

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-181

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-181
Submission Code	N
Letter Date	25 May, 2007
Stamp Date	25 May, 2007
PDUFA Goal Date	25 November, 2007
Reviewer Name	Ethan D. Hausman, MD
Through	Anne R. Pariser, MD, Clinical Team Leader
Review Completion Date	7 December, 2007
Established Name	Sapropterin; 6R-tetrahydrobiopterin (6R-BH4)
(Proposed) Trade Name	Kuvan
Applicant	BioMarin Pharmaceutical Inc.
Priority Designation	Priority
Formulation	Oral
Dosing Regimen	5, 10, and 20 mg /kg/day
Indication	To reduce blood phenylalanine levels in patients with hyperphenylalaninemia due to BH4-responsive phenylketonuria (PKU)
Intended Population	Patients with BH4-responsive PKU

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Partial List of Abbreviations Used in this Clinical Review

DAP	Daiichi Suntory Pharma
BH4	Tetrahydrobiopterin
Hyper-Phe	Hyper-phenylalaninemia
PAH	Phenylalanine hydroxylase
PHE	Phenylalanine
PKU	Phenylketonuria

**Appears This Way
On Original**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This Reviewer recommends Approval of Kuvan for the following indication:

“Kuvan is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe-restricted diet.”

The rationale for this recommendation is based on the efficacy results of the pivotal, double-blind, placebo-controlled Efficacy Study (PKU-003). In this study of patients with PKU, eight years and older, who were previously screened for potential BH4-responsiveness, the reduction in blood Phe in Kuvan-treated patients was superior to placebo-treated patients. The reduction in blood Phe in sapropterin-treated patients was clinically meaningful and statistically significant. It is recommended that since not all patients with PKU in clinical trials responded to Kuvan treatment, the treatment indication should be restricted to patients with BH4-responsive PKU.

The safety results from the short-term clinical trials with Kuvan showed a concerning safety signal for the risk of mild to moderate neutropenia. Otherwise, the type and incidence of AEs reported in Kuvan- and placebo-treated patients were similar, and were comprised of AEs commonly reported in the general population and otherwise healthy patients with PKU, such as headaches and upper respiratory tract infections. Safety assessments were limited to approximately 29 weeks of Kuvan treatment. The long-term safety of Kuvan in patients with BH4-responsive PKU has not been established.



1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No risk management activities are warranted at this time.

1.2.2 Required Phase 4 Commitments

The recommended indication for Kuvan is limited by the narrow scope of the clinical data submitted in support of this application, and a number of clinical areas need to be addressed by post-marketing commitments. It is recommended that Kuvan undergo further clinical evaluation in:

- Children with PKU who are younger than four years of age.
- The effect of sapropterin on growth and development of pediatric PKU patients over time.
- The effect of sapropterin on pregnancy, lactation, and the off-spring of pregnant women with PKU.
- The effect of sapropterin on cardiac safety (e.g., QT interval).
- Assessment of any association of genotype and clinical response to sapropterin treatment.
- The safety and efficacy of sapropterin on patients with primary BH4 deficiency.

Therefore, the following clinical post-marketing actions are recommended:

1. Design, implement, and complete a study of the safety, efficacy, and pharmacokinetics of Kuvan (sapropterin) in patients with PKU, who are less than or equal to four years of age at study entry. Efficacy is to be assessed by the pharmacodynamic measure of blood phenylalanine levels over a six-month period of treatment.
2. Design and implement a long-term study to assess growth and neurocognitive development in Kuvan treated patients who are less than or equal to eight years of age at study entry. This study is to include blinded assessments of growth (including standardized measurements of recumbent length, height, weight, and head circumference), and developmental testing (the scales used need to be prospectively agreed upon) at six- to twelve-month intervals over a seven year period.
3. Completion of the open-label extension study PKU-008, entitled “A Phase 3b, Multicenter, Open-Label Extension Study of Phenoptin™ in Subjects with Phenylketonuria Who Participated in Studies PKU-004 or PKU-006”. Patients are to be treated under PKU-008 for a minimum of two years of total treatment with Kuvan.
4. Design and implement a registry of patients with PKU being treated with Kuvan that will obtain long-term clinical status information. Information will be collected on patient demographics, specifics of treatment with Kuvan, clinical status, neurocognitive assessments, growth and development (for patients who are pre-pubertal at the start of treatment), and adverse events. This registry will be designed so that detailed clinical status information is collected at registry entry and on a six- to twelve-month basis for at least 15 years. The Sponsor is to conduct a sub-study within the registry that will evaluate the effect of Kuvan on pregnancy and lactation. The registry data will be analyzed at yearly intervals and the results will be submitted in annual reports to the Kuvan IND (#69,708).

5. Design, implement, and complete a thorough QT (TQT) study with Kuvan that complies with ICH E14.¹ The dose of Kuvan administered in the TQT study is to be selected so that it results in plasma concentrations that cover the expected high clinical exposure scenario in patients with BH4-responsive PKU, without compromising study patient or subject safety. This study may be a single-dose, positive- and placebo-controlled, cross-over study in healthy volunteers.
6. The analysis of the whole blood samples for *PAH* gene mutations that were collected during PKU-001 study, entitled “A Phase 2, multicenter, open-label study to evaluate the response to and safety of an 8-day course of Phenoptin™ (sapropterin dihydrochloride) treatment in subjects with phenylketonuria who have elevated phenylalanine levels” is to be completed. These samples are to be analyzed to determine whether patients with PKU with specific *PAH* mutations are likely to be responders (by change in blood phenylalanine levels) to treatment with Kuvan.
7. Completion of the open-label study PKU-007, entitled “A Phase 2, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Phenoptin™ in Subjects with Hyperphenylalaninemia Due to Primary BH4 Deficiency”. The core safety and efficacy portion of this study is complete and patients are continuing on in an extension study.

1.2.3 Other Phase 4 Requests

No risk management activities are warranted at this time.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Phenylketonuria (PKU) is a rare inherited disorder of phenylalanine (Phe) metabolism. Untreated patients experience adverse neurological outcomes including mental retardation and seizures. Current treatment options are limited to dietary Phe restriction, which lowers blood Phe and is associated with reduced incidence and severity of adverse neurologic outcomes. Long-term dietary Phe restriction is difficult to maintain. Therefore, a safe and effective drug that reduces blood Phe would be an important addition to the clinical armamentarium for the treatment of PKU.

This document reviews four safety and efficacy trials in patients with BH4-responsive PKU including: the Enrichment Study (PKU-001), the Efficacy Study (PKU-003), the Extension Study (PKU-004), and the Diet Study (PKU-006). Additionally, the expanded access program (EAP; SEAP-001) is reviewed for safety. These five studies comprise the entire sapropterin-PKU patient experience at the time of submission of the NDA and at receipt of the 120-day safety update.

1.3.2 Efficacy

The Enrichment, Efficacy, Extension, and Diet Studies were reviewed for efficacy. The Efficacy Study and Part II of the Diet Study were randomized, double-blind, placebo-controlled studies. The Enrichment and Extension Studies and Part I of the Diet Study were open-label, uncontrolled studies.

The Enrichment, Efficacy, and Extension Studies represent a continuum of 498 patients who were treated for one week in the uncontrolled Enrichment Study, 89 of whom were then studied under controlled conditions for six weeks during the Efficacy Study. Eighty patients from the Efficacy Study were then enrolled in the uncontrolled Extension Study. Daily Phe intake was not controlled in these three studies. In contrast dietary Phe was controlled in the Diet Study, which was a two-part study that screened patients for BH4 responsiveness (Part I) and assessed dietary Phe tolerance (Part II).

Efficacy results are summarized below.

- Enrichment Study (PKU-001): In this open-label (OL), uncontrolled study of 489 patients with PKU and screening blood Phe >450 uM, between eight and 49 years of age, patients were treated with sapropterin 10 mg/kg/day for eight days. Ninety-six patients (20%, 95% CI [16, 23]) had a $\geq 30\%$ reduction in blood Phe from Day 1 (Baseline) to Day 8 and were classified as Responders, and qualified for enrollment in the Efficacy Study. The study was adequately designed to identify patients for further study under controlled conditions in the Efficacy Study. These results can not be used to independently support efficacy.
- Efficacy Study (PKU-003): In this short-term, randomized, double-blind (DB), placebo-controlled (PC) study, 88 Responders from the Enrichment Study were randomized to receive sapropterin 10 mg/kg/day (N=41) or placebo (N=47) for six weeks. The primary efficacy analysis showed a difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) for the Intent to Treat (ITT) population of -245 uM (SE 53 uM), 95% CI [-350, -140]; $p < 0.001$. These primary efficacy findings show a clinically meaningful and statistically significant decrease in blood Phe in sapropterin- vs. placebo-treated patients with BH4-responsive PKU.

Important secondary efficacy endpoints were mean changes in blood Phe at Weeks 1, 2, and 4. Reduction in blood Phe was apparent at Week 1 and was sustained through Week 6. These important secondary efficacy findings demonstrate a clinically meaningful decrease in blood Phe in sapropterin- vs. placebo-treated patients with BH4-responsive PKU and support the primary efficacy findings.

- Diet Study (PKU-006): Part I was a short-term, OL, uncontrolled study of 89 patients with PKU on dietary Phe restriction, between four and twelve years of age, with a screening blood Phe <480 uM, who were treated with sapropterin 20 mg/kg/day for eight days. Fifty of 89 patients (56%) had a $\geq 30\%$ decrease in blood Phe from Day 1 (Baseline) to Day 8 and Day 8 blood Phe <300 uM. These patients were classified as

Responders and qualified for enrollment in Part II. These findings may be included in labeling in support of the percentage of the PKU population who may respond to sapropterin 20 mg/kg/day.

Part II was a 3:1 randomized, DB, PC study of sapropterin 20 mg/kg/day (N=33) vs. placebo (N=12) in patients who were Responders in Part I. After three weeks of DB treatment, dietary Phe supplement could be added to the patients' daily intake base on blood Phe results. The primary efficacy endpoint was the maximum dietary Phe supplement tolerated at Week 10 while maintaining blood Phe <360 uM. Phe supplement tolerated at Week 10 in sapropterin-treated patients was 21 mg/kg/day (SD 15) (p<0.001) and Phe supplement tolerated in placebo-treated patients was 3 mg/kg/day (SD 4) (p=0.03). The primary efficacy findings show a statistically greater amount of dietary Phe supplement was tolerated in sapropterin- vs. placebo-treated patients with BH4-responsive PKU. The primary efficacy endpoint from Part II, tolerated dietary Phe, is not recognized as a clinically meaningful endpoint and has not been demonstrated to be safe in long-term clinical studies. ~~_____~~

The important secondary efficacy endpoint of Part II was a comparison of mean change in blood Phe from Week 0 (Baseline) to Week 3 prior to first dietary Phe supplementation for sapropterin-treated patients. Mean change in blood Phe for sapropterin-treated patients was -149 uM (SD 134). This secondary efficacy finding supports the primary efficacy findings of the Efficacy Study.

- Extension Study (PKU-004): This was an open-label, uncontrolled study of 80 patients who received >80% of doses in the Efficacy Study. In Part I, patients were treated sequentially with sapropterin 5, 20, then 10 mg/kg/day for two weeks at each dose. In Part II, patients were treated with open-label sapropterin based on blood Phe during Part I when they were being treated with 5 (N=6), 10 (N=37), or 20 (N=37) mg/kg/day for 12 weeks.

The primary efficacy endpoint of Part I was change in blood Phe at the end of each two-week dose period (5, then 20, then 10 mg/kg/day) compared to Week 0 (Baseline). At the end of treatment with 5 mg/kg/day, mean change in blood Phe was -100 uM (SD 295). At the end of treatment with 10 mg/kg/day, mean change in blood Phe was -204 uM (SD 303). At the end of treatment with 20 mg/kg/day, mean change in blood Phe was -263 uM (SD 318). These findings show a clear dose-response effect of sapropterin treatment in patients with BH4-responsive PKU.

