?

We divided the literature addressing this question into three sections: studies of the relationship of blood Phe levels and intelligence quotient (IQ) in individuals with PKU, studies of the relationship of blood Phe levels and measures of executive function in individuals with PKU, and studies offspring of mothers with PKU (maternal PKU). Children in the latter group may or may not have PKU themselves but may experience intellectual disability, low birth weight, or other impairments as a result of the mother's PKU. We considered executive function to be defined as working memory, cognitive flexibility, inhibitory control, planning, or attention domains of executive function.[43]

In conducting a review of reviews to identify potential systematic reviews to answer this Key Question, we identified one review that used the same inclusion and exclusion criteria and sought to answer a nearly identical question.[59] However, this study was a meta-analysis of the correlation between blood Phe and IQ, and we sought to predict the probability of low IQ based on blood Phe level. Therefore, we used the existing, well-conducted review as a source of citations only.

Phe Levels and IQ Impairment in Individuals With PKU

Key Points

- Increasing blood Phe is clearly associated with decreased IQ, with a probability of having an IQ less than 85 exceeding the probability for the general population (approximately 15 percent) at a Phe level of over 400 μmol/L. This finding supports the typical target goal for Phe level in individuals with PKU (120 to 360 μmol/L).
- The probability of having an IQ of <85 does not continue to increase considerably above a blood Phe level of 2000 μmol/L.
- Historical measurements of Phe (taken more than 1 year prior to IQ testing) show a stronger correlation with the probability of having a lower IQ than do concurrent measurements. Even at the highest blood Phe measurement, observed effects differ by when the measurements are taken, both relative to IQ measurement and according to whether measurements were taken during the critical period (<6 years old).
- The best measure of blood Phe for assessing the potential impact on IQ is likely to be a historical measure of dietary control that is taken at least one year prior to the IQ test.
- The probability of low IQ (<85) increases faster with higher blood Phe measurement when historical measurements were taken during the critical period and associated with later IQ, although historical measurements taken after the critical period are also associated with risk of low IQ. Hence, control of blood Phe levels during the critical period is particularly important, but the need for dietary control continues beyond early childhood.
- The relatively modest increase in the probability of low IQ with blood Phe measurement in measurements taken concurrently during the critical period may suggest that effects are unlikely to be observed in this period, either because the IQ test is not stable for young children (under 5 years of age), or because the adverse effects take time to manifest.

From a clinical perspective, this provides a basis for being cautious in interpreting measures of cognitive outcomes as they relate to blood Phe in early childhood.

Overview of the Literature

Seventeen unique studies (reported in 21 publications) met our criteria and addressed the relationship between blood Phe levels and IQ (Table 3).[60-79] Age ranges and IQ levels varied widely across studies. Ten studies were conducted in Europe,[62-66, 69, 70, 73-75] six in the United States,[60, 71, 72, 78, 80, 81] and one in Iran.[61] We rated one study[67, 68] as good quality and five studies as fair quality.[63, 65, 71, 74, 79, 81] The remaining studies[60-62, 64, 66, 69, 70, 72, 73, 75-78] were rated as poor quality and typically did not document recruitment processes adequately, did not include all eligible participants in analyses, and/or did not assess confounding variables using valid and reliable measures.

Overall, the number of participants in the studies was low, ranging from 10 to 57. The studies included a total of 432 individuals with PKU. Of the studies that reported on disease classification, 10 included only participants with classic PKU, and the remainder did not provide the classification or included individuals with less severe PKU. Results are therefore most clearly applicable to individuals with classic PKU.

Table 3. Overview of studies addressing Phe levels and IQ

Study (Author/Year) Quality	Country	Disease Type	N (PKU)
Viau, 2011[81] Quality: Fair	United States	Classic Moderate Mild	55
Azadi, 2009[61] Quality: Poor	Iran	Classic	10
Anastasoaie, 2008[60] Quality: Poor	United States	Classic Moderate Mild Unclassified	46
Wasserstein, 2006[72] Quality: Poor	United States	Classic	10
Pfaender, 2005[66] Quality: Poor	Germany	NR	31
Rupp, 2001[69] Quality: Poor	Germany	Classic	17
Weglage, 2001 [73] Quality: Poor	Germany	Classic	15
Griffiths, 2000[63] Quality: Fair	United Kingdom	Classic	57
Weglage, 2000[74, 79] Quality: Fair	Germany	Classic	42
Cerone, 1999[62] Quality: Poor	Italy	Classic	16
Weglage,1995[75-77] Quality: Poor	Germany	NR	20
Leuzzi, 1998[65] Quality: Fair	Italy	NR	14

Table 3. Overview of studies addressing Phe levels and IQ (continued)

Study (Author/Year) Quality	Country	Disease Type	N (PKU)
Ris, 1994[67, 68] Quality: Good	United States	Classic	25
Jones, 1995[64] Quality: Poor	United Kingdom	Classic	32
Schmidt, 1994[70] Quality: Poor	Germany	NR	17
Welsh, 1990[78] Quality: Poor	United States	NR	11
Seashore, 1985[71] Quality: Fair	United States	Classic	14

N = number; NR = not reported; PKU = phenylketonuria

Participant ages ranged from 2 to 34 years. A majority of studies included primarily participants under age 25 at intake,[60-63, 65, 67, 70, 71, 74, 75, 78, 81] with five studies including only participants under age 15 at intake.[60, 63, 71, 75, 78] Dietary control varied among the studies, with five studies reporting that all participants were adhering to a restricted diet,[60, 61, 63, 72, 78] seven reporting a mix of dietary control (some participants on and some off a restricted diet),[64-70, 81] and three reporting that participants had discontinued a restricted diet.[62, 71, 73] Dietary status was not clearly reported in the remaining studies.[74-77] Table 4 outlines characteristics of study participants.

Table 4. Characteristics of participants in studies addressing Phe levels and IQ

Study (Author/ Year)	Type of Phe Measurement	PKU Subjects (N)	Age, Mean Years (Range)	Diet
Viau 2011[81]	Concurrent	55	Overall: 11.04 (6-22)	Mixed
	Historical & Critical	55		
	Historical & Non-critical (ages 7-12)	38		
	Historical & Non-critical (age >12 years)	15		
Azadi 2009[61]	Concurrent	10	13.28 (6.58-19.83)	Restricted
Anastasoaie 2008[60]	Critical	46	7.5 (2.9-15.5)	Restricted
Wasserstein 2006[72]	Concurrent	10	28.80 (23-35)	Restricted
	Historical		29.1 (23-35)	
	Critical		28.80 (23.00-35.00)	
Pfaendner 2005[66]	Historical	31	29 (18-40)	Mixed
	Critical		29 (18-40)	

Table 4. Characteristics of participants in studies addressing Phe levels and IQ (continued)

Study (Author/ Year)	Type of Phe Measurement	PKU Subjects (N)	Age, Mean Years (Range)	Diet
Rupp 2001[69]	Concurrent	17	22.24 (17-27)	
	Historical		22.24 (17-27)	Mixed
Weglage 2001[73]	Historical	15	18.47 (14-30)	Unrestricted
	Critical		18.47 (14-30)	
Griffiths 2000[63]	Critical	57	8.14	Restricted
Weglage 2000[74]	Concurrent	42	14.7 (10-18)	Not Clear
	Critical			
Cerone 1999[62]	Concurrent	16	11.1 (10-12)	Unrestricted
Weglage1995[75-77]	Historical	20	10.9(8.9-13.1)	Not Clear
Leuzzi 1998[65]	Historical	14	12.30 (9.00-17.60)	Mixed
Ris 1994, 1997[67]	Concurrent	25	22 (18-26)	Mixed
Jones 1995[64]	Concurrent	32	17.81 (7.50-29)	Mixed
Schmidt 1994[70]	Concurrent	17	20.5 (17-24)	Mixed
Welsh 1990[78]	Concurrent	11	4.64 (4.08-5.75)	Restricted
	Critical		4.64 (4.08-5.75)	
	Historical		4.64 (4.08-5.75)	
Seashore 1985[71]	Historical & Critical	14	11.33 (8.17-14.50)	Unrestricted

IQ = intelligence quotient; N = number; Phe = phenylalanine; PKU = phenylketonuria

IQ scores ranged from 44 to 148 across studies. Five studies reported concurrent measures of Phe levels (blood Phe measurement within 6 weeks of IQ measurement),[61, 62, 64, 67, 70] eight studies reported historical Phe measurements (blood Phe measurements taken more than 12 months before IQ measurement),[63, 65, 66, 71, 73-75, 78] and four reported both historical and concurrent measurements.[60, 69, 72, 81] Phe measurements were also taken in the critical period (blood Phe measurement before age 6) in seven studies (Table 5).[60, 63, 66, 71, 72, 78, 81] The one study that included very young children used developmental quotient as the outcome measurement for the young children.[60]

Table 5. Summary of results of studies addressing Phe levels and IQ

Study (Author/Year)	Type of Phe Measurement	Blood Phe, Mean ± SD µmol/L	IQ Mean ± SD (Range)	Correlation (p Value)
Viau 2011[81]	Concurrent	592 ± 355	Overall: 99.2 ± 13.6 (69-132)	-0.098 (0.476)
	Historical & Critical	365 ± 128		-0.157 (0.253)
	Historical & Non-critical (ages 7-12)	530 ± 209		-0.057 (0.732)
	Historical & Non-critical (age >12 years)	693 ± 257		-0.034 (0.905)
Azadi 2009[61]	Concurrent	1363.80 ± 410.44	108.40 ± 12.45	0.21 (0.57)
Anastasoaie 2008[60]	Critical	312 ± 132	104 ± 15 (68-143)	-0.17 (0.38)
Wasserstein 2006[72]	Concurrent	1137.00 ± 327.10	98.8 ± 18.13	-0.21 (0.56)
	Historical	607.6 ± 246.8	98.5 ± 18.1	-0.28 (0.24)
	Critical	433.2 ± 98.5	98.8 ± 18.1	-0.24 (0.51)
Pfaendner 2005[66]	Historical	399.3 ± 163.3	107.5 ± 18.7	-0.46 (<0.01)
	Critical	308.6 ± 102.2	107.5 ± 18.7	-0.52 (<0.01)
Rupp 2001[69]	Concurrent	1175.88 ± 319.61	104.06 ± 15.67	-0.60 (0.01)
	Historical	654.71 ± 184.73	104.06 ± 15.67	-0.65 (0.01)
Weglage 2001[73]	Historical	661.33 ± 267.62	98.4 ± 14.0	-0.36 (0.05)
	Critical	519.33 ± 198.58	98.40 ± 14.0	-0.70 (.005)
Griffiths 2000[63]	Critical	466 ± 154	85.8 ± 13.9	-.035 (<0.01)
Weglage 2000[74]	Concurrent	894 ± 360	100 ± 14	-0.25 (ns)
	Critical	528 ± 96	100 ± 14	-0.33 (<.05)
Cerone 1999[62]	Concurrent	1826.3 ± 462.9	104.9 ± 4.7	0.05 (0.84)
Weglage 1995[75-77]	Historical	11yrs: 474 ± 144	101.4 ± 10.2	-0.33 (ns)
		14 yrs: 534 ± 174	107.4 ± 10.2	-0.41 (<.05)
Leuzzi 1998[65]	Historical	543.79 ± 148.13	90.64 ± 13.52	-0.42 (0.13)
Ris 1994, 1997[67, 68]	Concurrent	1323.28 ± 445.29	89.80 ± 11.17	-0.35 (0.09)
Jones 1995[64]	Concurrent	1193.28 ± 425.21	91.91 ± 21.79	-0.20 (0.28)
Schmidt 1994[70]	Concurrent	1233.18 ± 390.16	110.00 ± 10.96	-0.42 (0.09)
Welsh 1990[78]	Concurrent	564.55 ± 256.58	104.73 ± 13.94	0.13 (0.70)
	Critical	570.55 ± 195.1	104.73 ± 13.6	-0.04 (0.86)
	Historical	576.55 ± 118.3	104.73 ± 13.94	-0.42 (0.19)
Seashore 1985[71]	Historical & Critical	1613.6 ± 245.2	90.0 ± 13.32	-0.56 (0.04)

IQ = intelligence quotient; Phe = phenylalanine; SD = standard deviation

The degree to which Phe was noted to be correlated with IQ varied across the studies, with some noting a significant negative correlation and others finding little to no relationship. At the individual study level, this variation in outcomes did not appear to be related to the population or when or how the measures were taken. The observed variation is possibly due, however, to the small size of the studies, a consideration that is mitigated by the meta-analysis, below.

Meta-analysis

We developed two meta-analytic models. The first represents the relationship of blood Phe and IQ when Phe was measured "historically" (more than 12 months before IQ measurement). In the second model, Phe and IQ were measured concurrently (within 6 weeks of IQ measurement). The key model parameters for the relationship between blood Phe and IQ from both models are presented in Table 6. The *baseline Phe effect* denotes the slope (correlation) of the linear relationship of Phe (either historical or concurrent) and IQ, when both are measured at or after 6 years of age; the *critical period effect*, then, is the additive effect of using Phe measurements that were taken in the critical period (prior to 6 years of age). The magnitude of association is strongest for the historical measurement of blood Phe versus that seen when Phe and IQ are measured concurrently.

Table 6. Estimates of key parameters by model

Model	Parameter	Median	SD	Lower 95% BCI	Upper 95% BCI
Historical	Critical period effect	-0.0100	0.0063	-0.0222	0.0025
	Baseline Phe effect	-0.0257	0.0067	-0.0393	-0.0128
Concurrent	Critical period effect	0.0071	0.0141	-0.0178	0.0353
	Baseline Phe effect	-0.0067	0.0035	-0.0138	0.0000

BCI = Bayesian credible intervals; SD = standard deviation

Note: The intervals shown in the last two columns are the 95% Bayesian credible intervals (BCI), which represent the shortest posterior 95% interval for the location of the parameter.

The implications of this relationship for a range of blood Phe levels measured at different points in life are described in Table 7. These probabilities can be used to estimate the chances of an individual's IQ being less than 85, based on blood Phe level, when Phe was measured, and the proximity of the Phe measurement to the IQ measurement. For example, Column 2 provides probabilities of the results of an IQ test showing an IQ less than 85 at different Phe levels when 1) the Phe is measured at least one year prior to the IQ, but 2) when the individual is 6 years old or greater. Note that these probabilities do not have associated levels of uncertainty, such as confidence intervals, because they were derived by integrating over the posterior distribution of the predicted IQ.

Table 7. Summary of probability (IQ<85) for various combinations of predictor variables

Phe (µmol/L)	Historical, Noncritical (Group 1)	Historical, Critical (Group 2)	Concurrent, Noncritical (Group 3)	Concurrent, Critical (Group 4)
200	0.095	0.110	0.107	0.098
400	0.140	0.187	0.118	0.094
600	0.202	0.299	0.138	0.109
800	0.279	0.427	0.157	0.125
1000	0.352	0.537	0.170	0.147
1200	0.430	0.642	0.192	0.163
1400	0.516	0.715	0.215	0.175
1600	0.563	0.783	0.234	0.198
1800	0.617	0.824	0.259	0.210

Table 7. Summary of probability (IQ<85) for various combinations of predictor variables (continued)

Phe (µmol/L)	Historical, Noncritical (Group 1)	Historical, Critical (Group 2)	Concurrent, Noncritical (Group 3)	Concurrent, Critical (Group 4)
2000	0.665	0.854	0.292	0.225
2200	0.700	0.879	0.310	0.245
2400	0.733	0.899	0.325	0.265
2600	0.762	0.915	0.354	0.273
2800	0.780	0.921	0.381	0.283
3000	0.796	0.931	0.408	0.295

IQ = intelligence quotient; Phe = phenylalanine

Conversely, Column 3 provides the probabilities for individuals for whom 1) the Phe is measured at least one year prior to IQ, but 2) in the critical period (prior to 6 years of age). As expected, increasing blood Phe in all cases is associated with increasing probability of a low IQ. However, our ability to see the relationship between Phe and IQ is attenuated by when both measurements are obtained. This suggests that although a relationship between high Phe and low IQ clearly exists, the effects may not be observed during early childhood, but become apparent later in life.

The columns in Table 7 provide probabilities for low IQ for four groups of individuals whose Phe levels have been measured at distinct time periods.

- Group 1 represents probabilities for low IQ for individuals who are tested for IQ whose reported blood Phe was measured *more than one year prior to* their IQ test and *at or after* age 6.
- Group 2 represents probabilities for low IQ for individuals who are tested for IQ whose reported blood Phe was measured *more than one year prior to* their IQ test and *before* age 6.
- Group 3 represents probabilities for low IQ for individuals who are tested for IQ testing whose blood Phe and IQ measurements are occurring *within* 6 weeks of one another and *at or after* age 6.
- Group 4 represents probabilities for low IQ for individuals who are tested for IQ testing whose blood Phe and IQ measurements are occurring *within* 6 weeks of one another and *before* age 6.

Across all groups, blood Phe of 200 µmol/L is associated with a low probability of about 0.10 (10 percent) of having an IQ less than 85. As Phe increases to 400, probability of low IQ increases considerably to 0.187 (19 percent) only in Group 2 in which Phe has been measured *more than one year prior to* IQ and *before* age 6.

The association of a high blood Phe level of 1,200 µmol/L with low IQ is most clearly captured when Phe and IQ measurements take place at least one year apart. The probability of having a low IQ is 0.642 (64 percent) for those individuals who had a Phe level of 1200 before age 6 (critical period) and at least one year before IQ testing. If the Phe level was measured at or after age 6 as opposed to in the critical period, the probability of a low IQ is 0.430 (43 percent).

A less dramatic effect is observed when the blood Phe and IQ measurements are taken concurrently. In individuals whose Phe and IQ are measured concurrently and at or after age 6, if the blood Phe is 1,200 µmol/L, then there is a 0.192 (19 percent) probability of low IQ,

compared with a probability of 0.163 (16 percent) when both measurements are taken concurrently in the critical period. This finding may represent tighter dietary control among individuals with frequent and concurrent measurement, or it may suggest that long-term effects of Phe on IQ cannot be seen when the two are measured too closely.

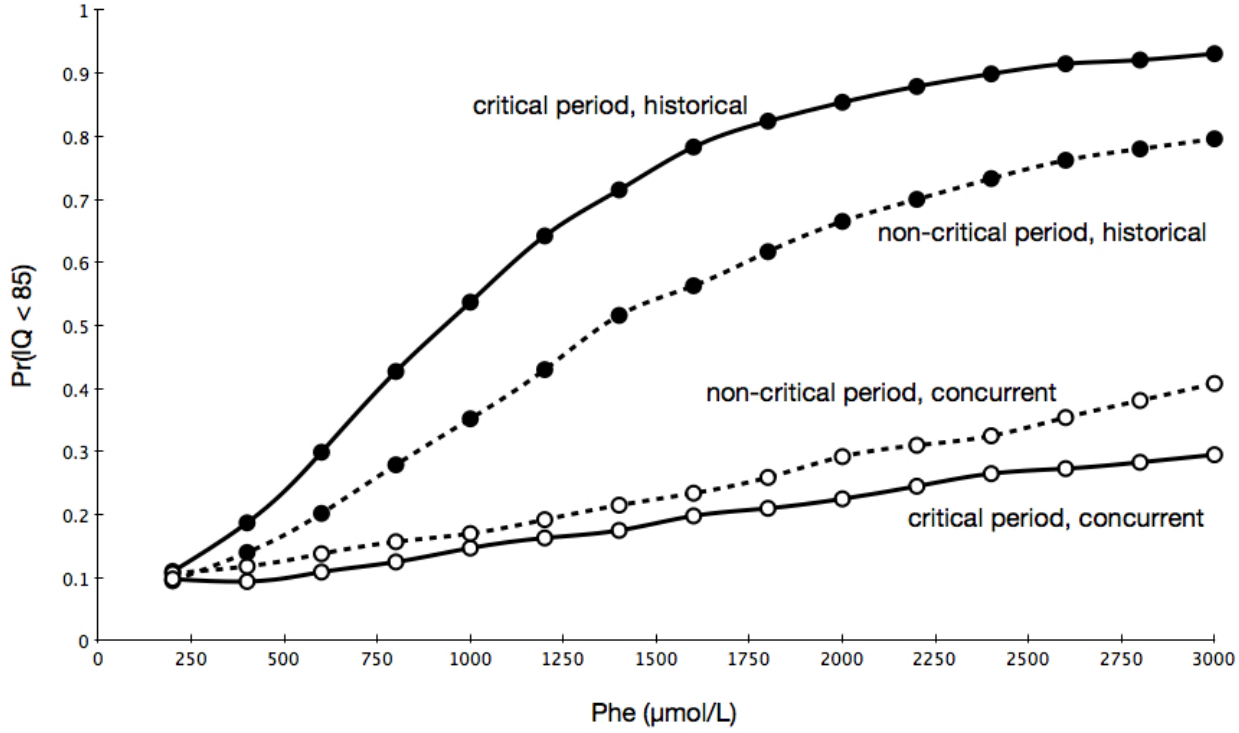
At the highest blood Phe level (3000 μmol/L), the probability of low IQ is substantially different across groups. When both are measured prior to age 6, the probability of low IQ is only 30 percent. This may be because the effects on IQ are not yet observable or because IQ measurements in this young age group are not stable. This also may reflect the fact children are more likely to be in compliance with diet when their diet is substantially controlled by the adults in their lives. Thus, of greater clinical importance is the historical effect of Phe on IQ over the longer term, as observed in Groups 1 and 2, in which earlier blood Phe measures of 3000 μmol/L are associated with approximately 80 and 90 percent probability, respectively, of low IQ measured later. However, even in Group 3, in which both measures are taken concurrently and after the critical period (i.e., in older children, adolescents and adults), very high Phe continues to be associated with low IQ, suggesting a continued effect into adulthood.

In summary, the observed influence of varying blood Phe on the probability of having an IQ <85 depends strongly on when Phe is measured relative to when IQ is tested, and whether or not the Phe measurement takes place in the critical period (before 6 years of age) (Figure 3).

Note that in Figure 3 the two lines depicting historical measures of blood Phe (top two lines) both demonstrate increasing probability of low IQ at higher blood Phe levels, regardless of whether IQ was measured during childhood (top line) or beyond (second line). The effect in early childhood is consistently stronger. Nonetheless, effects of Phe on IQ continue beyond early childhood. Therefore, the best measure of Phe for assessing the potential impact on IQ is likely to be a historical measure of dietary control that is taken at least one year prior to the IQ test. The probability of having an IQ <85 does not continue to increase considerably above a blood Phe level of 2,000 μmol/L.

The two lower lines in the figure describe the observed relationship of blood Phe and IQ when they are measured concurrently. The lack of strong association in measurements taken concurrently during the critical period may suggest that effects are unlikely to be observed in this period, either because the IQ test is not stable for young children (under 5 years of age), or because the adverse effects take time to manifest. From a clinical perspective, this provides a basis for being cautious in interpreting measures of cognitive outcomes as they relate to Phe in early childhood.

Figure 3. Probability of IQ <85 at varying blood Phe levels and Phe measurement times



IQ = intelligence quotient; Phe = phenylalanine; Pr = probability

Phe Levels and Impairments in Executive Function in Individuals With PKU

Key Points

- Too few studies of common outcomes are available to synthesize the relationship of specific Phe levels and executive function measures.
- Among individual studies, data are inconsistent in terms of the direction and degree of association between specific Phe levels and measures of planning ability, inhibitory control and attention.

Overview of the Literature

Nineteen unique studies, reported in 26 papers,[67, 68, 70, 72, 75-78, 82-99] provided data on blood Phe levels and on measures of executive function. We summarize data from these studies in Appendix H. Of the 19 studies providing Phe and executive function data, only three tests of executive function appeared in at least three studies, suggesting that we could potentially provide some synthesis on these nine studies (Table 8). The nine studies presented here include three using the Tower of London test to assess planning ability,[61, 78, 84, 85] three studies using a Flanker test for inhibitory control,[86-88, 90, 97] and three studies using the Color Word Interference Test as a measure of inhibitory control and attention.[75-77, 91-93] After reviewing these as possible candidates for meta-analysis, clinical and statistical experts determined that a meta-analysis would not be appropriate for any component of executive function.

Overall, while blood Phe levels correlate with various assessments of executive function in some papers, the degree to which they are correlated, and the correlation on individual measures, are not conclusive. For example, in the three studies of planning skills, one study found no correlation between higher blood Phe and improved planning skills,[61] one found a significant negative correlation,[78]and one did not measure the association.[84, 85] Two out of three studies of blood Phe and inhibitory control found no association. In none of these studies can a specific Phe threshold as a target be identified to answer the Key Question. Further, these studies cannot be meaningfully aggregated since the measures of executive function relevant for individuals with PKU have not yet been established (see Future Research section also).

Table 8. Summary of studies addressing measures of executive function and Phe levels

Domain / Test	Test Measures	Key Outcomes
Planning / Tower of London, Tower of Hanoi		
Anderson et al., 2004[84, 85]	• Number of mistakes over 12 trials used to assess planning ability	• 33 classic PKU participants, ages 7 to 18 years, mean age=11.18 ± 3.4. Mean IQ=90.97 ± 8.6 • Mean Tower of London score=7.72 (SE 0.7) • Impairments in executive function related to severity of white matter abnormalities in individuals with PKU • Negative correlation between composite measure of executive function and Phe
Azadi et al., 2009[61]	• Average number of moves to complete each set • Planning time (s) • Subsequent time to execute plan	• 10 early treated individuals with PKU, ages 6 to 20 years (mean=13.3), mean IQ=108.40 ± 12.44 • Average number of moves to complete 2 to 5 move problems ranged from 2.3 to 10.47. Mean planning and execution times ranged from 7.14 to 71.68 (unit of measurement not stated) • No significant correlations observed between Phe level and Tower of London measures
Welsh et al., 1990[78]	• Number of trials to complete task correctly using fewest moves possible	• 11 early treated individuals, mean age=4.64, IQ ranging from 82 to 120 • Mean Tower of Hanoi score=7.46 ± 7.74 • Significant correlations between composite measure of executive function and concurrent and mean lifetime Phe levels (-.54 and -.62 respectively, $p<0.05$)
Inhibitory Control / Flanker-Eriksen/Schultz		
Channon et al., 2004[86-88]	• Accuracy of performance • Speed of performance	• 25 early treated individuals (ages 18-38 years) on unrestricted diet since adolescence (mean IQ=101.48 ± 14.60) and 25 individuals (ages 18-38 years) continuing restricted diet (mean IQ=107.04 ± 12.01) • Percentage accuracy on compatible trials for on diet group=99.35, % on incompatible trials=97.65. Speed per item on compatible trials=0.45 and 0.47 on incompatible trials • No significant correlations for either group between cognitive measures and most Phe levels (concurrent, recent, and lifelong measures)

Table 8. Summary of studies addressing measures of executive function and Phe levels (continued)

Domain / Test	Test Measures	Key Outcomes
Inhibitory Control / Flanker-Eriksen/Schultz		
Christ et al., 2006[90]	• Reaction time • Accuracy error rate	• 26 early treated children, mean age 11.2 ± 3.1, mean IQ=102.2 ± 9.9 • Median reaction time (milliseconds) in neutral condition=766 ± 212 (error rate=5.8 ± 5.7), in inhibitory condition=777 ± 219 (error rate=7.1 ± 8.9), and in facilitatory condition=736 ± 195 (error rate=4.6 ± 6.1) • No significant correlations
Stemerdink et al., 1995[97]	• Reaction time (speed) • % error rate	• 33 individuals with early treated PKU between 7 and 16 years of age, mean IQ=100.8 ± 14.8 • Mean response times and error percentages greater in incongruent response condition compared with congruent and neutral conditions • Manipulation of target size increased mean response time and error percentage in incongruent and neutral response conditions but not in congruent condition • Reaction time (r=0.3)and error percentage (-0.004) and overall mean Phe level significantly correlated (p<0.05)
Attention / Color Word Interference Test		
Gassio et al., 2005[91]	• Stroop word reading • Color naming • Color word interference	• 37 early treated individuals with PKU, mean age 9.9 years, all adhering to dietary treatment • Mean word reading score=45 ± 8.0, mean color naming=40 ± 8.9, mean color word interference=42 ± 9.8 • Significant correlations between Stroop scores and Phe levels
Weglage et al., 1995[75-77]	• Stroop word reading • Color naming • Color word interference (time) • Mistakes (number)	• 20 early treated adolescents with PKU, mean IQ at 14 years=107.4 ± 10.2 • Mean time in seconds on word reading test=48.2 ± 11.1, on color naming test=83.5 ± 16.7, interference task=153.7 ± 45.9, and number of mistakes=15.4 ± 14.2 at 11 years of age • Mean time in seconds on reading of color words=41.4 ± 10.3, on color naming=67.4 ± 11.2, on interference task=110.6 ± 24.2, and number of mistakes=11.6 ± 11.7 at 14 years of age • Significant correlations between color word interference test and Phe at 11 years (r=0.39, p<0.05) and mistakes at 11 years (r=0.38, p<0.05)
Antschel et al., 2003[92, 93]	• Stroop word reading	• 46 children with PKU, mean age=10.9 ± 2.1 (mean IQ=104.2 ± 10.7) and 15 born to mothers with PKU, mean age=11.2 ± 2.4 (mean IQ=99.0 ± 15.5) • Mean T score=50.7 ± 8.3 for PKU group and 37.8 ± 10.7 for maternal PKU group • Significant correlation between Phe level and word reading task (r= -0.498, p<0.001)

IQ = intelligence quotient; Phe = phenylalanine; PKU = phenylketonuria

Phe Levels and Maternal PKU and Maternal PKU Syndrome

Key Points

- Data predominantly from one longitudinal study provide evidence for poor cognitive outcomes in the offspring of women who have high blood Phe during pregnancy.
- Several analyses of the data, including separate analyses for U.S. and German data, suggest that the time it takes for women to achieve dietary control is particularly influential on offspring outcomes, with relatively better outcomes associated with achieving control by 10 weeks postconception, but all studies recommending control as early as possible. Children of mothers with well-controlled PKU prior to pregnancy had the best outcomes.
- One complex analysis using structural equation modeling and splines was able to demonstrate that a threshold of 360 μmol/L of blood Phe is appropriate to prevent poor cognitive outcomes in offspring, and that a linear relationship exists after that threshold.

Overview of the Literature

We identified 20 papers from three unique study populations that provided some data on maternal blood Phe and cognitive outcomes in infants or children.[19, 21, 24, 31-33, 92, 93, 100-111] Most of the papers in this literature come from the international Maternal PKU (MPKU) Collaborative Study, which prospectively followed women with PKU who were pregnant or planning pregnancy and their offspring from 1984 to 2002 and provides the most complete data currently available on women with PKU and their offspring. The data reported were not suitable for meta-analysis; however, we summarize key findings below and present tables outlining cognitive outcome data in Appendix I.

Detailed Analysis

MPKU Collaborative Study

The MPKU Collaborative Study was initiated in 1984 to study the implications of maternal PKU, and specifically to assess outcomes when blood Phe is controlled in pregnant women. Initially, women were advised to maintain blood Phe levels of <600 μmol/L, but the target was changed to Phe <360 μmol/L. The study was conducted originally in the United States and Canada only. Germany, Austria, and Switzerland were added in 1992, and the study also expanded to include women with untreated mild hyperphenylalaninemia (defined as blood Phe concentrations between 240 and 599 μmol/L[21]), with hyperphenylalaninemia treated at different stages of pregnancy, and non-hyperphenylalaninemia controls. The study enrolled women at any time during their pregnancy and followed many of the women's offspring to test their cognition at 1, 2, 4, and 7 to 9 years. The entire study sample consisted of 572 pregnancies, 412 live births, with 416 offspring.[33]

Timing of maternal metabolic control, defined as the number of weeks gestation before plasma Phe levels remained consistently lower than 605 μmol/L, was associated with child cognitive scores at 4 years of age, including on the children's McCarthy General Cognitive Index and subscale scores. At four years of age, children whose mothers had not achieved dietary control by 20 weeks into their pregnancies had a mean General Cognitive Index score 2 standard deviations below the mean. Overall, children of mothers who were treated prior to pregnancy had the best outcomes, with a mean General Cognitive Index score of 99, compared with 107 in non-

hyperphenylalaninemia controls, and 59 in those who had not achieved dietary control by 20 weeks.[101]

At 7 years of age, 228 children were evaluated using the Wechsler Intelligence Scale for Children-Revised, Peabody Individual Achievement Test-Revised, Test of Language Development-2, Visual Motor Integration Test, Stroop Color Word Test, Home Observation for Measurement of the Environment, and Child Behavior Checklist 4 to 18.[100] At this point, 18 percent of the children were considered to have intellectual disability, 18 percent had borderline intellectual disability, and 64 percent were considered average in terms of intellectual ability. As at the younger ages, a decrease in children's scores for cognition, language, behavior, achievement, and visual motor skills was associated with time to maternal metabolic control.[100] A separate analysis of the German data found similar results, with consistently negative correlations between start of dietary control and Bayley Mental Developmental Index (r=-0.43) and Psychomotor Development Index (r=-0.60).[105]

The 48 women who had mild hyperphenylalaninemia had 58 pregnancies and an average blood Phe exposure during pregnancy of 270 ± 84 µmol/L in untreated women and 269 ± 136 µmol/L in treated women.[19] In the group of untreated women, 40 offspring received IQ testing; their scores were slightly below but not significantly different from mean IQ scores for controls (102 ± 15 vs. 109 ± 21).

Because they had access to the largest available dataset on maternal PKU, investigators were able to model the form of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood. They conducted a spline analysis accounting for potentially strong confounders including maternal IQ, education and socioeconomic status as maternal characteristics differed in the groups of women with and without PKU.[33] The use of a spline analysis allowed for the first time confirmation that the relationship between maternal Phe and offspring cognitive outcomes is not linear, and that a blood Phe threshold of 360 µmol/L is the level at which cognition begins to be impaired. Importantly, while other factors, including maternal characteristics and infant head circumference, contribute strongly to outcomes at 1 year of age, by age 2, maternal blood Phe strongly overtakes other factors in predicting cognitive impairment.

Additional Maternal PKU Studies

Two additional studies[24, 32] provide support for a relationship between maternal blood Phe and offspring IQ, but none adds additional information beyond that found in the high quality Maternal PKU Collaborative.

Key Question 1b. What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?

Too few studies provided data by age group to answer this question without combining the data quantitatively. Therefore, we explored the use of an age effect in the meta-analysis of the relationship between blood Phe and IQ. Any influence of age was adequately represented by whether the Phe measurements were historical or concurrent and whether they were taken in the critical period.

Key Question 2. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13-21 years old with PKU
- Adults >21 years old with PKU

Key Points

- Two multisite RCTs and three uncontrolled open-label trials were eligible for inclusion. Studies ranged in quality from fair to good. Four of the five trials include overlapping populations.
- Studies included between 29 and 90 children and adults who were responsive to BH4 in initial loading trials that included more than 500 individuals to assess initial response.
- Between 19 and 62 percent of participants screened for inclusion in the trials demonstrated initial response to BH4 and were therefore eligible for the efficacy studies.
- In five trials (RCTs and open label), blood Phe levels were reduced by at least 30 percent (the level used in studies submitted to the U.S. Food and Drug Administration (FDA) to assess responsiveness) in almost half of treated participants (42 percent to 49 percent) at dosages of 10 to 20 mg/kg/day and for up to 22 weeks of observation, compared with small reductions in Phe in the placebo groups (9 percent).
- A subset of participants in the RCTs were ultimately followed in an uncontrolled open label trial with 2.6 years of data; most participants had achieved Phe levels in the recommended treatment range by the end of the analysis period, and harms were mild and rare.
- The strength of evidence (confidence that the current effect estimate will not change with future research) for the effects of BH4 on reducing blood Phe levels to clinically acceptable levels among BH4 responders in the short term (12 weeks or less) is moderate based on few studies.
- The strength of evidence for the effect of Phe on IQ is moderate. Therefore, the strength of evidence for the indirect relationship of BH4 on IQ is low, based on a lack of direct measurement.
- Harms were noted to be rare and mild, and the strength of evidence for this observation is moderate.
- The strength of the evidence is insufficient for the direct effect of BH4 on improving all other outcomes (Phe tolerance and the ability to liberalize the diet, Phe variability, quality of life, and cognitive and nutritional outcomes).

Overview of the Literature

Ten studies evaluated the effects of BH4 in participants with PKU (Tables 9–10).[112-121] Although study populations overlap, the studies were conducted as separate studies and so are presented as such in our analysis. We note, however, those situations in which studies were

conducted using the same populations. Four of the studies described in this section are linked by common participants as follows. Two are multisite placebo-controlled randomized trials that contributed to FDA approval of BH4.[113, 115] One of the RCTs[113] had initially screened 490 individuals to assess initial responsiveness to the drug prior to inclusion in the efficacy study. Of these individuals, 96 demonstrated an initial reduction of ≥ 30 percent and were thus included in the efficacy trial reviewed here. This comparative efficacy trial was followed by an uncontrolled open label trial[114] that included 80 of the 87 completers from the comparative trial. Of the 79 completers in that extension study, 71 then were enrolled in a second open-label extension study,[112] as were 40 completers from the other RCT.[115]

One additional uncontrolled open label trial was conducted separately from the family of studies described above[116]as were one prospective cohort,[121] two retrospective case series,[117, 119] and two prospective case series.[118, 120] We did not conduct a meta-analysis of the studies examining BH4 because the most common outcome (blood Phe level) was measured at different time points in only two RCTs and the populations were substantially heterogeneous. Furthermore, the individual RCTs had adequate power to demonstrate the effect that each noted, so combining the data would have added little to the results.

No individual study included more than 80 participants in the treatment arm, and the total number of individuals in all studies was 284, after accounting for duplication in participants across studies. There were 135 total participants in the RCTs. In the three studies explicitly providing a classification of disease, 38 individuals had classic PKU and 51 had mild, moderate, or variant PKU.[116, 118, 119] All of the studies were performed in the United States, Canada, Australia, and Europe. Participants ranged in age from 3 to 58 years in the five trials and from 10 days to 34 years in the four case series. The cohort study analyzed blood samples collected from birth through roughly age 8 from individuals responsive and non-responsive to BH4.[121] Most participants had demonstrated responsiveness to BH4 in a loading study; however, the approach to assessing responsiveness varied by study (Table 9) and the base populations tested for initial responsiveness were not consistent.

Initial responsiveness to the drug at screening varied by blood Phe level prior to inclusion in the efficacy studies. For example, individuals screened for participation in the Levy study and Lee follow-on trial had a baseline blood Phe level of at least 450 µmol/L, and were nonadherent to diet. Although those screened had an overall response rate of about 20 percent, more than half (54 percent) of individuals with blood Phe <600 µmol/L had a positive response, compared with 10 percent of those with blood Phe >1200 µmol/L.[119]

Table 9. Variation in approach to assessing responsiveness to BH4

Study	Definition of BH4 Responsiveness	% Responders
Humphrey 2011[121]	Reduction in blood Phe of >30% 15 hours after BH4 loading at 20mg/kg/day	NR[a]
Trefz 2010[120]	Reduction in blood Phe of ≥30% after either a 20 mg/kg over 24 hour loading test or 20 mg/kg/day over 8 days	94
Levy 2007[113] Lee 2008[114] Burton 2011[112]	Reduction in blood Phe of ≥30% after 8 days of BH4 at 10mg/kg/day	19.8[b]
Trefz 2009[115]	Reduction in blood Phe of ≥30% after 8 days of BH4 at 20 mg/kg/day plus a blood Phe level ≤300 µmol/L on Day 8	56

Table 9. Variation in approach to assessing responsiveness to BH4 (continued)

Study	Definition of BH4 Responsiveness	% Responders
Vernon 2010[116]	Reduction of blood Phe level of at least 30% or reduction to <360 µmol/L after Day 7 on BH4 at 10/mg/kg/day or at 20 mg/kg/day for a total of 30 days	62 (classic PKU=27, variant PKU=100)
Lambruschini 2005[118]	Reduction in blood Phe of ≥30% after 24 hours of BH4 at 20 mg/kg/day	19.2
Burlina 2009[117]	Reduction in blood Phe of ≥30% after 24 hours of BH4 at 20 mg/kg/day, and among those with Phe >450µmol/ L	76,63[c]
Burton 2010[119]	Reduction in blood Phe of ≥25% after 2 weeks of BH4 at 20 mg/kg/day among those with good control of Phe, an increase of Phe tolerance ≥200 mg/day by 4 weeks of Rx	NR

NR = not reported; Phe = phenylalanine; PKU = phenylketonuria
[a]Responsiveness described in Muntau et al., 2002.[122]
[b]Data on responsiveness for this study provided in Burton et al., 2007.[123]
[c]All participants had previously demonstrated responsiveness.

BH4 was studied in doses ranging from 5 mg/kg/day to 20 mg/kg/day (Table 10). Some participants in multiple studies (including the extension studies) were exposed to the drug for up to 2.6 years, although the follow-up period for the two RCTs was 10 weeks. One case series followed participants up to 7 years,[118] although the average follow-up was 3.5 years. The mean treatment duration among participants in another case series[120] was 4 years and 8 months (range= 24 to 110 months). The degree to which participants were adherent to a restricted diet varied, and one study examined a differential effect in those who maintained a restricted diet versus those who did not.[116]

One RCT and its follow-on uncontrolled open label trial included participants with PKU who were at least 8 years old with a mean age of 20 years, were not on a restricted diet, and had baseline blood Phe levels >450 µmol/L.[113, 114] The second RCT in the "family" of studies examined the effect of 20 mg/kg/day of BH4 for 10 weeks in children ages 4 to 12 who were on a Phe-restricted diet with baseline blood Phe levels <480 µmol/L.[115] The unassociated uncontrolled open label trial included both adolescents and adults both on and off a restricted diet to compare relative effectiveness across these groups.

All randomized trials and three case series evaluated the short-term outcome of reduction in blood Phe levels. Two trials and three case series reported on Phe tolerance,[115-118, 120] and one cohort study[121] and one case series reported on Phe variability.[119] Only one case series[118] assessed longer term outcomes, including cognition and nutritional status. That study used cognitive outcome measures including the Brunet-Lezine test, the Kaufman Assessment Battery, and the Wechsler Intelligence Scale for Children-Revised.[118] Nutritional outcomes included brachial fat and muscular area, micronutrient levels and daily nutrient intake. No study evaluated quality of life. BioMarin, the pharmaceutical company that holds the patent for sapropterin, sponsored five of the ten studies, including two of the RCTs.

Table 10. Overview of studies addressing BH4

Author, Year Design Quality	Dosage, mg/kg/ Day	N	Age, Years Mean and/or Range	Biochemical Characteristics (Mean baseline Phe level, µmol/L)	Outcomes
Trefz 2009[115] RCT Quality: Fair	20	46	4–12	Treatment: 314 ± 107 Placebo: 303 ± 74	• Phe level • Phe tolerance
Levy 2007[113] RCT Quality: Good	10	89	20.4 (8–49)	Treatment: 842.7 ± 299.6 Placebo: 888.3 ± 323.1	• Phe level
Burton 2011[112] Uncontrolled open label[a] Quality: Fair	5-20	90	4-50	613.1 ± 328.5	• Phe level
Vernon 2010[116] Uncontrolled open label Quality: Good	10, 20	36	3–58	Restricted diet: 587.0 Unrestricted diet:1372.6	• Phe level • Phe tolerance
Lee 2008[114] Uncontrolled open label[b] Quality: Good	5, 10, 20	80	20.4 (8–49)	844 ± 398	• Phe level
Humphrey 2011[121] Prospective Cohort Quality: Poor	NR	34	Newborn – roughly 8 years	NR	• Tyrosine level • Phe/tyrosine ratio • Variability of Phe and tyrosine levels
Trefz 2010[120] Case series Quality: Poor	5-26	16	10 days -34 years	321 + 236 (responders)	• Phe level • Phe tolerance
Burton 2010[119] Case series Quality: Poor	20	37	1.5–32 months	400.2	• Phe level • Phe variability
Burlina 2009[117] Case series Quality: Poor	10, two times/day	12	2–16	433-1215 (range)	• Phe tolerance
Lambruschini 2005[118] Case series Quality: Poor	5, three times/day	14	2.4 months–12 years	382 ± 229	• Phe level • Phe tolerance • Liberalization of diet • IQ, DQ • Micronutrient/ plasma levels • Urine biopterin • Nutritional status

DQ = developmental quotient; IQ = intelligence quotient; N = number; Phe = phenylalanine[a]Includes participants from Lee 2008, Levy 2007, and Trefz 2009.
[b]Open label continuation of Levy 2007; therefore participants are not unique.

Effects of BH4 on Blood Phe Levels and Phe Tolerance

Phe levels were reduced by at least 30 percent in up to half of treated participants (32 to 50 percent) at dosages of 5 to 20 mg/kg/day and for up to 22 weeks of observation in comparative studies (Table 11). In the one RCT that compared the effect of placebo on likelihood of a 30 percent reduction in blood Phe, only 9 percent of those on placebo achieved this effect, compared with 44 percent of the treated group after 6 weeks.[113] Data from the uncontrolled open label trial[114] following this RCT[113] suggested a sustained response for up to 22 weeks' duration, with 46 percent achieving a 30 percent reduction in blood Phe levels with most participants receiving 10 and 20 mg/kg/day doses compared with 5 mg/kg/day.

Similarly positive effects were reported at a dosage of 20 mg/kg/day in children on Phe-restricted diets. Reduction in blood Phe levels sampled at week 3 (before supplemental medical foods began) was greater among those receiving BH4.[115] In the other nonrandomized clinical trial,[116] BH4 (7 to 20 mg/kg/day) was associated with a reduction of blood Phe levels among participants both on and off Phe-restricted diets. Overall, participants' responses to different dosages of BH4 varied, with individualized dose adjustments needed according to target plasma Phe and dietary intake. Dosages of 10 to 20 mg/kg/day were most effective across the studies. Response also varied by different baseline Phe levels, with those with the highest baseline levels having lower response rates. As noted above, some participants from the RCTs and extension study have now been followed for up to three years; almost all participants for whom data were available achieved Phe levels within clinically recommended ranges, although specific Phe levels are not reported.[112]

Studies of Phe tolerance (total Phe intake an individual can tolerate without raising blood Phe to an unacceptable level) all reported improvements over time.[115-118, 120] Data from the one RCT[115] measuring this outcome indicate that participants in the treatment group were able to increase the supplementary Phe added in controlled amounts to a patient's usual dietary intake from 0 mg/kg at baseline to 20.9 mg/kg/day, while maintaining blood Phe levels at <360 μmol/L, compared with an increase of 2.9 mg/kg/day in the placebo group. However, response varied substantially within the treatment group, with 33 percent tolerating an increase of between 31 and 50 mg/kg/day in medical food form, but the rest of the participants tolerating lower levels of supplementary Phe. Similarly, total Phe intake (medical food plus diet) in the treatment group doubled from baseline to a mean of 43.8 mg/kg/day, response varied substantially within the treatment group.[115] In the one open label trial that assessed changes in tolerance,[116] participants on a Phe-restricted diet taking 10 to 20 mg/kg of BH4 per day increased their Phe tolerance by an average of 21 to 41 mg/kg/day. Participants tolerated a wide range of dietary Phe, ranging from increases of 20 to 22 mg/kg/day up to a full non-protein restricted diet. For some individuals, increasing the dose of BH4 to 20 mg/kg/day allowed further liberalization of the diet. Trials did not evaluate the impact of increasing natural protein sources on micronutrient levels, nutritional status, or quality of life.

Three case series[117, 118, 120] also reported improved Phe tolerance. Among 11 children with mild or moderate PKU, participants reduced or discontinued Phe-free medical foods with 12 months of BH4 treatment. These reductions in special formula and replacement with unrestricted diet did not result in deficiencies of essential nutrients.

Although the mean blood Phe level is an important predictor of IQ, Phe variability may also be an important determinant. In one small retrospective case series (N=37), blood Phe variability as well as blood Phe levels decreased on BH4 20 mg/kg/day.[119]

Table 11. Summary of effects of BH4 on Phe in comparative studies

Study	N	Dose mg/kg/d	Week	Effect on Phe				
				Change in Blood Phe (µmol/L)	Mean Difference in Phe Change Between Groups ± SD	% Achieving ≥30% Reduction	% Achieving ≥50% Reduction	Increase in Phe Tolerance
Humphrey 2011[121]	9[r]	NR	Up to age 8	NR	NR	NR	NR	NR
	25[nr]	NR	Up to age 8	NR	NR	NR	NR	NR
Levy 2007[113]	42	10	6	-235.9 ± 257	-245 ± 52.5	44%	32%	NR
	47	Placebo	6	2.9 ± 239.5		9%	2%	NR
Trefz 2009[115]	33	20	3	-148.5 ± 134.2	-135.2 ± 26.9 (SE)	NR	NR	NR
	12	Placebo	3	-96.6 ± 243.6		NR	NR	NR
	33	20	10	NR		NR	NR	20.9 mg/kg/day (medical food)
	12	Placebo	10	NR		NR	NR	2.9 mg/kg/day (medical food)
Burton 2011[112]	90	5-20	2.6 years	NR[a]	NR	NR	NR	NR
Lee 2008[114]	80	5-20	22	NR	NA	NR	NR	NR
	80	10	22	NR		NR	NR	NR
	80	5-20	22	-190.5 ± 355.7		46% overall 50% for 5 mg dose 49% for 10 mg dose 42% for 20 mg dose		
Vernon 2010[116]	14[r]*	10	5	-258.8	NA	NR	NR	41 mg/kg/day (dietary)
	4[nr]^	10	5	-495.3		NR	NR	NR
	3[r]*	20	5	-85		NR	NR	NR
	8[nr]^	20	5	-69		NR	NR	NR

mg/kg/d=milligrams/kilogram/day; nr =nonresponder; NR=not reported; Phe-phenylalanine; r=responder; SD=standard deviation; SE=standard error

[a]In 50 percent of participants with baseline Phe above treatment guidelines, Phe was reduced to within target levels (level not specified).

*Restricted diet

^Unrestricted diet

Effect of BH4 on Longer Term Effectiveness

After nearly 3 years of following participants in the longer term extension study of BH4, most of the 90 study completers (of 111 enrolled) were reported to have reached clinical targets in Phe levels.[112] Only one small prospective case series (N=11) reported on IQ and nutritional outcomes following one year of 5 mg/kg/day BH4 treatment.[118] After one year of treatment, 11 participants with mild to moderate PKU discontinued use of a medical food and normalized their diet. IQ scores after 12 months on BH4 were maintained, or developmental quotients were within normal limits. Treatment was not adversely associated with anthropometric or nutritional status indicators, and all participants had normal levels of micronutrients. In another case series with 16 participants,[120] treatment duration ranged from 24 to 110 months (mean=56 months), 14 individuals responded to BH4 treatment (blood Phe reduction of ≥30 percent in loading test). Among these responders, the mean blood Phe decrease was 54.6 percent, and 13 were able to maintain Phe control while increasing Phe intake or eliminating dietary restrictions. The study noted that psychomotor development was in the normal range among children between 5 and 6 years of age.

Detailed Description of Individual Studies

Given the small number of studies available for review, we have provided detailed descriptions of each study below and summary information for comparative studies and open label trials in Table 12.

