OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	22-181/S-013	*Submission Date(s)*	9/10/2013,12/10/2013, 1/17/2014, 2/13/2014
Brand Name		Kuvan	
Generic Name		Sapropterin dihydrochloride	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
Pharmacometrics Reviewer		Jingyu "Jerry" Yu, Ph.D.	
PM Team Leader		Nitin Mehrotra, Ph.D.	
OCP Division		Division of Clinical Pharmacology 3 Division of Pharmacometrics	
OND Division		Division of Gastroenterology and Inborn Errors Products	
Sponsor		Biomarin Pharmaceutical Inc.	
Formulation;Strengths; <u>*Proposed*</u> *Regimen*		100 mg Tablet (b) (4) taken once daily with food and may be adjusted in the range of 5 to 20 mg/kg	
Indication		Reduction of phenylananine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydropbiopterin- (BH4) responsive Phenylketonuria (PKU)	

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1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology reviewed the submission and found acceptable from a clinical pharmacology standpoint.

We found the [redacted] (b) (4). Nevertheless the final decision on the optimal starting dose for all age groups should be made with the conclusion on safety assessment into consideration.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Kuvan (sapropterin dihydrochloride) is a Phenylalanine Hydroxylase activator and a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin (BH_4). Kuvan® is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to BH_4-responsive Phenylketonuria. Kuvan is to be used in conjunction with a Phe-restricted diet. The approved starting dose is 10 mg/kg once a day and the dose should be adjusted within the range of 5-20 mg/kg based on the control of blood Phe level.

In this supplement, the sponsor proposes to update the labeling regarding safety and efficacy of Kuvan in patients <4 years old based on a clinical trial conducted in response to the Written Request as well as in fulfilment of a Post-Marketing Commitment. [redacted] (b) (4) In the sponsor's new proposal, Kuvan should be discontinued in non-responders after one month of treatment at 20 mg/kg instead of screening for responders in a sequential treatment at 10 mg/kg/day followed by 20 mg/kg for up to one month at each dose.

Exposure (Dose)-Response Relationship

In Study PKU-015, only one dose level of 20 mg/kg was studied (patients <6 years old) and as such a dose-response relationship was not evaluated in patients < 6 years old. Nevertheless according to the analysis by Dr.Yu, a Pharmacometrics reviewer, a concentration-dependent increase in the proportion of responders (patients with > 30% decrease in blood Phe level from baseline after 4 week treatment) was observed. The E-R relationship for the proportion of responder indicates that efficacy reaches a

plateau at the higher end of concentration range by 20 mg/kg and there is a trend of loss of efficacy at lower concentrations in patients. Please see the attached Pharmacometrics Review for more details.

Previously a dose-response relationship was explored in patients older than 8 years in an open-label, forced dose-titration study in which patients were sequentially treated with Kuvan at 5 mg/kg, 20 mg/kg and 10 mg/kg for two weeks each (Study PKU-004 in the original submission). The clinical pharmacology review of original NDA22-181 noted the following[1]:

- The mean change in blood Phe level at 20 mg/kg was greater than 5 mg/kg and 10 mg/kg and statistically different ($p < 0.001$).
- The percentage of patients with a ≥ 30% reduction in blood Phe levels was 25%, 46%, 55% after dosing for 2 weeks with 5, 10, and 20 mg/kg/day, respectively.
- No apparent relationship between the dose of Kuvan and the incidence of AE was noted.

Starting Dose

(b) (4) with proper selection of patients for Kuvan treatment in addition to the dietary Phe management.

- In patients on Phe-controlled diet, one-week treatment with 20 mg/kg decreased the mean blood Phe concentration from 333 μmol/L to 143 μmol/L.
    - Similarly in a trial previously conducted in patients aged 4-12 years and on Phe-controlled diet, one-week treatment with 20 mg/kg decreased the mean blood Phe concentrations from 321 μmol/L to 110 μmol/L.

- In Study PKU-015, a plasma concentration-dependent increase in the proportion of responders[2] was observed. The decreasing trend of the proportion of responders in lower concentration range indicates that doses lower than 20 mg/kg may not be as efficacious as 20 mg/kg. In addition the E-R relationship indicates that potential responders at 20 mg/kg may not be identified at lower doses. This positive E-R relationship for the proportion of responders is consistent with the positive dose-response relationship observed in patients aged ≥8 years in a dose-titration study (PKU-003).
    - In patients aged < 8 years on Phe-controlled diet (included in Studies PKU-015 and PKU-006[3]), doses other than 20 mg/kg were not studied so the dose-response relationship in this age group on Phe-controlled diet was not evaluated.

- In Study PKU-015, some patients had blood Phe levels lower than 120 μmol/L during Kuvan treatment. After one week of treatment, blood Phe level was reduced to < 120 μmol/L in 60% (12/20), and 25% (13/52) of patients with blood Phe level of 120-240 μmol/L and >240 μmol/L at week 0, respectively. Therefore, the labeling should include languages to caution

[1] Page 5, Clinical pharmacology review of original NDA 22-181 by Dr. Hae-Young Ahn
[2] > 30% blood Phe reduction from baseline
[3] Submitted in the original NDA 22-181, Included patients aged > 4, and < 12 years old

about the decrease in blood Phe level lower than target range within one week treatment with 20 mg/kg especially for patients on Phe-controlled diet.

- In addition, in some patients (n=14), blood Phe fell below 120 μmol/L prior to the Kuvan treatment. It is unclear if an improved compliance to dietary control played a role in lowering blood Phe level prior to treatment while a significant fluctuation of blood Phe level within patients was generally observed. In those patients, an additional blood Phe measurement should have been performed to determine the necessity and timing of Kuvan treatment. As such a close monitoring of blood Phe level before and during Kuvan treatment should be performed and the dose for Kuvan should be adjusted accordingly. The review of the clinical management of blood Phe in PKU patients is deferred to the clinical review by Dr. Epps.

- As for the starting dose in other age groups, in patients for whom a rapid control of blood Phe is desired, a higher starting dose would be preferred. Non-responders to the dose of 10 mg/kg may respond to 20 mg/kg based on the positive exposure-response relationship for the proportion of responders. Starting at the dose of 20 mg/kg would eliminate the screening period with 10 mg/kg for potential responders who would respond to 20 mg/kg than 10 mg/kg and for non-responders for whom treatment with Kuvan should be discontinued. (b) (4) While the dose-related increase in adverse events was not apparent especially in patients who were not on Phe-restricted diets, there is a concern of exaggerated pharmacological effect of Kuvan to reduce blood Phe level lower than desired level in patients on Phe-controlled diets. The review of safety is deferred to the clinical review by Dr. Epps.

Dose adjustment within the range of 5-20 mg/kg/day

Although doses other than 20 mg/kg/day were not studied in pediatric patients younger than 8 years old for the efficacy, the dosage adjustment is reasonable with proper blood Phe monitoring.

Pharmacokinetic/ Biopharmaceutics Properties

In population PK analysis, the body weight but no other covariates were found to significantly affect clearance and volume of distribution supporting the body weight based dosing.

(b) (4) 20 mg/kg dose provides comparable Kuvan exposure levels across different weight groups among pediatric patients. Compared to the systemic exposure in adults, the AUC at steady-state following 20 mg/kg dosing was lower in pediatric patients 1-12 years old tended to be lower while it was similar in patients < 1 year old and >12 years old. Please see the Pharmacometrics Review in Appendix for more details.

In Study PKU-015, the approved Kuvan Tablets but no other formulations were used. Prior to administration, Kuvan was dissolved in as little as 5 ml water or apple juice and administered to patients using an oral syringe and a cup as appropriate. The protocol also allowed mixing Kuvan in

soft foods. Per reviewer's request, the sponsor clarified that patients' families were given the option to mix Kuvan into soft foods at 9 of the 18 sites. These foods included apple sauce, yogurt, porridge, pudding, and mashed potatoes. The sponsor also cited[4] a published literature on the stability of Kuvan in various food media including rice cereal and PKU compatible formula. As the mixing Kuvan in soft foods was allowed during the clinical trial and the publication of Kuvan stability in food media other than approved water and apple juice is available, the labeling update on the compatible food vehicle should be recommended. The review of stability of Kuvan in other food media is deferred to the CMC reviewer.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background to the current assessment of the clinical pharmacology of this drug?

Kuvan (sapropterin dihydrochloride) is a Phenylalanine Hydroxylase activator and a synthetic preparation of the dihydrochloride salt of naturally occurring tetrahydrobiopterin. Kuvan® is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia due to tetrahydrobiopterin-responsive Phenylketonuria. Kuvan is to be used in conjunction with a Phe-restricted diet. Kuvan® Tablet was originally approved in 2007 and Kuvan® Powder for oral solution was approved in 2013. The approved starting dose is 10 mg/kg once a day and dose should be adjusted within the range of 5-20 mg/kg/day based on the control of blood phenylalanine.

For this submission, Study PKU-015 which had two sub-studies was conducted in pediatric PKU patients as specified in the Written Request dated October 31, 2011. These sub-studies were also conducted in fulfillment of Postmarketing Commitment # 1 in the Kuvan NDA approval letter dated December 13, 2007 as below.