The efficacy endpoint of Part II was change in blood Phe at each dose level for the ITT at Weeks 12 through 22, irrespective of dose (5, or 10, or 20 mg/kg/day). The reduction in blood Phe from Baseline between Weeks 12 through 22 varied between -190 uM (SD 356) and -206 uM (SD 326). The reduction in blood Phe established in Part I was maintained through Part II. These findings show durability of treatment effect of sapropterin in patients with BH4-responsive PKU.

In conclusion, it is the overall assessment of this Reviewer that data from these four short-term clinical efficacy and safety studies conducted in patients four to 49 years old with PKU support the effectiveness of Kuvan in reducing blood Phe in patients with BH4-responsive PKU. Results in the Efficacy Study demonstrate short-term efficacy of sapropterin treatment at a dose of 10 mg/kg/day in patients eight to 49 years old. Results at Week 3 of the Diet Study, prior to dietary Phe supplementation, support short-term efficacy of sapropterin treatment at a dose of 20 mg/kg/day in patients four to 12 years old. Results from the open-label Enrichment Study and Part I of the Diet Study suggest that patients can be screened for response to sapropterin with doses of 10 or 20 mg/kg/day for periods as short as one week.

Long-term dietary Phe tolerance was not studied, and studies of short-term dietary Phe tolerance did not incorporate neurocognitive outcomes. Blood Phe was accepted as an efficacy outcome in these short-term studies because of a long history of PKU treatment with dietary Phe restriction, and the association of dietary Phe restriction with lowering blood Phe levels, and improved long-term neurocognitive development. Kuvan studies did not employ neurocognitive measures or neurocognitive outcomes. Labeling should state that long-term neurocognitive outcomes were not assessed in clinical trials. Neurocognitive outcomes should be evaluated in long-term post-marketing studies.

1.3.3 Safety

The safety information submitted in this NDA includes clinical information from nine studies performed with Kuvan, the Sponsor's product. These studies include the two controlled and two uncontrolled studies described in section 1.3.2 above, the EAP, two pharmacokinetic (PK) studies in healthy volunteers, an ongoing study of primary BH4 deficiency, and a study in patients with hypertension investigated under _____ (e.g., Kuvan Studies). These studies include 579 patients with PKU, 74 healthy volunteers, 12 patients with primary BH4 deficiency, and 116 patients with chronic hypertension. Treatment in these studies ranged from one day to 40 weeks. The gender composition in Kuvan studies was approximately equal, and the age range of patients exposed to sapropterin in Kuvan studies was from four to 49 years.

The Sponsor also submitted summary information from fourteen studies and the post-marketing experience of another product with the same active ingredient (sapropterin as Biopten). Three of these studies were PK studies in healthy volunteers (N=18), which were submitted in support of Kuvan. Supplemental information in controlled studies of Biopten are limited to 306 patients with autism (N=191 Biopten, N=115 placebo) and Machado-Joseph Disease (N=84 Biopten, N=89 placebo). An additional 305 patients were treated in uncontrolled studies of autism, primary BH4 deficiency, and Machado-Joseph Disease. Length of treatment in these studies range from one day to ten years.

The safety results are notable for the following:

- There were no deaths reported in patients treated with Kuvan or Biopten.

- Withdrawals: Seven patients withdrew. Four patients withdrew due to compliance. One patient each withdrew due to pregnancy, dysmenorrhea, and testicular neoplasm, none of which were related to treatment with sapropterin.
- Serious Adverse Events (SAEs):
 - In studies of PKU, the incidence of SAEs in Kuvan- and placebo-treated patients was 1% each. In the chronic hypertension study, the incidence of SAEs in Kuvan- and placebo-treated patients was 3% each. These SAEs were not apparently related to treatment with Kuvan. A list of SAEs occurring in Kuvan-treated patients with PKU is to be included in labeling, and includes: _____ urinary tract infection, _____, spinal cord injury, streptococcal pharyngitis, and testicular carcinoma.
 - A list of SAEs occurring in Kuvan- or Biopten-treated patients for diseases other than PKU, including primary neurologic disorders and _____ cardiovascular disease is to be included in labeling, and includes: myocardial infarction, respiratory failure, and post-procedural bleeding _____
- Common Adverse Events: In pooled, DB, PC Kuvan Studies (Efficacy and Part II of the Diet Study) the incidences of non-serious AEs in sapropterin- and placebo-treated patients (64% vs. 70%) were similar; although AEs were lowest in patients receiving sapropterin 10 mg/kg/day (51%), and highest in patients receiving 20 mg/kg/day (79%). The most common AEs in sapropterin-treated patients were headache (15% of patients), upper respiratory tract infection (12%), and rhinorrhea (11%), which are not meaningfully different from AEs reported in placebo-treated patients, or from common complaints in the general population or otherwise healthy patients with PKU.
- Special safety concerns:
 - Neutropenia occurred in 3% (17 of 579) of patients who were exposed to sapropterin in the Kuvan Studies. Since all patients were exposed to sapropterin in the Kuvan studies, and since no “challenge-dechallenge-rechallenge” information is available, no definitive association of Kuvan treatment with neutropenia can be made. However an association of Kuvan treatment with neutropenia should appear in labeling.
 - _____
 - Growth and development in pediatric patients with PKU were not assessed. Since Kuvan is intended for chronic (i.e., many years) administration to pediatric patients, during periods of growth and development, then growth and development assessments should be part of post-marketing study commitments. Patients should be

followed from birth through Tanner Stage IV or fifteen years of age, whichever occurs later.

- Thorough QT (TQT) studies and, cardiac safety assessments were not performed. Since Kuvan is a new molecular entity (NME) that is systemically available, a TQT study is to be performed. This TQT study may be performed as a post-marketing commitment
- The longest combined exposure to Kuvan in patients with PKU who participated in multiple clinical trials is 29 weeks (N=80), and mean exposure in the EAP was 23 (SD 9) weeks (N=108). This Reviewer concludes that duration of exposure was not adequate to support long-term safety. Since Kuvan is intended for chronic administration, long-term studies of at least two years are required and may be performed as post-marketing commitments.

Summary of clinical safety results with Biopten: The safety profile of Biopten in healthy volunteers and in patients with diseases other than PKU is substantially similar to the safety profile of Kuvan in patients with PKU. The only notable difference in controlled trials with Biopten occurred in patients with autism where polyuria was noted in 9% of sapropterin-treated patients vs. 3% of placebo-treated patients. Polyuria in these patients was not associated with other AEs or clinical laboratory abnormalities. Therefore, since polyuria was not noted in studies with Kuvan, the clinical relevance of polyuria to the PKU population is unclear

1.3.4 Dosing Regimen and Administration

The proposed starting dose of Kuvan is 10 mg/kg/day. If reduction in blood Phe does not occur after four weeks, while dietary Phe intake is unchanged, the dose may be increased to 20 mg/kg/day. If reduction in blood Phe does not occur after several weeks at 20 mg/kg/day, while dietary Phe intake is unchanged, these patients should be considered non-responders and treatment with Kuvan should be discontinued. For patients who show a response at 10 or 20 mg/kg/day, dose may be adjusted between 5, 10 and 20 mg/kg/day to achieve a desired reduction in blood Phe.

The recommended starting dose is supported by the data from the Enrichment Study and Part I of the Diet Study. In the Enrichment Study 90 of 489 (20%) patients with PKU, ages eight to 49 years, who were treated with Kuvan 10 mg/kg/day for eight days had a $\geq 30\%$ decrease in blood Phe from non-treatment Baseline. Diet was not controlled during this study. In Part I of the Diet Study 50 of 90 (56%) patients with PKU, ages four to 12 years, who were treated with Kuvan 20 mg/kg/day for eight days had a $\geq 30\%$ decrease in blood Phe from non-treatment Baseline. Diet was controlled during this study. Since Efficacy was demonstrated with the 10 mg/kg/day dose, this dose is recommended as the starting dose.

Overall efficacy for the reduction blood Phe in patients with BH4-responsive PKU was established in the Efficacy Study. In this study, the difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) for the ITT was -245 uM with a standard error of 53 uM, 95% CI [-350, -140]; $p < 0.001$. N=41 sapropterin; N=47 placebo. Diet was not controlled during this study.

In the open-label, uncontrolled Extension Study (PKU-004), treatment with 5 mg/kg/day resulted in a mean change in blood Phe of -100 uM (SD 295); treatment with 10 mg/kg/day resulted in mean change in blood Phe of -204 uM (SD 303); and treatment with 20 mg/kg/day resulted in a mean change in blood Phe was -263 uM (SD 318). N=80. Diet was not controlled during this study.

This Reviewer concludes the efficacy data summarized above support the proposed starting dose and dosage regimen of five to 20 mg/kg/day. Doses above 20 mg/kg/day have not been evaluated.

1.3.5 Drug-Drug Interactions

Potential drug-drug interactions include co-administration of Kuvan with folate inhibitors, nitric oxide mediated vaso-relaxants, and with levodopa. ~~_____~~

Theoretical drug-drug interactions could exist with sapropterin and drugs that affect metabolism, recycling, or mechanism of action of endogenous BH4. For example, sulfa-based antibiotics and folate inhibitors, such as methotrexate, should be taken with caution while taking sapropterin.

Theoretical drug-drug interactions could exist with sapropterin and drugs that affect nitric oxide (NO) metabolism or nitric oxide mediated vaso-relaxants (e.g. sildenafil, vardenafil, tadalafil) through the following mechanism. Sildenafil increases vasorelaxation through phosphodiesterase-5 (PDE5) inhibition, which decreases catabolism of cGMP to GMP. Sapropterin couples with endothelial nitric oxide synthase and regenerates NO stores. NO so generated binds to guanylate cyclase, increasing concentrations of cyclic guanosine monophosphate (cGMP) adding to the vasorelaxants effect of sildenafil. Therefore, co-administration of these drugs could result in decreased blood pressure and hypotension. The risk of co-administration of sildenafil and sapropterin in healthy volunteers or patients with PKU was not assessed.

Theoretical drug-drug interactions could exist with sapropterin and levodopa. Summaries of archival data and labeling of Biopten for treatment of dihydrobiopterin synthase and dihydropteridine reductase deficiencies indicate that in open-label, uncontrolled studies of 30 patients, central and peripheral nervous system events occurred in 17% of patients receiving sapropterin, myoclonus, alterations in consciousness, hypertonia, stammering, and convulsions. These events were more common in patients receiving concomitant levodopa therapy. Approximately 85% of these patients were receiving levodopa prior to treatment with Biopten.

The observed and theoretical risks of drug-drug interactions of sapropterin with levodopa, and NO-mediated vasorelaxants such as sildenafil should be addressed in labeling.

1.3.6 Special Populations

PKU is a rare, autosomal recessive disorder of amino acid metabolism and the Kuvan clinical development program included mostly PKU patients. PKU is an orphan disease and the population available for study was relatively small.

Gender composition in clinical studies of PKU was approximately equal, and gender did not appear to affect response to Kuvan. Patients from the United States, Asia, the Middle East, Europe, and South America were included in clinical studies and the expanded access protocol; however, since the clinical development program for Kuvan in patients with PKU is relatively small, insufficient information exists to determine a difference in response to PKU treatment by ethnic origin. Patients were predominantly Caucasian (96% of all PKU patients). This may be due to recognized difference in disease incidence by race. PKU occurs in approximately 1 in 8,000 Caucasians, 1 in 50,000 African American-Blacks, and 1 in 70,000 Asian Americans. Analyses of safety and efficacy by race could not be performed.

The PKU clinical program did not enroll patients younger than four years of age, and children with PKU younger than four years of age were not studied in these clinical trials. Virtually the entire newborn population in the US is screened for PKU. The majority of patients are detected in the first weeks of life and conventional treatment with dietary Phe restriction is started at, or soon after, diagnosis.

_____ the evaluation of PKU in patients less than four years of age is to be required as a condition of approval (i.e., as a post-marketing commitment). Labeling should state that children less than four years of age were not studied in clinical trials.

The PKU clinical program excluded patients with severe liver dysfunction. Patients with long-standing PKU may be at risk for liver dysfunction. Labeling should indicate that safety in patients with liver dysfunction was not assessed and that Kuvan administration should be carefully monitored in patients with underlying liver dysfunction.