Table 12. Comparative studies and open label trials of BH4 for the treatment of PKU

Author, Year, Dosage Treated Time Total N	Age, Mean (Years) ± SD	Key Outcomes
Randomized Controlled Trials		
Trefz 2009[115] 20 mg/kg/day once daily compared with placebo 10 weeks N=46	**G1:** 7.7 ± 2.8 **G2:** 7.1 ± 2.0	• Average blood Phe was lowered in the treatment group by 148.5 ± 134.2 µmol/L, compared with a decrease of 96.6 ± 243.6 µmol/L in the control group (p = 0.20) • Blood Phe levels in the treated group were lower than in the placebo group by 135.2 µmol/L at Week 3 (p<0.001) • Phe tolerance was increased to 20.9 ± 15.4 mg/kg/day (95% CI: 15.4 to 26.4) in the treated group vs. 2.9 mg/day in the controls
Levy 2007[113] 10 mg/kg/day once daily compared with placebo 6 weeks N=89	**G1:** 21.5 ± 9.5 **G2:** 19.5 ± 9.8	• Average blood Phe lowered in the treatment group by 235.9 ± 257 µmol/L vs. increase of 2.9 ± 239.5 µmol/L in controls (p <0.0001) • Estimated difference between groups in mean change in blood Phe was 245 ± 52.5, with a 95% CI of -350 to – 141 • 44% of the treated group had at least a 30% Phe reduction Phe vs. 9% of controls • 32% of the treated group had at least a 50% Phe reduction vs. 2 percent of controls

Table 12. Comparative studies and open label trials of BH4 for the treatment of PKU (continued)

Author, Year, Dosage Treated Time Total N	Age, Mean (Years) ± SD	Key Outcomes
Uncontrolled Open Label Trials		
Burton 2011[112] (includes participants from Levy 2007, Lee 2008, Trefz 2009) 5 – 20 mg/kg/day once daily 2.6 years N=90	**G1:** 16.4 ± 10.2	• Blood Phe concentrations were within target range for most subjects • In 50% of participants with baseline blood Phe levels above treatment guidelines, levels were reduced to "within range" (not defined) during the study • Transitory low blood Phe levels (≤26 µmol/L) were observed in 4.5% of subjects while 24% had blood Phe levels ≤ 120 µmol/L that resolved without any intervention
Lee 2008[114] (extension of Levy 2007) Week 1-6 (Phase 1): forced dose-titration (5, 20, and 10 mg/kg/day for 2 weeks each) Week 7-10 (Phase 2): 10 mg/kg/day Week 11-22 (Phase 3): 5, 10, or 20 mg/kg/day based on Phe concentration at week 2 and 6 22 weeks N=80	20.4 ± 9.6 (range 8-49)	• In Phase 1, all 3 doses (5, 10, 20 mg/kg/day) were associated with reduction in plasma Phe (p≤.01) • In Phase 2, 37 participants (46%) showed a decrease in plasma Phe of at least 30%, compared with Week 0 • In Phase 3, participants had a mean change in Phe from Week 0 of -190.5 ± 355.7 µmol/L • At Week 22, at least 30% reduction in Phe was seen by 46% of participants taking the 5 mg/kg/day dose, 50% of participants taking the 10 mg/kg/day does and 49% of participants taking the 20 mg/kg/day dose
Vernon 2010[116] **G1:** Completed trial, 29 **G1a:** Responders, 18 **G1b:** Nonresponders, 11 Days 1–7: 10 mg/kg/day Days 8–37: 20 mg/kg/day for nonresponders 37 days N=39	23.4 (range 3 – 58)	• Nonresponders had a change in blood Phe level of 1422.3 to 1332.6 µmol/L • Responders on a restricted diet had a reduction in blood Phe level from 484.9 to 226.1 µmol/L (p<0.001) • Responders not on a restricted diet had a decrease in blood Phe level from 1049 to 553.7 µmol/L (p<0.035) • Nonresponders on a restricted diet had a change in Phe level from 1063.7 to 978.7µmol/L • Nonresponders not on a restricted diet had a mean change in blood Phe level from 1534.4 to 1465.4 µmol/L • BH4 responders: 18 (62%) • Responders on a restricted diet achieved a Phe tolerance of 41 mg/kg/day compared with a starting tolerance of 21 mg/kg/day • Two individuals were able to liberalize from a restricted to an unrestricted diet

Table 12. Comparative studies and open label trials of BH4 for the treatment of PKU (continued)

Author, Year, Dosage Treated Time Total N	Age, Mean (Years) ± SD	Key Outcomes
Prospective Cohort Studies		
Humphrey 2011 [121] **G1:** Responders **G2:** Nonresponders Dosage NR 8 years N=34	Newborn to < 10 years	• Variation in Blood Phe greater in individuals nonresponsive to BH4 (Responsive to BH4: median 338µmol/L, 95% CI: 329–346, mean: 358 µmol/L, 95% CI 350– 366. Nonresponsive to BH4: median 338 µmol/L, 95% CI 332–344, mean: 370 µmol/L, 95%CI 364–376) • Phe < 400 µmol/L: Responsive to BH4: 66.7%, Nonresponsive to BH4: 62% • Phe > 600 µmol/L: Responsive to BH4: 7.5%, Nonresponsive to BH4: 12.7% • At Phe >600 µmol/L, median and mean tyrosine levels were higher among BH4-responsive individuals than those not responsive to BH4 • Variation in Phe/ Tyr ratio greater in individuals nonresponsive to BH4 (mean= 6.12, 95%CI 5.9-6.3) vs. mean=5.44 in individuals responsive to BH4 , 95%CI: 5.3-5.6, particularly at Phe > 600 µmol/L)

CI = confidence interval; G = group; Phe = phenylalanine; PKU = phenylketonuria

Clinical Trials

The first RCT[113] evaluating the efficacy of BH4 was carried out in 16 centers in North America and 14 centers in Europe. Between 2005 and 2006, 89 participants with PKU were randomized to receive either 10 mg/kg of BH4 (N=42) or placebo (N=47) once daily for 6 weeks. Eligible participants were responsive to BH4 in a previous phase I screening study, had a blood Phe of 450 µmol/L or more, were 8 years of age and older, and had relaxed or abandoned a strict low phenylalanine diet. The primary outcome was the change in blood Phe from baseline to week 6. Participants' mean age was 21.5 years in the treatment group and 19.5 years in the placebo group. Adherence to treatment was high, with 82 percent of participants taking all doses correctly during the 6 week period.

After 6 weeks of treatment, participants in the BH4 group had a significant decrease in mean blood Phe levels of -235.9 ± 257 µmol/L from baseline (843 µmol/L) compared with a 2.9 ± 239.5 µmol/L increase in mean Phe levels from baseline (888 µmol/L) in the control group ($p<0.0001$). The mean blood Phe decreased in the BH4 group at 1 week and remained at that lower level until the 6 week end point, when the mean Phe level was 607 µmol/L. The estimated difference between treatment and placebo groups in the mean change in blood Phe at 6 weeks compared with baseline was -245 ($p<0.0002$). A significantly higher proportion of participants receiving BH4 (44 percent) had a 30 percent or greater reduction in blood Phe levels compared with controls (9 percent).

The proportion of individuals in the BH4 group who had blood Phe levels under 600 µmol/L increased significantly from 17 percent at baseline to 54 percent at 6 weeks compared with controls (baseline: 19 percent, week 6: 23 percent). Almost all participants (16 of 17) for whom genotyping was performed had at least one mutation known to be associated with residual enzymatic activity. Responsiveness was not consistently linked to specific mutations. Despite enrolling only those participants who had at least a 30 percent reduction in blood Phe while taking BH4 in a one week loading test, not all participants were responsive to BH4 in the trial.

A 22 week uncontrolled open label trial[114] followed this RCT.[113] This was conducted in three parts: the first period was a 6 week forced dose titration phase in which all participants received doses of 5, 20, and 10 mg/kg/day of BH4 consecutively for 2 weeks each. This phase was followed by a dose analysis phase in which all participants received 10 mg/kg/day for 4 weeks followed by a 12 week fixed dose phase in which participants received doses of 5, 10, or 20 mg/kg/day based on their plasma Phe concentrations during the dose titration at weeks 2 and 6. All participants enrolled in the previous RCT were eligible if they had taken at least 80 percent of their scheduled does in the trial and were willing to continue their current diet during the study. The primary endpoint was mean plasma Phe levels at week 22 and mean changes from week 0. Plasma Phe levels at weeks 2, 4, and 6 were used to estimate the effects of dose on plasma Phe levels.

Of 87 participants who completed the previous RCT,[113] 80 were enrolled in the extension trial,[114] of whom 39 had previously received BH4 and 41 placebo. Participants' mean age was 20.4 years. Overall, 60 percent reported taking all doses correctly, 18 percent reported missing at least one dose and no incorrect doses, 9 percent took at least one dose incorrectly but did not miss any doses, and 14 percent took at least one dose incorrectly and missed at least one dose.

During the dose titration phase, individuals receiving 10 or 20 mg/kg/day had significantly greater mean reductions in blood Phe at week 6 compared with week 0 than those receiving 5 mg/kg/day. Additionally, those receiving 20 mg/kg/day had significantly greater reductions from week 6 to week 22 compared with week 0 than those receiving 10 mg/kg/day. By the end of the dose analysis phase with 10 weeks at 10 mg/kg/day, 46 percent of participants had a decrease in plasma Phe of at least 30 percent compared with week 0. During the fixed dose phase, most participants (92 percent) received either 10 (46 percent) or 20 mg/kg/day (46 percent). By week 22, plasma Phe was reduced by 190.5 µmol/L compared with week 0. The mean Phe level at 22 weeks for those on 5, 10, and 20 mg/kg/day was 438 µmol/L, 450 µmol/L, and 896 µmol/L, respectively.

Mean plasma Phe decreased from 844 µmol/L at baseline to 645 µmol/L at week 10 and was maintained at a mean of 652 µmol/L at week 22. At week 22, 46 percent of participants had achieved a 30 percent reduction in plasma Phe concentration compared with week 0. The corresponding reductions for those receiving 5, 10, and 20 mg/kg/day were 50 percent, 49 percent, and 42 percent respectively.

Another RCT[115] of fair quality was carried out in the United States, Germany, Spain, and Poland between 2005 and 2006 and enrolled children with PKU between 4 to 12 years of age who were on a Phe-restricted diet, had maintained blood Phe control (blood Phe level <480 µmol/L) and had an estimated Phe tolerance of ≤1000 mg/d. The objective was to determine the safety and efficacy of BH4 at 20 mg/kg/day for 10 weeks in increasing Phe tolerance while maintaining blood Phe control. Investigators randomized BH4 responders in a 3:1 ratio to receive either 20 mg/kg of BH4 or placebo once daily for 10 weeks. Participants maintained a stable, Phe-restricted diet, monitored by food diaries. Starting at the third week, a medical food was added or removed every 2 weeks based on Phe levels. Children with blood Phe level of ≥1200 µmol/L in 2 consecutive weeks were withdrawn from study drug treatment and received dietary counseling.

The primary endpoint was daily Phe tolerance at week 10 compared with week 0. Phe tolerance was defined as the cumulative increase or decrease in medical food at the last visit for which blood Phe level was ≤360 µmol/L. Secondary endpoints were the difference in blood Phe levels in the BH4 group between week 0 (before dosing) and week 3 (before Phe

supplementation), and the comparison of Phe tolerance between treatment and placebo groups at week 10. Thirty-three children were randomized to 20 mg/kg/day of BH4 for 10 weeks, and 12 children received a placebo. Baseline characteristics, including blood Phe levels, were similar between groups.

After 10 weeks of treatment, the total mean ± SD of medical food tolerated by participants on BH4 increased significantly from 0 mg/kg/day at baseline to 20.9 ± 15.4 mg/kg/day. In contrast, the placebo group tolerated only an increase of 2.9 mg/kg/day of medical food. The adjusted mean difference between the groups in Phe tolerance was 17.7 ± 4.5 mg/kg/day($p<0.001$). Total Phe intake (dietary Phe intake plus total medical food) also increased significantly from baseline in the BH4 group, approximately doubling to 43.8 mg/kg/day at 10 weeks. The placebo group had a slight increase in total Phe intake from 16.3 mg/kg/day at baseline to 23.5 ± 12.6 mg/kg/day at 10 weeks.

The BH4 group tolerated a range of medical food supplementation over the 10 weeks: 36 percent tolerated an increase of 10 mg/kg/day or less, 30 percent tolerated an 11 to 30 mg/kg/day increase and 33 percent tolerated an increase of 31 to 50 mg/kg/day. No one in the placebo group tolerated an increase of more than 10 mg/kg/day, and 58 percent could not tolerate any medical food supplement. Mean blood Phe levels decreased significantly in the BH4 group between baseline and the beginning of supplementation in week 3 (decrease of 148.5 ± 134.2 µmol/L). Some participants in the BH4 group had transient low blood Phe levels (<26 µmol/L) corrected with increased medical food supplementation.

More recently,[116] an uncontrolled open label trial of good quality conducted at one U.S. clinic from 2008 to 2009, included participants with classic or variant PKU with any Phe level or diet. Eligible subjects received 7 days of open label BH4 at 10 mg/kg/day with plasma Phe measurement on day 8 and weekly during a dietary modification period. The study defined response as a 30 percent reduction in plasma blood Phe or reduction to treatment range of <360 µmol/L after day 7. Investigators increased the dosage to 20 mg/kg/day for nonresponders and rechecked Phe levels after 8 days. Individuals who were still nonresponders continued on 20 mg/kg/day until day 30. Responders who were on a Phe-restricted diet underwent gradual liberalization of their diet to the maximum tolerated natural protein intake while still maintaining plasma levels in the range of 120 to 360 µmol/L.

Of the 36 participants (mean age 23.4) who began treatment with BH4, 29 (74 percent) completed the study. Of these 29 individuals, 59 percent were on some form of protein restricted diets and had a mean baseline blood Phe of 587 µmol/L. Forty-one percent were not following protein restricted diets and had a mean baseline blood Phe level of 1372 µmol/L. Overall, 62 percent were determined to be responders, with variable doses required for response; 14 participants required a dose of 7 to15 mg/kg/day, and four participants required a dose of 15 to 20 mg/kg/day. Four (29 percent) of the classic PKU participants (defined as off diet plasma Phe of >1200 µmol/L) were responders, and 100 percent of the variant PKU participants (>400 and <1200 µmol/L) were responders.

Of the 12 participants who were not on a Phe-restricted diet, 33 percent were responders with a significantly decreased mean blood Phe of 554 µmol/L compared with baseline Phe level (1049 µmol/L). Of the 17 participants who were on a Phe-restricted diet, 82 percent were responders with significantly reduced mean blood Phe level of 226 µmol/L compared with baseline (485 µmol/L). Among individuals who were responders and on a Phe-restricted diet, the average Phe tolerance increased from 21 to 41 mg/kg/day. However, responders' Phe tolerance varied widely from an increase of 20 to 22 mg/kg/day to a non-protein restricted diet in two participants. Of the

11 who were nonresponders, three were on a Phe-restricted diet with a mean blood Phe level at the end of the trial of 978 µmol/L (baseline mean=1363 µmol/L). Eight of the 11 nonresponders were on an unrestricted diet with an end of trial mean blood Phe level of 1465 µmol/L (baseline mean=1524 µmol/L). Overall, nonresponders had an end trial blood Phe of 1333 and a baseline of 1422 µmol/L compared with responders who had significant decrease in blood Phe from a baseline of 1049 µmol/L to an end of trial level of 554 µmol/L.

Prospective Cohort Study and Case Series

One poor quality prospective cohort study[121] assessed variability in blood Phe. Participants included nine children who were responsive to a 20 mg/kg BH4 loading test and 25 who were nonresponsive. Among those who were BH4 responsive, two were treated with BH4 alone and the rest also needed dietary modifications. From 2002 to 2010, there were 1384 blood samples available from BH4 responders and 4415 samples available from non-responders. Overall, there appeared to be no significant difference in mean and median blood Phe levels between the groups; however, above blood Phe levels of 600 µmol/L, confidence intervals around the mean were wider among BH4 nonresponsive participants. The authors equate these differences with variability in response.

Four poor-quality case series[117-120] evaluated dosages of BH4 ranging from 5 to 26 mg/kg/day for duration of 6 months to up to 9 years among BH4-responsive participants. All reported positive outcomes in terms of reduction in blood Phe and increased Phe tolerance. As reported above, one case series[118] also examined longer term functional outcomes, including IQ and developmental quotient after one year of treatment, reporting no adverse effects as participants' Phe tolerance increased and the diet was liberalized. Nutritional status was unchanged with the exception of increases in selenium. In another case series,[117] 12 participants were studied for up to 7 years on a dosage of 10 mg/kg twice a day. In this group, ranging in age from 2 to 16 years old, all participants eventually stopped medical food supplementation and relaxed dietary restrictions.

Another longer-term case series[120] assessed Phe levels and increase in Phe tolerance (presented as the number of times Phe intake increased from baseline level for those on dietary restriction) in 16 individuals receiving BH4 for between 24 months to 9 years (mean=56 months). Of the 16 patients, 15 (94 percent) patients were initial responders. The mean blood Phe level in responders was 321 $\pm$ 236 µmol/L, and the mean decrease in blood Phe was 54.6 percent (range 28.4 to 85.6 percent). Two patients, ages 10 and 13 years at the start of treatment, were non-responders and had high fluctuations in blood Phe levels. Seven patients had stable Phe control (defined as that recommended by the 2000 NIH consensus development panel), without any dietary restriction. Of the remaining seven patients who were on dietary restrictions, six increased their Phe intake from a baseline of 200 to 300 mg/day to 800 to 1000 mg/day. Psychomotor development, (measured using the Hamburg Wechsler Intelligence test-HAWIK III) among children 5 to 6 years of age was reported to be within normal range; however, results were not presented. Finally, one case series[119] provided data on Phe variability by measuring blood Phe at least six times before and after treatment initiation. Individual variability in Phe levels was lessened after treatment.

Key Question 3. What is the comparative effectiveness of BH4 with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

We did not identify any studies addressing this question.

Key Question 4. What is the comparative effectiveness of large neutral amino acids (LNAAs) with dietary intervention versus dietary intervention alone for affecting outcomes including measures of cognition (including executive function), quality of life, and nutritional status? Subgroups include the following:

- Infants with PKU
- Children ages 2 to 12 years old with PKU
- Adolescents ages 13-21 years old with PKU
- Adults >21 years old with PKU

Key Points

- With only three very small studies, and none of good quality, the strength of evidence is insufficient to draw conclusions about the effectiveness of LNAA formulations in affecting short- or long-term outcomes, including Phe level, Phe tolerance, IQ, executive function or quality of life.
- Studies used blood Phe level as the primary outcome.
- The longest followup period was 2 weeks, and the largest study included 20 participants.
- No RCTs evaluated infants or children younger than 11 years.

Overview of the Literature

This portion of the review focused on the use of LNAA formulations for treating PKU. We did not study the use of individual large neutral amino acids. Three studies addressed the effects of LNAAs,[16, 124, 125] including two RCTs[124, 125] and one uncontrolled open label trial.[16] The studies were very small, including a total of 47 participants, and were conducted in the United States, Brazil, Europe, and Australia. Participant numbers in the RCT treatment arms ranged from 16[124] to 20[125] while the uncontrolled open label trial included 11.[16] Participants were between 11 and 45 years of age, and typically had classic PKU. The trials were short, with treatment between 1 and 8 weeks, and dosages ranged from 250 mg/kg/day in three divided doses to 1g/kg/day. Two of the three studies measured reductions in blood Phe levels, and one assessed cognitive outcomes (Table 13).[124]

Table 13. Overview of studies and populations for research on LNAA formulations

Study Design Quality	Product Dosage	Formulation		N	Age, Years Mean and/or Range	Blood Phe Levels (µmol/L)	Outcomes
		Amino Acid	mg				
Schindeler 2007[124] RCT (crossover) Quality: Fair	250 mg/kg/d	L-Histidine L-Isoleucine L-Leucine L-Lysine L-Methionine L-Threonine L-Tryptophan L-Tyrosine L-Valine	15.11[a] 7.53 7.53 7.53 15.11 7.53 15.11 15.11 7.53	16	Median 24.9 (11–45)	>450 N=16	• Cognitive and affective outcomes • Phe level
Matalon 2007[125] RCT (crossover) Quality: Poor	0.5 g/kg/g	Tyrosine Tryptophan Methionine Isoleucine Threonine Valine Leucine Histidine Lysine Arginine	195 51 32 35 32 35 130 30 30 30	20	11-32	932.9	• Phe level
Matalon 2006[16] Open label Quality: Poor	0.5 g/kg/d*	Tyrosine Tryptophan Methionine Isoleucine Threonine Valine Leucine Histidine Lysine Arginine	195 51 32 35 32 35 130 30 30 30	8	20.5	957.4	• Phe level
	1.0 g/kg/d*			3	16.5	1230	

d = day; kg = kilogram; mg = milligram; N = number; Phe = phenylalanine
*Same formulation used at either dose
[a](g/100 g)

Summary of Effects

One RCT[124]enrolling 16 participants reported on measures of cognition, including executive functioning. The study reported that LNAAs supplementation had a positive effect on executive functioning, specifically improving verbal generativity, cognitive flexibility, and self-monitoring. Despite improvements in some aspects of executive functioning with LNAAs supplementation, studies reported considerable individual variation. In all three studies, blood Phe decreased after one week of treatment, but remained above clinically acceptable levels. The one trial that measured correlation between blood and brain Phe found no association.[124] Overall, participants who were using a Phe-free formula did not experience a decrease in blood Phe, although those not adhering to diet or not using Phe-free formula did. This finding suggests that LNAAs may be helpful in lowering blood Phe in participants unable to adhere to medical treatment, but current research suggests a lack of clinical impact.[16, 124, 125] Table 14 summarizes key outcomes of comparative studies.

Table 14. Comparative studies of LNAAs for the treatment of PKU

Author, Year, Formulation/Dosage Total N Quality	Age, Mean Years ± SD	Key Points
Crossover Trials		
Schindeler 2007[124] Phase 1: Phe-free medical food, Phe-restricted diet, LNAAs Phase 2: Phe-free medical food, Phe-restricted diet, placebo Phase 3: No Phe-free medical food, Phe-restricted diet, LNAAs Phase 4: No Phe-free medical food, Phe-restricted diet, placebo 250 mg/kg/day in 3 equal daily doses, each phase for 14 days with a 4 week washout period in between phases N = 16 Quality: Fair	24 years 9 months (median) 11 – 45 (range)	• All participants had early treated, classic PKU; none had excellent dietary control prior to treatment • Brain Phe levels did not differ by phase • Median plasma Phe levels increased from phase 1 (639 µmol/L, range 149-1044) to phase 4 (1180 µmol/L, range 641-1744), • Plasma Phe was reduced in most subjects (9/16) by an average of 25% during phase 1 during which they took LNAAs and Phe-free medical food. • No difference in plasma Phe reduction was observed with LNAAs plus formula or without LNAAs plus formula. In the absence of Phe-free medical food, LNAAs was associated with greater reductions in Phe than placebo. However, plasma Phe levels remained high for all participants, including those taking the LNAAs formulation (958 µmol for those not on Phe-free medical food).
Matalon 2007[125] **G1:** LNAA/Placebo **G2:** Placebo/LNAAs 0.5 g/kg/day in 3 doses taken with meals, for 1 week N=20 Quality: Poor	11 - 32	• Study was conducted in 6 centers in the U.S., Italy, Denmark, Russia and Brazil • Participants were instructed to continue diet while in the trial • Blood Phe levels were significantly reduced on LNAAs from a mean blood Phe of 932.9 µmol /L at baseline to 568.4 µmol/L at one week (39% decline) • Seven participants were adherent to Phe formula and had a decline from a baseline mean of 531.6 µmol /L to 281.5 µmol/L at one week, an average decline of 250.1 ± 173.7 (47% decline) • In comparison, blood Phe was not reduced on placebo
Matalon 2006[16] **G1:** 0.5 g/kg/day NeoPhe **G2:** 1.0 g/kg/day NeoPhe 0.5 g/kg/day or 1.0 g/kg/day of NeoPhe in 3 doses taken before meals, for 1 week N=11 Quality: Poor	**G1:** 20.5 **G2:** 16.5	• Participants were enrolled at 3 centers in Ukraine, Russia and the U.S. • Participants were not on a restricted diet; Phe intake was more than 500 mg/day • Of 11 participants enrolled in the trial, 8 received 0.5 mg/kg/day of LNAAs and 3 received 1.0 g/kg/day • In the 8 participants taking 0.5 g/kg/day, blood Phe levels decreased significantly from the baseline mean of 957.4 µmol/L to 458.4 µmol/L after one week on LNAAs, a decline of 52%. • Among the 3 participants who took 1 g/kg/day of LNAAs, the mean blood Phe level decreased from the baseline level of 1230 µmol/L to 549.0 µmol L, a decline of 55%.

LNAAs = large neutral amino acids; N = number; Phe = phenylalanine

Detailed Description of Individual Studies

Clinical Trials

One fair quality, double blind, randomized, crossover study[124] was carried out in one center in Australia. Sixteen participants with early treated, classic PKU (plasma Phe >1000 µmol/L) were enrolled. The objective was to evaluate the relationship between LNAAs supplementation and cognitive and affective outcomes under four different therapeutic combinations with PKU amino acid products. Participants followed their usual Phe-restricted diet and PKU Phe-free medical food. All subjects completed four phases, each lasting 14 days with a 4 week washout period between phases. Phase 1 consisted of taking their usual medical food, usual Phe-restricted diet and LNAAs at 250 mg/kg/day in three equal daily doses.

During Phase 2, participants maintained their usual medical food, usual Phe-restricted diet and placebo. In Phase 3, participants did not take their usual medical food, maintained their usual Phe-restricted diet and received LNAAs. In Phase 4, participants did not take their usual medical food, maintained their usual Phe-restricted diet and placebo. For the phases without medical food, advice was provided on energy supplements needed to replace energy intake usually obtained from a medical food. Blood Phe levels from the previous year were used to determine baseline Phe. Of the 16 participants, nine were determined to have good control (median Phe level 450 to 750 µmol/L), six participants had marginal control (median Phe level 750 to 1000 µmol/L), and two participants had poor control (median Phe level >1000 µmol/L).

Dietary analysis demonstrated that both total protein and LNAAs intake were highest in phase 1 followed by phase 2, phase 3, and lowest in phase 4, consistent with the phased study. There was no significant difference in brain Phe between the 4 phases (range 176 to 365 µmol/L). Brain Phe levels were determined by magnetic resonance spectroscopy. No participant was determined to have excellent control (median blood Phe level<450 µmol/L), and no difference in Phe reduction was observed with or without LNAAs as long as participants were on the Phe-free medical food. However, in the absence of medical food, the LNAAs arm was associated with greater reductions in Phe than placebo. However, plasma Phe levels remained high for all participants, including those taking the LNAAs formulation (958 for those not on Phe-free formula).

The second RCT[125] was a crossover trial of poor quality that was carried out in 6 centers located in the United States, Italy, Denmark, Ukraine, Russia, and Brazil. Blood Phe levels dropped significantly on LNAAs from a mean level of 932.9 µmol/L at baseline to 568.4 µmol/L at one week, an average decline of 365.5 ± 233.2 (39 percent). Seven participants who adhered to PKU formula had a significant reduction in blood Phe from a baseline mean of 531.6 µmol/L to 281.5 µmol/L at one week, an average decline of 250.1 ± 173.7 (47 percent). The average decline of Phe on placebo from a baseline mean of 932.9 µmol/L to 882.66 µmol/L at one week (5.4 percent) was not significant.

Uncontrolled Open-Label Trial

The third trial[16] was an uncontrolled open-label trial of poor quality that included 11 participants. Participants were not on a Phe-restricted diet and Phe intake was over 500 mg/day. Of 11 participants enrolled, eight received 0.5 mg/kg/day of LNAAs and three received 1.0 g/kg/day. Blood Phe levels decreased significantly from baseline after one week of LNAAs, an average decline of 601 µmol/L ± 370. In the eight participants taking 0.5 g/kg/day, Phe levels decreased significantly from the baseline mean of 957.4 µmol/L to 458.4 µmol/L, a decline of 52

percent. Among the three participants who took 1 g/kg/day of LNAAs, the mean blood Phe level decreased from the baseline level of 1230 µmol/L to 549.0 µmol/L, a decline of 55 percent.

Key Question 5. What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects?

We did not identify any studies addressing this question.

Key Question 6. What are the harms, including adverse events, associated with the use of BH4 or LNAAs in individuals with PKU?

Key Points

- Few studies of BH4 (N=4) or LNAAs (N=1) reported harms.
- Harms commonly reported in BH4 studies included headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, and nausea and vomiting.
- One study of BH4 reported that three subjects discontinued the treatment due to adverse events.
- Increased anxiety level was reported in one study of LNAAs.
- The strength of the evidence for a lack of significant harms associated with BH4 is moderate. The strength of the evidence for harms associated with LNAAs is insufficient.

Overview of the Literature

Of the ten studies examining the effectiveness of BH4 in participants with PKU, four studies with overlapping participants[112-115] reported any type of harm related to the intervention drug. Three studies[117, 118, 120] reported that no adverse events were observed during intervention, one study reported that BH4 was well tolerated with mild diarrhea occurring rarely,[121] and there was no mention of harms in two studies.[116, 119]

Among the BH4 studies reporting harms, two, including one RCT and following uncontrolled open label trial, predefined harms (Table 15),[113, 114] and two defined severe and serious events precisely.[112, 114] Two specified the number of deaths (N=0),[112, 115] and most included both active and passive collection of harms data.[112-115] All studies of BH4 specified details about the investigators collecting harms data and timing of data collection,[112-115]

The studies of BH4 also reported the number of participants who withdrew or were lost to follow up in each group as well as the total number of participants affected by harms in each group.[112-115]

Table 15. Overview of harms reported in studies of BH4

		BH4	Placebo
	N on intervention drug[a]	33[115] 41[113] 79[114] 111[112b]	12[115] 47[113]
		Range of % Subjects With Adverse Event (Number of Studies)	
	Any adverse event (in the total sample)	51-85 (4)	72-76 (2)
	Adverse events related to study drug	23-39 (4)	20-25 (2)
	Withdrawals due to adverse events	2.7 (1)	0
Serious events	Total	4.4-6.3 (2)	8.3 (1)
	Urinary tract infection	1.5 (1)	0
	Spinal cord injury	1.5 (1)	0
	Fractured tibia	1.5 (1)	0
	Streptococcal infection	3 (1)	0
	Appendicitis	0	8.3 (1)
	Gastroesophageal reflux	0.9 (1)	
	Testicular mass	0.9 (1)	
	Incontinence	0.9 (1)	
	Tonsillectomy	0.9 (1)	
	Menorrhagia	0.9 (1)	
	Dysmenorrhea	0.9 (1)	
	Neck injury	0.9 (1)	
Severe events	Tooth abscess	1.5 (1)	0
	Difficulty concentrating	0.9 (1)	0
	Mood swings	0.9 (1)	0

[a]Studies include overlapping participants.
[b]Harms are reported for the total population in this study (N=111) vs. only for those individuals completing the study (N=90).

The most common side effects reported during BH4 trials were headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, nausea and vomiting (Table 16).

Table 16. Harms with highest incidence in studies of BH4

Trial Type	Adverse Event	Levy 2007[113] BH4 / Placebo n (%)	Trefz 2009[115] BH4 / Placebo n (%)
RCTs	Upper respiratory infection	7 (17) / 13 (28)	2 (6) / 1 (8)
	Headache	4 (10) / 7 (15)	7 (21) / 1 (8)
	Vomiting	2 (5) / 4 (9)	4 (12) / 0 (0)
	Abdominal pain	1 (2) / 4 (9)	3 (9) / 1 (8)
	Diarrhea*	2 (5) / 3 (6)	4 (12) / 0 (0)
	Pyrexia	2 (5) / 2 (4)	3 (9) / 2 (17)

Table 16. Harms with highest incidence in studies of BH4 (continued)

Trial Type	Adverse Event	Levy 2007[113] BH4 / Placebo n (%)	Trefz 2009[115] BH4 / Placebo n (%)
RCTs	Low T4	1 (2) / 0 (0)	
	High Thyroid Stimulating Hormone	1 (2) / 0(0)	
	Liver enzyme changes	0 (0) / 2 (4)	
	Back pain	1 (2) / 3 (6)	
	Rhinorrhea		7 (21) / 0 (0)
	Cough		5 (15) / 0 (0)
	Pharyngolaryngeal pain		4 (12) / 1 (8)
	Contusion		3 (9) / 1 (8)
	Nasal congestion		3 (9) / 0 (0)
	Decreased appetite		2 (6) / 0 (0)
	Erythema		2 (6) / 0 (0)
	Excoriation		2 (6) / 0 (0)
	Lymphadenopathy		2 (6) / 0 (0)
	Streptococcal infection		2 (6) / 2 (17)
	Toothache		2 (6) / 0 (0)
	Neutropenia		7 (21) / 2 (17)
		Lee 2008[114] BH4 / Placebo n (%)	**Burton 2011[112] BH4 / Placebo n (%)**
Open-Label Trials	Headache	16 (20)	13 (11.7)
	Pharyngo-laryngeal pain	12 (15)	10 (9)
	Nasopharyngitis	11 (14)	20 (18)
	Vomiting	10 (13)	20 (18)
	Diarrhea	8 (10)	10 (9)
	Upper respiratory infection	8 (10)	22 (19.8)
	Cough	7 (9)	21 (18.9)
	Gastroenteritis	4 (5)	7 (6.3)
	Influenza	4 (5)	9 (8.1)
	Dysmenorrhea[a]	3(9)	
	Migraine	6 (8)	
	Back pain	4 (5)	

Note: One additional prospective cohort study reported that some participants occasionally experienced mild diarrhea but did not provide the number or proportion.[121]
[a] 3/33 female patients.

Harms probably or possibly related to study treatment (Table 17) were similar in both BH4 and placebo (23 vs. 20 percent[113], 27 vs. 25 percent[115]).

Table 17. Harms probably/possibly related to BH4 in studies assessed

Adverse Event	Open-Label Trials BH4	
	Lee 2008[114] N (%)	Burton 2011[112] N (%)
Headache	1 (3.2)	5 (4.5)
Vomiting	4 (12.9)	5 (4.5)
Diarrhea	2 (6.5)	3 (2.7)
Pharyngo-laryngeal pain	3 (9.7)	1 (0.9)
Cough	2 (6.5)	3 (2.7)
Upper abdominal pain	1 (3.2)	
Nausea	2 (6.5)	
Dizziness	1 (3.2)	
High Alanine Amino-Transferase	1 (3.2)	
Urinary tract infection	2 (6.5)	
Streptococcal infection	2 (6.5)	
Abdominal pain	2 (6.5)	
Headache	8 (25.8)	
Migraine	4 (12.9)	
Low neutrophil count	2 (6.5)	
Rash	2 (6.5)	
Infection and infestations		11 (9.9)
Upper respiratory infection		2 (1.8)
Nasopharyngitis		3 (2.7)
Influenza		1 (0.9)
Viral infection		1 (0.9)
Gastroenteritis viral		5 (4.5)
Gastrointestinal disorders		14 (12.6)
Respiratory, thoracic, and mediastinal disorders		4 (3.6)
General disorder and administration site conditions		4 (3.6)
Pyrexia		4 (3.6)
Nervous system disorders		6 (5.4)

One trial of LNAAs[124] assessed neuropsychological outcomes and reported higher rates of anxiety associated with LNAA use. This study was of fair quality, very small and short term, and did not provide any details on the prespecification or collection of harms data.

Key Question 7. What is the evidence for the effectiveness of the addition of BH4 or LNAAs to dietary intervention for affecting outcomes in subgroups of patients? The following are examples of potential defining characteristics of subgroups:

- Demographic
- Clinical
- Genotypic
- Adherence

To date, there is no evidence that predictable subgroups of individuals are likely to have a differential response to either BH4 or LNAAs. In part, the small size and research design of the studies have precluded appropriate analyses of subgroups. The following section on Grey Literature contains additional detail on current studies that may provide additional data on modifiers of effectiveness in the future.

Grey Literature

Regulatory Information

As part of the evaluation of the clinical evidence of the safety and efficacy of BH4, we examined grey literature sources to supplement the published literature. Specifically, we compared clinical trial data that were included in regulatory documents submitted to the U.S. FDA, Health Canada, and the European Medicines Agency as part of the approval process for sapropterin dihydrochloride to be marketed as Kuvan® by BioMarin. The materials obtained from the three agencies differed in content and level of detail. The material from the FDA included the following documentation: the letter granting approval for BioMarin to market sapropterin as Kuvan, administrative documents and correspondence between the FDA and BioMarin, chemistry and pharmacology reviews of BH4, clinical pharmacology and biopharmaceutics reviews, medical reviews of the efficacy clinical trials for BH4, a statistical review of company analysis of trial results, the proprietary name review, and review and approval of labeling information for consumers for BH4, as well as summary documents for the new drug application review process. The materials from the European Medicines Agency included the following documentation: a public summary of orphan designation for BH4, announcement of the drug's market approval, the report from the Committee for Medicinal Products for Human Use which provided detail about the clinical trials supporting the drug's approval, the European Public Assessment Report used to provide information to the public about BH4, and the labeling review and label information. The materials from Health Canada included only the Summary Basis of Decision report which described the evidence used to approve BH4 for the Canadian market. The information in the Committee for Medicinal Products for Human Use and Summary Basis of Decision reports mirrored information in the various documents from the FDA. Because there was significantly less detail in those reports, we decided to use only FDA documents for the grey literature analysis of the published literature.

While there is evidence of publication bias for some pharmaceuticals on the market when comparing the grey and published literatures,[126, 127] there was no such discrepancy for BH4. Our

review of regulatory documents found no missing studies. In order to compare the grey literature with the published literature, we extracted data from the FDA approval documents about the study design, patient characteristics, type of randomization, length of study, drug dosing protocol, pretreatment blood Phe levels, and the outcomes measured (Table 18). Information in these documents included summaries of the data submitted to the FDA as part of BioMarin's new drug application (NDA) for BH4. Next, we identified publications of those trials and compared the data submitted to the FDA with the information contained in the published literature. We examined the concordance between the published and grey literatures, looking for differences in how data were reported or the absence of grey literature data in the published literature. The published literature was essentially identical to the information on safety and efficacy provided to the FDA as part of the new drug application for its approval to the U.S. market. Further information on these studies is included in Appendix J.

Table 18. FDA documentation used for Kuvan approval process

Document Title	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007
Trial Number	PKU-001 / PKU-003	PKU-004	PKU-006, Part 2
Patient Characteristics -# screened for BH4 responsiveness -# at enrollment -# per protocol -Age range -Sex	-489 screened for BH4 -89 responders (≥30% blood Phe decrease from baseline to day 8), 88 participants randomized -8-49 years, mean 20 -51M, 37F	-Extension study of PKU-003 -80 participants who completed PKU-003 (39 who had received BH4, 41 who had received placebo) -8-49, mean 20 -47M, 33F	-Part 1 tested 90 PKU patients -45 responders(≥30% blood Phe decrease from baseline, and a blood Phe ≤300 on day 8) -4-12 yrs old (mean 7yrs) -26 (58%) male
Study Drug Comparison	BH4 vs. placebo (double blind)	Forced-dose titration	BH4 vs. placebo (double blind, placebo controlled)
Type of Randomization (x:x; #patients per drug vs. placebo)	1:1; 41 and 47	NA	3:1; 33 and 12
Drug Dosing Protocol	-BH4 10mg/kg/day once a day	-6 week open label forced dose-titration: 5mg/kg/day for 2 weeks, then 20 mg/kg/day for 2 weeks, then 10mg/kg/day for 2 weeks. Then maintained on 10mg/kg/day for 4 weeks. Then 12 weeks of BH4 dosed at 5 (N=6), 10 (N=37), or 20 (N=37) mg/kg/day based on individual patient's blood Phe from the forced dose-titration	-BH4 20 mg/kg/d

Table 18. FDA documentation used for Kuvan approval process (continued)

Document Title	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007	"Clinical Team Leader Summary Review of NDA 22-181 Kuvan for the treatment of PKU; 12-3-2007
Trial Number	PKU-001 / PKU-003	PKU-004	PKU-006, Part 2
Length of Study	6 weeks	22 weeks total BH4 use (with PKU-003 data)	10 weeks of treatment
Diet Controlled/Not	No dietary changes made	No dietary changes	No change for first 3 weeks of tx; at week 3, increased dietary Phe 5 mg/kg/day for 2 weeks if blood Phe ≤300. Further increase of dietary Phe at weeks 5, 7, and 9 with specific blood Phe levels while maintaining blood Phe at <360 micromol/L
Pretreatment Phe Levels Micromol/L (SD)	**G1:** 848 (300) **G2:** 888 (323)	844 (398)	**G1**: 314 (107) **G2**: 303 (74)
Outcomes Measured	**Primary:** Mean change in blood Phe from baseline at week 6 **Secondary:** Mean change from baseline in weekly blood Phe levels; proportion of patients who had blood Phe <600 µmol/L at week 6; AEs during tx	**Primary:** Change in blood Phe from baseline to weeks 10, 12, 16, 20, and 22 **Secondary:** Blood Phe at week 2, 4, 6. Safety and AEs	**Primary:** Mean dietary Phe tolerated after 10 weeks of double-blind treatment for each treatment group. **Secondary:** Difference in blood Phe from baseline to pre-Phe supplement; comparison of tx groups in amount of Phe supplement tolerated
Publication of Matched Data	Levy 2007[113]	Lee 2008[114]	Trefz 2009[115]

AE = adverse events; EU = European Union; FDA = Food and Drug Administration; NDA = New Drug Application; Phe = phenylalanine; PKU = phenylketonuria; tx = treatment
G1: BH4; G2: Placebo.

As part of the FDA approval process, BioMarin agreed to conduct the following postmarketing commitment studies (Table 19):

1. Assessment of the safety, efficacy, and pharmacokinetics of BH4 in children younger than 4 years old;
2. Assessment of growth and neurocognitive development with long-term use of BH4 in children eight years old or younger at study entry;
3. An open label extension with participants in the pivotal efficacy studies to continue the treatment period to 2 years;
4. The creation of a registry of individuals treated with BH4 to collect long-term clinical status information, including a substudy of the effects of BH4 on pregnancy and lactation;
5. Completion of a thorough cardiac study in healthy volunteers;
6. Completion of a PAH gene mutation study to identify treatment responders and

7. Assessment of the safety and efficacy of BH4 in individuals with hyperphenylalaninemia due to BH4 deficiency.

For commitment 1, the study of 61 PKU participants <4 years old is noted by the FDA as delayed (the due date has passed and no final report has been submitted). The study for commitment 2, with an estimated enrollment of 230, is in children with PKU 0 to 6 years of age and is ongoing. An open label extension of the NDA studies appears to meet the requirement of commitment 3; the study, PKU-008, is noted as "completed" by www.clinicaltrials.gov, "submitted" on the FDA Web site, and now has published results.[112]

BioMarin and Merck KGaA have set up U.S. (PKU Demographic, Outcomes, and Safety [PKUDOS] registry) and European (Kuvan Adult Maternal Pediatric European Registry [KAMPER]) registries, respectively, for commitment 4 that are recruiting and ongoing. The PKUDOS registry includes a substudy on pregnancy and lactation effects, including a subregistry of pregnant women with PKU (PKUMOMS); data from the PKUDOS and KAMPER registries are due for submission to the FDA in early 2025. A completed but as yet unpublished study in 56 healthy volunteers to evaluate BH4's effect on QT intervals is listed by the FDA as having fulfilled commitment 5. Commitment 6 requires analysis of blood samples for PAH gene mutation collected as part of an NDA study (PKU-001); it is listed as fulfilled, and some data are published in the Levy et al. RCT of BH4.[113] PKU-007, another open label extension of NDA studies in an estimated 12 individuals, has been completed and is listed by the FDA as submitted for commitment 7.

Table 19. Summary of Kuvan commitment studies

Study Description (Country/ID/Design/Date/Sponsor)	Intervention/Study Population (Disease Type/Age/Estimated Enrollment)	Outcomes
Commitment 1		
Austria, Belgium, Czech Republic, Germany, Italy, Netherlands, Portugal, Slovakia, Turkey, United Kingdom NCT01376908; EudraCT # 2009-015768-33 Randomized controlled trial NR Merck Serono SA – Geneva	Evaluate safety and efficacy of BH4 compared with placebo PKU <4 years N=61	Blood Phe level
Commitment 2		
Canada, United States NCT00838435 Nonrandomized open label 02/2009-12/2018 BioMarin	Evaluate efficacy of BH4 PKU 0-6 years N=230	Blood Phe level, neurocognitive function
Commitment 3		
Germany, Ireland, Italy, Spain, United Kingdom, United States NCT00332189 EudraCT # 2006-000839-10 Nonrandomized open label 07/2006-08/2009 BioMarin	Evaluate safety and efficacy of phenoptin (BH4) PKU ≥ 4 years N=111	Incidence of adverse effects, blood Phe level

Table 19. Summary of Kuvan commitment studies (continued)

Study Description (Country/ID/Design/Date/Sponsor)	Intervention/Study Population (Disease Type/Age/Estimated Enrollment)	Outcomes
Commitment 4		
United States NCT00778206 Prospective cohort NR BioMarin	PKUDOS: individuals with PKU who have either received BH4 therapy, currently receive BH4, or intend to begin receiving BH4 therapy PKU NR N=3500	NR
Switzerland NCT01016392 Prospective cohort 11/2009-07/2025 Merck KGaA	KAMPER: Kuvan Adult Maternal Pediatric European Registry PKU ≥ 4 years N=625	Incidence and description of adverse events and serious adverse events
Commitment 5		
United StatesNCT00789568 Randomized controlled trial 10/2008-10/2009 BioMarin	Evaluate QT interval effect of BH4 compared with placebo NR ≥18 years N=56	QT correction from baseline
Commitment 6		
United StatesNCT00104260 Open label study 12/2004-11/2005 BioMarin	Assess whether individuals with specific PAH mutations are likely to be responders to BH4 NR ≥ 8 years N=88	PAH mutations
Commitment 7		
Germany, United States NCT00355264 EudraCT # 2005-003778-13 Nonrandomized open label NR BioMarin	Evaluate safety and efficacy of phenoptin (BH4 dihydrochloride) Hyperphenylalaninemia due to BH4 deficiency NR N=12 (United States), 15 (Germany)	Blood Phe level

N = number; NR = not reported; PAH = phenylalanine hydroxylase; Phe = phenylalanine; PKU = phenylketonuria

A number of other postmarketing studies have been initiated and should provide some additional data regarding the use of BH4 in the treatment of PKU (Table 20). Two studies are looking at the efficacy of BH4 in individuals with PKU older than 4 years old. The ENDURE study, based in Denmark and Norway and sponsored by Merck KGaA / Merck Serono, is in 150 patients and is ongoing. The other study, sponsored by the University of Miami, is in 20 patients with an unknown status at the time of publication. One ongoing study sponsored by Graz Medical University in Austria includes 30 PKU participants 4 to 18 years old and uses blood Phe level to evaluate a test to identify BH4-responsive individuals. To evaluate the effect of BH4 on amino acids and fatty acid patterns, the Aragon Institute of Health Sciences in Spain has sponsored a study in 30 PKU participants that is noted as recruiting.

Two studies sponsored by U.S.-based academic centers are evaluating BH4 on cognitive effects. The first, sponsored by Tulane University School of Medicine, is looking at executive function and behavior in 30 participants with PKU between 2 and 21 years of age and is currently recruiting. Another study, sponsored by Washington University School of Medicine in collaboration with BioMarin and University of Missouri, Columbia, is using the Wechsler Abbreviated Intelligence Scale to study cognition in 35 participants with PKU ≥ 6 years of age and enrolling by invitation only.

Three studies are evaluating behavioral effects of BH4 in PKU. One BioMarin-sponsored study is a U.S.- and Canada-based RCT recruiting 200 individuals with PKU and ≥12 years of age to evaluate attention deficit hyperactivity disorder symptoms and BH4 use. The second is studying effect on behavior in 20 six to 18 year old individuals with PKU (sponsored by Washington University School of Medicine collaborating with BioMarin and the University of Missouri, Columbia, Northwestern University, and Oregon Health and Science University, enrolling by invitation only). The third study, from the University of Southern California collaborating with BioMarin, is evaluating behavior in 13 participants with PKU taking BH4 (enrollment by invitation only).

Three studies are evaluating the effect of BH4 on the brain. One focuses on brain glucose metabolism using positron emission tomography imaging in five adults with PKU (sponsored by Children's Hospital of Philadelphia and recruiting). The second uses magnetic resonance imaging to study the drug's effect on brain connectivity in 20 individuals ≥6 years of age (sponsored by University of Missouri, Columbia collaborating with BioMarin and enrolling by invitation only). The third study, sponsored by Emory University collaborating with BioMarin and the Clinical Interaction Network of the Atlanta Clinical and Translational Science Institute, is an ongoing study of the effect on neurotransmitter concentrations in 62 individuals with PKU ≥4 years of age (Table 20).

Table 20. Summary of additional Kuvan postmarketing studies

Study Description (Country/ID/Design/Date/Sponsor)	Intervention/Study Population (Disease Type/Age/Estimated Enrollment)	Outcomes
Efficacy and Effect of BH4		
Denmark, Norway NCT01082328 EudraCT # 2009-018168-81 Nonrandomized open label NR Merck KGaA / Merck Serono Norway	Evaluate efficacy of BH4 PKU ≥ 4 years N=150	Blood Phe level
United StatesNCT00841100 Nonrandomized open label 12/2008-02/2010 University of Miami	Evaluate effect of BH4 PKU ≥ 4 years N=20	Blood Phe level
Identifying BH4-Responsive Individuals		
Austria EudraCT # 2010-019767-11 NR NR Graz Medical University	Evaluate a test to identify BH4-responsive individuals PKU 4-18 years N=30	Blood Phe level

Table 20. Summary of additional Kuvan postmarketing studies (continued)

Study Description (Country/ID/Design/Date/Sponsor)	Intervention/Study Population (Disease Type/Age/Estimated Enrollment)	Outcomes
Amino Acids and Fatty Acids Effects		
Spain EudraCT # 2008-005394-35 ISRCTN77098312 Controlled, open label 03/2009-NR Aragon Institute of Health Sciences	Evaluate effect of BH4 on amino acids and fatty acids patterns PKU NR N=30	Amino acids, fatty acids levels
Cognitive Effects		
United StatesNCT01274026 Nonrandomized open label 01/2011-01/2012 Tulane University School of Medicine	Evaluate BH4 on executive function and behavior PKU 2-21 years N=30	Blood Phe level, executive function
United StatesNCT00730080 Prospective case control 07/2008-07/2009 Washington University School of Medicine (collaborating with BioMarin and University of Missouri-Columbia)	Evaluate BH4 effect on cognition PKU ≥6 years N=35	Wechsler Abbreviated Scale of Intelligence, various working memory and strategic processing tests
Behavioral Effects		
Canada, United States NCT01114737 Randomized controlled trial 06/2010-12/2011 BioMarin	Evaluate effect of BH4 compared with placebo on ADHD symptoms PKU ≥12 years N=200	Blood Phe level, ADHD symptoms
United StatesNCT00827762 Prospective case series 01/2009-01/2010 Washington University School of Medicine (collaborating with BioMarin and University of Missouri-Columbia Northwestern University, and Oregon Health and Science University)	Evaluate BH4 effect on behavior PKU 6-18 years N=20	Various behavioral assessments
United States NCT00728676 Prospective case control 08/2008-2/2010 University of Southern California (collaborating with BioMarin)	Evaluate BH4 effect on behavior PKU NR N=13	Vineland scale standard scores, Phe level

Table 20. Summary of additional Kuvan postmarketing studies (continued)

Study Description (Country/ID/Design/Date/Sponsor)	Intervention/Study Population (Disease Type/Age/Estimated Enrollment)	Outcomes
Brain Effects		
United StatesNCT00986973 Single blind 03/2010-09/2011 Children's Hospital of Philadelphia	Evaluate BH4 on glucose metabolism in the brain PKU ≥18 years N=5	Brain PET scan, Phe level
United StatesNCT00964236 Prospective case control 08/2009-08/2011 University of Missouri, Columbia (collaborating with BioMarin)	Evaluate BH4 effect on brain connectivity PKU ≥6 years N=20	Magnetic resonance imaging
United StatesNCT00688844 Prospective cohort 08/2008-02/2010 Emory University (collaborating with BioMarin and the Clinical Interaction Network of the Atlanta Clinical and Translational Science Institute)	Evaluate BH4 effect on neurotransmitter concentrations PKU ≥4 years N=62	Various biochemical analysis tests

ADHD = attention deficit hyperactivity disorder; N = number; PET = positron emission tomography; Phe = phenylalanine; PKU = phenylketonuria

Summary

The results of the commitment studies and the other ongoing clinical studies, especially those focusing on neurocognitive development and behavior, will be especially critical to shed light on the clinical utility of BH4 treatment for the management of PKU. It should be noted, however, that the majority of clinical studies are sponsored by BioMarin or Merck, with only 5 studies out of 24 being conducted independently of BH4 marketers. The efficacy studies for the drug used blood Phe levels as surrogate endpoints to assess the broader benefits of drug treatment. This fact indicates that additional research is needed to confirm that the drug (and any additional nutritional supplementation used in conjunction with drug therapy) has positive outcomes on the neurocognitive development of children with PKU.