> "BioMarin commits to designing and implementing a safety, efficacy, and pharmacokinetics study with Kuvan (sapropterin dihydrochloride) in patients with PKU who are four years of age or younger at study entry. Efficacy is to be assessed by the pharmacodynamic outcome measure of blood phenylalanine levels over a six-month period of treatment."

The original approval was based on studies in patients older than 4 years. The review of the original submission also noted that a limited number of patients 4 to 6 years of age were included. So the additional data was requested in patients 4 to 6 years of age in the Written Request.

[4] Striepeke et al., In Vitro Stability of Sapropterin Dihydrochloride from Crushed Tablets Mixed in Applesauce, Pudding, and Infant Formula". Infant, Child, & Adolescent Nutrition 2009; 1; 267

2.1.2 What are the highlights of the formulation of the drug product as they relate to clinical pharmacology review?

Kuvan is originally approved in Tablet formulation. Kuvan Tablets should be dissolved in 120-240 ml water or apple juice prior to administration. The administration of Kuvan as whole tablets and Kuvan Powder for oral solution was approved in 2013. In Study PKU-015, the administration of Kuvan Tablets after dissolving in water or apple juice was studied.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

(b) (4) dosage may be adjusted in the range of 5-20 mg/kg in all age groups.

The approved dosage is as follows:

> The recommended starting dose of Kuvan is 10 mg/kg/day taken once daily. Response to therapy is determined by change in blood Phe following treatment with Kuvan at 10 mg/kg/day for a period of up to 1 month. If blood Phe does not decrease from baseline at 10 mg/kg/day, the dose may be increased to 20 mg/kg/day. Patients whose blood Phe does not decrease after 1 month of treatment at 20 mg/kg/day are non-responders, and treatment with Kuvan should be discontinued in these patients. Once responsiveness to Kuvan has been established, the dosage may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

(b) (4) The clinical pharmacology review of original submission[5] noted following:

> (b) (4) Doses of Kuvan may be adjusted in the range of 5-20 mg/kg. It is, however, suggested that the 10 mg/kg/day be the starting dose and the patients be titrated up and down based on the response"
> The review noted that although there is clear dose-response relationship (i.e., the higher dose, the more efficacy), the dose of 10 mg/kg/day was used in the pivotal, controlled, phase 3 study (Study PKU-003) and proven to be efficacious. Please see the Clinical Pharmacology Review for original submission for more details.

At the time of approval, the long-term safety and efficacy was yet to be established.

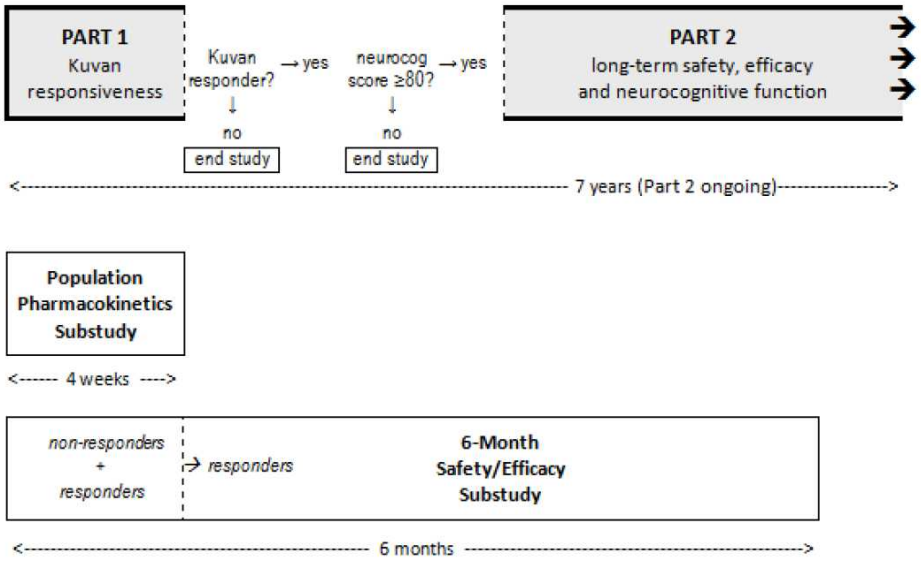
[5] The clinical pharmacology review of original NDA 22-181

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

For this submission, Study PKU-015 which had two sub-studies was conducted in pediatric PKU patients. Study PKU-015 is consisted of two parts: Part 1 to select potential responders to Kuvan and Part 2 for long-term safety and efficacy of Kuvan (Figure 1). In substudy Part 1 a change in blood phenylalanine (Phe) levels from baseline in response to treatment with Kuvan 20 mg/kg/day was examined in patients on Phe-controlled diet to identify potential responders to Kuvan treatment. In addition, a total of three or four plasma samples were to be collected from patients younger than 1 year old and from patients aged 1-4 years, respectively for population PK analysis.

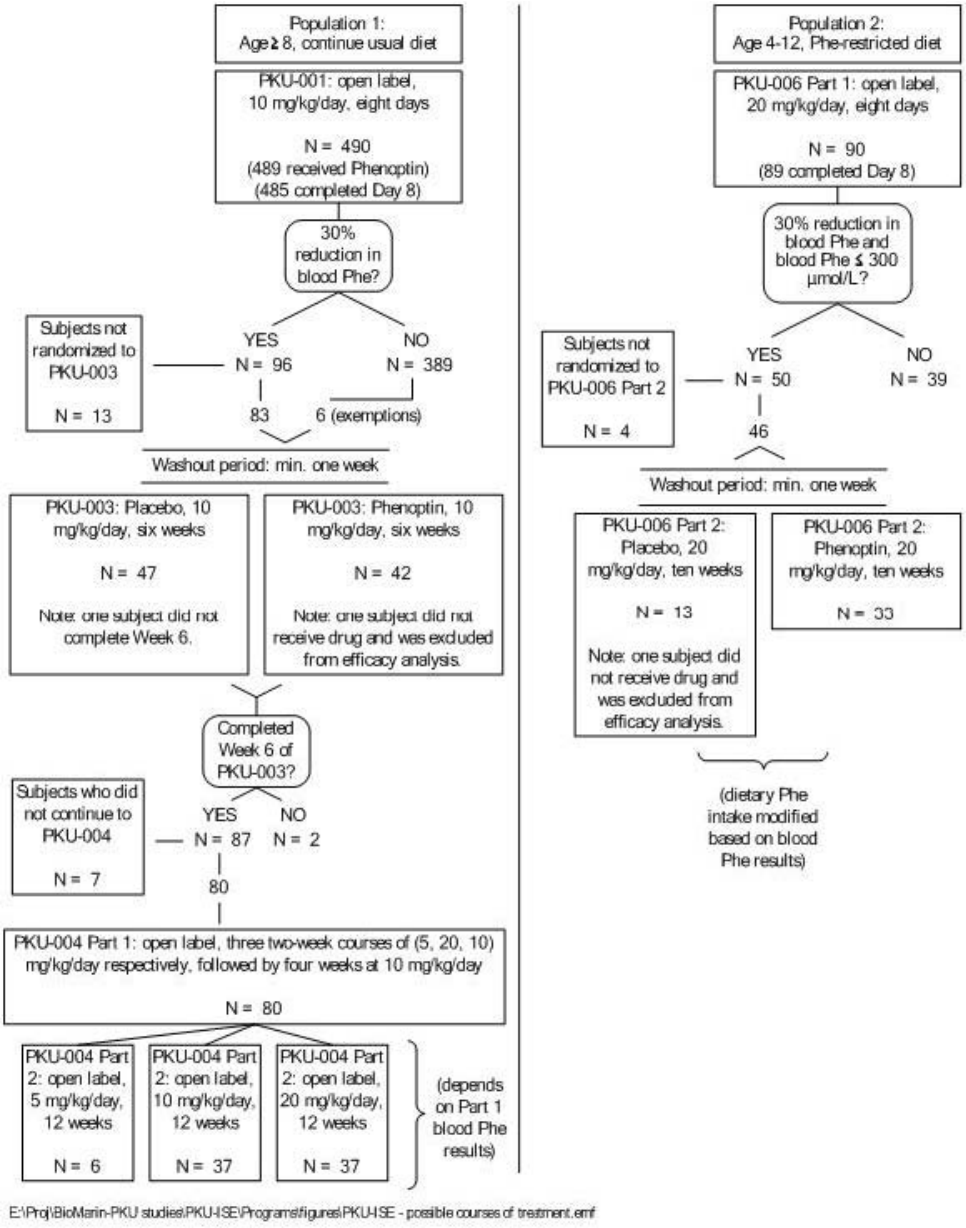
Figure 1. Study Scheme of PKU-015



Kuvan-responsive subjects who scored at least 80 on age-appropriate cognitive measures when tested within 6 weeks of determining Kuvan responsiveness continued to Part 2 of the ongoing study (up to 7 years), which is designed to investigate long-term safety and efficacy. This second substudy analyzes safety and efficacy after 6 months of Kuvan treatment at 20 mg/kg/day.

In addition to Study PKU-015, clinical trials conducted in support of the original approval were referred in support of the proposed labeling changes (Figure 2). For more information, please see the clinical pharmacology review of original NDA 22-181.