Labeling should indicate that pregnant or lactating women with PKU were not evaluated in clinical trials. It is expected that Kuvan will be prescribed to women of reproductive potential. It is also expected that Kuvan will be prescribed to pregnant women, since maternal PKU syndrome affects genetically normal infants of pregnant women with PKU who are not under good dietary control preceding and during pregnancy. Thus, the safety and efficacy of Kuvan in these women and their off-spring should be monitored by a post-approval registry, and the establishment of a pregnancy and lactation registry will be a condition of approval (i.e., a post-marketing commitment).

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The investigational agent studied in this application is sapropterin dihydrochloride. The Sponsor (BioMarin) intends to market sapropterin dihydrochloride under the trade name Kuvan®. Sapropterin dihydrochloride (6R-BH4) is an enantiomer of endogenous tetrahydrobiopterin (BH4). One function of endogenous BH4 is as a co-factor for phenylalanine hydroxylase (PAH), which converts phenylalanine into tyrosine. This activity takes place in the liver. Patients with PKU have deficient PAH activity. Kuvan is a new molecular entity (NME) being proposed as a treatment for patients with BH4-responsive PKU.

The precise mechanism of action of Kuvan is unknown; however, at least two possible mechanisms of action exist. Kuvan is a synthetic form of endogenous tetrahydrobiopterin and may allosterically force residual PAH into a more energetically favorable conformation.^{2,3} Data from *in vitro* assays indicate that some variant forms of PAH have improved enzyme kinetics in the presence of the synthetic analog 6R-BH4.^{2,3} Early clinical trials suggest that oral formulations of 6R-BH4 are absorbed and increase conversion of phenylalanine to tyrosine.^{4,5,6} This does not bypass PAH, and individuals with PAH null phenotypes are not expected to benefit from treatment with BH4 analogues.

Proposed doses of sapropterin are 5, 10, and 20 mg/kg/day in patients with BH4-responsive PKU, ages four years and older. Kuvan is not expected to decrease blood Phe in all patients with PKU, such as patients with mutations that produce no PAH enzyme (e.g., null mutations) and Kuvan is not indicated for use in these patients.

2.2 Currently Available Treatment for Indications

There is no other currently available drug or biologic treatment for reduction of blood Phe in patients with PKU. Current treatment is limited to dietary Phe restriction and supplementation with low-Phe medical foods. Dietary Phe restriction reduces blood Phe and is effective in reducing adverse neurocognitive outcomes, such as mental retardation, but dietary Phe restriction is difficult to maintain and patients commonly abandon treatment.

2.3 Availability of Proposed Active Ingredient in the United States

Kuvan is not a legally marketed product in the United States (US). Kuvan is available in the US under Investigational New Drug (IND) # 69,708 for investigation of reduction of blood Phe in patients with PKU

2.4 Important Issues With Pharmacologically Related Products

The majority of clinical experience with the Sponsor's formulation of sapropterin dihydrochloride is limited to patients studied under IND 69,708. Clinical experience with another sponsor's product [Biopten Granules, produced by Daiichi Suntory Pharma] not marketed in the US, is limited to approximately 800 persons, including healthy volunteers and patients with diseases other than PKU, and three patients with BH4-responsive hyper-Phe. Biopten has been marketed in Japan since 1992 for lowering blood Phe in patients with dihydrobiopterin synthase deficiency (DHBSD) or dihydropteridine reductase deficiency (DHPRD).

The post-marketing report for Biopten, submitted with the NDA, indicates that co-administration of levodopa with Biopten Granules has been associated with an increased incidence of excitability, irritability, and convulsions in patients with disorders of tetrahydrobiopterin metabolism; the report does not indicate the diseases for which these patients received Biopten. These events were not reported in clinical studies of Kuvan in patients with PKU, but the theoretical risk of co-administration of Kuvan with levodopa is to be addressed in labeling.

Theoretical drug-drug interactions with sapropterin and folate inhibitors, levodopa, and nitric oxide mediated vaso-relaxants are discussed in section 7.2.6 of this review.

2.5 Presubmission Regulatory Activity

The IND (69,708) for the investigation of sapropterin dihydrochloride for reduction in blood Phe for patients with BH4-responsive PKU was opened in August, 2004. IND 69,708 was transferred from CDER's Division of Metabolic and Endocrine Products to the Division of Gastroenterology Products (DGP) in October 2005. Orphan status was granted in January 2004, and fast track designation was given in January 2006. In November 2004, the Sponsor received access to non-clinical pharmacology/toxicology data, pharmacokinetic data, and clinical safety data collected by another manufacturer for investigation of the same active ingredient for diseases other than PKU. This other product, Biopten Granules, is produced by Daiichi Suntory Pharma and is not legally marketed in the US. The NDA was received 25-May-2007.

Pre-submission discussions between the Sponsor and FDA are notable for the following:

- At the "End of Phase 2" meeting, the Agency agreed to accept a pharmacodynamic efficacy endpoint (e.g., blood Phe).
- At the pre-NDA meeting, the Agency notified the Sponsor that increased dietary Phe tolerance would not be accepted as a clinical efficacy endpoint without long-term data that incorporated neurocognitive assessments.

2.6 Other Relevant Background Information

PKU is an autosomal recessive inborn error of amino acid metabolism caused by a deficiency in activity of phenylalanine hydroxylase (PAH). Patients with PKU can not metabolize dietary Phe, an essential amino acid found in most protein sources. The PAH gene is located on

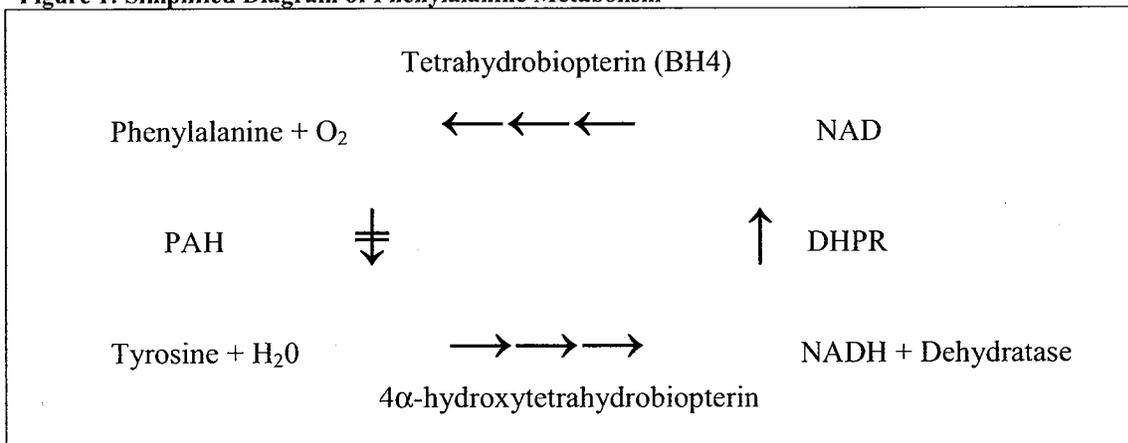
chromosome 12q24.1.⁷ Multiple gene defects have been identified that result either in a decreased amount of normal enzyme, or a decreased amount of abnormal enzyme, or a normal amount of functionally abnormal enzyme.

The incidence of PAH mutations leading to PKU differs by race and ethnicity. The overall incidence occurring in live born infants in the US is approximately 1 in 12,000 to 1 in 15,000. The approximate incidence by racial or ethnic category is 1 in 8,000 in Caucasians, 1 in 50,000 in African American-Blacks, and 1 in 70,000 in Asian Americans.⁸

Other causes of hyper-Phe include dihydropteridine reductase deficiency and dihydrobiopterin synthase deficiency. These disorders each occur in approximately 1 in 1,000,000 live birth in the US, and around 1 in 100,000 live births in China.

A simplified schema of phenylalanine metabolism is presented in Figure 1 below. The primary toxin is blood Phe (shown). The shunt metabolites phenylacetate (PA) and phenyllactate (PL) may also be toxic (not shown). The crossed arrow indicates abnormal PAH activity. Reduction of blood Phe by dietary control or liver transplant reduces blood Phe, which decreases PA and PL.

Figure 1: Simplified Diagram of Phenylalanine Metabolism



PAH: Phenylalanine hydroxylase
DHPR: Dihydropteridine reductase
NAD: Nicotine Adenine Dinucleotide
NADH: reduced NAD

PKU is usually diagnosed within the first month of life through state directed newborn screening programs. Screening for PKU is part of all current state newborn screening protocols.^{8,9}

Clinical signs and symptoms of untreated PKU include severe mental retardation and other behavioral abnormalities, microcephaly, seizures, and white matter changes. These changes are positively correlated with the degree of blood Phe elevation and length of time of elevation. Adverse neurologic outcome is ameliorated or prevented by blood Phe reduction associated with dietary Phe restriction. It is not possible to reverse established neurocognitive decline.

Another complication is maternal PKU, which is associated with pregnancies of women with PKU where blood Phe is severely elevated. These pregnancies are complicated by an increased risk of spontaneous abortion of genetically normal conceptuses, and increased risk of irreversible neurocognitive impairment and possible cardiac malformations in these genetically normal offspring. Stigmata of maternal PKU are not reversible and prevention is the treatment goal.

The only currently available therapy is a low Phe diet. Low-Phe medical formulae are available and low-Phe diets are commonly maintained through infancy. The diet is difficult to maintain and older children, adolescents, and adults commonly abandon diet restrictions. Data on percent of patients who abandon diet therapy are not available. Phe is found in nearly all protein sources; consequently, one complication of dietary Phe restriction is concomitant nutritional deficiency. Treatment goals for target blood Phe vary by region (for example, British, European, and NIH Consensus Guidelines exist). There is no blood Phe level below which risk is eliminated. Some sources recommend maintaining blood Phe below 600 μM to optimize neurocognitive development. Target blood Phe in pregnant women is between 120 and 360 μM .^{8, 10, 11}

Liver transplantation has cured disease, but is not a realistic therapeutic option for most patients with PKU. Other therapeutic options in development include microbial enzymes that act in the gut to bypass PAH.¹²

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

CMC data have been extensively reviewed by the Product Reviewer (Yichun Sun, Ph.D.). Please see the CMC review for the complete review of the product data. The CMC reviewer recommended approval.

3.2 Animal Pharmacology/Toxicology

The pre-clinical/non-clinical data have been extensively reviewed by the Pharmacology-Toxicology Reviewer (Fang Cai, Ph.D.). Please see the pharmacology/toxicology review for a complete review of the non-clinical data. Dr. Cai concludes the Sponsor conducted adequate non-clinical studies to determine the safety of sapropterin by the proposed route of administration. Notable findings from Dr. Cai's review include:

In rats at oral doses up to 400 mg/kg/day (about 3 times the maximum recommended human dose of 20 mg/kg) and in rabbits at oral doses up to 60 mg/kg/day (about 10 times the maximum recommended human dose)

- No teratogenicity was demonstrated in rats. There was a significant reduction in the number of live fetuses and a significant reduction in the body weights of live fetuses from

F1 dams treated with the 600 mg/kg/day dose (about 3 times the maximum recommended human dose, based on body surface area).

- In the rabbit teratogenicity study, there was a significant increase in the incidence of holoprosencephaly at the 600 mg/kg/day (about 10 times the maximum recommended human dose, based on body surface area) compared to controls.

Dr. Cai concludes there are no outstanding issues, and from a non-clinical standpoint the NDA is approvable. Since animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed, and Dr. Cai recommends a Pregnancy Category C classification.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

This application includes clinical efficacy or outcomes measures of Kuvan from four BioMarin-sponsored clinical studies in patients with hyper-Phe due to PKU, and two pharmacokinetic studies in healthy volunteers. Safety information was submitted from the same studies as well as the expanded access program (EAP) in patients with BH4-responsive PKU. Additional safety information with studies of Kuvan included a study in 12 patients with PBH4 deficiency investigated under IND # 69,708, and a study in 116 patients with chronic hypertension

Supportive safety data were also provided from 11 clinical studies and a post-marketing report of Biopten Granules in patients with diseases other than PKU, and three PK studies in healthy volunteers. These data included a variety of open-label and controlled study designs, and were of limited utility in establishing the safety of Kuvan in patients with BH4-responsive PKU. These studies, including three PK studies in healthy volunteers, were not reviewed for efficacy.