Conference Abstracts

We identified 46 abstracts that appeared to address adjuvant treatment for PKU; abstracts discussing the same population may have been presented at multiple conferences. Thirty-six abstracts appeared to be unpublished at this point (10 are now represented in the published literature, and 4 of these 10 studies are discussed in this review[112-114, 119]). Conference abstracts are considered unpublished or ongoing studies at this time, and because there is inadequate information to fully extract the studies or to assess quality, they cannot be integrated with the results in the review. Nonetheless, preliminary results appear consistent with the published literature and as these data are published, they should provide additional information on short-

and long-term efficacy, effects on behavior, and nutritional outcomes. We provide the abstracts in Appendix K as information for the reader.

Discussion

This section provides an overview of the state of the literature and outcomes for each Key Question, details the strength of evidence for the impact of each major intervention on relevant outcomes, and describes major issues and gaps in the current body of evidence.

State of the Literature

Summary of Outcomes by Key Question

Key Question 1a. Optimal Blood Phenylalanine (Phe) Levels for Minimizing/Avoiding Cognitive Impairment

Individuals with phenylketonuria (PKU), their families and their clinicians make continual decisions and treatment adjustments based on Phe measurements, with little information about the degree to which any course of treatment is providing protection against cognitive impairment. The precise relationship of blood Phe levels to intelligence quotient (IQ), and the timing of the effect have not been fully elucidated, in part because extant studies are small and sample populations in individual studies are sometimes selected to be homogenous. By combining information from a large number of studies that described the relationship between Phe and IQ, we provide further evidence of the relationship between specific blood Phe levels and IQ, the impact of the critical period on cognition and the best timing for Phe and IQ measurement in order to determine these effects. It is well established that high levels of blood Phe are associated with a lower IQ and that dietary control can mitigate the effects of high Phe,. The current analysis provides additional support for continuing dietary control through adolescence and into adulthood, although detailed information about the requisite level of control by age group and particularly into older age remains unknown.

Seventeen studies were included in the meta-analysis, providing data on 432 individuals who ranged from age 2 to 34 years. We modeled the association of IQ less than 85 with blood Phe level, accounting for time of Phe measurement relative to cognitive testing, and whether or not the measurement occurred in the critical period (<6 years of age). While intellectual disability is defined as IQ score lower than 70 (i.e., 2 standard deviations below the population mean) and impairment in activities of daily living, IQ scores within the normal range could be considered impairment if lower than the expected value of the general population. Though necessarily subjective, we believe that a reasonable candidate for impairment is a threshold of 1 standard deviation below the population mean, or an IQ score of 85. Subjects below this threshold would likely exhibit symptoms of cognitive impairment, such as poor language development, problem solving deficiencies, and memory deficits.

Increasing Phe is clearly associated with decreased IQ, with a probability of IQ less than 85 exceeding the population probability (approximately 15 percent) at blood Phe over 400 μmol/L and leveling off at about 80 percent at 2,000 μmol/L. This finding supports the typical target goal for blood Phe levels in individuals with PKU (120 to 360 μmol/L).[8]

Notably, the negative association between blood Phe and IQ is strongest when Phe is measured at least one year prior to IQ testing. The blood Phe level obtained more than one year before IQ testing is likely to be a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship lends support to the principle

that cognitive effects accumulate over a long time period, and thus concurrent measurements are poor predictors of a cognitive effect. The strongest associations are seen in the group for which historical measurements were taken during the critical period (<6 years old) and associated with later IQ, although historical measurements taken after the critical period are also associated with risk of low IQ. Hence, control of blood Phe levels during the critical period is particularly important, but the need for dietary control continues throughout the lifetime. Current clinical practice is to try to maintain tight Phe control even in adulthood, which is supported by this analysis and is consistent with the NIH recommendations of diet for life.

Note that the two lines corresponding to historical measures of blood Phe in Figure 3 (top two lines) both demonstrate increasing probability of low IQ at higher Phe measures, regardless of whether the effect is being measured during childhood (solid line) or beyond (dashed line), with a stronger association seen between blood Phe measured in early childhood and later IQ.

The two lower lines in the figure describe probability of IQ <85 as a function of blood Phe when measured concurrently. The lack of strong association in measurements taken concurrently during the critical period suggests that effects are unlikely to be observed in this period, either because the IQ test is not stable for young children (less than 5 years old) or because the adverse effects take time to manifest. From a clinical perspective, this provides a basis for being cautious in interpreting measures of cognitive outcomes during the critical period as they relate to blood Phe, and emphasizes the importance of well-controlled Phe levels during the critical period and over time.

Of note, these estimates may be biased because they are based on studies that include nonrandomly selected individuals from the PKU population. Insurance coverage and access to care for individuals with PKU, especially adults, is uneven across states and insurance companies. There is likely substantial unevenness in the degree to which patients access or use medical care, which would be the primary way that they would be recruited into studies. Thus if, the available studies exclude individuals not interacting with the healthcare system, the associations presented here may be conservative, as they may be especially likely to exclude people who are non-adherent to diet. Thus, we anticipate that clinicians can use these results to encourage parents and patients to maintain dietary control even in the absence of immediate, observable effects. Researchers considering the effect of Phe on IQ should know that when those measurements are taken concurrently, a relationship may not be apparent, and that a more accurate predictor may be historical measurements, such as an index of dietary control, which typically is calculated as the mean of annual mean or median Phe levels.

Optimal Phe Levels for Minimizing Impairments in Executive Function in Individuals With PKU

Studies of the association of blood Phe and executive function have targeted many specific outcomes, precluding straightforward quantitative analysis of the data. Some studies clearly suggest that elevated Phe is likely associated with poorer outcomes but data are inconsistent across types of measures. This is an important area for research, although there is currently insufficient strength of evidence to delineate a specific relationship between blood Phe levels in the individual and specific measures of executive function. To a large degree this is because no specific measures of executive function have been validated as sensitive to changes in Phe in the population with PKU, and thus this is a rich area for ongoing and future research.

Optimal Phe Levels for Minimizing Impairments Related to Maternal PKU and Maternal PKU Syndrome

Data also provide support for the increased risk observed of poor cognitive outcomes in the offspring of high maternal blood Phe. The Maternal PKU Collaborative Study was initiated in 1984 to study the implications of maternal PKU, and specifically to assess outcomes when Phe is controlled in pregnant women. The study demonstrated that timing of maternal metabolic control, defined as the number of weeks gestation before plasma Phe levels remained consistently lower than 605 μmol/L, was associated with child cognitive scores at 4 and 7 years of age. This is consistent with current recommendations that pregnant women achieve dietary control as early as possible in pregnancy, or before pregnancy, and maintain it until birth.

Because they had access to the largest available data set on maternal PKU, investigators were able to model the form of the association between maternal blood Phe levels during pregnancy and effect on offspring during childhood.[33] The analysis confirmed that the relationship between maternal blood Phe and offspring cognitive outcomes was not linear, and that a threshold of 360 μmol/L is the threshold level at which cognitive impairment was significantly more common in offspring of mothers with PKU than in controls, and that a linear relationship between Phe levels and impaired cognitive outcomes occurred after this threshold. Importantly, while other factors, including maternal characteristics, severity of mutations and head circumference, contributed strongly to outcomes at 1 year of age, by age 2, maternal Phe strongly overtook other factors in predicting cognitive impairment, supporting current recommendations that regarding the importance of dietary control for women who may become pregnant and for pregnant women.

Key Question 2. Effectiveness of BH4 as an Adjuvant Treatment With Diet Versus Diet Alone in Individuals With PKU

The treatment for PKU with dietary restriction of Phe in natural protein and use of Phe-free medical foods has been critical in reducing the incidence of irreversible neurocognitive impairment in individuals with PKU. However, especially as patients enter adolescence and adulthood, dietary adherence and supplement use can be difficult. As noted in Key Question 1, effects of Phe levels on cognitive outcomes can continue beyond the so-called critical period, making lifelong management the goal for people with PKU and some level of diet for life the current recommendation. However, little is known about rates of adherence to diet, especially as children age into adolescence and beyond.

To date, clinicians, patients and families have lacked therapeutic options other than a lifetime of strict dietary management. Importantly, the ability to liberalize the diet has the potential to affect the quality of life of individuals with PKU who must be constantly vigilant about what they consume. An optimal therapeutic adjunct to dietary management would increase Phe tolerance allowing for increased intake of dietary protein and reducing (but likely not eliminating) the necessity for Phe-free medical foods.

The targeted goal for treatment may differ by the degree to which an individual is able to maintain dietary control. The goal of an adjunct pharmacologic treatment in an individual already able to maintain good dietary control should be to liberalize the diet, with a focus on quality of life, as well as maintenance of cognitive function. The goal for an individual unable to achieve target blood Phe levels with dietary restrictions is to lower Phe levels directly.

As a potential adjuvant treatment approved by the U.S. Food and Drug Administration (FDA) in 2007, BH4 works by enhancing residual enzyme activity present in some individuals with PKU. Research to date is limited, with only two randomized controlled trials (RCTs) and

three uncontrolled open-label trials currently available in the literature. One of the open label trials is an extension of one of the RCTs. The largest of the studies included only 90 individuals.

These relatively small numbers are a reflection of how rare the disease is, which makes recruitment of patients challenging and means that clinical decision making may always need to be made on the basis of few, small studies put into context with other clinical information.

All potential study participants underwent an initial loading test and were only included in efficacy studies if they demonstrated an initial reduction in Phe levels. The proportion of those screened who met this criterion ranged from 19 to 62 percent. Screening responsiveness was to some degree associated with blood Phe level, and individuals diagnosed with mild PKU were most likely to show initial responsiveness. Some individuals with classic PKU and very high Phe (>1200 μmol/L) were responsive, but at a much lower rate than those with mild or moderate PKU. Each study in the review used somewhat different screening criteria, and no approach to assessing responsiveness has been shown to be optimal. As a result, study populations are potentially heterogeneous.

All studies evaluated intermediate outcomes (change in blood Phe levels and Phe tolerance). Almost no information is yet available, and none from RCTs, on longer term outcomes including cognitive impairment, quality of life, nutritional impact and status, and the ability to liberalize diet. In enriched populations (all participants had reduced Phe in initial loading tests), fewer than half of the participants had Phe reductions of at least 30 percent, and reductions in Phe were not related to clinical outcomes.

For example, one of the studies that formed the basis for FDA approval recruited only individuals with blood Phe levels higher than 450 μmol/L and did not require that participants successfully adhere to a restrictive diet.[113] This study population included adults who could be following current recommendations allowing for some liberalization of the diet.[8] Presumably, the clinical target for this group would be to reduce Phe through pharmacologic treatment. Indeed, significantly more treated participants achieved the 30 percent target reduction in blood Phe than did those in the placebo group (44 percent vs. 9 percent).[113] At the end of 6 weeks of treatment, 32 percent of the treated group had achieved Phe <360 μmol/L, compared with 2 percent in the placebo group ($p<0.001$). Thus, although the effect was substantial, a high proportion of treated participants who achieved a reduction in blood Phe of the study target of 30 percent continued to have Phe levels above the clinical target. There is no evidence that a 30 percent reduction is clinically meaningful if blood Phe levels remain above clinical targets. Nonetheless, an open label extension of this trial demonstrated that reductions in Phe observed early in treatment could be maintained up to 22 weeks.[114]

On the other hand, the clinical goal for individuals maintaining dietary control could be to improve their quality of life by liberalizing their diet. In the trial that targeted children with Phe <480 who were successfully maintaining a restricted diet, Phe tolerance was increased.[115] Total Phe intake (dietary Phe intake plus total medical food supplement to maintain blood Phe levels in the therapeutic range) increased from baseline in the BH4 group, approximately doubling to 43.8 mg/kg/day at 10 weeks. An example of the practical implication of this result for the typical 6 year old with PKU who weighs about 45 pounds (20 kilograms) is that while on BH4 for the 10 week duration of this study, she might be able to liberalize her daily diet by consuming an additional 8 ounces of milk, or adding about 1 ounce of meat, or one small serving of spaghetti without meat or cheese. The placebo group in this study had a slight increase in total Phe intake from 16.3 mg/kg/day at baseline to 23.5 ± 12.6 mg/kg/day at 10 weeks. Even so, the impact on Phe tolerance was not uniform across the study population; 36 percent tolerated an increase of 10

mg/kg/day or less, 30 percent tolerated an increase of 11 to 30 mg/kg/day and 33 percent tolerated an increase of 31 to 50 mg/kg/day. Some participants in the BH4 group had transient low blood Phe levels (<26 μmol/L) that were corrected with increased Phe supplementation. Although many of the participants could modestly increase their protein intake, none could be on an unrestricted diet.[114]

Phe tolerance was also assessed in the open label study not associated with an initial RCT.[116] For this study, participants began with a BH4 dose of 10 mg/kg/day, which was increased to 20 mg/kg/day if a 30 percent decrease in Phe or achievement of a target blood Phe level of 360 μmol/L was not observed within a week. Responders who were on a Phe-restricted diet underwent gradual liberalization of their diet to the maximum tolerated natural protein intake while still maintaining plasma levels in the range of 120 to 360 μmol/L. Among individuals who were responders and on a Phe-restricted diet, the average Phe tolerance increased from 21 to 41 mg/kg/day. However, responders' Phe tolerance varied widely from an increase of 20 to 22 mg/kg/day to a non-protein restricted diet in two participants. Of note, a number of conditions may affect Phe tolerance, including illness, type of mutation, degree of BH4 response among others; these are not assessed in the studies.

In all of the studies, compliance with BH4 was reported to be good over the short term. However, long term sustainability of compliance with both BH4 and dietary therapy, especially given the variability in response, has not been evaluated, nor has durability of treatment effects. Authors from the uncontrolled open label trial note that one responder reportedly discontinued BH4 after the trial as the small increases in Phe intake that BH4 allowed was not significant enough to warrant taking the medication. Certainly, as noted above in the summary of results, observed increases in Phe tolerance were moderate at best in classic PKU in terms of allowing changes in diet, and the decision about trade-offs between reliance on medication and carefully titrating liberalization of the diet will need to be made by patients and their clinicians on an individual basis that balances available evidence with the individual's context.

Key Question 3. Effectiveness of BH4 Versus Diet Alone in Maternal PKU

We did not identify any studies of the role of BH4 in pregnant women. Reports of three cases have been published, and a registry is ongoing. It is essential that individual clinicians publish data about their patients and provide data for the registry in order to build an evidence base.

Key Question 4. Effectiveness of LNAAs Versus Diet Alone in Individuals With PKU

In theory, supplementation of a Phe-restricted diet with large neutral amino acids (LNAAs) might have beneficial effect on cognition as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. Some researchers have postulated that this may explain why there are some PKU patients with high plasma Phe levels, low brain Phe levels and normal cognitive function. Similarly LNAAs and Phe, facilitated by a carrier protein, cross the intestinal mucosa. LNAAs, at much higher levels, may also compete with Phe for transport across the intestinal mucosa.

However, there is insufficient evidence to suggest that LNAAs could be a viable treatment option for improving neurologic outcomes or increasing Phe tolerance. There have been only three very small studies (total number of participants was only 47) with inconsistent results, and

there is no evidence that the treated individuals experienced clinically meaningful improvement in their cognitive or neurologic outcomes in the short time that they were studied.

Key Question 5. Effectiveness of LNAAs Versus Diet Alone in Maternal PKU

We did not locate any studies addressing this question.

Key Question 6. Harms of BH4 or LNAAs

Reported harms in trials of BH4 were mild and included headache, throat pain, upper respiratory infection, diarrhea, abdominal pain, nausea and vomiting at rates no greater than seen in placebo arms. Headache was more frequently observed in the placebo group compared with the BH4 group when BH4 was given at a dose of 10 mg/kg/day while a higher proportion (21 percent) taking BH4 at a dose of 20 mg/kg/day reported headache compared with those on placebo (8 percent). Pharyngolaryngeal pain was more frequently reported by the BH4 group at 20 mg/kg/day compared with the placebo group (12 percent vs. 8 percent, respectively) over 10 weeks. Three study participants withdrew from a study due to harms;[112] harms reported in this 2.6 year study were largely minor and in line with those reported in earlier studies with some overlapping participants.[113-115] The rates of harms by study group were compared statistically in only one study, which found 23 percent in the treated group and 20 percent in the placebo group experiencing a harm, probably related to treatment.[113]

Even though studies reporting harms consistently indicate that BH4 is well tolerated and without serious side effects, not all studies assess and report harms, and data are based on a small number of individuals, so ongoing registries will be important for supplementing these data. One fair quality study of LNAAs reported a higher rate of anxiety in the treatment arm, which was an unexpected event, but the study included few participants and studied effects over a short time period.[124]

Key Question 7. Effectiveness of BH4 or LNAAs Plus Diet in Subgroups of Individuals With PKU

Although all five trials enrolled only patients who were BH4-responsive, efficacy in terms of decreasing blood Phe level or increasing Phe tolerance was 44 percent to 62 percent even in this enriched study population. This suggests that there may be yet unidentified subgroups that are more likely to have a positive response to drug treatment. With only small studies published to date, the literature is unable to provide evidence of effectiveness in subgroups including differences seen in response by disease severity.

Strength of the Evidence for Effectiveness of Therapies

Overview

The degree of confidence that the observed effect of an intervention is unlikely to change is presented as strength of evidence and can be insufficient, low, moderate, or high. Strength of evidence describes the adequacy of the current research, in both quantity and quality, and whether the entire body of current research provides a consistent and precise estimate of effect. Interventions that have shown significant benefit in a small number of studies but have not yet been replicated using rigorous study designs will have insufficient or low strength of evidence,

despite potentially offering clinically important benefits. Future research may find that the intervention is either effective or ineffective.

Methods for applying strength of evidence assessments are established in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews[45] developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers (EPCs) and are based on consideration of four domains: risk of bias, consistency in direction of the effect, directness in measuring intended outcomes, and precision of effect. We determined the strength of evidence for the following outcomes: Phe level, tolerance, and variability; cognitive outcomes, nutritional outcomes, harms, and quality of life

Table 21 documents the strength of evidence for each domain of the major intervention–outcome combinations.

Strength of the Evidence

The strength of evidence (confidence that the observed effect will not change) for the relationship modeled of Phe and IQ in the meta-analysis is moderate. There were adequate numbers of studies, but they varied in quality. Additional studies with less risk of bias could strengthen our confidence that the relationship we saw accurately reflects the true effect.

The strength of evidence for a threshold effect of blood Phe of 360 μmol/L in affecting cognition in the offspring of women with PKU is low as it is based on one longitudinal study (Table 21). Further analysis is warranted to confirm and/or expand upon the observed relationship between maternal Phe and offspring IQ. This should not be construed to mean that an effect of Phe on infant outcomes was not seen; rather it specifies that 360 μmol/L may or may not be the ideal goal, and studies are clear in supporting the need for early dietary management for women with PKU considering pregnancy or who are pregnant.

In terms of treatment effects, we separately examined the strength of the evidence for short term effects on Phe, longer term effects on Phe, and direct effects on cognition. The strength of the evidence for a large and significant effect of BH4 on lowering Phe to clinically acceptable levels in the short term is moderate. Given the moderate strength of evidence of the Phe to IQ relationship noted above, and the therefore indirect effect of BH4 on IQ, the overall strength of the evidence for BH4 to improve cognition is low, pending additional data. Strength of evidence is currently insufficient for longer term outcomes, but additional data continue to be published, and ongoing registries will provide important information. The strength of evidence that harms associated with the treatment are minor and not significantly greater than those seen with placebo is moderate, again pending additional research and registry data. With more than 12 studies ongoing, additional data are likely to be available in the future. At this time, it is unclear whether these new studies are likely to corroborate current early outcomes; they will certainly provide additional information on a number of specific outcomes (e.g., measures of cognition) and in specific target populations (e.g., young children and pregnant women).

The strength of evidence for an effect of LNAAs on all outcomes is insufficient.

Table 21. Intervention, strength of evidence domains, and strength of evidence for key outcomes

Outcome / Intervention	Study Type (N Studies of Type Reporting Outcome)	Domains Pertaining to Strength of Evidence (SOE):				SOE
		Risk of Bias	Consistency	Directness	Precision	
Reduction in Phe Levels Over the Short Term (≤12 Weeks) in Responders						
BH4	RCT (2)[113, 115] Uncontrolled open label (3)[112, 114, 116] Case series (3)[118-120]	Medium	Consistent	Direct	Precise	Moderate
LNAAs	RCT (2)[124, 125] Uncontrolled open label (1)[16]	High	Inconsistent	Direct	Imprecise	Insufficient
Reduction in Phe Levels Over the Long Term (>12 weeks) in Responders						
BH4	Case series (4)[117-120]	High	Consistent	Direct	Imprecise	Insufficient data to calculate an effect
Phe Tolerance						
BH4	RCT (1)[115] Uncontrolled open label (1)[116] Case series (3)[117, 118, 120]	High	Consistent	Direct	Imprecise	Insufficient
LNAAs	NR	NR	NR	NR	NR	Insufficient
Phe Variability						
BH4	Case series (1)[119] Cohort study (1)[121]	High	Unknown	Direct	Imprecise	Insufficient
LNAAs	NR	NR	NR	NR	NR	Insufficient
Cognitive Outcomes						
BH4	Case series (1)[118] plus indirect evidence from RCTs plus meta-analysis	High	Unknown	Direct	Imprecise	Low
LNAAs	RCT (1)[124]	High	Unknown	Direct	Imprecise	Insufficient
Nutritional Status						
BH4	Case series (1)[118]	High	Unknown	Direct	Imprecise	Insufficient
LNAAs	NR	NR	NR	NR	NR	Insufficient
Lack of Significant Harms						
BH4	RCT (2)[113, 115] Uncontrolled open label (2)[112, 114] Cohort study (1)[121]	High	Consistent	Direct	Precise	Moderate
LNAAs	RCT (1)[124]	High	Unknown	Direct	Imprecise	Insufficient
Quality of Life						
BH4	NR	NR	NR	NA	NR	Insufficient
LNAAs	NR	NR	NR	NA	NR	Insufficient

LNAAs = large neutral amino acids; NA = not applicable; NR = not reported; RCT = randomized controlled trial; SOE = strength of the evidence

Applicability

The degree to which current research may not be applicable to the clinical population with PKU is a concern, given the small size and homogenous populations in each of the studies. For example, the two RCTs of BH4[113, 115] each focused on a distinctly different population; one on a slightly older population with naturally more variation in diet, and one on a somewhat younger group with tight dietary control. Both reflect important PKU populations, but because they are different, it is unclear whether the results should be synthesized, or whether either study can confirm the results of the other. The two RCTs do provide data on a range of patients who are similar to those seen in routine clinical practice. As is always the case with RCTs, they may not represent the patients less likely to receive regular medical care, or those with additional medical comorbidities. As noted previously, the degree to which care for PKU is available and covered by insurance varies substantially, and it seems likely that individuals unable to access care also may not be situated such that they are recruited into studies. If this is true, then the individuals in the studies may represent a group of patients most likely to be consistent users of medical care and advice; this has implications for the potential issues of adherence to any medical intervention. Little is known about the burden of adhering to medication and the degree to which patients in clinical practice outside of trials would adhere to a drug regimen.

Data are entirely lacking on the use of pharmacologic therapy in pregnancy, although this is likely an area of interest and need for those making clinical decisions. The lack of data may be due in part to characteristics of this patient population. Women with PKU are frequently off of dietary therapy for significant lengths of time before conception. There may also be delays in initiation of clinical metabolic care. Thus, the population available to study pharmacological therapy is small and fetal outcomes may be confounded by the effects of poor blood Phe control. Nonetheless, an ongoing registry should provide invaluable data.

As noted throughout this report, PKU is an exceedingly rare condition, making it challenging even to enroll enough participants in research studies, and even more so to include enough "types" of people to fully represent the patient population and provide applicable data for the full range of PKU patients.

Applicability of Studies Assessing BH4

Participants ranged in age from 10 days to 58 years in all studies and 4 to 49 years in RCTs. Most individuals were classified as having mild to moderate disease, which is appropriate given the expected mechanism of action (i.e., boosting the activity of residual phenylalanine hydroxylase). Studies typically included participants recruited from metabolic clinics at university/academic-affiliated clinics or research centers, which is generally where PKU treatment is available. Most individuals had demonstrated responsiveness to BH4 in a loading study, though there was variability in the loading study methods and the dosage required to produce a response according to study criteria. Participants' adherence to a restricted diet varied, with one RCT including participants with good compliance and one including participants with poor compliance and higher average Phe levels. In practice, patients range in their compliance, so studying the effects of BH4 across a range of dietary compliance is important to understand its potential effects.

BH4 was studied in doses that ranged from 5 mg/kg/day to 26 mg/kg/day. Duration of treatment ranged from 37 days to 2.6 years in randomized and uncontrolled open label trials and up to 9 years in one case series. Individual variation from dosing protocol was reported in some

studies, though overall compliance with the medication regimen was reported to be good in the short term, based on parent or patient report.

Studies primarily assessed short-term change in blood Phe levels and/or Phe tolerance (daily medical food supplement tolerated). One case series[119] and one cohort study[121] measured changes in Phe variability, and one examined clinically meaningful outcomes, including IQ, developmental quotient, and nutritional status.[118] Three case series also assessed participants' ability to liberalize their diets.[112, 117, 118] These case series were very small and of poor quality. Ultimately, to understand the applicability of this drug, substantially more data are needed on clinical and long-term outcomes established to be important to patients.

Evaluations occurred at the end of less than 6 months of treatment, with the exception of case series that followed participants for up to 9 years and one 2.6 year open label trial. Few studies assessed harms, and those that did reported mostly minor events (e.g., headache, throat pain). It is not clear whether these outcomes and harms predict longer-term results.

Applicability of Studies Assessing LNAAs

The use of LNAAs has been proposed primarily for patients unable to achieve dietary compliance. It is difficult to assess the applicability of current research, however, given the very small sample sizes and short-term outcomes measurement. Studies included a total of 47 individuals, most with classic PKU, between the ages of 11 and 45. Participants were on a restricted diet in two studies. In the third study the subjects had an unrestricted diet, and the average Phe intake exceeded 500 mg/day.

LNAA dosages ranged from 250 mg/kg/day to 1 g/kg/day, with many pills required each day. The degree to which it is likely that patients having difficulty maintaining a strict diet would respond positively to taking multiple pills has not been explored. Treatment duration ranged from 1 to 8 weeks, and no study followed participants for more than 1 week after treatment. Formulations of LNAAs varied: 2 studies used the NeoPhe formulation (Solace Nutrition), and one used a formulation manufactured by SHS International. The formulations contained largely the same amino acids with the exception of the addition of arginine in NeoPhe.

An RCT compared LNAAs with placebo with and without participants' usual medical food;[124] another RCT compared LNAAs plus usual diet with placebo and usual diet.[125] The uncontrolled open label study also examined LNAAs with continuation of participants' usual diet.[16]

All studies measured changes in blood Phe level. One RCT also assessed cognitive and affective outcomes and brain Phe.[124] Harms were not systematically assessed in any study. Evaluations occurred shortly after treatment ended, and it is not clear whether these intermediate outcomes predict longer-term outcomes.

Future Research

The existing research gaps related to the use of adjunct pharmacologic therapy in PKU are both substantive and methodologic. Specific deficiencies range from the substantive need for more trials that include more individuals to methodologic gaps in our understanding of the longer term implications of intermediate outcomes. In both cases, research is fundamentally challenging because the disease is so rare, making accrual of adequate numbers of participants difficult, if not impossible, for specific studies. Furthermore, in part because it affects so few people, funding for PKU research is limited, and to date, treatment research is almost exclusively supported by the pharmaceutical industry. Other rare conditions have benefited from an overall research agenda.

To this end, we recommend that a multi-collaborator process that includes a public-private partnership which could create a powerful tool for the future of PKU research in the form of a longer term (perhaps 10 year) research agenda. Furthermore, because the metabolic centers that treat patients with PKU are identifiable, and because PKU patients are almost inevitably treated in such a center if they are receiving care, there is tremendous potential for development of a multicenter research consortium to comprehensively evaluate the complete system of care for individuals with PKU.

Funding from private or public entities should help establish a long-term prospective registry through which the consortium could collect comprehensive and detailed data on subjects with PKU. This could include additional support or linkage with the existing registry that is specific to use of Kuvan, the PKUDOS. The expanded registry could include, but need not be limited to, data on short and long-term outcomes of treatment, such as executive functioning, nutritional status, growth, and quality of life. Ideally, this registry would include a biorepository that would help identify any genotype-phenotype correlations and provide a multidimensional perspective on the effectiveness in practice of treatments, both in the short and long term.

One corollary might be a committee of experts and individuals with PKU to focus on harmonizing data collection, standardized outcomes assessments, required specific and stringent standards for conducting double-blind placebo-controlled trials that adhere to high standards required for synthesis and use in treatment guidelines, and the selection and implementation of studies that clarify the short- and long-term outcomes of treatments and interventions for individuals with PKU, including psychological outcomes. For example, since dietary restriction is the essential cornerstone in the treatment of PKU, it would be helpful to study various methods that would improve adherence to dietary management and other intervention strategies in order to improve outcomes throughout the lifespan, especially for adolescents and adults with PKU. With the establishment of a multicenter consortium, registry, and biorepository, PKU could serve as a model for studying the short- and long-term outcomes of treated inborn metabolic diseases. The field already has a starting position, with the Maternal PKU Collaborative study a case in point.

Future Research on the Relationship of Phe and Cognition

A significant limitation in the current body of research on the relationship between blood Phe level and cognitive outcomes is the lack of consistent methodologies using standardized tools and measures and consistent data collection across centers. The result is that many studies provide incomplete data that cannot be used in meta-analyses, despite a clear need for research to occur across sites in order to accrue adequate numbers for analysis. The studies that were included for meta-analysis were those that met the criteria for data availability. Specifically, studies frequently lacked measures of variance and correlation. Complete reporting of data and results in future studies would ensure that future research can be considered in more robust meta-analyses and can contribute to an improved understanding of the relationship between Phe and IQ.

In addition, some studies that did provide appropriate data for inclusion did not provide information on potentially confounding or modifying factors in the relationship between Phe and IQ. In future research, details about familial IQ, socioeconomic status, maternal education, age at initial treatment and concurrent medications should be fully described so they might be used in a more extensive meta-analysis of Phe-IQ associations. One basic need is to better understand the degree to which the perceived association changes by age, with the practical implication of

understanding the degree of dietary control necessary across age groups. Certainly if patients are able to adhere to diet, then tight control is the standard of care, but understanding the specific implications of looser control, especially in older adults, is lacking and could inform clinical practice. Because tight control is important, an understanding is needed of the supports that might be helpful as individuals age over the lifespan. Related to this is the need for additional measures to assess adequate control beyond blood Phe. This requires an understanding of what outcomes are clinically important, and their relative value to patients and their families. For this to be possible, complete and accurate measure of Phe and cognition over fairly long periods of time is necessary, perhaps through a long-term follow up study or through the multisite collaboration suggested above. Finally, the effects of mild hyperphenylalaninemia as opposed to classic, mild and moderate PKU, should also be clarified, including the impact on cognition, executive functioning, attention, behavioral problems, and other psychological issues.

Ideally, future studies or a complete registry could provide repeated measures (e.g., index of dietary control) of blood Phe that can more precisely characterize an individual's Phe level over relevant time intervals, and standard deviations around those measures so that we can determine the effect of variation in Phe on IQ. Also, rather than relying solely on IQ, alternative outcomes could allow for modeling the degree to which increased Phe is associated with differences between an individual's realized and expected outcomes.

Although research is being conducted on executive function outcomes for individuals with PKU, there is no consensus on which measures of executive function are most appropriate. This highlights the need for fundamental research, because measures of executive function tend to be better reflections of success with day-to-day activities than targeted measures such as IQ. It is plausible that some measures of executive function may be more sensitive to changes in Phe than IQ, and therefore better at identifying impairment. By the same token, establishing the degree to which measures of executive function can and should be combined in analyses would be helpful for synthesizing the currently disparate body of literature. Nonetheless, the sensitivity, validity and acceptability of individual executive function measures in PKU has yet to be established or agreed upon, and current research reflects a reliance on a wide range of outcomes, making synthesis of relationships and pooling of results difficult.

Given the reported association between PKU and an increased incidence of inattention, anxiety and depressive symptoms, additional studies on these and other psychological issues in PKU are also warranted. Some of this work is ongoing, and we encourage more work examining the full range of outcomes associated with PKU.

Future Research on Pharmacologic and Other Adjuvant Treatment

BH4

Research on the use of BH4 as an adjuvant therapy in PKU management is relatively new and consists of small, tightly controlled multisite efficacy studies, two of which are RCTs. The greatest research need in this area is thus for larger studies that include adequate numbers of participants. Given the known difficulty of accruing large numbers of participants, however, researchers should also use existing datasets and, as recommended, use a consortium and multisite approach to gathering data. Ideally, studies will be conducted in both tightly controlled and nonadherent populations, and among different age groups, with appropriate design and power for subgroup analyses. Research should continue to include RCTs, but prospective cohort studies that may have the potential to provide additional effectiveness data—including outside of

a controlled clinical setting—adherence and longer term evidence would also be helpful to support understanding of the role of BH4 in clinical care. These studies should provide substantially more detail on the range of benefits and harms associated with treatment. For example, a better understanding is needed of the effects of BH4 in children less than 4 years of age and pregnant women, and while it may be challenging or inappropriate to conduct RCTs in these populations, observational cohorts or registry data should be considered essential.

Data are not currently available to understand potential modifiers of treatment effectiveness in order to select the best populations for targeting further research and treatment. Moreover, the significant variability in responsiveness to BH4 is unexplained, and subpopulations that have a unique response to this medication have not been well characterized. Causes of variability may be multifactorial and likely include individual patient and genotype differences, drug dose, and individual patient behavior such as dietary adherence. It is unclear, in particular, why a high proportion of individuals who have an initial response in loading studies do not have a durable response even over a few weeks in efficacy trials, even while those who do have a response demonstrate a significant effect. The degree to which this observed variation may be associated with suboptimal adherence should be assessed both in clinical trials and other types of studies.

Another area of potential research that could be explored in combination with studies of BH4 is the use of adherence supports for both drug and diet to optimize potentially positive outcomes. What types of clinical or social interventions might improve adherence to diet and drug, and be associated with improved longer term outcomes? It is assumed that support at familial, social, and system levels may be helpful and this idea should be empirically addressed.

Long-term efficacy outcomes beyond 22 weeks, and safety outcomes beyond three years are currently unavailable, as are measures of behavioral change and cognition and patient-reported outcomes including quality of life. The degree to which reductions in blood Phe are associated with measurable cognitive outcomes or even patient perception of increased mental clarity is unknown; foundational research should be done to identify target outcomes for additional studies. Furthermore, explicit assessment of the potential for liberalization of the diet, and the subsequent nutritional effects has yet to be conducted.

Future research should comprise larger studies designed to allow subgroup analysis of the effectiveness of adjuvant pharmacologic therapy for PKU. Although the current literature does not provide evidence for effectiveness in all target patients, some benefit (albeit of unclear clinical value) is seen in some patients. Whether these patients differ from the overall population in terms of genotype is an area of current research focus that has the potential to allow targeting of treatment to those most likely to benefit. Larger studies are also necessary to determine whether pharmacologic intervention is more advantageous in certain age groups or among individuals of varying dietary control of Phe or severity of disease. The two RCTs of BH4[113, 115] included substantially different study populations thus the two studies can neither be combined nor used to support one another.

A number of studies are reportedly underway to address gaps in the current literature. These include a long-term study of the effect of BH4 on neurocognitive function in young children, a study of the effect in adolescent patients with attention deficit hyperactivity disorder, and a registry that includes pregnant women (PKUMOMS). However, we stress the importance of making data available and note that several commitment studies have been listed as completed, but have yet to make findings available. These include the studies on cardiac effects of BH4. Another commitment study that is reported as fulfilled is an open label study to study the safety and efficacy of BH4 for treating patients with hyperphenylalaninemia, yet no results have been

made available. Finally, most of the published and ongoing studies are currently being funded by the drug companies that stand to gain financially from use of BH4; publicly-funded studies to confirm and expand on reported efficacy and effectiveness data are needed.

LNAAs

The three very small studies of LNAAs cannot be considered as more than proof of concept at this time, and if further work is to occur in this area, it should be done in well-conducted RCTs of adequate size. The mechanism by which LNAAs may work should be clarified, as should the optimal target population and specific treatment goals. The current formulations that have been tested require taking many pills per day and so the formulations should be made more palatable.

Conclusions

Blood Phe level is positively correlated with the probability of having an IQ of less than 85. This predicted probability exceeds the population probability (approximately 15 percent) at 400 µmol/L and reaches a maximum of about 80 percent at 2000 µmol/L. Thus, the commonly-used blood Phe target of 120 to 360 µmol/L is supported in our meta-analysis.[8] Notably, the negative association between Phe and IQ is strongest when Phe is measured at least one year prior to IQ testing. The Phe level obtained more than one year before IQ testing is likely a better indicator of how well Phe has been controlled over the long term, relative to concurrent measurements. This relationship lends support to the principle that cognitive effects accumulate over a long time period, that concurrent measurements are poor predictors of a cognitive effect, and that control should be continued into adulthood. Review of the research on maternal PKU supports the need for dietary control as early as possible before or in pregnancy, and maintenance of Phe control to prevent poor cognitive outcomes in infants.

Dietary management remains the mainstay of treatment for PKU, and as noted above, maintaining control over the lifetime is an appropriate goal. Nonetheless, there is potential for supporting patients in achieving their clinical goals and possibly liberalizing their diet with adjuvant therapy. As a potential adjuvant treatment approved by the U.S. FDA in 2007, BH4 works by enhancing residual enzyme activity present in some individuals with PKU. BH4 has been shown in two RCTs and three open label trials to reduce Phe levels in some patients, with significantly greater reductions seen in treated versus placebo groups.

We do not yet have the ability to reliably predict which patients are most likely to be responders, as all participants in the trials were initially responsive in screening tests, but not necessarily so in the efficacy studies. One RCT also demonstrated increased Phe tolerance using BH4 among children on restricted diets. Overall, harms associated with the drug were minor and did not occur more frequently in the treatment group than in placebo arms. To date, there are no data to directly establish the potential effects of BH4 on longer term clinically important outcomes, including cognition, executive function, and quality of life. Significant gaps in the evidence remain, including effectiveness of the drug in a range of patients outside of the clinical trial setting. Thus, while the strength of evidence is moderate for a large, positive effect of BH4 on reducing Phe levels over the short term in groups of patients showing initial responsiveness, evidence for the effect of BH4 on longer term clinical outcomes is low, and based on indirect associations, including our meta-analysis.

In theory, supplementation of a Phe-restricted diet with LNAAs might have a beneficial effect on cognition as LNAAs may competitively inhibit transportation of Phe through the blood-brain barrier, thereby offering protection by potentially decreasing brain Phe levels. However,

there is insufficient evidence to suggest that LNAAs could be a viable treatment option for reducing Phe levels or increasing Phe tolerance. There have been only three very small studies (total number of participants was only 47) with inconsistent results, and there is no evidence that Phe levels were reduced to clinically meaningful levels in the short time they were studied.

In particular, continued studies that include adequate numbers of participants should be conducted in both tightly controlled and nonadherent populations, and among different age groups for both types of adjuvant therapies. In addition, effectiveness in various groups of patients outside the clinical trial setting are needed, including those with variability in adherence,

Registries have been established and will provide important data in the future, as will ongoing studies that directly measure additional outcomes, including behavioral and psychiatric measures. Data are not currently available to understand potential modifiers of treatment effectiveness, including genotype, in order to select the best populations for targeting further research and treatment. Moreover, the significant variability in responsiveness to BH4 is unexplained. It is unclear, in particular, why a high proportion of individuals who have an initial response during screening do not have a durable response even over a few weeks in the efficacy trials.

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Acronyms and Abbreviations

ADHD	Attention deficit hyperactivity disorder
AE	Adverse effects
AHRQ	Agency for Healthcare Research and Quality
BCI	Bayesian credible intervals
CI	Confidence interval
DQ	Developmental quotient
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
G	Group
IQ	Intelligence quotient
KQ	Key Question
LNAAs	Large neutral amino acids
MCMC	Markov chain Monte Carlo
Mg/dl	Milligram/deciliter
Mg/kg/d	Milligrams/kilogram/day
N,n	Number
NA	Not applicable
NDA	New drug application
NIH	National Institutes of Health
NR	Not reported
PAH	Phenylalanine hydroxylase
PET	Positron emission tomography
Phe	Phenylalanine
PKU	Phenylketonuria
RCT	Randomized controlled trial
TEP	Technical Expert Panel
TOO	Task Order Officer
Tx	Treatment

Appendix A. Search Strategies

[Last updated August 1, 2011]

Table A-1. MEDLINE search strategies (pubmed.gov interface)

Search terms		Search results
#1	phenylketonurias[mh] OR phenylketonuria[tiab] OR phenylketonurias[tiab] OR phenylalanine hydroxylase deficiency[tiab] OR phenylalanine hydroxylase/deficiency[mh] OR pku[tiab] OR hyperphenylalaninemia[tiab]	6949
#2	therapy[sh] OR pharmaceutical preparations[mh] OR therapeutics[mh] OR diet therapy[mh] OR "diet therapy"[Subheading] OR diet[tiab] OR dietary[tiab] OR 5,6,7,8-tetrahydrobiopterin[nm] OR sapropterin[tiab] OR tetrahydrobiopterin[tiab] OR bh4[tiab] OR kuvan[tiab] OR amino acids, neutral[mh] OR large neutral amino acid[tiab] OR large neutral amino acids[tiab] OR lnaa[tiab]	6,456,812
#3	#1 AND #2 AND eng[la] AND humans[mh]	2281
#4	#3 AND editorial[pt]	23
#5	#3 AND letter[pt]	89
#6	#3 AND comment[pt]	48
#7	#3 AND case reports[pt]	260
#8	#3 AND review[pt]	315
#9	#3 AND news[pt]	6
#10	#3 AND practice guideline[pt]	6
#11	#3 AND meta-analysis[pt]	5
#12	#3 AND historical article[pt]	18
#13	#3 AND jsubsetk	2
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	699
#15	#3 NOT #14	1582

Key: jsubsetk consumer health subset; [la] language; [mh] medical subject heading; [nm] substance name; [sh] subheading; [tiab] keyword in title or abstract.

Table A-2. CINAHL search strategies (EBSCO Host interface)

Search terms		Search results
#1	(MH "Phenylketonuria+") OR phenylketonuria OR hyperphenylalaninemia OR pku OR phenylalanine hydroxylase deficiency	385
#2	(MH "Therapeutics+") OR therapeutics OR (MH "Drug Therapy+") OR drug therapy OR (MH "Amino Acids+") OR (MH "Nutritional Support+") OR (MH "Natural and Biologically Based Therapies+") OR (MH "Diet+") OR (MH "Diet Therapy+") OR (MH "Dietary Supplements+") OR diet OR diet therapy OR dietary OR sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan OR large neutral amino acids OR lnaa	744,844
#3	#1 AND #2	234
#4	#3 AND limiters: English language; Human	86
#5	#3 AND limiters: English language; Human; Exclude MEDLINE records	9

Table A-3. EMBASE Drugs and Pharmacology search strategies (Ovid interface)

	Search terms	Search results
#1	(phenylketonuria or pku or hyperphenylalaninemia).mp or exp phenylketonuria/ or exp hyperphenylalaninemia/	7703
#2	(therapy or therapies or treatment or treatments or management or diet or dietary or medical food or medical foods or nutriceutical or nutraceutical or therapeutic or therapeutics or sapropterin or tetrahydrobiopterin or bh4 or kuvan or large neutral amino acid or large neutral amino acids or lnaa).mp. or exp therapy/ or sapropterin/ or tetrahydrobiopterin/ or kuvan/	7,754,746
#3	1 and 2	3983
#4	limit 3 to human and English language	2527
#5	4 and review.pt	445
#6	4 and conference paper.pt	221
#7	4 and editorial.pt	39
#8	4 and letter.pt	72
#9	4 and note.pt	42
#10	4 and short survey.pt	36
#11	4 and case report/	266
#12	4 and practice guideline/	46
#13	4 and systematic review/	8
#14	4 and meta analysis/	6
#15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1104
#16	4 not 15	1423

Key: / all fields; exp explode term; .mp map term as keyword; .pt publication type.