Figure 2. Design of clinical trials included in the original NDA[6]



[6] PKU-001: A phase 2, multicenter, open-label study to evaluate the response to and safety of an 8-day course of Phenoptin (Kuvan) treatment in subjects with phenylketonuria who have elevated phenylalanine levels
PKU-003: A phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Phenoptin in subjects with phenylketonuria
PKU-004: A phase 3, multicenter, open-label extension study of Phenoptin in subjects with phenylketonuria who have elevated phenylalanine levels
PKU-006: A Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Phenoptin 20 mg/kg/day to increase phenylalanine tolerance in phenylketonuric children on a phenylalanine-restricted diet

2.2.2 What is the basis for selecting the blood phenylalanine and how are they measured in clinical pharmacology and clinical studies?

The high concentration of blood Phe is associated with neurotoxicity. In Study PKU-015, the response to Kuvan was determined based on the ≥ 30% reduction of blood Phe from baseline after 4 week treatment. The same criteria i.e. ≥ 30% reduction of blood Phe from baseline after 8 day treatment was employed to identify potential responders to Kuvan treatment in previous studies PKU-001 and PKU-004.

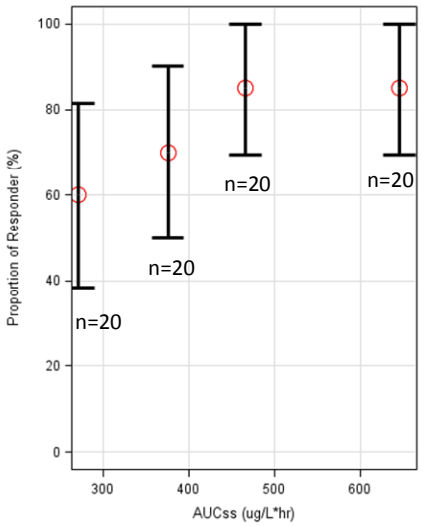
Reviewer's comments: Blood Phe was measured at each site with various bioanalytical assay methods (See 2.3.2. Analytical Section for more discussion)

2.2.3 Exposure-Response Evaluation

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

As only one dose i.e. 20 mg/kg was studied, a dose-response relationship was not evaluated in Study PKU-015 which included patients < 6 years old. The response is defined as > 30% reduction in blood Phe from baseline after 4 week treatment. According to the analysis by Dr. Yu, there was a concentration dependent increase in the proportion of responders[7] in Study PKU-015 (Figure 3). The decreasing trend of the proportion of responders in lower concentration range suggests lower doses may not be as efficacious as 20 mg/kg. This positive E-R relationship for the proportion of responders is consistent with the positive dose-response relationship observed in patients aged ≥8 years in a dose-titration study PKU-003. Of note, patients in PKU-015 were on Phe-controlled diet while patients in PKU-003 were not on Phe-controlled diet.

Figure 3. Proportion of Responders in patients younger than 6 years old by AUCss



[7] > 30% blood Phe reduction from baseline

Dose-response relationship in other age groups

A dose-response relationship was not studied in patients younger than 8 years. In study PKU-006[8] which included patients 4-12 years old, only one dose i.e. 20 mg/kg was studied and in this study patients were on a Phe-restricted diet.

In patients older than 8 years, a dose-response relationship was explored in an open-label, forced dose-titration study (Study PKU-004 in the original submission). The clinical pharmacology review of original NDA22-181 notes the following[9]:

- The mean change in blood Phe level at 20 mg/kg was greater than 5 mg/kg and 10 mg/kg and statistically different ($p < 0.001$).
- The percentage of patients with a ≥ 30% reduction in blood Phe levels was 25%, 46%, 55% after dosing for 2 weeks with 5, 10, and 20 mg/kg/day, respectively.
- In Study PKU-004, 85% of subjects experienced at least one AE. The sponsor reported that during the fixed-dose period, the percentage of subjects who had an AE was similar between the 5 mg/kg/day and the 20 mg/kg/day doses (50% and 57%), but slightly lower for the 10 mg/kg/day dose group (38%). There seemed to be no apparent relationship between the dose of Kuvan and the incidence of AE.

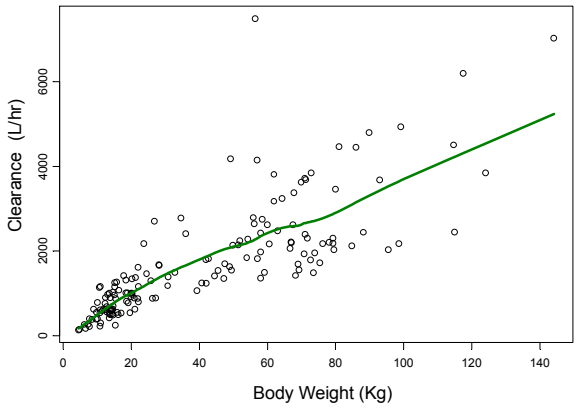
2.3 Factors that affect PK and PD response of Kuvan

2.3.1. Which intrinsic factors affect PK of Kuvan?

Population PK analysis showed that the body weight but no other covariates were found to significantly affect the clearance; therefore, body weight based dose is acceptable (Figure 4).

See the Pharmacometrics Review by Dr. Yu for more details.

Figure 4. Apparent total clearance by body weight following 20 mg/kg once daily dosing



[8] In original submission of NDA 22-181
[9] Page 5, Clinical pharmacology review of original NDA 22-181 by Dr. Hae-Young Ahn

(b) (4) 20 mg/kg dose provides comparable Kuvan exposure levels across different weight groups (Figure 5). In addition, the exposure levels in pediatric populations are lower or similar to that in adults following 20 mg/kg dose (Figure 6).

Figure 5. Kuvan systemic exposure across different body weight groups following 20 mg/kg once daily dosing

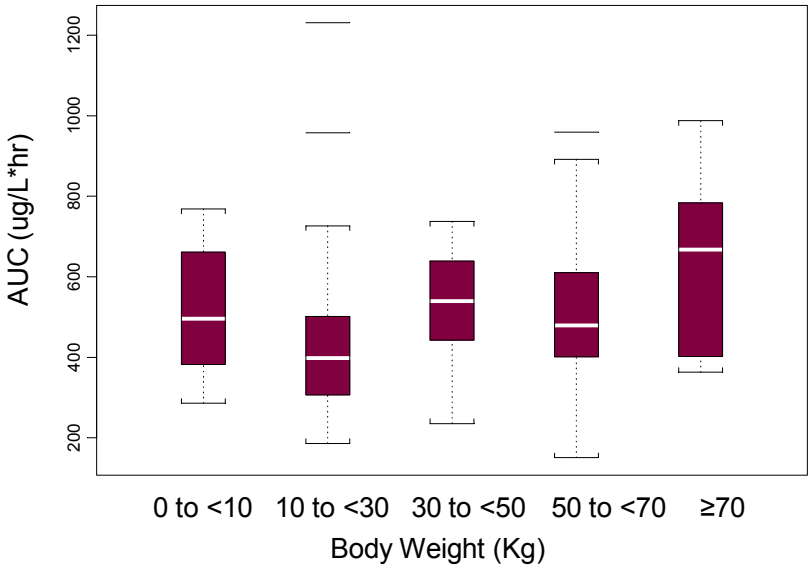
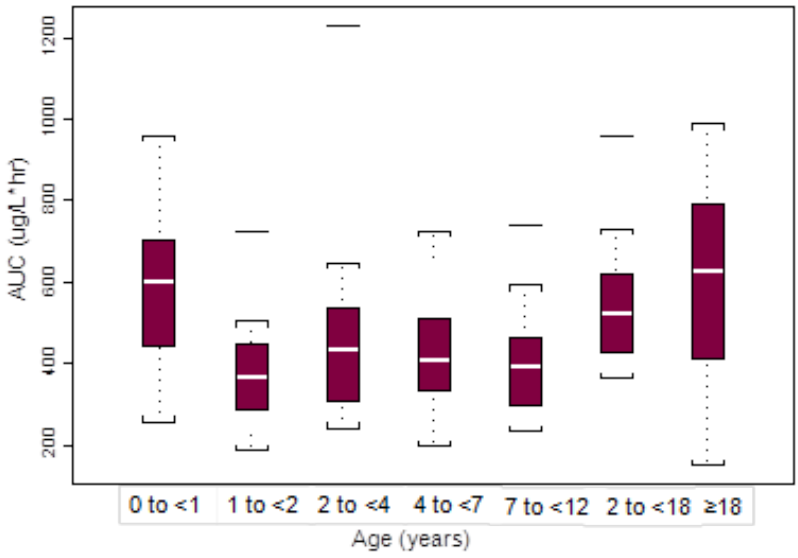


Figure 6. Kuvan exposure (AUCss) across different age groups following 20 mg/kg once daily dosing