4.2 Tables of Clinical Studies

The clinical studies and expanded access programs performed with the Sponsor's product in support of the safety and efficacy of Kuvan in patients with BH4-responsive PKU, including completed and ongoing studies, are summarized in Table 1.

Table 1: Studies with Kuvan

Study	Comment
Phenylketonuria	
Enrichment Study (PKU-001)	One-week, open-label (OL) study in patients with PKU, 8 to 49 years old; sapropterin 10 mg/kg/day; N=489
Efficacy Study (PKU-003)	Six-week, 1:1 randomized (R), DB, PC study in patients with PKU, 8 to 49 years old; Sapropterin 10 mg/kg/day, N=41; Placebo, N=47
Extension Study (PKU-004)	OL extension study of 80 patients who participated in PKU-003; Part I: 5, 10, and 20 mg/kg/day x two weeks at each dose; then 10 mg/kg/day for four

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Table 1: Studies with Kuvan

Study	Comment
	more weeks Part II: 12 weeks of 5 (N=6), or 10 (N=37) or 20 (N=37) mg/kg/day
Diet Study (PKU-006)	Part I: One-week, OL, study of patients with PKU, 4 to 12 years old: sapropterin 20 mg/kg/day; N=90 Part II: 10-week R, DB, PC; Sapropterin 20 mg/kg/day, N=33; Placebo, N=12. After Week 3, possible dietary Phe supplemented added per protocol
EAP (SEAP-001)	OL; expanded access with 5, 10, or 20 mg/kg/day until market approval; N=108
Healthy Volunteers	
PKU-005	OL, bioavailability (BA) study in healthy volunteers, 19 to 50 years old; sapropterin 10 mg/kg/day once per week x four weeks; N=28
PKU-009	OL, BA-study in healthy volunteers, 19 to 50 years old; sapropterin 10 mg/kg/day once per week x three weeks; N=44
Other	
BH4 Deficiency (PKU-007)	OL, uncontrolled study in 12 patients with primary BH4 deficiency; not completed at 120-day safety update. Part I observation; Part II 5 mg/kg/day x six weeks then two weeks of individualized dose; Part III 20 mg/kg/day x seven weeks.
Hypertension Study (HTN-001)	Eight-week, R, DB, PC study of 116 patients, 31 to 81 years old, with hypertension. Sapropterin 10 mg/kg/day, N=77; Placebo N=39.

These studies represent the entire known clinical experience with the Sponsor's product.

Clinical studies and post-marketing information with another manufacturer's product with the same active ingredient [Daiichi Suntory Pharma; Biopten Granules] submitted in support of safety are summarized in Table 2.

Table 2: Studies with Biopten

Study	Comment
Controlled	
FB1602 Healthy Volunteers	One-week single-blind (SB), pharmacokinetic (PK) study; Sapropterin 200 mg PO TID (10.1 - 11.2 mg/kg/day) or placebo x 7 days; Biopten, N=6; Placebo, N=2
D261 Autism	DB, PC 12-week study; 1 to 5 mg/kg/day PO x 5 to; Biopten, N =42; Placebo, N=42
ZD2201 Autism	R, DB, PC 12-week study in patients with autism; 0 to 3 mg/kg/day PO x 12 weeks; Biopten, N=149; Placebo, N=73
FB3701 Machado-Joseph Disease (MJD)	R, DB, PC, eight-week study, 200 mg PO TID; Biopten, N=84; Placebo, N=89
Uncontrolled	
FB1701 Healthy Volunteers	One-week OL treatment; 200 mg TID; N=6 (9.0 - 10.6 mg/kg/day)
P1501 Healthy Volunteers	One-week OL, PK study; 100 or 200 mg PO/week (1.4 - 3.3 mg/kg) x two weeks; N=6 vs. 100 mg PO TID (4.2 - 4.9 mg/kg/d) x seven days; N=6
D271 and D271b Autism	OL, 1-3 mg/kg/day; 12 to 24 weeks; N=99
D381 Autism	OL, 1-3 mg/kg/day x 12 to 24 weeks; N=138
D383 Autism	OL, 1-3 mg/kg/day x 3 months; N=7
D384 Autism	OL, 2.1-3.3 mg/kg/day x 12 to 20 weeks; N=9

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D272 BH4 Deficiency	OL, 1.5 to 10 mg/kg/day x 10 to 12 months; 3 months to 29 years old; N=16
Post market report BH4 Deficiency	5 to 20 mg/kg/day x 10 years
FB2501 MJD	OL, 1.0 to 5.0 mg/kg/day x four weeks; N=7
FB2601 MJD	OL, 100 or 200 mg PO TID x four weeks; N=16
FB2602 MJD	OL, 100 to 200 mg PO TID x 24 to 48 weeks; N=13

The above studies represent the entire safety experience of Biopten.

4.3 Review Strategy

The indication being reviewed is for Kuvan as a treatment for the reduction in blood Phe levels in patients with hyper-Phe due to BH4-responsive PKU. [REDACTED]

[REDACTED] Therefore, the review is restricted to the assessment of safety and efficacy of Kuvan in reducing blood Phe in patients with BH4-responsive PKU.

The most important clinical studies submitted to this application are:

- The Enrichment Study (PKU-001; dietary Phe not controlled)
- The Efficacy Study (PKU-003; dietary Phe not controlled)
- The Diet Study (PKU-006; dietary Phe controlled)
- The Extension Study (PKU-004; dietary Phe not controlled)

The efficacy endpoint reviewed in the Enrichment, Efficacy, and Extension studies was change in blood Phe during treatment compared to non-treatment Baseline (e.g., a pharmacodynamic endpoint). The efficacy endpoint reviewed in the Diet Study was dietary Phe supplement tolerated at the end of treatment, which was dependent on blood Phe levels at the end of treatment (e.g., <360 uM). In each study, safety assessments were collected through four weeks after the end of treatment. The comprehensive short-term (six to ten week) efficacy data, and combined 29-week safety data from exposure in multiple studies, permitted substantive clinical review.

- The Enrichment Study (PKU-001) was a multi-center, open-label study of 489 patients with PKU, ages ≥ 8 to 49 years who were not on dietary Phe restriction. Patients were treated with sapropterin 10 mg/kg/day for eight days. Patients with a $\geq 30\%$ decrease in blood Phe from Day 1 (Baseline) to Day 8 qualified enrollment in the Efficacy Study. The comprehensive data submitted to the application permitted substantive review. These open-label data are supportive but can not be relied upon to demonstrate efficacy.
- The Efficacy Study (PKU-003) is the pivotal clinical efficacy trial. This was a multi-center, randomized, double-blind, placebo-controlled study of 88 patients with PKU, ages

≥8 to 49 years, and who were not on dietary Phe restriction, who had a ≥30% decrease in blood Phe with sapropterin 10 mg/kg/day from Day 1 to Day 8 in the Enrichment Study (PKU-001). In the Efficacy Study patients were randomized 1:1 to receive sapropterin 10 mg/kg/day or placebo for six weeks. The primary efficacy endpoint was change in blood Phe from Week 0 (Baseline) to Week 6 of treatment (sapropterin minus placebo). The comprehensive safety and efficacy data from this trial permitted substantive review. The study showed a clinically meaningful decrease in blood Phe in sapropterin vs. placebo treated patients and the results were statistically significant.

- The Extension Study (PKU-004) was a multi-center, open-label study of 80 patients with PKU, ages >8 to 49 years, who received at least 80% of doses in the Efficacy Study, and who were not on dietary Phe restriction. In Part I, patients were treated with 5, 10, and 20 mg/kg/day for two weeks each. The efficacy endpoint of Part I was change in blood Phe at the end of each two week dose period compared to Week 0 (Baseline). In Part II, patients were treated with either 5, 10, or 20 mg/kg/day for 12 weeks according to blood Phe levels during Part I. The efficacy endpoint of Part II was maintenance of reduced blood Phe. The comprehensive data submitted to the application permitted substantive review. These open-label data are supportive but can not be relied upon to demonstrate efficacy.
- The Diet Study (PKU-006) was a multi-center, international study in patients, ages ≥4 to 12 years, with PKU who were on dietary Phe restriction. In Part I, 90 patients, ages ≥4 to 12 years old, and Screening blood Phe ≤480 uM were treated with open-label sapropterin 20 mg/kg/day for eight days. Patients with ≥30% decrease in blood Phe at Day 8 from Day 1 (Baseline) and Day 8 blood Phe <300 uM were designated as Responders and qualified for further treatment in Part II. In Part II, 45 patients were randomized 3:1 to receive sapropterin or placebo for 10 weeks. At Weeks 3, 5, 7, and 9, changes in daily supplemental dietary Phe could be made based on blood Phe from the preceding week (i.e., Weeks 2, 4, 6, and 8). The primary efficacy endpoint of Part II was supplemental dietary Phe tolerated at Week 10 defined as maximum supplement ingested while maintaining blood Phe <360 uM. The comprehensive data submitted to the application permitted substantive review for safety; however, as discussed in section 6.1.2 of this review, dietary Phe supplement is not an acceptable endpoint at this time, and these data can not be used to support efficacy.

Analyses of the above four studies were emphasized in this review, and comprehensive reviews of these studies are summarized in the Appendix section under the Individual Study Reports. The data submitted for the expanded access program (EAP) in patients with BH4-responsive PKU, and studies of Kuvan in patients with primary BH4 deficiency and chronic hypertension are reviewed for safety only in section 7 of this review, but were not supportive of efficacy for the treatment of BH4-responsive PKU.

For the clinical trials of Biopten Granules, the original study reports and primary datasets are not available for review; however, safety summaries and pooled AE and clinical laboratory datasets were provided and were reviewed for safety and are discussed in sections 7.2.2.1.4 and 7.2.2.2 of

this review. These studies were not reviewed for efficacy and are not considered supportive of efficacy for the treatment of BH4-responsive PKU.

4.4 Data Quality and Integrity

The individual study reports and datasets for studies performed with Kuvan were substantially complete and were reviewable for safety and efficacy.

The Division of Scientific Investigation (DSI) performed three clinical site audits for this application, including: Dr. B. Burton (Site # 0109), Chicago IL; Dr. D. Grange (Site # 0110), St. Louis MO; and Dr. D. Gruskin (Site # 0184), Decatur GA. These sites were selected for inspection because of their high enrollment. The overall observation noted by the DSI Inspector (Khairy Malek, MD) is that inspection of the “three sites reveals that the data from these sites are acceptable and can be used in support of the NDA.”

The study reports and datasets from the three PK studies of Biopten were substantially complete and reviewable. For the remaining 11 clinical trials of Biopten Granules for diseases other than PKU, original study reports and primary datasets were not available for review. Translated safety summaries and translated pooled AE and clinical laboratory datasets were provided and were reviewable. This Reviewer concludes these data are adequate to enrich the safety experience of Kuvan, but are not be used to support efficacy. The three of PK studies with Biopten were not relied upon to established PK for patients with PKU, and are not discussed in the Clinical Pharmacology review.

4.5 Compliance with Good Clinical Practices

The Sponsor states that all BioMarin-sponsored studies in the PKU development plan were conducted in accordance with Good Clinical Practices (GCP). The Sponsor certifies that no debarred investigators participated in BioMarin-sponsored clinical trials.

The Sponsor states that although “many” of the studies of Biopten were conducted before the International Conference on Harmonization (ICH) guidance on Good Clinical Practice (GCP) was available in April 1996, they were conducted in compliance with the good clinical practice standards of Japanese Pharmaceutical Affairs Law that were in effect at the time they were conducted. The Sponsor concludes that these studies were conducted “in the spirit of current Good Clinical Practice” and included: review and approval of all study protocols by ethics committees, provision of informed consent, recording of all clinical data in CRFs, and GCP and data audits by the Japanese Ministry of Health and Welfare. The results of those audits are not available. Since the clinical information from the Biopten studies are being reviewed for safety of sapropterin for diseases other than PKU, rather than to establish efficacy in patients with BH4-responsive PKU, this Reviewer concludes the data may be used to enrich the safety database.

