CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022-181/S13
Priority or Standard	Priority
Submit Date(s)	September 9, 2013
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Division / Office	DGIEP/ODE III
Reviewer Name(s)	Carla Epps, MD, MPH
Review Completion Date	March 6, 2014
Established Name	Sapropterin hydrochloride
(Proposed) Trade Name	Kuvan
Therapeutic Class	Phenylalanine hydroxylase activator
Applicant	BioMarin
Formulation(s)	Oral
Dosing Regimen	5, 10, and 20 mg/kg/day
Indication(s)	Reduction of blood Phe levels in patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria (PKU)
Intended Population(s)	Patients with BH4-responsive PKU

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

The applicant submitted Efficacy Supplement 13 to NDA 022-181. The supplement included the results of a population PK study (Sub-study 2) and a 6-month safety and efficacy trial (Sub-study 1) conducted as sub-studies of an ongoing 7-year study (PKU-015) to evaluate the safety of Kuvan on neurocognitive functioning in pediatric patients 6 years old or younger. The sub-studies were conducted to fulfill a post-marketing commitment (PMC #1) and in response to a Pediatric Written Request (PWR) issued October 31, 2011. The ongoing 7-year study is being conducted to fulfill another post-marketing commitment (PMC #2). The applicant is seeking a claim for safety and efficacy for pediatric patients 6 years and younger based on the results of the sub-studies. The applicant also proposes to update labeling to change dosing recommendations.

1.1 Recommendation on Regulatory Action

I recommend approval action for Efficacy Supplement 13 for NDA 22181. The recommended starting dose of Kuvan for patients 6 years and younger is 10 mg/kg/day. The recommended starting dose for patients 7 years and older is 20 mg/kg/day.

There is sufficient evidence of safety and short-term efficacy based on sub-studies for a pediatric trial (PKU-015) to support an indication in pediatric patients ages 6 years and younger with PKU that are tetrabiopterin (BH4)- responsive and to provide adequate directions for use. (b) (4) Evidence of safety is based on a database of 94 pediatric patients enrolled in In a phase 3 clinical trial (PKU-015) and a review of post-market safety reports for the period December 7, 2007 to December 12, 2012.

1.2 Risk Benefit Assessment

The efficacy data for PKU-015 Sub-study 1 indicated that there was a reduction in blood phenylalanine (Phe) levels following treatment with Kuvan for 4 weeks in pediatric patients ages 0 to 6 years who were maintained on a stable Phe diet.

(b) (4) . This reviewer notes that the long-term efficacy of Kuvan has not been established for any age group. All of the trials conducted to support the original submission were short-term (8 days to 6 weeks). The applicant has conducted an open-label long-term safety trial in older children and adults (PKU-008) that included blood Phe as a secondary endpoint. However, the trial was not adequately designed to evaluate efficacy because dietary

Phe intake was not controlled. For demonstration of long-term efficacy on reduction of blood Phe levels, this reviewer recommends that the applicant conduct a trial with patients on a stable Phe diet as the control arm and patients on a stable Phe diet and Kuvan as the treatment arm, with patients stratified by age.

Because a number of patients in the sub-study had blood Phe levels within or below the target range prior to treatment, this reviewer considers trends in blood Phe control status to be more informative of a clinically meaningful response than trends in blood Phe levels. Blood Phe levels decreased during the first four weeks of treatment and then increased over time in all age groups. However, blood Phe control status improved in the two younger age groups whereas blood Phe control status did not appear to improve in the two older age groups. I recommend that the labeling include information on blood Phe control results.

From a clinical and nutritional perspective, the ability to liberalize a patient's diet would provide significant clinical benefit. However, the trial was not adequately designed to evaluate for efficacy for increased Phe tolerance. (b) (4) for improved Phe tolerance, the applicant will need to conduct a trial that compares Phe levels of patients receiving increases in dietary Phe and patients receiving increases in dietary Phe and Kuvan, with patients stratified by age.

The observed safety profile of Kuvan in the trial data and post-marketing data provided by the applicant was consistent with the labeling for Kuvan. Kuvan labeling includes a precaution to monitor blood Phe level during treatment to prevent prolonged elevations in blood Phe levels or prolonged levels of blood Phe that are too low. Sixteen patients in Sub-study 1 experienced blood Phe levels below the age-based reference range; the majority of these events occurred during the first four weeks of treatment. Events of hypophenylalaninemia were also reported for five patients treated with Kuvan in PKU-008, a long-term safety trial in older children and adults. Of note, four of the five PKU-008 patients who experienced hypophenylalaninemia were children (ages ranged from 6 to 11 years) who were treated with Kuvan 20 mg/kg/day; the fifth patient was an adult who was treated with Kuvan 10 mg/kg/day.

(b) (4) . The current labeling recommends Kuvan dosing of 10 mg/kg/day for up to one month to determine whether a patient is BH4-responsive. The dose may be increased to 20 mg/kg/day for another month if there is no response at the lower dose. Patients whose blood Phe levels do not decrease after 1 month of treatment at 20 mg/kg/day are considered non-responders and therefore not candidates for treatment with Kuvan. (b) (4) Based on the observed increased incidence of hypophenylalanemia in younger children treated with Kuvan doses of 20 mg/kg/day, I do not recommend (b) (4) 20 mg/kg in children younger than 7 years old. The current labeling should be updated

to include information about the risk of hypophenylalaninemia in children younger than 7 years old.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Continuation of routine surveillance for adverse events is recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

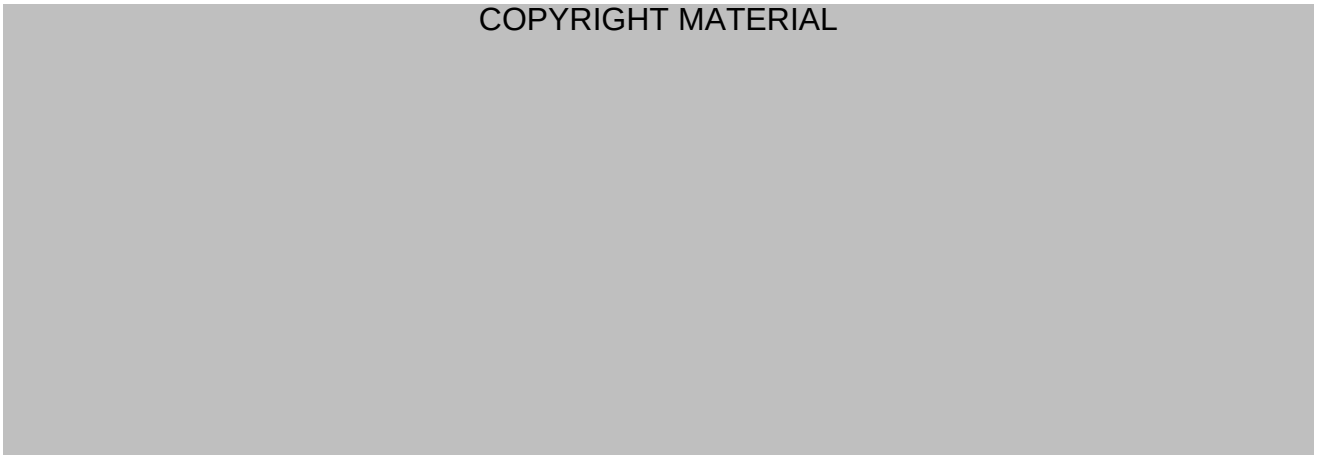
The clinical study report for the two PKU-015 sub-studies is adequate to fulfill PMC #1. At the time of this review, no additional PMCs were being negotiated with the applicant.

At the time of this review, the Pediatric Exclusivity Board was reviewing information from the sub-studies to determine whether the terms of the PWR were met. One key issue is whether study enrollment was adequate. The PWR stipulated a minimum enrollment of 60 BH4 responders for the 6-month safety/efficacy sub-study; however, only 57 patients were enrolled who met the protocol-defined criterion for Phe responder. In addition, the sub-study did not meet the minimum enrollment requirement of 20 patients ages 4 to 6 years (only 13 BH4 responders in this age group were enrolled). Other issues include whether PWR requirements for controlled dietary Phe intake and for safety monitoring were met. (b) (4)

2 Introduction and Regulatory Background

Hyperphenylalaninemia
Hyperphenylalaninemia (HPA) is an autosomal recessive disorder due to a deficiency of the enzyme phenylalanine hydroxylase (PAH). The deficiency results in the inability to convert the essential amino acid phenylalanine (Phe) to tyrosine (see Figure 1). Excessive levels of phenylalanine are neurotoxic and can result in neurocognitive impairment in untreated patients, with the most severe impact on neurocognitive development and functioning occurring during infancy and early childhood.

Figure 1: Metabolic Pathway for Phenylalanine



Source: van Calcar SC, Ney DM, Food products made with glycomacropepeptide, a low-phenylalanine whey protein, provide a new alternative to amino acid-based medical foods for nutrition management of phenylketonuria, *J Acad Nutr Diet* 2012; 112(8): 1201-1210.

The incidence of HPA varies widely between ethnic groups. The incidence in the US is approximately 1:10,000 to 1:20,000 for Caucasians and Asians; the incidence among African-Americans is much less.[1] Diagnosis of the disease can be established by genetic testing for the presence of mutations of the *PAH* gene. More than 400 gene mutations resulting in clinical disease have been identified. For the majority of patients with HPA, there is a strong genotype-phenotype correlation.[2] Genotype also may be helpful in predicting response to treatment with tetrahydrobiopterin (BH4).[3]

[1] http://www.npkua.org/index.php/pku-facts
[2] Blau N, Hennerman JB et al, Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies, *Mol Genet Metab* 2011; 104:S2-S9.
[3] http://www.ncbi.nlm.nih.gov/books/NBK1504/

HPA disorders are classified according to the degree of hyperphenylalaninemia.[4,5] Guldberg et al. proposed four classification categories, based on prediction of metabolic phenotype from genotype: classic PKU, moderate PKU, mild PKU, and mild HPA. Patients with classic phenylketonuria (PKU), the most severe variant of the disease, have absent or near-absent PAH activity.

Clinical manifestations in children with classic PKU include: microcephaly, epilepsy, a musty body odor, decreased skin and hair pigmentation, eczema, severe cognitive impairment, and behavior problems. In adulthood, these patients may also develop neurologic abnormalities (increased deep tendon reflexes, tremor, and paraplegia or hemiplegia) and psychiatric disorders (depression, anxiety, and phobias). Patients with less severe PKU phenotypes have a lower risk of cognitive impairment. Patients with PKU also have a high incidence of osteopenia. However, it is unclear whether this finding is inherent to the disease or secondary to dietary restrictions. Individuals with mild HPA (also known as non-PKU HPA) do not have a higher risk of cognitive, neurologic, or neuropsychological impairment than individuals without PAH deficiency.

Infants of mothers with PKU are at risk of congenital heart disease, microcephaly, growth retardation, and cognitive impairment. The risk is dependent on the time and the dose of exposure to Phe in utero.

Diagnosis
Newborn screening for HPA is universal in the US. HPA can be diagnosed by newborn screening for the presence of elevated Phe levels (>1000 µmol/L in untreated PKU patients; above normal [i.e., > 120 µmol/L] but <1000 µmol/L in patients with mild HPA when on a normal diet). Patients who have a positive screen should also be tested to exclude a disorder of BH4 metabolism, which can also cause elevated Phe levels. About 2% of newborns with elevated Phe levels on newborn screening have a BH4 deficiency and require different treatment.[6] The BH4 loading test is used both to identify patients with BH4 deficiency and to identify a subgroup of patients with HPA that are responsive to treatment with BH4. The frequency of BH4-responsiveness is highest in patients with milder phenotypic disease. Genetic mutation analysis is performed to predict the level of dietary Phe restriction that will be required and responsiveness to treatment with BH4.

Treatment
Dietary intervention is the mainstay treatment of HPA and includes restriction of dietary Phe. Because a Phe-restricted diet is very low in total protein, patients with HPA require supplementation with a medical food containing Phe-free amino acids to provide an

[4] Ibid.
[5] Guldberg P, Rey F et al., A European multicenter study of phenylalanine hydroxylase deficiency: Classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype, *Am J Hum Genet* 1998; 63:71-79.
[6] Blau N, Hennermann JB et al., Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies, *Mol Genet Metab* 2011; 104:S2-S9.

adequate protein source for growth and protein turnover. The therapeutic goal of dietary management of HPA is to achieve normal or near-normal concentrations of Phe and tyrosine in the blood. Although PAH genotype is helpful in predicting phenotype, Phe tolerance (i.e., the amount of daily Phe intake that does not increase blood Phe level above the upper target range) should be evaluated in each individual patient.

Treatment is initiated as soon as possible after birth and is continued at least into adolescence to prevent cognitive deficits. Waisbren et al. performed a meta-analysis of data for 3361 patients with PKU that showed a reduction in IQ of 1.9 to 3.8 points for every 100 µmol/L increase in lifetime blood Phe level.[7] Studies have indicated that even early- and well-treated patients may have impaired executive function (e.g., planning, organizing) and psychosocial difficulties during childhood and adulthood.[8] Thus, an expert panel convened by the National Institutes of Health in 2000 noted that lifelong dietary restriction of Phe "probably is medically necessary for almost all patients with classic PKU."[9] Conversely, patient with mild HPA who consistently maintain blood Phe levels below 600 µmol/L do not appear to require dietary restrictions (see Table 1). Compliance with a Phe-restricted diet presents a significant challenge to optimal disease management in older pediatric patients and adults.

Table 1: Guidelines for Restriction of Dietary Phenylalanine by HPA Phenotype

Category	Daily dietary Phe allowance
Classic PKU	< 250-300 mg/day
Moderate PKU	350-400 mg/day
Mild PKU	400-600 mg/day
Mild HPA (non-PKU HPA)	Normal diet

PAH=phenylalanine hydroxylase; Phe=phenylalanine; PKU=phenylketonuria; HPA=hyperphenylalaninemia
Source: http://www.ncbi.nlm.nih.gov/books/NBK1504/

Although there is worldwide consensus on the importance of early dietary intervention, there are no universal guidelines for dietary treatment or age-specific criteria for target Phe levels. These criteria differ among treatment centers in the United States and across different countries.[10] The European Society of Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESKPU) recently published a survey of treatment practices in countries participating in the ESPKU. The survey revealed that about one-third of centers used their own guidelines and one-half of centers used national guidelines. Target blood Phe levels in the responding centers ranged from 60-400

[7] Waisbren SE, Noel K et al., Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systemic literature review and meta-analysis, *Mol Genet Metab* 2007; 92(1-2): 63-70.
[8] Gentile JK, Ten Hoedt AE, Bosch AM, Psychosocial aspects of PKU: Hidden disabilities-A review, *Mol Genet Metab* 2010; 99: S64-67.
[9] National Institutes of Health Consensus Development Panel, National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16-18, 2000, *Pediatrics* 2001; 108:972-982
[10] Ibid.

µmol/L.[11] In both the US and abroad, target blood Phe levels vary depending upon patient age (target Phe levels are lowest for young children and highest for adults) and pregnancy status (target Phe levels for pregnant women are similar to those for young children).

Currently, Kuvan is the sole drug product approved for treatment of PKU. Investigative therapies include treatment with large neutral amino acids (LNAA) transporters to reduce Phe transport across the blood-brain barrier and with the enzyme phenylalanine ammonia lyase (degrades Phe to trans-cinnamic acid and ammonia).

2.1 Product Information

Kuvan was approved in 2007 for the treatment of patients with HPA due to BH4-responsive PKU. The labeling for Kuvan notes that the product is to be used in conjunction with a Phe-restricted diet.

The efficacy and safety of Kuvan were evaluated in 4 clinical studies in patients with PKU ages 4 to 48 years. Study 1 was an 8-day open-label uncontrolled enrichment study conducted in patients with PKU who were not on dietary restriction and was designed to identify patients for further study in a controlled efficacy trial. Of 489 patients (age range 8-48 years); 96 patients (20%) were determined to be responsive to treatment with Kuvan (defined as ≥30% decrease in blood Phe). Study 2 was the pivotal study for Kuvan and was a 6-week double-blind, placebo-controlled trial in 88 patients with PKU. The primary endpoint for the trial was mean change in blood Phe level. Study 3 was a 6-week open-label, extension trial in 80 patients who were identified as responders to Kuvan in Study 1 and completed study 2. Patients were treated for 3 consecutive 2-week courses with 3 different doses of Kuvan (5, 10, and 20 mg). Study 4 was an 8-day, open-label, uncontrolled diet study conducted in pediatric patients (age range 4-12 years) with PKU who were on a Phe-restricted diet. Of 89 patients, 50 patients (56%) were determined to be responders. Because these were short-term trials, the long-term efficacy of Kuvan on blood Phe levels remains unknown. In addition, these clinical trials did not evaluate the efficacy of Kuvan on neurocognitive, growth and development, or nutritional status.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Treatments for PKU

Name	Formulation	Indication
Kuvan (sapropterin dihydrochloride)	Oral 100 mg tablets	Reduce blood Phe levels in patients with HPA due to BH4-responsive PKU

[11] van Spronsen FJ, Kiaer Ahring K, Gizewska M, PKU- What is daily practice in various centres in Europe?, *J Inherit Metab Dis* 2009; 32:58-64.

2.3 Availability of Proposed Active Ingredient in the United States

There have been no reported drug shortages for Kuvan in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

The labeling for Kuvan notes that convulsions and exacerbation of convulsions were reported during clinical trials and post-marketing for patients treated with a different formulation of sapropterin for non-PKU indications.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- **May 25, 2007:** NDA 22181 was submitted.
- **December 13, 2007:** NDA 22181 was approved. The Agency approval letter listed seven post-marketing commitments, including agreement by the applicant to conduct the following pediatric studies
    - A safety, efficacy (based on pharmacodynamic outcome of blood Phe levels over a 6-month treatment period) and pharmacokinetics (PK) trial in PKU patients ages 4 years and younger (PMC #1)
    - A long-term efficacy trial to assess growth and neurocognitive development in PKU patients ages 8 years and younger (PMC #2)
- **January 14, 2008:** Division issued Pediatric Written Request (PWR) pertaining to the studies specified in PMC #1 and PMC #2
- **June 4, 2008:** Applicant submitted protocol for PKU-015 to IND 069,708
- **September 15, 2008:** Type C meeting was held with applicant to discuss revisions to PWR. Agreed-upon revisions included lowering the age limit from 8 to 6 years for the 7-year neurocognitive trial and decreasing minimum enrollment from 80 to 60 patients.
- **December 11, 2008:** Applicant submitted amended protocol for PKU-015 to IND 069,708
- **February 5, 2009:** Applicant submitted proposed revisions to PWR based on discussions during September 15, 2008 meeting.
- **May 31, 2009:** Original PWR expired prior to Agency review of amended protocol and issuance of an updated PWR
- **May 5, 2010:** Applicant submitted PPSR.
- **October 31, 2011:** Agency issued second PWR.
    - Clinical trials were already near completion at the time that the revised PWR was issued to the applicant. The applicant states that the two sub-studies included in this submission were conducted based upon protocol revisions that were agreed upon with the Agency during the September 2008 Type C meeting.
- **September 10, 2013:** Supplement 13 was submitted.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was an electronic submission. The overall quality of the data submitted by the applicant was adequate for comprehensive review of the data.

Two major protocol amendments were issued during the trial:

Amendment 1 (dated November 25, 2008)
Amendment 1 included the following revisions agreed upon with the Division during the Type C meeting held on September 15, 2008:

- Lowered age limit from 8 to 6 years and adjusted sample sizes for age cohorts
- Provided additional information regarding control of blood Phe during the trial, including a specific definition of adequate blood Phe control (blood Phe $\leq$ 240 µmol/L); maintenance of diet records, and specific instructions for modifying dietary Phe intake
- Changed method of administration to dissolved tablets only and provided Kuvan dosing chart for patients weighing < 20 kg.
- Added electrocardiogram assessment after initial Kuvan dose
- Added Bayley testing every 6 months for patients ages 0 to 2.5 years as a secondary objective to the safety and efficacy sub-study

Additional revisions included:

- Added vital signs assessment after initial Kuvan dose
- Removed long-term Phe control as an objective of the 7-year trial
- Clarified PK sampling times and added a post-dose sample for patients aged 0 to 1 year, and a total biopterin sample in the event of a treatment-related serious adverse event
- Added additional tyrosine and tryptophan sampling times

Amendment 2 (dated November 30, 2010)

- Added use of phosphodiesterase type 5 (PDE5) inhibitors as an exclusion criterion
- Modified age group sizes in the Population PK sub-study due to high responder rates (decreased size of < 1 year age group from 30 to 10 patients and increased size of 1 to 6 years age group from 50 to 70 patients)

The applicant conducted an analysis of pooled data from PKU-015 and another trial (PKU-004) for the population PK sub-study analysis rather than the planned analysis using only PKU-015 population PK data. The PK data from PKU-004 included data in older children and adults. The applicant stated that there were no changes in the

analysis plan for the 6-month safety/efficacy sub-study. However, the applicant performed additional sensitivity analyses of the efficacy data to assess for differences between the overall efficacy population, which included patients who were not BH4 responders as defined by the protocol, and the subset of patients who protocol-defined BH4 responders.

Reviewer Comments:
As discussed later, the safety-efficacy sub-study did not meet the minimum enrollment of 60 patients who were BH4 responders stipulated in the PWR. Although minimum enrollment targets were met for the other age groups, the sub-study did not met the minimum enrollment requirement of 20 patients for the 4 to <7 age group (only 13 patients were enrolled in this age group). The smaller sample size of BH4 responders in this age group was one of several factors that limited the interpretability of the data. As discussed later, other factors included the significant proportion of patients with major protocol deviations, and a dietary protocol that allowed changes in dietary Phe during the course of the sub-study.