Table A-4. AGRICOLA results (National Agricultural Library interface, keyword search)

Search terms		Search results
#1	(phenylketonuria phenylketonurias pku hyperphenylalaninemia) AND (therapy therapies treatment treatments management diet diets dietary medicine medication medications therapeutic therapeutics sapropterin tetrahydrobiopterin bh4 kuvan large neutral amino acid large neutral amino acids lnaa) Note: limited to English language, terms searched as any of these, keywords anywhere	262

Table A-5. PsycINFO results (CSA Illumina interface)

Search terms		Search results
#1	DE=phenylketonuria OR phenylketonuria OR "phenylalanine hydroxylase deficiency" OR pku OR hyperphenylalaninemia	1963
#2	DE="drug therapy" OR DE="medical treatment general" OR "dietary restraint" OR "medical management" OR "diet therapy" OR dietary OR "drug therapy" OR sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan OR "large neutral amino acid" OR "large neutral amino acids" OR lnaa	127,501
#3	#1 and #2	377
#4	limit #3 to human and English language	314
#5	#4 AND (PT=(abstract collection) or PT=(authored book) or PT=(bibliography) or PT=(book) or PT=(chapter) or PT=(classic book) or PT=(column/opinion) or PT=(comment/reply) or PT=(dissertation abstract) or PT=(dissertation) or PT=(edited book) or PT=(editorial) or PT=(electronic collection) or PT=(encyclopedia entry) or PT=(encyclopedia) or PT=(handbook/manual) or PT=(letter) or PT=(obituary) or PT=(publication information) or PT=(reference book) or PT=(reprint) or PT=(review-book) or PT=(review-media) or PT=(review-software) or PT=(textbook/study guide) or PT=(conference proceedings))	113
#6	#4 AND (PT=(journal article) or PT=(journal) or PT=(peer reviewed journal) or PT=(peer-reviewed status-unknown))	207*

Key: DE descriptor; PT publication type
*articles may be indexed as more than one publication type

Appendix B. Data Extraction Forms

Treatment for Phenylketonuria (PKU)
Abstract Review Form

First Author, Year: _____ Reference #_____ Abstractor Initials: _____

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude editorials, commentaries, letter, reviews, etc.)	Yes	No	Cannot Determine
2. Study includes any of the following: - Infants with PKU <2 years of age: - Children with PKU 2-12 years of age - Adolescents with PKU 13-21 years of age - Adults with PKU 21+ years of age - Pregnant women with PKU	Yes	No	Cannot Determine
3. Eligible study size (N ≥ 10) **N=_____** (please record even if < 10)	Yes	No	Cannot Determine
4. Assesses effectiveness of the following interventions: __a. Sapropterin Dihydrochloride (Kuvan) __b. Large Neutral Amino Acids (LNAAs) __c. Dietary intervention (medical foods/formulas, nutritional supplements, Phe-restricted diet) AND / OR Addresses one or both of these key questions: __**KQ1a.** What is the evidence that any specific phenylalanine (Phe) levels are optimal for minimizing or avoiding cognitive impairment in individuals with phenylketonuria (PKU)? __**KQ1b.** What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?	Yes	No	Cannot Determine

Retain for: _____BACKGROUND/DISCUSSION _____REVIEW OF REFERENCES _____Other

Reason for Other: _____

COMMENTS:

Treatment for Phenylketonuria (PKU)
Full Text Review Form

First Author, Year: _____ Reference #_____ Abstractor Initials: _____

1. Original research (exclude editorials, commentaries, letter, reviews, etc.)	Yes	No
2. (A) Study includes relevant population: __PKU __Hyperphenylalaninemia __BOTH PKU & Hyperphenylalaninemia	Yes	No
(B) Please check subgroups that apply: __Infants <2 years of age __Children 2-12 years of age __Adolescents 13-21 years of age __Adults 21+ years of age __Pregnant women	--	--
3. Eligible study size (N ≥ 10 individuals with PKU and/or Hyperphe) N =_____ (please record if < 10)	Yes	No
4. Study includes assessment of phenylalanine (Phe) levels AND a measure of cognitive function for: __KQ1a: What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU? __KQ1b: What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?	Yes	No
5. Study addresses one or more of the following key questions (check applicable KQ below):	Yes	No
__KQ2: What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone for affecting outcomes, including measures of cognition (including executive function), quality of life, and nutritional status, in individuals with PKU? __KQ3: What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects? __KQ4: What is the comparative effectiveness of large neutral amino acids (LNAAs) with dietary intervention versus dietary intervention alone for affecting outcomes, including measures of cognition (including executive function), quality of life, and nutritional status, in individuals with PKU? __KQ5: What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects? __KQ6: What are the harms, including adverse events, associated with the use of sapropterin dihydrochloride, LNAAs, and/or dietary intervention in individuals with PKU? __KQ7: What is the evidence for the effectiveness of the addition of sapropterin dihydrochloride or LNAAs to dietary intervention for affecting outcomes in subgroups of patients (e.g. demographic, clinical, genotypic, adherence, etc.)?		
6. For comparative effectiveness studies (answered "Yes" to #5), eligible study design __Randomized controlled trial (RCT) __Prospective cohort __Retrospective cohort __Case series __Case control __Non-randomized controlled trial	NA	Yes	No
7. Study published in English		Yes	No

8. Review the reference list (included papers only) and list author name/year for EPC to verify if included in database: _____9. If excluded, retain for ____Background/Discussion ____Other: _____

Comments

Appendix C. Evidence Tables

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Burton et al., 2011 **Country:** US, Canada, Poland, Germany, UK, Spain, France, Ireland, Italy **Enrollment period:** 7/2006[2] **Funding:** BioMarin Pharmaceutical, Inc. **Author industry relationship disclosures:** Received grant support, honoraria, consulting fees, former / current employee & shareholders of BioMarin Pharmaceutical **Design:** Uncontrolled Open label extension study	**Intervention:** Multicentre, multinational, Phase 3b, extension trial of BH4 (PKU-008) **G1:** Sapropterin Dosage & duration: 5-20 mg/kg BH4 orally once daily for 3 years or until one of the following occurred: subject withdrew consent and discontinued the study; discontinued the study at the discretion of the investigator and in accordance with the investigator's clinical judgment; the drug became available via the appropriate marketing approval; or the study was terminated All subjects from PKU-004 began PKU-008 at the dose they were taking at the end of PKU-004. Subjects enrolled from PKU-006 began PKU-008 at 20 mg/kg/day BH4 despite PKU-006 Rx assignment (BH4 or placebo). Dose levels adjusted in increments of 5 mg/kg/day within a range of 5-20 mg/kg/day in accordance with local clinical site recommendations. Formulation: BH4 dissolved in 120-240 mL of water / apple juice for at least first 3 months. Modified later to allow intact tablets: taken before morning meal. **No dietary restriction** **Assessments:** Drug safety at 3 month intervals for adverse events (AEs) and serious AEs , Blood Phe measures (2.5-5 hrs after meal), clinical lab	**Inclusion criteria:** • BH4 responders who completed either PKU-004 or PKU-006 or subjects in PKU-006 who terminated early due to elevated Phe after increases in Phe intake Exclusion criteria: • Screening alanine aminotransferase value > 2× upper limit of normal • Concurrent use of levodopa or folate inhibitors • Pregnant females or subjects of childbearing potential not currently using or unwilling to continue with birth control. **Age, mean/yrs ± SD (range):** **G1:** 16.4 ± 10.2 (4-50) **Other characteristics, mean days ± SD (range):** Overall exposure to drug: **G1:** 658.7 ± 221.3 (56-953) median = 595 While on dissolved tablet: **G1:** 472.2 ± 284.2 While on intact tablet: **G1:** 378.0 ± 185 **Mean dose, mg/kg/day:** Overall: **G1:** 16.4 ± 4.4 While on dissolved tablet: **G1:** 16.2 ± 4.6 While on intact tablet: **G1:** 16.8 ± 4.4	**Cognitive:** **IQ:** NR **Phe level, mean µmol/L ± SD (range):** **G1:** 613.1 ± 328.5 (10-1533) **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level (µmol/L), n (%):** Transitory low Phe levels after Rx: ≤ 26 **G1:** 5 (4.5) ≤120 **G1:** 27 (24.0) Overall, BH4 controlled blood Phe levels throughout the study **Nutritional:** NR **Quality of Life:** NR **Harms:** Any adverse event, %: **G1:** 84 Drug-related AEs 37 (33.3%) Most common drug-related AEs: viral gastroenteritis, vomiting, and headache (each 4.5) Adverse events in ≥ 5% of patients: headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, and vomiting (commonly reported and consistent with PKU-004 & 006) **Treatment emergent adverse events (TEAEs), n subjects [# events] (%):** Infection and infestations: **All[1]:** 74 [198] (66.7) d-r*: 11 [27] (9.9) URI: **All[1]:** 22 [28] (19.8) d-r: 2 [2] (1.8)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Burton et al., 2011 (continued)	evaluations, physical & vital sign measurements **Primary endpoint**: Safety of long term exposure to sapropterin **Secondary endpoints:** NR **RX compliance**: Minor deviations in compliance reported. 94.6% of subjects were at least 80% compliant. **Length of follow-up:** End of 3 years **Groups, n at enrollment:** **G1:** 111 (71 from PKU-004; 40 from PKU-006) **N at follow-up:** G1: 90			Nasopharyngitis: **All[1]:** 20 [30] (18.0) d-r: 3 [6] (2.7) Influenza: **All[1]:** 9 [15] (8.1) d-r: 1 [2] (0.9) Viral infection: **All[1]:** 8 [12] (7.2) d-r: 1 [1] (0.9) Gastroenteritis viral: **All[1]:** 8 [9] (7.2) d-r: 5 [6] (4.5) Pharyngitis: **All[1]:** 7 [13] (6.3) d-r: 0 Gastroenteritis: **All[1]:** 7 [7] (6.3) d-r: 0 Bronchitis: **All[1]:** 6 [7] (5.4) d-r: 0 Gastrointestinal disorders: **All[1]:** 43 [73] (38.7) d-r: 14 [18] (12.6) Vomiting: **All[1]:** 20 [24] (18.0) d-r: 5 [6] (4.5) Diarrhea: **All[1]:** 10 [16] (9.0) d-r: 3 [3] (2.7) Respiratory, thoracic,and mediastinal disorders: **All[1]:** 36 [77] (32.4) d-r: 4 [9] (3.6) Cough: **All[1]:** 21 [28] (18.9) d-r: 3 [5] (2.7) Pharyngolaryngeal pain: **All[1]:** 10 [15] (9.0) d-r: 1 [4] (0.9) Nasal congestion: **All[1]:** 9 [13] (8.1) d-r: 0 Rhinorrhoea: **All[1]:** 6 [8] (5.4)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Burton et al., 2011 (continued)				d-r: 0 General disorders and administration site conditions **All[1]:** 25 [33] (22.5) d-r: 4 [5] (3.6) Pyrexia: **All[1]:** 18 [25] (16.2) d-r: 4 [5] (3.6) Nervous system disorders: **All[1]:** 16 [53] (14.4) d-r: 6 [25] (5.4) Headache: **All[1]**: 13 [48] (11.7) d-r: 5 [23] (4.5) **Total: n = 111** **AEs by tablet type, n (%):** Dissolved: **G1:** 29 (26.4) Intact: **G1:**11 (19.6) [n = 56] **Withdrawal / discontinued Rx, n (%):** **G1:** 3 (2.7) One each of difficulty concentrating, decreased platelet count, and intermittent diarrhea. One patient with possible idiopathic thrombocytopenic purpura had consistently low platelet counts that were considered possibly related to study drug and resulted in study withdrawal)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Burton et al., 2011 (continued)				**Severe AE, n subjects:** **G1: 6 (**1 subject had difficulty concentrating and mood swings which resolved with altering timing of BH4 to avoid coinciding with levothyroxin medication) **Serious AEs, n subjects:** **G1:** 7 1 hospitalization for gastroesophageal reflux; patient had concomitant use of ibuprofen. Other serious AEs reported include a testicular mass and subsequent lymphadenectomy, incontinence required surgical correction, tonsillectomy. menorrhagia and dysmenorrheal, neck injury due to a traffic accident, and gastroesophageal reflux. No deaths or discontinuation due to serious AEs. No age specific differences in AE reporting. **Lab values:** 2 patients had clinically significant ALT and AST values, that decreased after early terminiation N=3 with Neutrophil counts < 1.0 x 10^9 N=24 < 1.5 x 10^9 All decreased in neutrophil count

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Burton et al., 2011 (continued)				were transitory N=13 with platelet counts below lower limit of normal. N=4 platelet count < 100 x 10 [9,] **Modifiers:** NR

Comments:

Subjects here are from study # 800 (PKU-003), #771 (PKU-004) OR #1346 (PKU-006)
[1] All = all reported TEAEs; d-r = drug-related TEAEs
No. (%) subjects who reported the event, No of events
[2] reported as 3-year extension trial that began in July 2006.

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Humphrey, 2011 **Country:** Australia **Enrollment period:** 10/2002 to 12/2010 **Funding:** NR **Author industry relationship disclosures:** NR **Design:** Prospective Cohort	**Intervention:** Tetrahydrobiopterin **Groups:** **G1:** BH4 responders **G2:** BH4 non-responders Mean Dosage: NR Mean duration of Rx: NR Formulation: NR **Assessments:** Blood Phe levels, tyrosine levels, Phe/Tyr ratios along with their variability, at different ranges of Phe levels **Primary endpoint**: Comparison of BH4 Rx effect on blood Phe/Tyr ratios and Phe variability over time in BH4 responders and BH4 non-responders **Secondary endpoints:** Comparison of BH4 Rx effect on tyrosine level and variability over time in BH4 responders and BH4 non-responders, and on Phe levels, tyrosine levels, Phe/Tyr ratios and variability at different ranges of Phe concentrations L**ength of follow-up:** End of Rx **Groups, N at enrollment:** **G1:** 9 (1384 blood samples) **G2:** 25 (4415 blood samples) **N at follow-up:** **G1:** 9 (1384 blood samples) **G2:** 25 (4415 blood samples)	**Inclusion criteria:** All newborn babies with hyperphenylalaninaemia > 400 µmol/L on initial screening and a BH4 load of 20 mg/kg prior to starting treatment Blood samples collected over time from both responders & non-responders during treatment with BH4 Exclusion criteria: See inclusion criteria **Age, mean/yrs ± SD:** NR **Other characteristics:** On BH4 only: n=2 Dietary modification: n=32	**Cognitive:** **IQ:** NR **Phe level, range, µmol/L:** **G1:** 566-1200 (n=7 subjects) > 1200 (n=2 subjects) **G2:** NR **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level,** Median (95% CI), Mean (95% CI), N samples, µmol/L: Phe: **G1:** 338 (329–346) 358 (350–366), 1384 **G2:** 337 (332–344), 370 (332–344) 4415 t-test *P* = 0.025 Per Table 1 and Results section text the median is 337; per the abstract the median is 338. Per Table 1 the CI for the mean is 332-344; per the abstract the CI for the mean is 364-376. **Phe level by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples, µmol/L: Phe: For Phe range 0-200 µmol/L: **G1:** 160 (155-166), 153 (148–158), 187 **G2:** 136 (133-138), 130 (127–133), 1183 t-test *P* < 0.000137 For Phe range 201-400 µmol/L: **G1:** 306 (302-310), 304 (300-308), 745 **G2:** 302 (300-304), 302 (300-304), 2624

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Humphrey, 2011 (continued)				t-test *P* = 0.31 For Phe range 401-600 µmol/L: **G1:** 469 (464-475), 477 (471-482), 349 **G2:** 482 (479-485), 488 (486-491), 1730 t-test *P* = 0.00019 For Phe range 601-800 µmol/L: **G1:** 659 (648-670), 669 (658-680), 78 **G2:** 678 (673-682), 682 (678-686), 629 t-test *P* = 0.034 For Phe >800 µmol/L: **G1:** 872 (800-943), 959 (888-1031), 20 **G2:** 898 (876-920), 963 (941-985), 307 t-test Not done Variation in blood Phe greater in G2 Phe < 400 µmol/L, N samples (%): **G1:** 934 (66.7)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Humphrey, 2011 (continued)				**G2:** 2409 (62) Phe > 600 µmol/L, N samples (%): **G1:** 94 (7.5) **G2:** 493 (12.7) **Tyrosine level,** Median (95% CI), Mean (95% CI), N samples, µmol/L: **Tyrosine:** **G1:** 59 (58–61), 67 (66–69), 1384 **G2:** 62 (61–63), 70 (69–71), 4415 t-test *P* = 0.0083 **Tyrosine level by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples, µmol/L: Tyrosine: For Phe range 0-200 µmol/L: **G1:** 56 (52-60), 63 (59-67), 187 **G2:** 64 (62-66), 73 (70-75), 1183 t-test *P* < 0.000345 For Phe range 201-400 µmol/L: **G1:** 57 (55-59), 64 (62-65), 745

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Humphrey, 2011 (continued)				**G2:** 59 (58-60), 67 (66-68), 2624 t-test *P* = 0.0031 For Phe range 401-600 µmol/L: **G1:** 64 (60-67), 72 (68-75), 349 **G2:** 58 (57-59), 65 (64-66), 1730 t-test *P* = 0.0004 For Phe range 601-800 µmol/L: **G1:** 79 (71-86), 84 (77-92), 78 **G2:** 62 (59-66), 70 (67-74), 629 t-test *P* = 0.0012 For Phe > 800 µmol/L: **G1:** 85 (72-98), 87 (74-100), 20 **G2:** 64 (58-69), 74 (70-79), 307 t-test Not done

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Humphrey, 2011 (continued)				Variation in Tyr levels greater in G2 **Phe/Tyr ratio:** Median (95% CI), Mean (95% CI), N samples: Phe/Tyr ratio: **G1:** 5.4 (5.3–5.6), 6.1 (5.9–6.3), 1384 **G2:** 5.4 (5.2–5.5), 6.4 (6.3–6.6), 4415 t-test *P* = 0.0042 **Phe/Tyr ratio by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples: Phe/Tyr ratio: For Phe range 0-200 µmol/L: **G1:** 2.6 (2.4-2.8), 2.8 (2.6-3.0), 187 **G2:** 1.9 (1.9-2.0), 2.2 (2.1-2.3), 1183 t-test *P* < 0.000173 For Phe range 201-400 µmol/L: **G1:** 5.1 (5.0-5.3), 5.6 (5.4-5.7), 745 **G2:** 5.0 (4.9-5.1), 5.4 (5.3-6.5),

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
				2624 t-test *P* = 0.047 For Phe range 401-600 µmol/L: **G1:** 7.4 (7.0-7.7), 7.9 (7.6-8.3), 349 **G2:** 8.4 (8.2-8.6), 9.0 (8.8-9.1), 1730 t-test *P* < 0.000551 For Phe range 601-800 µmol/L: **G1:** 8.7 (7.8-9.5), 9.2 (8.4-10.1), 78 **G2:** 11.0 (10.6-11.4), 11.7 (11.3-12.1), 629 t-test *P* < 0.000453 For Phe > 800 µmol/L: **G1:** 12.5 (10.6-14.5), 12.3 (10.4-14.3), 20 **G2:** 14.5 (13.8-15.2), 15.4 (14.7-16.1) 307 t-test *P* = 0.007 Phe/Tyr ratio difference noticeable at blood Phe levels > 400 µmol/L and

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
				widened as Phe increased **Genotype**: NR **Nutritional:** NR **Quality of Life:** NR **Harms:** **G1& G2:** Mild diarrhea **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Burton, 2010 **Country:** US **Enrollment period:** 9/2003 to 9/2009 **Funding:** BioMarin **Author industry relationship disclosures:** BioMarin **Design:** Retrospective case series	**Intervention:** Sapropterin: Dosage: 20mg/kg/day, single dose rounded up to the next 100mg increment Duration: mean=19 months (range: 12-31 months) **Assessments:** Blood Phe every 2 weeks for those < 12 years of age and once a month for ages over 12 years, Compliance with dietary therapy by 3 day diet records Compliance with BH4 , questioned at clinic visits & over the telephone but not by any pill count Dietary phe intake was increased to the maximum level tolerated while maintaining blood Phe levels less than 360 umol/L **Length of follow-up:** End of treatment **Groups**: **G1:** Sapropterin **Groups, N at enrollment:** **G1:** 37 **N at follow-up:** **G1:** 37 **Responsiveness:** A decline in blood phe of ≥ 30% after 2 weeks of treatment for those subjects with baseline blood phe of at least 3 mg/dl or a decline in blood phe of 25% and improvement in Symptoms. Those with baseline Phe < 3mg/dl were considered responsive if dietary Phe tolerance was ≥ 200mg/day by 4 wks of treatment	**Inclusion criteria:** • Diagnosis of PKU and were receiving care in the PKU Clinic at Children's Memorial Hospital • Those responsive to BH4 during a 2- to 4-week treatment trial • On BH4 therapy for a minimum of 1yr at the time of data collection • To have a minimum of six blood phe levels available before and six after starting BH4 therapy **Exclusion criteria:** See inclusion criteria **Age, mean/yrs :** **G1:** 12.6 (range: 1.5-32) **Other character-istics, n :** Mild to moderate PKU: 22 Classical PKU: 17	**Cognitive:** **IQ:** NR **Phe level, mean ± SD:** **G1:** 6.67 ± 4.2 mg/dl **Phe Variability:** **G1:** Within-subject variance: 6.897 (0.43) **Nutritional:** NR **Quality of Life:** NR	**Post treatment:** **Cognitive:** **IQ:** NR **Phe level, mean ± SD:** **G1:** 5.16 ± 3.78 Post Rx/ BL, *P* = 0.0002 **Phe Variability:** **G1:** Within-subject variance: 4.799 (0.27) Post RX/BL, significantly different (likelihood ratio test, chi-square=12.7, df = 2, *P* = 0.0017). **Nutritional:** NR **Quality of Life:** NR **Harms:** NR **Modifiers:** Increasing age associated with increasing phe variability , with older ages associated with higher levels of phe (for each 1 year increase in age, phe increases by 0.24 (0.05), p < .0001 after adjusting for repeated measurements). A clear increase in variance in older subjects Phe variability as a function of age: Between subjects Age < 3: 1.4708 Between subjects Age 3-10: 6.2798

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Burton, 2010 (continued)				Between subjects Age > 10: 7.6354 Within subjects: Age < 3: 3.6962 Within subjects: Age 3–10: 8.7274 Within subjects age ≥ 10: 9.4995

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Trefz, 2010 **Country:** Germany **Enrollment period:** NR **Funding:** NR[1] **Author industry relationship disclosures:** NR **Design:** Prospective case series	**Intervention:** **G1:** Tetrahydobiopterin Mean Dosage: 16mg/kg/ day (range: 5-26 mg/kg) Mean duration of Rx: 56 months (range: 24-110 months) Dietary restriction: n=7 Formulation: Tablets dissolved in a glass of water & taken once in the morning **Assessments:** Blood Phe measures at weekly intervals during 1st year of life, twice monthly from 2nd year & once / month in adults **Primary endpoint:** NR **Secondary endpoints:** Long-term effects of BH4 treatment (Phe levels & Phe tolerance) **Poor Dietary compliance:** N = 2 **Length of follow-up:** End of Rx **Groups, N at enrollment:** **G1:** 16 **N at follow-up:** **G1:** 16	**Inclusion criteria:** • Patients with Phenylketonuria • All patients must have received treatment for PKU in accordance with treatment guidelines: infants and children with Phe levels > 600µmol/l; adolescents and adults with Blood Phe of > 1200 µmol/L • Required a clear response to BH4 treatment with a > 30% reduction in blood Phe levels evident after either an acute BH4 -overload test (20 mg/kg body weight over 24 h) or long BH4 -overload test (20 mg/kg body weight over 8 days) Exclusion criteria: See inclusion criteria **Age:** **G1:** Range: 2-38.3 years (n=16) **Other characteristics:** BH4 therapy over 9 years: n=1 Diet + BH4 : n=9/16	**Cognitive:** **IQ:** NR **Phe level, mean ± SD, µmol/L:** **G1:** range: 828-1454 (n=16) **Phe intake** (among those with continued dietary restriction): N = 7 200-300 mg/day **Nutritional:** **G1:** Body weight & height: 3rd percentile (n=1) **Quality of Life:** NR	**Cognitive:** **IQ:** **G1:** Psychomotor development was within normal range in those with ages 5-6 years (HAWIK III) 14/16 achieved long-term Phe control (87.5%) BH4 Responders: n=14 Non-responders: n=2 **Phe level , mean ± SD, µmol/L:** **G1:** 321 ± 236, n=14 Phe decrease from BL: **G1:** 54.6% (range: 28.4-85.6 %, n=16) **Not dietary restriction and stable Phe control**; N=7 **Continued dietary restriction with increased Phe intake** h) to 800-1000 mg/day (n=6) Phe tolerance increased 4 times (n=5) 3 times(n=1) 2 times (n=1) None (n=2) **Genotype**: PAH genotype: p.R261Q/p.R243L (n=1) p.R158Q/IVS4+5G>T (n=1) account for high (blood Phe) fluctuation index **Nutritional:** **G1:** Body weight &

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Trefz, 2010 (continued)				height increased to > 50th percentile after relaxation of diet with a higher content of natural protein (n=1) & increased body weight observed after an increase of BH4 dose to 10mg/kg/day (n=1) **Quality of Life:** NR **Harms:** No Rx related side effects were observed; BH4 was well tolerated **Modifiers:** NR

Comments:
[1] BH4 provided from Schircks laboratories, Switzerland: For 3 subjects BH4 was provided by BioMarin Pharmaceutical Inc.
HAWIK III=Hamburg Wechsler Intelligence test fur Kinder

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Vernon, 2010 **Country:** US **Enrollment period**: 1/2008 to 9/2009 **Funding:** NCRR, NIH **Author industry relationship disclosures:** NR **Design**: Uncontrolled open label trial	**Intervention:** Started with a 7-day trial of BH4 at 10 mg/kg/day. At day 8, plasma phe measured. Responders were those with a 30% reduction in plasma Phe or reduction to treatment range of < 360 µmol/L after day 7. BH4 increased to 20 mg/kg/day for non-responders, and levels rechecked again in 8 days. Patients who were not responders at this time continued BH4 for a total of 30 days and had Phe levels checked. Responders on a Phe-restricted diet underwent gradual liberalization of their diet to the maximum tolerated natural protein intake while still maintaining plasma levels in the range of 120–360 lmol/L **Groups:** **G1:** Completed trial **G1a:** Responders **G1b:** Non-responders **Dose required for response: G1a:** 7-15mg/kg/day: n=14 15-20mg/kg/day: n=4 Formulation: 100 mg pill dose closest to 10 mg/kg **Assessments:** Plasma Phe levels **Length of follow-up:** After the end of 30 days Rx **Groups, N at enrollment:** 36 **N at follow-up:** **G1:** 29 **G1a:** 18 **G1b:** 11	**Inclusion criteria:** Patients with Variant (plasma Phe 401-1199 µmol/L) OR Classical PKU (plasma Phe of > 1200 µmol/L) No limiting dietary / trial baseline plasma Phe criteria **Exclusion criteria:** See inclusion criteris **Age, years:** mean=23.4, median=19, range: 3-58, n=39 **Other characteristics: n (%):** Disease classification: Classical PKU: 15 (52) Variant PKU: 14 (48)	**Cognitive:** **IQ:** NR **Phe level, µmol/L:** Those on restricted diet, n (%): **G1:** 17 (59), Phe=587.0 Range: 225-1363 Among those not on Phe-restricted diet, n: **G1:** 12 Phe=1372.6 Range: 444-1847 G1a & Phe-restricted diet , 14: Phe=484.9 Range: 225-1061 G1a & not on diet, 4: Phe=1049 Range: 444-1461 G1b: Phe=1422.3 Range: 783-1847 G1b & on protein-restricted diet, 3: Phe=1063.7 Range: 783-1363 G1b & on unrestricted diet, 8: Phe=1534.4 Range:1363-1847 **Phe tolerance:** G1a on restricted diet: 21 mg/kg/day **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **G1a, n (%):** 18 (62) Classical PKU, 4/15 (26.6) Variant PKU, 14/14 (100) Not on Phe-restricted diet, 4/12 (33.3) On Phe-restricted diet, 14/17 (82.3) **Phe level: Means, µmol/L:** G1a & on Phe-restricted diet : Phe=226.1 Range: 28-696 (*P* < 0.0001) & G1a & not on Phe-restricted diet : Phe=553.7 Range: 162-793 (*P* = 0.035, paired T-test) G1b, n (%): 11 (38) Phe=1332.6 Range: 731-1798 G1b & on protein-restricted diet, n=3: Phe=978.7 Range: 731-1304 G1b & on unrestricted diet, n=8: Phe=1465.4 Range: 1148-1798 **Phe Tolerance** G1a on restricted diet: 41 mg/kg/day Able to liberalize to unrestricted diet (n=2) Positive behavioral improvements in 1 severely affected

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Vernon, 2010 (continued)				untreated PKU **Nutritional:** NR **Quality of Life:** NR **Harms:** NR **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Burlina, 2009 **Country:** Italy **Enrollment period:** NR **Funding:** Centro Regionale Malattie Metaboliche Ereditarie, Regione Veneto and COMETAASMME, Italy & in part by the Swiss National Science Foundation Grant **Author industry relationship disclosures:** NR **Design:** Retrospective case series	**Intervention:** **G1:** Long-term 6R BH4 treatment given to patients with PKU & Phe levels > 450 µmol/L and positive at BH4 loading Dosage:10mg/kg, twice a day Diet was relaxed based on Phe concentration **Assessments:** Blood Phe measured by tandem mass spectrometry Dietary Phe tolerance by repeated 3- day dietary protocols **Length of follow-up**: 6 months – 7 years **Groups, N at enrollment:** **G1:** 12 **N at follow-up:** **G1:** 12	**Inclusion criteria:** • Known mutations in the PAH gene • Normal pterin profile and dihydropteridine reductase activity (no BH4 deficiency) • Patient or parental agreement with the BH4 loading tests • Patients who previously responded positively to the BH4 loading test performed after 6 months of age • Patients who do not fully comply with a Phe restricted diet Exclusion criteria: See inclusion criteria **Age, mean/yrs ± SD:** **G1:** 5.5 ± 4.7, range: 2-16 Other characteristics**, n (%)**: Normal Psychomotor development: 2 (16.7) **Study group**: Mild-moderate PKU	**Cognitive:** **IQ:** NR **Phe level:** **G1:** range: µmol/L 433-1215 **Phe tolerance: n (%)** < 700mg/day: 11 (91.7) ≥ 700 mg/day: 1 (8.3) **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe tolerance** on BH4 (mg/day) Increased up to 2 to 3 fold from 498 $\pm$ 49 to 1475 $\pm$ 155 mg/day Range: 800-2700 A combined diet with Phe intake of 100mg/kg needed to maintain blood levels < 360 µmol/L in 5 patients 50% were BH4 responders with Phe levels of 450-900 µmol/L **Genotype:** Mutations reported to be BH4 responsive were p.E390G, p.L48S, p.V388M, p.R158Q, p.G48S, IVS10-11g >a and p.I65V **Nutritional:** NR **Quality of Life:** **G1:** Report great improvement by patients & their families, no other data reported **Harms:** No side-effects were observed **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Trefz, 2009 **Country:** US, Germany, Spain & Poland **Enrollment period:** 2/2006-11/2006 **Funding:** BioMarin **Author industry relationship disclosures:** National PKU advisory Board, Bio-Marin & Merck Serono S.A.-Geneva **Design:** RCT	**Intervention:** Phase III, double-blind, randomized placebo-controlled trial of BH4 Part 2: After a washout period of ≥ 1 week, responders from Part 1 * were randomized (3:1) to receive a 10-week course of sapropterin, 20 mg/kg/d, or placebo tablets, once daily. Subjects with a blood Phe concentration of ≥1200 µmol/L in 2 consecutive weekly recordings were instructed to discontinue study drug treatment and receive dietary counseling. At the week 10 visit, follow-up visit was scheduled for Wk 14. A stable Phe-restricted diet to be maintained throughout the study After three weeks a dietary Phe supplement was added or removed every weeks according to Phe level Formulation: BH4 (100mg) tablets were dissolved in 120 to 240 mL of water or apple juice and the solution was administered within 30 minutes. **Groups:** **G1:** BH4 **G2:** Placebo **Assessments:** • Phe levels at wkly intervals from wk 0 to wk 10 • Medical & dietary history • Use of concomitant medications • Blood chemistries • Hematology, urine analysis	**Inclusion criteria:** • 4 to 12 years of age, had a diagnosis of PKU with PAH deficiency, an estimated Phe tolerance ≤1000 mg/d, • Under dietary control with a Phe-restricted diet, as evidenced by a mean blood Phe ≤ 480 µmol/L over the 6 months before study enrollment, as well as at screening **Exclusion criteria:** • History of organ transplantation, use of any investigational agent within 30 days before screening, serum alanine aminotransferase levels of > twice the upper limit of normal • Concurrent disease that might interfere with participation (including untreated neuropsychiatric disorders) • A requirement for treatment with any drug that inhibits folate synthesis, • Concurrent use of levodopa, or a diagnosis of primary BH4 deficiency **Age, mean/yrs ± SD:** **G1:** 7.7 ± 2.8 **G2:** 7.1 ± 2.0 **Other characteristics:** NR	**Cognitive:** **IQ:** NR **Phe level, µmol/L:** Over prior 6 months, mean ± SD: **G1:** 314 ± 107 **G2:** 303 ± 74 Range: **G1:** 112-474 **G2:** 176-447 Mean blood Phe < 300 over prior 6 months, n (%): **G1:**16 (48) **G2:** 5 (42) **Part 2:** Wk 0: Phe, mean ± SD: **G1:** 275.7 ± 135.2 **G2:** NR **Dietary Phe intake (mg/kg/day), mean ± SD:** **G1:** 16.3 ± 8.4, n=30 **G2:** 16.8 ± 7.6, n=9 **Tolerance, mg/kg/day:** **G1:** 0 **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Part 2:** Week 10: Phe supplement tolerated at last visit when blood Phe < 360umol/L, mean ± SD: **G1:** 20.9 ± 15.4 mg/kg/d (95 % CI: 15.4 to 26.4) (*P* < 0.001 vs. BL) **G2:** 2.9mg/kg/d Adjusted Mean ± SE of RX difference in tolerated supplement =17.7 ± 4.5 mg/kg/d, 95%CI: 9-27 (*P* < 0.001) Tolerance range, n (%) 10mg/kg/d: **G1:** 12/33 (36) **G2:** NR 11-30mg/kg/d: **G1:** 10 (30) **G2:** 0 31-50mg/kg/d: **G1:** 11 (33) **G2:** 0 Could not tolerate any supplement: **G1:** 5 (15) **G2:** 7/12 (58) Total Phe intake at wk 10: (dietary Phe intake plus total Phe supplement taken) **G1:** 43.8 (24.6) mg/kg/d (*P* < 0.0001 vs. BL) **G2:** 23.5 (12.6)mg/kg/d (*P* = ns) **Phe level, µmol/L:** Wk3: Phe level, mean ± SD: **G1:** 127.2 ± 89.6 Difference between wk 3 & BL: **G1:** -148.5 ± 134.2.

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Trefz, 2009 (continued)	• Adverse events **Primary endpoints:** Phe tolerance (Phe tolerance defined as the cumulative increase or decrease in Phe supplement at which blood phe is ≤ 360 µmol/L) **Secondary endpoints:** Difference in blood Phe in G1 between week 0 (before dosing) and week 3 (before Phe supplementation) and the comparison of G1 & G2 in the amount of Phe supplement tolerated at wk 10 **Length of follow-up: end of treatment 10 wks** **Groups, N at enrollment:** Part 2: Total N, 46 **G1:** 34 **G2:** 12 **N at follow-up:** Part 2: **G1:** 33 **G2:** 12			*P* < 0.001 **G2:** -96.6 ± 243.6, *P* = 0.20 WK 10: Phe level, mean ± SD: **G1:** 340 ± 235 **G2:** 461 ± 235 Mean ± SE difference in Blood Phe between G1& G2 at wk 3: -135.2 ± 26.9 µmol/L (*P* < 0.001) **Nutritional:** NR **Quality of Life:** NR **Harms, n (%):** Highest incidence (> 5% in G1) during part 2 of the study: Rhinorrhea: **G1:** 7 (21) **G2:** 0 (0) Headache: **G1:** 7 (21) **G2:** 1 (8) Cough: **G1:** 5 (15) **G2:** 0 (0) Pharyngolaryngeal pain: **G1:** 4 (12) **G2:** 1 (8) Diarrhea: **G1:** 4 (12) **G2:** 0 (0) Vomiting: **G1:** 4 (12) **G2:** 0 (0) Abdominal pain **G1:** 3 (9) **G2:** 1 (8) Contusion **G1:** 3 (9) **G2:** 1 (8) Nasal congestion: **G1:** 3 (9) **G2:** 0

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Trefz, 2009 (continued)				Pyrexia: **G1:** 3 (9) **G2:** 2 (17) Decreased appetite: **G1:** 2 (6) **G2:** 0 (0) Erythema: **G1:** 2 (6) **G2:** 0 (0) Excoriation: **G1:** 2 (6) **G2:** 0 (0) Lymphadenopathy: **G1:** 2 (6) **G2:** 0 (0) Streptococcal infection: **G1:** 2 (6) **G2:** 2 (17) Toothache: **G1:** 2 (6) **G2:** 0 (0) URI: **G1:** 2(6) **G2:** 1(8) AEs considered to be related to study Rx: **G1:** 27% **G2:** 25% Serious AE: **G1:** 1 streptococcal infection **G2:** 1 appendicitis (probably not related to study drug) Severe AE: None **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lee, 2008 See Levy et al., 2007 **Country:** UK, Ireland, Canada, US, France, Germany, Italy, Poland **Enrollment period:** NR **Funding:** BioMarin Pharmaceutical **Author industry relationship disclosures:** PKU advisory board, BioMarin **Design:** Open label extension study	**Intervention:** **G1:** Phase III, Multicenter, study of BH4 **G1a:** 6-week forced dose-titration phase (5, 20, and 10 mg/kg/day of study drug consecutively for 2 weeks each) **G1b:** 4-week dose-analysis phase (10 mg/kg/day) **G1c:** 12-week fixed-dose phase (patients received doses of 5, 10, or 20 mg/kg/day based on their plasma Phe concentrations during the dose titration at weeks 2 & 6) **Dose during fixed dose period:** 5 mg/kg/day: < 600 umol/L at week 2 and < 240 umol/L at week 6 10 mg/kg/day: > 600 umol/L at week 2 and > 240 umol/L at week 6 or > 240 umol/L and < 600 umol/L at week 6 20 mg/kg/day: > 600 umol/L at week 6 Duration: 22 weeks Formulation: 100 mg tablet of BH4 which contains 77 mg BH4 base, dissolved in 120–240 ml water, orange juice or apple juice. Doses were calculated by multiplying the patient's weight in kilograms (at week 0) by the assigned dose (5, 10, or 20 mg/kg/day) and rounding up to the next 100 mg unit dose **Assessments:** Blood phe collected at 0, 2, 4, 6,10, 12, 16, 20, 22 weeks	**Inclusion criteria:** • ≥ 8 years of age with PKU and hyperphenylalanemia who had been enrolled in the previous 6-wk RCT study where blood Phe level of ≥ 600 or 450 mmol/L after a protocol amendment at screening, after achieving ≥ 30% reduction in plasma Phe concentration during a previous 8-day treatment course with sapropterin • Received at least 80% of the scheduled doses in the previous RCT • Negative urine pregnancy test & using acceptable measures of contraception for Female patients of child-bearing age • Willing to continue with their current diet during study **Exclusion criteria:** • Discontinued the previous study for any reason other than withdrawal because of high plasma Phe concentrations, or if they were expected to require any investigational product or vaccine prior to completion of the study • Pregnancy (or intended pregnancy) or lactation • Concurrent medical conditions or diseases that would interfere with the conduct of the study; the use of dihydrofolate reductase inhibitors, levodopa, • Or other medications that could influence the **Age, mean/yrs ± SD (range):** 20.4 ± 9.6 (8-49)	**Cognitive:** **IQ:** NR **Phe level, mean ± SD:** **G1:** 844 ± 398 µmol/L **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level, mean ± SD (µmol/L):** **G1a** (6 weeks): 639.9 ± 381.8 **G1b** (10weeks): 645.2 ± 393.4 **G1c** (week 22): 652.2 ± 382.5 **Difference in the mean (SE) of the change in Phe from week 0:** **G1a:** Receiving 5 & 10 mg/kg/day: 104 ± 22.2 ($P < 0.0001$) Receiving 5 & 20 mg/kg/day: 163 ± 22.2, ($P < 0.0001$) Receiving 10 & 20 mg/kg/day: 59 ± 22.2, ($P = 0.009$) **G1b:** 37 patients (46%) showed a decrease in plasma Phe of at least 30%, compared with week 0 **G1c:** mean change from week 0: Overall: -190.5 ± 355.7 **Phe concentration** Among those on 5mg/kg/day (n=6): 437.8 ± 260.5 10mg/kg/day (n=37): 449.9 ± 193.1 20mg/kg/day (n=37): 895.7 ± 407.2 **Week 22:** Among those on 5mg/10mg/20 mg kg/day, the n (%) with ≥30% Phe reductions were 3(50%), 18(49%), 15 (42%) respectively & overall (G1) 36

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Lee, 2008 (continued)	Safety assessed by medical hx, monitoring of adverse events by MedDRA & severity of AEs **RX compliance (self report), n (%):** Took all doses correctly: 48 (60) Missed at least one does and took no incorrect doses: 14 (18) Took at least one does incorrectly and did not miss a dose: 7 (9) Took at least one dose incorrectly and missed at least one dose: 11 (14) No patient took any dose higher than that prescribed. **Dietary compliance**: (19 reported changes in their diet) During the study, 4 patients reported a decrease in Phe intake for a period of > 3 days, and 12 patients reported a total of 15 incidences of increased in Phe intake lasting > 3 days. **Length of follow-up:** 22 weeks **Groups, N at enrollment:** **G1:** 80 **N at follow-up:** **G1:** 79	Other characteristics: NR		(46%) **Nutritional:** NR **Quality of Life:** NR **Harms:** **G1:** A total 260 AEs were reported by 68 (85%) of patients All AE were mild or moderate except 1 Severe event, n: Tooth abscess: 1 82 (32%) AEs in 31 (39%) were possibly or probably related to sapropterin No patient withdrew from the study because of AEs **Most commonly reported AEs, n (%):** Headache: 16 (20) Pharyngo-laryngeal pain: 12 (15) Nasopharyngitis: 11 (14) Vomiting: 10 (13) Diarrhea: 8 (10) Upper respiratory tract infection: 8 (10) Cough: 7 (9) Dysmenorrheaa: 3 (9) Migraine: 6 (8) Back pain: 4 (5) Gastroenteritis: 4 (5) Influenza: 4 (5) **AEs considered probably related to BH4 include, n:** Upper abdominal pain: 1

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Lee, 2008 (continued)				Nausea: 2 Headache: 1 Dizziness: 1 Increased alanine amino-transferase: 1 Moderate nausea: 1 **AEs that were considered to be possibly related to BH4 and were reported by more than one patient included, n:** Urinary tract: 2 Streptococcal infections: 2 Vomiting: 4 Diarrhea: 2 Abdominal pain: 2 Headache: 8 Migraine: 4 Pharyngolaryngeal pain: 3 Cough: 2 Decreased neutrophil counts: 2 Rash: 2 31 AEs possibly related to BH4 were reported by 1 patient each. One serious AE during the study (n=3). Two of these events, urinary tract infection & spinal cord injury, occurred during G1c & the third event, tibia fracture, occurred after the week-22 visit. **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Levy, 2007 See Lee et al., 2008 **Country:** US, Canada, Poland, Germany, France , UK **Enrollment period:** 3/2005-2/2006 **Funding:** BioMarin pharmaceutical , Merck Serono, The Children's Hospital Boston General Clinical Research Centre, the University of Mineesota GCRC, NIH **Author industry relationship disclosures:** PKU advisory board BioMarin pharmaceutical **Design:** RCT, double-blind	**Intervention:** Multicentre, Phase III, placebo-controlled trial of tetrahydobiopterin, 6R-BH4 **G1:** BH4 **G2:** Placebo Dosage: 10mg/kg BH4 & placebo orally once daily for 6 weeks Formulation: BH4 & placebo dissolved in 120-240 mL of water, apple juice or orange juice. Diet to be continued without any modification **Assessments:** Blood Phe measures at screening, at 2 baseline assessments (1&2 wks before randomization), & at Rx weeks 0, 1, 2, 4 & 6 **Primary endpoint**: Change in Phe concentration from baseline to week 6. **Secondary endpoints:** Changes in Phe concentrations in blood at each of the 6 wks of Rx, and the proportion of patients who had blood Phe < 600 µmol/L at wk 6. Compare adverse events and serious adverse events (classified as per MDRA) between G1 & G2 PAH genotype at screening **RX compliance**: 82% (72/88) took all doses of the study drug **Dietary compliance**: Deviations, n (%): **G1:** 7/14 (17) **G2:** 12/47 (26)	**Inclusion criteria:** • Patients with Phenylketonuria • Responsiveness in PKU-001 (previous phase-1 screening study) defined as a reduction of ≥ 30% in blood Phe after 8 days of treatment with BH4 at a dose of 10mg/kg/day • Blood Phe of ≥ 600 µmol/L or ≥450 µmol/L after a protocol amendment at screening • Age of ≥ 8 years • Willingness and ability to comply with study procedures and to adhere to their current diet. • Negative urine pregnancy test • Sexually active men and women had to adopt acceptable birth control measures to prevent pregnancy Exclusion criteria: See inclusion criteria **Age, mean/yrs ± SD:** **G1:** 21.5 ± 9.5 **G2:** 19.5 ± 9.8 **Other characteristics:** NR	**Cognitive:** **IQ:** NR **Phe level, mean ± SD, µmol/L:** **G1:** 842.7 ± 299.6 **G2:** 888.3 ± 323.1 **Phe <600 µmol/L at screening, n (%):** **G1:** 7 (17) **G2:** 9 (19) **Phe ≥600 µmol/L, n (%):** **G1:** 34 (83) **G2:** 38 (81) **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level (6 weeks), mean ± SD, µmol/L:** **G1:** 606.9 ± 377 Mean change from BL ± SD, µmol/L at 6 weeks: **G1:** -235.9 ± 257 **G2:** 2.9 ± 239.5, *P* < 0.0001 **G1 vs. G2:** Mean diff between groups ± SD at wk 6: -245 ± 52.5, 95% CI: -350 to -141 Secondary endpoint (weekly Phe levels) mean difference: -230, 95% CI: -317 to -144 6wks: 11-29% reduction in blood Phe, n: **G1:** 12 **G2:** 10 ≥ 30% reduction of blood phe, n (5%): **G1:** 18/41 (44), 95% CI: 28-60 **G2:** 4/47 (9), 95%CI: 2-20, ≥ 50% reduction in phe, n (%): **G1:** 13/41 (32) 95% CI: 18–48 **G2:** 1/47 (2) 95% CI: 0–11 63% reduction in phe, n: **G1:** 1 Increased Blood phe, n (5): **G1:** 7 (17) **G2:** 21 (45)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Levy, 2007 (continued)	**Length of follow-up:** End of 6 weeks **Groups, N at enrollment:** **G1:** 42 **G2:** 47 **N at follow-up:** **G1:** 41 **G2:** 46			Efficacy at 6 wks from screening: Phe < 600 µmol/L, n (%): **G1:** 22/41 (54), 95%CI: 38-69 (*P* = 0.004) **G2:** 11/47 (23), 95%CI: 11-36 Phe < 600 at wk 6 & ≥ 600 µmol/L at screening, n (%): **G1:** 15/34 (44) **G2:** 4/38 (11) *P* = 0.003 Phe <360 µmol/L at wk 6, n (%): **G1:** 13/41 (32) **G2:**1/47 (2), *P* < 0.001 **Genotype:** 16/17 fully genotyped had at least 1 non-null mutation. 6 mutations were associated with both responsiveness & non-reponsiveness 1 had two PAH mutations (IVS10-3C->T and G272X), (presumably null) , & had 63% reduction in Phe after 6 weeks of treatment with sapropterin **Nutritional:** NR **Quality of Life:** NR **Harms:** Drug related, n (%): **G1:** 11/47 (23) **G2:** 8/41 (20), *P* = 0.80 Adverse effects, n (%):

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Levy, 2007 (continued)				Any adverse event on or after 1st dose: **G1:** 21 (51) **G2:** 34 (72) Adverse events in ≥ 5% of patients: URI: **G1:** 7 (17) **G2:** 13 (28) Headache: **G1:** 4(10) **G2:** 7 (15) Vomiting: **G1:** 2 (5) **G2:** 4 (9) Abdominal pain: **G1:** 1(2) **G2:** 4 (9) Diarrhea: **G1:** 2 (5) **G2:** 3(6) Pyrexia: **G1:** 2 (5) **G2:** 2(4) Back pain: **G1:** 1(2) **G2:** 3 (6) Significant changes in liver enzymes, n: **G1:** 0 **G2:** 2 Low T4 at wk 0 & 6, n: **G1:** 1 High TSH at 6 wks, n: **G1:** 1 No serious event No deaths **Modifiers:** NR

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lambruschini, 2005 **Country:** Spain **Enrollment period:** NR **Funding:** REDEMETH, INERGEN (C03/05), and FIS-021450 **Author industry relationship disclosures:** NR **Design:** Prospective case series	**Intervention:** BH4 50mg tablet Start dose of 5 mg/kg/day, given in 3 daily doses. Phe- restricted diet progressively liberalized by adding 200mg Phe/day for 2 months, while gradually reducing the formula (from a mean ±SD of 51 ± 40 g/day) until complete removal was achieved. BH4 therapy discontinued when tolerance could not be increased > 400mg Phe/day and formula could not be completely removed **Assessments:** Anthropometric (ht and wt), nutritional status (brachial fat and muscle, nutrient intake micronutrient levels, genetic & neuropsychological evaluation Intelligence by K-ABC WISC-R, Brunet-Lezine Plasma Phe & tyrosine by chromatography Phe intake by 3 day QNR Phe tolerance before the start of BH4 therapy & whenever an increase in daily Phe intake Phe tolerance defined as the highest phe intake tolerated while keeping blood phe within 120-360 µmol/L Index of dietary control calculated as the mean of the Median of all Phe values for 1 year **Length of follow-up:** After 1 year of Rx **Groups, N at enrollment:** **G1:**14	**Disease classification:** Mild PKU (tolerance: 400–600mg Phe/day, n=9) Moderate PKU (tolerance: 350–400mg Phe/day, n=4) Classic PKU (tolerance: < 350mg Phe/day, n=1) **Inclusion criteria:** Mild/ moderate PKU patients with good response(45-94% decrease in plasma Phe) to the BH4 loading test Exclusion criteria: Defect in BH4 synthesis or recycling **Age, range in years:** G1: 0.2-12.2 **Other characteristics:** Anthropometric measurements were within age- and sex-specific percentiles for a healthy population	**Cognitive:** **IQ, mean ± SD:** **G1:** 102 ± 9, range: 91-112 (older patients) **Developmental quotient:** NR **Phe level:** **G1:** 382 ± 229 µmol/L **Phe tolerance (n=11) mean ± SD (range):** **G1:** 356 ± 172 mg/day (201–600) **Nutritional:** **G1:** Selenium intake, mean=47.1 µg/day **Plasma selenium:** **G1:** 61.6 ± 21.1 µg/L **% of Urine Biopterin:** **G1:** 39.4 ± 12.3 **Quality of Life:** NR	**Cognitive:** **IQ, mean ± SD:** **G1:** 108 ± 9; range: 96-118 (*P* = NS) (older patients) No alterations in attention, executive function tests **Developmental quotient (ages < 3 yrs), mean ± SD (range):** **G1:** 104 ± 3 (100-106) **After 1 yr Rx:** Phe level: **G1:** 442 ± 141 (*P* = NS) IDC (n=10) within the safe range with BH4 therapy at 5mg/kg/day **Phe tolerance: mean ± SD (range): G1:** 1546 ± 192 mg/day (1240–1801) (*P* =0.004). PKU formula could be removed (n=11) **Genotype**: P275S mutation (n=1) associated with long-term BH4 responsiveness (no other data reported) **Nutritional:** Selenium intake (n=11), mean: **G1:** 56.2 µg/day (*P* = NS) **Plasma selenium (n=11), mean, ± SD:** **G1:** 85 ± 21.4 µg/L (*P* = 0.02)

Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Lambruschini, 2005 (continued)	**N at follow-up:** **G1:**11 (9 mild PKU, 2 Moderate PKU)			**% of Urine Biopterin, mean ± SD:** **G1:** 69.6 ± 17.7 (*P* = 0.028) No difference observed in vitamin, oligo-element daily intake **Quality of Life:** NR **Harms:** No adverse effects reported **Modifiers:** NR

Comments:
K-ABC=Kaufman Assessment Battery, WISC-R=Wechsler Intelligence Scale for Children-Revised, QNR=questionnaire, IDC=Index of dietary control

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Matalon, 2007 **Country:** Russia, Ukraine, US, Italy, Brazil, Denmark **Enrollment period:** NR **Funding:** Genetics Research Trust, the Mid-Atlantic Connection for PKU and Allied Disorders (MACPAD), the South Texas Association for PKU and Allied Disorders (STAPAD), and PKU and Allied Disorders of Wisconsin (PADOW), PreKUNil and NeoPhe by PreKU lab, Denmark **Author industry relationship disclosures:** None **Design:** RCT	**Intervention:** Double-blind placebo controlled crossover trial of tablets of Large neutral Amino Acid (LNAA-NeoPhe) & placebo, with a random order of placebo & LNAA **Groups:** **G1:** LNAA / placebo **G2:** Placebo /LNAA **Dosage**: **G1:** 0.5 g/kg/day in 3 divided doses to be taken with meals, which is about one tablet/ kg/day. **G2:** same as G1 & contained lactose monohydrate, microcrystalline cellulose and colloidal hydrated silica. 1 week washout period prior to the next week of crossover trial Diet was continued as before the trial **Assessments:** Blood Phe determined at the beginning & then twice weekly **Length of follow-up:** A week after treatment **Groups, N at enrollment:** **G1/G2:** 20 **N at follow-up:** **G1/G2:** 20	**Inclusion criteria:** Should have PKU and old enough to swallow pills **Exclusion criteria:** See inclusion criteria **Age:** **G1/G2:** range (11-32 years) Other characteristics, n: Disease classification: Classical PKU, 19	**Cognitive:** **IQ:** NR **Phe level, mean:** **G1/G2:** 932.9 µmol/L Those adhered to PKU formula (n=7): 531.6 µmol /L **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level, mean ± SD:** (µmol/L) **G1:** 568.4 (average decline of 364.5 ± 232.),39% reduction (P < 0.0001) **G1 and adhered to formula:** 281.5 (average decline of 250.1 ± 173.7), 47% reduction (P = 0.009) **G2**: 882.66 (decline of 5.4%) (P = 0.07) **Nutritional:** NR **Quality of Life:** NR **Harms:** NR **Modifiers:** NR

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Schindeler, 2007 **Country:** Australia **Enrollment period:** NR **Funding:** SHS International **Author industry relationship disclosures:** NR **Design:** RCT	**Intervention:** Double-blind, randomized crossover study with LNAA Dosage: 250mg/kg/day of LNAA, 3 equal daily doses 4 phases of study: **G1A:** Phase 1: Usual Medical product, usual Phe restricted diet & LNAA tablets **G1B:** Phase 2: Usual Medical product, usual Phe restricted diet & placebo tablets **G1C:** Phase 3: No Medical product, took usual Phe restricted diet & energy intake, LNAA tablets **G1D:** Phase 4: No Medical product, took usual Phe restricted diet & energy intake, Placebo tablets Duration: Each phase for 14 days with a 4 week washout period between phases **Assessments:** Brain Phe by MRS Plasma Phe at the completion of each phase 3 day food diary to assess intake of dietary protein Intelligence by WASI Components of attention & executive function by CPT-II, CANTAB, D-KEFS Self-report of mood ratings by DASS Length of follow-up: end of each phase All on diet & medical products for PKU At the end of each phase: median (min,max), Phe intake mg/kg/day **G1A:** 18.6 (5.3, 27.9) **G1B:** 18.5 (6.4, 43.9) **G1C:** 17.5 (4.5, 29.7) **G1D:** 21.8 (6.2, 27.9)	**Inclusion criteria:** Early treated Classical PKU (plasma Phe at some stage >1000 µmol/L) Currently on diet & medical products for PKU **Exclusion criteria:** see inclusion **Age, median/yrs:** 24y 9 m, range (11y 8m to 45y 1m) Other characteristics**, n (%)**: Classical PKU subjects=16 (100)	**Cognitive:** **IQ: mean (SD)** 101 (16) **Phe level:** Previous year Median blood Phe levels used as baseline Excellent control (<450 µmol/L), n=0 Good control (450-750 µmol/L), n=9 Marginal control (750-1000 µmol/L), n=6 Poor control (>1000 µmol/L), n=1 **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** G1C vs. G1D: Better performance on measures of verbal generativity (*t*=2.657, *P* = 0.018) and non verbal cognitive flexibility (*t*=2.66, *P* = .018) G1C vs. G1A: Better verbal self monitoring (*t*=2.179, *p*=0.046) G1A & G1B vs. G1C & G1D: better performances on attention measures (*F*=23.64, *p*=0.000) **Phe level:** Brain Phe, µmol/L, range: 176-365 (no significant differences between phases) Plasma Phe µmol/L, at the end of each phase, median (min,max): G1A: 639 (149, 1044) G1B: 734 (19, 1231) G1C:958 (553, 1500) G1D: 1180 (641, 1744) Significant differences in plasma Phe between G1C & G1D (p=0.001), between G1A & and G1C (*P* = 0.001), between G1A & G1D (*P* < 0.0005), between

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Schindeler, 2007 (continued)	Protein total g/kg/day **G1A:** 1.62 (0.96, 2.10) **G1B:** 1.43 (0.88, 1.85) **G1C:** 0.63 (0.34,0.93) **G1D:** 0.51 (0.17,0.62) LNAA total g/kg/day **G1A:** 0.90 (0.53, 1.27) **G1B:** 0.75 (0.32, 1.05) **G1C:** 0.35 (0.24,0.46) **G1D:** 0.15 (0.05,0.21) Compliance on LNAA supplement - good **Groups, N at enrollment:** **Total:** 16 **N at follow-up:** **Total:** 16			G1B and G1D (p=0.001), and between G1B and G1C (p=0.023). There was no significant difference between G1A and G1B (p=0.22), however, plasma Phe was reduced in most subjects (9 of 16) by an average of 24.9% during G1A **Plasma Phe/Tyr ratio:** median (min,max) ; G1A: 10 (1.2, 17.9) G1B:14 (0.2, 27.5) G1C:18 (8.6, 36.6) G1D: 30 (11.9, 52.1) **Plasma Phe/Tyr ratio:** significant differences between G1A and G1B (*p*=0.017), between phase G1C and G1D (*p*=0.001), between G1A and G1C (*p*=0.02), between G1A and G1D (*p*<0.001),and between G1B and G1D (*p*<0.001) No significant diff between G1B & G1C (p=.23) **Nutritional:** G1A:NR G1B:NR G1C: NR G1D: NR **Quality of Life:** G1A:NR G1B:NR G1C: NR

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Schindeler, 2007 (continued)				G1D: NR **Harms:** Higher levels of anxiety symptoms while on LNAA (F=5.2, p=.039), G1A & G1C compared to G1B & G1D **Modifiers:** No correlation between Plasma & brain Phe when Plasma Phe <1200 µmol/L G1D: Significant correlation between plasma & brain phe (r=0.90, p=.04, where phe ≥1200 µmol/L n=5) No significant correlations Between plasma Phe or Phe/Tyr ratio with total dietary LNAA intake, or dietary Phe intake G1A: significant negative correlations were obtained between plasma Phe and semantic verbal Fluency (VF-Category; r=- 0.525, p=0.018. G1B: plasma Phe and inattention Negatively correlated (CPT-Errors, r = - 0.441, *p*=.044). G1C: a negative correlation between spatial working memory and plasma Phe (SWM, r= - 0.464, *p*=0.035).