4.6 Financial Disclosures

All investigators and sub-investigators in studies used to support the indication were listed on FDA form 3454 and no financial interests were disclosed.

5 CLINICAL PHARMACOLOGY

The recommendation of the Clinical Pharmacology reviewer (Hae-Young Ahn, PhD) is that the clinical pharmacology and biopharmaceutics information submitted to the NDA are acceptable, provided that labeling is agreed upon between the Sponsor and FDA. Important findings from the Clinical Pharmacology Review by Hae-Young Ahn, PhD are summarized below. Please see Dr Ahn's review for full discussion of PK, PD and exposure-response relationships.

5.1 Pharmacokinetics

In healthy volunteers, T_{max} and $t_{1/2}$ (10 mg/kg/dose) were each approximately four hours. Administration with or after a high fat, high-calorie meal resulted in increased absorption compared to administration under fasted conditions.

In healthy volunteers, administration of intact tablets at (10 mg/kg/dose) resulted in approximately 20% greater absorption compared to dissolved tablets.

A population PK sub-study in patients with BH4-responsive PKU was performed (PKU-004 sub-study 002). Patients received either 5 mg/kg/day (N=6), 10 mg/kg/day (N=37), or 20 mg/kg/day (N=34). The only apparent variable that affected PK was total body weight; gender and age did not significantly affect PK. Mean terminal $t_{1/2}$ was 6.7 hours (range 3.9 to 16.6 hours). Intrinsic factors, such as hepatic and renal impairment, were not assessed.

5.2 Pharmacodynamics

The PD effect of Kuvan is assessed by change in blood Phe. The ability to maintain stable blood Phe over 24 hours with once daily dosing was assessed in two sub-studies. In PKU-001 sub-study 001, PD was assessed in 11 patients receiving 10 mg/kg/day for eight days. In this study, mean blood Phe levels were stable over 24 hours, there was large inter-patient variability, and many data points were missing. In PKU-004 sub-study 01, PD was assessed in 12 patients receiving 10 mg/kg/day for four weeks. In this study, mean blood Phe levels were stable over 24 hours, there was large inter-patient variability, but intra-patient variations in blood Phe were minimal. Thus, these data support once daily dosing.

5.3 Exposure-Response Relationships

Efficacy findings of exposure-response are detailed in section 6 of this review. Notable findings are summarized below.

Exposure-response relationships for change in blood Phe were studied in Part I of the open-label Extension Study (PKU-004), which was an open-label forced dose-titration study. The Clinical Pharmacology review (Hae-Young Ahn, PhD) assessed dose response by determining the percentage of patients who had a $\geq 30\%$ reduction in blood Phe levels from Baseline. Dr. Ahn's analysis showed the following:

- At 5 mg/kg/day, 25% of patients had $\geq 30\%$ reduction in blood Phe from Baseline.
- At 10 mg/kg/day, 46% of patients had $\geq 30\%$ reduction in blood Phe from Baseline.
- At 20 mg/kg/day, 55% of patients had $\geq 30\%$ reduction in blood Phe from Baseline.

In the Efficacy Study sapropterin-treated patients (10 mg/kg/day) had a greater decrease in blood Phe from Baseline than placebo-treated patients.

This Reviewer concludes that efficacy of Kuvan 5, 10, and 20 mg/kg/day is supported for the reduction of blood Phe in patients with BH4-reponsive PKU.

There were no notable safety findings related exposure-response. Please see section 7 of this review for a detailed discussion of safety findings.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The Sponsor proposed the wording:

“Kuvan™ is _____ indicated to reduce blood phenylalanine (Phe) levels _____
_____ in patients with hyperphenylalaninemia (hyper-Phe) due to
Phenylketonuria (PKU). _____
_____”

6.1.1 Methods

This original NDA submission includes clinical efficacy measures from four clinical trials of sapropterin (e.g., the study drug) in patients with hyper-Phe due to PKU, and interim data from a single open-label study of twelve patients with primary BH4 deficiency (Study PKU-007) submitted with the 120-day safety update.

The PKU studies included two Phase 3, randomized, double blind, placebo-controlled studies (the Efficacy Study, and the Diet Study) and two open-label, uncontrolled studies (the Enrichment Study and the Extension Study). Sub-studies of the Enrichment and Extension Studies evaluated blood Phe over 24 hours, and population pharmacokinetics (PK).

The clinical development program focused on the treatment of patients with hyper-Phe due to PKU. Two groups were studied.

The first group was composed of patients aged 8 to 48 years with hyper-Phe due to PKU with unregulated diets; therefore, some patients were on Phe restriction and some were not. This population was evaluated in the Enrichment Study (PKU-001). A subset of patients (20%) from the Enrichment Study who showed a $\geq 30\%$ reduction in blood Phe with open-label sapropterin treatment were selected for further study in the Efficacy Study (PKU-003), and the Extension Study (PKU-004). The maximum continuous exposure to drug in these studies was for 22 weeks in the Extension Study. The primary efficacy variable in these three studies was blood Phe.

The second group was composed of patients aged 4 to 12 years with hyper-Phe due to PKU who were following dietary Phe restriction (PKU-006). After eight days of open-label treatment with sapropterin (Part I), 50 patients (56% of patients treated) showed a $\geq 30\%$ reduction in blood Phe and concomitant Day 8 blood Phe of < 480 μM , and were selected for further study of dietary Phe supplement (Part II). The primary efficacy variable in this study was dietary Phe tolerated at the end of the study. Exposure to drug in this study was for 10 continuous weeks. The secondary efficacy variable in this study was blood Phe.

Comprehensive efficacy and safety data from the Efficacy Study (N=90) and the Diet Study (N=80) permitted substantive review. Supportive efficacy and safety information from the open label Enrichment (N=489) and Extension (N=80) Studies were also reviewed.

The remaining five clinical studies in the PKU development program were Phase 1 studies. Of these five Phase 1 studies two were conducted with the Sponsor's product and three were conducted with another manufacturer's product. These five studies were not reviewed for efficacy, but are reviewed for safety as a component of the ISS.

The ongoing primary BH4 Deficiency Study (BH4 Study; PKU-007) is evaluating twelve patients with primary BH4 deficiency under open-label, uncontrolled conditions, with individualized doses of 5 to 20 mg/kg/day. Minimal efficacy data limited to a tabular listing of blood Phe at different treatment visits was presented. This study is not reviewed for efficacy.

6.1.2 General Discussion of Endpoints

Blood Phe was the primary efficacy variable in the Enrichment, Efficacy, and Extension studies. The primary efficacy endpoint in the Enrichment Study was percent change in blood Phe from Baseline during treatment. The primary efficacy endpoint in the Efficacy and Extension Studies was percent change in blood Phe from Baseline during treatment.

These primary efficacy endpoints are appropriate for the following reasons:

- Patients with PKU have decreased hepatic phenylalanine hydroxylase (PAH) activity.
- Patients absorb, but do not metabolize, dietary Phe.
- Blood Phe becomes elevated up to ≥ 30 times the upper limit of normal.
- In patients, changes in diet affect blood Phe within hours.
- Elevated blood Phe causes progressive neurocognitive decline with mental retardation and seizure unless early (e.g., neonatal) diagnosis is made and dietary Phe restriction are rapidly instituted. There is no blood Phe level below which normal neurocognitive development is assured; however, current NIH guidelines (2000) suggest maintenance of blood Phe < 600 μM reduces risk of neurocognitive impairment.³
- Current treatment is limited to reduction of dietary Phe, which decreases blood Phe and reduces neurological sequelae.³
- Dietary Phe restriction is difficult to maintain, and abandonment of diet is associated with return of elevated blood Phe and neurological impairment.^{3, 13}
- Resumption of diet may again arrest progression of long-term neurologic damage; however, the patient is at risk for irreversible neurologic impairment.^{13, 14}
- Pregnant women with PKU and elevated blood Phe can birth genetically normal children with a microcephaly and irreversible mental retardation called maternal PKU syndrome.
- Reduction of blood Phe in the three months prior to, and during pregnancy, can reduce the risk of maternal PKU syndrome.

Use of a $\geq 30\%$ decrease in blood Phe to define a potentially responsive population is arbitrary. It was chosen during negotiations between the Sponsor and the Division of Metabolic and Endocrine Drug Products prior to the transfer of the IND for sapropterin (IND 69,708) to the Division of Gastroenterology Drug Products for the following reasons:

- Over 400 PAH mutations have been described resulting in decreased activity of functional PAH. Mutations result in normal concentration of abnormal enzyme, decreased concentration of normal enzyme, decreased concentration of abnormal enzyme, or null mutations. Clinical response based on genotype is incompletely characterized.
 - In non-clinical studies, all mutations resulted in catalytic defects. Synthetic BH4 bound to several mutant alleles and prolonged their half-life in cell-free preparations. Some, but not all, mutant enzymes had improved substrate activity in the presence of synthetic BH4.¹⁵
 - In one clinical study, 38 patients with hyper-Phe were studied under fasted conditions, to establish Phe controlled diet. Patients were then given 100 mg/kg oral Phe followed one hour later by 20 mg/kg of synthetic BH4. Twenty three patients (60%) showed a $> 30\%$ reduction in blood Phe from BH4 treatment. The authors concluded that response was correlated with genotype in some but not all patients.¹⁶
- Under uncontrolled conditions, dietary Phe intake and blood Phe fluctuate. While a group's mean/median blood Phe might be stable, any individual's blood Phe would be

just as likely to increase as decrease. Therefore, if an unselected PKU patient population without diet control were to show a mean decrease in blood Phe, selecting the sub-population with greatest decrease (e.g., $\geq 30\%$) would increase the likelihood that patients chosen for further study were patients who responded to drug rather than undocumented changes in diet.

- If the $\geq 30\%$ decrease in blood Phe were reconfirmed under placebo-controlled and diet-controlled conditions, such information could be used to support efficacy.

The primary efficacy variable of the Diet Study was supplemental dietary Phe tolerated at Week 10 of therapy. This endpoint was not suitable to establish efficacy and the Division was not willing to allow this endpoint [REDACTED] at the current time due to the following:

- Increased dietary Phe supplementation or tolerance is not an established clinical endpoint.
- Current treatment with dietary Phe reduction is intended to prevent neurological sequelae.
- Long term neurocognitive endpoints were not evaluated in this study.

The Division previously informed the Sponsor that long-term studies incorporating neurocognitive outcomes would be required [REDACTED]

In conclusion, blood Phe is an established biomarker in patients with PKU and hyper-PHE, and control of blood Phe with diet is associated with prevention or amelioration of neurological sequelae. Change in blood Phe and percent change in blood Phe are appropriate primary and secondary efficacy variables. In an uncontrolled study, a $\geq 30\%$ decrease in blood Phe may identify patients for further study under controlled conditions. If the $\geq 30\%$ decrease in blood Phe were reconfirmed under placebo-controlled and diet-controlled conditions this information could be used to support efficacy.

This Reviewer recommends that supplemental Phe tolerance be evaluated in long-term studies of at least several years duration. Such studies should incorporate validated long term neurocognitive outcome measures and long-term tracking of blood Phe levels. These studies may be performed as a post-marketing commitment.

6.1.3 Study Design

The Enrichment, Efficacy, Diet, and Extension Studies are reviewed in detail. The reader is directed to the individual study reports located in appendices 10.1.1, 10.1.2, 10.1.3, and 10.1.4, respectively, for a detailed discussion of these studies.

For reviews of the pharmacokinetic sub-studies of the Enrichment and Extension Studies, please refer to the Clinical Pharmacology review by Dr. Hae-Young Ahn.

6.1.3.1 Enrichment Study (PKU-001)

The Enrichment Study is presented first because it identified potential responders for study in the Efficacy Study. Efficacy findings from the Enrichment Study do not independently support efficacy.