3.2 Compliance with Good Clinical Practices

The applicant stated that this trial was conducted in accordance with Good Clinical Practice (GCP) as described in 21 CFR, the International Conference on Harmonisation (ICH) GCP guideline (ICH E6), and the Declaration of Helsinki.

The Division of Scientific Investigations (DSI) was consulted to determine the reliability of data by evaluating US and foreign clinical sites with the most enrolled patients for PKU-015. A total of two clinical sites were inspected (see Table 3). These sites were selected for inspection because of their high enrollment and geographic location (one domestic and one foreign site). The DSI inspector (Susan Leibenhaut, M.D.) reported that no significant regulatory violations were noted and concluded that data from the two sites could be used in support of the NDA.

Table 3: DSI Site Inspections

Site/Investigator	Protocol ID	Number of Subjects
Site 0124 Nicola Longo, MD, PhD University of Utah 2C412 SOM, 50 N. Mario Capecchi Drive Salt Lake City, UT 84132 USA	PKU-015	20
Site 0129 Komudi Siriwardena, MD The Hospital for Sick Children 555 University Avenue Toronto, Ontario M5G 1X8 CANADA	PKU-015	17

3.3 Financial Disclosures

No financial interests were disclosure for investigators and sub-investigators in PKU-015. The applicant noted that the study is ongoing and that investigators are periodically queried for changes in financial disclosure information.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The applicant provided information on the stability of Kuvan in a number of soft food in an amendment to the submission dated January 22, 2014. The CMC reviewer, Libaniel Rodriguez, Ph.D., concluded that the stability data supported including administration of Kuvan dissolved in soft foods or 5 mL of water in labeling. All other CMC data for this product were reviewed by Yichun Sun, Ph.D. during the review cycle for the original NDA submission (see Quality Review dated November 19, 2007 for further details).

Reviewer Comments:
The PWR stated that the applicant must use or develop an age-appropriate formulation in the sub-studies. During the trial, Kuvan was administered as a dissolved tablet in soft food or water (the current labeling for Kuvan states that Kuvan can be administered with food or dissolved in 4 ounces of water of apple juice). For patients weighing less than ≤5 kg, a solution of Kuvan prepared by dissolving a tablet (200 mg) in 5 mL of water and a portion of the dissolved tablet was administered to the patient (for example, a 20 mg/kg/dose for a patient weighing 5 kg was 2.5 mL (100 mg). The applicant stated that use of dissolved tablets was an age-appropriate formulation for the age groups in the sub-studies. A powder formulation for Kuvan was also approved in December 2013. Both the dissolved tablet and powder formulations are age-appropriate for children under 7 years of age.

4.2 Clinical Microbiology

Clinical microbiology considerations do not apply to this application because Kuvan is not an antimicrobial agent.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical pharmacology and toxicology data were submitted for this application. The nonclinical program for this product was reviewed by Fang Cai, Ph.D. during the review cycle for the original NDA submission Dr. Cai concluded that the non-clinical data were adequate to determine the safety of Kuvan by the proposed route of administration. Dr. Cai recommended a Pregnancy Category C classification in labeling due to the following findings in animal reproduction studies:

- increased fetal loss and reduced body weight of live fetuses in rats at doses up to 400 mg/kg/day (equivalent to about 3 times the maximum recommended human dose of 20 mg/kg/day)
- teratogenicity in rabbits (increased incidence of holoprosencephaly) at a dose of 600 mg/kg/day (equivalent to about 10 times the maximum recommended human dose of 20 mg/kg/day)

Please refer to Dr. Cai's review dated November 27, 2007) and addendum to the review (dated December 4, 2007) for further details.

Reviewer Comment:
The labeling for Kuvan was recently revised to structure information regarding reproductive and pregnancy risks as specified in the Proposed Pregnancy and Lactation Labeling Rule (see current label dated December 19, 2013).

4.4 Clinical Pharmacology

The clinical pharmacology information for this submission was reviewed by the Clinical Pharmacology reviewer, Insook Kim, Ph.D. and the Pharmacometrics reviewer, Jingyu Yu, Ph.D. (see Clinical Pharmacology review dated February 18, 2014 for further details). Based on the observed exposure-response relationship, Dr. Kim and Dr. Yu concluded that the data supported use of a Kuvan dose of 20 mg/kg in pediatric patients less than 8 years old.

4.4.1 Mechanism of Action

Kuvan is a synthetic form of tetrahydrobiopterin (BH4), the cofactor for the enzyme involved in the metabolism of Phe. The labeling for Kuvan notes that treatment with BH4 can activate residual phenylalanine hydroxylase enzyme and thus improve the metabolism of Phe in a subset of patients.

4.4.2 Pharmacodynamics

Blood Phe levels are elevated in patients with PKU. Normal Phe levels vary by age. Blood Phe level was evaluated as a secondary endpoint in the population PK sub-study and the 6-month safety/efficacy sub-study.

Dr. Kim analyzed patterns of response in Phe levels and noted that considerable variability in response was observed in the sub-study (see Figure 2). In patients with blood Phe levels <120 µmol/L at baseline (Week 0), mean blood Phe dropped from screening to Week 0, and subsequently increased over time. In patients with blood Phe levels between 120 and 240 µmol/L (the target blood Phe range for the sub-study) at Week 0, mean blood Phe decreased after 1 week of treatment and subsequently increased. In patients with blood Phe levels >240 µmol/L, mean blood Phe decreased over the 4-week treatment period for the population PK sub-study and was maintained during Part 2 of PKU-015. Dr. Kim also noted intra-patient variation, with some patients experiencing significant blood Phe fluctuations even while maintaining stable dietary Phe intake.

Figure 2: Mean (5%CI) Blood Phe Level (µmol/L) in Subgroups Based on Blood Phe Level at Week 0

Included all patients (responder and non-responders)

Source: Clinical Pharmacology review dated February 18, 2014, Figure 8

Reviewer Comments:
The reason for the variability in blood Phe response is unclear. Dr. Kim raised the possibility of variations in dietary compliance as the cause for variability. However, based on DSI review of dietary records maintained at the two major clinic sites for the sub-study, dietary compliance appeared to be high. I reviewed AEs, in particular intercurrent infections such as upper respiratory tract infections, as a potential extrinsic factor contributing to variability in response. There did not appear to be a clear relationship between intercurrent illness and difference in Phe response. This trial did not collect information on intrinsic factors, such as genotype, that may potentially impact blood Phe response.

Dr. Kim also commented on the acceptability of the assays used for biopterin and blood Phe levels. She reviewed the validation information for the biopterin assay used in the trial and found the assay method to be acceptable. She noted that use of multiple local laboratories to measure blood Phe levels was acceptable since individual patients were assessed in a consistent manner and served as their own references. The applicant also provided information from a phenylalanine testing equivalency analysis that was conducted by the applicant for a prior trial. The report demonstrated comparable results across local laboratories used in Kuvan trials (see the clinical pharmacology review of

the original submission for more details). The applicant also cited published reports comparing various analytical methods and collection methods for measuring blood Phe. These reports demonstrated that variation in Phe levels across methods ranged from 10 to 15%.[12]

4.4.3 Pharmacokinetics

(b) (4)

Figure 3: PKU-015 Population PK Sub-study- Proportion of Responders at Week 4 vs. Kuvan exposure (AUC_{ss})

300

Source: Clinical Pharmacology review dated February 18, 2014, Figure 3

[12] NDA 22-181 SD-369 Response to FDA Information Request submitted January 17, 2014

Dr. Kim summarized exposure-response information in other age groups, noting that a dose-response relationship has not been studied in patients younger than 8 years. She cited the dose-response relationship findings for PKU-004, a prior open-label, forced dose-titration study in patients older than 8 years that was reviewed during the original submission. Statistically significant differences were observed in mean change in blood Phe between dose groups (5,10, and 20 mg/kg/day). In addition, the percentage of patients who were Phe responders increased as the dose increased. No apparent relationship was observed between Kuvan and the incidence of AEs.

4.4.4 Metabolism

The current labeling for Kuvan includes a warning of potential drug interactions with drugs that inhibit dihydropteridine reductase (DHPR) and information on the metabolic pathway of BH4. Outstanding PMCs for Kuvan include the following *in vitro* studies:

- Evaluation of potential inhibitory effects of Kuvan on activity of major cytochrome P450 enzymes including but not limited to CYP3A4
- Evaluation to determine if Kuvan is an inducer of CYP3A4
- Evaluation of potential effects of Kuvan on activity of transporters including p-glycoprotein and breast-cancer-resistance protein

4.4.5 Clinical Pharmacology Labeling Recommendations

Starting Dose

(b) (4)

given the observed decreases in blood Phe below the target range for blood Phe control, Dr. Kim recommended that the labeling include language about excessive decrease in blood Phe levels in addition to language about close monitoring of blood Phe levels.

Method of Administration

Dr. Kim noted that Kuvan was administered to PKU-015 patients in smaller amounts of liquid (5mL or less) and in addition foods than those included in the current labeling. She recommended that labeling be updated to include the methods of administration used in the trial, pending review and approval of stability data by CMC.

Reviewer Comments:
This reviewer has some concerns about the risk-benefit profile of Kuvan in children, particularly children younger than 7 years old, at the higher starting dose of 20 mg/kg. As discussed later, events of hypophenylalaninemia were reported for this trial and a prior clinical trial (PKU-0004) in children treated with Kuvan doses of 20 mg/kg. The

reported events underscore the need for adequate blood Phe monitoring in pediatric patients. Because Phe is an essential amino acid necessary for growth and development, children are particularly vulnerable to the deleterious effects of both elevated Phe levels and very low Phe levels. This reviewer acknowledges that some patients will not respond to a 10 mg/kg dose. However, the current labeling states that the dose of Kuvan may be increased from 10 mg/kg to 20 mg/kg if there is no response to the lower dose. Therefore, from a safety perspective I do not recommend (b) (4) *20 mg/kg in children younger than 7 years old.*

I agree with Dr.Kim's recommendations regarding adding language about monitoring for excessively low Phe levels as well elevated Phe levels. I also concur with her recommendation to update labeling regarding compatible foods for administration of Kuvan.

4.4.6 Clinical Pharmacology Action Recommendation

Approval (pending agreement upon product labeling)

5 Sources of Clinical Data

The applicant submitted the final clinical study report (dated July 21, 2013) for two sub-studies for trial PKU-015, including a population PK study and a safety/efficacy study. PKU-015 is a 7-year trial to evaluate the safety and efficacy of Kuvan on neurocognitive outcomes, blood Phe concentration, and growth on children ages 0 to 6 years. The applicant also referenced all Period Drug Adverse Event Reports (PADERs) filed since market approval up through the most recent reporting period prior to submission of this efficacy supplement (from December 2007 to December 2012).

5.1 Tables of Studies/Clinical Trials

The clinical development program for Kuvan for hyperphenylalaninemia includes 10 Phase 1 PK studies, nine Phase 2 and 3 clinical trials to evaluate safety and efficacy, and three post-marketing registries to evaluate long-term safety (see Table 4). With the exception of PKU-015, all pre-marketing clinical trials have been completed. Post-marketing registries include a general patient registry, a pregnancy registry, and a registry for neurocognitive outcomes in pediatric patients. The applicant also listed the completed post-marketing registry for Biopten (a sapropterin formulation that has marketing approval in Japan).

Table 4: Kuvan Clinical Trials

Trial	Phase	N	Design	Type of Study	Sapropterin Dosing (mg/kg/day)	Study population	Duration	Status
PK studies								
PKU-005	1	28	OL, R, Crossover	PK fed vs. fasted orange juice vs. water	10 mg/kg X1 dose PO	Healthy adults	4 single doses 7 days apart	completed
PKU-009	1	12	OL, R, Crossover	PK Intact vs. dissolved Fed vs. fasted	10 mg/kg X1 dose PO	Healthy adults	3 single doses 7 days apart	completed
P1501 **PHN-111-PK-SR** (safety report for P1501)	1	12 6 single dose/ 6 repeat dose	OL, R	PK Metabolism Safety	100 or 200 mg X 1 dose PO or 100 mg TID PO	Healthy adults	2 single doses 7 days apart Repeat dose 7 days	completed
FB1602	1	6	PC,R	PK Safety	200 mg TID PO	Healthy adults	7 days	completed
FB1701	1	6	OL	PK Safety	200 mg TID PO	Healthy adults	7 days	completed
PKU-004 Substudy 02	2	78	OL	PK	5-20 mg/kg repeat dose PO	PKU patients	26 weeks	completed
PKU-001 Substudy 01	2	11	OL	PK	10 mg/kg single dose PO	PKU patients	24 hours	completed
PKU-004 Substudy 01	2	12	OL	PK	10 mg/kg single dose PO	PKU patients	24 hours	completed
PKU-0013	1	32	OL, R, Crossover	PK Intact vs. dissolved Fed vs. Fasted	10 mg/kg single dose PO	PKU patients	3 single doses 7 days apart	completed
PKU-015 Substudy 2	3	94	OL	Population PK	20 mg/kg repeat dose PO	PKU patients ages 0-6 years	4 weeks	completed

Table 4: Kuvan Clinical Trials (cont'd)

Trial	Phase	N	Design	Type of Study	Sapropterin Dosing (mg/kg/day)	Study population	Duration	Status
Efficacy & Safety								
PKU-003	3	88 (41 active) (47 placebo)	PC, R, DB	Efficacy Safety	10 mg/kg repeat dose PO	PKU Patients	6 weeks	completed
PKU-006	3	Part 1: 90 Part 2: 46 (33 active) (12 placebo)	Part 1:OL Part 2: PC, R, DB	Efficacy Safety	20 mg/kg repeat dose PO	PKU Patients	Part 1: 8 days Part 2: 10 weeks	completed
PKU-001	2	489	OL	Efficacy Safety	10 mg/kg repeat dose PO	PKU Patients	8 days	completed
PKU-004	3	80	OL	Efficacy Safety Dose Ranging	5-20 mg/kg repeat dose PO	PKU Patients	Part 1: 10 weeks Part 2: 12 weeks	completed
PKU-007	2	12	OL	Efficacy Safety	2.5-20 mg/kg repeat dose PO	BH4 deficiency patients	147 days to 960 days	completed
PKU-015	3	95	OL	Long-term Efficacy & Safety	20 mg/kg repeat dose PO	PKU patients ages 0-6 years	7 years	Ongoing
PKU-015 Substudy 1	3	95	OL	Efficacy Safety	20 mg/kg repeat dose PO	PKU patients ages 0-6 years	6 months	Completed
Safety								
PKU-008	3	111	OL	Long-term Safety	5-20 mg/kg repeat dose PO	PKU patients	56 days to 953 days	Completed
SEAP-01	3	Up to 500	Expanded Access Program	Long-term safety	5-20 mg/kg repeat dose PO	PKU patients	Until commercially available	Completed

Table 4: Kuvan Clinical Trials (cont'd)

Trial	Phase	N	Design	Type of Study	Sapropterin Dosing (mg/kg/day)	Study population	Duration	Status
Post-marketing								
PKU-011	4	~100	Post-market Registry	Safety (Pregnancy)	5-20 mg/kg repeat dose PO	PKU patients	Until 1 month post-delivery	Status not provided
PKU-012	4	~60	Post-market Registry	Long-term safety (Neurocognitive Outcomes)	5-20 mg/kg repeat dose PO	PKU patients	Up to 10 years, or until patient is 15 years old	Ongoing
PKUDOS	4	Up to 5000	Post-market Registry	Long-term safety	2.5-20 mg/kg repeat dose PO	PKU & BH4 deficiency patients	Up to 10 years	Ongoing
20040503*		30	Post-market Registry	Long-term safety	Not available	PKU & BH4 deficiency patients	10 years	Completed

*Post-marketing surveillance study for Biopten- a sapropterin formulation that has marketing approval in Japan.

5.2 Review Strategy

This section provides a brief description of the trial design for the population PK sub-study (Sub-study 2) and a detailed discussion of trial design and efficacy results for the 6 month safety/efficacy sub-study (Sub-study 1). I will refer to the sub-substudies by number (i.e., Sub-study 1 or Sub-study 2) for the remainder of this review.[13] Results for Sub-study 2 are reviewed in Section 4.4. Safety data for both sub-studies are reviewed in Section 7.

Safety data for both trials are discussed in Section 7.

5.3 Discussion of Individual Studies/Clinical Trials

PKU-015 is an ongoing Phase 3b, multicenter, multinational, open-label trial to evaluate the effect of Kuvan on neurocognitive function, maintenance of blood Phe concentrations, safety, and population PK in pediatric patients with PKU ages 0 to 6 years. The trial is comprised of 2 parts, including a 4-week trial designed to identify BH4-responders (Part 1) and a 7-year trial to evaluate long-term neurocognitive function (Part 2). PKU-015 is being conducted at 20 sites in the United States (12 sites) and Canada (8 sites).

The two stub-studies were conducted as part of the long-term trial (see Figure 4). The trial period for the two sub-studies was from May 27, 2009 to September 19, 2012.

[13] N.B. These are the sub-study numbers as per the study protocol for PKU-015. The PWR refers to the population PK sub-study as Study 1 and the 6-month safety/efficacy study as Sub-study 2.

Figure 4: Schematic Diagram of PKU-015 Including Patient Disposition for Sub-studies 1 & 2

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Figure 9.1

5.3.1 PKU-015 Sub-study 2 (Population PK Study)

This was a 4-week open-label PK study. Pediatric patients 6 years and younger at study entry were eligible for participation. Trial participants received Kuvan 20 mg/kg/day as a single dose for 4 weeks. Safety assessments were the same for Sub-study 1 and Sub-study 2 (see Section 5.3.2 for further details).

Of 94 enrolled patients, 93 patients (99%) completed the sub-study; 80 patients (86%) were included in the population PK analysis. Patient excluded from the population PK analysis included one patient whose post-dose blood sample was not collected and 13 patients whose blood samples were not analyzed within the established 161-day stability period. Fifty-seven patients who met the protocol criterion for Kuvan responder (.i.e., ≥30% reduction in blood Phe) were enrolled in the 6-month safety/efficacy sub-study. Six Kuvan responders discontinued after completing Sub-study 2 due to: noncompliance with the study protocol (3 patients), an AE, patient erroneously classified as non-responder, and outlying blood Phe level (1 patient each). Eight patients who were non-responders as defined by the protocol were deemed to be "clinical responders." Seven of the eight patients were determined to have elevated Phe levels due to: dietary Phe overcorrection (4 patients), illness (1 patient), or post-operatively (1 patient); six patients were granted an exemption based on an alternative blood Phe reading that met protocol criteria.[14] The eighth "clinical responder" was a patient who had a 29% blood Phe reduction. The eight "clinical responders" also were enrolled in Sub-study 1 after completion of Sub-study 2.

Major protocol deviations were documented for 18/93 patients (19%), including study assessment performed outside the time window (11 patients), procedures not performed (5 patients), and eligibility criteria not met (3 patients).[15] Clinic visits that occurred >3 days outside of the visit window for the weekly study visits were considered to be major protocol violations. Other major deviations categorized as outside of the visit window and/or procedures not done included missed baseline urinalysis assessments. Minor protocol deviations were documented for 88/93 patients (95%), including procedures not done (87%), study assessment performed outside the time window (55%), and dosing irregularities (17%).

As noted earlier, the population PK analysis was performed using data pooled from PKU-004 and PKU-015. The sub-study was powered to achieve confidence intervals for clearance (CL/F) and volume of distribution (V/F) for each age group that were within

[14] The four patients who experienced an "overcorrection" of dietary Phe all experienced blood Phe levels <120 µmol/L during the first two weeks of treatment that were treated by an increase in dietary Phe; three of the 4 patients had blood Phe levels <240 µmol/L at Week 0. The patients' blood Phe levels following the increases in dietary Phe were <30% lower than their baseline blood Phe levels.

[15] Two patients had received Kuvan within 30 days of screening (an exclusion criterion) and were granted exemptions after an abbreviated Kuvan washout period. A third patient had only one blood Phe level to document blood Phe control (two were required per protocol) at screening and was granted an exemption because blood Phe was controlled rapidly in response to parenteral change in dietary Phe.

60% to 166% of the geometric mean. The results of Sub-study 2 are summarized in Section 4.4 (also see the Clinical Pharmacology review for further details).

Reviewer Comments:
As noted earlier, the two sub-studies were conducted to fulfill a post-marketing commitment (PMC #1) and the PWR. In this reviewer's opinion, the application has fulfilled the requirements for PMC #1 but has not fulfilled all of the requirements for the PWC. Specifically, Sub-study 2 did not fulfill a key requirement of the PWR: enrollment of sufficient numbers of patients in the population PK study to ensure adequate enrollment for the safety-efficacy study (Sub-study 1). The PWR for Kuvan stated that a minimum of 60 patients who are BH4-responders (defined as a >30% decrease from baseline blood Phe levels after 4 weeks of treatment) must be enrolled in the 6-month safety/efficacy study. As noted above, only 57 patients met the criterion for BH4 response. As a result, overall enrollment requirements for Sub-study 1 were not met. In addition, the minimum enrollment requirement for patients in the 4 to <7 age group was not met.

Protocol deviations are another potential issue in regard to meeting the terms of the PWR. The PWR required intensive monitoring after receipt of the first dose of Kuvan, including vital signs and electrocardiogram monitoring performed at specific time intervals up to 3 hours and 6 hours post-dose, respectively. The applicant classified the missed vital signs as minor protocol deviations. Because the missed assessments did not impair the ability to evaluate for safety, this reviewer agrees with the applicant's assessment that these were minor deviations. Furthermore, from a practical standpoint, this reviewer notes that it is not always possible to obtain frequent, accurate vital signs (the PWR required vital signs monitoring every 15 minutes for the first hour) in babies and young children, who may be crying or struggling during assessments. Therefore, in this reviewer's opinion, the applicant made a good faith effort to comply with this particular safety monitoring requirements. I did not identify any other issues regarding the PWR's specifications for safety monitoring.