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Schindeler, 2007 (continued)				G1D: no significant correlations **Across phases,** Statistically significant negative correlations between plasma Phe and verbal generativity (VF-Letters; r= - 0.465, (*p*=0.035) and non-verbal self monitoring (DF-reps, r = -0.488, *p*=0.027).

Table C-2. Adjuvant treatment for phenylketonuria (PKU) – LNAA evidence tables (continued)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Matalon, 2006 **Country:** US, Ukraine, Russia **Enrollment period:** NR **Funding:** Genetics Research Trust **Author industry relationship disclosures:** None **Design:** Uncontrolled open label trial	**Intervention:** Open-label study of LNAAs (NeoPhe) **Groups : G1:** 0.5g/kg/day of NeoPhe **G2:** 1.0 g/kg/day of NeoPhe Duration: 1 week Formulation: NeoPhe divided into 3 doses and taken before meals Instructed to continue with their diet as before the trial **Assessments:** Blood Phe at baseline, 1 wk and 1 week after Rx **Length of follow-up:** 1 week after the end of Rx **Groups, N at enrollment:** **G1:** 8 **G2:** 3 **N at follow-up:** **G1:** 8 **G2:** 3	**Inclusion criteria:** •Should have PKU •Old enough to swallow pills **Exclusion criteria:** See inclusion criteria **Age, mean/yrs :** **G1:** 20.5 **G2:** 16.5 **Other characteristics: G1+G2:** All 11 patients were classical PKU 2 responded to BH4 loading, none were on BH4 during study	**Cognitive:** **IQ:** NR **Phe level, mean µmol/L:** **G1:** 957.4 **G2:** 1,230 **Nutritional:** NR **Quality of Life:** NR	**Cognitive:** **IQ:** NR **Phe level, mean µmol/L ± SD:** **G1:** 458.4 **G2:** 549 Drop in Phe, mean ± SD: 601 + 370, n=11, (P = 0.0003) **% decline in Phe:** **G1:** 52 **G2:** 55 **G1/BL:** *P* = .004 **Nutritional:** NR **Quality of Life:** NR **Harms:** NR **Modifiers:** NR

Table C-3. Studies addressing Phe levels and IQ

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Viau 2011	Concurrent	Classic moderate mild	55	Overall: 11.04 ±4.59 (6-22)	Overall: Mixed	592 ± 355 (42-1774)	Wechsler	Overall: 99.2 ± 13.6 (69 -132)	-0.098 (0.476)
	Historical critical		55			365 ± 128 (162-809)			-0.157 (0.253)
	Historical, non-critical (Age 7-12 years)		38			530 ± 209 (172-1115)			-0.057 (0.732)
	Historical, non-critical (Age > 12 years)		15			693 ± 257 (372-1329)			-0.034 (0.905)
Azadi 2009	Concurrent	Classic	10	13.28 ± 4.13 (6.58-19.83)	Restricted	1363.80 ± 410.44 (704-2025)	Raven	108.40 ± 12.45 (90-128)	0.21 (0.57)
Anastasoaie 2008	Critical	Classic, moderate, mild, unclassified	46	7.5 ± 3.3 (2.9-15.5)	Restricted	312 ± 132 (125-852)	Wechsler	104±15 (68-143)	-0.17 (0.38)

Table C-3. Studies addressing Phe levels and IQ (continued)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Wasserstein 2006	Concurrent	Classic	10	28.80 ± 3.82 (23-35)	Restricted	1137.00 ± 327.10 (408-1584)	NR	98.8 ± 18.13 (74-124)	-0.21 (0.56)
	Historical			29.1 ± 3.64 (23-35)		607.6 ± 246.8 (282-1170)		98.5 ± 18.1 (74-124)	-0.28 (0.24)
	Critical			28.80 ± 3.82 (23.00-35.00)		433.2 ± 98.5 (282-576)		98.8 ± 18.1 (74-124)	-0.24 (0.51)
Pfaendner 2005	Historical	NR	31	29 (18-40)	Mixed	399.3 ± 163.3 (208.1-686.1)	Hamburg Wechsler	107.5 ±18.7 (64-148)	-0.46 (<0.01)
	Critical			29 (18-40)		308.6 ± 102.2 (181.5-570.5)		107.5 ±18.7 (64-148)	-0.52 (<0.01)
Rupp 2001	Concurrent		17	22.24 ± 2.54 (17-27)		1175.88 ± 319.61 (660-1780)		104.06 ± 15.67 (61-129)	-0.60 (0.01)
	Historical	Classic		22.24 ± 2.54 (17-27)	Mixed	654.71 ± 184.73 (420-970)	WAIS-R	104.06 ± 15.67 (61-129)	-0.65 (0.01)
Weglage 2001	Historical,	Classic	15	18.47 ± 3.96 (14-30)	Unrestricted	661.33 ± 267.62 (230-1420)	CFT20	98.4 ± 14.0 (77-132)	-0.36 (0.05)
	Critical			18.47 ± 4.03 (14-30)		519.33 ± 198.58 (230-880)		98.40 ± 14.0 (77-132)	-0.70 (.005)

Table C-3. Studies addressing Phe levels and IQ (continued)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Griffiths 2000	Critical	Classic	57	8.14 ±0.3	Restricted	466 ±154	Multiple	85.8 ±13.9	-.035 (<0.01)
Weglage 2000	Concurrent	Classic	42	14.7± 2.9 (10-18)	Not Clear	894 ± 360	CFT20	100 ±14 (76-127)	-0.25 (ns)
	Critical					528 ± 96		100 ±14 (76-127)	-0.33 (<.05)
Cerone 1999	Concurrent	Classic	16	11.1 ± 0.72(10-12)	Unrestricted	1826.3 ± 462.9 (1320-3000)	Multiple	104.9 ± 4.7 (98-114)	0.05 (0.84)
Weglage 1995	Historical	NR	20	10y11m ±1.3 (8.9-13.1)	Not Clear	11yrs:474±144 (282-810) 14 yrs:534 ± 174 (276-1014)	CFT20	101.4 ±10.2 (88-121) 107.4±10.2 (88-135)	-0.33 (ns) -0.41 (<.05)
Leuzzi 1998	Historical	NR	14	12.30 ± 2.50 (9.00-17.60)	Mixed	543.79 ± 148.13 (230-800)	WISC-R WAIS	90.64 ± 13.52 (59-110)	-0.42 (0.13)
Ris 1994	Concurrent	Classic	25	22 (18-26)	Mixed	1323.28 ± 445.29 (254-2252)	WAIS-R	89.80 ± 11.17 (71-119)	-0.35 (0.09)
Jones 1995	Concurrent	Classic	32	17.81 ± 6.31 (7.50-29)	Mixed	1193.28 ± 425.21 (348-2010)	Multiple	91.91 ± 21.79 (44-127)	-0.20 (0.28)
Schmidt 1994	Concurrent	NR	17	20.5 (17-24)	Mixed	1233.18 ± 390.16 (564-1932)	WAIS	110.00 ± 10.96 (89-132)	-0.42 (0.09)

Table C-3. Studies addressing Phe levels and IQ (continued)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Welsh 1990	Concurrent	NR	11	4.64 ± 0.47 (4.08-5.75)	Restricted	564.55 ± 256.58 (66-1074)	Multiple	104.73 ± 13.94 (82-120)	0.13 (0.70)
	Critical			4.64 ± 0.46 (4.08-5.75) 4.64 ± 0.47 (4.08-5.75)		570.55 ± 195.1 (66-1074)		104.73 ± 13.6 (82-120)	-0.04 (0.86)
	Historical					576.55 ± 118.3 (438-840)		104.73 ± 13.94 (82-120)	-0.42 (0.19)
Seashore 1985*	Historical & Critical	Classic	14	11.33 ± 2.19 (8.17-14.50)	Unrestricted	1613.6 ± 245.2 (1080-2040)*	Multiple	90.0 ± 13.32 (68-112)	-0.56 (0.04)

CFT=Culture Fair Intelligence Test; IQ=intelligence quotient; NR=not reported; Phe=phenylalanine; PKU=phenylketonuria; WAIS=Wechsler Adult Intelligence Scale; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WISC=Wechsler Intelligence Scale for Children; WISC-R=Wechsler Intelligence Scale for Children-Revised

* Imputed Phe values

Mixed diet=some participants adhering to restricted diet and some not adhering to restricted diet

Appendix D. Tools Used To Assess the Quality of the Literature

Quality Assessment Form: Studies Addressing IQ and Phe Levels

Question	NA	-	+
1. Was the approach to recruiting participants into the study clearly documented and applied consistently?			
2. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?			
3. Was there a high rate of attrition?			
4. Were all eligible participants included in the analysis?			
5. Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?			
6. Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?			
7. Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
8. Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?			
9. Are the potential outcomes pre-specified by the researchers?			
10. Are all pre-specified outcomes reported?			

Comments:

Quality Assessment Form: Before-and-After Studies

Reviewer initials:	Date:	Study ID:
1. Were patients enrolled consecutively?		
☐ Yes -"Consecutive enrollment" was explicitly stated; OR - All, or a random sample of, patients treated within a given date range were included	☐ Unclear - No information on the enrollment process was reported	☐ No - Patients were selected by the investigator
Notes:		
2. Were incomplete outcome data adequately addressed?		
☐ Yes - ≤ 10% of enrolled patients withdrew/ dropped out of the study before the last outcome assessment; OR - ≤ 25% of enrolled patients withdrew/ dropped out *and* reasons for withdrawal were described and unrelated to treatment	☐ Unclear - Proportion of patients that withdrew from study was unclear; OR - 10% < x <25% of enrolled patients withdrew, but reasons were not reported	☐ No - 10% < x <25% of enrolled patients withdrew and reasons were related to treatment; OR - >25% of enrolled patients withdrew
Notes:		
3. Was a standardized approach used to assess outcomes?		
☐ Yes - One or more key outcomes were assessed blindly, in duplicate, or by an independent observer	☐ Unclear - Approach to outcome assessment was not reported	☐ No - Outcomes were assessed by the investigator or treatment provider; OR - All outcomes were patient self-reported
Notes:		

Quality Assessment Form: RCTs and Other Intervention Studies

Risk of Bias	Criterion
Selection bias and confounding	Was treatment adequately randomized (e.g., random number table, computer-generated randomization)?
	Was the allocation of treatment adequately concealed (e.g.,. pharmacy- controlled randomization or use of sequentially numbered sealed envelopes)?
	Are baseline characteristics similar between groups?
	Does the analysis control for baseline differences between groups?
	Did the strategy for recruiting participants into the study differ across study groups?
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
	Did variation from the study protocol compromise the conclusions of the study?
	Was there a high rate of differential or overall attrition?
	Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?
	Is the analysis conducted on an intention-to-treat (ITT) basis?
Detection bias	Were the outcome assessors blinded to the intervention or exposure status of participants?
	Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
	Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
	Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Reporting bias	Are the potential outcomes, including harms, pre-specified by the researchers?
	Are all pre-specified outcomes reported?

+, -, NA, Cannot Determine

Quality Assessment Form: Harms Reporting

1. Were the harms PRE-DEFINED using standardized or precise definitions?
2. Were SERIOUS events precisely defined?
3. Were SEVERE events precisely defined?
4. Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?
5. Was the mode of harms collection specified as ACTIVE?
6. Was the mode of harms collection specified as PASSIVE?
7. Did the study specify WHO collected the harms?
8. Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?
9. Did the study specify the TIMING and FREQUENCY of collection of the harms?
10. Did the author(s) use STANDARD scale(s) or checklists(s) for harms collection?
11. Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?
12. Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?
13. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?
14. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?
15. Did the author(s) specify the type of analyses undertaken for harms data?

+, -, NA

Appendix E. Quality of the Literature

Randomized Trials

Table E-1. Quality assessment of randomized trials addressing adjuvant treatment of PKU

Domain	Selection bias & confounding					Performance bias	Attrition bias			Detection bias				Reporting bias		Final rating
Author, Year	Random assignment adequate	Allocation adequately concealed	Baseline characteristics similar between groups	Analysis controlled for baseline differences	Recruitment strategy differed across groups	Impact of concurrent interventions ruled out	High rate of attrition	Attrition resulted in group differences	ITT analysis	Outcome assessors blinded to intervention status	Inclusion/exclusion criteria measured with valid & reliable instruments	Interventions assessed with valid & reliable measures	Outcomes assessed with valid & reliable measures	Outcomes and harms pre-specified	Pre-specified outcomes reported	
BH4																
Trefz 2009[1]	+	+	+	+	-	+	-	NA	-	+	+	+	+	-	+	Fair
Levy 2007[2]	+	+	+	NA	-	+	-	NA	+	+	+	+	+	+	+	Good
LNAAs																
Schindeler 2007[3]	+	+	NA	NA	-	+	-	NA	+	+	+	+	+	-	+	Fair
Matalon 2007[4]	-	-	NA	NA	-	+	-	NA	NA	+	+	+	+	-	+	Poor

+=yes/positive, -=no/negative; LNAAs=large neutral amino acids

Open Label Trials

Table E-2. Quality assessment of open label trials addressing adjuvant treatment of PKU

Author, Year	Consecutive enrollment	Incomplete outcome data adequately addressed	Standard approach for outcome assessment	Final rating
BH4				
Burton 2011[5]	+	+	-	Fair
Vernon 2010[6]	+	+	+	Good
Lee 2008[7]	+	+	+	Good
LNAAs				
Matalon 2006[8]	-	+	-	Poor

+=yes, -=no; LNAAs=large neutral amino acids

BH4 Case Series

Table E-3. Quality assessment of case series addressing BH4

Domain	Selection bias & confounding		Performance bias	Attrition bias		Detection bias						Reporting bias		Final Rating
Author, Year	Confounding and modifying variables considered		Impact of concurrent interventions ruled out	High rate of attrition	Attrition resulted in group differences	Outcome assessors blinded	Inclusion/exclusion assessed with valid & reliable measures	Interventions measured with valid & reliable measures	Outcomes assessed with valid & reliable measures	Confounders assessed with valid & reliable measures	Accounted for secular trends & regression to mean	Outcomes and harms pre-specified	Pre-specified outcomes reported	
Trefz 2011[9]	-		-	-	NA	-	-	+	+	-	NA	-	+	Poor
Burton 2010[10]	+		+	-	NA	-	+	-	-	+	NA	-	+	Poor
Burlina 2009[11]	-		+	-	NA	-	+	+	+	+	-	-	+	Poor
Lambruschini 2005[12]	+		+	+	+	-	+	+	+	+	NA	+	+	Poor

+=yes, -=no, NA=not applicable

BH4 Cohort Studies

Table E-4. Quality assessment of cohort studies addressing BH4

Domain	Selection bias & confounding							Performance bias	Attrition bias				Detection bias					Reporting bias		Final Rating
Author, Year	Allocation balanced between groups	Inclusion/exclusion criteria uniformly applied	Comparison group appropriate	Baseline characteristics similar between groups	Analysis controlled for baseline differences	Recruitment strategy differed between groups	Confounding/modifying variables taken into account	Impact of concurrent interventions ruled out	Length of follow-up different between groups	High rate of attrition	Attrition resulted in group differences	ITT analysis	Outcome assessors blinded	Inclusion/exclusion assessed with valid & reliable measures	Interventions measured with valid & reliable measures	Outcomes assessed with valid & reliable measures	Confounders assessed with valid & reliable measures	Outcomes and harms pre-specified	Pre-specified outcomes reported	
Humphrey 2011[13]	-	+	+	-	-	-	+	+	-	-	-	-	-	+	+	+	-	-	+	Poor

+=yes, -=no, NA=not applicable

Harms Reporting in Studies of BH4 and LNAAs

Table E-5. Quality assessment of studies reporting harms of adjuvant therapies for PKU

Author, Year	Harms predefined using standardized/precise definitions	Serious events precisely defined	Severe events precisely defined	Deaths/group specified	Active harms collection	Passive harms collection	Specified who collected harms	Training/background of individuals(s) collecting harms specified	Timing of harms collection specified	Standard scale for harms collection used	Specified whether reported harms encompass all events collected	Number participants withdrawing/lost to followup reported by group	Total number participants affected by harms specified by group	Number for each type of harm specified by group	Analyses for harms data specified
BH4															
Humphrey 2011[13]															
Burton 2011[14]	-	+	+	+	+	+	-	-	+	-	+	+	+	+	+
Burton 2010[10]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Vernon 2010[6]	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
Burlina 2009[11]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Trefz 2009[1]	-	U	-	-	+	+	+	+	+	-	+	+	+	+	+
Lee 2008[7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	U
Levy 2007[2]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Lambruschini 2005[12]	-	-	-	-	U	U	+	-	-	-	NA	+	NA	NA	NA
LNAAs															
Schindeler 2007[3]	-	-	-	-	-	+	-	-	-	U	-	NA	-	-	-
Matalon 2007[4]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Matalon 2006[8]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-

+= yes/positive; -=no/negative; LNAA=large neutral amino acids; NA=not applicable; U=unsure

Studies Addressing Phe Levels and IQ

Table E-6. Quality assessment of studies addressing Phe levels and IQ in individuals with PKU

Author, Year	Recruitment approach clearly documented	Impact of concurrent intervention ruled out	High rate of attrition	All eligible participants included in analysis	Attrition resulted in group differences	Inclusion/exclusion criteria measured with valid &reliable instruments	Outcomes assessed with valid & reliable instruments	Confounders assessed with valid & reliable instruments	Outcomes pre-specified	Pre-specified outcomes reported	Final Rating
Viau 2011[15]	-	+	-	-	NA	+	+	+	+	+	Fair
Azadi 2009[16]	-	+	-	-	NA	+	+	-	+	+	Poor
Anastasoie 2008[17]	-	-	NA	-	-	+	+	-	+	+	Poor
Wasserstein 2006[18]	-	+	-	-	NA	+	-	-	+	+	Poor
Pfaender 2005[19]	-	+	-	-	NA	+	+	-	+	+	Poor
Rupp 2001[20]	+	+	+	-	NA	+	+	-	+	+	Poor
Weglage 2001[21]	-	+	NA	-	NA	-	+	-	+	+	Poor
Griffiths 2000[22]	-	+	NA	-	NA	+	+	+	+	+	Fair
Weglage 2000[23, 24]	-	+	-	-	NA	+	+	+	+	+	Fair
Cerone 1999 [25]	-	+	NA	-	NA	+	+	-	+	+	Poor
Weglage 1995[26-28]	-	+	-	-	NA	CD	+	-	+	+	Poor
Leuzzi 1998[29]	+	+	-	-	NA	+	+	-	+	+	Fair
Ris 1997[30, 31]	+	+	-	+	NA	+	+	+	+	+	Good
Jones 1995[32]	-	+	-	-	NA	+	+	-	+	+	Poor
Schmidt 1994[33]	-	+	+	-	CD	+	+	-	+	+	Poor
Welsh 1990[34]	-	+	-	-	NA	+	+	-	+	+	Poor

Author, Year	Recruitment approach clearly documented	Impact of concurrent intervention ruled out	High rate of attrition	All eligible participants included in analysis	Attrition resulted in group differences	Inclusion/exclusion criteria measured with valid &reliable instruments	Outcomes assessed with valid & reliable instruments	Confounders assessed with valid & reliable instruments	Outcomes pre-specified	Pre-specified outcomes reported	Final Rating
Seashore 1985[35]	+	+	-	-	NA	+	+	-	+	+	Fair

+=yes, -=no, CD=cannot determine, NA=not applicable

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Appendix F. Meta-analysis Methods

The association of blood phenylalanine levels with IQ was meta-analyzed using a hierarchical mixed-effects model, estimated using Markov chain Monte Carlo (MCMC) methods[1]. The advantages of using a Bayesian approach to meta-analysis were recognized over a decade ago[2] and they have been applied extensively ever since[3,4,5,6,7,8,9,10]. It allows for straightforward probabilistic inference across studies, and readily combines both fixed and random effects. In contrast to the more indirect measures of inference afforded by classical methods, all inference from Bayesian models is in the form of probability statements that describe the uncertainty in the unknown quantities of interest (θ), given the information at hand (y):

$$\Pr(\theta y) \propto \Pr(y\theta)\ \Pr(\theta)$$

The left side of this equation is the posterior distribution of all unknown parameters in the model, while right side shows that this posterior quantity is the product of a data likelihood and the prior distribution (i.e. before data are observed) of the model. While the use of priors allows for the incorporation of extant information into the analysis, we used uninformative priors on all parameters, allowing the results from the included studies to provide all the evidence.

Using random effects for meta-analysis permits us to abandon the tenuous assumption that the effects across studies are independent and identically distributed. Rather, we view them as *exchangeable* samples from a "population" of PKU studies. This conditional independence (i.e., conditional on population parameters) assumption avoids either having to combine studies in a single estimate (which assumes they are identical) or keeping them entirely separate (which assumes they are completely different), but rather, allows for some mixture of the two extremes. In contrast, fixed effects models force one of these unlikely extremes. Moreover, the degree to which studies are pooled is dictated by the heterogeneity across studies, rather than via arbitrary weighting factors.

We specified random effects for the intercept and slope parameters of a linear relationship between blood Phe level and IQ. Importantly, this allowed each study to have its own parameters, each sampled from a notional population of parameters. Those with smaller sample sizes were automatically shrunk towards the population means for each parameter, with larger studies influencing the estimate of the population mean more than being influenced by it. In turn, the magnitude of the effect (*i.e.* slope) was specified partly as a function of a fixed effect for whether measurements of Phe were carried out during the critical period. Hence, the overall model was a hierarchical mixed effects model. Bayesian hierarchical models are very easily estimated using Markov chain Monte Carlo (MCMC) methods[11].

The core of the model is a linear relationship between the expected IQ ( ) and Phe (x):

$$\mu_i = \beta_{0j[i]} + \beta_{1i} x_i$$

The subscript *j[i]* denote parameters for study *j* corresponding to observation *i*. Hence, both the intercept and slope are allowed to vary by study. Note that by "observation" we refer here not to

individuals, but to groups of individuals within a study that share a characteristic. For example, within the same study, one group of individuals might have been measured for Phe in the critical period, and others not; these groups were considered separate observations in this analysis. One study[12] reported a range of Phe measurements, rather than a single value, so we imputed values by randomly sampling at every iteration from a uniform distribution across the reported range.

Though age was included as an additional linear predictor in early versions of the model, it did not appear to be an important covariate, and models in which it was included did not exhibit good convergence. Hence, age was omitted from the final model. We suspect that the important aspects of age might be adequately characterized by the four combinations of historical or concurrent Phe measurement and measurement in or outside the critical period.

The intercept was modeled as a random effect, where each study is assumed to be an exchangeable sample from a population of PKU studies:

$$\beta_{0j[i]} \sim N(\mu_\beta, \tau_\beta)$$

The slope of the relationship included a study-level random effect and fixed effects corresponding to whether the Phe measurement was concurrent with the measurement of IQ (an indicator variable):

$$\beta_{1i} = \alpha_{0i} + \alpha_1 \boldsymbol{crit}_{j[i]}$$
$$\alpha_{0i} \sim N(\mu_\alpha, \tau_\alpha)$$

Finally, the expected value of IQ was used to model the distribution of observed IQ values y_i, with error described by the inverse variance □

$$y_i \sim N(\mu_i, \tau)$$

Twelve studies provided only summarized data, with no individual measurements of Phe or IQ. For studies that provided only data summaries, we were unable to estimate the quantities as specified above. Instead, we employed reported correlation coefficients to obtain additional inference regarding the relationship of these variables. Inference regarding the linear relationship (slope) between Phe and IQ can be obtained from the correlation coefficient (□), using the Fisher transformation. Here, the hyperbolic function can be used to transform the correlation to a normally-distributed random variable:

$$\operatorname{arctanh}(r_j) \sim N\left(\operatorname{arctanh}(\rho_j), \frac{1}{\sqrt{n_j - 3}}\right)$$

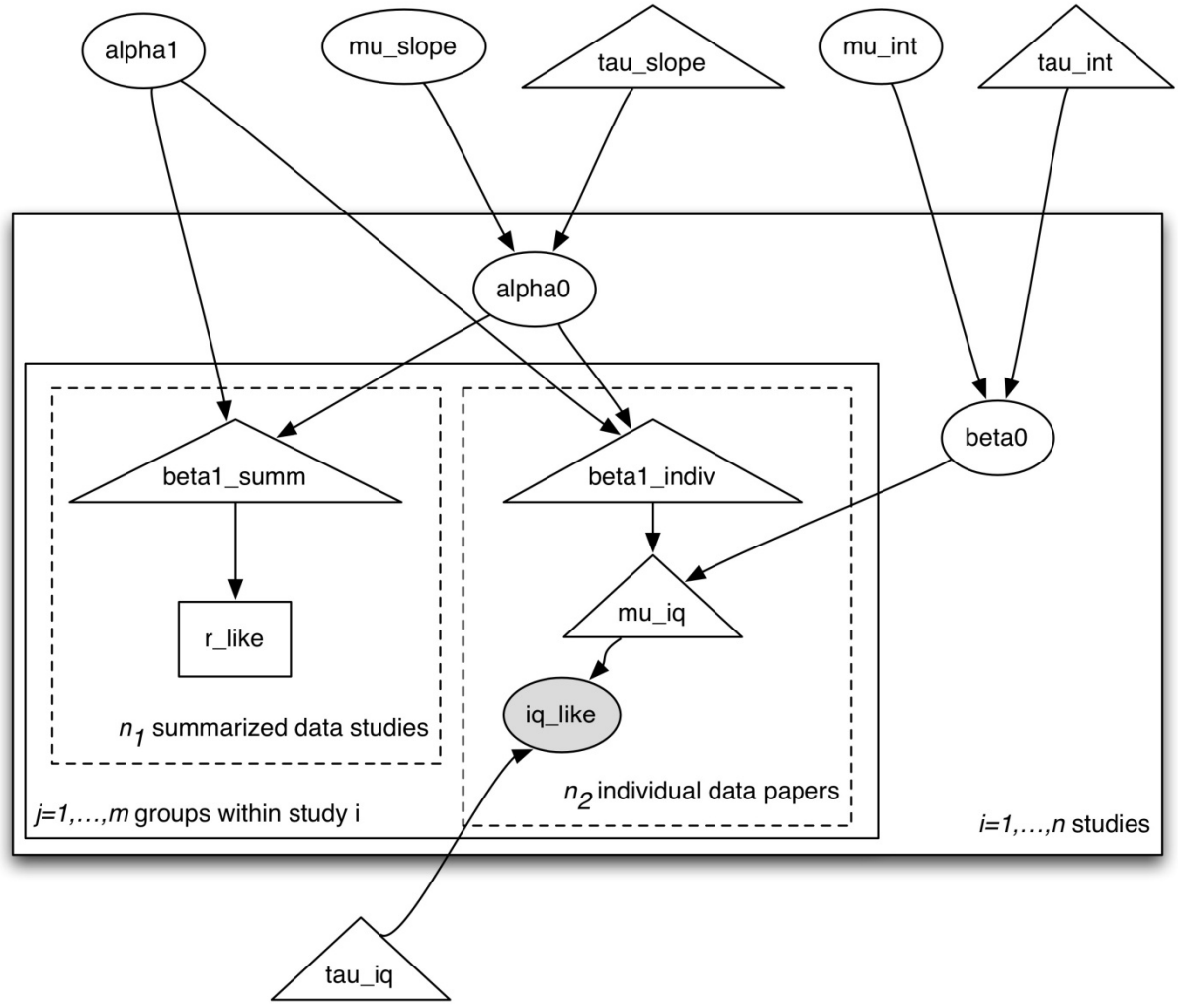
where r_j is the reported Pearson correlation from study j, with a standard error that is solely a function of the corresponding sample size (for a Spearman correlation, the standard error is the inverse square root of n-2). This provides a measure of precision for the reported correlations, which in turn becomes a measure of precision for the slope of the relationship between Phe and IQ. The expected value of the slope is obtained in the model by converting □ using the fundamental relationship:

$$\beta_{1j} = \rho_j \left(\frac{s_{yj}}{s_{xj}} \right)$$

where s_{xj} and s_{yj} are the reported standard deviations of the Phe levels and IQs, respectively, for study j.

The full model structure is illustrated in Figure F-1. Note the distinction between the influence of studies with group-summarized data and that of studies with individual-level data.

Figure F-1. Directed acyclic graph (DAG) showing the meta-analysis model structure



Note: Unfilled circles represent stochastic nodes, shaded circles represent data, triangles represent deterministic nodes and squares represent factor potentials (arbitrary log-probability terms).The large enclosing square represents the collection of n unique studies in the meta-analysis; the smaller enclosing box represents the distinct groups (i.e. subsets that had distinct covariates) within each study. Different information was contributed depending on whether the study provided group-summarized data (n_1 studies) or individual-level data (n_2 studies), as indicated by the dashed boxes; group-level data provided inference on the slope parameter only, while individual-level data informed both the slope and intercept.

All stochastic parameters were specified using diffuse prior distributions. For continuous parameters on the real line (e.g. linear model coefficients), a normal distribution with mean zero and precision (inverse-variance) 0.01 was used. For precision parameters, the standard deviation was modeled uniformly on the interval (0, 1000) and then transformed to inverse variance; this provides a better non-informative prior than modeling the precision directly[13].

In order to evaluate the effect of particular levels of Phe on the likelihood of cognitive impairment, we chose a threshold value of IQ to bound the definition of impairment. While discretizing a continuous variable into one dichotomous variable is subjective and problematic, we felt that for a standardized measure like IQ, a boundary of one standard deviation below the mean (IQ=85) was a reasonable choice. This threshold value was used to define indicator variables that were set to one if the value of the predicted IQ was below 85 during the current iteration of the MCMC sampler, and zero otherwise. Hence, the total number of ones divided by the number of MCMC iterations represents a posterior probability of observing IQ<85. This corresponds to the integral of the posterior distribution of IQ up to an 85 score. To illustrate the variation of this probability in response to Phe, this probability was calculated for a range of blood Phe levels from 200 to 3000 μmol/L, in increments of 200. This was done for critical period and non-critical period Phe measurement, under both the historical and concurrent measurement models.

This model was coded in PyMC version 2.1[14], which implements several MCMC algorithms for fitting Bayesian hierarchical models. The model was run for one million iterations, with the first 900,000 discarded as a burn-in interval. The remaining sample was thinned by a factor of ten to account for autocorrelation, yielding 10,000 samples for inference. Convergence of the chain was checked through visual inspection of the traces of all parameters, and via the Geweke[15] diagnostic. Posterior predictive checks[1] were performed, which compare data simulated from the posterior distribution to the observed data. This exercise showed no substantial lack of fit for any of the studies included in the dataset.

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Appendix G. Excluded Studies

Reasons for exclusion:

X-1=Not original research
X-2=Ineligible population
X-3=Ineligible study size
X-4=Not relevant to Key Question 1
X-5= Not relevant to Key Questions 2-7
X-6=Ineligible study design
X-7=Unable to obtain study

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Appendix H. Studies Addressing Executive Function

Table H-1. Key outcomes of studies addressing Phe levels and executive function in individuals with PKU

Azadi, 2009[1] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
Iran Cross Sectional **G1:** PKU subjects	**G1:** 10/10 Concurrent PKU classification: : NR **G1:** 13.3 ± 4.1 (6.6 – 19.8)	**Concurrent Phe (µmol/l):** Patient 1: 704 Patient 2: 1418 Patient 3: 1402 Patient 4: 1207 Patient 5: 2025 Patient 6: 1600 Patient 7: 704 Patient 8: 1487 Patient 9: 1400 Patient 10: 1691	**Tower of London (TOL) - Average number of moves to complete:** **2-move problems:** **G1:** 2.3 ± 0.51 **3-move problems:** **G1:** 4.12 ± 1.12 **4-move problems:** **G1:** 8.85 ± 3.38 **5-move problems:** **G1:** 10.47 ± 4.24 **TOL - Planning times (s):** **2-move problems:** **G1:** 7.14 ± 3.43 **3-move problems:** **G1:** 10.84 ± 8.19 **4-move problems:** **G1:** 9.45 ± 8.78 **5-move problems:** **G1:** 8.38 ± 4.29 **TOL - Subsequent thinking times (s):** **2-move problems:** **G1:** 17.16 ± 8.03 **3-move problems:** **G1:** 32.11 ± 19.66	**Spearman correlations:** **Concurrent phe and:** **TOL - Average number of moves to complete:** **2-move problems:** **G1:** 0.17 **3-move problems:** **G1:** -0.14 **4-move problems:** **G1:** 0.06 **5-move problems:** **G1:** 0.23 **TOL - Planning times:** **2-move problems:** **G1:** -0.09 **3-move problems:** **G1:** 0.08 **4-move problems:** **G1:** 0.17 **5-move problems:** **G1:** -0.01 **TOL -Subsequent thinking times:** **2-move problems:** **G1:** 0.07

Azadi, 2009[1] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			4-move problems: **G1:** 60.69 ± 27.46 **5-move problems:** **G1:** 71.68 ± 31.18 **Continuous Performance Test (CPT):** **Commission errors (number):** **G1:** 5.50 ± 3.59 **Omission errors (number):** **G1:** 4.80 ± 2.97 **Mean reaction time (s):** **G1:** 0.79 ± 0.22 **Successfully recognized matches (number):** **G1:** 67.7 ± 19.90 **Stroop single-task test:** **Time in dots card (s):** **G1:** 19.32 ± 7.79 **Errors in dots card (number):** **G1:** 0.11 ± 0.33 **Time in word card (s):** **G1:** 31.33 ± 18.45 **Errors in word card (number):** **G1:** 0.11 ± 0.33 **Time in color card (s):** **G1:** 41.77 ± 15.73 **Errors in color card (number):** **G1:** 0.33 ± 0.70 **Difference index:** **G1:** 22.78 ± 11.87	**3-move problems:** **G1:** 0.03 **4-move problems:** **G1:** 0.3 **5-move problems:** **G1:** 0.4 **Continuous Performance Test (CPT):** **Commission errors (number):** **G1:** 0.27 **Omission errors (number):** **G1:** 0.15 **Mean reaction time:** **G1:** -0.03 **Successfully recognized matches (number):** **G1:** -0.15 **Stroop single test:** **Time in dots card:** **G1:** 0.02 **Errors in dots card (number):** **G1:** 0.27 **Time in word card:** **G1:** 0.03 **Errors in word card (number):**

Azadi, 2009[1] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				G1: -0.27 **Time in color card:** **G1:** 0.2 **Errors in color card (number):** **G1:** 0.43 **Difference index:** **G1:** 0.41

Sharman, 2009[2] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
Australia Prospective Cohort **G1:** PKU subjects	**G1:** 12/10 PKU classification: NR Age (years): Baseline: **G1:** 14.4 ± 2.08 Follow-up: **G1:** 14.4 ± 2.16	**Baseline (Jan. 2006) concurrent phe (µmols):** 601.30 ± 204.95 (270.00-970.00) **Follow-up (Mar. 2006) concurrent phe (µmols):** 478.00 ± 274.26 (210.00-1100.00) **Mean average phe age < 12 years (µmols):** **G1:** 383.00 ± 96.91 (267.00-580.00) **Mean average phe age > 12 years (µmols):** **G1:** 491.75 ± 127.83 (367.00-742.00) **Mean lifetime phe (µmols):** **G1:** 395.80 ± 102.83 (276.00-626.00) **Average phe in 2005:** **G1:** NR	**BRIEF Inhibit Scale T-scores:** **Baseline:** **G1:** 54.30 ± 14.38 **Follow-up:** **G1:** 58.40 ± 17.59	**Phe level in 2005 and BRIEF Inhibit scale:** **Baseline:** **G1:** 0.671, $p < 0.05$ **Follow-up:** **G1:** 0.752, $p < 0.05$ **Lifetime phe and BRIEF Inhibit scale:** **Baseline:** **G1:** 0.737, $p < 0.01$ **Baseline:** **G1:** 0.883, $p < 0.01$

Moyle, 2007[3] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
Australia Cross Sectional **G1:** PKU patients	**G1:** 12/12 PKU classification: NR Lifetime, Recent Age (years) ± SE: **G1:** 28.5 ± 3.3	**Lifetime phe level:** **G1:** NR **Phe level obtained most recently before assessment:** **G1:** NR	**Wechsler Adult Intelligence Scale-III (WAIS-III) mean scores ± SE:** **Working Memory Index (WMI):** **G1:** 103 ± 5.7 **Wechsler Memory Scale Third Edition (WMS-III) mean scores ± SE:** **Working Memory (WM):** **G1:** 104 ± 6.0 **Trail Making Test Part A (TMT-A):** **G1:** 35 ± 4.8 **Trail Making Test Part B (TMT-B):** **G1:** 75 ± 14.9	**Lifetime phe with:** **WAIS-III - Working Memory Index (WMI):** **G1:** -.50 **WMS-III - Working Memory (WM):** **G1:** -.51 **Trail Making Test Part A (TMT-A):** **G1:** .20 **Trail Making Test Part B (TMT-B):** **G1:** .54 **Phe level obtained most recently before assessment with:** **WAIS-III - Working Memory Index (WMI):** **G1:** -.24 **WMS-III - Working Memory (WM):** **G1:** -.35 **Trail Making Test Part A (TMT-A):** **G1:** .38 **Trail Making Test Part B (TMT-B):** **G1:** .68*, $p < .05$

Moyle, 2007[3] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation

*Text in the Results section states “r(11) = -.68, p=.02.”

Author/Year Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Christ, 2006[4] USA Prospective Cohort **G1:** PKU subjects	**G1:** 26/26 Concurrent PKU classification: NR **G1:** 11.2 ± 3.1 years (6-18)	**Recent Phe (mg/dL):** **G1:** 7.0 ± 5.6 (0.2-20.2)	**Go/no-go:** **Reaction time (milliseconds):** **Neutral:** **G1:** 335 ± 60 **Inhibitory:** **G1:** 443 ± 67 **Error rate (%):** **Neutral:** **G1:** 2.0 ± 2.0 **Inhibitory :** **G1:** 31.7 ± 17.4 **Antisaccade:** **Reaction time (msec):** **Neutral:** **G1:** 306 ± 61 **Inhibitory :** **G1:** 392 ± 77 **Error rate (%):** **Neutral:** **G1:** 0.3 ± 0.7 **Inhibitory :** **G1:** 12.1 ± 11.5 **Flanker:** **Reaction time (msec):** **Neutral:** **G1:** 766 ± 212 **Inhibitory:** **G1:** 777 ± 219 **Facilitatory:** **G1:** 736 ± 195	**Correlation of Phe levels with Go/no-go, antisaccade, Flanker, and Stroop tests:** NR

	Error rate (%): **Neutral:** **G1:** 5.8 ± 5.7 **Inhibitory :** **G1:** 7.1 ± 8.9 **Facilitatory:** **G1:** 4.6 ± 6.1 **Stroop:** **Reaction time (msec):** **Neutral:** **G1:** 811 ± 173 **Inhibitory:** **G1:** 875 ± 186 **Facilitatory:** **G1:** 785 ± 164 **Error rate (%):** **Neutral:** **G1:** 1.1 ± 2.0 **Inhibitory:** **G1:** 2.2 ± 3.2 **Facilitatory:** **G1:** 0.6 ± 1.1

Wasserstein, 2006[5] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
USA Cross Sectional **G1:** PKU patients	**G1:** 10/10 Concurrent, lifetime Classic Age: Mean NR Age at test (years): Patient 1 – 26 Patient 2 – 23 Patient 3 – 27 Patient 4 – 30 Patient 5 – 30 Patient 6 – 29 Patient 7 – 35 Patient 8 – 24 Patient 9 – 33 Patient 10 – 31	**Concurrent Phe (mg/dl):** Patient 1 – 17.1 Patient 2 – 17.6 Patient 3 – 17.5 Patient 4 – 25.8 Patient 5 – 19.2 Patient 6 – 6.8 Patient 7 – 18.1 Patient 8 – 22.0 Patient 9 – 26.4 Patient 10 – 19.0 **Phe level from birth to 12 years (mg/dl):** Patient 1 – 6.2 Patient 2 – 5.6 Patient 3 – 6.3 Patient 4 – 6.5 Patient 5 – 9.6 Patient 6 – 8.5 Patient 7 – 9.5 Patient 8 – 7.7 Patient 9 – 4.7 Patient 10 – 7.6 **Phe level over 12 years (mg/dl):** Patient 1 – 15 Patient 2 – 11.8 Patient 3 – 9.6 Patient 4 – 7.8 Patient 5 – 19.5	**California Verbal Learning Test Words remembered correctly:** **G1:** 11.02, SD-NR **Dependence on semantic clues:** **G1:** 6.11, SD-NR	**Phe levels and CVLT test outcomes:** NR

Wasserstein, 2006[5] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		Patient 6 – 12.1 Patient 7 – 16.8 Patient 8 – NR Patient 9 – 13.4 Patient 10 – 14.2		

Gassio, 2005[6] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Spain Cross Sectional **G1:** individuals with PKU **G2:** individuals with hyper-phenyl-alanemia	**G1:** 37/37 **G2:** 35/35 Concurrent, Historical **G1:** PKU classification: NR **G2:**Hyperphenylalanemia **G1:** 9.75 ± 5.25 years (2.7- 19.3) **G2:** 7.8 ± 3.2 years (2.7-17.25)	**Phe from the day of study (µmol/l):** **G1:** 388 ± 205 (123-1013) **G2:** 237 ± 86 (98-413) **Phe at diagnosis (µmol/l):** **G1:** 1504 ± 739 (371-2802) **G2:** 253 ± 106 (112-544) **Index of Dietary Control** (IDC, average of medians of plasma phe obtained every 6 months)**, most recent 6-mo period:** **G1:** 427 ± 191 (116-880) **G2:** 231 ± 76 (106-359) **IDC, first 6 yrs of life:** **G1:** 354 ± 113 (182-656) **G2:** NR **IDC, 7 to 12 yrs of life:** **G1:** 444 ± 145 (250-820) **G2:** NR	**Wisconsin Card Sorting test, preservative errors:** **G1:** 50 ± 11.2 **G2:** 48 ± 10.5 **Trail Making Test:** **Trail A:** **G1:** 43 ± 12.4 **G2:** 48 ± 14.1 **Trail B:** **G1:** 44 ± 12.3 **G2:** 50 ± 10.1 **Conners' Continuous Performance Test (CPT):** **Omissions:** **G1:** 56 ± 11.5 **G2:** 56 ± 9.1 **Commissions:** **G1:** 51 ± 10.3 **G2:** 48 ± 11.7 **Stroop:** **Word reading:** **G1:** 45 ± 8.0 **G2:** 50 ± 8.3 **Color naming:** **G1:** 40 ± 8.9 **G2:** 48 ± 6.9 **Color word interference:** **G1:** 42 ± 9.8 **G2:** 50 ± 6.6	**Phe day of study with Stroop color:** **G1:** r=-0.457, p=0.019 **Phe day of study with Stroop color word interference:** **G1:** r=-0.462, p=0.018 **IDC first 6 yrs of life with Stroop color-word interference:** **G1:** r=-0.547, p=0.013 **IDC 7-12 yrs of life with Stroop Word reading:** **G1:** r=-0.423, p=0.035 **IDC 7-12 yrs of life with Stroop color-word interference:** **G1:** r=-0.413, p=0.04

Gassio, 2005[6] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			Resistance to interference: **G1:** 49 ± 6.4 **G2:** 51 ± 5.7	

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Australia Cross Sectional **G1:** PKU participants **G1a:** PKU participants with MRI **G1b:** PKU participants with MRI and with no white matter abnormalities **G1c:** PKU participants with MRI and mild white matter abnormalities **G1d:** PKU participants with MRI and moderate white matter abnormalities **G1e:** PKU participants with MRI and no white	**G1:** 33 **G1a:** 32 **G1b:** 6 **G1c:** 12 **G1d:** 14 **G1e:** 5 **G1f:** 9 **G1g:** 5 Historical, Concurrent Classic **G1:** 11.18 ± 3.4 **G1a:** 11.2 ± 3.5 **G1b:** 9.1 ± 2 **G1c:** 9.8 ± 2.1 **G1d:** 13.2 ± 3.9 **G1e:** 8.3 ± 0.7 **G1f:** 8.9 ± 1.5 **G1g:** 9.2 ± 2.6	**Concurrent phe (µmol/l) ± SD:** **G1:** NR **G1a:** NR **G1b:** 400.3 ± 131.5 **G1c:** 435.3 ± 196.4 **G1d:** 786.2 ± 284.4 **Concurrent phe (µmol/l) ± SE:** **G1e:** 362.20 ± 92.3 **G1f:** 372.00 ± 68.8 **G1g:** 665.20 ± 92.3 **Lifetime phe (average of yearly median) (µmol/l) ± SD:** **G1:** NR **G1a:** NR **G1b:** 330.8 ± 42.2 **G1c:** 369.8 ± 46.2 **G1d:** 542.5 ± 132.7 **Lifetime phe (average of yearly median) (µmol/l) ± SE:** **G1e:** 354.05 ± 35.3 **G1f:** 380.03 ± 26.3 **G1g:** 451.23 ± 35.3 **Early phe (first 6 months) (µmol/l) ± SE:** **G1:** NR	**Neuropsychological Measures**:** **TEA-Ch-Sky Search ± SE:** **G1:** 17.6 ± 0.5 **G1a:** NR **G1b:** 17.9 ± 1.1 **G1c:** 18.5 ± 0.8 **G1d:** 16.5 ± 0.8 **TEA-Ch-Code Transmission ± SE:** **G1:** 35.21 ± 0.8 **G1a:** NR **G1b:** 37.7 ± 2 **G1c:** 34.7 ± 1.3 **G1d:** 34.6 ± 1.3 **TEA-Ch-Digital Distraction ± SE:** **G1:** 3.56 ± 0.3 **G1a:** NR **G1b:** 3.7 ± 0.7 **G1c:** 3.7 ± 0.4 **G1d:** 3.4 ± 0.3 **TEA-Ch-Sky Search Dual Task ± SE:** **G1:** 125.12 ± 6.7 **G1a:** NR **G1b:** 118.6 ± 17.2 **G1c:** 116.6 ± 11 **G1d:** 137.7 ± 11.2 **WISC III - Digit span – forwards ± SE:** **G1:** 5.32 ± 0.2	**Lifetime Phe with:** **Working memory (Digit span):** **G1a:** R=-0.40, p=0.05 **Mental flexibility (CNT errors and self-corrections):** **G1a:** R=0.55, p=0.005 **Early Phe (first 6 months) with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.09 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.22 **Executive Function:** **G1:** r=-.08 **Recent Phe (previous 12 months) with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
matter abnormalities - on strict dietary restrictions **G1f:** PKU participants with MRI and mild white matter abnormalities -on strict dietary restrictions **G1g:** PKU participants with MRI and moderate white matter abnormalities - on strict dietary restrictions		**G1a-d:** NR **G1e:** 356.00 ± 51.7 **G1f:** 401.33 ± 38.5 **G1g:** 396.00 ± 51.7 **Recent phe (previous 12 months) (µmol/l ± SE:** **G1:** NR **G1a-d:** NR **G1e:** 383.00 ± 62.0 **G1f:** 352.67 ± 46.2 **G1g:** 592.00 ± 62.0	**G1a-d:** NR **WISC III - Digit span – backwards ± SE:** **G1:** 3.27 ± 0.2 **G1a-d:** NR **WAIS-III or WISC-III Digit Span ± SE:** **G1:** NR **G1a:** NR **G1b:** 9 ± 1.3 **G1c:** 8.3 ± 0.9 **G1d:** 8.3 ± 0.9 **Tower of London (TOL) extra attempts ± SE:** **G1:** 7.72 ± 0.7 **G1a:** NR **G1b:** 5.8 ± 1.8 **G1c:** 7.9 ± 1.2 **G1d:** 8.5 ± 1.2 **Contingency Naming Test (CNT) - errors and self-corrections ± SE:** **G1:** 23.50 ± 2.8 **G1a:** NR **G1b:** 19.3 ± 7.2 **G1c:** 15.7 ± 4.6 **G1d:** 32.7 ± 4.6 **Means for G1b, G1c, and G1d adjusted for age at testing and socioeconomic status. Means for G1	Distraction, and Dual Task)**:** **G1:** r=-.20 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.22 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:** **G1:** r=-.37 **Concurrent Phe with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.19 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.29 **Executive Function** (TOL extra attempts,