6.1.3.1.1 Design, Treatment, and Population

The Enrichment Study (PKU-001) was an eight-day, Phase 2, multi-center, open-label (OL), uncontrolled study in 489 patients with PKU, ≥ 8 years. The objective was to identify potential sapropterin-responsive patients for enrollment in the Efficacy Trial. Response was defined as a $\geq 30\%$ decrease in blood Phe from Baseline to Day 8. Sapropterin 10 mg/kg/day was administered to all patients as dissolved tablets in one daily dose each day for eight days. Efficacy was assessed by comparing blood Phe at Day 8 of treatment to Day 1 (Baseline) prior to administration of the first dose.

Patients must not have been on dietary Phe restriction at entry, and diet was not to be changed from Screening through completion of study procedures. Dietary Phe was monitored by patient/caregiver diary review at the Day 8 visit.

A sub-study (PKU-001 Sub-study 01) was conducted at one study site to evaluate effect of sapropterin treatment on blood Phe over a 24-hour period. This was not a primary efficacy assessment. Please see the Clinical Pharmacology review for discussion of this sub-study.

A limitation of this study identified by the Reviewer is the lack of dietary control may have affected the results. However, the lack of dietary control does not prevent the identification of a potentially responsive population for further study under placebo-controlled conditions in the Efficacy Study (PKU-003; discussed in section 6.1.3.2 and appendix 10.1.2). Diet was not controlled in the Efficacy Study.

6.1.3.1.2 Objectives and Outcomes Measures

The ITT was defined as all patients who received ≥ 1 dose of sapropterin. The Analysis population (AP) was defined as all patients who received >1 dose and who had Day 1 and Day 8 blood Phe determinations. Safety assessments were performed on the ITT, and efficacy assessments were performed on the AP.

The primary objective of this study was to identify Responders for further study in the Efficacy Study (PKU-003). Response was defined as a $\geq 30\%$ decrease in blood Phe, calculated by:

$$\frac{[\text{Day 8 Treatment Blood Phe} - \text{Day 1 (Baseline) Blood Phe}]}{\text{Day 1 Blood Phe}} \times 100$$

Secondary efficacy objectives were exploratory and included:

Determination of the percentage of Responders by Day 1 blood Phe stratum (<600 vs. ≥600 uM) to explore the likelihood of Response based on pre-treatment blood Phe. This analysis was pre-specified by the Sponsor.

An analysis of change in blood Phe for the AP and by Day 1 blood Phe (<600 vs. ≥600 uM) to evaluate magnitude of change in blood Phe based on pre-treatment blood Phe. This analysis was not pre-specified by the Sponsor.

Safety was evaluated by changes from Baseline in medical history, physical examinations, and safety laboratory analyses (e.g., chemistry panel and hematology), and the occurrence during treatment of adverse events.

6.1.3.1.3 Patient Eligibility/Inclusion and Exclusion Criteria

To be eligible for the study, patients must have been diagnosed with PKU, had a Screening blood Phe ≥600 uM (initial protocol inclusion criterion) or ≥450 uM (after protocol Amendment 2), and must have been ages eight or older at study entry. All patients must have been willing to avoid changes in their diet from Screening through completion of study procedures.

Patients were excluded from study participation if there was a diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, use of any investigational agents within 30 days prior to screening, or required use of investigational agents prior to end of study, pregnancy or breast feeding, blood alanine amino-transferase (ALT) > 5 times the upper limit of normal ULN), or serious illness such as, but not limited to, uncontrolled neuropsychiatric disorders. The method of differentiating PKU from primary BH4 deficiency was not stated.

6.1.3.1.4 Concomitant and Prohibited Medications

Use of levodopa or folate inhibitors, such as methotrexate, at entry and during the study was prohibited. Any other required medicine could be used and, except for folate inhibitors or levodopa, was not reason for removal from the study. Doses and dates of use of concomitant medications and medicines used within 30 days of enrollment through completion of follow-up at Day 36 were recorded in the Case Report Forms (CRFs).

6.1.3.2 Efficacy Study (PKU-003)

6.1.3.2.1 Design, Treatment, and Population

The Efficacy Study (PKU-003) was a Phase 3, ten week, multi-center, randomized, double-blind (DB), placebo-controlled (PC) trial of sapropterin in patients with PKU, ≥ 8 years old. Patients received treatment for the first six weeks and safety assessments were collected for the entire ten week study period. To be eligible, patients must have had a ≥30% decrease in blood Phe with sapropterin treatment in the Enrichment Study. Patients were randomized 1:1 to receive sapropterin or placebo. Of 89 randomized patients, 88 randomized patients received ≥ 1 dose of

DB study medication (N=88). Treatments were oral sapropterin (10 mg/kg/day) or placebo as one daily dose dissolved in water, apple juice or orange juice each day for six weeks. Dietary Phe was not restricted from Screening through completion of all study procedures; however, patients were to maintain their usual pre-study diets from Screening through the end of treatment Week 6. Final safety assessments were performed at Week 10.

The efficacy measure was blood Phe at Baseline and at each weekly treatment visit or on early withdrawal. Baseline Phe was defined as the mean of three pre-treatment blood Phe analyses. Two of the baseline samples were taken within the month preceding the study, at least one week apart, and the final sample was taken at Week 0 prior to 1:1 randomization. Of 89 randomized patients, 88 received ≥ 1 dose of DB medication and were included in safety and efficacy analyses.

All patients were to have undergone a wash-out period between the end of the Enrichment Study (PKU-001) and the enrollment in the Efficacy Study (PKU-003). The length of the wash-out period was not specified in either study report.

6.1.3.2.2 Objectives and Outcomes Measures

The primary efficacy objective of the Efficacy Study was to evaluate the efficacy of sapropterin in reducing blood Phe in patients with PKU after six weeks of treatment.

The primary efficacy endpoint was change (reduction) in blood Phe at the end of treatment (Week 6) compared to Week 0 (Baseline), calculated as [Week 6 blood Phe – Baseline blood Phe].

Secondary efficacy assessments were:

- The mean change from Baseline in blood Phe at Weeks 1, 2, and 4
- The proportion of patients with blood Phe <600 uM at Week 6 compared to Screening (not Baseline)

For all primary and secondary endpoints, mean change in blood Phe in sapropterin-treated patients was compared to the mean change in blood Phe in placebo-treated patients. There was no definition of response (e.g., >30% decrease from Baseline).

Safety was evaluated by changes from Baseline in medical history, physical examinations, and safety laboratory analyses (e.g., chemistry panel and hematology), and the occurrence adverse events. SAEs were collected between signing of informed consent through the final safety assessment at Week 10. Non-serious AEs were collected from administration of the first dose through the final safety assessment at Week 10.

6.1.3.2.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients with PKU were eligible for study participation if they were ages eight years and older, and had a Screening blood Phe ≥ 600 uM (initial protocol inclusion criterion, N=73) or ≥ 450 uM

(after protocol Amendment 2, N=16). Patients must have received seven of eight doses of sapropterin during the Enrichment Study (PKU-001), and must have had a $\geq 30\%$ reduction in blood Phe from Day 1 to Day 8 in the Enrichment Study. All patients must have been willing to avoid changes in their diet from Screening through completion of study procedures.

Patients were excluded if there was a diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, use of investigational agents within 30 days of Screening, or required use of investigational agents prior to end of study, pregnancy or breast feeding, blood ALT > 5 times the ULN, or serious illness such as, but not limited to, uncontrolled neuropsychiatric disorders.

Patients were removed from the study if any of the following criteria were met:

- Age ≥ 8 to ≤ 12 years; remove if blood Phe $\geq 1,500$ μM any time after Screening
- Age > 12 years; if Baseline Phe was $< 1,500$, remove if any subsequent Phe $\geq 1,800$ μM
- Age > 12 years; if Baseline Phe $> 1,500$, remove if any subsequent Phe $\geq 1,800$, and $\geq 30\%$ higher than baseline

The method of differentiating PKU from primary BH4 deficiency was not stated.

6.1.3.2.4 Concomitant and Prohibited Medications

Use of levodopa or folate inhibitors, such as methotrexate, at entry and during the study was prohibited. Any other required medicine could be used and, except for folate inhibitors or levodopa, was not reason for removal from the study. Doses and dates of use of concomitant medications and medicines used within 30 days of Screening through completion of follow-up at Week 10 were recorded in the CRFs.

6.1.3.3 Diet Study (PKU-006)

6.1.3.3.1 Design, Treatment, and Population

The Diet Study (PKU-006) was a Phase 3, two-part, multi-center, randomized, DB, PC study in children, four to twelve years old, with PKU on Phe-restricted diets, and with blood Phe ≤ 480 μM at Screening. The objective was to evaluate the ability of sapropterin 20 mg/kg/day to increase dietary phenylalanine tolerance. In Parts I and II, sapropterin and placebo treatments were administered as tablets dissolved in water or apple juice in one daily dose.

Except as directed by the study protocol described below, dietary Phe was not to be modified from Screening through last dose of sapropterin or placebo (Week 10 of Part II). Final safety assessments were performed four weeks later (Week 14 of Part II).

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Part I: Ninety patients received open-label sapropterin 20 mg/kg/day for 8 days. Patients whose blood Phe levels met both of the following criteria were designated Responsive and eligible for Part II:

- A reduction in blood Phe level $\geq 30\%$ from Day 1 (Baseline) to Day 8 of treatment.
- Blood Phe level ≤ 300 uM on Day 8.

Patients who did not meet the above criteria were not eligible for enrollment in Part II and were withdrawn from study.

Part II: After a one week washout period, 46 of 50 Responders were randomized (3:1) to receive double-blinded treatment with either sapropterin 20 mg/kg/day (N=34) or placebo (N=12). Sapropterin and placebo treatments were administered for 10 weeks. Safety assessments were collected for an additional four weeks (14 weeks total). After Week 3 laboratory assessments, patients who had blood Phe ≤ 300 uM at the preceding (Week 2) visit had dietary Phe intake (supplement) increased by 5 mg/kg/day by adding a specified quantity of Phe-containing powder (in the form of non-fat dry milk or dried egg whites); patients with blood Phe of ≥ 301 uM at the preceding (Week 2) visit were to have no Phe supplement added at that time. Dietary Phe intake could also be modified at Weeks 5, 7, and 9 based on blood Phe levels from Weeks 4, 6, and 8 as outlined in Tables 3 and 4.

Table 3: Change in Dietary Phe Supplementation Based on Blood Phe

Blood Phe at Week 2 (uM)	Action after Week 3 blood sampling	
0 \leq 300	Add dietary Phe supplement (5 mg/kg/day)	
301 \leq 480	No change in Phe supplement intake	
481 and higher	No change in Phe supplement intake and monitor blood Phe level at the next visit	
Blood Phe at Week 4, 6, and 8 (uM)	Action at Next Visit's Blood Sampling	
0 \leq 180	Increase Phe supplement by 15 mg/kg/day	
181 \leq 240	Increase Phe supplement by 10 mg/kg/day	
241 \leq 300	Increase Phe supplement by 5 mg/kg/day	
301 \leq 359	No change in Phe supplement intake	
360 and greater	Query: Did patient have prior Phe supplement increase(s)	
	YES ↓	NO ↓
	Remove Phe supplement in reverse order, beginning with the amount of the most recent increase	No change in Phe supplement intake
481 \leq 1,199	<ul style="list-style-type: none"> • If first occasion at this level, monitor blood Phe level at the next visit • If second occasion at this level provide dietary counseling 	
1,200 and greater	<ul style="list-style-type: none"> • If first occasion at this level, provide dietary counseling and monitor blood Phe level at the next visit • If second occasion at this level, provide dietary counseling and terminate from study drug 	

Supplemental Phe modifications based on blood Phe at Weeks 2, 4, 8 are instituted at the following week's visit (e.g., Week 3, 5, 7, 9).

Two examples of change in dietary Phe supplement based on blood Phe levels are provided in Table 4 below.