5.3.2 PKU-015: Sub-study 1 (6-month Safety & Efficacy Study)

A. General Design and Objectives

This trial was a 6-month, open-label, one-arm trial to evaluate safety, efficacy, and baseline neurocognitive function in patients with PKU ages 0 to 6 years. Neurocognitive function was measured using an age-appropriate instrument (Bayley Scales of Infant and Toddler Development-3rd edition, Wechsler Intelligence Scale for Children [WISC]-4th edition, and Wechsler Preschool and Primary Scale of Intelligence

[WPPSI]-3rd edition). Patients who had completed Sub-study 2 and were BH4-responders were eligible for participation.[16]

As noted earlier, amendments to the trial included revisions to the age criterion and size of age cohorts, additional information regarding control of blood Phe during the trial, changed method of administration (dissolved tablets only), additional safety assessments, and additional neurocognitive assessments (Bayley every 6 months for patients up to age 2.5 years).

The PWR stipulated that a minimum of 60 BH4-responsive patients must be enrolled in a 6-month safety and efficacy study, with at least 10 patients under one year of age, at least 20 patients under 2 years of age, 20 patients age 2-4 years and 20 patients age 4-6 years at the time of entry into the study.

Study Objectives

The primary objective of Sub-study 1 was to evaluate the safety of Kuvan in BH4-responsive children with PKU ages 0 to 6 years, inclusive, at trial entry. The secondary objectives of the sub-study were:

- to evaluate the efficacy of Kuvan in controlling blood Phe concentration below 240 µmol/L in children with PKU ages 0 to 6 years, inclusive, at trial entry
- to provide baseline neurocognitive data for BH4-responsive patients and 6 month Bayley data for patients ages 0 to 2 years old, inclusive, at trial entry

B. Inclusion Criteria

- Age 0 to 6 years inclusive at trial entry
- Established diagnosis of PKU (based on at least 2 blood Phe concentration > ≥360 µmol/L obtained at least 3 days apart)
- Documented blood Phe control (as defined by the standard used at each treatment center) and willingness to adhere to a prescribed Phe-restricted diet in order to maintain blood Phe concentration ≤ 240 µmol/L
- Completion of Week 4 visit in Part 1 (i.e., completion of Sub-study 2)
- Response to Kuvan during Part 1 (Sub-study 2)- defined as ≥ 30% average reduction in blood Phe concentration calculated as the mean of the weekly percent change from baseline in blood Phe concentration at Weeks 1, 2, 3, and 4
- Baseline score >80 on the cognitive sub-score (Bayley) or full scale IQ (WPPSI or WISC) for participation in Part 2 of PKU-015 (including Sub-study 1)

[16] One patient refused participation in the PK study but enrolled in the 6-month sub-study and continued treatment in the ongoing long-term trial.

C. Exclusion Criteria

- Known hypersensitivity to Kuvan or its excipients
- Use of Kuvan or any investigation agent within 30 day of screening or during study
- Concurrent disease or condition that would interfere with trial participation, compliance or safety, or patients (or parents) perceived to be unreliable or unavailable for trial participation
- Concomitant use of inhibitors of folate synthesis (e.g., methotrexate) or phosphodiesterase type 5 inhibitors (PDE5 inhibitors; e.g., sildenafil)
- Established diagnosis of primary BH4 deficiency
- History of organ transplantation
- Serious neuropsychiatric illness (e.g., major depression) not currently under medical control
- Non-responders to Kuvan

Individual Patient Withdrawal Criteria

- Serious or intolerable AE
- Clinically significant laboratory abnormality
- Protocol-prohibited medication required
- Failure to adhere to protocol-specified study requirement
- Failure to meet entry criteria or erroneous study enrollment
- Loss to follow-up
- Pregnancy

Study Stopping Criteria

The protocol did not list specific study stopping criteria.

D. Endpoints

The primary endpoint for the trial was safety. The primary efficacy endpoint for the sub-study was change in blood Phe level from baseline to 6 months. Other efficacy endpoints included growth and neurocognitive development.

E. Treatment

Dosing and Method of Administration

Patients received Kuvan doses of 20 mg/kg/day administered as a dissolved or crushed tablet in water, juice, or soft food. Dosing was determined using a weight-based dosing table for infants up to 10 kg. For infants weighing $\leq$ 5 kg, a single Kuvan table (i.e., 200 mg) was dissolved in 5 ml of water or apple juice and a portion of the solution corresponding to 20 mg/kg was administered with an oral dosing syringe. For patients

weighing > 10 kg who were able to take medication from a cup or glass, the calculated weight-based dose could be rounded to the nearest whole tablet. Patients were instructed to take the Kuvan dose within 15 minutes of dissolving or mixing the tablet.

Kuvan dosing for patients in Sub-study 1 began during Part 1 (Week 0 to Week 4) of the 7-year neurocognitive trial. The first Kuvan dose in Week 0 was administered under observation at the clinic site. The remaining doses in Part 1 were administered daily with food. Patients were instructed to take Kuvan at the same time each day. No dose adjustments were allowed during Part 1 without consultation with the medical monitor. After Week 5, at the investigator's discretion, a dose reduction was allowed for patients who did not tolerate 20 mg/kg/day.

Dietary Protocol Restrictions

Patients were instructed to adhere to a Phe-restricted diet with no changes for the first four weeks of the trial.[17] Patients were instructed to record a diet record for the 3 days preceding each clinic visit. At each clinic visit, a study dietician reviewed dietary records and modified prescribed Phe as per clinic guidelines as needed to maintain adequate intake for growth and development. For patients with blood Phe levels outside the target range of 120 to 240 µmol/L, prescribed Phe intake was modified by gradually increasing or decreasing Phe supplements (5 to 20 mg/kg/day). Patients with adequate Phe supplementation could be prescribed natural protein foods rather than Phe-containing supplements.[18]

Reviewer Comments:
The PWR required that all patients in both the population PK study and the 6-month safety and efficacy study must have their diet controlled for Phe intake at entry and throughout the study. The PWR did not provide specific criteria for achieving dietary control, such as a requirement for patients to remain on a stable amount of dietary Phe or a requirement that the same definition of dietary Phe control be applied to both sub-studies. Furthermore, there do not appear to have been any specific discussions or recommendations regarding this issue during the Division's meeting with the applicant in September 2008, which was held to discuss revisions to the sub-study protocols. Therefore, the applicant was given some discretion on how to define controlled dietary Phe intake.

The applicant defined dietary control as documented blood Phe control (<u>as defined by the standard used at each treatment center</u> [underlined for emphasis]) and adherence to a prescribed Phe-restricted diet to maintain control. Note that the protocol only

[17] Prescribed increases in dietary Phe were allowed during the first four weeks of the trial if a patient's blood Phe level decreased to <120 µmol/L.
[18] Adequate Phe supplementation was defined as four stable Phe values (obtained during study or non-study visits) without diet supplementation.

required patients to maintain a stable diet during the first four weeks of the sub-study. Dietary Phe increases were allowed at any point during the trial to maintain blood Phe levels above 120 µmol/L and dietary Phe decreases were allowed after Week 5 to reduce blood Phe level to below 240 µmol/L or due to intolerability.

This reviewer considers the applicant's definition of dietary Phe control to be a plausible interpretation of the PWR's dietary Phe restriction requirement for the study. However, a review of Sub-study 1 dietary Phe management data indicates that there were 10/65 patients (15%) who had diet modifications at some point that were not per protocol (see Table 5). Thus, because the sub-study did not adequately maintain the applicant's own specifications for dietary Phe control, this reviewer does not feel that the sub-study met the PWR requirement that patients maintain controlled dietary Phe intake throughout the study.

Table 5: PKU-015 Sub-study 1- Dietary Phe Modifications That Were Not Per Protocol

Patient ID	Study Day	Modification Description	Reason
0109-1002	115	Reduced Phenex 2 formula intake	Patient not on dietary Phe restriction
0124-1020	29, 56, 86, 113, 148, 183	Increased dietary Phe (estimated intake)	Dietary Phe not prescribed; patient breastfed
0129-1003	33	Increased dietary Phe	Less than typical formula intake
0146-1001	44	Increased dietary Phe	Blood Phe 120 µmol/L; parent & PI agreed to liberalize diet
0146-1002	80 117 136	Increased dietary Phe Decreased dietary Phe Increased dietary Phe	Liberalize diet Parental adjustment Increased to reflect actual intake
0321-1001	89 141	Increased dietary Phe Increased dietary Phe	As per study dietician- no explanation provided As per study dietician- no explanation provided
1017-1001	111	Increased dietary Phe	Phe level was better
1018-1004	69	Decreased dietary Phe	Febrile illness
1018-1006	27	Increased dietary Phe	Food records indicated liberalized diet
1063-1001	70	Increased dietary Phe	Accidental increase X 3 days

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), *Listing 16.2.6.2.1*

Irrespective of PWR requirements, the applicant's definition of dietary Phe control is inadequate for assessing whether treatment with Kuvan provides additional clinical

benefit compared to dietary intervention alone. As discussed later, because a significant proportion of patients were not on a stable Phe diet throughout the sub-study, the ability to evaluate efficacy based on blood Phe results was limited.

Trial Schedule of Assessments

The sub-study was comprised of a screening period, a treatment period, and a termination/early withdrawal visit. Table 7 summarizes the schedule of assessments.

- **Screening**

Screening assessments included vital signs, height, weight, head circumference, physical examination, laboratory testing (hematology, serum chemistry, and urinalysis), electrocardiogram (ECG), pregnancy testing, blood Phe, tryptophan, and tyrosine concentrations, and concomitant medications.

- **Treatment Period**

During the treatment period, clinic visits and trial assessments were scheduled weekly for the first four weeks (Week 0 to Week 4) and then monthly up to Month 6. Vital signs, weight, blood Phe, concomitant medications, and adverse events (AEs) were assessed at every visit. Laboratory tests (hematology, serum chemistry, and urinalysis) were assessed at every visit except Week 2. Height, head circumference, and physical examination were assessed at Week 0, Week 4, Month 3, and Month 6. Pregnancy testing was assessed at Week 0, Week 4, and Month 6. ECG was assessed at Week 0 after the first Kuvan dose. Neurocognitive function testing was performed at Months 2 and 6. Tryptophan and tyrosine concentrations were assessed at Week 4 and Months 3 and 6. PK sampling was performed for Sub-study 2 at Week 0 to Week 4.

Urinalysis, blood Phe, and erythrocyte sedimentation rate (ESR) assessments for the sub-study were analyzed at each site's local laboratory. All other laboratory assessments were analyzed at central laboratories (see Table 6).

Table 6: Central Laboratories for PKU-015

Laboratory	Assessments
(b) (4)	Plasma Kuvan concentration
	Blood chemistry Hematology Tryptophan/tyrosine
	Blood chemistry Hematology Tryptophan/tyrosine

- **Termination/Early Withdrawal and Follow-up for SAEs**

Patients who completed the sub-study were contacted by telephone for follow-up to assess adverse events and concomitant medications. For patients who terminated early, early termination visit assessments included vital signs, weight, height, head circumference, physical examination, laboratory tests, pregnancy test, tryptophan and tyrosine concentrations, adverse events and concomitant medications. Patients with ongoing serious adverse events (SAEs) at the time of termination were followed up until resolution or stabilization of the event.

Table 7: PKU-015 Schedule of Assessments

Assessment	Screening	Part One					Part Two (7 years, ongoing)						
		6-Month Safety/Efficacy (Sub-study 1)										Neurocognitive Function and Long-term Safety	Follow-up or Early Termination
Sub-study Month		1					2	3	4	5	6		
		4-week Pop PK (Sub-study 2)											
Sub-study Week		0	1	2	3	4							
Informed consent	X												
Medical history/ demographics	X												
Entry criteria	X						X						
Vital signs	X	X	X	X	X	X	X	X	X	X	X		X
Weight	X	X	X	X	X	X	X	X	X	X	X		X
Height/head circumference	X	X				X		X			X		X
Physical Examination	X	X				X		X			X		X
Laboratory tests	X	X	X		X	X	X	X	X	X	X		X
Electrocardiogram		X											
Pregnancy test	X	X											X
Phe concentration	X	X	X	X	X	X	X	X	X	X	X		
Tryptophan/tyrosine concentration	X					X		X			X		X
Dispense Kuvan		X	X	X	X	X	X	X	X	X	X		
Phe prescription	X	X	X	X	X	X	X	X	X	X	X		X
PK sampling		X	X	X	X	X							
Neurocognitive test							X				X	X	
Adverse events		←											→
Concomitant medications	X	←											→
Telephone contact													X

Reviewer Comments:
The schedule of assessments was adequate for assessing safety. However, the trial was not designed adequately to assess for long-term efficacy based on changes in blood Phe levels. As noted earlier, patients were maintained on a stable Phe diet only for the first four weeks of the trials. Although the majority of patients remained on the same Kuvan dietary Phe intake or had increases of ≤10 mg/kg/day, a significant proportion of patients received larger increases in dietary Phe intake (range was 23% of patients age 4 to <7 to 60% of patients ages 0 to <1). Thus, there was limited ability to interpret the degree to which changes in dietary Phe intake versus treatment with Kuvan affected blood Phe levels.

Concomitant Medications
All medications taken during the trial were recorded. Patients were prohibited from taking drugs known to inhibit folate synthesis (e.g., methotrexate). As noted earlier, patients taking levodopa were excluded from the trial.

Safety Considerations/Monitoring
Safety was evaluated through the assessment of AEs, vital signs, electrocardiogram, and physical examination. Clinical safety laboratory analyses included serum chemistry, urinalysis, hematology, and blood Phe concentration. Pregnancy screening was performed for female patients of childbearing potential. The safety monitoring period was from the time that a patient provided informed consent until the patient's final study visit. Patients with ongoing SAEs at the time of termination from the trial were followed until the events were resolved or stabilized. Patients with unresolved AEs that were not SAEs could be followed up beyond the conclusion of the trial, if the investigator and trial medical monitor jointly determined that continued follow-up was warranted. There was no Data Monitoring Committee for the ongoing PKU-015 trial or the sub-studies.

The protocol noted that the trial could be discontinued at any time for clinical or administrative reasons but did not provide specify safety-related study stopping criteria. Safety-related individual patient withdrawal criteria were:

- Patient experiences a serious or intolerable AE
- Patient experiences a clinically significant laboratory abnormality
- Patient requires medication prohibited by the protocol
- Patient does not adhere to protocol requirements
- Erroneous admission into the trial or failure to meet eligibility criteria
- Patient lost to follow-up
- Patient becomes pregnant

F. Statistical Analysis Plan

The statistical analysis plan (SAP) consisted of summary statistics for safety, including summaries of AEs by method of study drug administration (dissolved versus intact tablets). The initial SAP also included summary statistics for blood Phe levels, including the proportion of patients and percentage of laboratory values for each patient that remained within the target range specified in local clinical site guidelines.

Analysis population

The analysis population for the trial included all patients who received at least one dose of trial medication.

Determination of Sample Size

The sample size calculation for the sub-study was based on the primary efficacy endpoint (neurocognitive function as measured by IQ score) for the 7-year trial, which assumed that each patient would have two two post-dose results from tests administered at least two years apart. A minimum sample size of 60 patients was selected for Sub-study 1 to achieve a sample size of 45 patients for the long-term trial (sample size required to achieve 90% power based on a mean baseline IQ score of 100 [±15] and a 2-sided type I error rate of 0.05). As noted earlier, the minimum numbers of patients in each age group were agreed upon with the Division.

Additional Analyses

Although the applicant stated that there were no changes to or deviations from the SAP for the sub-study, the efficacy analyses, which included both protocol-defined Phe responders and "clinical responders," constitute a deviation from the original SAP. The applicant also performed sensitivity analyses for the efficacy endpoints that excluded the patients classified as "clinical responders."

Missing Data

Statistical analyses were based on observed data only.

G. Patient Disposition

Patient Disposition

A total of 65 patients participated Sub-study 1¸ including 8 patients that did not meet the protocol definition of Phe responder who were granted exemptions to enroll. Sixty-three patients (97%) completed the trial; two patients (3%) discontinued after experiencing an adverse event (abdominal pain and hoarseness).

Table 8: PKU-015 Sub-study 1- Patient Disposition

Disposition	Protocol-Defined Phe Responders	"Clinical" Phe Responders	Total N (%)
Enrollment in trial	57(100%)	8 (100	65(100%)
Completion of trial	55 (96%)	8 (100%)	63(97%)
Discontinuations Reason: • AE	2 (4%) 2 (4%)	0	2(3%) 2 (3%)

Reviewer Comments:
The PWR stipulated a minimum enrollment of 60 patients who were Phe responders for the 6-month safety and efficacy study. Because only 57 patients met the protocol definition of Phe responder, Sub-study 1 does not fulfill the PWR minimum requirement for overall enrollment. In addition, only 13 patient were enrolled in the 4 to <7 age group (minimum enrollment for this age group was 20 patients). There were sufficient numbers of patients enrolled to meet the minimum PWR enrollment requirements in all other age groups. See Section 9.4 to view the Pediatric Written Request (dated October 31, 2011).

Patient Compliance
Measurements of patient compliance included diet recording, pill count, and attendance at required study visits. The applicant analyzed patient compliance based on the percentage of prescribed Kuvan dose administered, percentage of planned days taking the correct Kuvan dosage, and percentage of planned days taking Kuvan. Patient compliance was reported as 98% to 99% for all age groups for the three compliance analyses. Based on percentage of prescribed Kuvan dose administeredand percentage of planned days taking Kuvan, all patients achieved ≥80% compliance. Based on percentage of planned days taking the correct Kuvan dosage, all but one patient achieved ≥80% compliance; compliance for the remaining patient was 31%.

Reviewer Comments:
The applicant's analyses demonstrated high compliance with the treatment regimen.

Protocol Deviations
Thirty-nine of 65 patients (60%) in Sub-study 1 had at least one major protocol deviation; all 65 patients had at least one minor protocol deviation. Major protocol deviations included procedure or clinic visit that occurred outside of the protocol window (30 patients; 46%), eligibility criteria not met (11 patients; 17%), and procedure not done (7 patients; 11%). Table 10 summarizes major protocol deviations reported for the 6-month safety/efficacy sub-study.

The patients with eligibility criteria deviations were granted exceptions to participate in the sub-study; the majority of these patients were patients who were considered to be

"clinical responders" (see Table 9). Clinic visits that occurred >3 days outside of the visit window for the weekly study visits or >7 days outside the window for the monthly study visits were considered to be major protocol violations. Neurocognitive assessments that were missed or that were performed outside the scheduled window also were considered to be major protocol deviations. Other major deviations categorized as outside of the visit window and/or procedures not done include missed baseline urinalysis assessments and incomplete informed consent procedures (e.g., failure to obtain assent from patients starting at age 7 years; missed signatures on consent forms, etc.).

All other missed or late assessments were considered to be minor protocol deviations. Minor protocol deviations reported in >50% of patients included procedure not done (62 patients; 95%), and procedure or clinic visit that occurred outside of the protocol window (51 patients; 79%). Dosing irregularities, consisting primarily of missed doses, were reported for 26 patients (40%).