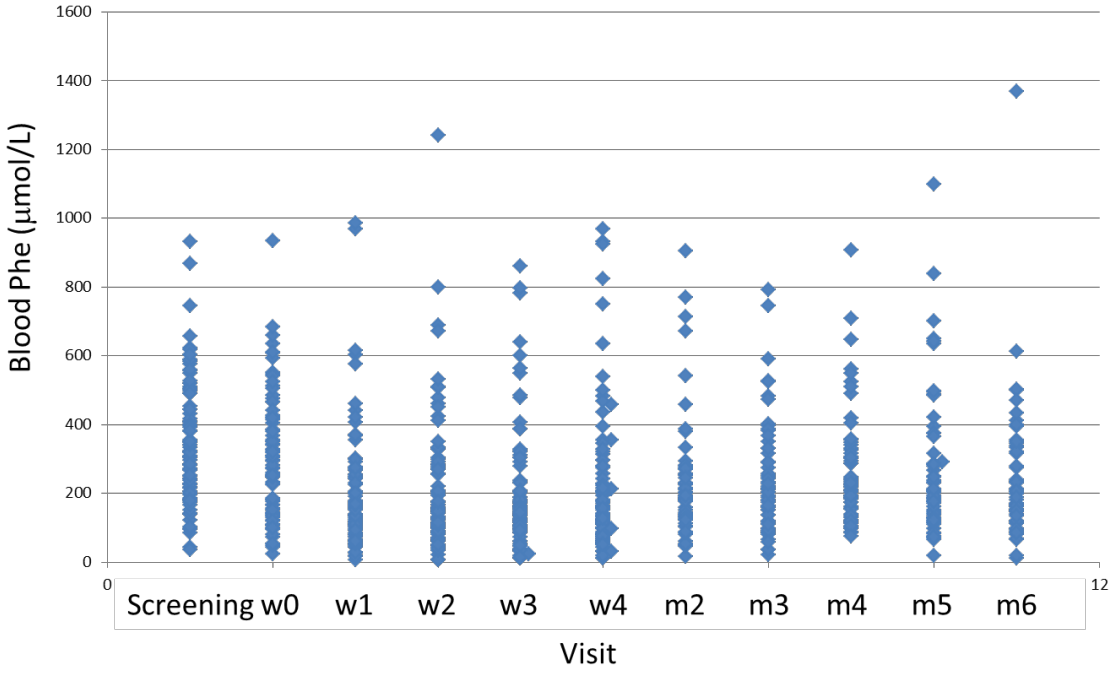


2.3.2. How Kuvan treatment affects the blood Phe level?

Blood Phe levels vary significantly within and among patients before and during Kuvan treatment (Figure 7). In addition blood Phe level changed by dietary intake of Phe. In Study PKU-015, the adjustment in dietary Phe was allowed especially in Part 2 while the dose of Kuvan remained the same and the blood Phe level increased as the prescribed dietary Phe increased.

While the comparison of blood Phe between patients is limited by the use of various assay methods for blood Phe analysis at each study site, per the sponsor for a patient blood Phe level was monitored using a same method over the trial.

Figure 7. Distribution of blood Phe at each visit



In Study PKU-015, upon treatment of Kuvan the substantial reduction of blood Phe was observed at week 1 visit in patients who responded to Kuvan. The mean blood Phe level decreased upon Kuvan treatment and overall the mean value remained below 360 µmol/L with dietary Phe adjustment over time. In Part 1, the extent of blood Phe reduction was similar with the results in Study PKU-006 which included patients aged 4-12 years on a Phe-controlled diet (Table 1). It was noted that some patients had blood Phe level within or below the target range i.e. 120-240 µmol/L immediately prior to Kuvan treatment i.e. week 0.

In some patients, blood Phe fell below 120 µmol/L before Kuvan treatment. In these patients whose blood Phe was <120 µmol/L prior to Kuvan treatment, another blood Phe measurement should have

been performed before treatment with Kuvan to determine the necessity and the timing of Kuvan treatment. In patients whose blood Phe was lower than 120 µmol/L, mean blood Phe stayed below <120 µmol/L for weeks (Figure 8) raising a concern of insufficient Phe level for growth and development. Especially in responders, mean blood Phe further decreased after Kuvan treatment started (Figure 9 (A)). To compensate for the low blood Phe, the prescribed dietary Phe was increased in case blood Phe decreased <120 µmol/L. On the other hand, in the subgroup of patients whose blood Phe > 240 µmol/L among those enrolled in Part 2, the mean blood Phe level after one-week treatment was about 200 µmol/L indicating that the reduction of blood Phe below the target range is also dependent on the baseline blood Phe level prior to Kuvan treatment.

In Part 1 study,

- In patients whose blood Phe was < 120 µmol/L, 64% (9/14) patients had blood Phe level < 120 µmol/L after one week treatment with Kuvan at 20 mg/kg.
- In patients whose blood Phe was between 120 and 240 µmol/L, 60% (12/20) patients had blood Phe level < 120 µmol/L after one week treatment with Kuvan at 20 mg/kg.
- In patients whose blood Phe was > 240 µmol/L, 25% (13/52) patients had blood Phe level < 120 µmol/L after one week treatment with Kuvan at 20 mg/kg.

Table 1. Mean Blood Phe concentration (PKU-003, PKU-006, and PKU-015)

Blood Phe, µmol/L (SD)	**PKU-003**		**PKU-006 Part 2**		**PKU-015**
	Placebo (n=47)	**Phenoptin** (n=41)	**Placebo** (n=12)	**Phenoptin** (n=33)	**Kuvan** (n=65)
PKU-001/PKU-006 Part1 [a]					
Day 1	817 (326)	825 (300)	320 (172)	322 (178)	
Day 8	425 (216)	441 (252)	116 (70)	108 (74)	
PKU-003/PKU-006 Part 2					
Baseline [b]	888 (323)	843 (300)	326 (235)	276 (135)	333.0 (135.03)
Week 1	863 (346)	620 (355)	290 (169)	112 (76)	142.7 (93.35)
Week 2	863 (325)	616 (340) [c]	269 (161)	116 (97)	177.8 (197.04)
Week 3	na	na	230 (116)	127 (90)	145.1 (124.05)
Week 4	907 (341)	587 (375)	na	na	154.1 (145.40)

n, number of subjects; na, not applicable; SD, standard deviation

[a] All subjects received Phenoptin during PKU-001 and PKU-006 Part 1.

[b] In PKU-003, baseline was calculated as mean of pre-treatment measurements taken at Baseline Visits 1 and 2 and Week 0. In PKU-006, baseline was the Week 0 value. In PKU-015, baseline was calculated as mean pre-treatment measurements taken Screening and Week 0.

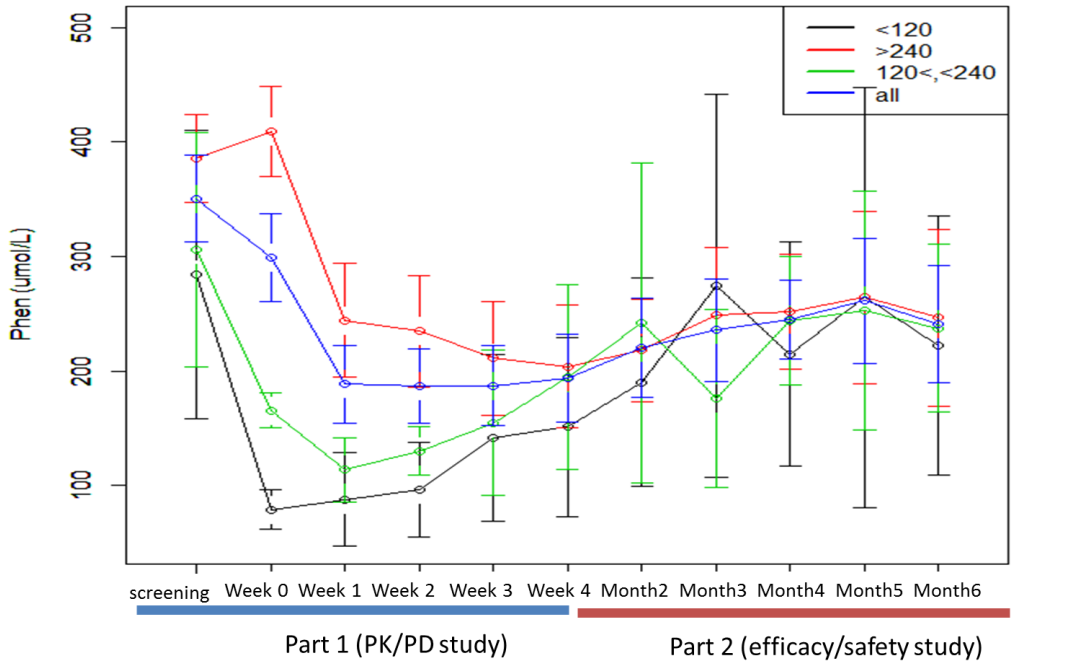
[c] One subject missing blood Phe results for this visit is excluded.

Source: Phenoptin NDA, Table 2.7.3.3.2.3.1.

PKU-003: > 8 years old not on Phe-restricted diet (10 mg/kg/day)
PKU-006: 4-12 years old on Phe-restricted diet (20 mg/kg/day)

Reviewer's comments: In Study PKU-015, for most of patients, screening was done within one week before the week 0 visit but in some cases the interval between screening and week 0 was longer than one week but shorter than a month.