Table 4: Examples of Change in Supplement by Blood Phe

Blood Phe		Change in Phe Supplement Prescribed	
Week	uM	Week	mg/kg/day supplement
Example 1			
2	265	3	+ 5
4	238	5	+10
6	362	7	-10
8	360	9	-5
Example 2			
2	302	3	0
4	290	5	+5
6	362	7	-5
8	350	9	0

Phe supplementation recommendations were performed by study personnel blinded to drug/placebo treatment.

6.1.3.3.2 Objectives and Outcomes Measures

Part I: The primary efficacy objective was to identify patients with PKU under dietary Phe control who had a $\geq 30\%$ reduction in blood Phe from Baseline to Day 8 when treated with sapropterin treatment (20 mg/kg/day) in order to qualify for randomization into Part II.

Part II: The primary efficacy objective was to determine the maximum dietary Phe supplement tolerated during maintenance of an otherwise Phe-restricted diet. Tolerated supplement was defined as the amount of supplement (maximum 50 mg/kg/day) prescribed and consumed at the Week 10 visit while maintaining blood Phe < 360 uM.

Part II had three secondary efficacy objectives:

1. To evaluate the ability of sapropterin to reduce blood Phe levels in children with PKU who are following a Phe-restricted diet.
2. To compare the ability of sapropterin versus placebo to increase Phe tolerance in children with PKU who are following a Phe-restricted diet.
3. To explore the potential reduction in the cost of medical foods and Phe-free formulas.

Safety was evaluated by changes from Baseline in medical history, physical examinations, and safety laboratory analyses (e.g., chemistry panel and hematology), and the occurrence during treatment of adverse events. SAEs were collected between signing of informed consent and the final safety assessment at Week 14 of Part II. Non-serious AEs were collected from administration of the first treatment dose through the final safety assessment at Week 14 of Part II.

The Division previously notified the Sponsor that substantive data from long-term studies of several years duration that incorporate neurocognitive outcomes would be required to support claims regarding diet liberalization (e.g., allowance increase in dietary Phe). Therefore, this Reviewer concludes the most useful information to be obtained from this study is the mean change in blood Phe between Baseline and Week 3 prior to addition of supplemental Phe.

Cost reduction of treatment of disease is desirable but does not fall under FDA's regulatory authority. Explorations of cost reduction will not be assessed.

6.1.3.3.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients with PKU were eligible for Part I if they were ages ≥ 4 to ≤ 12 years, and had:

- Clinical diagnosis of PKU with hyperphenylalaninemia documented by at least one blood Phe measurement ≥ 360 uM (6 mg/dL); PKU diagnosis was by blood Phe analysis not DNA testing.
- Blood Phe level ≤ 480 uM at Screening
- Dietary control with a Phe-restricted diet was required as demonstrated by:
 - Estimated daily dietary Phe tolerance ≤ 1000 mg/day by diet review; and
 - At least six months of blood Phe control (mean level of ≤ 480 uM) prior to Screening

Patients were excluded if there was a diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, use of investigational agents within 30 days of Screening, or required use of investigational agents prior to end of study, pregnancy or breast feeding, blood ALT >2 times the ULN, or any serious medical disorder not under medical control.

The method of differentiating PKU from primary BH4 deficiency was not stated.

6.1.3.3.4 Concomitant and Prohibited Medications

Use of levodopa or folate inhibitors, such as methotrexate, at entry and during the study was prohibited. Any other required medicine could be used and, except for folate inhibitors or levodopa, was not reason for removal from the study. Doses and dates of use of concomitant medications and medicines used within 30 days of enrollment through completion of follow-up (Part II, Week 14) were recorded in the CRFs.

6.1.3.4 Extension Study (PKU-004)

6.1.3.4.1 Design, Treatment, and Population

The Extension Study (PKU-004) was a 26-week, multi-national, open-label (OL), safety, efficacy, and dose-titration study of 80 patients with PKU who completed the Efficacy Study and

received $\geq 80\%$ of doses in the Efficacy Study. The Extension study was designed to evaluate the long-term safety and efficacy of three different doses of sapropterin in 80 patients with PKU. The study was conducted in two parts.

Part I: Patients received sapropterin in three consecutive two-week courses of single daily doses: 5 mg/kg/day for two weeks, followed by 20 mg/kg/day for two weeks, and then 10 mg/kg/day for two weeks. Following this six-week forced dose-titration period, patients continued to receive 10 mg/kg/day for four weeks during which time blood Phe levels from Baseline through Week 6 were analyzed. Results of the Phe analyses were called dose-analysis and were used to assign each patient's fixed dose for Part II (Week 11 through Week 22).

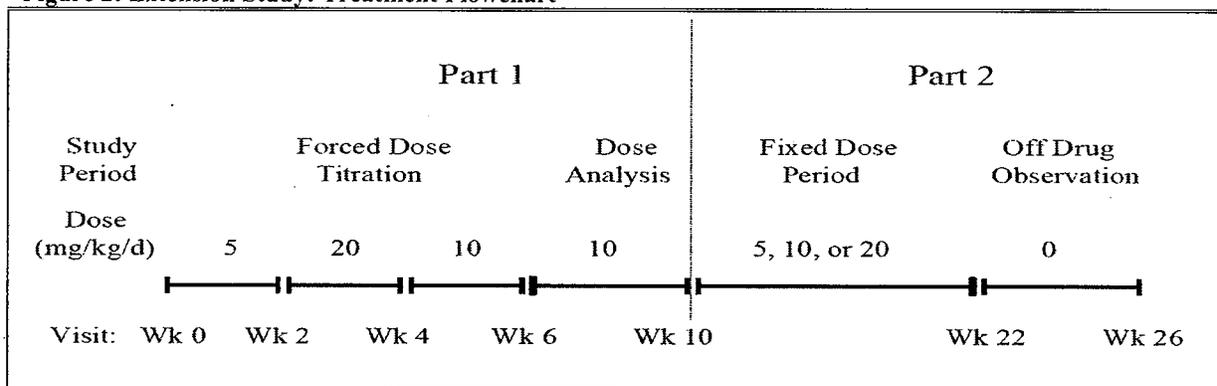
Part II: This was a 12-week fixed-dose period. Each patient's daily dose of drug was set at 5, or 10, or 20 mg/kg/day based on the following guidelines:

- If blood Phe was < 240 uM at the Week 6 visit and < 600 uM at the Week 2 visit, then provide a fixed dose of 5 mg/kg/day.
- If blood Phe was < 240 uM at the Week 6 visit and ≥ 600 uM at the Week 2 visit, then provide a fixed dose 10 mg/kg/day.
- If blood Phe at Week 6 was ≥ 240 uM and < 600 uM, provide a fixed dose of 10 mg/kg/day
- If blood Phe at Week 6 was ≥ 600 uM, then provide a fixed dose of 20 mg/kg/day

Patients assigned to receive 5 mg/kg/day, but whose blood Phe at the Week 12 visit was ≥ 600 uM were instructed increase their dose to 10 mg/kg/day for the remainder of the study.

A flowchart of treatments is summarized in Figure 2 below; copied from page 36 of the study report.

Figure 2: Extension Study: Treatment Flowchart



6.1.3.4.2 Objectives and Outcomes Measures

The primary objective was to evaluate the safety of sapropterin treatment in patients with BH4-responsive PKU over 22 weeks.

According to the sponsor, efficacy objectives were secondary. They included:

- Comparison of dose effect of three doses of sapropterin in reducing blood Phe in patients with BH4-reponsive PKU (Part I)
- To investigate persistence of blood Phe reduction over 22 weeks (Parts I and II).

Other objectives included evaluation of population PK and 24 hour PD, which are discussed in the Clinical Pharmacology review.

6.1.3.4.3 Patient Eligibility/Inclusion and Exclusion Criteria

Patients with PKU were eligible for study participation if they were ages eight years and older and had received $\geq 80\%$ of the scheduled doses in the Efficacy Study (PKU-003). Patients who were removed from the Efficacy Study due to exceeding maximum allowable Phe levels were allowed to enroll in the Extension Study. The blood Phe criteria for removing patients from the Efficacy Study were:

- Age >8 to <12 years; remove if blood Phe $>1,500$ uM any time after Screening
- Age >12 years; if Baseline Phe was $<1,500$, remove if any subsequent Phe $>1,800$ uM
- Age >12 years; if Baseline Phe $>1,500$, remove if any subsequent Phe $>1,800$, and $>30\%$ higher than baseline

Patients must have been willing to continue current diet unchanged during the study

Patients were excluded if there was a diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, use of any investigational agents within 30 days of screening, or required use of investigational agents prior to end of study, pregnancy or breast feeding, or serious illness including neuropsychiatric disorders, conditions requiring oral or parenteral corticosteroid, or insulin-dependent diabetes.

The method of exclusion of primary BH4 deficiency was not provided.

6.1.3.4.4 Concomitant and Prohibited Medications

Use of levodopa or folate inhibitors, such as methotrexate, at entry and during the study was prohibited. Any other required medicine could be used and, except for folate inhibitors or levodopa, was not reason for removal from the study. Doses and dates of use of concomitant medications and medicines used within 30 days of enrollment through completion of follow-up (Week 26) were recorded in the CRFs.

6.1.4 Efficacy Findings

Key efficacy findings are summarized below. Detailed reviews of the efficacy findings from the Enrichment, Efficacy, Diet, and Extension studies were performed and are summarized in Appendix section 10.1 of this review.

The determination of efficacy is based solely on change in blood Phe.

6.1.4.1 Enrichment Study (PKU-001)

6.1.4.1.1 Disposition and Demographics

Of 490 patients who completed all Screening procedures, 489 patients received ≥ 1 dose (ITT), and 485 patients had Day 1 and Day 8 blood Phe levels recorded (Analysis Population; AP).

Racial composition was predominantly Caucasian (96%), followed by Hispanic (2%), Asian/Pacific (1%), and other (1%), which is not inconsistent with the demographics of PKU. Thirteen percent of patients were ≥ 8 to ≤ 12 years old, 26% were from 13 to < 17 years old, and 60% were 18 to 48 years old. Gender distribution was 51% female and 49% male, which is compatible with the autosomal transmission of PKU.

Responders in this study comprise the same population studied in the Efficacy and Extension Studies (PKU-003 and PKU-004, respectively).

6.1.4.1.2 Primary Efficacy Analysis

The primary efficacy endpoint was to identify patients with a $\geq 30\%$ decrease in blood Phe from Baseline at Day 1 to Day 8. Efficacy analysis was performed on patients with blood Phe results reported for Screening, Day 1, and Day 8 (AP).

Of patients in the AP, 20% (95% CI 16%, 23%) had a decrease in blood Phe $\geq 30\%$ and were designated Responders (source: FDA statistical reviewer, Stella Grosser, PhD).

Blood Phe for the AP (Responders and Non-Responders) and by Day 1 blood Phe (< 600 and ≥ 600 uM) were assessed and compared. For the AP, Responders' blood Phe decreased 50% (SD 16) and Non-Responders' blood Phe decreased 2% (SD 17). Of patients with Day 1 blood Phe ≥ 600 uM, Responders' blood Phe decreased 48% (SD 15) and Non-Responders' blood Phe decreased 3% (SD 16). Of patients with Day 1 blood Phe < 600 uM, Responders' blood Phe decreased 55% (SD 17) and Non-Responders' blood Phe increased 10% (SD 27). Responders had a greater percent decrease in blood Phe than Non-Responders. These results are summarized in Table 5.