Table 9: PKU Sub-study 1- Inclusion and/or Exclusion Criteria Deviations

Patient ID	Age (years)	Site ID	Week 1 Blood Phe (µmol/L)	Category	Deviation
0009-1001	4.5	0009	403	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
0109-1005	6.5	0109	297	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
0109-1007	3.7	0109	551	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
0124-1001	2.5	0124	180	Inclusion	Blood Phe not controlled by diet (had 1 high Phe level)
0124-1007	4.8	0124	94	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
0124-1008	6.5	0124	934	Exclusion	Kuvan treatment within 30 days of study
0124-1013	5.7	0124	384	Exclusion	Kuvan treatment within 30 days of study
0129-1002	6.0	019	252	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
0325-1004	4.5	0325	144	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
1018-1001	5.2	1018	151	Inclusion	Non-responder (i.e. <30% blood Phe reduction)
1067-1002	6.97	1067	252	Inclusion	Non-responder (i.e. <30% blood Phe reduction)

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Listing 16.2.2.1.2

Table 10: PKU-015 Sub-study 1- Major Protocol Deviations

Patient ID	Deviation Category	Description of Deviation
0009-1001	Out of Window Out of Window	Month 4 visit done 8 days outside of window Month 5 visit not done
0109-1005	Eligibility Criteria	Patient exempted as a “clinical responder”
0109-1007	Eligibility Criteria	Patient exempted as a “clinical responder”
0123-1001	Procedure not done	Urinalysis not done at Screening and Week 0
0124-1001	Eligibility Criteria	Patient exempted based on previous Phe levels
0124-1002	Out of Window	Patient not reconsented on revised consent at next study visit during enrollment
0124-1006	Out of Window	Patient not reconsented on revised consent at next study visit during enrollment
0124-1007	Out of Window Eligibility Criteria	Month 2 neurocognitive evaluation completed after Month 3 visit Patient exempted as a “clinical responder”
0124-1008	Eligibility Criteria	Patient exempted for Kuvan use within 30 days of study
0124-1013	Eligibility Criteria	Patient exempted for Kuvan use within 30 days of study
0124-1017	Out of Window	Patient’s parent did not sign revised consent when patient was reconsented
0124-1018	Out of Window	Month 2 neurocognitive evaluation completed after Month 3 visit
0129-1001	Out of Window	Month 3 visit done 13 days outside of window
0129-1002	Eligibility Criteria	Patient exempted as a “clinical responder”
0129-1007	Out of Window Out of Window Out of Window Out of Window	Month 3 visit done 14 days outside of window Month 4 visit done 16 days outside of window Month 5 visit done 14 days outside of window Month 6 visit done 13 days outside of window
0129-1010	Out of Window Out of Window Out of Window	Month 4 visit done 9 days outside of window Month 5 visit done 9 days outside of window Month 6 visit done 8 days outside of window
0129-1014	Out of Window	Month 6 visit done 13 days outside of window
0129-1015	Out of Window Out of Window	Month 5 visit done 12 days outside of window Month 6 visit done 10 days outside of window
0129-1018	Out of Window	Month 5 visit done 8 days outside of window
0146-1001	Out of Window	Week 2 visit done 4 days outside of window
0146-1002	Out of Window Out of Window	Week 3 visit done 4 days outside of window Month 4 visit done 12 days outside of window
0146-1003	Out of Window Out of Window Out of Window Out of Window	Week 1 visit done 4 days outside of window Week 2 visit done 4 days outside of window Week 3 visit done 9 days outside of window Week 4 visit done 7 days outside of window

Table 10: PKU-015 Sub-study 1- Major Protocol Deviations (cont'd)

Patient ID	Deviation Category	Description of Deviation
0146-1004	Out of Window	Month 5 visit done 8 days outside of window
0313-1001	Out of Window	Month 2 neurocognitive evaluation completed after Month 3 visit
0313-1002	Out of Window	Month 2 neurocognitive evaluation completed after Month 3 visit
0325-1001	Out of Window	Month 6 visit done 11 days outside of window
0325-1002	Out of Window Out of Window	Month 4 visit done 10 days outside of window Month 5 visit done 9 days outside of window
0325-1003	Out of Window Out of Window	Month 5 visit done 8 days outside of window Month 6 visit done 15 days outside of window
0325-1004	Eligibility Criteria Out of Window	Patient exempted as a "clinical responder" Month 4 visit done 8 days outside of window
0325-1005	Out of Window	Week 2 visit done 4 days outside of window
0325-1006	Out of Window Procedure not done	Week 2 visit done 4 days outside of window Incorrect neurocognitive assessment done (Bayley was done instead of WPPSI-III)
0325-1008	Out of Window Out of Window Out of Window Out of Window	Week 2 visit done 8 days outside of window Week 3 visit done 7 days outside of window Week 4 visit done 7 days outside of window Month 5 visit done 8 days outside of window
0325-1009	Out of Window	Month 5 visit done 12 days outside of window
0325-1010	Procedure not done	Urinalysis not done at Screening and Week 0
1017-1001	Out of Window	Month 6 visit done 8 days outside of window
1018-1001	Eligibility Criteria Procedure not done	Patient exempted as a "clinical responder" Patient's parent did not sign revised consent when patient was reconsented
1018-1002	Procedure not done Out of Window Procedure not done	Month 3 visit not done due to family emergency Month 4 visit done 13 days outside of window Assent form not given to patient when patient turned 7
1018-1004	Dosing Irregularity	Patient missed 17 doses
1018-1007	Procedure not done	Assent form not given to patient when patient turned 7
1063-1001	Out of Window	Month 6 visit done 11 days outside of window
1067-1002	Out of Window Eligibility Criteria	Week 1 visit done 4 days outside of window Patient exempted as a "clinical responder"
1067-1005	Out of Window Out of Window	Month 4 visit done 23 days outside of window Month 6 visit done 24 days outside of window

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Listing 16.2.2.2

Reviewer Comments:
This reviewer notes that the eligibility deviations reduced the overall sample size of BH4-responsive patients, most significantly for the 4 to <7 age group. The smaller sample size may have implications for the planned the neurocognitive efficacy analysis for the 7-year trial. As noted earlier, the planned enrollment of 60 patients was selected to account for dropouts and provide a sample size of 45 patients.

The applicant provided sensitivity analyses for blood Phe results that excluded patients who were not protocol-defined BH4 responders. Because efficacy endpoints were secondary study endpoints, all efficacy analyses for the sub-study can only be considered as supportive evidence for an efficacy claim.

Based on my review of the safety data, the reported protocol deviations did not appear to affect safety analyses.

H. Demographics
The median age for the overall population for Sub-study 1 was 2.97 years (2 years 11 months) and the age range was from 0.1 years (1 month) to 6.97 years (6 years 11 months). Of 65 enrolled patients, 40 patients were female and 25 patients were male. The majority of patients enrolled in the sub-study were white (85%). The applicant noted that the sub-study population reflected overall PKU incidence and epidemiology as described in published literature.

Table11 summarizes baseline patient characteristics for the Sub-study 1 enrollees. Baseline mean and median values for height and weight percentiles for age were slightly above average (i.e., above 50th percentile) for all age cohorts in the trial; overall mean and median height percentiles were 64th and 79th percentile, respectively, and overall mean and median weight percentiles were 65th percentile and 72nd percentile, respectively. Head circumference was measured in children < 3 years old (up to 2.5 years old). Baseline mean and median head circumferences percentiles for age were near average for all age cohorts between 0 and <3 years of age. Overall mean and median head circumference percentiles for children <3 years of age were 48th percentile and 50% percentile, respectively. Baseline dietary Phe intake ranged from 8 to 98 mg/kg/day. Baseline dietary Phe intake decreased with age; mean dietary Phe intake was 38 mg/kg/day for infants, 26 to 28 mg/kg/day for children younger than 4 years old, and 17 mg/kg/day for children older than 4 years old.

Table 11: PKU-015 Sub-study 1- Baseline Patient Characteristics

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Age at Study Entry (years)					
Mean ± SD	**0.5 ± 0.3**	**1.4 ± 0.3**	**3.0 ± 0.7**	**5.6 ± 1.0**	**3.1 ± 2.0**
Median	0.4	1.2	3.1	5.7	3.0
Min, Max	0.11, 0.98	1.04, 1.97	2.03, 3.99	4.14, 6.97	0.11, 6.97
Sex (N[%])					
Male	6 (55%)	5 (45%)	15 (65%)	14 (70%)	25 (38%)
Female	5 (45%)	6 (55%)	8 (35%)	6 (30%)	40 (62%)
Race (N[%])					
White	9 (82%)	9 (82%)	18 (78%)	18 (90%)	54 (83%)
Asian	1 (9%)	1 (9%)	0	1 (5%)	3(5%)
Black	0	0	1 (4%)	0	1 (<2%)
Other	1(9%)	1(9%)	4 (17%)	1 (5%)	7(11%)
Ethnicity N[%])					
Hispanic	0	0	3 (13%)	0	3 (5%)
Non-Hispanic	11 (100%)	11 (100%)	20 (87%)	20 (100%)	62 (95%)
Country (N[%])					
Canada	5 (45%)	6 (55%)	8 (35%)	10 (50%)	29 (45%)
United States	6 (55%)	5 (45%)	15 (65%)	10 (50%)	36 (55%0
Height (cm)					
Mean ± SD	**64.8 ± 5.7**	**81.0 ± 3.8**	**96.0 ± 7.2**	**114.8 ± 0.3**	**94.0 ± 18.7**
Median	65.5	80.0	95.9	117.0	93.5
Min, Max	56.0, 72.7	77.0, 88.5	81.2, 106.5	103.0, 124.2	56.0, 124.2
Height Percentile					
Mean ± SD	**66± 27**	**66 ± 20**	**62 ± 30**	**64 ± 24**	**64 ± 26**
Median	71	73	68	68	70
Min, Max	<1, 97	32, 98	7, 99	28, >99	<1, >99
Weight (kg)					
Mean ± SD	**7.3 ± 2.0**	**11.1 ± 1.6**	**15.2 ± 2.3**	**21.9 ± 3.5**	**15.2 ± 5.9**
Median	7.4	10.9	14.6	20.7	14.6
Min, Max	4.5, 10.8	8.9, 14.2	12.4, 21.3	18.1, 30.6	4.5, 30.6
Weight Percentile					
Mean ± SD	**63 ± 29**	**52 ± 29**	**66 ± 23**	**71 ± 22**	**65 ± 25**
Median	74	61	70	78	72
Min, Max	8, 97	7, 86	15, 98	27, 99	7, 99
Head Circumference (cm)	(n=11)	(n=11)	(n=11)		(n=33)
Mean ± SD	**42.1 ± 2.9**	**47.3 ± 1.5**	**49.1 ± 1.9**	**N/A**	**46.2 ± 3.7**
Median	43.6	48.0	49.5		47
Min, Max	36.5, 45.0	44.0, 49.5	44.5, 51.5		36.5, 51.5
Head Circumference Percentile	(n=11)	(n=11)	(n=11)		(n=33)
Mean ± SD	**54 ± 21**	**65 ± 27**	**66 ± 31**	**N/A**	**61 ± 27**
Median	55	65	73		64
Min, Max	21, 92	2, 97	1, 99		1, 99

Table 11: PKU-015 Sub-study 1- Baseline Patient Characteristics (cont'd)

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Blood Phe (µmol/L)					
Mean ± SD	**298 ± 120**	**367 ± 107**	**337 ± 135**	**332 ± 159**	**334 ± 135**
Median	298	345	333	331	331
Min, Max	139, 457	228, 589	223, 453	58, 769	58, 769
Dietary Phe (mg/kg/day)					
Mean + SD	**38 ± 18**	**28 ± 6**	**26 ± 17**	**17 ± 5**	**26 ± 15**
Median	33	28	22	17	22
Min, Max	15, 71	22, 39	12, 98	8, 29	8, 98

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013),

Table 12 summarizes the baseline characteristics for the 54 patients who met all eligibility criteria for enrollment. The table excludes the 11 patients that were granted enrollment exemptions, including 2 patients in the 2 to < 4 age group and 9 patients in the 4 to < 7 age group. Note that all patients in the 0 to <1 and 1 to < 2 age groups met all eligibility criteria; baseline values for these age groups are unchanged

In the 4 to <7 age group, baseline blood Phe was slightly higher for fully eligible patients (371 µmol/L) than for the overall age group (332 µmol/L). Otherwise, baseline values were the same or very similar for the fully eligible patients compared to the values for the overall age group in the 2 to <4 and the 4 to <7 age groups.

Table 12: PKU-015 Sub-study 1- Baseline Patient Characteristics for Per-Protocol Eligible Enrollees

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=21)	4 to <7 (n=11)	(n=54)
Age at Study Entry (years)					
Mean ± SD	**0.5 ± 0.3**	**1.4 ± 0.3**	**3.0 ± 0.7**	**5.6 ± 1.0**	**3.1 ± 2.0**
Median	0.4	1.2	3.1	5.7	3.0
Min, Max	0.11, 0.98	1.04, 1.97	2.03, 3.99	4.14, 6.97	0.11, 6.97
Sex (N[%])					
Male	6 (55%)	5 (45%)	15 (71%)	4 (36%)	30 (56%)
Female	5 (45%)	6 (55%)	6 (29%)	7(64%)	24 (44%)
Race (N[%])					
White	9 (82%)	9 (82%)	16(76%)	11 (100%)	45 (83%)
Asian	1 (9%)	1 (9%)	0	0	2 (4%)
Black	0	0	1 (4%)	0	1 (2%)
Other	1(9%)	1(9%)	4 (19%)	0	6 (11%)
Ethnicity N[%])					
Hispanic	0	0	3 (14%)	0	3 (6%)
Non-Hispanic	11 (100%)	11 (100%)	18 (86%)	11 (100%)	51 (94%)
Country (N[%])					
Canada	5 (45%)	6 (55%)	8 (38%)	7 (64%)	26 (48%)
United States	6 (55%)	5 (45%)	13 (62%)	4 (36%)	28 (52%)
Height (cm)					
Mean ± SD	**64.8 ± 5.7**	**81.0 ± 3.8**	**95.9± 7.3**	**115.6 ± 5.9**	**90.5 ± 18.3**
Median	65.5	80.0	95.9	116.3	90.4
Min, Max	56.0, 70.5	77.0, 88.5	81.2, 106.5	106.0, 123.0	56.0, 123.0
Height Percentile					
Mean ± SD	**66± 27**	**67 ± 20**	**61 ± 31**	**67 ± 25**	**64 ± 26**
Median	71	73	68	74	72
Min, Max	<1, 97	32, 98	7, 99	28, >99	<1, >99
Weight (kg)					
Mean ± SD	**7.3 ± 2.0**	**11.1 ± 1.6**	**15.2 ± 2.3**	**22.1± 3.7**	**14.1 ± 5.6**
Median	7.4	10.9	14.6	20.2	13.8
Min, Max	4.5, 10.8	8.9, 14.2	12.4, 21.3	18.1, 30.6	4.5, 30.6
Weight Percentile					
Mean ± SD	**63 ± 29**	**52 ± 29**	**65 ± 24**	**71 ± 21**	**63 ± 26**
Median	74	61	68	78	69
Min, Max	8, 97	7, 86	15, 98	30, 99	7, 99
Head Circumference (cm)	(n=11)	(n=11)	(n=10)		(n=32)
Mean ± SD	**42.1 ± 2.9**	**47.3 ± 1.5**	**49.3 ± 2.1**	**N/A**	**46.1± 3.7**
Median	43.6	48.0	49.8		47
Min, Max	36.5, 45.0	44.0, 49.5	44.5, 51.5		36.5, 51.5
Head Circumference Percentile	(n=11)	(n=11)	(n=10)		(n=32)
Mean ± SD	**54 ± 21**	**65 ± 27**	**64 ± 32**	**N/A**	**61 ± 27**
Median	55	65	73		64
Min, Max	21, 92	2, 97	1, 99		1, 99

Table 12: PKU-015 Sub-study 1- Baseline Patient Characteristics for Per-Protocol Eligible Enrollees (cont'd)

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=21)	4 to <7 (n=11)	(n=54)
Blood Phe (µmol/L)					
Mean ± SD	**298 ± 120**	**367 ± 107**	**339 ± 135**	**371 ± 112**	**334 ± 135**
Median	298	345	333	158	331
Min, Max	139, 457	228, 589	109, 587	533, 385	58, 769
Dietary Phe (mg/kg/day)					
Mean + SD	**38 ± 18**	**28 ± 6**	**26 ± 18**	**17 ± 4**	**26 ± 15**
Median	33	28	21	17	22
Min, Max	15, 71	22, 39	12, 98	11, 24	8, 98

All enrolled patients had a baseline IQ score of at least 80. Table 13 summarizes neurocognitive scores at baseline for the full safety-efficacy population.

Table 13: PKU-015 Sub-study 1- Baseline Neurocognitive Scores

	BAYLEY			WPPSI	WISC
Score:	**Cognitive**	**Language**	**Motor**	**Full Scale IQ**	**Full Scale IQ**
n	27	27	27	34	4
Mean ± SD	**102 ± 9**	**101 ± 13**	**105 ± 12**	**101 ± 11**	**113 ± 10**
Median	105	100	107	102	115
Min, Max	80, 115	79, 127	88, 148	81, 127	101, 122

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 11.2.4

Reviewer Comments:
I reanalyzed neurocognitive results after excluding scores for exempted patients and one patient (patient 0124-0007) who was administered the incorrect neurocognitive test. With the exception of a 1-point difference on the language component of the Bayley (mean score was 100 instead of 101), score results were identical.

I. Concomitant Medications

Concomitant medications were recorded using standardized WHO Anatomical Therapeutic Chemical (ATC) classification codes. The majority of patients (56/65 patients; 86%) reported at least one prior medication, the most common being nutrients without Phe (39%), combinations containing fat, carbohydrates proteins, minerals and/or vitamins (i.e., PKU medical foods; 19%), and anilides (14%). All but one of the 65 enrolled patients reported at least one concomitant medication; the most common therapeutic classes of concomitant medications in the trial were anilides (59%),

nutrients without Phe (39%), proprionic acid derivatives (29%), penicillins with extended spectrum (23%), and influenza vaccines (20%).

Review of Efficacy

Efficacy Summary

The primary efficacy analysis for Sub-study 1 was change from baseline in blood Phe level. Prior to treatment, mean blood Phe levels in all age groups were above the protocol-defined blood Phe control target range (120 to 240 µmol/L) and the overall percentage of patients with blood phe levels > 240 µmol/L was 64 %. At week 4, blood Phe levels were below or within the target range in all age groups and the overall percentage of patients with blood phe levels > 240 µmol/L was 11 %.

Patients were on a stable Phe diet during the first four weeks of treatment and there was adequate and reliable documentation of dietary information and treatment compliance. Thus, the data for this portion of the sub-study are adequate to evaluate whether Kuvan provided additional benefit over dietary management alone. The findings are supportive of short-term efficacy in this patient population.

The study data were inadequate to determine long-term efficacy. Analyses of change in mean blood Phe levels suggest that there is not a sustained response to Kuvan. At month 6, mean blood Phe levels were above the target range in all age groups except for the 2 to <4 age group. At Month 6, the overall percentage of patients with blood phe levels > 240 µmol/L was 29%.

For patients with PKU, the treatment goal is to maintain blood Phe level within a target range. Thus, for patients who had blood Phe levels within or below the target range, there is no clinical benefit in further reduction of the blood Phe levels. Because a number of patients in the sub-study had blood Phe levels within or below the target range prior to treatment, this reviewer considers trends in blood Phe control status to be more informative of a clinically meaningful response than trends in blood Phe levels. Blood Phe levels decreased during the first four weeks of treatment and then increased over time in all age groups. However,blood Phe control status improved in the two younger age groups whereas blood Phe control status did not appear to improve in the two older age groups. These results suggest that there may be age-related differences in treatment response.

However, because diet was not controlled during the remainder of the sub-study, it is unclear whether the observed trends in Phe levels and in changes in blood Phe control were due to increased dietary Phe intake or a reduced response to Kuvan treatment over time. There were additional factors limiting the interpretability of these data,

including the inclusion of patients who were not BH4-responders as defined by the protocol.

This reviewer notes that the long-term efficacy of Kuvan has not been established for any age group. All of the trials conducted to support the original submission were short-term (8 days to 6 weeks). The applicant has conducted an open-label long-term safety trial in older children and adults (PKU-008) that included blood Phe as a secondary endpoint. However, the trial was not adequately designed to evaluate efficacy because dietary Phe intake was not controlled. For demonstration of long-term efficacy on reduction of blood Phe levels, this reviewer recommends that the applicant conduct a trial using a placebo control group (dietary Phe restriction only) with stratification by age.

From a clinical and nutritional perspective, the ability to liberalize a patient's diet would provide significant clinical benefit. However, the trial was not adequately designed to evaluate for efficacy for increased Phe tolerance. (b) (4) the applicant will need to conduct a trial that compares Phe levels of patients receiving increases in dietary Phe and patients receiving increases in dietary Phe and Kuvan with patients stratified by age.

1. Blood Phe Concentration

Baseline mean blood Phe levels at baseline were above the target range of 120 to 240 µmol/L for all age groups. Mean blood Phe for the overall population decreased to within the target range at week 4 (154 µmol/L) and then increased to the upper limit or near the upper limit of the target range at Months 3 (overall mean blood Phe was 240 µmol/L) and Month 6 (overall mean blood Phe was 238 µmol/L).

At week 4, mean blood Phe decreased to below the target range in the 0 to <1 year age group (96 µmol/L). In the other age groups, mean blood Phe decreased to within the target range.

At Month 3, mean blood Phe increased but remained within the target range for all age groups except the 2 to <4 age group (mean blood Phe was 282 µmol/L).

At Month 6, mean blood Phe further increased to just beyond the target range in all age groups except the 2 to <4 year age group. In the the 2 to <4 year age group, mean blood Phe decreased to within the target range at Month 6 (199 µmol/L).

At all time points except Month 6, the lowest mean blood Phe levels were observed in the 0 to <1 age group. At Month 6, the lowest mean blood Phe levels were observed in the 2 to <4 age group.

Table 14 summarizes blood Phe levels by age group.

Table 14: PKU-015 Sub-study 1- Mean Blood Phe levels (µmol/L) by Age Group

	Age Groups				Overall
	0 to <1 (n=11)	**1 to <2 (n=11)**	**2 to <4 (n=23)**	**4 to <7 (n=20)**	**(n=65)**
Baseline					
n	11	11	23	20	65
Mean ± SD	**298 ± 120**	**366 ± 107**	**337 ± 135**	**332 ± 159**	**334 ± 135**
Median	298	345	333	331	331
(Min, Max)	139, 457	(228, 589)	223, 453	58, 769	58, 769
Week 4					
n	11	11	23	20	65
Mean ± SD	**96 ± 53**	**144 ± 99**	**146 ± 165**	**201 ± 169**	**154 ± 145**
Median	79	115	109	147	115
(Min, Max)	(51, 228)	(31, 355)	(12, 823)	(24, 634)	(12, 823)
Month 3					
n	10	11	22	19	62
Mean ± SD	**183 ± 164**	**210± 130**	**282 ± 205**	**240 ± 114**	**240 ± 162**
Median	126	209	238	216	210
(Min, Max)	(35, 591)	(85, 483)	(21, 791)	(81, 527)	(21, 791)
Month 6					
n	11	10	21	20	62
Mean ± SD	**241 ± 146**	**264 ± 391**	**199 ± 140**	**265 ± 122**	**238 ± 195**
Median	212	148	154	223	193
(Min, Max)	(68, 502)	(85, 1370)	(12, 612)	(95, 499)	(12, 1370)

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.2.4

Table 15 summarizes blood Phe levels by age group for protocol-defined BH4 responsive patients. The analysis excludes eight patients (one patient in the 2 to < 4 age group and 7 patients in the 4 to < 7 age group) who were classified as “clinical responders”; all patients in the 0 to <1 and 1 to < 2 age groups were protocol-defined BH4-responders. In the 4 to < 7 age group, baseline blood Phe was slightly higher in BH4-responders (394 µmol/L) compared to the full age group (332 µmol/L). Otherwise, mean blood Phe values for BH4-responders were similar at all time points to mean blood Phe values for the full age group.