Figure 8. Mean blood Phe level in subgroups based on blood Phe level at week 0

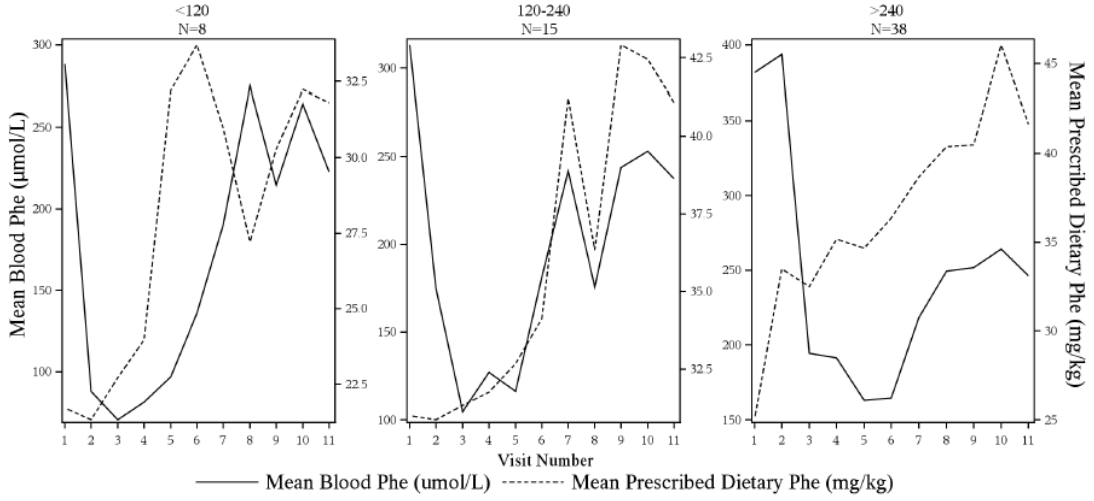


Included all patients (responder and non-responders)

In those patients the adjustment of dietary Phe was allowed at the discretion of principal investigators to maintain blood Phe level within the target range (Figures 9 and 10).

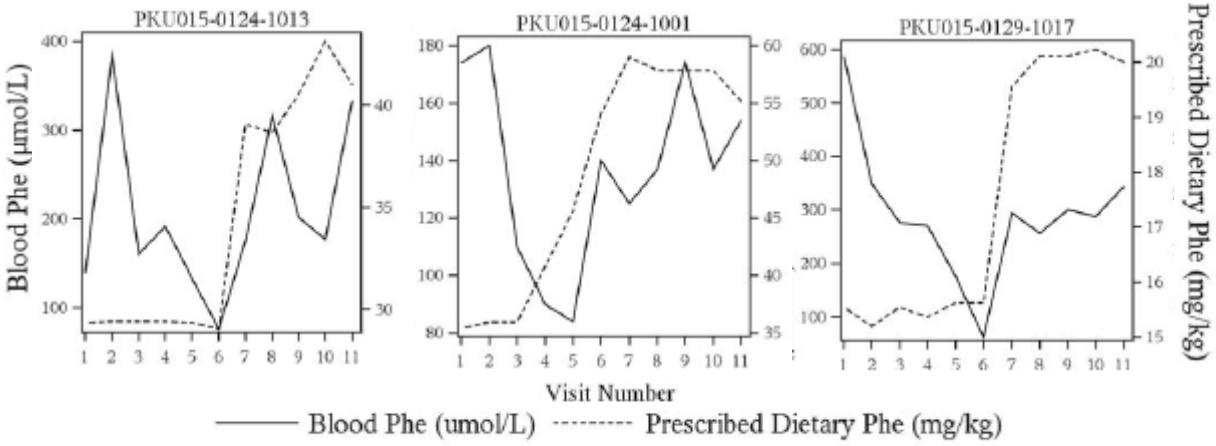
Figure 9. <u>Mean</u> Blood Phe Concentration- and Mean Prescribed Dietary Phe by Visit in Patients Subgrouped by Blood Phe Level at Week 0 * (only included patients enrolled in Part 2)

(A) (B) (C)



- Scheduled Visits: 1=Screening, 2=Week 0, 3=Week 1, 4=Week 2, 5=Week 3, 6=Week 4 (End of Part 1), 7=Month 2, 8=Month 3, 9=Month 4, 10=Month 5, 11=Month 6
- Note that the scales of y-axis are not consistent among figures (In amendment 7 submitted on 1/23/14)

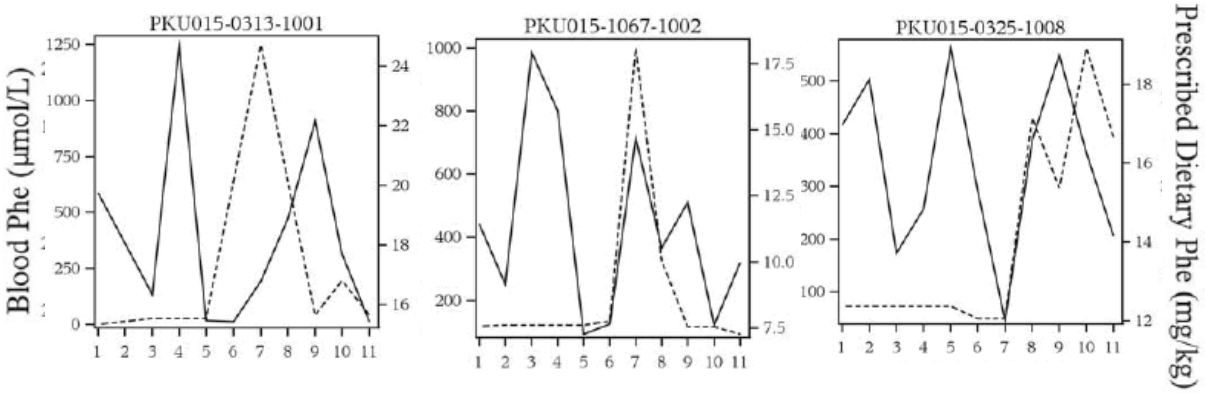
Figure 10. Blood Phe concentration and Prescribed Dietary Phe Time Profile in Selected Patients



- Scheduled Visits: 1=Screening, 2=Week 0, 3=Week 1, 4=Week 2, 5=Week 3, **6=Week 4 (End of Part 1)**, 7=Month 2, 8=Month 3, 9=Month 4, 10=Month 5, 11=Month 6
- Note that the scales of y-axis are not consistent among figures (In amendment 7 submitted on 1/23/14)

In some patients, the blood Phe significantly fluctuated within patients even during the period when the prescribed dietary Phe remained constant. It is unclear if it was due to the non-compliance to dietary Phe restriction (Figure 11).

Figure 11. Blood Phe concentration and Prescribed Dietary Phe Time Profile in Selected Patients



- Solid line: Blood Phe; dotted line: Prescribed dietary Phe (mg/kg)
- Scheduled Visits: 1=Screening, 2=Week 0, 3=Week 1, 4=Week 2, 5=Week 3, **6=Week 4 (End of Part 1)**, 7=Month 2, 8=Month 3, 9=Month 4, 10=Month 5, 11=Month 6
- Note that the scales of y-axis are not consistent among figures (In amendment 7 submitted on 1/23/14)

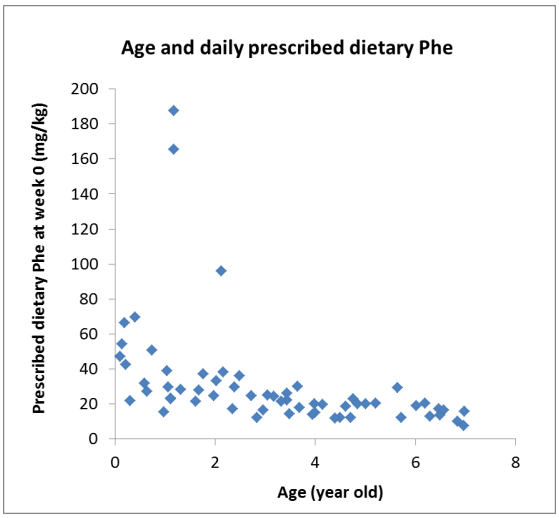
Reviewer's comments: The sponsor stated that for a patient, blood Phe was assayed with the same method over time.

2.3.3. Which extrinsic factors affect the pharmacodynamics effects of Kuvan?

Kuvan is recommended to be used with Phe-controlled diet. As the approved indication states, not all patients are expected to respond to Kuvan treatment. In Study PKU-015, patients were to be on Phe-controlled diet at least during the Part I to identify responders to Kuvan. On the other hand in Part 2 of Study PKU-015, per protocol the adjustment in prescribed dietary Phe by 5 mg/kg was allowed at a discretion of principal investigators when blood Phe level falls out of the target range. In general, the total prescribed dietary Phe amount was increased over time especially during the part 2 when the adjustment of dietary Phe was allowed. During PKU-015, 64.6% of the prescribed dietary Phe modifications were increases because blood Phe concentration fell < 120 µmol/L (73.8%).

Prior to initiation of Kuvan treatment, the range of prescribed dietary Phe per body weight was similar across age group with a trend of higher dietary Phe prescription for infants than for older children (Figure 12).

Figure 12. Prescribed ietary Phe by Age before Kuvan treatment in patients who were enrolled in Part 2 Study



A relationship between the prescribed dietary Phe at week 0 and baseline blood Phe (mean of blood Phe at screening and baseline) was not apparent (Figure 13). When patients were subgrouped by the blood Phe level at week 0, the mean dietary Phe was lower in patients with blood Phe < 120 µmol/L than in patients with higher blood Phe (Table 3).