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			adjusted for age **Cognitive Domains***:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task) **± SE:** **G1:** NR **G1a:** NR **G1b:** -0.02 ± 0.3 **G1c:** -0.12 ± 0.2 **G1d:** -0.60 ± 0.2 **G1e:** 0.49 ± 0.5 **G1f:** -0.74 ± 0.4 **G1g:** -1.46 ± 0.4 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals) **± SE:** **G1:** NR **G1a:** NR **G1b:** -0.23 ± 0.4 **G1c:** -0.27 ± 0.2 **G1d:** -0.56 ± 0.2 **G1e:** -0.48 ± 0.5 **G1f:** -0.66 ± 0.3 **G1g:** -1.12 ± 0.4 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words) **± SE:** **G1:** NR	RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:** **G1:** r=-.19 **Lifetime Phe with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.32 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.49, p<.01 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:** **G1:** r=-.40

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			G1a: NR **G1b:** -0.10 ± 0.4 **G1c:** -0.01 ± 0.2 **G1d:** -0.70 ± 0.2 **G1e:** -0.68 ± 0.3 **G1f:** -0.62 ± 0.2 **G1g:** -1.26 ± 0.3 *** Means adjusted for age, socioeconomic status and gender	

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
UK Cross Sectional **G1:** off-diet PKU subjects **G2:** on-diet PKU subjects **G3:** PKU subjects continuously treated	**G1:** 25 **G2:** 25 **G3:** 20 Lifetime, Recent, Concurrent Classic, atypical **G1:** 27.48 ± 4.55 (18-38) **G2:** 26.68 ± 4.92 (18-33) **G3:** 24.60 ± 4.62 (18-33)	**Mean Phe (µmol/l):** **1-4 years of age:** **G1:** 460.59 ± 181.91 (171.75-786.69) **G2:** 450.58 ± 123.97(255.75-727.5) **G3:** 418.13 ± 94.35 (255.75-596.67) **5-8 years of age:** **G1:** 586.5 ± 199.91 (276-986.25) **G2:** 456.85 ± 127.3 (237.13-740) **G3:** 430.64 ± 127.75 (225.00-680.00) **9-12 years of age:** **G1:** 917.69 ± 209.53 (430-1380) **G2:** 697.3 ± 280.65 (175-1275) **G3:** 715.34 ± 280.96 (175.00-1275.00) **13-16 years of age:** **G1:** 1153.24 ± 242.91 (859-1710) **G2:** 775.7 ± 255.9 (422.25-1411.5) **G3:** 790.72 ± 265.98 (453.38-1411.50)	**N-back percentage accuracy:** **0-back:** **G1:** 97.08 ± 2.46 **G2:** 98.83 ± 1.09 **G3:** NR **1-back:** **G1:** 95.65 ± 3.24 **G2:** 97.78 ± 1.53 **G3:** NR **2-back:** **G1:** 84.55 ± 7.62 **G2:** 88.93 ± 5.69 **G3:** NR **N-back speed per item (s):** **0-back:** **G1:** 0.43 ± 0.05 **G2:** 0.45 ± 0.08 **G3:** NR **1-back:** **G1:** 0.60 ± 0.15 **G2:** 0.55 ± 0.13 **G3:** NR **2-back:** **G1:** 1.54 ± 1.17 **G2:** 1.34 ± 0.67 **G3:** NR **Flanker percentage accuracy:** **Compatible trials:** **G1:** 98 ± 1.57 **G2:** 99.35 ± 1.03	**N-back accuracy:** **0-back with:** **mean phe level age 1-4:** **G1:** r=-0.19 **G2:** 0.29 **mean phe level age 5-8:** **G1:** -0.05 **G2:** 0.23 **mean phe level age 9-12:** **G1:** 0.16 **G2:** -0.41 **mean phe level age 13-16:** **G1:** 0.15 **G2:** -0.17 **mean phe level age 17-20:** **G1:** -0.09 **G2:** -0.15 **mean phe level age 21-24:** **G1:** -0.11 **G2:** -0.26 **mean phe level age 25-28:** **G1:** -0.10 **G2:** -0.36 **mean phe level age 29-32:** **G1:** -0.29

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		17-20 years of age: **G1:** 1345.79 ± 282.26 (845-2013) **G2:** 867.73 ± 248.89 (448.00-1443.13) **G3:** 891.88 ± 251.19 (448.00-1443.13) **21-24 years of age:** **G1:** 1362.55 ± 268.87 (850-1774.5) **G2:** 850.74 ± 229.44 (323.75-1216.81) **G3:** 818.46 ± 238.35 (323.75-1216.81) **25-28 years of age:** **G1:** 1408.19 ± 426.96 (989-2815.5) **G2:** 868.63 ± 187.40 (572-1170.79) **G3:** 878.94 ± 194.34 (493.56-1170.09) **29-32 years of age:** **G1:** 1320.46 ± 262.99 (995-1736) **G2:** 795.75 ± 228.62 (470.32-1194.25) **G3:** NR **Concurrent Phe (µmol/l):** **G1:** 1285.68 ± 197.83 (990-1651)	**G3:** NR **Incompatible trials:** **G1:** 97.05 ± 2.28 **G2:** 97.65 ± 3.41 **G3:** NR **Flanker speed per item (s):** **Compatible trials:** **G1:** 0.49 ± 0.07 **G2:** 0.45 ± 0.06 **G3:** NR **Incompatible trials:** **G1:** 0.52 ± 0.08 **G2:** 0.47 ± 0.05 **G3:** NR **Attention:** **Telephone search per minute:** **G1:** NR **G2:** NR **G3:** 19.94 ± 4.82 **Telephone search and counting per minute:** **G1:** NR **G2:** NR **G3:** 18.46 ± 4.88 **Self-ordered pointing:** **6-word trials per minute:** **G1:** NR **G2:** NR **G3:** 15.45 ± 4.17 **9-word trials per minute:**	**G2:** -0.56 **Concurrent phe level:** **G1:** -0.07 **G2:** -0.33 **Recent phe level:** **G1:** -0.08 **G2:** -0.38 **1-back with**: **mean phe level age 1-4:** **G1:** -0.12 **G2:** -0.47 **mean phe level age 5-8:** **G1:** 0.04 **G2:** -0.48 **mean phe level age 9-12:** **G1:** 0.44 **G2:** -0.01 **mean phe level age 13-16:** **G1:** 0.21 **G2:** 0.13 **mean phe level age 17-20:** **G1:** -0.15 **G2:** 0.18 **mean phe level age 21-24:** **G1:** -0.54 **G2:** 0.02 **mean phe level age 25-**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		G2: 758.79 ± 261.27 (221.00-1233.00) **G3:** 858.80 ± 285.28 (333.00-1432.00) **Recent Phe (year preceding test) (µmol/l):** **G1:** 1317.77 ± 221.78 (1013.67-1710) **G2:** 797.62 ± 240.80 (283.40-1153.00) **G3:** 788.90 ± 225.24 (338.09-1208.75)	**G1:** NR **G2:** NR **G3:** 12.90 ± 2.64 **12-word trials per minute:** **G1:** NR **G2:** NR **G3:** 12.25 ± 2.70	**28:** **G1:** -0.12 **G2:** 0.20 **mean phe level age 29-32:** **G1:** -0.25 **G2:** -0.04 **Concurrent phe level:** **G1:** -0.24 **G2:** -0.14 **Recent phe level:** **G1:** -0.19 **G2:** -0.07 **2-back with:** **mean phe level age 1-4:** **G1:** 0.13 **G2:** -0.21 **mean phe level age 5-8:** **G1:** 0.02 **G2:** -0.11 **mean phe level age 9-12:** **G1:** 0.24 **G2:** 0.21 **mean phe level age 13-16:** **G1:** -0.17 **G2:** 0.39 **mean phe level age 17-20:** **G1:** -0.24

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				G2: 0.34 **mean phe level age 21-24:** **G1:** -0.26 **G2:** 0.22 **mean phe level age 25-28:** **G1:** -0.49 **G2:** 0.59 **mean phe level age 29-32:** **G1:** -0.22 **G2:** 0.32 **Concurrent phe level:** **G1:** -0.24 **G2:** -0.07 **Recent phe level:** **G1:** -0.19 **G2:** -0.08 **N-back speed:** **0-back with:** **mean phe level age 1-4**: **G1:** -0.58, p<0.01 **G2:** 0.36 **mean phe level age 5-8:** **G1:** -0.46 **G2:** 0.55, p<0.01 **mean phe level age 9-12:** **G1:** 0.01 **G2:** 0.03

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				mean phe level age 13-16: **G1:** -0.14 **G2:** 0.09 **mean phe level age 17-20:** **G1:** -0.04 **G2:** 0.10 **mean phe level age 21-24:** **G1:** 0.37 **G2:** 0.11 **mean phe level age 25-28:** **G1:** 0.10 **G2:** -0.17 **mean phe level age 29-32:** **G1:** 0.33 **G2:** -0.64 **Concurrent phe level:** **G1:** 0.55, p<0.01 **G2:** 0.22 **Recent phe level:** **G1:** 0.44 **G2:** -0.37 **1-back with:** **mean phe level age 1-4:** **G1:** -0.45 **G2:** -0.03 **mean phe level age 5-8:**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				G1: -0.38 **G2:** 0.19 **mean phe level age 9-12:** **G1:** -0.19 **G2:** 0.02 **mean phe level age 13-16:** **G1:** -0.14 **G2:** 0.13 **mean phe level age 17-20:** **G1:** 0.09 **G2:** 0.13 **mean phe level age 21-24:** **G1:** 0.28 **G2:** 0.05 **mean phe level age 25-28:** **G1:** 0.11 **G2:** -0.24 **mean phe level age 29-32:** **G1:** 0.38 **G2:** -0.38 **Concurrent phe level:** **G1:** 0.38 **G2:** 0.26 **Recent phe level:** **G1:** 0.31

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				G2: 0.06 **2-back with:** **mean phe level age 1-4:** **G1:** -0.14 **G2:** -0.39 **mean phe level age 5-8:** **G1:** -0.30 **G2:** -0.15 **mean phe level age 9-12:** **G1:** 0.01 **G2:** 0.17 **mean phe level age 13-16:** **G1:** -0.54, p<0.01 **G2:** 0.10 **mean phe level age 17-20:** **G1:** -0.53 **G2:** -0.18 **mean phe level age 21-24** **G1:** 0.07 **G2:** -0.30 **mean phe level age 25-28:** **G1:** -0.43 **G2:** -0.01 **mean phe level age 29-32:** **G1:** -0.11

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				G2: -0.29 **Concurrent phe level:** **G1:** -0.06 **G2:** 0.23 **Recent phe level:** **G1:** -0.14 **G2:** 0.08 **Flanker speed:** **Compatible trials with:** **mean phe level age 1-4:** **G1:** -0.36 **G2:** 0.24 **mean phe level age 5-8:** **G1:** -0.40 **G2:** 0.41 **mean phe level age 9-12:** **G1:** -0.32 **G2:** -0.11 **mean phe level age 13-16:** **G1:** -0.10 **G2:** 0.15 **mean phe level age 17-20:** **G1:** -0.08 **G2:** 0.18 **mean phe level age 21-24** **G1:** 0.35 **G2:** 0.22

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				mean phe level age 25-28: **G1:** 0.26 **G2:** 0.17 **mean phe level age 29-32:** **G1:** 0.43 **G2:** -0.59 **Concurrent phe level:** **G1:** 0.44 **G2:** -0.18 **Recent phe level:** **G1:** 0.41 **G2:** -0.20 **Flanker speed: Incompatible trials with:** **mean phe level age 1-4:** **G1:** -0.38 **G2:** 0.27 **mean phe level age 5-8:** **G1:** -0.41 **G2:** 0.33 **mean phe level age 9-12:** **G1:** -0.26 **G2:** -0.13 **mean phe level age 13-16:** **G1:** -0.11 **G2:** 0.08

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				mean phe level age 17-20: **G1:** -0.13 **G2:** 0.08 **mean phe level age 21-24** **G1:** 0.28 **G2:** 0.19 **mean phe level age 25-28:** **G1:** 0.26 **G2:** 0.03 **mean phe level age 29-32**: **G1:** 0.25 **G2:** -0.63 **Concurrent phe level:** **G1:** 0.38 **G2:** -0.24 **Recent phe level:** **G1:** 0.32 **G2:**-0.21 **Correlations between N-back accuracy, N-back speed, and Flanker speed with phe levels for G3:** NR **Attention (combined Telephone search and**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				Telephone search with counting) and: **mean phe level age 1-4:** **G3:** .19 **mean phe level age 5-8:** **G3:** .18 **mean phe level age 9-12:** **G3:** .21 **mean phe level age 13-16:** **G3:** -.06 **mean phe level age 17-20:** **G3:** -.03 **mean phe level age 21-24:** **G3:** -.18 **mean phe level age 25-28:** **G3:** -.59, p<0.05 **Concurrent phe level:** **G3:** -.16 **Recent phe level:** **G3:** -.19 **Self-ordered pointing (combined levels) and mean phe level age 1-4:** **G3:** .03 **mean phe level age 5-8:** **G3:** -.06

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				mean phe level age 9-12: **G3:** -.01 **mean phe level age 13-16:** **G3:** -.13 **mean phe level age 17-20:** **G3:** .44 **mean phe level age 21-24:** **G3:** -.63, p<.05 **mean phe level age 25-28:** **G3:** -.77, p<.01 **Concurrent phe level:** **G3:** -.49, p<.05 **Recent phe level:** **G3:** -.67, p<.01 **Correlations between attention and self-ordered pointing for G1 and G2:** NR

Antshel 2003[12, 13] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
United States Cross Sectional **G1:** participants with PKU	**G1:** 46 Current PKU classification: NR **G1:** 10.75 ± 2.1 years (8-14)	**Current Phe (mg/dl)** **G1:** 8.1 ± 6.2 (0.9 – 22.8)	**California Verbal Learning Test – Children's Version (CVLT-C) Semantic Cluster Ratio:** **G1:** 39.9 ± 7.4 **CVLT-C Trial 5 Number Correct:** **G1:** 40.3 ± 9.2 **Stroop Color and Word Test Interference trial:** **G1:** 50.7 ± 8.3 **Stroop Word Reading T score:** **G1:** 44.0 ± 9.9	**Current Phe level with: CVLT-C Semantic Cluster Ratio:** **G1:** r = -.543, p<.001 **CVLT-C Trial 5 Number Correct:** **G1:** r = -.291, p<.001 **Stroop Word Reading:** **G1:** r = -.498, p<.001

Huijbregts 2002[14] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Netherlands Retro-spective case series **G1:** PKU subjects **G1a:** PKU subjects age <11 **G1b:** PKU subjects age ≥11 **G1c:** PKU subjects with concurrent phe≤360 µmol/l **G1d:** PKU subjects with concurrent phe≤360 µmol/l age<11 **G1e:** PKU subjects with concurrent phe≤360 µmol/l age ≥11	**G1:** 57 **G1a:** 27 **G1b:** 30 **G1c:** 22 **G1d:** 11 **G1e**:11 **G1f:** 35 **G1g:** 16 **G1h:** 19 Lifetime, Concurrent Classical **G1:** 11.0 ± 2.1 **G1a:** 9.1 ± 1.1 **G1b:** 12.7 ± 1.1 **G1c:** 11.2 ± 2.2 **G1d:** 9.4 ± 1.4 **G1e:** 12.9 ± 1.3 **G1f:** 10.9 ± 2.1 **G1g:** 8.9 ± 0.9 **G1h:** 12.6 ± 1.0	**Concurrent phe (µmol/l):** **G1:** 461 ± 259 **G1a:** 424 ± 218 **G1b:** 494 ± 291 **G1c:** 206 ± 99 **G1d:** 218 ± 77 **G1e:** 194 ± 119 **G1f:** 621 ± 190 **G1g:** 566 ± 161 **G1h:** 668 ± 203 **IDC (mean of all half-year median phe levels) (µmol/l):** **G1:** 344 ± 115 **G1a:** 354 ± 150 **G1b:** 335 ± 75 **G1c:** 295 ± 67 **G1d:** 281 ± 64 **G1e:** 307 ± 70 **G1f:** 372 ± 128 **G1g:** 396 ± 169 **G1h:** 351 ± 75	**ANT Mean RT sustained attention (ms):** **G1d:** 1331, SD-NR **G1e:** 1040, SD-NR **G1g:** 1658, SD-NR **G1h:** 1110, SD-NR **Mean series time (MST); see following set of values for SD:** **G1d:** 15.98 **G1e:** 12.48 **G1g:** 19.90 **G1h:** 13.32 **Standard deviation of Mean series time (a measure for the stability of performance (Fluctuation in Tempo)):** **G1d:** 2.77 **G1e:** 1.98 **G1g:** 3.77 **G1h:** 2.24 **MST Corrected for Accuracy:** **G1d:** 17.04, SD-NR **G1e:** 13.23, SD-NR **G1g:** 21.62, SD-NR **G1h:** 14.15, SD-NR **Mean number of false alarms 3 dots (FA3):**	**Tempo (Mean series time corrected for accuracy) with:** **Phe between ages 5 and 7:** r=0.36, p=0.004 **IDC:** r=0.27, p=0.026 **Phe between ages 2.5 and 4:** r=0.26, p=0.029 **Fluctuation in Tempo with:** **Phe between ages 5 and 7:** r=0.38, p=0.002 **IDC:** r=0.28, p=0.021 **Phe between ages 2.5 and 4:** r=0.24, p=0.045 **Bias with** **Phe between ages 5 and 7:** r=0.29, p=0.019 **IDC:** r=0.29, p=0.018 **Concurrent phe:** r=0.24 p=0.043

Huijbregts 2002[14] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
G1f: PKU subjects concurrent phe>360 µmol/l G1g: PKU subjects concurrent phe>360 µmol/l age<11 G1h: PKU subjects concurrent phe>360 µmol/l age≥11			**G1d:** 7.5, SD-NR **G1e:** 5.6, SD-NR **G1g:** 8.8, SD-NR **G1h:** 4.8, SD-NR **Mean number of Misses 4 dots (MISS):** **G1d:** 20.1, SD-NR **G1e:** 16.7, SD-NR **G1g:** 28.4, SD-NR **G1h:** 22.1, SD-NR **Mean number of false alarms 5 dots (FA5):** **G1d:** 10.7, SD-NR **G1e:** 10.9, SD-NR **G1g:** 13.0, SD-NR **G1h:** 9.8, SD-NR **Number of misses – number of false alarms (BIAS):** **G1d:** 11.0, SD-NR **G1e:** 8.5, SD-NR **G1g:** 16.3, SD-NR **G1h:** 13.2, SD-NR	**Bias over time with:** **phe level between ages 5 and 7:** r=0.40, p=0.002 **phe level between ages 2.5 and 4:** r=0.28, p=0.023 **IDC:** r=0.35, p=0.007

Luciana 2001[15] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
United States Cross Sectional **G1:** PKU patients	**G1:** 18 Classic Lifetime, Recent (within 6 months prior to cognitive assessment) 17.88 ± 2.74 years	**Recent phe (mg/dl):** **G1:** 16.3 ± 6.8 (5.3-28.8) **Phe averages for 0-2 years, 3-4 years, 5-8 years, 9-13 years and 14-15 years of life:** **G1:** NR	**Spatial working memory:** **Easy-item errors:** **G1:** .71 ± 1.7 **Hard-item errors:** **G1:** 21.6 ± 16.8 **Strategy score:** **G1:** 32.6 ± 4.6 **Tower of London planning:** **Minimum move solutions:** **G1:** 7.8 ± 1.8 **Average moves to complete 3-move problems:** **G1:** 3.2 ± .4 **Average moves to complete 4-move problems:** **G1:** 5.7 ± 1.2 **Average moves to complete 5-move problems:** **G1:** 7.3 ± 1.9 **Planning Times:** **3- move problems:** **G1:** 5911.9 ± 4383.0 **4-move problems:** **G1:** 9535.7 ± 6772.7 **5-move problems:** **G1:** 8895.0 ± 5755.9 **ID/ED set shifting:** **Stage reached:** **G1:** 8.1 ± 2.0 **ID errors:**	**Spatial Working Memory-Strategy and: Phe within past 6 months:** **G1:** .71, p<.01 **Phe 0-2 years:** **G1:** -.11 **Phe 3-4 years:** **G1:** .38, p<.10 **Phe 5-8 years:** **G1:** .23 **Phe 9-13 years:** **G1:** .39, p<.10 **Phe 14-15 years:** **G1:** .65, p<.05 **Spatial Working Memory-Errors and Phe within past 6 months:** **G1:** .13 **Phe 0-2 years:** **G1:** -.44, p<.10 **Phe 3-4 years:** **G1:** .26 **Phe 5-8 years:** **G1:** .18 **Phe 9-13 years:** **G1:** .30 **Phe 14-15 years:**

Luciana 2001[15] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			G1: 4.4 ± 7.9 **ID trials:** **G1:** 10.5 ± 7.6 **ED errors:** **G1:** 5.5 ± 7.9 **ED trials:** **G1:** 13.3 ± 10.6 **Reversal errors:** **G1:** 5.75 ± 2.8	**G1:** .15 **Set shifting-Stage and Phe within past 6 months:** **G1:** NR **Phe 0-2 years:** **G1:** .24 **Phe 3-4 years:** **G1:** -.41, p<.10 **Phe 5-8 years:** **G1:** -.49, p<.05 **Phe 9-13 years:** **G1:** -.57, p<.05 **Phe 14-15 years:** **G1:** .03 **Tower of London-Perfect solutions and Phe within past 6 months:** **G1:** -.30 **Phe 0-2 years:** **G1:** .54, p<.05 **Phe 3-4 years:** **G1:** -.05 **Phe 5-8 years:** **G1:** -.09 **Phe 9-13 years:** **G1:** -.30 **Phe 14-15 years:** **G1:** .04

Griffiths 1998[16] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
UK Retro-spective case series **G1:** individuals with PKU	**G1:** 11 Concurrent, lifetime Classic Median Age (years): **G1:** 8.83 (5.11-11.92)	**Phe level birth to age 5 years (µmol/l):** **G1:** 342 ± 126 **Lifetime phe (µmol/l):** **G1:** 341 ± 125 (224-600) **Concurrent phe (µmol/l):** **G1:** 388 ± 127 (193-562)	**One-back continuous performance test (CPT):** **Overall mean hit rate out of 80:** **G1:** 72.18 ± 7.17 **Overall mean false alarm frequency:** **G1:** 8.36 ± 7.24 **Overall mean reaction time (milliseconds):** **G1:** 499 ± 81 **Two-back continuous performance test (CPT):** **Overall mean hit rate:** **G1:** 64.55 ± 7.54 **Overall mean false alarm frequency:** **G1:** 9.64 ± 5.89 **Overall mean reaction time (milliseconds):** **G1:** 509 ± 72	**Lifetime phe with any one-back measure or two-back measure:** **G1:** NS **Phe for first 5 years of life with any one-back measure or two-back measure:** **G1:** NS **Concurrent phe with any one-back measure or two-back measure:** **G1:** NS

Pietz 1998[17] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
Germany Cross Sectional **G1:** PKU subjects	**G1:** 57 Classic Lifetime, Concurrent 23.6 ± 3.4 (17-33)	**Phe $_{0\text{-adult}}$ (mean of all half-year medians) (µmol/l):** **G1:** 676 ± 157 (388-994) **Phe $_{0\text{-}12}$ (mean of all half-year medians for first 12 years) (µmol/l):** **G1:** 424 ± 158 (206-806) **Phe $_{12\text{-adult}}$ (mean of all half-year medians from 12 years of age up to adulthood) (µmol/l):** **G1:** 964 ± 194 (642-1424) **Concurrent phe (µmol/l):** **G1:** 1085 ± 303 (362-1733)	**Slow videotracking level (distance):** **G1:** 17.2 ± 6.7 **Slow videotracking stability (distance):** **G1:** 6.5 ± 3.0 **Fast videotracking level (distance):** **G1:** 37.9 ± 15.2 **Fast videotracking stability (distance):** **G1:** 16.6 ± 11.8	**Phe after 12 years of age with videotracking performance:** **G1:** r=-0.34, p<.05 **Concurrent phe with videotracking performance:** **G1:** r=-0.37, p<.01

Stemerdink 1995[18] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Netherlands Prospective Cohort **G1:** PKU patients	**G1:** 33 Classical Lifetime 11.8 ± 2.9 years (7.3-16.8)	**Phe levels first 4 years (µmol/l):** **G1:** 408, SD-NR (222-650) **Phe levels 2 years preceding testing (µmol/l):** **G1:** 374, SD-NR (125-701)	**Eriksen and Schultz task performance:** **Response times:** **G1:** NR **Error percentages:** **G1:** NR **Memory Search Task:** **Response times:** **G1:** NR **Error percentages:** **G1:** NR	**Mean Phe for first 4 years and:** **Eriksen and Schultz task performance:** **Response times:** **G1:** 0.33, p<0.05 **Error percentage:** **G1:** -0.004 **Memory Search Task:** **Response times:** **G1:** 0.03 **Error percentage:** **G1:** 0.12 **Mean Phe 2 years before testing and:** **Eriksen and Schultz task performance:** **Response times:** **G1:** 0.33, p<0.05 **Error percentages:** **G1:** -0.08 **Memory Search Task:** **Response times:** **G1:** 0.03 **Error percentage:** **G1:** -0.07

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Germany Prospective Cohort **G1:** PKU patients	**G1:** 20/20 Concurrent, lifetime Classic Age: **G1:** **Test time 1:** 10 years, 11 mos ± 1.3 years (8.9-13.1) (reported as median and mean of 10 years, 11 mos ± 1.3 years in Weglage 1996 and mean of 10.11 ± 1.3 years in Weglage 1995) **Test time 2:** 14 yrs, SD-NR	**Concurrent phe (µmol/l):** **G1:** **Test time 1:** 582 ± 372 (84-1710) (583 ± 377 (85-1709) in Weglage 1995 and 1996) **Test time 2:** 744 ± 456 (66-1944) **Lifetime phe (mean of yearly medians) (µmol/l):** **G1:** **Test time 1:** 474 ± 144 (282-810) (476 ± 144 (279-818) in Weglage 1995 and 1996) **Test time 2:** 534 ± 174 (276-1014) **Phe 6 months prior to test (mean of monthly medians) (µmol/l):** **G1:** **Test time 1:** 624 ± 328 (80-1563) **Test time 2:** NR **Mean of yearly medians between test times 1 and 2 (µmol/l):** **G1:** 576 ± 174 (276-1014)	**Test-d-2 (percentile scores):** **G1:** **Number of items completed:** **Test time 1:** 37.2 ± 26.2 (8.1-90.3) **Test time 2:** 60.0 ± 25.8 **Errors:** **Test time 1:** 57.0 ± 27.6 (15.9-93.3) **Test time 2:** 81.2 ± 26.8 **Number of items completed - errors:** **Test time 1:** 35.5 ± 26.6 (3.0-76.0) **Test time 2:** 65.8 ± 34.9 **CWIT-Stroop tasks:** **G1:** **Reading of color words (sec):** **Test time 1:** 48.2 ± 11.1 (SD=10.6 with a range of (31-81) in Weglage 1996; NR in Weglage 1995) **Test time 2:** 41.1 ± 10.3 **Color naming (sec):** **Test time 1:** 83.5 ± 16.7 (57-121) **Test time 2:** 67.4 ± 11.2 **Interference task time (sec):** **Test time 1:** 153.7 ± 45.9 (105-300) **Test time 2:** 110.6 ± 24.2 **Interference task mistakes (number):** **Test time 1:** 15.4 ± 14.2 (0-45) **Test time 2:** 11.6 ± 11.7	**Concurrent phe with Number of items completed:** **Test time 1:** r=0.41, p<0.05 (r=-0.41, p<0.05 in Weglage 1996) **Test time 2:** r=-2.42, p<0.05 **Errors:** **Test time 1:** r=-0.38, p<0.05 **Test time 2:** r=-2.39, p<0.05 **Number of items completed - errors:** **Test time 1:** r=-0.39, p<0.05 (reported as r=0.38, p<0.05 in Weglage 1995) **Test time 2:** r=-2.40, p<0.05 **Lifetime phe with Number of items completed:** **Test time 1:** NS **Test time 2:** NS **Errors:** **Test time 1:** NS **Test time 2:** NS **Number of items**

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			WISC-R (short term memory): **Test time 1:** 10.2 ± 2.2 (6-14) **Test time 2:** NR	**completed - errors:** **Test time 1:** NS **Test time 2:** NS **Phe 6 months prior to test with** **Number of items completed:** **Test time 1:** NR **Test time 2:** NR **Errors:** **Test time 1:** NR **Test time 2:** NR **Number of items completed - errors:** **Test time 1:** r=-0.39, p<0.05 **Test time 2:** NR **Concurrent phe and:** **reading of color words:** **Test time 1:** NS **Test time 2:** NS **Color naming:** **Test time 1:** NS **Test time 2:** NS **Interference task time:** **Test time 1:** r=0.39, p<0.05 **Test time 2:** NS **Mistakes (number):**

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				Test time 1: r=0.38, p<0.05 **Test time 2:** NS **Lifetime phe and: reading of color words:** **Test time 1:** NS **Test time 2:** NS **Color naming:** **Test time 1:** NS **Test time 2:** NS **Interference task time:** **Test time 1:** NS **Test time 2:** NS **Mistakes (number):** **Test time 1:** NS **Test time 2:** NS **Correlation of differences in CWIT performances between test times 1 and 2 and mean phe during the 3-year interval:** NS **Concurrent phe with WISC-R (short term memory):** **Test time 1:** NS **Test time 2:** NR

Weglage 1995[19-21] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**			**Lifetime phe with WISC-R (short term memory):** **Test time 1:** NS **Test time 2:** NR

Ris 1994[22, 23] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes**	**Correlation**
USA Prospective cohort **G1:** PKU subjects **G1a:** PKU subjects with unaffected siblings	**G1:** 25 **G1a:**10 Concurrent Classic **G1:** 22 years, SD-NR **G1a:** NR	**Concurrent phe (mg/dl):** **G1:** 22, SD-NR **Individual Concurrent Phe (µmol/l):** Subject 1: 993 Subject 2: 1102 Subject 3: 1665 Subject 4: 1968 Subject 5: 1380 Subject 6: 1538 Subject 7: 920 Subject 8: 1162 Subject 9: 1120 Subject 10: 1483 Subject 11: 1084 Subject 12: 1635 Subject 13: 1659 Subject 14: 1804 Subject 15: 503 Subject 16: 1399 Subject 17: 254 Subject 18: 1586 Subject 19: 2252 Subject 20: 1164 Subject 21: 1284 Subject 22: 1810 Subject 23: 1011 Subject 24: 1368 Subject 25: 938	**WCST-Perseverative Responses (raw scores):** **G1:** 21 ± 32 **G1a:** 22 ± 39 **Attention Diagnostic Method (seconds):** **G1:** 461 ± 132 **G1a:** 439 ± 125 **Individual WCST-Perseverative Responses:** Subject 1: NR Subject 2: 5 Subject 3: 7 Subject 4: 123 Subject 5: 11 Subject 6: 28 Subject 7: 8 Subject 8: 13 Subject 9: 39 Subject 10: 5 Subject 11: 17 Subject 12: 14 Subject 13: 9 Subject 14: 22 Subject 15: 6 Subject 16: 12 Subject 17: 6 Subject 18: 4 Subject 19: 115	**Concurrent phe with WCST-Perseverative Responses:** **G1:** 0.59, $p<0.01$ **Concurrent phe with Attention Diagnostic Method:** **G1:** 0.34, $p<0.10$

Ris 1994[22, 23] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
			Subject 20: 4 Subject 21: 16 Subject 22: NR Subject 23: 7 Subject 24: 18 Subject 25: 3	

Schmidt 1994[24] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Germany Prospective Cohort **G1:** PKU subjects **G1a:** PKU subjects who completed tests and were able to keep their Phe-levels according to high-low-high study design	**G1:** 19/14 **G1a:**14/14 Concurrent PKU classification: NR Age: **G1:** 20.5 years SD-NR (17-24) **G1a:** NR	**Mean Phe level (mg/dl):** Test time 1: **G1:** 23.4, SD-NR (12-30) **G1a:** 22.0 ± 5.7 Test time 2: **G1:** NR **G1a:** 10.5 ± 3.7 Test time 3: **G1:** NR **G1a:** 23.5 ± 6.1 **Individual phe at Test Time 1 (mg/dl):** Patient 1: 19.1 Patient 2: 19.0* Patient 3: 25.4 Patient 4: 23.1* Patient 5: 15.0 Patient 6: 21.0 Patient 7: 26.7 Patient 8: 24.7 Patient 9: 25.4 Patient 10: 16.8 Patient 11: 16.3* Patient 12: 12.4* Patient 13: 18.7 Patient 14: 29.7 Patient 15: 25.3 Patient 16: 16.6 Patient 17: 12.0 Patient 18: 9.4*	**Dot Pattern Exercise (DPE):** **Mean RT of 50 series (level of performance) (s):** **Test time 1:** **G1a:** 10.1 **Test time 2:** **G1a:** 8.09 **Test time 3:** **G1a:** 9.32 **SD of 50 series times (ms) (stability of performance):** **Test time 1:** **G1a:** 1381 **Test time 2:** **G1a:** 777 **Test time 3:** **G1a:** 1356 **Number of Errors (sum of misses, false alarms 3 and false alarms 5 dots):** **Test time 1:** **G1a:** 51.9 **Test time 2:** **G1a:** 36.8 **Test time 3:** **G1a:** 43.0 **Percentage of Errors:**	**Phe levels with DPE test outcomes:** NR

Schmidt 1994[24] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		Patient 19: 32.2 **Individual phe at Test Time 2 (mg/dl):** Patient 1: 11.0 Patient 2: 16.8* Patient 3: 16.1 Patient 4: 8.5* Patient 5: 7.4 Patient 6: 6.1 Patient 7: 16.8 Patient 8: 11.6 Patient 9: 10.9 Patient 10: 7.5 Patient 11: 13.7* Patient 12: 2.0* Patient 13: 4.6 Patient 14: 16.3 Patient 15: 10.4 Patient 16: 8.5 Patient 17: 7.0 Patient 18: 12.4* Patient 19: 12.0 **Individual phe at Test Time 3 (mg/dl):** Patient 1: 16.1 Patient 2: NR* Patient 3: 23.0 Patient 4:18.7* Patient 5: 35.2 Patient 6: 25.2	**Test time 1:** **G1a:** 8.7 **Test time 2:** **G1a:** 6.1 **Test time 3:** **G1a:** 7.2 DPE test outcomes for **G1:** NR	

Schmidt 1994[24] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		Patient 7: 25.9 Patient 8: 17.4 Patient 9: 18.4 Patient 10: 20.0 Patient 11: 14.8* Patient 12: 6.5* Patient 13: 20.9 Patient 14: 20.0 Patient 15: 36.6 Patient 16: 18.9 Patient 17: 25.4 Patient 18: 14.3* Patient 19: 25.3 *Data from patients 2, 4, 11, 12 and 18 not included in data analysis.		

de Sonneville 1990[25] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
Germany Prospective Cohort **G1:** PKU patients **G1a:** PKU patients with median concurrent Phe >9.5 mg/dl **G1b:** PKU patients with median concurrent Phe <9.5 mg/dl	**G1:** 32 **G1a:** NR **G1b:** NR PKU classification: NR Lifetime, concurrent **G1:** 8.7 years SD-NR **G1a:** NR **G1b:** NR	**Concurrent phe:** **G1:** NR **G1a:** NR **G1b:** NR **Lifetime phe:** **G1:** NR **G1a:** NR **G1b:** NR	**Dot Pattern Exercise:** **Mean times per series:** **G1:** 19.8 ± 3.7 **G1a:** 22.5 ± 5.3 **G1b:** 17.0 ± 2.5 **Accuracy (%) for false alarms to 3-dot patterns:** **G1:** 4.0, SD-NR **G1a:** NR **G1b:** NR **Accuracy (%) for Miss:** **G1:** 4.0, SD-NR **G1a:** NR **G1b:** NR **Accuracy (%) for false alarms to 5-dot patterns:** **G1:** 4.5, SD-NR **G1a:** NR **G1b:** NR **Calculation exercise (CAE) performance:** **Number of errors-simple additions:** **G1:** 0.9, SD-NR **Number of errors-complex additions:** **G1**: 2.5, SD-NR	**Eight median phe levels (measured at 6-month intervals since birth) with highest correlations with:** **DPE SD series:** Median 18: r=.75, p=.01 Median 14: r=.65, p=.01 Median 17: r=.64, p=.01 Median 04: r=.55, p=.01 Median 15: r=.51, p=.02 Median 12: r=.48, p=.02 Concurrent: r=.47, p=.01 Median 16: r=.47, p=.02 **DPE mean time over series:** Median 18: r=.58, p=.04 Median 14: r=.51, p=.02 Median 17: r=.48, p=.05 Median 16: r=.46, p=.03 Median 01: r=.46, p=.02 Median 04: r=.45, p=.02 Median 15: r=.45, p=.04 Concurrent: r=.37, p=.05 **Calculation exercises simple additions:** Median 16: r=.46, p=.02 Median 18: r=.42, p=.12

de Sonneville 1990[25] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
				Concurrent: r=.42, p=.02 Median 02: r=.34, p=.05 Median 01: r=.32, p=.07 Median 10: r=.31, p=.09 Median 05: r=.31, p=.09 Median 12: r=.27, p=.16 **Calculation Exercises complex additions:** Concurrent: r=.45, p=.01 Median 15: r=.29, p=.15 Median 01: r=.27, p=.15 Median 18: r=.24, p=.40 Median 13: r=.24, p=.24 Median 02: r=.20, p=.27 Median 12: r=.16, p=.40 Median 06: r=.16, p=.38

Welsh 1990[26] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
USA Prospective cohort **G1:** PKU subjects	**G1:** 11/11 Lifetime, Concurrent PKU classification: NR Mean age (years): 4.64, SD-NR (4.08-5.75) Individual Age (years): Subject 1: 4.25 Subject 2: 5.75 Subject 3: 4.08 Subject 4: 5.17 Subject 5: 4.50 Subject 6: 4.83 Subject 7: 4.50 Subject 8: 4.67 Subject 9: 4.42 Subject 10: 4.33 Subject 11: 4.50	**Concurrent phe:** **G1:**NR Subject 1: 13.0 Subject 2: 8.4 Subject 3: 10.6 Subject 4: 9.9 Subject 5: 9.9 Subject 6: 4.9 Subject 7: 17.9 Subject 8: 9.5 Subject 9: 7.5 Subject 10: 10.9 Subject 11: 1.1 **Mean lifetime phe:** **G1:** NR Subject 1: 9.2 Subject 2: 9.9 Subject 3: 7.9 Subject 4: 10.5 Subject 5: 11.4 Subject 6: 10.3 Subject 7: 14.0 Subject 8: 7.3 Subject 9: 8.3 Subject 10: 7.4 Subject 11: 9.5 **Highest phe level during infancy, before diet initiation:**	**Tower of Hanoi:** **G1:** 7.46 ± 7.74	**Tower of Hanoi with:** **Concurrent phe:** **G1:** r=-.46, **Mean phe:** **G1:** r=-.06 **Infant phe:** **G1:** r=-.46

Welsh 1990[26] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes	Correlation
		G1: NR Subject 1: 44.5 Subject 2: 45.3 Subject 3: 36.1 Subject 4: 31.9 Subject 5: 51.1 Subject 6: 31.9 Subject 7: 50.1 Subject 8: 20.0 Subject 9: NR Subject 10: 19.1 Subject 11: 43.0		

* All quantities expressed as **mean ± 1 SD (range)** unless otherwise noted.

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Appendix I. Studies Addressing Maternal PKU

Table I-1. Overview of Maternal PKU Collaborative Study (MPKUCS) papers

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
		Studies Reporting Cognitive Outcomes				
Rouse et al., 2004[1]	Effect of High Maternal Blood Phenylalanine on Offspring Congenital Anomalies and Developmental Outcome at Ages 4 and 6 Years: The Importance of Strict Dietary Control Preconception and Throughout Pregnancy	NR	US Canada	526 100 matched controls	576 413 live births	• McCarthy at 4 yrs • WISC-R at 6 yrs
Guttler et al., 2003[2]	Impact of the Phenylalanine Hydroxylase Gene on Maternal Phenylketonuria Outcome	NR	US Canada Germany	196 fully evaluated; 236 genotyped	308 pregnancies; 253 live births; 196 offspring fully evaluated	• WISC-R at 6-7 yrs or later
Levy et al., 2003[3]	Pregnancy Experiences in the Woman With Mild Hyperphenylalaninemia	NR	US Canada Germany	48	58	• WISC-R at 2 years • McCarthy Scales of Children's Abilities • Bayley Scales of Infant Development
Waisbren et al., 2003[4]	Cognitive and Behavioral Development in Maternal Phenylketonuria Offspring	NR	US Canada Germany	NR	NR; 228 offspring; 70 controls	• WISC-R at 7 years • Test of Language Development, 2nd edition • Peabody Individual Achievement Test-Revised • Stroop Interference • Visual Motor Integration • Child Behavior Checklist
Koch et al., 2003[5]	The Maternal Phenylketonuria International Study: 1984-2002	1984-2002	US Canada Germany	382	572	• McCarthy at 4yrs • WISC-R at 7 yrs • WISC-R at 10 yrs
Widaman et	Relation of Prenatal	NR	US	NR	572 pregnancies;	• Bayley at 1 year

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
al., 2003[6]	Phenylalanine Exposure to Infant and Childhood Cognitive Outcomes: Results From the International Maternal PKU Collaborative Study		Canada Germany		413 offspring evaluated	• McCarthy at 4 years • TOLD CSLQ at 4 years • WISC-R at 7 years
Antshel et al., 2003[7, 8]	Developmental Timing of Exposure to Elevated Levels of Phenylalanine is Associated with ADHD Symptom Expression	NR	US	NR	15 MPKU offspring; 46 PKU patients; 18 controls	• ADHD symptoms • FSIQ
Platt et al., 2000[9]	The International Study of Pregnancy Outcome in Women with Maternal Phenylketonuria: Report of a 12-year study	1984-1999	US Canada Germany	PKU NR; 101 controls	576 pregnancies; 414 live births	• Bayley at 2 yrs • McCarthy at 4-5 yrs • WISC-R data presented on children who had reached age 7
Koch et al., 2000[10]	The international collaborative study of maternal phenylketonuria: status report 1998	1984-1998	US Canada	NR	572 HPA 99 control	• Congenital anomalies • McCarthy at 4 years
Waisbren et al., 2000[11]	Outcome at Age 4 Years in Offspring of Women With Maternal Phenylketonuria: The Maternal PKU Collaborative Study	1984-2000	US Canada	205 253 offspring received preschool evaluation	572 pregnancies; 412 offspring	• McCarthy at 3-5 years • Test of language development at 4 years • Achenbach at 4 years • Vineland at 4 years • Bayley at 2 yrs
Waisbren, et al., 1998[12]	Neonatal neurological assessment of offspring in maternal phenylketonuria	NR	US	NR	56 PKU offspring; 45 control offspring	• Dubowitz Neurological Assessment of the Preterm and Full-Term Newborn Infant • Bayley Mental and Motor Scales at 1 year • Receptive-Expressive Emergent Language Scales at 1 year
Hanley et al., 1996[13]	The North American Maternal Phenylketonuria Collaborative Study, developmental assessment of the offspring: preliminary report	1984-1994	US Canada	NR	134 HPA offspring; 58 control offspring	• Bayley at 2 yrs • McCarthy at 4 yrs
Cipcic-Schmidt	German Maternal	1989-1994,	Germany	275	43 pregnancies;	• Bayley tests at 2 yrs

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
et al., 1996[14]	Phenylketonuria Study	worked with North American study since 1992	Austria		34 live births	
Koch et al., 1994[15]	The international collaborative study of maternal phenylketonuria: status report 1994	1984-1994 (US) 1986-1994 (Canada) 1993-1994 (Germany)	US Canada Germany	NR	402 pregnancies; 99 control	• Bayley Scales and McCarthy at 3.5 to 4.5 yrs
Koch et al., 1993[16]	The North American Collaborative Study of Maternal Phenylketonuria: Status Report 1993	1984-1992	US Canada	379 HPA	318 HPA; 59 control	• Bayley scale at 12-24 mos • McCarthy Scale between 3.5-5yrs

ADHD=attention deficit hyperactivity disorder; FSIQ=full scale intelligence quotient; MPKU=maternal phenylketonuria; NR=not reported; PKU=phenylketonuria; TOLD CSLQ=Test of Language Development Spoken Language Component; WISC-R=Wechsler Intelligence Scale for Children-Revised

Table I-2. Overview of additional Maternal PKU studies

Author, Year	Title	Study Date	Country	# of Women	# of Pregnancies	Cognitive Outcomes Reported
Studies Reporting Cognitive Outcomes						
Maillot et al., 2008[17, 18]	Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine & Maternal Phenylketonuria: Experiences From the United Kingdom	1977-2005	UK	67	105 offspring	• Griffiths Developmental Quotient at 1 year • McCarthy at 4 years • WISC-III at 8 and 14 years
Levy et al.,1983[19]	Effects of Untreated Maternal Phenylketonuria and Hyperphenylalaninemia on the Fetus	1971-1981	US	22	59 pregnancies 53 offspring	• IQ for children ≥3yrs • DQ for children<3yrs (Bayley, McCarthy, Wechsler, and Stanford-Binet) • Visual-motor coordination (Beery or Bender) • Congenital anomalies

DQ=developmental quotient; IQ=intelligence quotient; WISC-III-=Wechsler Intelligence Scale for Children, Third edition

Table I-3. Summary of maternal PKU studies reporting cognitive outcomes

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
Maternal PKU Collaborative Study Papers					
Koch et al., 2003[5]	NR/572/414	Pre-pregnancy treatment: 148 (25.9%) Treated in 1st trimester: 263 (46%) Treated in the 2nd trimester: 52 (9.1%) Treated in 3rd trimester: 4 (0.7%) Mild HPA, no treatment offered: 57	NR	NR	**Mental retardation among MPKUCS per maternal off-diet Phe (µmol/L), % affected** ≥1200: 28 901-1199: 8 601-900: 15 180-600: 2 Non-PKU=4.3
Levy et al., 2003[20]	48/58/NR	APL is assigned blood Phe selected as the highest of 2 or 3 plasma Phe on an unrestricted diet measured by amino acid analyzer or fluorometrically when the subject was not pregnant, µmol/L	APL=408±114 Maternal Phe: Average Phe exposure: untreated=270±84 (n=50); treated=269 ± 136 (n=8)	WISC-R, mean±SD (range)	Maternal MHP (n=40): 102±15 (65-125) Controls (n=64): 109±21 (35-147) P=0.07
Antshel et al., 2003[7, 8]	NR/NR/15	Maternal metabolic control defined by number of weeks gestation that elapsed until all subsequent blood phe was <10 mg/dL.	Mean=10.4 wks±4.9wks	Inattentive symptoms: number total of nine on ADHD Rating Scale-IV Hyperactive/Impulsive symptoms=number total of nine on ADHD Rating Scale-IV	**Mean (SD) Inattentive:** 5.9 (1.5) **Mean (SD) Hyperactive/Impulsive:** 6.3 (1.4) **Spearman rank coefficients for MPKU offspring ADHD Rating Scale-IV symptoms:** **Age**: -0.37, p<0.001 **Socioeconomic status**: -0.11 **FSIQ estimate**: -0.28, p<0.01 **Weeks to maternal metabolic control**: 0.63, p<0.001 **Maternal IQ**: -0.48, p<0.001

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
Waisbren et al., 1998[12]	NR/NR/56 with PKU, 45 controls	Mild HPA,no dietary intervention: 13% Metabolic control pre-pregnancy: 20% First trimester: 22% 2nd or 3rd trimester: 45%	NR	Dubowitz Neurological Assessment (relationship with other variables determined using Kruskal-Wallace chi-square test); Bayley Scales of Infant Development; Receptive-Expressive Emergent Language Scale; Home Observation for Measurement of the Environment	**Maternal Phe and Dubowitz**: r=4.4, p=0.11 **Maternal Phe and HOME Scale**: r=-.26, p=0.10 **Maternal Phe and DQ**: r=-.24, p=0.09 **Maternal Phe and language score**: r=-.23, p=0.12 **Weeks gestation diet started and Dubowitz rating**: r=2.1, p=0.35 **Weeks gestation diet started and HOME Scale**: r=-.19, p=0.30 **Weeks gestation diet started and DQ**: r=-.35, p=0.02 **Weeks gestation diet started and language score**: r=-.43, p=0.006 **Weeks gestation Phe <600 µmol/L and Dubowitz rating**: r=8.9, p=0.01 **Weeks gestation Phe <600 µmol/L and HOME Scale**: r=-.52, p=0.0008 **Weeks gestation Phe <600 µmol/L and DQ**: r=-.46, p=0.001 **Weeks gestation Phe <600 µmol/L and language score**: r=-.27, p=0.07 **Logistic regression analysis risk for having DQ <85 if metabolic control attained after pregnancy began**: OR=1.06, CI: 0.97-1.16, p=0.2
Hanley et al., 1996[4, 11, 13, 21]	NR/576/414	Maternal metabolic control=plasma Phe <10mg/dL (605 µmol/L) **G1:** Untreated mild HPA on a normal diet, treatment not recommended **G2:** Prior to pregnancy **G3:** 0-10 wks pregnancy **G4:** 10-20 wks pregnancy **G5:** >20 wks pregnancy	Phe (mg/dL) (n=253)	Peabody Individual Achievement Test Developmental Test of Visual Motor Integration Test of Language Development Child Behavior Checklist McCarthy General Cognitive Index WISC-R Bayley	**Waisbren 2000** **McCarthy Scales of Children's Abilities: n, GCI score** **G1:** n=33, 99 (14) **G2:** n=17, 99 (13) **G3:** n=26, 89 (17) **G4:** n=47, 84 (18) **G5:** n=59, 71 (19) **G6:** n=71, 107 (20) **Bayley Scales, Mean±SD:** **Mental Index:** **G1-G5** (n=134): 96±23 **G6** (n=53): 114±18 **Motor index:** **G1-G5** (n=134): 98±19 **G6** (n=53):110±16 **McCarthy Scales, Mean±SD**

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
		G6: Non-HPA control			**General Cognitive Index:** **G1-G5 (**n=134): 85±21 **G6** (n=53**):** 110±20 **Motor scale:** **G1-G5** (n=134): 91 ±17 **G6 (**n=53): 106±15 **Logistic regressions for risk of low GCI (≤86) in treated maternal PKU pregnancies (n=132): OR (95%CI), p** Low maternal IQ (≤85 vs. >85): 2.9(1.3-6.8), p=0.01 Maternal plasma Phe on normal diet (>20 vs ≤20 mg/dL [>1210 vs ≤1210 µmol/L]) [assigned Phe]: 2.5 (1.0-6.2), p=.04 Low HOME (Home Observation for Measurement of the Environment) Score (≤85 vs >85%): 2.0 (0.8-4.6) p=.13 Weeks to metabolic control (vs. metabolic control prior to pregnancy) 0-10 weeks: 2.6 (0.6-11.3) p=.20 10-20 wks: 3.2 (1.0-10.4) p=.06 >20 or never in control: 7.4 (2.3-24.4) p=.001 **Waisbren 2003** **Cognitive:** **FSIQ (on WISC-R), Mean±SD: n applicable to all WISC-R scores** **G1 (n=36):** 106±65–125 **G2** (n=39): 105±73–126 **G3** (n=46): 100±74–139 **G4** (n=44): 93±35–123 **G5** (n=70): 72±35–133 **G6** (n=63): 109±39–147 **Verbal score on WISC-R, Mean±SD:** **G1:** 105±67–125 **G2**: 103±75–129 **G3**: 98±65–142 **G4**: 93±40–122 **G5**: 77±40–127 **G6**: 108±46–154