Table 15: PKU-015 Sub-study 1- Mean Blood Phe levels (µmol/L) by Age Group for Protocol-Defined BH4-Responders

	Age Groups				Overall
	0 to <1 (n=11)	**1 to <2 (n=11)**	**2 to <4 (n=22)**	**4 to <7 (n=13)**	**(n=57)**
Baseline					
n	11	11	22	13	57
Mean ± SD	**298 ± 120**	**366 ± 107**	**332 ± 136**	**394 ± 155**	**346 ± 134**
Median	298	345	318	385	334
(Min, Max)	139, 457	(228, 589)	109, 587	158, 769	109, 769
Week 4					
n	11	11	22	13	57
Mean ± SD	**96 ± 53**	**144 ± 99**	**116 ± 76**	**175 ± 136**	**131 ± 96**
Median	79	115	105	155	109
(Min, Max)	(51, 228)	(31, 355)	(12, 313)	(51, 563)	(12, 563)
Month 3					
n	10	11	21	12	54
Mean ± SD	**183 ± 164**	**210± 130**	**282 ± 210**	**208 ± 88**	**232 ± 166**
Median	126	209	219	210	206
(Min, Max)	(35, 591)	(85, 483)	(21, 791)	(85, 388)	(21, 791)
Month 6					
n	11	10	20	13	54
Mean ± SD	**241 ± 146**	**264 ± 391**	**198 ± 143**	**289 ± 1214**	**238 ± 195**
Median	212	148	153	278	193
(Min, Max)	(68, 502)	(85, 1370)	(12, 612)	(112, 499)	(12, 1370)

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.2.14

2. Mean Change in Blood Phe

Table 16 summarizes mean change in blood Phe levels by age group for the overall Sub-study 1 population. Mean change in blood Phe from baseline was greatest at Week 4 for all age groups. Mean change in blood Phe was similar for children under 4 years (range was -191 to -222 µmol/L) and slightly less in children over 4 years (mean change was -131 µmol/L). Mean change in blood Phe from baseline subsequently decreased at all time points up to Month 6 for all age groups except the 2 to < 4 age group. For the 2 to < 4 age group, mean change in blood Phe decreased from Week 4 (-191 µmol/L) to Month 3 (-63 µmol/L) and then increased at Month 6 (-135 µmol/L).

Table 16: PKU-015 Sub-study 1- Change from Baseline in Mean Blood Phe Levels (µmol/L) by Age Group

	Age Groups				Overall
	0 to <1 (n=11)	**1 to <2 (n=11)**	**2 to <4 (n=23)**	**4 to <7 (n=20)**	**(n=65)**
Baseline					
n	11	11	23	20	65
Mean ± SD	**298 ± 120**	**367 ± 107**	**337 ± 135**	**332 ± 159**	**334 ± 135**
Median	298	345	333	331	331
(Min, Max)	139, 457	228, 589	281, 393	58, 769	58, 769
Week 4					
n	11	11	23	20	65
Mean ± SD	**-202 ± 119**	**-223 ± 139**	**-191 ± 198**	**-131 ± 233**	**-180 ± 190**
Median	-166	-194	-177	-172	-173
(Min, Max)	-316, -88	-558, -69	-575, 372	-659, 363	-659, 372
Month 3					
n	10	11	22	19	62
Mean ± SD	**-131 ± 236**	**-156 ± 93**	**-63 ± 187**	**-81 ± 197**	**-96 ± 185**
Median	-180	-164	-86	-72	-119
(Min, Max)	-392, 453	-360, 38	-397, 337	-576, 296	-576, 453
Month 6					
n	11	10	21	20	62
Mean ± SD	**-58 ± 207**	**-101 ± 319**	**-135 ± 187**	**-67 ± 174**	**-94 ± 210**
Median	-162	-181	-104	-52	-104
(Min, Max)	-274, 295	-354, 781	-575, 162	-559, 240	-575, 781

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.2.5

Table 17 summarizes mean change in blood Phe levels by age group for protocol-defined BH4-responders. In the 2 <4 age group, mean change in blood Phe over time was similar in BH4-responders compared to the overall age group. In the 4 to < 7 age group, baseline blood Phe was higher but mean change in blood Phe was greater at all time points compared to the overall age group.

Table 17: PKU-015 Sub-study 1- Change from Baseline in Blood Phe Levels (µmol/L) by Age Group (Protocol-Defined BH4-Responders)

	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=22)	4 to <7 (n=13)	(n=57)
Baseline					
n	11	11	22	13	57
Mean ± SD	**298 ± 120**	**367 ± 107**	**332 ± 136**	**394 ± 155**	346 ± 134
Median	298	345	318	385	334
(Min, Max)	139, 457	228, 589	109, 587	158, 769	109, 769
Week 4					
n	11	11	22	13	57
Mean ± SD	**-202 ± 119**	**-223 ± 139**	**-216 ± 159**	**-218 ± 187**	-215 ± 152
Median	-166	-194	-177	-173	-175
(Min, Max)	-316, -88	-558, -69	-575, 10	-659, 103	-659, 103
Month 3					
n	10	11	21	12	54
Mean ± SD	**-131 ± 236**	**-156 ± 93**	**-58 ± 190**	**-174 ± 170**	-117 ± 182
Median	-180	-164	-85	-154	-134
(Min, Max)	-392, 453	-360, 38	-397, 337	-576, 55	-576, 453
Month 6					
n	11	10	20	13	54
Mean ± SD	**-58 ± 207**	**-101 ± 319**	**-131 ± 191**	**-105 ± 183**	**-104 ± 216**
Median	-162	-181	-104	-56	-109
(Min, Max)	-274, 295	-354, 781	-575, 162	-559, 170	-575, 781

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.2.15

3. Blood Phe Control

Tables 17 to 19 summarize the percentage of BH4-responders who achieved blood Phe levels within and outside of the defined blood Phe control range of 120 to 240 µmol/L. Prior to treatment (Week 0) about 11% of all BH4 responders had blood Phe levels below the blood Phe control range (see Table 18). Percentage varied by age group (no patients in the 1 to <2 and the 4 to < 7 age groups had blood Phe levels below the target range; 20%-21% of patients in the 0 to <1 and 2 to <4 age groups had blood Phe levels below the target range). At Week 1 and Week 4, the percentage of patients with blood Phe levels below the target range increased significantly in all age groups, with the highest percentage observed in the 0 to < 1 age group (91%) at Week 1. The percentage of patients with blood Phe levels below the target range decreased from Week 4 to Month 3 in all age groups. At Month 6, the percentage of patients with blood Phe levels below the target range continued to decrease in all age groups except the 1 to <2 age group.

Table 18: PKU-015 Sub-study 1- Percentage of BH4-Responders with Post-Treatment Blood Phe Levels < 120 µmol/L

	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=22)	4 to <7 (n=13)	(n=57)
Week 0					
n/N(%) Mean ± SD Min, Max	2/10 (20%) **91± 13** 81, 100	0/11 (0) -- --	4/19 (21%) **89 ± 44** 24, 119	0/13 (0) -- --	6/53 (11%) **90 ± 34** 24, 119
Week 1					
n/N(%) Mean ± SD Min, Max	10/11 (91%) **69 ± 32** 19, 100	1/11 (9%) **113** --	12/22 (52%) **84 ± 34** 15, 119	6/13 (46%) **59 ±11** 48, 80	29/57 (51%) **75 ± 31** 15, 119
Week 4					
n/N(%) Mean ± SD Min, Max	8/11 (73%) **70 ± 17** 51, 100	6/11 (55%) **71 ± 28** 31, 115	13/22 (59%) **69 ± 35** 12, 115	6/13 (46%) **86 ± 30** 51, 116	33/57 (58%) **73 ± 29** 12, 116
Month 3					
n/N(%) Mean ± SD Min, Max	5/10 (50%) **73 ± 24** 35, 91	4/11 (36%) **100 ± 12** 85, 111	3/20 (15%) **38 ± 19** 21, 58	4/12 (33%) **95 ± 16** 81, 117	16/53 (30%) **79 ± 28** 21, 117
Month 6					
n/N(%) Mean ± SD Min, Max	2/11 (18%) **74 ± 8** 68, 80	5/11 (45%) **103 ± 14** 85, 118	7/20 (35%) **72 ± 1344** 12, 119	1/13 (8%) **112** --	15/55 (27%) **85 ± 34** 12, 119

Table 19 summarizes the percentage of BH4-responders who achieved blood Phe levels in the target range. Approximately 25% of BH4-responders had controlled blood Phe levels at Week 0, with the highest percentage of patients with controlled blood phe in the 4 to < 7 age group (38%) and the lowest percentage in the 1 to < 2 age group (9%). The largest increases in percentage of patients with controlled blood Phe from Week 0 to Month 6 were observed in the 0 to <1 age group (increased from 20% to 50%) and the 1 to < 2 age group (increased from 9% to 45%). There was a slight increase in the percentage of patients with controlled blood Phe from Week 0 to Month 6 in the two older age groups.

Table 19: PKU-015 Sub-study 1- Percentage of BH4-Responders with Post-Treatment Blood Phe Levels 120 to 240 µmol/L

	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=22)	4 to <7 (n=13)	(n=57)
Week 0					
n/N(%)	2/10 (20%)	1/11 (9%)	5/19 (26%)	5/13 (38%)	13/53 (25%)
Mean ± SD	**168 ±18**	**232**	**176 ± 33**	**177 ± 33**	**179 ± 32**
Min, Max	155, 180	--	140, 226	133, 224	133, 232
Week 4					
n/N(%)	3/11 (27%)	3/11 (27%)	7/22 (29%)	5/13 (38%)	18/57 (32%)
Mean ± SD	**166 ±54**	**181 ± 25**	**151 ± 25**	**181 ± 28**	**167 ± 32**
Min, Max	134, 228	159, 208	120, 194	155, 228	120, 228
Month 3					
n/N(%)	3/10 (30%)	4/11 (36%)	8/20 (40%)	4/12 (33%)	19/53 (36%)
Mean ± SD	**194 ±36**	**186 ± 44**	**171 ± 32**	**210 ± 14**	**186 ± 34**
Min, Max	161, 232	120, 212	137, 219	193, 226	120, 232
Month 6					
n/N(%)	6/11 (55%)	5/11 (45%)	7/20 (35%)	6/13 (46%)	24/55 (44%)
Mean ± SD	**192 ± 41**	**175 ± 36**	**172 ± 28**	**189 ± 36**	**182 ± 34**
Min, Max	138, 239	146, 235	147, 206	135, 234	135, 239

Table 20 summarizes the percentage of patients who had blood Phe levels above the target range. Over 60% of all patients had blood Phe levels above the target range at Week 0; over 90% of patients in the 1 to <2 age group had blood Phe levels above the target range at Week 0. At week 4, the percentage of patients with high blood Phe levels decreased in all age groups (range was 0 to 23%). At Month 3, the percentage of patients with high blood Phe levels trended upwards in all age groups (range was 20% to 45%). From Month 3 to Month 6, the percentage of patients with high blood Phe levels increased slightly in the 0 to <1 age group and 4 to <7 age group and decreased in the 1 to <2 age group and 2 to <4 age group.

Table 20: PKU-015 Sub-study 1- Percentage of BH4-Responders with Post-Treatment Blood Phe Levels >240 µmol/L by Age Group

	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=22)	4 to <7 (n=13)	(n=57)
Week 0					
n/N(%)	6/10 (60%)	10/11 (91%)	10/19 (53%)	8/13 (62%)	34/53 (64%)
Mean ± SD	**376 ±123**	**401 ± 117**	**348 ± 95**	**470 ± 209**	**397 ± 14**
Min, Max	275, 592	297, 659	248, 525	254, 934	248, 934
Week 4					
n/N(%)	0/11 (0%)	2/11 (18%)	2/22 (9%)	2/13 (23%)	6/57 (11%)
Mean ± SD	--	**306 ± 70**	**296 ± 25**	**296 ± 1**	**299 ± 34**
Min, Max	--	256, 355	278, 313	295, 297	256, 355
Month 3					
n/N(%)	2/10 (20%)	3/11 (27%)	9/20 (45%)	4/12 (33%)	18/53 (34%)
Mean ± SD	**440 ±214**	**377 ± 120**	**464 ± 193**	**299 ± 68**	**410 ± 166**
Min, Max	288, 591	246, 483	256, 791	242, 388	242, 791
Month 6					
n/N(%)	3/11 (27%)	1/11 (9%)	6/20 (30%)	6/13 (46%)	16/55 (29%)
Mean ± SD	**449 ±18**	**1370**	**373 ± 120**	**376 ± 75**	**451 ± 261**
Min, Max	411, 502	--	274, 612	278, 499	274, 1370

Reviewer Comments:
All of the blood Phe analyses demonstrated a reduction in blood Phe during the initial 4 weeks of treatment in all age groups. Specifically, mean blood Phe decreased to below or within the target range in all age groups and the percentage of patients with blood Phe levels above the target range decreased significantly in all age groups. Note that patients were on a stable Phe diet during this portion of the sub-study and that there was adequate and reliable documentation of dietary information and treatment compliance. Thus, the data are adequate to evaluate whether Kuvan provided additional benefit over dietary management alone. The findings for this portion of the sub-study are supportive of short-term efficacy in this patient population.

The observed increases in mean blood Phe levels from Week 4 to Month 6 suggest that response to Kuvan waned over the course of the sub-study. However, the trends in blood Phe control status suggest that responses to Kuvan varied among age groups. In the two youngest age groups, the percentage of patients with blood Phe levels in the target range improved at all time points. Similarly, the percentage of patients in these age groups with blood Phe levels above the target range decreased over time. These trends suggest that there was continued response to Kuvan in these age groups.
For the two older age groups, although the percentage of patients with blood Phe levels within the target range increased slightly from Week 0 to Week 4, the percentage of patients with blood Phe levels above the target range also increased, suggesting that response decreased over time in these age groups.

This reviewer notes that all of the trials conducted to support the original submission were short-term (8 days to 6 weeks). The applicant has conducted an open-label long-term safety trial in older children and adults (PKU-008) that included blood Phe as a secondary endpoint. However, the trial was not adequately designed to evaluate efficacy because dietary Phe intake was not controlled.

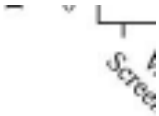
4. Dietary Phe Intake

Qantitative information on prescribed dietary Phe and dietary Phe intake was collected during the trial. Patients were instructed to record dietary Phe intake for the three days prior to each study visit.

Figure 5 presents prescribed daily dietary Phe intake for the overall population (n=65) by age group over the course of Sub-study 1. Baseline daily dietary Phe intake by weight (mg/kg) was highest in the 0 to < 1 age group and decreased with each successive age group.

Dietary Phe intake increased for in all age groups, with slightly higher increases in mean dietary Phe intake observed in the 0 to <1 age group and the 1 to < 2 age group (mean increase was 11 mg/kg/day and 14 mg/kg/day, respectively) compared to the 2 to <4 age group and the 4 to < 7 age group (mean increase was 8 mg/kg/day and 7 mg/kg/day, respectively). With the exception of the 0 to <1 age group, the majority of patients in each age group remained on fairly stable dietary Phe intake over the course of treatment (the percentage of patients whose Kuvan dose was unchanged or changed by ≤10 mg/kg/day ranged from 70% to 77% for patients 1 to <7 years old). In the 0 to <1 age group, 40% of patients remained on the same dose or received a dose change of ≤10 mg/kg/day and 60% of patients received a dose change of >10 mg/kg/day. As noted earlier, DSI inspected dietary records for the sub-study and concluded that dietary data were reliable.

Figure 5: PKU-105 Substudy 1- Prescribed Daily Dietary Phe (mg/kg) by Age Group



o= outlier; ◊= median

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Figure 14.2.12

Reviewer Comment:
Dietary Phe requirements are based on age and developmental considerations; infants require higher dietary Phe intake than older children to maintain adequate growth.

5. Subpopulations

A majority (83%) of the patients in PKU-015 were white. Therefore, there were insufficient numbers of patients in other race categories to perform subpopulation analyses by race. There were no apparent gender differences in blood Phe levels. As discussed, there may be some age differences in response to Kuvan. No neonates were enrolled in the sub-study; therefore no data are available on neonatal response to Kuvan.

6. Analysis of Clinical Information Relevant to Dosing Recommendations

Only one dose was used in the sub-studies and therefore no dose-response analysis was performed.

Reviewer Comments:

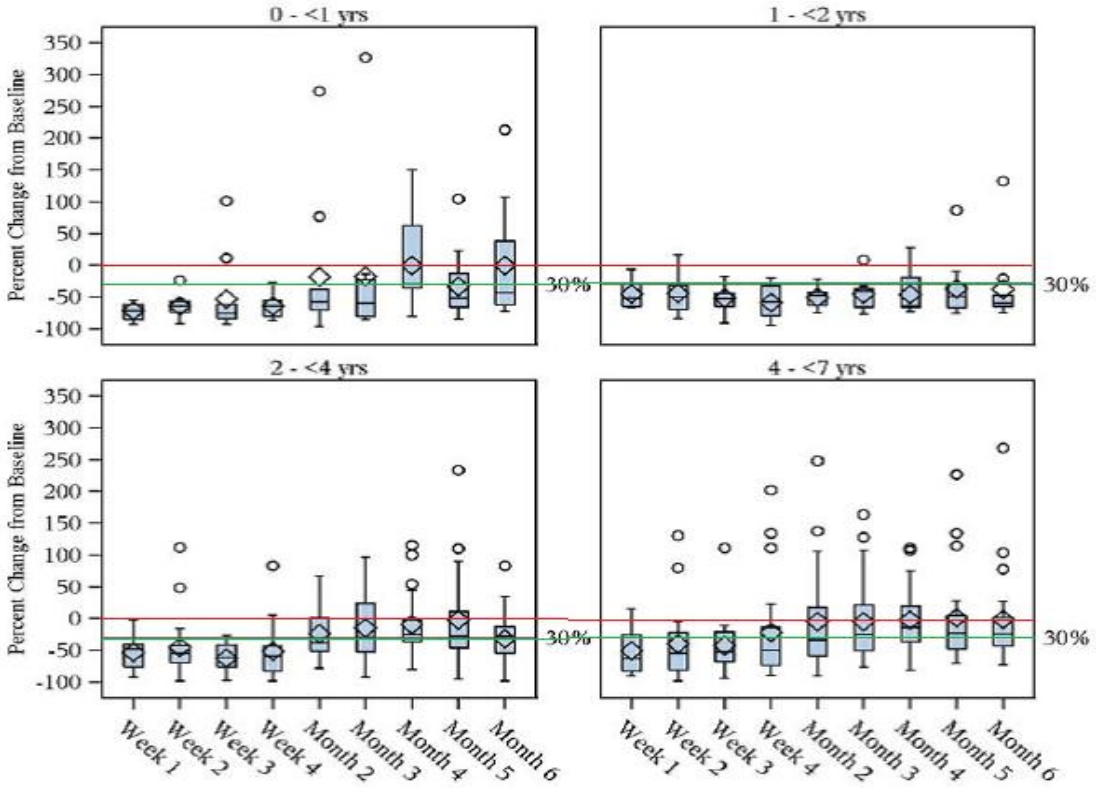
(b) (4)

, due to the risk of clinically significant hypophenylalaninemia in children under 7years old (see Section 7.3.5), I recommend that the current labeled dose of 10 mg/kg/day be used in children under 7 years old. I recommend a starting dose of 10 to 20 mg/kg/day for older children and adults.

7. Discussion of Persistence of Efficacy and/or Tolerance Effects

As discussed earlier, mean blood Phe levels decreased from baseline at Month 12 and then trended upward towards baseline in all age cohorts. Figure 6 summaries the percent change from baseline in blood Phe concentration by age group. Note that for age groups 0 to <1 age group and 4 to <7, the median percent change from baseline in blood Phe concentration was at or near 0 (marked by solid red line) at Month 6. For age groups 1 to <2 and 2 to <4, median percent change from baseline in blood Phe concentration decreased over time but remained at or below the responder threshold of 30% reduction (marked by green line) at Month 6.

Figure 6: PKU-015 Sub-Study 1- Percent Change in Blood Phe Levels from Baseline over Time by Age Group

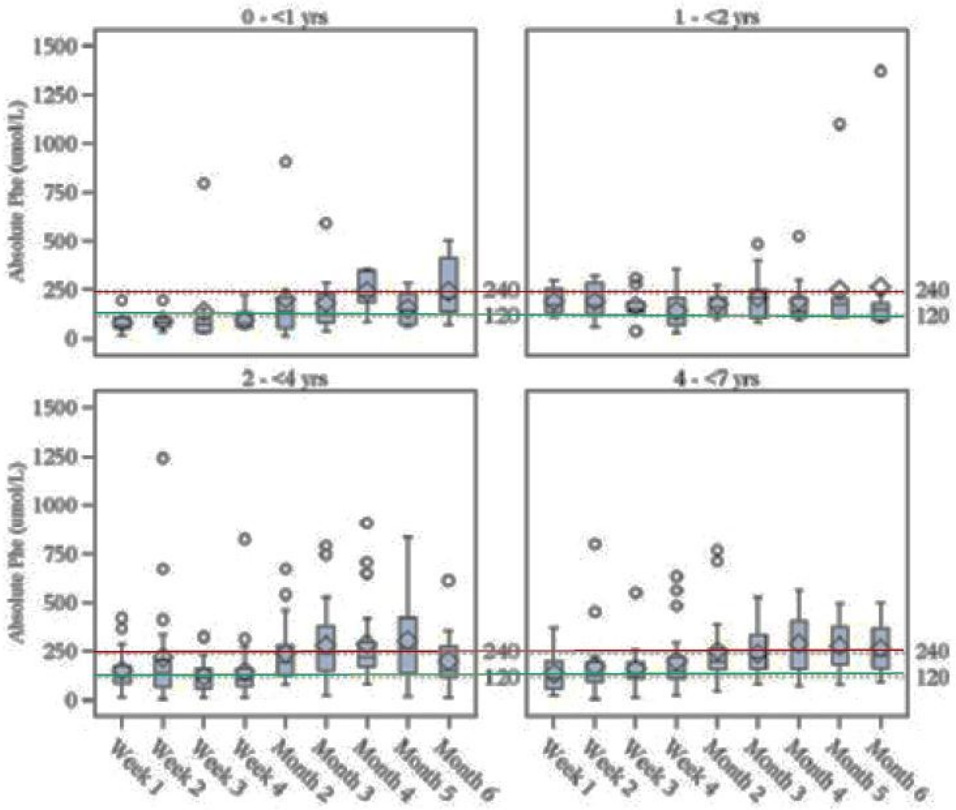


o= outlier; ◊= median

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Figure 14.2.9

Figure 7 presents absolute blood Phe levels over time by age group. Note that the median absolute blood Phe level was below or within the target range (lower limit and upper limit of target range are marked by green line and red line, respectively) for the first 4 weeks for all age group. At Month 6, the median absolute blood Phe level was within the target range for the 0 to <1 and 2 to <4 age groups and above the target range for the 1 to <2 and 4 to <7 age groups.