Figure 13. Baseline blood Phe by Daily Prescribed Dietary Phe before Kuvan treatment in patients who were enrolled in Part 2 Study

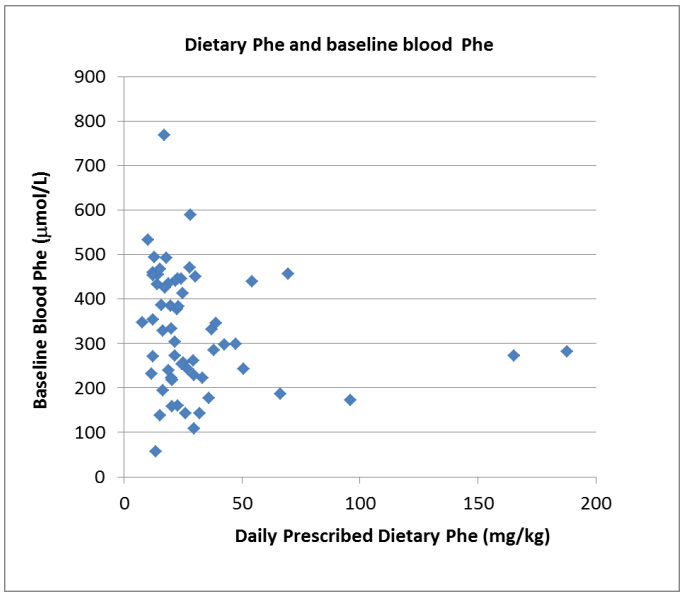


Table 3. Mean Daily Prescribed Dietary Phe at week 0 in patients enrolled in Part 2 by blood Phe at week 0

Subgroup Blood Phe at week 0 (μmol/L)	Mean Daily Prescribed Dietary Phe at week 0	
	mg/kg	mg
< 120 (n=8)	21.32	331.5
120 – 240 (n=36)	30.6	398.3
>240 (n=15)	33.48	389.4

2.4 Analytical Section

2.4.1. How are the active moieties identified and measured in the plasma?

Sapropterin concentrations were obtained indirectly from measurement of L-biopterin due to the instability of BH_4 in human plasma and also the fact that BH_4 can be oxidized to L-biopterin under basic conditions. The LC/MS/MS method was validated to indirectly determine the concentration of "BH_4" by measuring the concentration of L-biopterin and applying a correction factor. The correction factor, 2.150 is calculated according to the conversion ratio of the spiked BH_4 concentration in treated human plasma to the determined concentration of L-biopterin in human plasma.

The BH_4 conversion ratio was calculated as the molar ratio:

$$\textbf{\%BH}_4\textbf{ Conversion Ratio} = \frac{\text{Mean of Biopterin Found}}{\text{Nominal BH}_4\text{ Concentration}} \times \frac{MW_{BH_4}}{MW_{Biopterin}} \times 100$$

where $MW_{BH_4} = 241.2$ and $MW_{Biopterin} = 237.2$

This analysis was carried out by the method outlined in (b) (4) Study Number 146-0402 entitled "Determination of Tetrahydrobiopterin (BH_4) in Human Plasma By LC/MS/MS." The same method was used in other clinical pharmacology studies that previously submitted for review.

Reviewer's comments: Of these 93 subjects, 80 were included in the population PK analysis; of the 345 blood samples collected, 53 samples from 13 subjects were analyzed beyond the established 161-day stability period and, therefore, were excluded from the Population PK analysis. It is acceptable.

2.4.2 How is blood Phenylalanine level measured?

In Study PKU-015, blood phenylalanine was measured at local laboratories certified by the College of American Pathologists (CAP) Laboratory Accreditation or CLIA (Clinical Laboratory Improvement Act) and the 7 Canadian sites were certified by provincial health authorities.
The sponsor clarified that clinical sites were consistent in their use of local laboratories throughout the 6-Month study period. And individual local laboratories used the same method of blood Phe analysis during the 6-Month study period.

According to the sponsor, although individual local laboratories used the same method throughout the study, there was variation in the type of method used between some local laboratories. The type of method, number of sites utilizing each method and the affected patient number (that enrolled in the 6-Month study) is listed as follows: Tandem Mass Spectrometry (MS/MS), 7 sites (n=21); High-Performance Liquid Chromatography (HPLC) 4 sites (n=9); Amino Acid Analyzer (AAA), 3 sites (n=2); Ion Exchange Chromatography (IEC), 2 sites (n=15); Colorimetry, 1 site (n=2); MS/MS or Ultra HPLC, 1 site (n=16) depending on whether they needed Phe and Tyrosine levels only or a complete amino acid panel, respectively. Fifty percent of sites (25 patients) used a filter paper method to collect whole blood for analysis and 50% of sites (40 patients) sent plasma samples for analysis.

***Reviewer's comment*:** The details for different blood Phe assays were not submitted. Use of various methods for blood Phe analysis makes comparison of blood Phe between patients at different sites unreliable so it is not ideal. However, it is not considered invalidating the study results because the blood Phe levels in individual patients were assessed consistently and each patient served as their own reference. The sponsor referred a study report titled "Phenylalanine Testing Equivalency Report" which was previously submitted in the original NDA (#22-181) with the PKU-006 Clinical Study Report. This study evaluated IEC, HPLC, Fluorimetric, and MS/MS methods at 17 local laboratories and found a high level of consistency across methods and laboratories. The clinical pharmacology review of the equivalency report noted that the report demonstrated comparable results. Please see the clinical pharmacology review of original NDA 22-181 by Dr. Ahn for more details.

2.4.3. What is the range of the standard curve for L-biopterin? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

Standard curve concentrations were 5, 15, 50, 100, 300, 500 and 1000 ng/mL and quality control samples levels were 5, 15, 150 and 800 ng/mL. The LLOQ and ULOQ were the same concentration as

the lowest and height calibration standard. Pooled K2 EDTA human plasma was used as the blank matrix throughout the validation.

The results for interday precision and accuracy were within the acceptable range. The precision and accuracy data for 5 ng/mL of L-biopterin spiked in six different lots of K2 EDTA human plasma was within the acceptable range (Table 4).

Table 4. Validation summary for L-biopterin

Table 5. In-study QC results for L-biopterin

concentration (ng/ml)	15 (n=30)	30 (n=30)	150 (n=29)	800 (n=30)
Mean	14.807	29.653	163.746	797.549
S.D.	1.619	2.705	98.476	49.518
%C.V.	10.9	9.1	60.1*	6.2
%RE	-1.3	-1.2	9.2	-0.3

Percent Relative Error (%RE) = (Determined Concentration - Nominal Concentration)/ Nominal Concentration x 100

Reviewer's comment: The inter-day accuracy (% Difference) was acceptable (Table 5). The inter-day precision for QC samples was within acceptable range except for the QC sample of 150 ng/ml.
For the QC sample of 150 ng/ml, % C.V. of 60.1% was reported. The high %CV was due to one measurement with the value of 673.057 ng/ml for nominal concentration of 150 ng/ml. The sponsor did not exclude the value for the % C.V. calculation. The %CV from the calibration standards covering the concentration of 150 ng/ml ranged from 5.2-7.7% and was found acceptable (Table 6).

Table 6. In-study inter-day precision and accuracy for L-biopterin in calibration standards

	5.000	15.000	50.000	100.000	300.000	500.000	1000.000
Mean	5.029	14.758	50.447	100.089	296.508	503.894	1005.007
S.D.	0.387	0.984	2.771	5.505	14.931	29.404	52.719
%CV	7.7	6.7	5.5	5.5	5.0	5.8	5.2
%Diff	0.6	-1.6	0.9	0.1	-1.2	0.8	0.5
n	21	27	29	30	28	27	29

3 Appendices

3.1 Major Labeling Comments

- The labeling should include languages to caution about the decrease in blood Phe level lower than target range within one week treatment with 20 mg/kg in patients on a Phe-controlled diet.

- As the mixing Kuvan in soft foods was allowed during the clinical trial and the publication of Kuvan stability in food media other than approved water and apple juice is available, the labeling update on the compatible food vehicle should be recommended.

3.2. Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the proposed [(b) (4)] dose for pediatric patients aged 0-4 years supported by population PK analysis and exposure-response (E-R) analysis?

Yes. All three dose levels of 5, 10 and 20 mg/kg are approved for patients above 4 years old. The starting dose approved in patients above 4 years old is 10 mg/kg and titrated based on phenylalanine (phe) levels, a pharmacodynamic marker for efficacy. However, sponsor only evaluated a starting dose of 20 mg/kg in < 4 year patients (PKU-015) with titration to lower doses based on phenylalanine levels. From a clinical pharmacology perspective, [(b) (4)]

[(b) (4)]

1. Population PK analysis showed that the body weight (and no other covariates) substantially affects clearance (Figure 1); therefore, body weight based dose is acceptable.
2. The proposed [(b) (4)] dose provides comparable kuvan exposure levels across different weight groups (Figure 2). In addition, the exposure levels in pediatric populations are lower or similar to that in adults following [(b) (4)] (Figure 3).
3. [(b) (4)]

A considerable variability in response of Phe levels was observed in the study PKU-015. Hence, a dose adjustment from 5-20 mg/kg is recommended with regular monitoring the phenylalanine (Phe) levels. As stated above, it is worthwhile to note that all the patients in study PKU-015 (< 4 year old patients) had a starting dose of 20 mg/kg. Whether [(b) (4)] mg/kg is optimal as a starting dose needs further assessment from clinical perspective.