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					Performance score on WISC-R, Mean±SD: **G1:** 104±71–129 **G2**: 102±72–129 **G3**: 95±69–128 **G4**: 96±40–129 **G5**: 72±40–131 **G6**: 111±44–142 **TOLD-2 Total Language, Median scores (ranges):** **G1 (n=29):** 96 (70–123) **G2** (n=23): 94 (74–119) **G3** (n=32): 92 (71–121) **G4** (n=41): 85 (64–117) **G5** (n=60): 74 (34–112) **G6** (n=59): 103 (44–136) **Stroop Interference, Median scores (ranges):** **G1** (n=13): 51 (22–64) **G2** (n=9): 51 (47–54) **G3** (n=10): 51 (37–62) **G4** (n=9): 56 (45–65) **G5** (n=7): 55 (47–70) **G6** (n=20): 50 (43–57) **PIAT-R Total Achievement, Median Scores (ranges):** **G1** (n=22): 94 (75–114) **G2** (n=21): 91 (80–132) **G3** (n=31): 92 (72–143) **G4** (n=32): 82 (65–103) **G5** (n=44): 73 (55–104) **G6** (n=43): 100 (56–145) **VMI, median scores (ranges):** **G1** (n=28): 97 (75–114) **G2** (n=36): 99(80–132) **G3** (n=41): 99(72–143) **G4** (n=35): 92 (73–118) **G5** (n=56): 77 (54–114) **G6** (n=44): 103 (55–134) **CBCL, median scores (ranges): n applicable for**

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					all CBCL scores Internalizing: **G1** (n=35): 49 (33–72) **G2** (n=39): 51 (33–67) **G3** (n=42): 50 (33–80) **G4** (n=43): 48 (33–69) **G5** (n=67): 55 (33–76) **G6** (n=61): 49 (33–76) Externalizing: **G1**: 49 (30–68) **G2**: 51 (30–70) **G3**: 53 (37–71) **G4**: 55 (30–73) **G5**: 56 (43–57) **G6**: 47 (30–77) Total Behavior: **G1**: 49 (30–73) **G2**: 51 (24–65) **G3**: 52 (24–74) **G4**: 54 (24–74) **G5**: 61 (32–81) **G6**: 48 (29–76)
Cipcic-Schmidt et al., 1996[14]	NR/43/34	Time at which Phe was <360 µmol/L	PKU: Pre-pregnancy: 11 (46%) 1-10 wks: 8 (33%) 11-20 wks: 2 (8%) >21 wks: 3 (13%) HPA: No diet: 2 (20%) Pre-pregnancy: 4 (40%) 1-10 wks: 1 (10%) 11-20 wks: 0 >21 wks: 3 (30%)	Bayley Scales of Infant Development	**Mean MDI**: 96.4 (60-140) **Mean PDI**: 90.2 (49-128) **Start of dietary control and developmental quotients**: rMDI=-.43 rPDI=-.60
Additional Maternal PKU Studies					
Lee et al., 2003[17, 18]	67/107/109	Phe during pregnancy, mean ± SD, µmol/L: **G1**: diet begun	**G1:** 203.5 ± 58 **G2:** 269 ± 115 P=0.0003	Griffiths DQ at 1 yr McCarthy GCI at 4 yrs WISC-III IQ at 8 yrs	**DQ:** **G1 (n=73):** 107± 13.8 **G2 (n=27):** 99.3 ± 13.3 P=0.014 **GCI**:

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
		preconception **G2**: diet begun postconception			**G1 (n=54):** 95.2 ± 16.6 **G2 (n=14):** 85.9 ± 28.9 P=NS **IQ**: **G1 (n=30):** 110.6 ± 14.8 **G2 (n=9):** 91.2 ± 23.9 P=0.005 **Pregnancies with mean blood Phe in the target range for the entire pregnancy, SDs for Phe and:** **4 yr GCI**: r=0.362 (n=53); P=0.008 **8 yr IQ**: r=0.446 (n=30); P=0.014 **14 yr IQ**: r=0.761 (n=7); P=0.047 **1 yr DQ**: r=0.057 (n=73); P=NS **SDs for Phe during pregnancy, and:** **4 yr GCI**: r=-0.385 (n=65); p=0.002 **8 year IQ**: r=-0.433 (n=36); p=0.008 **14 year IQ**: r=-0.712 (n=9); p=0.031 **Proportion of time with Phe in target range and:** **4 yr GCI**: r=0.269 (n=77); p=0.041 **8 year IQ**: r=0.437 (n=58); p=0.012 **Time during pregnancy when mean Phe > 300:** **Griffiths DQ**: r=0.036, p=NS **McCarthy GCI**: r=-0.219, p=NS **WISC-III IQ at 8 yrs**: r=-0.564, p=0.001 **WISC-III IQ at 14 yrs**: r=-0.75, p=0.032 **Time during pregnancy when mean Phe > 400 and:** **Griffiths DQ**: r=0, p=NS **McCarthy GCI**: r=-0.334, p=0.01 **WISC-III IQ at 8 yrs**: r=-0.566, p=0.001 **WISC-III IQ at 14 yrs**: r=-0.687, p=0.06 **Mean maternal Phe and developmental outcome** **Trimester 1:** **1 yr Griffiths DQ**: r=-0.019 (n= 90); p=NS **4 yrs McCarthy GCI**: r=-0.365 (n=65); p=0.003 **8 yr WISC-III IQ:** r=-0.593 (n=36); p<0.0005 **14 y WISC-III IQ**: r=-0.73 (n=9); p=0.026 **Trimester 2**: **1 yr Griffiths DQ**: r=-0.134 (n=91); p=NS

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					4 yrs McCarthy GCI: r=-0.106 (n=65); P=NS **8 yr WISC-III IQ:** r=-0.274 (n=36); p=NS **14 y WISC-III IQ**: r=0.249 (n=9); P=NS **Trimester 3**: **1 yr Griffiths DQ**: r=0.069 (n=90); p=NS **4 yrs McCarthy GCI:** r=-0.037 (n=63); p=NS **8 yr WISC-III IQ**: r=-0.46 (n=35); p=0.005 **14 y WISC-III IQ**: r=-0.709 (n=8); p=0.049
Levy et al., 1983[19]	22/59/53	Mean of two maternal Phe levels drawn at times of child evaluation	Range: 165-1370 µmol/L; mean: 697.3 µmol/L	Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, Wechsler Intelligence Scale for Children-Revised; Standford-Binet Intelligence Test; Visual Motor Coordination by Beery Visual Motor Integration Test or Bender Gestalt Test	**Maternal blood Phe and IQ:** r=-0.82, p<0.001 (n=28)

ADHD=attention deficit hyperactivity disorder; APL=assigned blood phenylalanine level ; CBCL=Child Behavior Checklist ; cm=centimeter; DQ= developmental quotient ; FSIQ=full scale intelligence quotient ; G=group; GCI=McCarthy Global Cognitive Index; HC=head circumference; HOME= Home Observation for Measurement of the Environment; HPA=hyper phenylalaninemia;; IQ=intelligence quotient; MDI= Bayley Mental Development Index; MHP=maternal hyperphenylalaninemia; MPKU=maternal phenylketonuria; MPKUCS= Maternal PKU Collaborative Study; MR=mental retardation; n=number; PDI=Bayley Psychological Development Index ; Phe=phenylalanine; PIAT= Peabody Individual Achievement Test; PKU=phenylketonuria; TOLD=Test of Language Development; VMI=visual motor integration; WISC=Weschler Intelligence Scale for Children

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Appendix J. Summary of New Drug Application Studies of Sapropterin

Table J-1. Summary of New Drug Application studies

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
A Phase 2, Multicenter, Open-Label Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin Treatment in Subjects With Phenylketonuria Who Have Elevated Phenylalanine Levels (PKU-001) Germany, Italy, US Completed Sapropterin **Note:** Phenoptin is sapropterin	Primary Outcomes: • Evaluate the degree and frequency of response to Phenoptin, as demonstrated by a reduction in blood Phe level among subjects with PKU who have elevated Phe levels Secondary Outcomes: • Evaluate the safety of Phenoptin treatment in this subject population, and identify individuals in this subject population who respond to Phenoptin treatment with a reduction in blood Phe level	Inclusion Criteria: Age ≥ 8 years Blood Phe level ≥ 450 umol/L at screening Clinical diagnosis of PKU with hyperphenylalaninemia documented by past medical history of at least one blood Phe measurement ≥ 360 umol/L (6 mg/dL) Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian, after the nature of the study has been explained Negative urine pregnancy test at screening (non-sterile females of child-bearing potential only) Male and Female subjects of childbearing potential (if sexually active and non-sterile) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study Willing and able to comply with study procedures Willing to continue current diet unchanged while participating in the study Exclusion Criteria: Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable Use of any investigational agent within 30 days prior	Trial ID: NCT00104260; EudraCT # 2004-002071-16 Study design: non-randomized open label safety/efficacy study Time frame: NR Enrollment: 489 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		to screening, or requirement for any investigational agent or vaccine prior to completion of all scheduled study assessments Pregnant or breastfeeding, or considering pregnancy ALT > 5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid–dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation) Serious neuropsychiatric illness (e.g., major depression) not currently under medical control Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) Concurrent use of levodopa Clinical diagnosis of primary BH4 deficiency	
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin in Subjects With Phenylketonuria Who Have Elevated Phenylalanine Levels (PKU-003) Ireland, Italy, United Kingdom, US Completed Sapropterin **Note:** Phenoptin is sapropterin. "Subjects who complete protocol PKU-003 will have the opportunity to be	Primary Outcomes: • Change in blood Phe levels from baseline to week 6 [US-based sites] • To evaluate the efficacy of Phenoptin in reducing blood Phe levels in subjects with phenylketonuria. The primary efficacy endpoint is the Phe level at Week 6, which will be compared by testing the difference in mean blood Phe levels in the placebo and Phenoptin treatment groups at Week 6. The Week 6 mean blood Phe levels in each group will be compared using an	Inclusion Criteria: 8 years of age and older Received at least 7 out of 8 scheduled doses in Study PKU 001 Responsive to Phenoptin in Study PKU-001, defined as a reduction in blood Phenylalanine level of ≥30% compared with baseline Blood Phenylalanine level ≥450 µmol/L at screening Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian,	Trial ID: NCT00104247; EudraCT # 2004-004512-23 Study design: RCT Time frame: NR Enrollment: 88 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
enrolled in an open-label extension study of Phenoptin."	analysis of covariance model with baseline Phe level and treatment as the only covariates. The model will utilize a last observation carried forward (LOCF) imputation approach to deal with missing data. Secondary Outcomes: • NR [US-based sites] • To evaluate the safety of Phenoptin versus placebo in this subject population. • To evaluate the efficacy of Phenoptin versus placebo in this subject population with respect to: the mean change in weekly blood Phe levels during the 6 weeks of treatment; the proportion of subjects who have blood Phe levels ≤600 µmol/L at Week 6.	after the nature of the study has been explained Negative urine pregnancy test at screening (females of child-bearing potential) Male and Female subjects of childbearing potential (if sexually active) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study Willing and able to comply with study procedures Willing to continue current diet unchanged while participating in the study Exclusion Criteria: Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable Use of any investigational agent other than Phenoptin within 30 days prior to screening, or requirement for any investigational agent or investigational vaccine prior to completion of all scheduled study assessments Pregnant or breastfeeding, or considering pregnancy ALT >5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation	

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		recipient) Serious neuropsychiatric illness (e.g., major depression) not currently under medical management Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) Concurrent use of levodopa Clinical diagnosis of primary BH4 deficiency	
A Phase 3, Multicenter, Open-Label Extension Study of Phenoptin in Subjects With PKU Who Have Elevated Phenylalanine Levels (PKU-004) Ireland, Italy, US Completed Sapropterin **Note:** Phenoptin is sapropterin	Primary Outcomes: • To evaluate the safety and tolerability of long-term Phenoptin treatment in subjects with PKU Secondary Outcomes: • To compare the safety and tolerability of three different doses of Phenoptin treatment in subjects with PKU • To determine the effect of various doses of Phenoptin on blood phenylalanine (Phe) levels • To evaluate the population pharmacokinetics of Phenoptin • To evaluate the ability of Phenoptin to reduce phenylalanine (Phe) levels over a 24-hour period • To evaluate the persistence of benefit of Phenoptin treatment in the subject population as evidenced by long-term control of blood Phe levels	Inclusion Criteria: 8 years of age and older Prior successful participation in Study PKU-003 Willing and able to provide written informed consent or assent and written informed consent (if required) by a parent or legal guardian For females of child-bearing potential only: Negative urine pregnancy test within 24 hours prior to enrollment. Women using acceptable birth control measures must agree to continue to use those measures while participating in the study Willing and able to comply with study procedures Willing to continue current diet unchanged while participating in the study Exclusion Criteria: Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable Withdrew from, or otherwise did not successfully complete, study PKU-003, except for subjects who were removed from the study because their blood Phe exceeded the alert level Expected to require any investigational agent or vaccine prior to	Trial ID: NCT00225615; EudraCT # 2004-004513-41 Study design: non-randomized safety/efficacy study Time frame: NR Enrollment: 80 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		completion of all scheduled study assessments Pregnant or breastfeeding, or planning pregnancy Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes) Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) Concurrent use of levodopa	
A Phase 3, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Phenoptin to Increase Phenylalanine Tolerance in Phenylketonuric Children on a Phenylalanine-restricted Diet (PKU-006) Germany, Spain, US Completed Sapropterin in 100 mg tablets equivalent to 20 mg/mg per day or placebo **Note:** Phenoptin is sapropterin.	Primary Outcomes: • Amount of dietary supplemented phenylalanine (Phe) tolerated in children with PKU [US-based sites] • To evaluate the ability of Phenoptin to increase phenylalanine (Phe) tolerance in children with phenylketonuria who are following a Phe-restricted diet Secondary Outcomes: • Change in Phe levels from baseline to week 3 [US-based sites] • To evaluate the ability of Phenoptin to reduce blood Phe levels in children with phenylketonuria who are following a Phe-restricted diet • To compare the ability of Phenoptin versus placebo to increase Phe tolerance in children with phenylketonuria who are following a Phe-restricted diet • To evaluate the safety of Phenoptin as compared with placebo in this subject population • To explore the potential	Inclusion Criteria: Clinical diagnosis of PKU with hyperphenylalaninemia (HPA) documented by at least one blood Phe measurement ≥360 umol/L (6 mg/dL) Under dietary control with a Phe-restricted diet as evidenced by:· Estimated daily Phe tolerance ≤1000 mg/day At least 6 months of blood Phe control (mean level of ≤480 µmol/L) prior to enrolling in the study Aged 4 to 12 years inclusive at screening A blood Phe level ≤ 480 µmol/L at screening Female subjects of childbearing potential (as determined by the principal investigator) must have a negative blood or urine pregnancy test at entry (prior to the first dose). Note: All female subjects of childbearing potential and sexually mature male subjects must be advised to use a medically accepted method of contraception throughout the study. Female subjects of childbearing	Trial ID: NCT00272792; EudraCT # 2005-003777-24 Study design: RCT Time frame: NR Enrollment: 45 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
	reduction in the cost of medical foods and Phe-free formulas	potential must be willing to undergo periodic pregnancy tests during the course of the study Willing and able to comply with all study procedures Willing to provide written assent (if applicable) and written informed consent by a parent or legal guardian after the nature of the study has been explained and prior to any research-related procedures Exclusion Criteria: Any condition that, in the view of the PI, renders the subject at high risk from treatment compliance and/or completing the study Prior history of organ transplantation Perceived to be unreliable or unavailable for study participation or have parents or legal guardians who are perceived to be unreliable or unavailable Use of any investigational agent within 30 days prior to screening, or requirement for any investigational agent or vaccine prior to completion of all scheduled study assessments ALT > 2 times the upper limit of normal (i.e., Grade 1 or higher based on World Health Organization Toxicity Criteria) at screening Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes)	
Sapropterin Expanded Access Program US	Primary Outcomes: • NR	Inclusion Criteria: Patient has hyperphenylalaninemia	Trial ID: NCT00484991 Study design: expanded

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
Unknown; status lasted updated April 11, 2008 Sapropterin	Secondary Outcomes: • NR "The Purpose of this study is to provide patients with hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU) access to sapropterin dihydrochloride and to collect more information about the safety of the drug in an expanded access program (EAP) until commercial product is available."	due to PKU, a rare and serious disease Patient is not participating in a sapropterin dihydrochloride clinical study Patient is older than 8 years of age Patient is willing and able to provide written informed consent or, in the case of under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian If female and of child bearing potential, the patient has a negative urine pregnancy test within 24 hours prior to enrollment (females of child-bearing potential only) and will be using adequate contraceptive methods to avoid pregnancy while participating in the program Patient is willing and able to comply with program procedures Patient lives in the United States Exclusion Criteria: Patient is perceived to be unreliable or unwilling to comply with program participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unwilling to comply with program participation Patient has a concurrent disease or condition that would interfere with program participation or safety Patient is 8 years old or younger Patients is eligible for enrolling in PKU-010 Patient is participating in an ongoing study with sapropterin dihydrochloride Patient is pregnant, breast	access program Time frame: NR Estimated Enrollment: NR Start date: NR Estimated completion date: NR Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		feeding or considering pregnancy Patient is taking levodopa	

ALT=alanine aminotransferase; EAP=expanded access program; HPA=hyperphenylalaninemia; NR=not reported; Phe=phenylalanine; PI=principal investigator; PKU=phenylketonuria

Appendix K. Recent Conference Abstracts Addressing Adjuvant Treatment

Table K-1. Recent conference abstracts addressing adjuvant treatment

Conference	Year	Published	Title	Abstract
American College of Medical Genetics	2011	Not found	Diet Challenge as a Method for Determining Responsiveness to Sapropterin Dihydrochloride in a Patient with Well Controlled Phenylketonuria	Phenylketonuria (PKU) is a metabolic disorder caused by the deficiency of phenylalanine hydroxylase (PAH), the enzyme responsible for converting phenylalanine (Phe) to tyrosine (Tyr). To be effective, PAH depends on a cofactor, tetrahydrobiopterin (BH4). The currently accepted management of PKU involves a low-protein diet, supplemented with a phenylalanine-free amino acid formula. Recent advances, however, have included treatment with a synthetic version of BH4, sapropterin dihydrochloride. The introduction of sapropterin dihydrochloride may improve the function of any existent PAH thus increasing the patient's dietary Phe tolerance. Early studies have shown BH4 responsiveness in 30-50% of individuals with PKU, allowing their diets to be liberalized and their use of medical formula reduced. Current practice for use of this medication specifies that the dose should be started at 20 mg/kg. After one month at 20 mg/kg, patients whose Phe levels have not decreased from their baseline are determined to be non-responsive and the treatment is discontinued. We report here the case of a 25-year-old male with PKU who is being successfully treated with sapropterin dihydrochloride in an atypical manner. The patient reached and maintained the dose of 20 mg/kg, and his Phe level remained unchanged. According to the current recommendations this would categorize him as a non-responder. At the beginning of the trial his Phe levels were on the low end of the normal treatment range (120-360 µmol/L, 2-6 mg/dL) so instead of discontinuing the treatment when he did not appear to respond, the medical team decided to initiate a Phe challenge. The addition of sapropterin dihydrochloride has allowed this patient to double his phenylalanine intake and decrease his medical formula. He has been able to incorporate regular grains, dairy and occasional portions of fish and poultry into his diet, improving his perceived quality of life. This case raises the question of whether patients who maintain a steady but acceptable Phe level with the addition of sapropterin dihydrochloride should be challenged with diet to test for a change in their Phe tolerance. The clear benefit to this patient is a strong indication for further investigation. These findings have the potential to uncover a population of patients who would otherwise have been labeled non-responsive and had a truly beneficial treatment discontinued.
American College of Medical Genetics	2011	Not found	Interim Report of Study PKU-015: a Phase 3b Study of Sapropterin Dihydrochloride (Kuvan®) in Young Children with PKU	Background: Phenylketonuria (PKU) is an inherited metabolic disease characterized by the accumulation of phenylalanine (Phe) leading to neurocognitive dysfunction. The brain is more sensitive to the toxic effects of Phe during periods of rapid growth, such as during childhood. Among PKU patients, maintenance of adequate Phe levels is the strongest determinant of IQ. Clinical study PKU-015 examines whether sapropterin dihydrochloride (sapropterin, Kuvan®) in conjunction with dietary control in young children is safe and as effective as diet alone in preserving neurocognitive function and normal growth. As of this interim data cut (October 2010), the study was still enrolling. This study also collects data on long-term safety and ability to maintain blood Phe levels within acceptable ranges. Methods: In Part 1, children aged 0 - 6 years with PKU are evaluated over 4 weeks for sapropterin (20 mg/kg/day) responsiveness, defined in this study as a ≥30% mean decrease from baseline in blood Phe levels. Sapropterin responders are allowed to enroll in Part 2, a 7-year evaluation of neurocognitive outcomes, safety, and blood Phe control. Enrollment is balanced across ages. An inclusion criterion requires subjects to have adequate blood Phe control at enrollment as defined by local standards or the investigator.

Conference	Year	Published	Title	Abstract
				Results: Demographic information, baseline characteristics, sapropterin responsiveness, and adverse events are presented for the first 80 enrolled subjects. Subjects were 58% female and 83% white. Mean height and weight were compared with average values on the CDC growth curve, resulting in a mean body mass index of 0.6±0.93 SD above the fiftieth percentile. Mean blood Phe level at enrollment was 310±176 µmol/L. Of the 78 subjects with mean blood Phe level data for the first 4 weeks of dosing (Part 1), 59% were sapropterin responders. Median duration of study participation at the interim data cut was 175 days (range, 29 - 394 days), including non-responders who discontinued after completion of Part 1. Only one adverse event was reported in ≥5% of subjects: vomiting in 5.0%. Other reported adverse events, including infections, fever, and rash, are common symptoms in this population. The only reported serious adverse event (convulsion in one case) was not considered related to study drug. Conclusions: PKU-015 is exploring safety and response to sapropterin in young children with PKU. Interim data analysis indicates that a relatively high percentage (59%) responded to sapropterin with a favorable safety profile. Serial evaluation of neurocognitive function over time will determine the effect of sapropterin on development.
Society for Inherited Metabolic Disorders	2011	Not found	Baseline Characteristics of PKU Patients Enrolled in the PKUDOS Registry	Background: The PKUDOS registry was designed to provide 15 years of data on PKU patients of all ages who are currently or previously treated with sapropterin dihydrochloride (sapropterin, Kuvan®) or who plan to initiate treatment with sapropterin. Baseline data were provided by participating centers. Results: Baseline characteristics are presented for the 589 patients enrolled at 45 centers across the United States during the first 2 years after launch of the registry. This PKUDOS population was aged 0–55 years (median=14 years) at enrollment, evenly distributed between males and females, and 89% white. Age at PKU diagnosis ranged from 0 to 49 years (median=3 days). Overall median height (n=552) was slightly below and weight (n=562) was slightly above the 50% CDC growth curve resulting in a median BMI (n=553) of +0.7 SD above the 50% CDC growth curve. Prescribed phenylalanine (Phe) free medical foods and formulas, large neutral amino acids, and nutrient supplements (tyrosine [Tyr], vitamins, minerals, energy, and dietary Phe) were recorded. At enrollment, 315 (53%) patients were taking sapropterin, 188 (32%) had prior sapropterin exposure (not currently taking sapropterin), and 86 (15%) were to begin treatment with sapropterin per registry enrollment criteria. Median duration of exposure for both current and prior sapropterin users (n=457) was 15.5 months with a median dose level of 20 mg/kg/day. For patients with daily Phe intake reported, median daily prescribed Phe and actual Phe intake were approximately 30–50% higher in patients taking sapropterin than in patients with prior sapropterin exposure and patients that were to begin sapropterin treatment. Median blood Phe levels at enrollment were 333, 666 and 598 µmol/L among patients currently taking sapropterin, patients with prior sapropterin exposure and patients that were to begin sapropterin treatment, respectively. Phe/Tyr ratios showed a similar trend, with values of 6.7, 11.6 and 10.3 among patients taking sapropterin, patients with prior sapropterin exposure and patients that were to begin sapropterin treatment, respectively. Conclusions: The PKUDOS registry allows the longitudinal follow up of patients with PKU. Patients had mildly increased BMI compared with CDC growth curves. Patients taking sapropterin had higher prescribed and actual dietary Phe intake while maintaining lower Phe levels and Phe/ Tyr ratios. The PKUDOS registry is an opportunity for healthcare providers to engage in active research regarding management and long-term outcomes of PKU patients who have had, or will have, exposure to sapropterin.

Conference	Year	Published	Title	Abstract
Society for Inherited Metabolic Disorders	2011	Not found	Bone Mineral Density in a Cohort of PKU Patients: Comparison Between Responders and Non-responders to Kuvan Treatment	Background: Patients with phenylketonuria (PKU) are at greater risk of fractures, osteopenia, and osteoporosis than those without PKU. Kuvan, a BH4 analog, is an adjunct therapy for PKU, but its effect on bone mineral density has yet to be explored. The objective of this analysis was to determine the effect of Kuvan on total bone mineral density (tBMD) in a group of PKU patients (N4 years old) after 1 year of treatment, as well as to examine differences between responders and non-responders and differences between gender. Methods: tBMD was measured with dual-energy X-ray absorptiometry (DXA) at baseline and at 12 months in 35 male and 23 female patients between the ages of 6 and 49. PKU patients were categorized as either responders (≥15% decrease in blood Phe levels) or non-responders at the 4-week follow-up visit after the start of treatment. Responders to Kuvan treatment were kept on drug for the duration of the study, whereas those found to be non-responders were simply asked to continue following diet therapy. Z-score values were used for within- and between-group comparisons; 2-sample t-tests were used for the analysis, and the level of significance was pb0.05. Results: Baseline and 12-month DXA results are available for 41 patients, with 12-month results pending for 2 patients. Thirty-six percent (36%) of patients were considered responders based on the defined criteria. Average total bone density Z-scores were similar between responders and non-responders at baseline (−0.42±0.9 vs. −0.59±1.0, respectively). At baseline, the prevalence of tBMD z-scores≤−1 was 33%, and 67% had Z-scores over−1. When divided by age group, 22% of children (5–11), 54% of adolescents (12–18), and 33% of adults (19+) had Z-scores≤−1. A 2-sample t-test revealed that there was a non-significant difference (pN0.847) in Z-score from baseline to endpoint between responder and non-responder groups. The change in Z-score between males and females, regardless of treatment group, was also not significant (pN0.160). Within the group of responders, females had a greater change in Z-scores than males (mean 0.3000 vs.−0.0455, pN0.0587). Within the group of non-responders, females and males were similar in Z-score change (mean 0.129 vs. 0.125, pN0.987). Conclusions: In this pilot study, we saw small but not significant differences when comparing by treatment groups and by gender. In the responder group, women had a higher Z-score change than men, and even though this change was non-significant (pN0.0587), it could point to a correlation between treatment and gender. Comparing baseline and endpoint Z-scores, the only significant difference was found in female responders (p=0.04), lending more weight to a possible gender-specific effect. Larger studies are needed to confirm this observation.
Society for Inherited Metabolic Disorders	2011	Not found	Change in Timing of Sapropterin Dose Results in Inappropriate Liberalization of Diet in 10 Year old Patient with PKU	Phenylketonuria (PKU), an autosomal recessive disorder due to defects in the enzyme phenylalanine hydroxylase (PAH), results in accumulation of phenylalanine in the body. The mainstay of treatment is dietary intervention to limit the phenylalanine in the diet. Tetrahydrobiopterin (BH4) is a required cofactor for enzymatic activity. Sapropterin dihydrochloride, a synthetic tetrahydrobiopterin (BH4), has been shown to be effective in the treatment of PKU by activating residual PAH activity in responsive patients. The medication is labeled to be administered with food, preferably at the same time each day. Once-daily dosing of sapropterin has been reported to show stable levels of blood phenylalanine levels over a 24 hour period. Case report: We describe a 10 year old, Caucasian male, with historically extremely well-controlled PKUon diet, who had an unexpected response to a dose administration change. Sapropterin (20 mg/kg/day) was initially taken in the morning with food, followed by a regular phe-restricted dietary regimen throughout the day. After ten days, he began taking it int he evenings, with food, and phenylalanine levels were obtained following an overnight fast. Based on these levels, his response to this medication was determined to be an 82% decrease in

Conference	Year	Published	Title	Abstract
				fasting phe level after 2 weeks on therapy, at which time his diet was significantly liberalized. However, when he again began taking it in the morning, with no additional dietary changes, his measured phenylalanine level tripled, suggesting that measurement of fasting phenylalanine levels after evening dosage might result in a spuriously low phenylalanine level and erroneous identification of responder status, resulting in inappropriate liberalization of the diet. Conclusion: The findings in this case suggest that the pharmacokinetics of once-daily sapropterin dosage may be different from previously reported pharmacokinetics, and particularly dependent upon timing of dose and prolonged fasting after dosing.
Society for Inherited Metabolic Disorders	2011	Not found	Factors Influencing Adherence to Long Term Sapropterin Therapy	A recent patient survey examined why patients responsive to sapropterin dihydrochloride (sapropterin, Kuvan®) failed to adhere to long term therapy. In December 2009, 38 English speaking patients were surveyed to determine factors influencing adherence based on the five dimensions of adherence defined by the World Health Organization (2003): social and economic, health care system, condition related, therapy related, and patient related. Twenty patients (52%) had been on sapropterin therapy for one year (active patients) and 18 (48%) who had discontinued therapy (inactive patients) after nine months of treatment. Mean age for inactive patients was 15.9 years and 61% (11) were male. Mean age for active patients was 17.5 years and 61% (12) were female. Marked differences in dietary adherence, support systems, perception of disease on their life, and use of health care services were seen between the two groups. Only 72% (13) of inactive patients used medical foods and formulas to control their phe levels versus 90% (18) of active patients. Only 5% (1) of active patients versus 28% (5) of inactive patients reported that PKU was a burden and interfered with their ability to attain their full potential. Active patients had a larger support system including parents, teachers, and clinic staff whereas inactive patients relied primarily on their parents. Active patients also had shorter driving distances to clinics and more regular clinic visits. This data provides insight into factors that influence long-term adherence to sapropterin therapy.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	The Effect of LNAA on Diet Intake for PKU Patients	Background: Supplementation of large neutral amino acid (LNAA) and a semi-free (SF) diet has been shown to have a positive effect on well-being on adults with PKU. However, patients are used to low protein diet and find it often difficult to eat sufficient natural protein. This can result in malnutrition. The aim of this study was among others to determine the effect on diet intake from LNAA in different dosages and combinations. Material (Patients) and methods: This was a prospective, double-blind, cross-over study consisting of four consecutive 3-week phases. Twelve subjects (6 males, 6 females) with PKU were recruited, 11 completed the study. Two different brands of LNAA (A and B) were tested. Each phase consisted of LNAA A or B, either in low or high dosage. Subjects were instructed to follow their usual SF diet and complete a 3-day food record at start, and at the end of each period. Results: Protein intake varied from 76–102 grams/day (mean) and energy intake was 9341–10098 kilojoules/day (mean). There was no correlation between protein- and energy intake and the amount or brand of LNAA. Conclusions: LNAA A & B in different dosages or combinations do not affect protein or energy intake.

Conference	Year	Published	Title	Abstract
Society for the Study of Inborn Errors of Metabolism	2011	Not found	Tetrahydrobiopterin Reduces Plasma Prolactin Concentrations in PKU Patients	Background: Reduced cerebral neurotransmitter concentrations may contribute to cognitive dysfunction and mood disturbances in PKU. Some patients report improved executive functioning and mood during BH4 treatment at comparable plasma Phe concencentrations. We hypothesized that BH4 increases cerebral neurotransmitter synthesis in PKU patients. Methods: BH4 treatment effects were studied in 18 several-week BH4-responsive subjects (age 17.5±9.6 years, 9 male). Plasma concentrations of prolactin (a marker of cerebral dopamine availability), monoaminergic neurotransmitters, and neurotransmitter metabolites prior to BH4 treatment were compared to long-term stabilization concentrations. Results: BH4 significantly reduced prolactin in male patients (270±168 vs. 195±132 mE/L , p=0.008), but not in female patients (295±192 vs. 249±99 mE/L, p=0.329). Unexpectedly, adrenalin and metanephrine were significantly reduced after BH4 treatment (p=0.034 and p<0.001). A similar trend was observed for noradrenalin (p=0.091). Serotonin concentrations were unaffected by BH4 (p=0.251). Dopamine was undetectable. Conclusions: BH4 treatment reduces plasma prolactin concentrations in male patients. This reduction is consistent with increased cerebral dopamine availability, possibly caused by BH4 treatment. Follow-up studies should investigate executive function and mood prior to and during BH4 treatment, as well as the cerebral effects of several-week BH4 treatment in non-responsive PKU patients. Conflict of Interest declared.
Society for the Study of Inborn Errors of Metabolism	2011	Shintaku 2008 [1]	Efficacy and Safety of Sapropterin Dihydrochloride in Long-term Follow-up of Patients with Tetrahydrobiopterin-responsive Mild Phenylketonuria in Japan	Background: Sapropterin dihydrochloride (Biopten.) is first synthesized in Japan as a 6R-isomer of tetrahydrobiopterin (BH4), a natural cofactor for phenylalanine hydroxylase (PAH) in 1982. In Japan, Biopten. is first approved for the treatment of BH4 deficiency in 1992, and then for BH4- responsive PAH deficiency (BRPD) in 2008. Objectives: To evaluate efficacy and safety of BH4 treatment in patients with BRPD, we followed up development and examined side effects. Patients and Methods: We examined serum phenylalanine levels, EEG, MRI, and complications in 33 BRPD yearly at 22 medical centers in Japan. Results: Among 33 BRPD 14 were treated with BH4 only, and 19 were treated with BH4 plus low phenylalanine diet. An initial age of BH4 treatment was 4.9 years (15 patients were less than 4 years old), and their mean age at end of follow-up was 7.8 years. Average duration of treatment with BH4 (mean, 8.5 mg/kg/day) was 7 years (range, 1–14 years). No abnormalities of height and weight were observed in all patients. No unwarranted side effects were reported throughout the long-term course of treatment. Conclusion: Biopten. therapy in BRPD is highly efficacious for reducing serum phenylalanine levels and provides excellent safety with no unwarranted side effects.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	Brain MRI Features in Patients with Phenylketonuria (PKU) in Long-term Treatment with Tetrahydrobioperin	Aim: To examine the presence of brain white matter involvement in tetrahydrobiopterin (BH4) responsive PKU patients. Material and Methods: Brain MRIs (T2, FLAIR and DWI sequences) were assessed in 7 PKU BH4-responsive patients (age range 7–23 years; plasma phenylalanine levels 500–1200 µmol/L, and phenylalanine tolerance 350–700 mg/day before starting BH4), receiving BH4 (Schircks Inc. and Kuvan., 10mg/kg) for a period of 5–8 years. Four patients were on unrestricted diet and 3 were on a mild phenylalanine-restricted diet at the moment of the study. Results: We detected normal MRI in 3 out of 7 patients (age range 7–9 yrs, treatment period range 6–8 yrs, mean blood phenylalanine levels 295± 58 µmol/l, phenylalanine tolerance 800–2700 mg/day). In the remaining 4 patients (age range 8–23 yrs, treatment period range 5–8 yrs, mean blood phenylalanine levels 292±44 µmol/l, phenylalanine tolerance 1000–1600 mg/day) minimal white matter abnormalities (in posterior areas in 3 patients, in frontal area and centrum semiovale in one patient) were detected. Conclusions The lower blood phenylalanine levels and the increasing dietary phenylalanine intake achieved by means of long-term BH4 treatment, might protect the brain from the white matter lesions we reported previously in classic-PKU patients (Manara R, 2009). Further research is needed to reach definitive

Conference	Year	Published	Title	Abstract
				conclusions.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	The Kuvan Adult Maternal Paediatric European Registry (KAMPER): Patient Characteristics	Objectives: KAMPER aims at providing information on the long-term outcomes of approximately 625 Kuvan treated patients with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) or BH4 deficiency, over the course of 15 years. Methods: Observational, multi-centre, drug registry, including a maternal subregistry. Results: First year interim analysis included data from 73 patients (PKU n=58, BH4-deficiency n=15). All results are presented as median (Q1–Q3). Baseline mean Phenylalanine concentration (µmol/L): 550 (288–641) (n=39) and 232 (54–1493) (n=11); in PKU and BH4-deficiency patients, respectively. Identified by newborn screening: 93% of PKU patients; Phenylalanine concentrations (µmol/L) 483 (371–727) and at confirmatory test 793 (478–1150). Identified by newborn screening: 87% of BH4-deficiency patients; Phenylalanine concentration (µmol/L) 467 (336–727) and at confirmatory test 888 (466–1574). Mean Kuvan doses are 15 (10–20) mg/kg/day and 3.6 (1.5–9.6) mg/kg/day in PKU and BH4-deficiency patients, respectively. The majority of patients were tested for BH4 responsiveness following a 24-hr loading test. Phenylalanine concentrations decreased≥30% in 51/55 of PKU and 9/9 of BH4-deficiency patients. Mild/moderate adverse events were reported in 9% of PKU patients (not drug related). Conclusion: KAMPER will increase knowledge on current treatment practises of HPA patients with either PKU or BH4 deficiency across Europe. Conflict of Interest declared.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	Use of Tetrahydrobiopterin (BH4) in Patients with Phenylketonuria: Impact on Metabolic Control, Nutrition Habits and Quality of Life	Background: We investigated metabolic control, nutrition habits and health-related quality of life (HRQoL) in potentially BH4 sensitive phenylketonuria (PKU) under BH4 treatment. Subjects and Methods: Of 41 patients screened, 19 were potentially BH4 sensitive (neonatal BH4 test, mutation analysis; 9 females, 4–18 yrs). We analysed phenylalanine concentrations in dried blood (phe), nutrition protocols and HRQoL (KINDL®) beginning one year before, during the first six weeks and after three months of BH4 therapy. Results: 8/19 patients could increase phe tolerance (629+/−476 mg vs. 2131+/−1084 mg, p=0.006) while maintaining good metabolic control (phe concentration 283+/−145 µM vs. 304+/−136 µM, p=1.0). Intake of vitamine D (110%+/−22 vs 30%+/−19, p=0.001), iron (140%+/−26 vs 71%+/−31, p=0.01), iodine (118%+/−23 vs 37%+/−24, p=0.006) and calcium (136%+/−19 vs 62%+/−38, p=0.042; % of German recommendations) was significantly lower during BH4 treatment. BH4 sensitive patients had HRQoL scores comparable to age-matched healthy children; no change of HRQoL under BH4 treatment, although available questionnaires appear inappropriate to detect aspects relevant to PKU.

Conference	Year	Published	Title	Abstract
				Conclusion: The unexpected deficiency in micronutrient intake should be verified prospectively. Substitution seems necessary independent of the substitution of phe-free amino acid mixtures. Specific HRQoL questionnaires should be developed for PKU. Conflict of Interest declared.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	Sapropterin Treatment in Perphenylalaninemic Patients Below Four Years of Age	Background: The main treatment for PKU is lifelong dietary phenylalanine restriction. Early dietary treatment is effective in hyperphenylalaninemia, but this Phe restricted diet has negative aspects. A subset of patients shows a clinically significant reduction in blood phenylalanine when treated with pharmacological doses of Sapropterin. Sapropterin has been approved for the treatment of hyperphenylalaninaemia in patients>or=4 years of age. Objective: Assessing the treatment with sapropterin in children less than four years. Patients: PAH deficiency patients younger than 4 years treated with sapropterin. Results: Six children less than 4 years have been treated with sapropterin. All of them but one were responsiveness. Two of them began the treatment from the newborn period and the other three began it above one year. Considering all together, the Phe (nmol/ml) mean and SD was 215,4+ 108,49; the Phe intake (mg) mean and SD was 1025+745. Children who began when they were more than one year old, the Phe intake (mg) mean nd SD before sapropterin treatment was 570,14+324,83 and after treatment was 1340,96+978,86. There has been no side effects. Comments. Sapropterin treatment is a valid alternative to the treatment with a diet limited in phenylalanine in hyperphenylalaninemia in patients less than 4 years.
Society for the Study of Inborn Errors of Metabolism	2011	Not found	Nutritional Assessment of Tetrahydrobiopterin (BH4) Treated Patients with Phenylketonuria (PKU)	Background: In BH4-treated patients the primary outcome measure has been improvements in plasma phenylalanine (phe) concentrations, while the effect of dietary intake and nutritional status, have not been sufficiently elucidated. Objectives: To assess the nutritional status of PKU patients undergoing BH4 therapy. Methods: Six weeks before and during the treatment, phe tolerance were evaluated twice a week to fortnightly. Weight and height Z-scores; daily consumption of macro and micronutrients including phe, tyrosine and protein were calculated. Results: Five BH4 responsive (≥ 30% reduction in phe levels) patients were followed for 7,3±5 months. The patients received sapropterin 15± 6,5 mg/kg/day. The increase in phe tolerance was 217%. Vitamin A, E, B1, B6, folate and iron consumptions supplied the RDA. Vitamin B12 consumption decreased from 96% to 86% RDA due to reduction of special formula consumption. Calcium, phosphorus and zinc intakes were increased to 87%, 92%, 62,8% of RDA, respectively. Conclusions: Long-term dietary guidance and monitoring of the nutritional status of patients with PKU should be part of a follow-up programme in BH4 treatment.

Conference	Year	Published	Title	Abstract
American College of Medical Genetics	2010	Not found	Case Report of Gastric Lap-band Surgery in a 25 Year Old Female with PKU: Impact on Phenylalanine Levels	Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism, occurring in approximately 1 in 10,000 live births in the United States. PKU is caused by mutations in the PAH gene; this gene is required to convert phenylalanine (phe) into tyrosine. In infants with PKU, phe accumulates in the bloodstream and crosses the blood brain barrier, leading to irreversible mental retardation. The mainstay of PKU treatment involves lifelong diet modification to prevent cognitive impairment. Treatment typically includes an amino acid formula that does not contain phe, while providing the majority of a person's protein needs to promote growth. The amount of phe an individual patient can consume is variable, dependent on both genotype and metabolic phenotype. A person's metabolic phenotype, or tolerance for phe, is usually determined by frequent measurement of blood phe levels. We report a 25-year old female with PKU, who underwent gastric lap-band surgery. JV was diagnosed at birth with PKU through newborn screening, and remained on a PKU diet until 3 years of age. The diet was discontinued from 3-14 years of age. Off diet, her phe levels averaged 15-17 mg/dl (900-1020 umol/L), with her highest phe level equal to 19 mg/dl. Dietary compliance after 14 years of age was inconsistent, mainly because of social and family factors. Poor dietary compliance likely played a role in her failing grade 7, and poor performance in grade 8. In May 2008, at 24 years of age, a trial of Kuvan was initiated to attempt to obtain metabolic control. At that time, JV was on a modified diet, with no PKU formula, and one serving of meat per day. Baseline phe level was established at 11.61 mg/dL. Kuvan was initiated at a dose of 20 mg/kg, and phe levels post-Kuvan treatment were 1.98, 1.25, and 1.82 mg/dL. The Kuvan dose was then decreased to 10 mg/kg, and the phe level was 3.56 mg/dl or lower. She was maintained on 10 mg/kg of Kuvan until January 2009. JV discontinued Kuvan at the time of her gastric lap band surgery in January 2009. Her pre-surgery BMI was 38. As of November 2009, she has lost 73 pounds over an 11 month period (34% of her body weight), with a current BMI of 24. She has not restarted Kuvan to date. Her diet consists of frequent small meals high in protein totaling approximately 1200 calories, with an estimated daily phe intake of 23 mg/kg, similar to a woman's daily intake of phe in the general population. Her phe levels are 6.18, 4.2, and 6.8 mg/dL, 3, 6, and 11 months post surgery, respectively, without any treatment. We hypothesize her increased phe tolerance may be the result of a combination of factors, including decreased BMI with an increase in lean body mass, increasing age, and overall low calorie diet. Another possibility is that her weight loss has improved her insulin sensitivity leading to improved protein utilization, especially protein synthesis.
American College of Medical Genetics	2010	Not found	Treatment of PKU Patients with Kuvan: Experience in an Inner-City Safety-net Hospital	Phenylketonuria (PKU) is the most common inborn error of amino acid metabolism, occurring in approximately 1 in 10,000 live births in the United States. PKU is caused by mutations in the PAH gene; this gene is required to convert phenylalanine (phe) into tyrosine, with tetrahydrobiopterin (BH4) needed as a cofactor. In infants with PKU, phe accumulates in the bloodstream and crosses the blood brain barrier, leading to irreversible mental retardation. PKU treatment involves lifelong diet modification to prevent cognitive impairment, and typically includes an amino acid formula that does not contain phe, while providing the majority of a person's protein needs to promote growth. The amount of phe an individual patient can consume is variable, dependent on both genotype and metabolic phenotype. A person's metabolic phenotype, or tolerance for phe, is usually determined by frequent measurement of blood phe levels. In 2007, the FDA approved Kuvan (sapropterin dihydrochloride), a synthetic form of BH4, for treatment of PKU. Published reports indicate that at least 30% of patients with PKU will respond to therapy with Kuvan. Methods: 13 patients with PKU are followed in our clinic. One patient was not offered Kuvan

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				therapy because of immigration issues and two declined therapy. One patient has not initiated a trial of Kuvan, because of social issues. Our remaining 9 patients (2 males, 7 females) initiated the process for a trial of Kuvan. All were age 6 or older, nonpregnant, and provided written consent or assent if younger than 18 years of age. Baseline weight, phe, and tyr blood concentrations were obtained. A once daily dose of 20 mg/kg of Kuvan was given, and blood phe and tyr levels were obtained at 1, 2, and 3 weeks after starting the medication. All patients were encouraged to make no dietary changes during the trial period. Results: 6 of 9 patients completed at least two weeks of treatment with Kuvan and associated testing. One patient responded with a reduction in phe levels of > 90% and continued on Kuvan until she had gastric lapband surgery. Three were non-responders (50%). One patient responded with a 30% reduction, and continues with Kuvan to bring his phe levels into good control without diet modification. One patient had a 40% reduction in phe levels, translating into an additional 4 exchanges of protein per day. The family discontinued therapy, as they felt the increase in the number of exchanges was not significant. The remaining 3 patients have been unable to establish a baseline phe level, because of a variety of issues, including psychological disorders and social issues. Conclusions: Kuvan has shown a dramatic benefit in 1 of 9 patients with PKU, followed in an inner-city hospital. Kuvan has shown mild benefits in two patients. The availability of Kuvan therapy has not been helpful in 6 of 9 (67%) patients. Only 2 of 13 patients were in good metabolic control prior to Kuvan therapy becoming available. The challenges in treating PKU are compounded by social, financial and environmental issues, especially in our high-risk population. For these patients, treatment may not be feasible, regardless of availability or effectiveness.
American College of Medical Genetics	2010	Burton 2010 [2]	Treatment with Sapropterin Results in Increased Stability of Blood Phenylalanine (Phe) Levels in BH4-Responsive Patients with Phenylketonuria (PKU)	Background/Objectives: It has recently been demonstrated that variability in blood phe levels is inversely correlated with IQ and is a better predictor of IQ in early and continuously treated patients with PKU than mean blood phe levels (Anastasoie, et al, Mol Genet Metab 2008; 95:17). If this is true, then stability of blood phe should be a therapeutic goal in patients with PKU. The purpose of this study was to determine if treatment in patients of BH4-responsive PKU with sapropterin would increase the stability of blood phe levels. Methods: The records of all patients treated with sapropterin (Kuvan®, Biomarin Pharmaceutical) in the PKU Clinic at Children's Memorial Hospital in Chicago were examined retrospectively after IRB approval was obtained. Patients were included in the study if they were responsive to sapropterin during a 2-4 week challenge (reduction of blood phe of at least 25% after 2 weeks of therapy or, in the case of patients with well-controlled blood phe at the time of testing, increased phe tolerance by 4 weeks of treatment). A total of 37 subjects were eligible for inclusion (16 male; 21 female); the mean age was 12.6 years (range 1.5-32.0). The total number of observations (phe levels) for all subjects was 1391 with a mean of 39 per subject (range 9-96 per subject). Linear mixed modeling was utilized to estimate variances of phe before (pre) and after (post) starting sapropterin. Likelihood test was used to evaluate the difference between variability pre and post. Statistical analysis was performed using SAS 9.1. Results: Means and standard deviations for phe as estimated by the model were pre: 6.67 mg/dl (4.20) and post 5.16 mg/dl (3.78). The mean blood phe post-sapropterin was significantly lower (p=.0002). The within-subject variances (and SE of variance) of phe were: pre 6.897 (0.43) and post 4.799 (0.27). These two variances are significantly different with a p=.0017. Conclusions: Sapropterin therapy results in increased stability of blood phe levels in patients with BH4- responsive PKU. This effect is likely to improve cognitive outcome in patients treated with sapropterin.