Figure 7: PKU-015 Sub-study 1- Absolute Blood Phe Levels (µmol/L) from Baseline over Time by Age Group



o= outlier; ◊= median

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Figure 14.2.10

Reviewer Comments:
The primary efficacy analysis for Sub-study 1 was change from baseline in blood Phe level. However, from a clinical perspective, the goal of treatment is to maintain blood Phe level within a target range. Thus, for patients who had blood Phe levels within or below the target range, there was no clinical benefit in further reduction of the blood Phe levels. Because a number of patients in the sub-study had blood Phe levels within or below the target range prior to treatment, this reviewer considers trends in blood Phe control status to be more informative of a clinically meaningful response than trends in blood Phe levels. As noted earlier, although blood Phe levels increased over time in all age groups, blood Phe control status improved in the two younger age groups whereas blood Phe control status did not appear to improve in the two older age groups.

From a clinical and nutritional perspective, the ability to liberalize a patient's diet would provide significant clinical benefit. However, the trial was not adequately designed to evaluate for efficacy for increased Phe tolerance. (b) (4) *, the applicant will need to conduct a trial that compares Phe levels of patients receiving increases in dietary Phe and patients receiving increases in dietary Phe and Kuvan with patients stratified by age.* (b) (4) *, the applicant will need to conduct a trial with patients on a stable Phe diet as the control arm and patients on a stable Phe diet and Kuvan as the treatment arm with patients stratified by age.*

6 Review of Efficacy

Efficacy Summary

Efficacy results are discussed in Section 5.3.2.

6.1 Indication

Kuvan is indicated to reduce blood Phe levels in patient with HPA due to BH4-responsive PKU. The applicant's proposed changes to labeling include the following:

Highlights

- (b) (4)

2. Dosage and administration

- Change (b) (4)
- Include statement recommending periodic blood monitoring
- Add method of administration for (b) (4)

5. Warnings and Precautions

- Update information in section regarding non-responders to Kuvan treatment to include data from PKU-015 to state that Kuvan treatment should be discontinued in patients who do not respond to a dose of 20 mg/kg/day

6. Adverse Reactions

- Update the section to include clinical trial information from PKU-15

8.4. Pediatric Use

- Update the section to include clinical trial information from PKU-015

12. Clinical Pharmacology

- Update Sections 12.2 and 12.3 to include information regarding Kuvan exposure-response relationship from PKU-004 and population PK information from PKU-015

14. Clinical Studies

- Update section to include clinical trial information from PKU-015

17. Patient Counseling Information

- Update section to include information regarding non-responders to Kuvan treatment, (b) (4) and status of disease and pregnancy registries.

Patient Information

- Include instructions on Kuvan administration [redacted] (b) (4)

See Section 4.4 and Section 5 for discussions of the data submitted to support the applicant's proposed labeling changes and Section 9.2 for labeling recommendations.

7 Review of Safety

Safety Summary

The safety profile for Kuvan observed in the two PKU-015 sub-studies was consistent with safety information contained in the current labeling for Kuvan. Twenty-five of 93 patients (26%) enrolled in Sub-study 2 and 19/65 patients (29%) enrolled in Sub-study 1 experienced adverse events that were reported as treatment-related. The most commonly reported treatment-related events in both sub-studies were vomiting, abdominal pain/stomach ache, and diarrhea. Two patients were discontinued after completion of Sub-study 2 due to AEs (psychogenic vomiting and elevated alkaline phosphatase). Two patients were discontinued from Sub-study 1 due to AEs (abdominal pain and hoarseness). All AEs reported for the trials were mild or moderate in severity. One patient experienced a SAE of gastroenteritis that was considered to be unrelated to treatment. There were no deaths reported for the trials reviewed for this submission.

Sixteen of 65 patients (25%) enrolled in Sub-study 1 experienced blood Phe levels below the age-based reference range. None of these events were reported as AEs. Events of hypophenylalaninemia in children were reported previously in PKU-008, the long-term safety trial in older children and adults. The data from PKU-008 and PKU-015 raise a concern about the safety of (b) (4) 20 mg/kg/day, particularly in young children.

Based on review of the safety data available for this review cycle, my independent safety analysis did not uncover major discrepancies compared with the applicant's analysis.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety information for this clinical review includes safety data from PKU-015. Post-marketing safety data are reviewed in Section 8.

7.1.2 Categorization of Adverse Events

The applicant coded AEs by System Organ Class (SOC) and AE preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA). I revised AE preferred terms and SOC terms so that AE terms were clustered together to allow for a more meaningful description of the AE profile of Kuvan. For example, abdominal pain and stomach ache were grouped together.

Reporting of adverse events included information such as classification of AE using standard medical terminology (MedDRA Version 15.1), system organ class (SOC), classification of relationship to study medication, classification of severity of AE, and date of onset and resolution of AE. These appear to be adequate to assess the safety profile of Kuvan.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

PKU-015 was the sole clinical trial reviewed in this submission. Data for the two sub-studies were analyzed separately due to the differences in study population (inclusion of non-BH4 responders in Sub-study 2 versus BH4-responders only in Sub- study 1).

7.2 Adequacy of Safety Assessments

Safety parameters for clinical studies and trials reviewed included physical examination, vital signs, ECG, safety laboratory analyses (serum chemistry, hematology, urinalyses, and blood Phe levels), and adverse events. In addition, pregnancy screening was performed for female patients of childbearing potential. These safety parameters appear to be adequate to assess the safety profile of Kuvan.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety data base for this review includes 95 pediatric patients with PKU enrolled in PKU-015.[19] For Sub-study 2, duration of exposure ranged from 21 days to 83 days, with a median duration of 56 days (see Table 21). This exposure period included time after sub-study completion as well as the time during which Kuvan responsiveness and eligibility for Part 2 of the long-term study were being determined. For Sub-study 1, duration of exposure ranged from 78 days to 219 days (median duration was 182 days); exposure was similar across age groups (see Table 22).

Table 21: PKU-015 Sub-study 2- Exposure to Kuvan

Responder Category	Phe Non-Responder (n=24)	Phe Responder (n=69)		Overall (n=93)
		Not Enrolled in Part 2	Enrolled in Part 2	
Total Duration (days)				
n	24	6	63	93
Mean ± SD	**37 ± 11**	**54 ± 20**	**59 ± 9**	**53 ± 14**
Median	33	52	57	56
Min, Max	21, 71	32, 80	42, 83	21, 83

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.3.6.4.

[19] Of 95 patients enrolled in PKU-015, 93 patients were included in Sub-study 2. Two patients were excluded from the Sub-study 2 safety population analysis but included in the Sub-study 1 safety population analysis, including one patient who declined enrollment in Sub-study 2 and one patient in Sub-Study 2 with missing PK samples.

Table 22: PKU-015 Sub-study 1- Exposure to Kuvan

Age Group	0 to <1	1 to <2	2 to <4	4 to <7	Overall
Total Duration (days)					
n	11	11	23	20	65
Mean ± SD	**192 ± 13**	**185 ± 15**	**172 ± 27**	**183 ± 9**	**181 ± 20**
Median	190	182	176	183	182
Min, Max	177, 219	172, 219	78, 212	169, 207	78, 219

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.3.6.4.2

Table 23 summarizes daily Kuvan dosing for the 2 sub-studies. For Sub-study 2, mean actual daily dose was 20.3 mg/kg/day (range was 15.9 to 27.3 mg/kg/day). For Sub-study 1, mean actual daily dose was 20.3 mg/kg/day (range was 15.4 to 23.3 mg/kg/day).[20]

For Sub-study 2, the majority of patients were on an unchanged dose of Kuvan (i.e., no change in mg/kg/day of Kuvan) over the 4-week duration. Twelve of 93 (13%) patients had dose adjustments of 5% or less during the course of the sub-study.

For Sub-study 1, 26/65 patients (60%) were on an unchanged dose of Kuvan. Thirty-eight of 65 (60%) patients had dose adjustments of 5% or less during the course of the sub-study. One patient (Patient1018-1008) in Sub-study 1 had a dose increase of 49% on Day 32 and then remained on the same dose for the remainder of the sub-study.

Table 23: PKU-015: Kuvan Dose (mg/kg/day) by Sub-study and Age Group

Sub-study 2					
Age Group	**0 to <1**	**1 to <2**	**2 to <4**	**4 to <7**	**Overall**
Dose (mg/kg/day)					
n	13	14	37	29	93
Mean ± SD	20.5 ± 0.8	20.3 ± 2.4	20.3 ± 1.2	20.0 ± 1.1	20.3 ± 1.3
Median	20.5	20.2	20.1	20	20.2
Min, Max	19.1, 21.9	15.9, 27.3	18.6, 23.3	18.1, 22.1	15.9, 27.3
Sub-study 1					
Age Group	**0 to <1**	**1 to <2**	**2 to <4**	**4 to <7**	**Overall**
Dose (mg/kg/day)					
n	11	11	23	20	65
Mean ± SD	20.1 ± 1.7	20.2 ± 0.6	20.6 ± 1.1	20.3 ± 1.0	20.3 ± 1.1
Median	20.3	20.2	20.3	20.3	20.2
Min, Max	15.4, 21.9	19.2, 21.5	18.8, 23.3	18.2, 22.1	15.4, 23.3

Source: PKU-015 Sub-studies Clinical Study Report (dated July 21, 2013), Table 14.3.6.4.1

[20] Mean actual daily dose was calculated as the sum of total amount of Kuvan intake in mg divided by dosing weight and total number of days on Kuvan.

Table 24 and Table 25 summarize the baseline characteristics of the Sub-study 2 and Sub-study 1 safety populations respectively.

Table 24: PKU-015 Sub-study 2 Safety Population

Baseline Characteristics	Age Groups				Overall Population
	0 to <1 (n=13)	1 to <2 (n=14)	2 to <4 (n=37)	4 to <7 (n=29)	(n=93)
Age at Study Entry (years)					
Mean ± SD	**0.5 ± 0.3**	**1.4 ± 0.3**	**2.9 ± 0.6**	**5.6 ± 1.0**	**3.2 ± 1.9**
Median	0.4	1.4	2.8	5.7	2.9
Min, Max	0.11, 0.98	1.04, 1.97	2.03, 3.99	4.14, 6.98	0.11, 6.98
Sex (N[%])					
Male	6 (46%)	7 (50%)	14 (38%)	9 (31%)	36 (39%)
Female	7 (54%)	7 (50%)	23 (62%)	20 (69%)	57 (61%)
Race (N[%])					
White	11 (85%)	11 (79%)	29 (78%)	26 (90%)	77 (83%)
Asian	1 (7.5%)	2(14%)	1 (3%)	1 (3%)	5(5%)
Black	0	0	2 (5%)	0	2 (2%)
Other	1(7.5%)	1(7%)	5(14%)	2 (7%)	9(10%)
Ethnicity N[%])					
Hispanic	0	1 (7%)	4 (11%)	1 (3%)	6 (6%)
Non-Hispanic	13 (100%)	13 (93%)	33 (89%)	28 (97%)	87 (94%)
Country (N[%])					
Canada	8 (62%)	8 (57%)	13 (35%)	13 (45%)	37 (40%)
United States	5 (38%)	6 (43%)	24 (65%)	16 (55%)	56 (60%)
Height (cm)					
Mean ± SD	**65.3 ± 5.3**	**80.5 ± 4.0**	**94.9 ± 6.3**	**114.8 ± 7.5**	**94.8 ± 17.8**
Median	67.0	79.8	94.5	117.7	94.8
Min, Max	56.0, 72.7	73.7, 88.5	81.2, 106.5	99.5, 127.9	56.0, 127.9
Height Percentile					
Mean ± SD	**63± 30**	**55 ± 22**	**61 ± 29**	**66 ± 24**	**62 ± 26**
Median	71	59	66	71	68
Min, Max	<1, 97	14, 83	7, 99	18, >99	<1, >99
Weight (kg)					
Mean ± SD	**7.5 ± 2.0**	**11.1 ± 1.4**	**14.9 ± 2.0**	**22.3 ± 5.2**	**15.6 ± 6.1**
Median	7.7	11.0	14.6	21	14.6
Min, Max	4.5, 10.8	8.9, 14.2	12.1, 21.3	15.2, 41.9	4.5, 41.9
Weight Percentile					
Mean ± SD	**66 ± 28**	**49 ± 25**	**65 ± 23**	**71 ± 23**	**65 ± 25**
Median	74	46	68	78	69
Min, Max	8, 97	7, 86	15, 99	24, >99	7, >99
Blood Phe (µmol/L)					
Mean ± SD	**308 ± 118**	**357 ± 115**	**316 ± 150**	**323 ± 166**	**323 ± 145**
Median	298	348	312	275	311
Min, Max	139, 457	170, 589	74, 653	58, 769	58, 769

Table 25: PKU-015 Sub-study 1 Safety Population

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Age at Study Entry (years)					
Mean ± SD	**0.5 ± 0.3**	**1.4 ± 0.3**	**3.0 ± 0.7**	**5.6 ± 1.0**	**3.1 ± 2.0**
Median	0.4	1.2	3.1	5.7	3.0
Min, Max	0.11, 0.98	1.04, 1.97	2.03, 3.99	4.14, 6.97	0.11, 6.97
Sex (N[%])					
Male	6 (55%)	5 (45%)	15 (65%)	14 (70%)	25 (38%)
Female	5 (45%)	6 (55%)	8 (35%)	6 (30%)	40 (62%)
Race (N[%])					
White	9 (82%)	9 (82%)	18 (78%)	18 (90%)	54 (83%)
Asian	1 (9%)	1 (9%)	0	1 (5%)	3(5%)
Black	0	0	1 (4%)	0	1 (<2%)
Other	1(9%)	1(9%)	4 (17%)	1 (5%)	7(11%)
Ethnicity N[%])					
Hispanic	0	0	3 (13%)	0	3 (5%)
Non-Hispanic	11 (100%)	11 (100%)	20 (87%)	20 (100%)	62 (95%)
Country (N[%])					
Canada	5 (45%)	6 (55%)	8 (35%)	10 (50%)	29 (45%)
United States	6 (55%)	5 (45%)	15 (65%)	10 (50%)	36 (55%)
Height (cm)					
Mean ± SD	**64.8 ± 5.7**	**81.0 ± 3.8**	**96.0 ± 7.2**	**114.8 ± 0.3**	**94.0 ± 18.7**
Median	65.5	80.0	95.9	117.0	93.5
Min, Max	56.0, 70.5	77.0, 88.5	81.2, 106.5	103.0, 124.2	56.0, 124.2
Height Percentile					
Mean ± SD	**66± 27**	**67 ± 20**	**62 ± 30**	**64 ± 24**	**64 ± 26**
Median	71	73	68	68	70
Min, Max	<1, 97	32, 98	7, 99	28, >99	<1, >99
Weight (kg)					
Mean ± SD	**7.3 ± 2.0**	**11.1 ± 1.6**	**15.2 ± 2.3**	**21.9 ± 3.5**	**15.2 ± 5.9**
Median	7.4	10.9	14.6	20.7	14.6
Min, Max	4.5, 10.8	8.9, 14.2	12.4, 21.3	18.1, 30.6	4.5, 30.6
Weight Percentile					
Mean ± SD	**63 ± 29**	**52 ± 29**	**66 ± 23**	**71 ± 22**	**65 ± 25**
Median	74	61	70	78	72
Min, Max	8, 97	7, 86	15, 98	27, 99	7, 99
Head Circumference (cm)	(n=11)	(n=11)	(n=11)		(n=33)
Mean + SD	**42.1 + 2.9**	**47.3 + 1.5**	**49.1 + 1.9**	**N/A**	**46.2 + 3.7**
Median	43.6	48.0	49.5		47.0
Min, Max	36.5, 45.0	44.0, 49.5	44.5, 51.5		36.5, 51.5
Head Circumference Percentile	(n=11)	(n=11)	(n=11)	**N/A**	(n=33)
Mean + SD	**54 + 21**	**65 + 27**	**66 + 31**		**61 + 27**
Median	55	65	73		64
Min, Max	21, 92	2, 97	1, 99		1, 99

Table 25: PKU-015 Sub-study 1 Safety Population (cont'd)

Baseline Characteristics	Age Groups				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Blood Phe (µmol/L)					
Mean ± SD	**298 ± 120**	**367 ± 107**	**337 ± 135**	**332 ± 159**	**334 ± 135**
Median	298	345	333	331	331
Min, Max	139, 457	228, 589	223, 453	58, 769	58, 769

7.2.2 Explorations for Dose Response

All patients received a Kuvan dose of 20 mg/kg/day; therefore, no evaluation for dose response for safety was performed.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

Safety assessments included laboratory testing for hematology, serum chemistry, urinalysis, blood Phe levels, and pregnancy testing. With the exception of urinalysis, blood Phe levels, and erythrocyte sedimentation rate, safety laboratory assessments for PKU-015 were analyzed at a central laboratory. Laboratory results are discussed in Section 7.4.2.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new metabolic, clearance or drug-drug interaction studies were submitted. As noted earlier, outstanding PMCs include additional drug-drug interaction studies (see Section 4.4.4).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Currently there are no other BH4 products approved for PKU in the US. In the original submission, the applicant provided post-marketing safety data for 30 patients treated with a sapropterin formulation that has marketing approval in Japan including 22 patients with dihydrobiopterin synthase deficiency, 5 patients with dihydropteridine reductase, and 3 patients with BH4-response PKU (off-label use). The most commonly reported AEs were convulsions or exacerbation of convulsions (10%) and increased GGT (7%). See the clinical review for the original submission for further details.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported during PKU-015.

7.3.2 Nonfatal Serious Adverse Events

One patient in Sub-study 2 experienced an event of gastroenteritis that was assessed as unrelated to treatment:

Patient 0253-1002
SAE: gastroenteritis
The patient was a 23 month-old male with household contacts with upper respiratory symptoms and gastroenteritis, including an aunt hospitalized for gastroenteritis and dehydration. The patient presented to the emergency department (ED) with a history of fever, decreased oral intake for 2 days. One day prior to presenting to the ED, the patient had vomited immediately after taking Kuvan. Physical examination and diagnostic work-up in the ED were remarkable for fever 102 to 104°F, rhinorrhea without cough, and a blood Phe level of 7.7 mg/dL. The patient was diagnosed with acute gastroenteritis and treated with ondansetron. The event resolved five days later. The investigator assessed the event as unrelated to treatment with Kuvan.

Comment: This reviewer agrees with the investigator's assessment.

7.3.3 Dropouts and/or Discontinuations

There were no discontinuations due to death or SAEs reported for PKU-015. Four patients discontinued due to AEs. All AEs resulting in discontinuation were assessed as related to treatment and of mild severity. Two patients discontinued due to AEs after completion of Sub-study 2 but prior to determination of their eligibility for enrollment in Part 2:

- Patient 0325-1005 experienced psychogenic vomiting. The event began on Day 42 and was resolved on Day 49.
- Patient 1063-1002 experienced an elevated alkaline phosphatase. The event began on Day 23 and was resolved on Day 59.

Two patients discontinued from Sub-study 1 due to AEs:

- Patient 1067-1004 experienced abdominal pain. The event began on Day 112 and was resolved on Day 121.
- Patient 0123-1001 experienced hoarseness after approximately 3.5 months of treatment. The patient had also experienced hoarseness during Sub-study 2.

7.3.4 Significant Adverse Events

The applicant monitored for identified and potential risks with Kuvan treatment, including:

- Hypophenylalaninemia
- Rebound
- Convulsions
- Serious hypersensitivity reactions
- Epigastric ulcer
- Nephrotoxicity
- Drug interactions

No AEs were reported related to these safety concerns. However, although there were no reported AEs of hypophenylalaninemia, some patients experienced blood Phe levels below the lower limits of normal for age (see Section 7.3.5).

No severe AEs were reported for either sub-study.