Figure 1. Kuvan clearance vs body weight

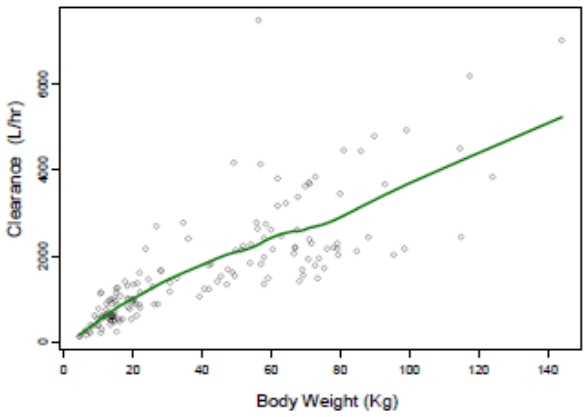


Figure 2. Kuvan exposure (AUCss) across different body weight groups following 20 mg/kg QD dose

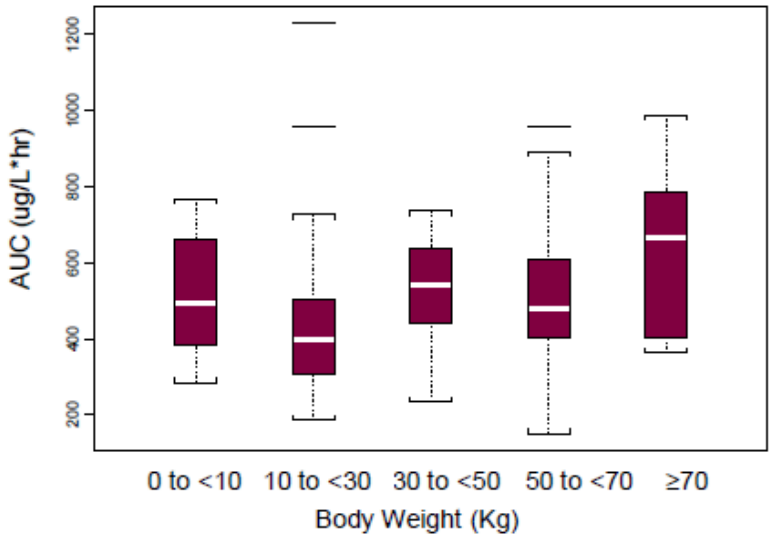


Figure 3. Kuvan exposure (AUCss) across different age groups following 20 mg/kg QD dose

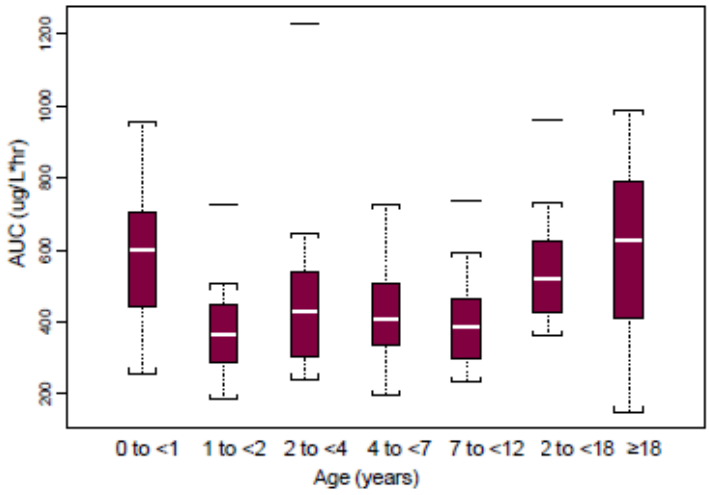
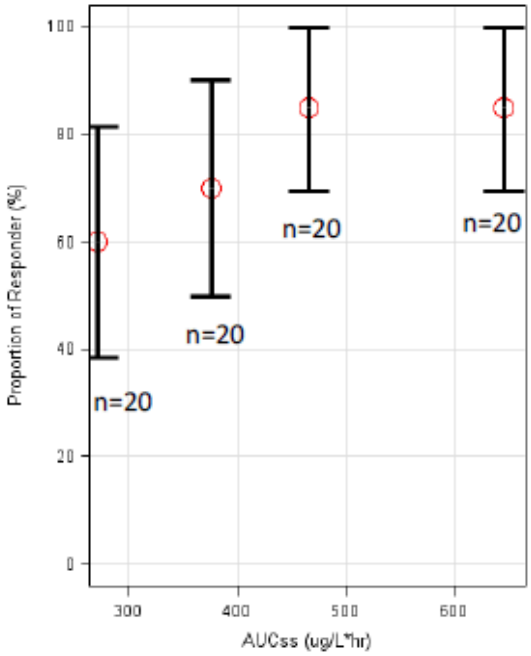


Figure 4. Proportion of Responders at Week 4 vs Kuvan exposure (AUCss) in Study PKU-015



1.2 Recommendations

Division of Pharmacometrics has reviewed this application and recommends approval of kuvan in pediatric patients < 4 years old. Discussions regarding optimal starting dose are ongoing with the clinical review team

1.3 Label Statements

See labeling recommendations in section 4.1 in clinical pharmacology review

2 PERTINENT REGULATORY BACKGROUND

Approval of Kuvan in the US was based on four clinical studies (PKU-001, PKU-003,PKU-004, and PKU-006) evaluating safety and efficacy in PKU patients aged 4 years and older. As part of this approval, the FDA requested that BioMarin fulfill post-marketing commitments. One post-marketing commitment was to conduct a safety, efficacy, and pharmacokinetics (PK) study with Kuvan treatment in PKU patients 4 years of age or younger at study entry; additional data in PKU patients 4 to 6 years of age were requested in a Written Request. PKU-015 study was conducted to meet these FDA requirements. This review focuses on the population PK reports for study PKU-015 in this submission.

3 RESULTS OF SPONSOR'S ANALYSIS

Sponsor conducted population PK analysis to characterize the PK and identify the factors affecting the PK in pediatric patients. The PK data collected from study PKU-015 (0-7 years) and PKU-004 (9-50 years) were pooled together for population PK analysis (Table 1).

Table 1: Demographics in population PK analysis dataset

Demographic	Study PKU-004	Study PKU-015	Pooled
Age at enrollment, years			
n	76	80	156
Geometric mean	19.3	2.45	6.69
Mean (SD)	21.2 (9.73)	3.28 (2.01)	12 (11.3)
CV	45.9	61.4	94.5
Min, Max	9, 50	0.107, 6.98	0.107, 50
Age category, n			
<1 year		10	10
1 to <2 years		14	14
2 to <4 years		28	28
4 to <7 years		28	28
7 to <12 years	10		10
≥12 years	66		66
Sex			
Female	31	49	80
Male	45	31	76
Ethnicity			
Hispanic	2	2	4
Not Hispanic	74	78	152

CV, coefficient of variation; n, number; Max, maximum; Min, minimum; SD, standard deviation

Subjects with:	Study PKU-004	Study PKU-015	Pooled
Weight, kg			
n	76	80	156
Geometric mean	63.8	14.7	30.1
Mean (SD)	67.2 (22)	15.9 (6.36)	40.9 (30.3)
CV	32.8	40	74.1
Min, Max	28.2, 144	4.5, 41.9	4.5, 144
Height, cm			
n	76	80	156
Geometric mean	164	93.8	123
Mean (SD)	165 (13.4)	95.6 (18.3)	129 (38.2)
CV	8.16	19.1	29.5
Min, Max	126, 191	56, 128	56, 191
Body surface area, m^2			
n	76	80	156
Geometric mean	1.7	0.606	1
Mean (SD)	1.72 (0.312)	0.635 (0.19)	1.17 (0.604)
CV	18.1	29.9	51.8
Min, Max	1.05, 2.65	0.259, 1.18	0.259, 2.65
Body mass index, kg/m^2			
n	76	80	156
Geometric mean	23.7	16.7	19.8
Mean (SD)	24.4 (6.08)	16.8 (2.13)	20.5 (5.88)
CV	24.9	12.7	28.7
Min, Max	15.2, 45.5	12.5, 25.6	12.5, 45.5
Phenylalanine, µmol/L			
n	76	80	156
Geometric mean	709	292	450
Mean (SD)	813 (388)	324 (140)	562 (378)
CV	47.7	43.2	67.2
Min, Max	53, 2190	57.5, 768	53, 2190

CV, coefficient of variation; n, number; Max, maximum; Min, minimum; SD, standard deviation

Sources: CSR-PKU-015 Population Pharmacokinetics Substudy and PKU-015 6-Month Safety/Efficacy Substudy, page 83

The final PK model was a one-compartment model with first-order input following an absorption lag time and first-order elimination. Model parameters included CL/F, V/F, first order Ka, ALAG, and C0. Effects of weight on clearance and volume of distribution were described using a power function. No other covariates were identified to explain the inter-subject variability. The estimates for the final population PK model are provided in Table 2.