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Society for the Study of Inborn Errors of Metabolism	2010	Not found	Prediction of Long-term Responsiveness to Tetrahydrobiopterin in Phenylketonuria	BH4 responsive phenylketonuria (PKU) has been described more than 10 years ago. Though, criteria for the identification of PKU patients, who benefit from long-term treatment with BH4, have not yet been established. In our center, 20 patients with mild or classic PKU were treated over a medium period of 30 months (3–77 months) with BH4 in a medium dose of 17 mg/kg/day (10–20 mg/kg/day). Criteria for treatment with BH4 were defined by i. positive BH4 loading test, ii. identification of at least one milder BH4 responsive PAH mutation and/or iii. mild clinical phenotype. Three criteria were positive in 7 patients, two in 11 patients, and one in 2 patients. 15/20 patients showed long-term response to BH4 resulting in an increase of medium phenylalanine tolerance to 1013 mg/day (350–1840 mg/day), corresponding to 31 mg/kg/day (6–96 mg/kg/day). 9/15 patients still needed a phenylalanine-free amino acid mixture. In 5 patients long-term BH4 treatment was stopped due to missing response; furthermore, one of them complained of recurrent headache. All patients with three positive criteria showed long term response to BH4. 7 of 11 patients with two positive criteria responded to long-term treatment with BH4, but none of those patients with only one positive criterion. Thus, at least two of the designated criteria have to be positive to attain BH4 long-term responsiveness. No single criterion was specific enough to prognosticate long-term BH4 responsiveness.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	315-P Phenylketonuria—The Effects on Quality of Life and Plasma Concentrations of Phenylalanine and Tyrosine of Two Different Amino-Acid-Supplementations in Different Concentrations	Background: Supplementation of large neutral amino acid (LNAA) and a semi-free (SF) diet has been shown to have a positive effect on well being on adults with PKU. The aim of this study was to determine the effects of 2 different products (LN1 and LN2), containing LNAA in different combinations on plasma Phe levels and other metabolites in early treated adults with PKU, and to investigate the relationship between these metabolites and well being. Material (Patients) and methods: This was a prospective, double blind, cross over study consisting of four consecutive three-week phases. Twelve subjects (6 males, 6 females) with PKU were recruited, 11 completed the study. Each phase consisted of either LN1 or LN2, either in low or high dosage. Subjects were instructed to follow their usual SF diet, maintain energy intake, and complete a 3-day food record and a SF36 scheme during each phase and to take blood samples every day for the week of each period. At the end of each phase, plasma amino acid profile was quantified and other metabolites were measured. Results: There was no correlation between plasma Phe level and LNAA dosage or type of LNAA supplement. However, 2 patients stated that they felt better when taking LN 2 in high dosage. Conclusions: LN1 & 2 in higher dosage than usual do not lower Phe level. However, LNAA supplementation has been used for PKU patients > 18 years for 25 years in Denmark and proved to be a useful alternative for adults with PKU.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	328-O Efficacy and Safety of Treatment with BH4 Before the Age of 4 Years in Patients with Mild Phenylketonuria	Background: Sapropterin dihydrochloride, an EMEA-approved synthetic formulation of BH4, is available in France since 2009 for PKU-patients older than 4-years. We report 13 patients treated before the age of 4-years and demonstrate the safety and efficacy of this treatment. Methods: PKU-patients treated with BH4 before the age of 4-years were screened in West and East regions of France. Results: Thirteen patients (7 females) were enrolled in this retrospective study. Mean phenylalaninemia at diagnosis was 552±175 µM. A positive response to BH4 was assessed by (i)a 24 h-BH4 loading test (20 mg/kg/d), performed during the neonatal period (n=9) or before 1-year of age (n=4) and inducing a 78±13%-decrease of phenylalaninemia, (ii)and genotyping. Long-term therapy with BH4 was initiated during the neonatal period (n=5) or at the age of 13±13 months (n=8), with BH4 (Schircks., n=5) or Kuvan. (Merck-Serono., n=8). All patients are actually treated with Kuvan.. The mean duration of treatment was 27±25 months. BH4-therapy

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				drastically improved diet phenylalanine tolerance (from 465±194 to 1525±621 mg/day, p<0.0001) and allowed to stop (or not start) phenylalanine-free amino acid supplementation in 11 patients. Additionally, in the 8 patients treated after few months of diet therapy, BH4 treatment improved metabolic control, significantly decreasing phenylalaninemia (331±76 to 243±75 μM, p<0.05) and increasing percentage of phenylalaninemia tests into therapeutic targets (120–300 μM, 67±17% with BH4 vs 37±21% before BH4, p<0.05). Finally, no side effects were reported. Conclusion: BH4-therapy improved phenylalanine tolerance and metabolic control with no side effects in BH4-responder PKU-patients before the age of 4-years.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	339-P Brain Function in Individuals with PKU Treated with Kuvan: Evidence from Functional Magnetic Resonance Imaging	Background: Phenylketonuria (PKU) is a genetic disorder characterized by inefficient metabolism of phenylalanine. Early and continuous dietary control prevents the severe neurologic and cognitive consequences once associated with PKU. Kuvan (sapropterin dihydrodichloride, BH4) represents a new supplemental pharmacologic treatment for PKU. In the present study, the researchers utilized functional MRI to examine neurocognitive functioning in individuals with and without PKU. The potential impact of Kuvan treatment on neural activity in PKU was also explored. Methods: Brain imaging data was collected from 7 individuals with early treated PKU (mean age = 21.9 years) immediately before treatment with Kuvan and then again after 4 weeks of Kuvan treatment. For comparison purposes, data was also collected from 5 non-PKU individuals (mean age = 20.0 years). At each timepoint, neural activity was recorded during performance of a working memory task. Results: Analysis of the pre-treatment data revealed PKU-related irregularities in neural activation in prefrontal cortex (PFC) and other brain regions, $F(1, 10) > 5.53$, $p < .05$ FDR-corrected. At the 4-week evaluation, two participants had responded to Kuvan with a >20% reduction in phenylalanine levels. Both also showed improved activation for a region in orbitomedial PFC. Findings for other brain regions were mixed. Conclusion: The present results provide evidence of brain dysfunction in individuals with early-treated PKU. Whereas the initial findings on Kuvan treatment are promising, additional data is needed to fully evaluate its benefits for brain function in PKU.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	342-P Neurocognitive Findings in Individuals with Phenylketonuria and Treatment with Sapropterin Dihydrochloride (BH4)	Background: Phenylketonuria (PKU) is a disorder in which phenylalanine (Phe) metabolism is disrupted. The disorder is associated with dopamine disregulation and white matter abnormalities in the brain. Impairments in cognition (particularly executive abilities) are common, even in patients treated early/continuously with dietary Phe restriction. Sapropterin dihydrochloride (BH4) is a pharmaceutical agent that lowers Phe in BH4 responders. We are evaluating changes in brain and cognition that occur during BH4 treatment. Methods: Brain and cognition are evaluated in PKU patients at baseline before BH4 treatment (20 mg/kg/day) using MRI/DTI (diffusion tensor imaging) and neuropsychological tests focused on executive abilities. For BH4 responders, follow-up evaluation is conducted after 6 months of BH4 treatment. Data collection is ongoing. At this time, participant ages range from 7 to 35 years (M=18; SD=8). Evaluation at baseline has been conducted with 19 PKU patients and 12 controls, and at follow-up with 5 PKU patients and 5 controls. Results and Conclusions: Baseline findings to date indicate that executive performance is significantly poorer for PKU patients than controls across a range of tasks assessing abilities such as inhibitory control (go/no-go, p=.04; stimulus-response compatibility, p=.03), strategic processing (verbal fluency, p=.007; word list learning, p=.001), and working memory (2-back, p=.001). These results reflect specific and pervasive impairments in executive abilities prior to treatment with BH4. Follow-up findings provide evidence of improvement in executive abilities during treatment with BH4. At the conference, baseline findings from newly enrolled patients

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				will be presented, as well as specific findings from follow-up neuropsychological assessment and MRI/DTI.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	352-P Changes in Neuro-Pyschometric Measures in a Sapropterin Responsive Adolescent Patient with PKU	Introduction: In PKU, although Sapropterin dihydrochloride (6R-BH4) (Merck Serona) reduces blood phenylalanine concentrations, it is unknown if it improves the subtle deficits observed in executive function, speed processing and social and emotional difficulties. Case Study: A boy aged 14y with well-controlled PKU (mutations F39L/ IVS 12+1G>A), was compliant with dietary treatment, despite neophobia to low protein foods. He was thin and complained of frequent hunger pains. He had previous psychological intervention due to family disputes he caused about diet. A carefully controlled trial with 10 mg/kg/day Sapropterin demonstrated that his blood phenylalanine concentrations reduced by 40% by day 5, to consistently less than 350 µmol/l. His phenylalanine tolerance increased from 450 mg/daily to 1000 mg/daily. He had neuro-pyschometric testing pre and 4 weeks post-Sapropterin. The case study reported him to be 'calmer,' 'less hyper' and socially 'more normal' and his self-esteem improved. His carer reported mood changes; he was happier, more relaxed, no longer an 'angry, young man,' and improvements in attention and concentration were reflected both at home and school. On repeat psychometric testing, only 4 weeks post-Sapropterin, there was subtle improvements across indices of attention measures, speed of inhibition and switching, and immediate memory span. His energy intake increased from 1600 kcal/d to 2200 kcal/d. Conclusions: In the short term, Sapropterin therapy appeared to result in subtle improvements in attention, executive function, mood and nutritional status in a previously well-controlled boy with PKU. Further longitudinal, controlled studies are required to study neurocognitive changes with Sapropterin.
Society for the Study of Inborn Errors of Metabolism	2010	Not found	359-P Pilot Study to Evaluate the Effects of Kuvan on Adult Individuals with Phenylketonuria with Measurable Maladaptive Behaviors	Background: We report 12 month data on a pilot study to evaluate changes in behavior while on Kuvan. (BH4). is a drug that is used for the treatment of PKU. Kuvan. is a co-factor for phenylalanine (phe), tyrosine, and tryptophan hydroxylases. BH4 may affect tyrosine and tryptophan hydroxylases in the brain and affect behavior without a reduction in blood phe levels. Aim: To evaluate effects of Kuvan. on maladaptive behavior in patients with PKU. Methods: Ten subjects (>18 years) with maladaptive behavior were enrolled in a 12-month study. Kuvan. was given at 20 mg/kg/day. Baseline and quarterly measures of plasma amino acids, as well as baseline, sixmonth and 12-month evaluation of the Vineland II Adaptive Behavior Scales (VABS-II) and a PKU Behavior Check List were obtained. Results: Comparison of 12-month data to baseline showed no change in blood phe levels ($p=0.33$), but increased blood tyrosine levels ($p=0.05$) and decreased blood phe/tyrosine ratio ($p=0.067$). The VABS-II showed no change in communication, daily living skills, socialization, or motor skills, but significant improvement for internal behavior including anxiety, nervousness, and unexplained sadness ($p=0.018$). On the PKU Behavior Check List, subjects showed significant improvement in the sum of scores over the 15 negative behaviors ($p<0.0001$). Conclusion: PKU subjects who did not respond to Kuvan in blood phe level, showed significant improvement in maladaptive behavior, may suggest effects of Kuvan in the CNS. Long term evaluation of CNS effects of Kuvan is warranted.

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American College of Medical Genetics	2009	Not found	Diet Liberalization in a 2 Year Old Child with PKU after Treatment with Sapropterin Dihydrochloride	Infants and children with untreated classical PKU are at risk for seizures, intellectual impairment and behavioral disorders. Although dietary restriction of phenylalanine remains the foundation of treatment, sapropterin dihydrochloride (Kuvan, Biomarin) is an adjunct treatment of hyperphenlylalaninemia independent of dietary intake. Current clinical indications for the use of Kuvan are limited to patients over the age of 4 years. We report on a 30-month-old female with classical PKU who was supplemented with Kuvan (20 mg/kg/day) for 7 months while following her routine dietary management for PKU. Her initial phenylalanine level on Newborn Metabolic testing at 59 hours of life measured 6.4mg/dL. Confirmatory testing performed at day-of-life 9 yielded a phenylalanine level of 20.1 mg/dL. Urine pterins and serum dihydropteridine reductase levels were normal. Phenylalanine/tyrosine level was elevated at 3.9μM. The primary management included a low-Phe formula plus other foods estimated to provide 175 mg/day of phenylalanine. This management protocol resulted in biweekly blood Phe levels that ranged between 3 and 8 mg/dl. The parents were very motivated and compliant. The blood Phe levels following the addition of Kuvan averaged between 2 and 4 mg/dl in spite of increasing the phenylalanine content of the diet to 275 mg/day of phenylalanine. Growth parameters remained stable following diet liberalization and the addition of Kuvan. Additionally, this child had neurocognitive testing (BDI-2) done at 33 months of age which revealed above average performance. No untoward side effects were reported. Target populations for treatment of patients with BH4-responsive PKU should include young children at important early permanent stages of functional cognitive development. Further studies to delineate the effect of early intervention with Kuvan in developing children with PKU are needed at this time.
American College of Medical Genetics	2009	Not found	The Effect of Sapropterin on Blood Phenylalanine Concentrations in Patients with Classical Phenylketonuria Followed at Akron Children's Hospital	Background: Information regarding the sapropterin expanded access program (SEAP) was provided to patients and families with phenylketonuria (PKU) followed at the metabolic clinic at Akron Children's Hospital, Ohio. Thirteen patients with classical PKU, defined as having a history of phenylalanine blood (phe) concentration greater than 1000 μmol/L, met eligibility criteria for the trial and were enrolled. Three patients were unable to continue in the study for nonmedical reasons. Methods: Every patient enrolled in the trial fulfilled inclusion criteria including having hyperphenylalaninemia due to PKU, being 9 years or older, nonpregnant, and providing written consent or assent if younger than 18 years. Baseline weights and phe and tyrosine (tyr) blood concentrations were obtained. A once daily dose of 20 mg/kg of sapropterin was given and blood phe and tyr levels were obtained at 24 hours and one week after starting the medication. All patients were on phenylalanine-restricted diets and were encouraged to make no dietary changes during the first week of treatment. Results: Ten patients completed at least one week of treatment with sapropterin and associated testing. One patient's blood phe concentration remained elevated at 24 hours and one week and he was deemed a nonresponder. One patient had an abnormally low baseline phe requiring dietary adjustments which made it difficult to determine response to medication. The remaining eight patients all had decreased blood phenylalanine concentrations after 24 hours of treatment. The decrease in blood phe concentrations persisted after one week of treatment and ranged from 8.3 – 87.2%. Six of these eight patients (75%) experienced a decrease of more than 39%. Of interest to note is that the smallest decrease (8.3%) was in an identical twin whose co-twin sister had a decrease of 40.9%. This emphasizes the multifactorial nature of this disease. Conclusion: Short term treatment of PKU with sapropterin resulted in a significant decrease in blood phenylalanine for the majority of patients in this study.

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American College of Medical Genetics	2009	Burton 2011[3]	PKU-008: A Long-Term, Open-Label Study of Sapropterin Dihydrochloride (Kuvan®) in PKU Subjects	Objective: We evaluated the safety of long-term treatment with sapropterin dihydrochloride (sapropterin) Kuvan®, a pharmaceutical preparation of 6R-BH4, in phenylketonuria (PKU) subjects who had participated in two Phase 3 studies. Methods: PKU subjects who participated in PKU-004 or PKU-006 and had a positive response to sapropterin were enrolled in this multicenter, open-label extension study and followed every 3 months. Safety was assessed with medical history, physical exam and laboratory tests (chemistry, hematology, blood Phe concentration, and urinalysis). At enrollment, the sapropterin dose was equivalent to the prescribed dose of the previous study. All subjects received dissolved tablets for 3 months then could take intact tablets. Dose was adjusted within 5 to 20 mg/kg/day to control blood Phe. Subjects were asked to keep diet unchanged. Results: Of the 111 subjects, 71 (64%) enrolled from PKU-004 and 40 (36%) from PKU-006. 108 subjects were Caucasian. The mean ± SD age was 16.4 ± 10.2 years (range 4 to 50 years), 44 (40%) were females. After dose adjustment, 71% of the subjects received 20 mg/kg/day. The mean ± SD duration of sapropterin exposure was 507 ± 114 days (56 to 649 days). The mean ± SD blood Phe concentration while on treatment at the start of the study of 614.2 ± 333.3 µmol/L decreased to 504.6 ± 316.3 µmol/L at Month 3 and remained at levels between 485.3 ± 308.8 µmol/L and 529.5 ± 332.1 µmol/L at subsequent visits. Approximately half of the subjects whose baseline blood Phe concentration was above treatment guidelines at enrollment shifted to within NIH recommended control range. 71% (79 of 111) of the subjects reported an adverse event (AE). Most AEs were mild and were not dose-dependent. Only 1 serious adverse event of gastroesophageal reflux was considered related to treatment. Two subjects withdrew from the study due to an AE (difficulty concentrating and intermittent diarrhea). No deaths occurred in the study. The most common treatment-emergent AEs were cough (16.2%), pyrexia (14.4%), and nasopharyngitis (13.5%). There were no clinically relevant mean changes for any hematology, chemistry, or urine analysis parameters. Seven subjects experienced 9 AEs that were temporally associated with neutropenia. All were typical of symptoms of viral infections that can cause neutropenia, none were severe, unusual, or difficult to treat. Twenty subjects with transient neutropenia did not have temporally associated AEs. In these subjects, neutropenia resolved without intervention or stopping of study drug. Conclusions: The results of the safety analysis of this study show that sapropterin taken for up to nearly two years as dissolved or intact tablets is well tolerated and has a favorable safety profile.
American Society of Human Genetics	2009	Not found	Neuropsychological Function in Individuals with Phenylketonuria Treated with Kuvan.	Phenylketonuria (PKU) is a hereditary disorder resulting in disrupted metabolism of phenylalanine (Phe). The profound effects of elevated Phe once associated with PKU, such as mental retardation and seizures, have largely been eliminated through dietary restriction of Phe. However, Phe often remains elevated even in patients considered to be well treated by diet alone. As a result, although more subtle than in the past, PKU patients continue to exhibit neurologic abnormalities and impaired cognition. Kuvan (sapropterin dihydrochloride/BH4) is a pharmaceutical treatment that lowers Phe in BH4 responders and holds promise for improving brain function and cognition. In our study, brain and cognition are examined in PKU patients immediately before beginning treatment with Kuvan (20 mg/kg/day) using MRI and neuropsychological tests of intelligence (IQ), executive abilities, and reaction time (RT). For patients who respond to Kuvan with a reduction of ≥20% in Phe within 4 weeks of beginning treatment, brain and cognition are again examined after 6 months of Kuvan treatment. We hypothesize that improvements in brain and cognition will occur with Kuvan treatment. Here we report results from the baseline neuropsychological evaluation of the first 7 PKU patients enrolled. Patients are from 9 to 20 years of age (M=14, SD=4), with Phe ≥360µmol/L. Patients' neuropsychological performance is compared with that of 10 normal controls from 8 to 22 years

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				of age (M=15, SD=5). Our findings indicate that PKU patients have significantly poorer IQ and executive abilities than controls. The IQ of PKU patients ranged from 75 to 109 (M=92, SD=12), whereas the IQ of controls ranged from 89 to 117 (M=107, SD=9), t(15)=2.7, p<.05. Regarding executive abilities, PKU patients performed more poorly than controls on tests of inhibitory control, working memory, and strategic processing, t(15)≥3.0, p<.01 in all instances. The PKU and control groups, however, were not significantly different on measures of simple RT (p>.05). These results reflect specific impairments in intelligence and executive abilities in PKU patients treated with diet alone prior to treatment with Kuvan. Data collection is ongoing. At the conference, baseline findings from newly enrolled patients will be presented. In addition, findings from 6 month evaluations of BH4 responsive patients will be presented to evaluate whether improvements in brain and cognition are associated with Kuvan treatment.
American Society of Human Genetics	2009	Not found	Neurocognitive Findings in Individuals with Phenylketonuria and Treatment with Sapropterin Dihydrochloride (BH4).	Background/Objective: Phenylketonuria (PKU) is a disorder in which phenylalanine (Phe) metabolism is disrupted. The disorder is associated with dopamine disregulation and white matter abnormalities in the brain. Impairments in cognition (particularly executive abilities) are common, even in patients treated early and continuously with dietary Phe restriction. Sapropterin dihydrochloride (BH4) is a pharmaceutical agent that lowers Phe in BH4 responders. We are evaluating changes in brain and cognition that occur following BH4 treatment. Method: Brain and cognition are evaluated in PKU patients at baseline before BH4 treatment (20mg/kg/day) using MRI/DTI (diffusion tensor imaging) and neuropsychological tests focused on executive abilities. For BH4 responders, follow-up evaluation is conducted after 6 months of BH4 treatment. Data collection is ongoing. At this time, participant ages range from 7 to 35 years (M=18; SD=8). Evaluation at baseline has been conducted with 19 PKU patients and 12 controls, and at follow-up with 5 PKU patients and 5 controls. Results/Conclusions: Baseline findings to date indicate that executive performance is significantly poorer for PKU patients than controls across a range of tasks assessing abilities such as inhibitory control (go/no-go, p=.04; stimulus-response compatibility, p=.03), strategic processing (verbal fluency, p=.007; word list learning, p=.001), and working memory (2-back, p=.001). These results reflect specific and pervasive impairments in executive abilities prior to treatment with BH4. Follow-up findings provide evidence of improvement in executive abilities following treatment with BH4. Baseline findings from newly enrolled patients will be presented, as well as specific findings from the follow-up neuropsychological assessments and MRI/DTI data.
American Society of Human Genetics	2009	Not found	Pilot Study to Evaluate the Effects of Sapropterin on Adult Individuals with Phenylketonuria with Measurable Maladaptive Behaviors.	Background: We report 12 month data on a pilot study to evaluate changes in behavior while on sapropterin (Kuvan®), a drug that is used for the treatment of PKU. Kuvan® functions like BH4, a co-factor for phenylalanine (phe), tyrosine, and tryptophan hydroxylases. Kuvan® may affect tyrosine and tryptophan hydroxylases in the brain and affect behavior without a reduction in blood phe levels. Objectives: To evaluate effects of Kuvan® on maladaptive behavior in patients with PKU. Material and methods: Ten subjects (>18 years) with maladaptive behavior were enrolled in a 12-month study. Kuvan® was given at 20mg/kg/day. Baseline and quarterly measures of plasma amino acids, as well as baseline, six-month and 12-month evaluation of the Vineland II Adaptive Behavior Scales (VABS-II) and a PKU Behavior Check List were obtained. Results: Comparison of 12-month data to baseline showed no change in blood phe levels (p=0.33), but increased blood tyrosine levels (p=0.05) and decreased blood phe/tyrosine ratio (p=0.067). The VABS-II showed no change in communication, daily living skills, socialization, or motor skills, but significant improvement for internal behavior including anxiety, nervousness, and unexplained sadness (p=0.018). On the PKU Behavior Check List, subjects showed significant improvement in the sum of scores over the 15 negative behaviors (p<0.0001). Conclusion: PKU subjects who did not respond to Kuvan in blood phe level, showed significant improvement in maladaptive behavior, may suggest effects of Kuvan in the

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				CNS. Long term evaluation of CNS effects of Kuvan is warranted.
American Society of Human Genetics	2009	Not found	Brain Function in Individuals with PKU Treated with Kuvan: Evidence from Functional Magnetic Resonance Imaging.	Background: Phenylketonuria (PKU) is a genetic disorder characterized inefficient metabolism of phenylalanine. Early and continuous dietary control prevents the severe neurologic and cognitive consequences once associated with PKU. Kuvan (sapropterin dihydrodichloride, BH4) represents a new supplemental pharmacologic treatment for PKU. In the present study, the researchers utilized functional MRI to examine neurocognitive functioning in individuals with and without PKU. The potential impact of Kuvan treatment on neural activity in PKU was also explored. Methods: Brain imaging data was collected from 7 individuals with early-treated PKU (mean age = 21.9 years) immediately before treatment with Kuvan and then again after 4 weeks of Kuvan treatment. For comparison purposes, data was also collected from 5 non-PKU individuals (mean age = 20.0 years). At each timepoint, neural activity was recorded during performance of a working memory task. Results: Analysis of the pre-treatment data revealed PKU-related irregularities in neural activation in prefrontal cortex (PFC) and other brain regions, $F(1, 10) > 5.53$, $p < .05$ FDR-corrected. At the 4-week evaluation, two participants had responded to Kuvan with a >20% reduction in phenylalanine levels. Both also showed improved activation for a region in orbitomedial PFC. Findings for other brain regions were mixed. Conclusion: The present results provide evidence of brain dysfunction in individuals with early-treated PKU. Whereas the initial findings on Kuvan treatment are promising, additional data is needed to fully evaluate its benefits for brain function in PKU.
American Society of Human Genetics	2009	Not found	The KUVAN® Adult Maternal Paediatric European Registry (KAMPER): Interim Results on Mutation Frequencies of PKU Patients.	Objectives: KAMPER aims at providing information on the long-term safety of Kuvan treated patients with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU) or BH4 deficiency, over the course of 15 years. Data from approximately 625 patients on growth, neurocognitive outcomes, adherence to diet, long-term sensitivity to Kuvan and pregnancy outcomes are expected. Methods: Observational, multi-centre, drug registry, including a maternal subregistry. Results: At first year interim analysis, four countries contributed a total of 58 patients with phenylalanine hydroxylase (PAH) deficiency and 15 with BH4-deficiency. This report includes results from PAH-deficient patients only. Patients were so far recruited in Germany (n=24), France (n=19), Spain (n=13) and Italy (n=2). All results are expressed as median (Q1-Q3). The median age of recruited PKU patients was 9.7 years (6.4-14.9). Of these, 53% were male and 47% female. Most PKU patients (93%) were identified by newborn screening. Phenylalanine (Phe) concentration at newborn screening was 483 (371-727) µmol/L. A confirmatory test was performed in 86% of patients, the Phe concentration at this time point was 793 (478-1150) µmol/L. Information on the PAH genotype was available in 34 patients resulting in a total of 27 different genotypes. The majority of the reported genotypes were compound heterozygotes (25/27), while the most frequently encountered one was p.R261Q homozygous (n=4). Further analyses using the BIOPKU database to predict expected response showed that 18 genotypes could be classified as BH4-responders, 1 as slow responder and 3 as non-responders. Five of the reported genotypes have not been previously described in BIOPKU. According to the

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				database, most of the genotypes found in KAMPER patients are associated with mild PKU/mild HPA. Almost all patients (95%) were tested for BH4 responsiveness, with the majority (64%) following a 24-hr loading test. Phe concentrations were reduced by ≥30% in 51 of 55 patients tested. The mean daily Kuvan dose was 15 (10-20) mg/kg/day. Mild/moderate adverse events were reported in 3 PKU patients, which were deemed as not drug related. Conclusions: KAMPER provides a unique opportunity to gather a large collection of long-term follow up data related to BH4-responsive HPA in about 10 European countries. Future analyses will attempt to establish a link between the mutations and the metabolic status of the patients.
American Society of Human Genetics	2008	Koch 2005[4]	PKU Treatment with Tetrahydrobiopterin (sapropterin) During Pregnancy.	Tetrahydrobiopterin (BH4) has been shown to significantly reduce the level of plasma phenylalanine (PHE) in 30-50% of PKU patients. The drug was recently FDA-approved for treatment of PKU individuals in conjunction with traditional dietary therapy. Treatment of adult phenylketonuria with BH4 (sapropterin) during pregnancy has not been systematically studied and only one case has previously been reported. In the FDA use in pregnancy ratings, BH4 is classified as Class C because no pregnant animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. We report a case of a 29-year old pregnant PKU patient treated with BH4 during the pregnancy. She demonstrated responsiveness to BH4 prior to becoming pregnant. In the preconception period she was counseled regarding the risks and benefits of use of this medication in pregnancy. After counseling, she elected to continue BH4 administration throughout the pregnancy. Mean plasma PHE prior to BH4 administration was 480 mcM (SD=90), substantially higher than the recommended range of 120-360 mcM; after starting BH4, plasma PHE dropped to 210 mcM (SD=36) from 10 weeks prior to pregnancy and throughout pregnancy (week 16 at the time of this abstract) without any dietary modification. The patient did experience anorrhexia and nausea of the first trimester of pregnancy and had decreased caloric intake during this period according to food diaries. Despite endogenous protein catabolism, the plasma PHE value remained normal in the first trimester. The patient has tolerated BH4 well. Second trimester targeted ultrasound has revealed no fetal anomalies or growth abnormalities. Subsequent course, PHE values, ultrasounds, and birth data will be presented.
American Society of Human Genetics	2008	Not found	Sapropterin (Kuvan®) is Safe and Effective in Patients Under 4 Years of Age with Phenylketonuria (PKU).	In December, 2007, Kuvan® was approved by the FDA for use in patients with hyperphenylalaninemia due to tetrahydrobiopterin(BH4)-responsive PKU. Clinical trials of Kuvan® did not include children under 4 years of age. Since FDA approval, 11 children under 4 years of age (range 7 mo- 4 yrs) with PKU have been treated with Kuvan® in the PKU Clinic at Children's Memorial Hospital in Chicago. All were well-controlled with mean blood phenylalanine (phe) levels below 360 umol/L at the time of initiation of drug therapy. Blood phe levels and diet records were obtained at baseline, 24 hrs, 1 wk and 2 wks; the dose used was 20 mg/kg/day given in apple juice. Response was defined as a decline in the blood phe level of > 30% below baseline. 7 pts were responders; 2 non-responders and 2 not yet determined. The mean decline in blood phe among responders was 58% (range 32-74). One pt. experienced diarrhea when drug was initiated; this resolved within one wk. on continued treatment. No other adverse events were reported. Total length of time on therapy for all patients ranged from 1-5 months. A 2 yo responsive pt on a medical food (formula) was able to discontinue this and is now on an unrestricted diet. Two infants with mild PKU under one year of age were started on Kuvan® without dietary restrictions when their blood phe levels reached a threshold requiring intervention. They remain on unrestricted diets with blood phe levels in the near normal range. The other 4 responsive patients have had their diets liberalized to varying degrees while

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				maintaining excellent blood phe control. We conclude that Kuvan® can be safely and effectively used in children under 4 years of age. Significant diet liberalization can be achieved in many patients without sacrificing blood phe control. In some patients, Kuvan® alone can provide excellent blood phe control without the need to institute dietary restrictions.
Society for Inherited Metabolic Disorders	2008	Not found	Experience with Long Term Use of LNAA in the Treatment of Phenylketonuria.	Objective: Short term treatment trials of Phenylketonuria (PKU) with large neutral amino acids (LNAA) done in our centers resulted in lowering of blood Phenylalanine (PKU). These trials have been reported, but were not followed by long term studies. The purpose of this trial is to examine long term safety, efficacy and acceptability of LNAA tablets, and to find out whether the effect of lowering blood Phe with LNAA (NeoPhe) is sustained over a one year period. Methods: Four patients with classical Phenylketonuria (PKU), three females and one male, ages 25–38 years, were enrolled in the long term trial. Patients were not taking medical food for more than ten years. Their mean blood Phe level was 1507 lmol/L. Patients were given NeoPhe tablets, 0.5 g/kg/day and were instructed to divide the pills equally with the three meals. Blood amino acids and Phe were determined once a month. Results: The mean blood Phe levels declined for each of the subjects during the study period: 642, 707, 899 and 869 lmol/L, from the mean level of 1507 lmol/L. The mean change from pre-and during NeoPhe trial was statistically significant (paired t-test: P = 0.002). Patients reached blood Phe level within the NIH Consensus Conference recommendations. None of the patients gained or lost any weight beyond minor fluctuations of +/0.2 kg. The acceptability of the pills was monitored during the monthly visit and through a check-list given to the patients for any complaints. There were no reports of abdominal discomfort, nausea or change in bowel movements. All patients felt encouraged by the drop of their blood Phe concentrations, and indicated that they felt ‘‘more focused’’ at work and asked to continue to be on NeoPhe beyond the trial period. Conclusions: The data from the four patients show that LNAA can be used to lower blood Phe in patients with PKU and can be taken for a long time without any adverse side effects. Future studies should include larger number of patients and also include neuropsychological tests to document improvement in such parameters as executive functioning and concentration.
Society for Inherited Metabolic Disorders	2008	Burton 2011[3]	Preliminary Findings from the Sapropterin Expanded Access Program for PKU.	Background: The Sapropterin Expanded Access Program (SEAP) is an FDA-approved program providing sapropterin dihydrochloride, prior to launch of drug (Kuvan), to patients with hyperphenylalaninemia (HPA) due to phenylketonuria (PKU), aged = 9 years, who did not participate in sapropterin clinical trials nor were enrolled in compassionate/temporary use programs. Objective: The SEAP provides data including adverse events (AEs) documented by treating physicians using Medical Dictionary for Regulatory Activities (MedDRA) terminology. All safety and program-retention data will be analyzed and described. Methods: Confirmed PKU patients will be enrolled in the SEAP from commencement of the program in June, 2007 until approximately February, 2008 or two months after commercialization of drug (Kuvan). Patients will receive a daily dosage of sapropterin dihydrochloride between 5 mg/kg/day and 20 mg/kg/day for variable lengths of time. Throughout the SEAP, time on drug, safety data pertaining to AEs such as MedDRA terms, severity, seriousness, relatedness to drug, action required and outcome will be analyzed. Results: As of November 6, 2007, a total of approximately 111 patients began therapy = 30 days, (between June, 2007 and October 6, 2007). Twenty of 111 (18%) patients who discontinued therapy were withdrawn for either non-response (12 patients; 11%); or non-compliance (4 patients; 3.6%), or AEs (4 patients; 3.6%: nausea [2], vomiting [1], diarrhea [1], fatigue [1], abdominal cramps [1] and abdominal pain [1]). For all patients enrolled during SEAP up to October 6, 2007, AEs occurred in 22 of 111 (20%) patients, including 4 patients who withdrew from the SEAP. All AEs

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				were mild to moderate in severity, belonged mostly to the gastrointestinal system order class, most of which were possibly related to sapropterin dihydrochloride. Conclusions: Discussion and definitive conclusions of the final set of results will be presented. Preliminary findings suggest that 91 (82%) of patients who were initiated on drug before October 6, 2007, were retained on drug up to November 6, 2007, whereas 20 (18%) of patients withdrew for reasons associated with non-response to drug, or due to non-compliance or due to AEs. Sapropterin dihydrochloride was well tolerated at doses between 5 and 20 mg/kg/day with mostly mild to moderate gastrointestinal-related AEs.
Society for Inherited Metabolic Disorders	2008	Not found	The Long Term Impact of Tetrahydrobiopterin Therapy in Phenylketonuria: Dietary and Nutritional Implications.	Objective: While improvements in plasma phenylalanine (Phe) concentrations have been the primary outcome measure of tetrahydrobiopterin (BH4) responsiveness thus far, the implications for diet and nutrition status are lacking. The objective of this study is to investigate the impact of BH4 on Phe tolerance, long-term dietary patterns, medical food continuation and nutritional status. Methods: At the Emory Genetics Clinic, 7 of 9 children with well-controlled phenylketonuria (PKU) responded to a dose of 20 mg/kg/day of BH4 (sapropterin dihydrochloride) with a =30% decrease in plasma Phe concentrations after 8 days (p = 0.014). Six of the responders were enrolled in a 6-month follow-up study to evaluate further the impact of BH4 on Phe tolerance and nutritional status. Maximum dietary Phe tolerance was determined by progressively increasing milk or egg powder over a six-week period while maintaining plasma Phe concentrations between 120 and 360 lmol/L. Subsequently, protein from medical food was decreased by 25% each week provided that plasma Phe concentrations and nutrition status markers remained within the therapeutic range and the average protein intake met or exceeded US Dietary Reference Intakes (DRIs). Results: Six weeks: Dietary Phe tolerance increased to a mean ± SD of 1380 ± 395 mg/d (baseline 575 mg/d ± 215) (p = 0.001). Six months: Mean plasma Phe concentrations persisted within the therapeutic range of 120–360 lmol/L throughout the 6-month follow-up period while the mean dietary Phe tolerance was 1595 ± 615 mg/d. Four of the six patients were able to completely eliminate medical food from their diet, while the remaining two took medical food below baseline intakes. While mean total protein intake did not significantly decrease and continued to exceed DRIs for each patient, vitamin and mineral supplementation was required for those who discontinued formula to meet micronutrient DRIs. There was no significant change in mean energy intake; weight percentiles; and concentrations of prealbumin, hemoglobin and hematocrit. Conclusions: These results demonstrate the need to systematically reduce medical food to maintain nutrient adequacy of the diet while maintaining plasma Phe levels within therapeutic range and to personalize diet recommendations. Vitamin and mineral supplementation may be necessary, particularly if medical food has been discontinued.

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Society for Inherited Metabolic Disorders	2008	Not found	Phenylalanine (Phe) Control in Patients with Phenylketonuria (PKU) Consuming a Novel Metabolic Medical Food (Add Ins).	Background: Amino acid-based medical food products are effective in nutrition management of phenylketonuria (PKU), however, long term compliance can be poor. A flavorless novel medical food (Add Ins*) was developed, and contains free amino acids, excluding phenylalanine (PHE), encapsulated in a lipid coating. These coated amino acids (CAAs) were designed to be incorporated into low protein foods in the PHE-restricted diet. Objectives: Primary outcome was quantitation of plasma amino acid concentrations and protein status indices; secondary outcome variables were to assess compliance using an acceptability questionnaire and dietary intakes compared to current medical food. Serum lipids profiles were also quantitated. Methods: Ten patients with PKU replaced at least 1/3 of their medical food requirements with CAAs for 28 days. Baseline, 2 and 4 week data were analyzed. Results: Patients (16 ± 7 yrs) were prescribed on average 2 sachets (1 sachet contains 10g protein equivalents) daily of CAAs. There was no significant difference in mean baseline (24.3kg/m2 + 7.9) and post intervention Body Mass Index results (23.1kg/m2 + 7.3) (p = 0.70). Mean baseline plasma Phe concentration (587 ± 443 lmol/L) did not statistically differ at 28 days (586 ± 322 lmol/L). Plasma tyrosine (14 and 28 days), protein status indices and serum lipid concentrations (28 day) were not statistically different from baseline and were in normal reference ranges for age. Acceptance: one major limitation identified by patients included the gritty texture of CAAs which required preparation of foods to mask texture, thus making it inconvenient for some patients. Overall, 70% of study completers rated taste of CAAs, when added to foods, as ‘‘good’’, ‘‘very good’’ or ‘‘excellent’’. Additional comments included ‘it’s simple and easy’, ‘food was the taste, rather than the product’, and ‘no detectable odor, which is good’. Conclusion: CAAs were found to be safe and effective in supporting normal nutrition status indices as part of a PHE-restricted diet and may help to ‘‘normalize’’ diet regimen in patients with PKU. CAAs may help compliance as an alternative flavorless and flexible medical food compared to traditional powders or liquids. Acceptability comments were helpful in identifying the best types and amounts of low protein foods to which CAAs can be successfully added to the diet. *CAAs and Add Ins are known as Phlexy-10 Add Ins in USA.
American College of Medical Genetics	2007	Not found	Industry Supported Symposia (Biomarin): Breakthrough Research in Tetrahydrobiopterin Therapy for PKU: Diet Liberalization	Clinical studies have demonstrated that a significant subset of patients with PKU respond to treatment with sapropterin dihydrochloride (tetrahydrobiopterin or 6R-BH4) with a significant decline in blood phenylalanine levels. Long term therapy of PKU patients with this drug has been described in only a limited number of cases, however. The extent to which protein and phenylalanine restriction can be liberalized in patients who respond to tetrahydrobiopterin varies and has only recently been studied in a controlled fashion. In this session, a number of brief case summaries will be reviewed, each illustrating the impact of tetrahydrobiopterin therapy on an individual patient and collectively emphasizing the wide range of outcomes that may be observed in responsive patients. A 19 year old classical PKU patient will be reported who was on a phenylalanine restricted diet, limited to 400 mg phenylalanine/day prior to starting on tetrahydrobiopterin (Phenoptin, Biomarin). His blood phenylalanine levels averaged 12-14 mg%. He is now on a completely unrestricted diet with a recent blood phenylalanine level of 7 mg%. A second patient is a 5 year old boy with mild PKU who was receiving 450 mg phenylalanine/day prior to beginning Phenoptin therapy. He is now tolerating 1865 mg phenylalanine/day with good control of blood phenylalanine levels. A third patient, an 11 year old boy, was receiving 375 mg phenylalanine/day prior to starting treatment. He is now on 700 mg/day and probably cannot be liberalized further. Several other patients will also be described, each with different circumstances. The reactions of the patients and the families to diet liberalization will be discussed. One patient will be described who was not on dietary therapy prior to initiating treatment with Phenoptin but experienced resolution of neuropsychiatric symptoms as his blood phenylalanine levels were brought under control.

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American College of Medical Genetics	2007	Burton 2007 [5]	Sapropterin Dihydrochloride Reduces Phenylalanine Levels in Patients with Phenylketonuria: Results of an Open-label, Multicenter, Screening Study	Previous studies have shown that BH4 (tetrahydrobiopterin) decreases blood phenylalanine (Phe) levels and increases Phe tolerance in phenylketonuria (PKU) patients. We designed a Phase 2, open-label study to evaluate the safety and response to sapropterin dihydrochloride (a formulation of BH4) in PKU patients with elevated blood Phe levels. PKU patients who met criteria for responsiveness were offered participation in a Phase 3 clinical trial. Patients ≥8 years old who were non-compliant with a Phe-restricted diet and had Phe levels ≥450 µmol/L at screening received 10 mg/kg of oral sapropterin dihydrochloride, once daily for 8 days. The primary endpoint was the proportion of patients who achieved a ≥30% reduction in blood Phe (prospectively defined as a response to treatment); the proportions of patients experiencing ≥20% and ≥10% reductions in Phe were also evaluated in post hoc analyses. Adverse events (AEs) and serious AEs (SAEs) were assessed. In total, 99% (485/490) of patients completed the study. Response to sapropterin was seen across baseline blood Phe level subgroups: 54% (31/57) of patients with Phe level <600 µmol/L; 24% (38/157) of patients with Phe level 600 to <900 µmol/L; 10% (14/135) of patients with Phe level 900 to <1200 µmol/L; and 10% (13/136) of patients with Phe level ≥1200 µmol/L. A ≥20% and ≥10% reduction in Phe occurred in 65% (37/57) and 68% (39/57) of patients with baseline Phe level <600 µmol/L; 31% (90/292) and 49% (143/292) of patients with baseline Phe level 600 to <1200 µmol/L; and 16% (22/136) and 39% (53/136) of patients with baseline Phe level ≥1200 µmol/L, respectively. Sapropterin was well tolerated. No deaths were reported; one SAE unrelated to Sapropterin was reported and one subject withdrew from the study due to an AE (pregnancy). The most frequent AEs observed were gastrointestinal symptoms (abdominal pain, diarrhea). Sapropterin was well tolerated and reduced blood Phe levels across a wide spectrum of phenotypes in PKU patients. If shown to be safe and effective in long-term studies, Sapropterin may become an important tool in the care of PKU patients.
American College of Medical Genetics	2007	Not found	The Outcome of Long Term Treatment with Sapropterin Dihydrochloride in Patients with Phenylketonuria (PKU)	Nine patients with PKU have been treated with sapropterin dihydrochloride (Kuvan tm, Biomarin Pharmaceuticals, Inc., Novato, CA) for nineteen months in an extension study that followed clinical trials previously reported. During this time, safety data were gathered under a specified protocol but dietary changes and all other treatment decisions were at the discretion of the individual investigator. Patients ranged in age from 5 to 29 years of age and were treated with a dose of 10- 20 mg/kg/day. In one patient who was not on any dietary treatment prior to enrollment in the clinical trials, the goal of continued treatment was control of blood phenylalanine (phe) levels while in the remaining 8 patients, the goal was diet liberalization. The 29 yr old man who was not on dietary therapy lowered his mean blood phe from 1178 umol/L to 370 umol/L and reported decreased anxiety & anger and improved sleep and mental clarity. All 8 pts on dietary therapy achieved diet liberalization ranging from a 2-5 fold increase in phe tolerance while maintaining blood phe levels in the acceptable range for age. Most patients eliminated low protein foods from the diet; medical food requirements were decreased in two although most continued to require some medical food. Detailed information regarding diet prescriptions before and after Kuvan will be presented for all patients along with patient demographics and mutation data, where available. All patients have reported a significant improvement in their quality of life. In summary, long term treatment with sapropterin can benefit patients with PKU in several ways: either through improved control of blood phe levels and relief of symptoms of PKU or through increased phe tolerance and diet liberalization.

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American Society of Human Genetics	2007	Lee 2008[6]	Safety and Efficacy of Sapropterin Dihydrochloride (Sapropterin) Treatment over 22 Weeks in Patients with Phenylketonuria (PKU).	Intro:Sapropterin, an oral formulation of tetrahydrobiopterin, can decrease blood phenylalanine (Phe) levels in some patients with PKU. We report 22-week efficacy and safety data from an open-label Ph 3 extension study of sapropterin in PKU patients who previously responded to sapropterin. Methods:80 patients (≥8yrs) with PKU, elevated blood Phe (≥600µmol/L) and who had relaxed or abandoned a Phe-restricted diet were enrolled. Design: 6-wk forced-dose titration phase (all patients received 3 consecutive 2-wk courses of sapropterin at 5, 20 and finally 10mg/kg/day), followed by a 4-wk dose-analysis phase (sapropterin maintained at 10mg/kg/day) and 12-wk fixed-dose phase (patients received 5, 10 or 20mg/kg/day based on their blood Phe level at Wk 2 and 6 visits). Results:Mean(SD) age was 20.4(9.6)yrs; 59%37; patients were male; 79 patients completed the study. Mean(SD) blood Phe concentration decreased from 844(398)µmol/L (14.1[6.6]mg/dL) at Wk 0 to 645(393)µmol/L (10.8[6.6]mg/dL) at Wk 10 and 652(383)µmol/L (10.9[6.4]mg/dL) at Wk 22 (end of fixed-dose phase). At Wk 22, 46%(36/79) patients had a ≥30% reduction in blood Phe compared with Wk 0. Adverse events (AEs) were reported by 68/80 patients (85%); all but one (tooth abscess considered to be unrelated to study drug) were mild/moderate in severity, no patient withdrew due to AEs, and 31 (39%) patients reported an AE considered possibly/probably related to study drug. Most commonly reported AEs during the study were headache (20% patients), pharyngolaryngeal pain (15%), nasopharyngitis (14% vomiting (13%), diarrhea (10%) and upper respiratory tract infections (10%). Concl:Sapropterin (5, 10 and 20mg/kg/day) reduces blood Phe levels in PKU patients through 22 weeks of treatment with an acceptable safety profile.
American Society of Human Genetics	2007	Lee 2008[6]	Dose-related Effect of Sapropterin Dihydrochloride (Sapropterin) on Blood Phenylalanine (Phe) in Patients with Phenylketonuria (PKU).	Intro:Sapropterin, an oral formulation of tetrahydrobiopterin, can decrease blood Phe levels in patients with PKU. We report the effects of 3 sapropterin dose levels on blood Phe in PKU patients who previously responded to sapropterin. Methods:80 patients(≥8yrs) with PKU and elevated blood Phe(≥600µmol/L), who had relaxed/abandoned a Phe-restricted diet entered the forced-dose titration phase of an open-label study and received 3 consecutive 2-wk courses of sapropterin, 5,20 and 10mg/kg/day (od). Mean(SD) change from Wk 0 in blood Phe level was calculated at Wks 2, 4 and 6 after 5,20 and 10mg/kg/day respectively, and analyzed using a longitudinal model (subjects served as their own controls). Results:Subjects were 98% Caucasian, 59% male, with mean(SD) age of 20.4(9.6)yrs. Mean(SD) decreases in blood Phe from Wk 0 at Wks 2, 4 and 6 after treatment with 5,20 and 10mg/kg/day were -100(295), -263(318) and -204(303)µmol/L respectively. Mean change in blood Phe was related to dose, shown by a statistically significant difference in effect when comparing doses ($p<0.01$ for all pairwise comparisons). Proportion of subjects with ≥30% decrease from Wk 0 in blood Phe was 25%, 55% and 46%, for 5,20 and 10mg/kg/day respectively. All dose levels were well tolerated (Randolph et al.) with no apparent relationship between dose and safety profile. Concl:In this forced-dose titration phase, sapropterin (5,10 and 20mg/kg/day) effectively reduced blood Phe in subjects with PKU in a dose-related manner with an acceptable safety profile. 20 mg/kg/day produced significantly greater decreases in blood Phe than lower doses.
American Society of Human Genetics	2007	Lee 2008[6], Levy 2007[7]	Sapropterin Dihydrochloride (Sapropterin) Increases Phenylalanine (Phe) Tolerance in Children with Phenylketonuria (PKU) Maintained on a Phe-restricted Diet.	Intro:Current PKU management focuses on blood Phe control using a Phe-restricted diet, but non-compliance with the diet may increase as children approach adolescence. This double-blind, placebo-controlled, Phase 3 study investigated the efficacy of sapropterin on Phe tolerance in children with PKU on diet therapy who respond to sapropterin. Methods:In Part 1, 90 subjects (4-12 yrs) with a diagnosis of PKU with hyperphenylalaninemia (≥1 blood Phe measurement ≥360µmol/L) and controlled (blood Phe ≤480µmol/L) on a Phe-restricted diet for

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				≥6 months received sapropterin 20mg/kg/day, for 8 days. Responders (≥30% reduction in blood Phe and blood Phe 300µmol/L[5mg/dL] on Day 8, arbitrarily defined) entered Part 2 and were randomized 3:1 to sapropterin or placebo for 10 weeks. Phe supplement was prescribed at Wk 3 and adjusted bi-weekly according to blood Phe levels. Primary endpoint was daily Phe supplement tolerated during 10 weeks while maintaining adequate blood Phe control (≤360µmol/L[6mg/dL]). Results:Of 89/90 patients in Part 1, 50 were responders eligible for Part 2, 46 were randomized (sapropterin=33;placebo=12) and 1 did not receive drug. At Wk 3 prior to Phe supplementation, mean (SD) decrease in blood Phe compared with Wk 0 was 148.5(134.2)µmol/L with sapropterin (p<0.001) and 96.6(243.6)µmol/L with placebo (p=0.2). By Wk 10, mean (SD) daily Phe supplement tolerated was significantly increased from Wk 0 (0 mg/kg/day) with sapropterin (20.9[15.4]mg/kg/day; p<0.001) and with placebo (2.9[4.0]mg/kg/day;p=0.027). Mean (SD) daily Phe intake (dietary+supplement) increased (Wk 0-Wk 10) from 16.8(7.6) to 43.8(24.6)mg/kg/day with sapropterin (p<0.001), and from 16.3(8.4) to 23.5(12.6)mg/kg/day with placebo (p=0.079). In the sapropterin group, mean (SD) blood Phe at Wk 10 was 340.0(234.5)µmol/L. Sapropterin had an acceptable safety profile (Grange et al). Concl:Sapropterin significantly increases Phe tolerance while maintaining adequate blood Phe control in children with PKU on a Phe-restricted diet.
American Society of Human Genetics	2006	Levy 2007[7]	A Phase 3 Study of the Efficacy of Sapropterin Dihydrochloride (Tetrahydrobiopterin, 6R-BH4) in Reducing PHE Levels in Subjects with Phenylketonuria.	Strict dietary management of Phenylketonuria (PKU) is the only option to prevent mental retardation. Major challenges remain to achieve optimal outcomes. We studied Sapropterin, a synthetic form of BH4, as a new treatment for PKU that could potentially improve long-term care. Patients previously screened for BH4 response enrolled in a Phase 3, multicenter, randomized, double-blind, placebo controlled trial. Safety and efficacy in reducing blood phenylalanine (Phe) were compared in PKU patients treated with oral sapropterin 10 mg/kg, or placebo, once daily for 6 weeks. Of the 89 subjects enrolled, 87 completed treatment. Age ranged from 8 to 49 years (mean 20±9.7). At baseline, mean (±SE) blood Phe was 843 (±47) µM and 888 (±47) µM in the sapropterin and placebo groups, respectively. After 6 weeks of treatment, sapropterin-treated patients achieved a mean blood Phe decrease of 236 (±40) µM (-29%) compared with a 3 (±35) µM (+3%) increase in the placebo group (p<0.0001). At week 6, the percentages of subjects with blood Phe levels ≤600 µM were 54% and 23% for the sapropterin and placebo groups, respectively (versus 17% and 19% at baseline). There was a consistent reduction over time in the average mean change in weekly blood Phe levels in the sapropterin group compared to the placebo group (p<0.001). The type and incidence of adverse events were similar in the two study arms. Sapropterin was well tolerated and effective in significantly reducing blood Phe levels in PKU patients previously screened for BH4 responsiveness.

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Society for the Study of Inborn Errors of Metabolism		Not found	PKU Diet Relaxtion Influences Fatty Acid Intake Pattern	Background: After diet relaxation due to BH4 therapy or previous overtreatment, PKU patients consume less fruits and vegetables, but considerable amounts of meat, milk, normal bread and pasta. Objective: Investigation of the influence of emerging consumption patterns of patients on relaxed PKU diets on their fatty acid intake. Methods: The intake of total fat, saturated (SFA), monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids of 16 PKU patients (7–22 years, 9 on BH4 therapy) with phe intakes from 570–2700 mg, was investigated by food protocol analysis (excluding protein supplements) using a nutrient calculation programme. Patients were assigned to group A (< 1500 mg phe intake, n=12) or group B (> 1500 mg phe intake, n=4). Results: Patients of group A have statistically significant lower intake of total fat and all fatty acid groups compared to group B. Mean values: total fat 40 g/d vs. 71.9 g/d, p=0.031; SFA 13.8 g/d vs. 32.2 g/d, p=0.013; MUFA 8.6 g/d vs. 23.7 g/d, p<0.002; PUFA 4.6 g/d vs. 8.3 g/d, p=0.039. Total fat and SFA as %energy of group B are above recommendations and above healthy peer groups (DONALD study). Conclusion: Diet relaxation leads to less favorable fatty acid patterns. Conflict of Interest declared.

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