7.3.5 Submission Specific Primary Safety Concerns

Hypophenylalaninemia
I performed an independent analysis of events of hypophenylalaninemia during the two substudies. Blood Phe levels were not analyzed at a central laboratory site. In addition, the laboratory data listings did not include reference range values for phenylalanine for the local laboratories. However, as noted earlier, the variability for Phe values is small across various Phe assay methods. The (b) (4) was the central laboratory used for blood Phe analyses in prior Kuvan trials. Therefore, I used the (b) (4) age-based reference ranges for phenylalanine for my analysis. Table 26 lists the (b) (4) reference ranges for pediatric and adult blood Phe concentrations:

Table 26: (b) (4) Clinical Reference Ranges for Plasma Phenylalanine (µmol/L)

Age	Reference Range (plasma)
Premature	98-213 µmol/L
0-1 month	38-137 µmol/L
1-24 months	31-75 µmol/L
2-18 years	26-91 µmol/L
Adults	35-85 µmol/L

Source: PKU-008 Final Study Report (dated April 19, 2010), Appendix 16.1.10.2- Phe Validation Report (dated October 12, 2007)

Sixteen patients experienced 24 events of blood Phe levels below the normal range for age (see Table 27). The majority of these patients had blood Phe levels within or below the blood Phe control target range of 120 to 240 µmol/L at Week 0. All of these patients were treated by increasing their prescribed dietary Phe intake to achieve blood Phe levels within the target range. None of these events were reported as AEs.

Table 27: PKU-015 Patients with Blood Phe Concentrations < 26 µmol/L

Patient ID	Sex	Age (years)	Pre-Treament (Week 0) Blood Phe (µmol/L)	Visit	Blood Phe (µmol/L)
0003-1001	Male	3.1	327	Month 3	21
0009-1001	Female	4.5	403	Week 2	6
0124-1002	Male	0.2	155	Week 1	19
0124-1007	Male	4.8	94	Week 1 Week 2	25 22
0124-1015	Female	3.2	24	Week 0 Week 3	24 12
0124-1018	Female	0.4	592	Month 2	16
0129-1019	Female	2.9	130	Week 4	12
0146-1001	Female	2.4	182	Week 3	12
0146-1003	Female	4.5	48	Week 2	6
0146-1004	Male	4.0	309	Week 2 Week 3 Month 5	6 12 18
0313-1001	Male	3.8	NA (Week 1 was 133)	Week 3 Week 4 Month 6	18 12 12
0313-1002	Female	2.2	NA (Week 1 was 291)	Week 4 Month 6	18 18
0325-1001	Female	3.0	107	Week1 Week 2	15 6
0325-1002	Male	0.6	NA (Screening was 396)	Week 1	28
0325-1004	Female	4.4	144	Week 4 (unscheduled visit)	24
1067-1005	Female	5	186	Week 3	13

NA=not available

Reviewer Comments:
The majority of patients (11/16 patients; 69%) who experienced blood Phe levels below the age-based reference range were 4 years old or younger. Events of hypophenylalaninemia were also reported for 5/11 patients treated with Kuvan in PKU-008, the long-term safety trial in older children and adults. Of note, four of the five PKU-008 patients who experienced hypophenylalaninemia were children (ages ranged from 6 to 11 years) who were treated with Kuvan 20 mg/kg/day; the fifth patient was an adult who was treated with Kuvan 10 mg/kg/day. The data from PKU-008 and PKU-015 raise a concern about the safety (b) (4) of 20 mg/kg/day, particularly in young children. Therefore, from a safety perspective I do not recommend (b) (4) 20 mg/kg in children younger than 7 years old.

Neutropenia
Neutropenia has been reported in prior PKU trials. 24 patients experienced low neutrophil counts during the 6-month safety-efficacy sub-study, including seven patients who had low baseline neutrophil counts. The majority of patients (14/24 patients; 58%) experienced low neutrophil counts during the first four weeks of treatment. Two patients experienced AEs of low neutrophil counts. Four patients experienced clinically significant transient neutropenia (neutrophil count < 1,000/m^3), including two patients who had neutrophil counts of 200 at baseline.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 28 and Table 29 summarize the most commonly reported AEs for Sub-study 2 and Sub-study 1, respectively. The most commonly reported AEs (≥10% of patients) for the overall Sub-Study 2 population were URI/cold/nasopharyngitis (26%), vomiting (24%), diarrhea and cough (19% each), fever/pyrexia (18%), and rhinorrhea (16%).

The most commonly reported AEs (≥10% of patients) for the overall Sub-Study 1 population were URI/cold/nasopharyngitis (54%), vomiting (39%), fever/pyrexia (37%), rhinorrhea (32%), diarrhea (31%), cough and ear infection/otitis media(25% each).

During Sub-study 2, 81/93 patients (87%) experienced a total of 275 AEs. During Sub-study, 63/65 patients (97%) experienced a total of 248 AES. All AEs were assessed as mild or moderate in severity.

Table 28: PKU-015 Sub-study 2- Most Commonly Reported Adverse Events (≥2 patients)

Preferred Term	Non-responders (n=24)	Responders (n=69)		Overall (N=93)
		Not Enrolled in Part 2 (n=6)	Enrolled in Part 2 (n=63)	
URI/cold/nasopharyngitis	7 (29%)	1 (17%)	20 (32%)	24 (26%)
Vomiting	5 (21%)	1 (17%)	16 (25%)	22 (24%)
Diarrhea	5 (21%)	0	13 (21%)	18 (19%)
Cough	4 (17%)	2 (33%)	12 (19%)	18 (19%)
Fever/pyrexia	3 (13%)	2 (33%)	12 (19%)	17 (18%)
Rhinorrhea	2 (8%)	1 (17%)	12 19%)	15 (16%)
Abdominal pain/stomach ache	3 (13%)	1 (17%)	5 (8%)	9 (10%)
Influenza	1 (4%)	2 (33%)	3 (5%)	6 (7%)
Nasal congestion	3 (13%)	0	3 (5%)	6 (7%)
Decreased appetite	4 (17%)	0	1 (2%)	5 (5%)

Table 29: PKU-015 Sub-study 1- Most Commonly Reported Adverse Events (≥2 patients)

Preferred Term	Age Group				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Nasopharyngitis/cold/URI	8 (73%)	4 (36%)	11 (48%)	12 (60%)	35 (54%)
Vomiting	4 (36%)	4 (36%)	9 (39%)	8 (40%)	25 (39%)
Fever/Pyrexia	5 (46%)	5 (46%)	7 (30%)	7 (35%)	24 (37%)
Rhinorrhea	5 (46%)	5 (46%)	6 (26%)	5 (25%)	21 (32%)
Diarrhea	4 (36%)	2 (18%)	10 (44%)	4 (20%	20 (31%)
Cough	1 (9%)	3 (27%)	6 (30%)	6 (30%)	16 (25%)
Ear infection/otitis media	5 (46%)	4 (36%)	6 (30%)	1 (5%)	16 (25%)
Teething	4 (36%)	1 (9%)	0	0	5 (8%)
Oropharyngeal pain	0	0	0	5 (25%)	5 (8%)
Rash	0	3 (27%)	2 (10%)	0	5 (8%)
Decreased appetite	1 (9%)	0	3 (13)	0	4 (6%)
Hand-foot-mouth disease	0	2 (18%)	1 (5%)	0	3 (5%)
Headache	0	0	1 (5%)	2 (10%)	3 (5%)
Neutrophil count decreased	2 (18%)	0	0	0	2 (3%)

Table 30 and Table 31 summarize the most commonly reported adverse reactions for Sub-study 2 and Sub-study 1, respectively. Twenty-five of 93 patients (26%) enrolled in Sub-study 2 and 19/65 patients (29%) enrolled in Sub-study 1 experienced adverse events that were reported as treatment-related. The most commonly reported treatment-related events in both sub-studies were vomiting, abdominal pain/stomach ache, and diarrhea.

Table 30: PKU-015 Sub-study 2- Most Commonly Reported Kuvan-Related Adverse Events (≥ 2 patients)

Preferred Term	Non-responders (n=24)	Responders (n=69)		Overall (N=93)
		Not in Part 2 (n=6)	In Part 2 (n=63)	
Any reported Kuvan-related AE:	10 (42%)	2 (33%)	12 (19%)	25 (26%)
Vomiting	4 (17%)	0	4 6%)	8 (9%)
Abdominal pain/stomach ache	2 (8%)	1 (17%)	20(3%)	5 (5%)
Diarrhea	3 (13%)	0	1 (2%)	4 (4%)

Table 31: PKU-015 Sub-study 1- Most Commonly Reported Kuvan-related Adverse Events (≥ 2 patients)

Preferred Term	Age Group				Overall
	0 to <1 (n=11)	1 to <2 (n=11)	2 to <4 (n=23)	4 to <7 (n=20)	(n=65)
Any reported Kuvan-related AE:	3 (27%)	2 (18%)	9 (39%)	5 (25%)	19 (29%)
Vomiting	1 (9%)	1 (9%)	3 (13%)	1 (5%)	
Abdominal pain/stomach ache	0	0	5	2 (20%)	7 (11%)
Diarrhea	0	0	3 (13%)	0	3 (5%)
Neutrophil count decreased	2 (18%)	0	0	0	2 (3%)

Reviewer Comments:
The safety profile of Kuvan observed in these trials is consistent with the clinical experience in previous clinical trials, including previous placebo-controlled trials.

7.4.2 Laboratory Findings

During Sub-study 2, 10 patients experienced 16 laboratory AEs. Three patients experienced AEs assessed as treatment-related (elevated alkaline phosphatase; low platelet count; decreased calcium and carbon dioxide levels). Laboratory AEs occurring in 2 or more patients included elevated alkaline phosphatase and low platelet count (2 patients each). All laboratory AEs were assessed as mild in severity. As noted earlier, one patient was discontinued due to elevated alkaline phosphatase, with resolution of the event after Kuvan withdrawal. All other laboratory AEs were resolved without changes in Kuvan dosing by the end of the sub-study.

During Sub-study 1, four patients experienced 5 laboratory AEs; including low absolute neutrophils (three events in 2 patients), elevated alkaline phosphatase, and elevated blood tyrosine levels (one patient each). All laboratory AEs were assessed as treatment-related and mild in severity. All laboratory AEs were resolved without intervention by the end of the sub-study.

7.4.3 Vital Signs

There were no clinically relevant changes in vital signs compared to baseline observed in either of the sub-studies.

7.4.4 Electrocardiograms (ECGs)

During Week 0 of Sub-study 2, an ECG was performed after the first Kuvan dose for the first 80 patients enrolled in the sub-study. Of 80 patients, 10 patients were reported to have abnormal ECG findings. An AE of abnormal ECG findings (left axis deviation, junctional escape beats, and sinus arrhythmia) was reported for one patient (Patient

0325-1008). The patient had a past medical history of tachycardia. The findings were assessed as clinically significant by the investigator and resulted in interruption of Kuvan dosing for 6 days. Similar ECG findings were reported on the patient's follow-up ECG obtained one week later. These findings were assesses as not clinically significant and the patient is continuing on treatment in the ongoing 7-year study.

None of the remaining nine patients had a past medical history of cardiac disease or cardiac rhythm abnormalities. ECG findings for the remaining nine patients included two patients with sinus bradycardia (Patient 0124-1020 and Patient 0325-1005), and one patient each with sinus tachycardia (Patient 0124-1009), left and right ventricular hypertrophy (Patient 0109-1001), septal hypertrophy (Patient 0109-1002), dextrocardia (Patient 0124-1019), prolonged QT interval with right bundle branch block(Patient 0310-1001) , left and right ventricular hypertrophy with deep Q wave plus sinus bradycardia (Patient 1067-1001), and moderate left ventricular hypertrophy with short PR interval (Patient 0325-1003). None of these findings were assessed as clinical significant. Six of nine patients are continuing to receive treatment in the ongoing 7-year trial. Two patients (Patient 0124-1019 and Patient 0310-1001) were not responsive to Kuvan and therefore were not enrolled into Part 2 of the ongoing trial. One patient (Patient 0325-1005) was discontinued following completion of Sub-study 2 due to an AE of psychogenic vomiting.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All patients received a Kuvan dose of 20 mg/kg/day; therefore, no evaluation for dose dependency for AEs was performed. Kuvan dosing was interrupted or withdrawn in 11 patients due to AEs, including five patients who experienced AEs assessed as being treatment-related.

7.5.2 Time Dependency for Adverse Events

There were seasonal variations in the occurrence of infectious disease AEs (URIs, influenza, etc.). There did not appear to be any temporal pattern for adverse events related to study drug. As noted earlier, most events of hypophenylalaninemia occurred during the first four weeks of treatment.

7.5.3 Drug-Demographic Interactions

The most frequently reported AEs for the trial included common conditions (nasopharyngitis/cold/URI, rhinorrhea, fever/pyrexia, cough, ear infections) in pediatric patients ages 0 to 6 years old. The most commonly reported adverse reactions for the trial (vomiting, abdominal pain/stomach ache, diarrhea, and low neutrophil count) are labelled adverse reactions for Kuvan. There do not appear to be any significant

differences in adverse events based on gender. No safety subgroup analyses were performed for race since the majority of patients were white.

7.5.4 Drug-Disease Interactions

No new information regarding drug-disease interactions was submitted. The current labeling for Kuvan includes the following information in the *Warnings and Precautions* section:

(b) (4)

7.5.5 Drug-Drug Interactions

No new information regarding drug-drug interactions was submitted. The current labeling for Kuvan includes information in the *Warnings and Precautions* section regarding concomitant use of Kuvan and the following medications:

- drugs that affect nitric oxide-mediated vasorelaxation(e.g., PDE-5 inhibitors such as sildenafil)
- drugs that inhibit folate metabolism (e.g., methotrexate)
- levodopa

As noted earlier, there are outstanding PMCs for additional *in vitro* studies to evaluate potential drug-drug interaction as PMCs (see Section 4.4.4).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was no evidence of human carcinogenicity in the safety evaluation.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported during the trials reviewed in this submission. Post-marketing information on pregnancy outcomes is reviewed in Section 8.

Reviewer Comments:
As noted earlier, the current labeling for Kuvan includes information specified by the Proposed Pregnancy and Lactation Labeling Rule. No further revisions to the labeling regarding human reproduction and pregnancy are needed at this time.

7.6.3 Pediatrics and Assessment of Effects on Growth

Table 32 summarizes growth measurements for Sub-study 1.The majority of patients had baseline growth measurements that were above the lower limits for normal for age

(i.e., ≥5th percentile), with 63/65 (97%) patients having baseline height and weight percentile values ≥5th percentile and 31/33 patients (94%) having baseline head circumference values ≥5th percentile for age. Mean values for growth, height, and head circumference percentiles were similar across age groups and were stable from baseline to month 6. For the overall safety/efficacy population, mean weight percentile was 65th percentile (range was 7th to 99th percentile) at baseline and 63rd percentile (range was 11th to >99th percentile) at Month 6. Mean height percentile was baseline 62nd percentile (range was <1st to >99th percentile) and 64th percentile at Month 6 (range was <1st to 99th percentile). Mean head circumference was 62nd percentile at baseline (range was <1st to 99th percentile) and 57th percentile at Month 6 (range was <1st to 97th percentile).

Table 32: PKU-015 Sub-study 1- Weight, Height, & Head Circumference Percentiles Over Time by Age Groups

	Age Groups				Overall
	0 to <1	1 to <2	2 to <4	4 to <7	
Weight Percentile					
Baseline					
N	11	11	23	20	65
Mean ± SD	**63 ± 29**	**52 ± 29**	**66 ± 23**	**71 ± 22**	**65 ± 25**
Median	74	61	70	78	72
Min, Max	8, 97	7, 86	15, 98	27, 99	7, 99
Month 6					
N	11	11	21	20	63
Mean ± SD	**52 ± 21**	**55 ± 26**	**69 ± 21**	**71 ± 21**	**64 ± 23**
Median	53	54	68	78	66
(Min, Max)	(19, 86)	(19, 87)	(11, 98)	(24, >99)	(11, >99)
Height Percentile					
Baseline					
N	11	11	23	20	65
Mean ± SD	**61 ± 25**	**65 ± 21**	**61 ± 30**	**62 ± 25**	**62 ± 26**
Median	64	69	67	66	65
(Min, Max)	(<1, 95)	(29, 98)	(7, 99)	(26, >99)	(<1, >99)
Month 6					
N	11	10	20	18	59
Mean ± SD	**61 ± 24**	**72 ± 18**	**66 ± 27**	**59 ± 25**	**64 ± 26**
Median	64	74	78	64	65
(Min, Max)	(<1, 97)	(38, 98)	(11, 94)	(29, 99)	(<1, 99)
Head Circumference Percentile					
Baseline					
N	11	11	11	N/A	33
Mean ± SD	**49± 22**	**64 ± 27**	**66 ± 31**		**60 ± 27**
Median	50	63	73		61
(Min, Max)	(16, 90)	(2, 96)	(<1, 99)		(<1, 99)
Month 6					
N	11	11	6	N/A	28
Mean ± SD	**45± 22**	**63 ± 28**	**67 ± 19**		**57 ± 25**
Median	37	72	71		55
(Min, Max)	(15, 96)	(<1, 97)	(33, 87)		(<1, 97)

Reviewer Comments:
The trial results indicate that there is no adverse impact on growth with up to 6 months of Kuvan treatment. The long-term impact of Kuvan on growth is being evaluated in the ongoing 7-year trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One patient was reported to have received an overdose of Kuvan in clinical trials. The patient received 36 mg/kg instead of 20 mg/kg. He reported a mild headache and dizziness that resolved within one hour of taking the dose (see Section 7.1.16 of the clinical review for the original submission for further details).

No withdrawal or abuse potential has been identified.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

The applicant referenced all Period Adverse Drug Experience Reports (PADERs) filed since market approval up through the most recent reporting period prior to submission of this efficacy supplement (from December 2007 to December 2012). These included 12 quarterly reports and two annual reports. No regulatory actions have been taken for safety or efficacy reasons in the US or other regulatory regions since marketing approval.

The most recent PADER (PADER 14 for the period December 13, 2011 to December 12, 2012) reported 251 unique cases with 440 AEs for the reporting period. The applicant did not provide a cumulative total of cases and AEs since marketing approval. Note that the PADER reports included reports for all patients treated with Kuvan, including patients treated for other indications such as BH4 deficiency.

8.1 Deaths

Five deaths have been reported to date for patients treated with Kuvan, including 1 patient with PKU who developed pneumonia and died of organ failure, 1 patient with BH4 deficiency whose death was attributed to disease progression, and two patients treated off-label (1 patient with an unspecified "neurotransmitter disease" and 1 patient with rabies). All of these cases were assess as unrelated to treatment with Kuvan. One additional patient died for whom no diagnostic or clinical data were available.

Reviewer Comment: This reviewer agrees, that based on the available information, the reported patient deaths do not appear to be related to treatment with Kuvan.

8.2 Pregnancy Outcomes

There were a total of 50 reports of maternal exposure during pregnancy from December 2007 to December 2012; all reports were for patients with PKU. Reported pregnancy outcomes included 5 live births, seven spontaneous abortions and one elective abortion. Of the five live births, all were reported to be healthy and/or to have a normal physical examination; one of the five newborns was reported to be a healthy baby with a low head circumference measurement. The most frequently reported pregnancy outcome disorders were spontaneous abortion (7 cases) and fetal distress syndrome (5 cases). The most commonly reported congenital and familial disorders were atrial septal defect and microcephaly (2 cases).

Reviewer's Comment:
There do not appear to be any new safety signals for pregnancy outcomes. The reported SAEs are all known complications of maternal PKU. The applicant has established a pregnancy registry as part of a disease registry for the overall PKU population as a post-marketing commitment (PMC #4). Data collection for the pregnancy registry is ongoing.

8.3 Serious Adverse Events

Table 33 summarizes SAEs reported from December 2007 to December 2012. Note that the The most commonly reported SAEs were seizures/convulsions (17 cases), vomiting (13 cases), abdominal pain (9 cases), skin infections/abscesses/cellulitis, fever/pyrexia, tremor (8 cases each), diarrhea, dehydration (6 cases each), decreased spontaneous abortion (7 cases),deaths, hypotension/orthostatic hypotension, URI/pharyngitis, and fetal distress syndrome (5 cases). Most cases were unrelated to treatment with Kuvan or represented events already identified in Kuvan labeling. Some of the reports did not provide sufficient information to assess the relationship of the event to treatment with Kuvan.

Reviewer Comments:
Based on my independent review of the cases for which clinical data were available, the cases were unrelated to treatment with Kuvan or represented known adverse reactions to Kuvan. All of the reports for seizures/convulsions appeared to be for patients with a known seizure disorder. As noted earlier, there is an ongoing registry study for PKU patients that is being conducted as a post-marketing commitment (PMC #4).