Table 2: Parameter Estimates in final population PK model

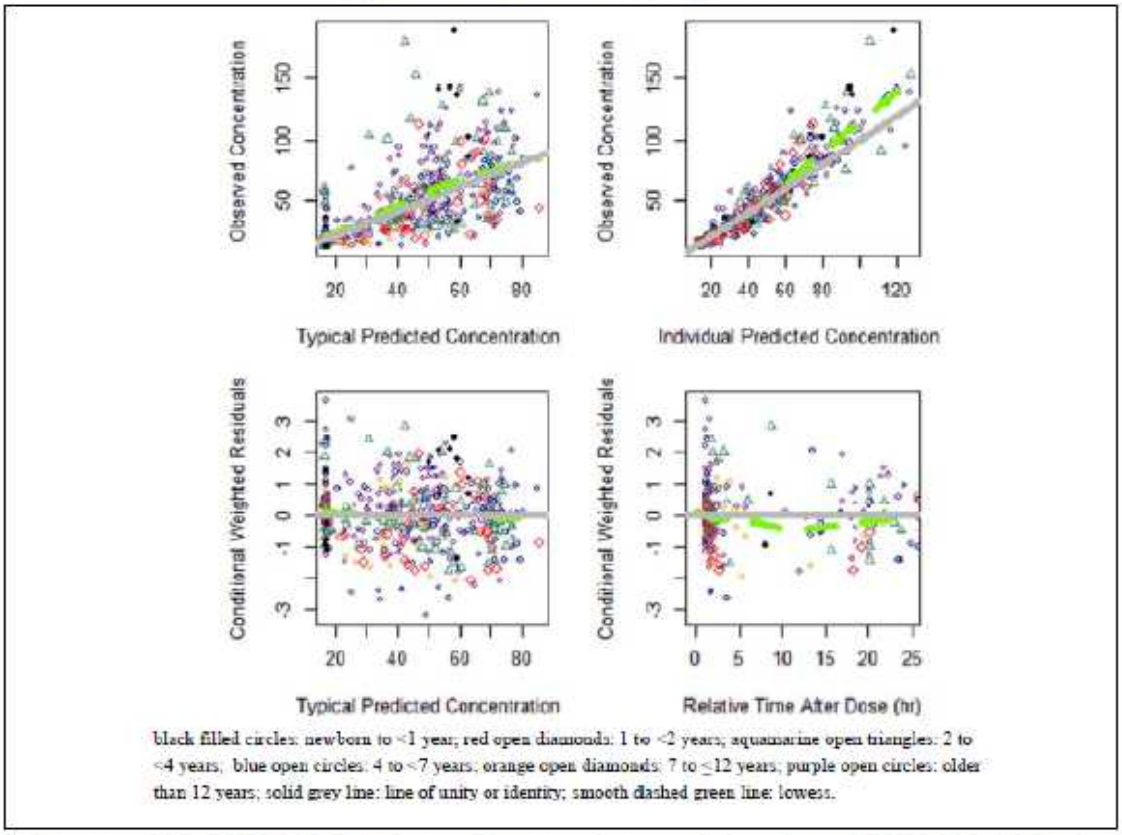
Parameter (units)	Parameter	Estimated Value	Standard Error (%)
CL/F (L/hour)	θ1	2710	9.8
Effect of weight on CL/F	θ6	0.864	7.3
V/F (L)	θ2	3010	43.9
Effect of weight on V/F	θ7	0.644	18.9
Ka (1/hour)	θ3	0.235	23.8
ALAG (hour)	θ4	0.321	11.2
C0 (µg/L)	θ5	16.6	4.1
Residual error study, PKU-004 (%CV)	θ8	21.1	9.2
Residual error study, PKU-015 (%CV)	θ9	30.2	12.0
IIVCL (%CV)	η1	45.61	23.3
IIVV2 (%CV)	η2	56.57	39.4
IIVC0 (%CV)	η3	36.47	30.0
Corr (CL,V)		0.469	NE

ALAG, absorption lag time; CL/F, clearance; C0, baseline endogenous Kuvan concentration; Corr, correlation between parameters; CV, coefficient of variation; IIV, inter-individual variability; Ka, absorption rate constant; NE, not estimated; V/F, volume of distribution

Sources: CSR-PKU-015 Population Pharmacokinetics Substudy and PKU-015 6-Month Safety/Efficacy Substudy, page 91

Reviewer's comments: The final model can adequately describe the observed PK data across different age groups (Figure 5). Based on the estimate (THETA6=0.864) of exponent for body weight effect on clearance, it is expected the body weight based dosing regimen will provide comparable exposure and minimize the variability in Kuvan exposure across different body weight groups. See section 1 for results from reviewer's analysis.

Figure 5: Goodness of fit, final model



Sources: CSR-PKU-015 Population Pharmacokinetics Substudy and PKU-015 6-Month Safety/Efficacy Substudy, page 93

4 REVIEWER'S ANALYSIS

4.1 Objectives

Analysis objectives are:

1. Examine the kuvan exposure levels across different body weight groups and age groups.
2. Graphically explore the exposure-response relationship for patients 0-6 years based on 4-weeks efficacy results in PKU-015 study.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 3.

Table 3. Analysis Data Sets

Study Number	Name	Link to EDR
PKU-015	Pharmacokinetics Substudy and PKU-015 6-Month Safety/Efficacy Substudy	\\cdsesub1\evsprod\nda022181\0087\m5\datasets\pku-015\analysis\adam\datasets\adsl.xpt
		\\cdsesub1\evsprod\nda022181\0093\m5\datasets\pku-015-poppk\analysis\legacy\datasets\base-wtclv.fit

4.2.2 Software

SAS 9.2 and SPLUS were used for data process and graphics.

4.3 Results

See section 1.1.1 for results.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
AUC_lot.ssc	Plot script	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Kuvan_NDA022181_JYU\PPK_Analyses

3.3. OCP Filing Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-181	Brand Name	Kuvan
OCP Division (I, II, III, IV, V)	DCP3	Generic Name	Sapropterin dihydrochloride
Medical Division	DGIEP	Drug Class	
OCP Reviewer	Insook Kim, Ph.D.	Indication(s)	Reduction of phenylananine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydropbiopterin- (BH4) responsive Phenylketonuria (PKU)
OCP Team Leader	Sue-Chih Lee, Ph.D.	Dosage Form	Tablet
Pharmacometrics Reviewer	Jingyu (Jerry) Yu, Ph.D. TL:Nitin Merhorta, Ph.D.	Dosing Regimen	Once daily
Date of Submission	September 10, 2013	Route of Administration	Oral
Estimated Due Date of OCP Review	February 10, 2014	Sponsor	Biomarin
Medical Division Due Date		Priority Classification	P
PDUFA Due Date	March 10, 2014		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods		2		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	x			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		**Study PKU 015 is a new study conducted in patients younger than 4 years old.** **PKU 004 was a study in patients older than 8 year and previously submitted. The sponsor refers the study results for labeling update in pharmacodynamics section. For Pop PK analysis, data from PKU 015 and 004was combined.**
Population Analyses -				
Data rich:				
Data sparse:	x	1		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**6**		**Two new studies and two previously submitted studies were referenced for the proposed changes in dosing and labeling languages**

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	x			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Fileable___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this point

Filing Memo (not to be conveyed to the sponsor)

Submitted is an efficacy supplement for pediatric patients [redacted] (b) (4) (b) (4) to fulfill a Postmarketing Commitment. The sponsor has completed two substudies in pediatric PKU patients as specified in the Written Requested dated October 31, 2011 and Postmarketing Commitment 1 in the Kuvan NDA approval letter dated December 13, 2007 as below.

- Substudy 1 - *PKU-015 Population Pharmacokinetics Substudy*: 4 week population pharmacokinetics study in children with PKU aged newborn to six years old
- Substudy 2 - *PKU-015 6-Month Safety/Efficacy Substudy*: 6 month open label study designed to evaluate safety and efficacy of Kuvan in children with PKU aged newborn to six years old

Significant labeling changes relevant to clinical pharmacology requested in this PAS are as below: Findings from PKU-015 substudies have been incorporated into proposed prescribing information (PI). The PKU-015 substudy results in PKU patients from newborn to 6 years old were similar to clinical findings in previous clinical studies in older children and adults (PKU-006 study aged 4 to 12 years old and PKU-004 study with patients aged 8 to 49). Based on new and available study results, the sponsor proposes [redacted] (b) (4) dose as an appropriate starting dose for all age groups.

Dosage and Administration:

- [redacted] (b) (4) The proposed PI still allows for dose adjustment within the range of 5 to 20 mg/kg/day once responsiveness is established.
- The Administration section has been updated to provide instructions for administration to infants, consistent with the PKU-015 protocol. It allows for dissolving Kuvan in as little as 5 mL of water or apple juice for patients that weigh 5 kg or less. This has also been added to the section [redacted] (b) (4) (b) (4)

Clinical Pharmacology

- The Pharmacodynamics section provides the dose-response relationship for Kuvan supported by the PKU-004 results.
- The Pharmacokinetics section incorporates results from PKU-015 study population pharmacokinetic analysis indicating that no effect of age on sapropterin dihydrochloride pharmacokinetics , and to clarify that body weight is the only covariate substantially affecting

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clearance or distribution volume, which is supported by results from pediatric studies PKU-015 and PKU-004.

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Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	10/28/13
Team Leader	Date

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