Table 33: Kuvan Safety Database- SAE Reports by System Organ Class

System Organ Class	Cases (N)	Event
Gastrointestinal Disorders	42	Vomiting (13 cases) Abdominal pain (9 cases) Diarrhea (6 cases) Nausea (4 cases) Gastroesophageal reflux disease (2 cases) Esophageal disorder (2cases) Anal fistula, dyspepsia, diabetic gastroparesis, flatulence, esophagitis, esophageal ulcer, gastritis, gastric ulcer, hematemesis, pancreatitis, peptic ulcer, perforated ulcer, rectal prolapse, retching, ulcerative colitis (1 case each)
Nervous System Disorders	38	Convulsions/seizures (17 cases) Tremors (8 cases) Cerebrovascular accident, dizziness, epilepsy/ status epilepticus, headache, lethargy, migraine (2 cases each) Cerebral calcification, gait disturbance, loss of consciousness, memory impairment, mental impairment, motor dysfunction, sensory disturbance, unresponsive to stimuli (1 case each)
Infections and Infestations	37	Skin infection/abscess/cellulitis (8 cases) URI/nasopharyngitis (5 cases) Appendicitis (3 cases) Dengue fever, ear infection, Epstein Barr virus, gastroenteritis, infection, influenza, pneumonia, sinusitis- (2 cases each) Diverticulitis, laryngitis, pharyngitis, viral infection, sepsis, staphylococcal infection (1 case each)
Respiratory	26	Dyspnea (4 cases) Asthma, cough (3 cases each) Aspiration, respiratory distress, wheezing (2 cases each) Acute respiratory distress syndrome, apnea, choking, dysphonia, epistaxis, hiccups, oropharyngeal pain, respiratory disorder, neonatal respiratory distress syndrome, throat irritation, throat tightness (1 case each)
General Disorders & Administrative Site Conditions	25	Fever/pyrexia (8 cases) Death (5 cases) Drug ineffective, fatigue, pain, peripheral edema (2 cases each) Asthenia/chills, discomfort, drug interaction, drug intolerance, general health deterioration, irritability, organ failure, pain (1 case each)
Psychiatric Disorders	22	Altered mood, anxiety, abnormal behavior, eating disorder, insomnia, suicidal behavior, suicidal ideation (2 cases each) Agitation, aggression, communication disorder, depressed mood/depression, dysphemia, intentional self-injury, increased libido, mental disorder, mental status changes, oppositional defiant disorder, psychotic behavior, schizophrenia, suicide attempt (1 case each)

Table 33: Kuvan Safety Database- SAE Reports by System Organ Class

System Organ Class	Cases (N)	Event
Pregnancy Related Disorders	18	Spontaneous abortion (7 cases)) Fetal distress syndrome (5 cases) Premature labor (2 cases) Blighted ovum Caesarean Section Fetal growth restriction Premature baby
Investigations	13	Decreased weight (4 cases) Increased amino acid level (2 cases) Abnormal MRI, anticonvulsant level below therapeutic, blood urine present, cardia murmur, increased BP, increased respiratory rate, increased weight (1 case each)
Injury, Poisoning & Procedural Complications	12	Drug exposure during pregnancy (3 cases) Accidental exposure, airway complication of anesthesia, foreign body trauma, head injury, incision site erythema, injuries from MVA, skin injury, sports injury, traumatic pneumothorax (1 case each)
Metabolic and Nutritional Disorders	12	Dehydration (6) Decreased appetite (3 cases) Diabetes mellitus, hypernatremia, gestational diabetes, hypophagia (1 case each)
Renal Disorders	10	Nephrolithiasis (6 cases) Renal disorder (2 cases) Acute renal failure Hydronephrosis Obstructive uropathy Nephritis
Congenital, Familial & Genetic Disorders	8	Atrial septal defect, microcephaly (2 cases each) Infant born with PKU Dysmorphism Medicum-chain acety-coenyzme A dehydrogenase deficiency Duodenal atresia
Cardiac Disorders	7	Tachycardia (3 cases) Arrhythmia Cardiac arrest Cyanosis Myocardial infarction
Vascular	7	Hypotension/orthostatic hypotension (5 cases) Hypertension Pallor
Blood & Lymphatic Disorders	5	Lymphadenitis (2 cases) Anemia Decreased platelet count Leukocytosis
Neoplasms Benign, Malignant & Unspecified	4	Thyroid neoplasm Breast cancer Malignant melanoma Fibroadenoma of breast

Table 33: Kuvan Safety Database- SAE Reports by System Organ Class

System Organ Class	Cases (N)	Event
Musculoskeletal & Connective Tissue Disorders	3	Muscle tightness/stiffness Neck pain Joint swelling
Immune System Disorders	3	Hypersensitivity (3 cases)
Endocrine Disorders	2	Thyroid disorder Subacute thyroiditis Thyroid neoplasm
Reproductive Disorders	2	Vaginal hemorrhage
Eye Disorders	2	Photophobia Eye movement disorder
Skin & Subcutaneous Tissue Disorders	2	Erythema Urticaria
Ear & Labyrinth Disorders	1	Middle ear infusion
Surgical & Medical Procedures	1	Hysterectomy Salpingo-oophorectomy
Hepatobiliary	1	Cholelithiasis

9 Appendices

9.1 Literature Review/References

1. Blau N, Sapropterin dihydrochloride for the treatment of hyperphenylalaninemias, *Expert Opin Drug Metab Toxicol* 201; 9(9): 1207-1218.
2. Blau N, Hennerman JB et al., Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies, *Mol Genet Metab* 2011; 104:S2-S9.
3. Gentile JK, Ten Hoedt AE, Bosch AM, Psychosocial aspects of PKU: Hidden disabilities-A review, *Mol Genet Metab* 2010; 99: S64-67.
4. Guldberg P, Rey F et al., A European multicenter study of phenylalanine hydroxylase deficiency: Classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype, *Am J Hum Genet* 1998; 63:71-79.
5. Hennermann JB, Buhrer C et al., Long-term treatment with tetrahydrobiopterin increases phenylalanine tolerance in children with severe phenotype of phenylketonuria, *Mol Genet Metab* 2005; 86 (Suppl):86-90.
6. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022181lbl.pdf
7. http://www.ncbi.nlm.nih.gov/books/NBK1504/
8. http://www.npkua.org/index.php/pku-facts
9. Huemer M, Huemer C et al., Growth and body composition in children with classical phenylketonuria: Results in 34 patients and review of the literature, *J Inherit Metab Dis* 2007; 30: 694-699.
10. Konstantopoulou A, Tsikrikas S et al., Mechanisms of drug-induced proarrhythmia in clinical practice, *World J Cardiol 2013; 5(6): 175-185.*
11. National Institutes of Health Consensus Development Panel, National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16-18, 2000, *Pediatrics* 2001; 108:972-982
12. Shintaku H, Kure S et al., Diagnosis and long-term treatment of tetra-hydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene, *J Inherit Metab Dis* 2003; 26 -Suppl 2.
13. van Spronsen FJ, Kiaer Ahring K, Gizewska M, PKU- What is daily practice in various centres in Europe?, *J Inherit Metab Dis* 2009; 32:58-64.
14. Waisbren SE, Noel K et al., Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systemic literature review and meta-analysis, *Mol Genet Metab* 2007; 92(1-2): 63-70.

9.2 Labeling Recommendations

The labeling will be in PLR format. Content and formatting were reviewed to meet the latest best practices. The final labeling contains all of the labeling revisions negotiated with the applicant.

I recommend the following edits to the applicant's proposed changes to the current labeling for Kuvan:

- **Section 2.1 (Dosage and Administration)**

Recommendation:

(b) (4) Due to the reported events of hypophenylalaninemia in patients 6 years and younger who received a starting dose of 20 mg/kg/day, I recommend a starting dose of 10 mg/kg/day for children 6 years and younger , which is the current labeled dose for Kuvan. I recommend a starting dose of 10-20 mg/kg/day for patients 7 years and older. Dosing instructions should also state that treatment should be discontinued in patients whose blood Phe des not decrease after 1 month of treatment at 20 mg/kg/day.

I agree with the applicant's proposal to include information on administration of Kuvan in soft foods and information on administration of Kuvan to patients weighing 5 kg or less.

- **5 (Warnings and Precautions)**

Recommendation:
I recommend revising Section 5.3 to state that anaphylaxis has been reported in patients taking Kuvan. The current labeling states that hypophenylalaninemia occurs more frequently in children 6 years and younger treated with Kuvan doses of 20 mg/kg/day.

- **Section 6.1 (Adverse Reactions- Clinical Trials Experience)**

Recommendation:
I recommend that this section be revised to include information about events of hypophenylalaninemia.

- **Section 8.4 (Pediatric Use)**

Recommendation:
I recommend adding language that hypophenylalaninemia occurs more frequently in children than in adults.

- **Section 12 Clinical Pharmacology**

Recommendation:
I agree with the applicant's proposal to add information on the Kuvan exposure-response relationship in Section 12.2 (Pharmacodynamics) and population PK analyses in Section 12.3 (Pharmacokinetics).

- **Section 14 Clinical Studies**

Recommendation:
I agree with the applicant's proposal to include information on long-term safety in Section 14 (b) (4)
(b) (4)

- **Section 17 Patient Counseling Information**

Recommendation:
I recommend that the counseling information in Section 17 be revised to include information on the recommended starting dose for children 6 years and younger, and the risk of hypophenylalaninemia in children.

- **Patient Information**

Recommendation:
Patient information should include specific instructions on the administration of Kuvan to patients weighing 5 kg or less, include what liquids may be used for dissolving Kuvan and how to calculate the amount of Kuvan solution (as measured in milliliters) to be administered.

9.3 Advisory Committee Meeting

No advisory committee was held for this submission.

9.4 Pediatric Written Request

The Pediatric Written Request for Kuvan was issued October 31, 2011 (see attached document).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022181

WRITTEN REQUEST

BioMarin Pharmaceutical, Inc.
Attention: Ben Dewees
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Mr. Dewees:

Reference is made to your May 5, 2010, Proposed Pediatric Study Request (PPSR) for Kuvan (sapropterin dihydrochloride).

BACKGROUND:

These studies investigate the potential use of sapropterin dihydrochloride in the treatment of pediatric patients with tetrahydrobiopterin- (BH4) responsive phenylketonuria (PKU), ages 0 months (birth) through six years of age, inclusive. Effectiveness will be extrapolated from studies in older pediatric patients using a proven surrogate endpoint, since the pathophysiology of PKU is the same in all age groups.

PKU is a rare, autosomal recessive disorder that occurs as a result of reduced or absent activity of the enzyme phenylalanine hydroxylase. PKU affects approximately 1 in 10,000 to 1 in 15,000 people in the United States. Affected infants are normal at birth. However, untreated patients develop elevated blood phenylalanine (Phe) levels and subsequent adverse neurological symptoms including severe mental retardation, hyperactivity and seizures. PKU is usually diagnosed in the newborn period because newborn screening for PKU is conducted in all states. Adverse neurological outcomes are ameliorated or prevented by decreasing blood phenylalanine with dietary phenylalanine restriction. However, it is not possible to reverse established neurocognitive decline. Prior to the approval of sapropterin dihydrochloride, PKU was managed exclusively with a low-phenylalanine diet. Sapropterin dihydrochloride is a synthetic form of tetrahydrobiopterin (BH4) and was approved in 2007 to reduce blood Phe levels in patients with BH4-responsive PKU. Early intervention with sapropterin dihydrochloride may improve clinical outcomes by lowering blood Phe levels in those patients with BH4-responsive PKU.

Approval of sapropterin dihydrochloride was based on 4 clinical studies evaluating the efficacy and safety of the drug in PKU patients ages 4 years and older. However, no clinical trials have been performed to evaluate the efficacy and safety in PKU patients birth to 4 years of age. The product is intended to be used in pediatric populations as early as the newborn period to avoid serious neurocognitive sequelae. Therefore, clinical trials should be conducted in this patient population. Additionally, only one clinical study submitted in the original NDA included

patients 4-8 years of age (n=90). The mean age of patients enrolled in this study (PKU-006) was 7.3 (± 2.5) years. Therefore, additional data in patients 4-6 years of age are also necessary.

It should be noted that this Pediatric Written Request (WR) is the second WR issued for Kuvan. The original WR was issued on January 14, 2008. A Type C meeting was held on September 15, 2008 to discuss your requested revisions to the WR. Based on agreements obtained at this meeting, an amendment to the WR was submitted on February 4, 2009. However, the amendments to the WR were not reviewed and approved prior to the expiration of the original WR on May 31, 2009. Therefore, the FDA review division communicated to you via email on January 25, 2010 that a new PPSR should be submitted so that a new WR could be issued. This communication also included specific recommendations for the PPSR based on agreements reached during the September 2008 Type C meeting. A new PPSR was submitted on May 5, 2010. However, studies were initiated under the amended WR based on the agreements reached during the Type C meeting, and in fact, the studies are near completion at this time. The current WR is being issued to include agreements made during the Type C meeting held on September 15, 2008 and to replace the WR that expired on May 31, 2009.

To obtain needed pediatric information on sapropterin dihydrochloride, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

***Nonclinical studies*:**

Nonclinical toxicology studies were conducted in rats (104 weeks duration) and mice (78 weeks duration) to support the original NDA for sapropterin dihydrochloride. In both groups, sapropterin doses of 25, 80, and 250 mg/kg/day were used. According to current labeling, sapropterin at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose, based on body surface area) was found to have no effect on fertility and reproductive function of male and female rats. Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

Study 1: PK-PD and Tolerability Study

A 4-Week Pharmacokinetic/Pharmacodynamic (PK-PD) and tolerability study in pediatric patients birth to 6 years with PKU. All patients must have their diet controlled for Phe intake at entry and throughout the study. Patients will receive sapropterin dihydrochloride at 20 mg/kg/day. Response to treatment will be defined as a $\geq$ 30% decrease from baseline blood Phe levels (measured at point of entry into the PD study) at the end of the PD study (e.g., 4 weeks of treatment). Patients who are tetrahydrobiopterin- (BH4) responders will be enrolled in the 6-month, open-label efficacy and safety study (Study 2). Patients who are unable to achieve the target exposures due to tolerability issues will need to receive a total of 6 months of exposure at the last tolerated dose that provided an acceptable response to treatment.

Study 2: Safety and Efficacy Study
A 6-month, open-label, uncontrolled, efficacy and safety study of sapropterin dihydrochloride in pediatric patients birth to 6 years with BH4-responsive PKU. All patients must have their diet controlled for Phe intake at entry and throughout the study. Patients who completed the 4 week PK/PD study (Study 1) and were found to be responders will be enrolled in this study. Patients (BH4 responders) will receive sapropterin dihydrochloride for an additional 5 months on Study 2 for a total of 6 months at doses expected to achieve exposures of sapropterin observed in older pediatric patients. Patients who are unable to achieve the target exposures due to tolerability issues will need to receive a total of 6 months of exposure at the last tolerated dose that provided acceptable response to treatment. Effectiveness will be extrapolated from studies in older pediatric patients using a proven surrogate endpoint since the pathophysiology of PKU is similar in all pediatric age groups.

A minimum of 60 BH4-responsive patients with PKU (responders) from Study 1 will be enrolled in Study 2. Patients will receive a total of six months of treatment with sapropterin dihydrochloride. The number of patients enrolled into Study 1 should be estimated based on the projected number of responders (defined as patients who demonstrate a ≥ 30% decrease in blood Phe from baseline at the end of Study 1), and on the projected number of drop-outs over the course of Study 1 and Study 2.

Objective of each study:

Study 1: PK-PD and Tolerability Study
To evaluate the population pharmacokinetics of sapropterin dihydrochloride administration for up to 4 weeks of treatment in pediatric patients ages 0 months to 6 years.

To evaluate safety and identify those pediatric patients ages 0 months to six years who will respond to sapropterin dihydrochloride (as defined as a ≥ 30% decrease from baseline blood Phe Levels) after 4 weeks of treatment.

Study 2: Safety and Efficacy Study
To evaluate the safety and tolerability of sapropterin dihydrochloride administration for a total of six months of treatment to pediatric patients with PKU, ages 0 months to six years. The efficacy outcome variable is the change in blood Phe level from baseline (no treatment) at the end of six months of treatment in the subgroup of patients who respond to treatment with sapropterin dihydrochloride (BH4 responders) in Study 1. Safety assessments must include, at minimum, physical examinations (to include, at a minimum, height, weight, and head circumference), medical history, and safety laboratory collections (including, at minimum, chemistry panel, complete blood count, and urinalysis) at baseline and at intervals during treatment, and the collection of Adverse Events during treatment.

Growth and neurocognitive development must be assessed periodically as age-appropriate. Standardized and replicated measurements of head circumference (less than 3 years of age), weight and length/height must be obtained. Neurocognitive development must be assessed using well validated and age-appropriate measures, including the Bayley III.

Indication to be studied:

Treatment to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU.

Patients to be studied:

Study 1: PK-PD and Tolerability Study
Pediatric patients ages 0 months to 6 years who have PKU.

Study 2: Safety and Efficacy Study
Pediatric patients ages 0 months to 6 years who have completed PK-PD Study (Study 1) and have BH4-responsive PKU.
Age group in which studies will be performed:

Birth to <1 year
1 year to 2 years
2 years to 4 years
4 years to 6 years

Number of patients to be studied:

Study 1: PK-PD and Tolerability Study
The number of patients should be estimated based on the projected number of responders, and on the projected number of drop-outs over the course of the study to ensure adequate enrollment for the Safety and Efficacy Study (Study 2). BH4-responsive patients will be defined as patients who demonstrate a ≥ 30% decrease in blood Phe from baseline at the end of Study 1 (while on a PKU-controlled diet).

For an adequate population pharmacokinetic analysis, the study must be prospectively powered to achieve precise estimates of clearance and volume of distribution for sapropterin dihydrochloride in each age group (birth to <1 years, 1-2 years, 2-4 years and 4-6 years).

Study 2: Safety and Efficacy Study
A minimum of 60 BH4-responsive patients with PKU (responders) will enroll in the Safety and Efficacy Study (Study 2). Of the patients enrolled in the Safety and Efficacy Study (Study 2), at least ten (10) must be less than one year of age, at least twenty (20) must be less than two years of age, 20 patients must be age 2-4 years, and 20 patients must be age 4-6 years at the time of entry into the study.

Representation of Ethnic and Racial Minorities:

The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an

adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Study endpoints:

Study 1: PK-PD and Tolerability Study

Pharmacokinetic Endpoints:
Population PK study will evaluate the population pharmacokinetics (PK) of sapropterin dihydrochloride in young children 0 months to 6 years of age. The sampling time should be optimized to allow adequate characterization of the PK profile. In addition, investigators will be asked to collect a blood sample for total biopterin testing with the occurrence of a serious adverse event, if possible, if it is considered by the investigator to be probably or possibly related to sapropterin dihydrochloride.

Pharmacodynamic Endpoints:
Sapropterin dihydrochloride responsiveness must be assessed by a ≥ 30% decrease in blood Phe from baseline (pretreatment) to the end of the study (e.g., 4 weeks) while on a PKU controlled diet.

Safety Endpoints:
Safety assessments must include adverse events, tolerability, vital signs, laboratory parameters and growth and development parameters. The following adverse events must be actively monitored:

- Changes in liver enzymes.
- All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- The following adverse events must be captured when spontaneously reported: Arrhythmias, syncope, palpitations, chest pain, shortness of breath, cyanosis, paresthesias, and sudden death. All other adverse events must also be captured when spontaneously reported.

Study 2: Safety and Efficacy Study

Efficacy Endpoints:
The primary efficacy endpoint will be effectiveness of sapropterin dihydrochloride treatment over 6 months and must be assessed by the change in blood Phe levels from baseline (no treatment) at the end of 6 months.

Important secondary endpoints must include age appropriate neurocognitive developmental assessments and must be assessed using well-validated and age-appropriate measures, including the Bayley III. Standardized and replicated measurements of head circumference (less than 3 years of age), weight and length/height must be assessed.

Measures of compliance must include diet recording, pill count, and attendance at required study visits.

Safety Endpoints:
Safety outcomes must include adverse events, tolerability, vital signs, laboratory parameters, and growth and development parameters. The following adverse events must be actively monitored:

- Changes in liver enzymes.
- All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- The following adverse events must be captured when spontaneously reported: arrhythmias, syncope, palpitations, chest pain, shortness of breath, cyanosis, paresthesias, and sudden death. All other adverse events must also be captured when spontaneously reported.

Known Drug Safety concerns and monitoring:

Your safety monitoring plan will include a baseline medical history, vital signs, physical examination, including measurements of growth (i.e., height and weight, and head circumference for patients less than two years of age), developmental assessments (e.g., Bayley III, etc.), and clinical laboratory tests (chemistry, hematology, and urinalysis).

Patients will remain at the study site for three hours after receipt of the first dose, with vital signs taken pre-dose, and 15, 30, 45, 60, 90, 120, and 180 minutes post-dose. Electrocardiograms will be performed 2 to 6 hours post-dose (estimated time of maximum concentration). Vital signs include seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured in mm Hg, heart rate in beats per minute, respiration rate in breaths per minute, and temperature. Vital signs will be measured weekly for the first month of dosing, then monthly until the completion of the study. Medical history will be taken at the screening visit. Physical examinations will be taken at the Screening, Week 0, Week 4, Month 3 and Month 6 visits. Clinical laboratory tests should be performed weekly for the first month of dosing (except the Week 2 visit), then monthly until the completion of the study. Neurocognitive testing will be performed within 6 weeks after a subject is determined to be sapropterin dihydrochloride responsive and after six months of treatment with sapropterin dihydrochloride in patients less than 2 years of age.

Blood chemistry analysis must include, at minimum, liver enzyme tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and gamma-glutamyl transferase (GGT). Hematology testing must include, at minimum, a complete blood count (CBC), including hemoglobin, hematocrit, platelet count, and white blood cell count (WBC) with differential.

Safety will be assessed by evaluating the number and type of adverse events occurring during the study, and by changes from baseline in vital signs, physical examinations, clinical laboratory testing, and developmental assessment results.

Extraordinary results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug information:

- *dosage form*
  Fully dissolvable tablets, fully dissolvable powder, or liquid may be administered. Whole tablet formulations are not appropriate for the ages being studied.

- *route of administration*
  Oral

- *regimen*
  Sapropterin dihydrochloride will be administered at a starting dose of 20 mg/kg/day once daily. Dosing adjustments will be made to achieve exposures observed in older pediatric patients, as tolerated.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must

submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Statistical information:

Descriptive analysis of the pharmacokinetic parameters of tetrahydrobiopterin must be provided.

Safety and effectiveness: Provide a statistical test of the null hypothesis that the mean change from baseline in blood Phe levels at the end of the treatment phase equals zero. Use descriptive statistics for other measures.

Labeling that may result from the study(ies):

You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that sapropterin dihydrochloride is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted:

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-

market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before September 13, 2013. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.
Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type

at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at 301-796-3924.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARLA L EPPS
03/06/2014
NDA 22181 Supplement 13 Clinical Review

LARA DIMICK-SANTOS
03/07/2014

ANDREW E MULBERG
03/07/2014