Table 5: Enrichment Study: Percent Change in Blood Phe; Analysis Population

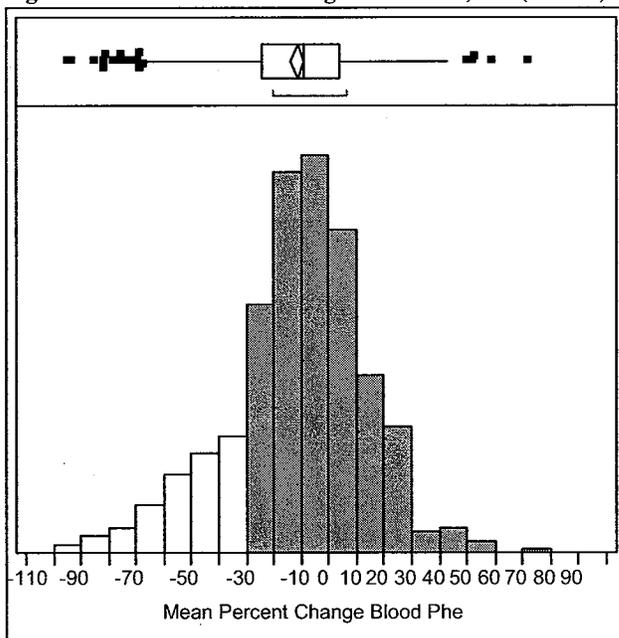
Blood Phe (uM)	Day 1 Blood Phe (uM)		AP N=485
	<600 N=57	≥600 N=432	
PRIMARY Efficacy Endpoint			
Percent Change Day 1 to Day 8; Responders			
Day 8 - Day 1 (n)	31	65	96
Mean (SD)	-55 (17)	-48 (15)	-50 (16)
Median	-51	-42	-45
Percentiles (25 th , 75 th)	-66, -44	-57, -35	-59, -36
Range (min, max)	-95, -32	-94, -30	-95, -30
Percent Change Day 1 to Day 8; Non-Responders			
Day 8 - Day 1 (n)	26	363	389
Mean (SD)	10 (27)	-3 (16)	-2 (17)
Median	15	-5	-4
Percentiles (25 th , 75 th)	-16, 26	-15, -6	-15, 7
Range (min, max)	-29, 59	-29, 72	-29, 72

In summary, 20% (95% CI [16, 23]) of patients were Responders. There was no difference in response by age or gender (data not shown).

The mean percent change in blood Phe for the AP is presented in Figure 2 below. The horizontal axis displays mean percent change in blood Phe from Day 1 to Day 8. Open vertical bars are Responders. Shaded vertical bars are Non-Responders. The height of each bar is proportional the number of patients showing a magnitude of change in 10% increments. The horizontal box in upper portion of the figure delimits the median percent change (-9%) within the 25th (-24%) and 75th (4%) percentiles for the AP. The vertical line to the right of the diamond in the upper box indicates the mean percent change (11%, 95% CI -13, -9). The horizontal stems in the upper portion of the figure delimit the central 95th percentile of percent change and black boxes to the left and right of the stems represent outliers outside of the central 95th.

*Appears This Way
 On Original*

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



This figure also demonstrates that percent change in blood Phe occurs across a spectrum. This is consistent with known pathophysiology of PKU, which is a spectrum disorder with over 400 known mutations in the gene encoding PAH, which can result in variable loss of enzyme activity, and variable potential response to synthetic BH4.

The figure also demonstrated that mean percent change in blood Phe increased in some patients. This may be due to unrecorded increases in dietary Phe.

In summary, of 485 patients in the AP, 96 patients (20%) achieved a $\geq 30\%$ decrease in blood Phe (Responders). Percent change in blood Phe appeared across a spectrum. There was no difference in response by age or gender. This Reviewer concludes this open-label, uncontrolled study successfully identified 96 patients for further study under controlled conditions in the Efficacy Study (PKU-003). Since diet and drug treatment were not controlled, these data can not be used to independently demonstrate efficacy. However, because results of the Efficacy Study, discussed in section 6.1.4.2 of this review, demonstrate efficacy of sapropterin in reducing blood Phe in patients with BH4-responsive PKU, the findings in the Enrichment Study are supportive in demonstrating that patients with PKU may be screened for BH4-responsive PKU with a one week trial of sapropterin 10 mg/kg/day, optimally when dietary Phe intake is held constant.

6.1.4.1.3 Secondary Efficacy Analyses

6.1.4.1.3.1 Percentage of Responders by Day 1 Blood Phe Stratum

The Sponsor performed an exploratory analysis by Day 1 blood Phe stratum (<600 uM vs. ≥600 uM), to determine if Response was related to pre-treatment blood Phe. Of 57 patients with Day 1 blood <600 uM, 54% (95% CI 41, 68) were Responders. Of 428 patients with Day 1 blood Phe ≥600 uM, 15% (95% CI 12, 19) were Responders. These results are summarized in Table 6.

Table 6: Enrichment Study, Responders by Day 1 blood Phe <600 uM vs. ≥600 uM

Analysis Population, n=485	Day 1 Blood Phe <600 uM n =57	Day 1 Blood Phe ≥600 uM n =428
Responders, n (%)	31 (54)	65 (15)
95% CI	(41, 68)	(12, 19)

Source: Clinical Reviewer's Analysis

These data suggest that likelihood of Response may be related to pre-treatment blood Phe; however, these findings would need to be corroborated in a controlled trial.

6.1.4.1.3.2 Change in Blood Phe, Analysis Population

This Reviewer performed a supplementary analysis of change in blood Phe from Day 1 to Day 8.

In the AP, mean blood Phe for Responders decreased 392 uM (SD 185) and mean blood Phe for Non-Responders decreased 27 uM (SD 159). For patients with Day 1 blood Phe ≥600 uM, Responders' mean blood Phe decreased 442 uM (SD 199) and Non-Responders' mean blood Phe decreased 32 uM (SD 160). For patients with Day 1 blood Phe <600 uM, Responders' mean blood Phe decreased 286 uM (SD 84) and Non-Responders' mean blood Phe increased 47 uM (SD 135). These findings are summarized in Table 7.

Table 7: Enrichment Study: Change in Blood Phe; Analysis Population

Blood Phe (uM)	Day 1 Blood Phe (uM)		AP
	<600	≥600	
	N=57	N=432	N=485
Responders			
Day 8 - Day 1 (n)	31	65	96
Mean (SD)	-286 (84)	-442 (199)	-392 (185)
Median	-271	-410	-356
Percentiles (25 th , 75 th)	-333, -215	-500, -306	-456, -273
Range (min, max)	-480, -164	-1312, -187	-1312, -164
Non-Responders			
Day 8 - Day 1 (n)	26	363	389
Mean (SD)	47 (135)	-32 (160)	-27 (159)
Median	70	-52	46
Percentiles (25 th , 75 th)	-73, 146	-150, 65	-147, 77
Range (min, max)	-163, 287	-387, 521	-387, 521

These findings demonstrate that in Responders, mean change in blood Phe was greater in patients with Baseline blood Phe ≥600 uM. This finding is not in conflict with the findings in section 6.1.4.1.3.1 above for the following reason: response was defined as a mean percent change (decrease) in blood Phe ≥30%, rather than absolute change in blood Phe. Therefore, a

decrease in blood Phe of 150 uM is a 30% decrease for a patient with a Baseline blood Phe of 450 uM, and is a 15% decrease for a patient with a Baseline blood Phe of 900 uM. These results are not discussed further.

6.1.4.1.4 Conclusions

In summary, the primary analysis indicates 20% (95% CI 16, 23) of patients were Responders and were eligible for enrollment in the Efficacy Study (PKU-003). In this sub-set of patients, mean percent change in blood Phe was -50% (SD 16, 95% CI -47, -53), and mean change in blood Phe was -392 uM (SD 185). Age and gender did not appear to affect likelihood of Response.

Secondary analyses indicate Responder status may be related to pre-treatment blood Phe.

- Of 57 patients with Day 1 blood <600 uM, 54% (95% CI 41, 68) were Responders.
- Of 428 patients with Day 1 blood Phe \geq 600 uM, 15% (95% CI 12, 19) were Responders.

These data suggest a subset of patients with PKU and elevated blood Phe may respond to sapropterin. The Sponsor succeeded in identifying a population for further study in controlled trials. Because diet and drug treatment were not controlled, these data can not be used to support efficacy.

6.1.4.2 Efficacy Study (PKU-003)

The primary efficacy endpoint of the Efficacy Study was the mean change in blood Phe from Baseline to Week 6 in the sapropterin- vs. placebo-treated groups.

The secondary efficacy endpoints were mean change in blood Phe from Baseline to Weeks 1, 2, and 4 in the sapropterin- vs. placebo-treated groups, and the proportion of patients with blood Phe <600 uM at Week 6.

6.1.4.2.1 Patient Disposition and Demographics

Of 89 randomized patients, 88 patients received \geq 1 dose (ITT=88; 41 sapropterin vs. 47 placebo). The placebo group was 51% males and the sapropterin group was 66% males. Mean patient age was 20.4 years (SD 9.7; range eight to 49 years), and the age distribution in the two treatment groups was similar. All but two patients were Caucasian. The proportion of patients with Baseline blood Phe levels \geq 600 uM was similar in the two groups (81% placebo; 83% sapropterin). In conclusion the randomization groups were similar.

6.1.4.2.2 Primary Efficacy Analysis

The primary efficacy endpoint was the mean change in blood Phe from Baseline to Week 6. Baseline blood Phe was designated as the average of three blood Phe measurements collected at

least one week apart, within four weeks preceding the first treatment dose. The first two measurements for Baseline were collected after signing informed consent for the current study and the third measurement for Baseline was drawn at the Week 0 visit. Missing Week 6 blood Phe level for one patient was imputed with the last post-Baseline observation (last observation carried forward, LOCF).

The statistician’s preliminary review (Stella Grosser, PhD) concludes the difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) for the ITT was -245 uM with a standard error of 53 uM, 95% CI [-350, -140]; p<0.001. A sensitivity analysis of Completers (N=87) was performed, which showed a difference in mean change at Week 6 (sapropterin minus placebo) of -247 uM (SE 53), 95% CI [-353, -142]; p<0.001.

Table 8 displays the results of the primary efficacy endpoint by mode of analysis. It displays results including results from the single placebo-treated patient with missing Week 6 blood Phe (N=88). It also contains a sensitivity analysis restricted to patients who completed all study procedures (N=87).

Table 8: Efficacy of Sapropterin—Primary Efficacy Analysis; Change in Blood Phe at Week 6 from Baseline

Mode of Analysis	Placebo (N=47)		Sapropterin (N=41)		Effect of Sapropterin		
	N	Change in blood Phe uM; mean ±SE ¹	N	Change in blood Phe uM; mean ±SE	Difference (Sapropterin – placebo) mean ± SE	95% Confidence Interval	p-value
Primary Efficacy; LOCF for missing data (n=1) ²	47	6 ± 36	41	-239 ± 38	-245 ± 53	(-350, -141)	<0.001
Completer Analysis ³	46	7 ± 36	41	-240 ± 39	-247 ± 53	(-353, -142)	<0.001

Source: FDA statistical review

¹ Least squared means and standard errors (SE) are presented

² ANCOVA model; change from baseline as response variable; treatment group and baseline blood Phe as covariates; LOCF (last observation carried forward for one missing blood Phe value).

³ ANCOVA model; as above restricted to completers with blood Phe reported at Week 6.

This Reviewer concludes that in a population of PKU patients pre-screened for BH4-responsiveness, sapropterin-treated patients had a statistically greater reduction in blood Phe than placebo-treated patients. This Reviewer concludes a 245 uM (SE 53) reduction in blood Phe is clinically meaningful.

This Reviewer performed an exploratory analysis of mean change, and mean percent change in blood Phe for descriptive purposes.

Mean Baseline blood Phe in sapropterin-treated patients (N=41) was 843 uM (SD 300, 95% CI [748, 937]) and mean Week 6 blood Phe was 607 uM (SD 377, 95% CI [488, 725]). Mean change in blood Phe was -236 uM (SD 257), and mean percent change was -29% (SD 32).

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Mean Baseline blood Phe in placebo-treated patients (N=47) was 888 uM (SD 323, 95% CI [793, 983]), and mean Week 6 blood Phe was 891 uM (SD 348, 95% CI [789, 993]). Mean change in blood Phe was 3 uM (SD 239), and mean percent change was 3% (SD 33).

These findings support the efficacy of sapropterin over placebo in reducing blood Phe in a subset of patients with PKU who are not on controlled diets. These results, summarized in Table 9 below, include a last observation carried forward for one placebo-treated patient with missing Week 6 data.

Table 9: Blood Phe at Baseline and Week 6; Change in Blood Phe, and Percent Change in Blood Phe

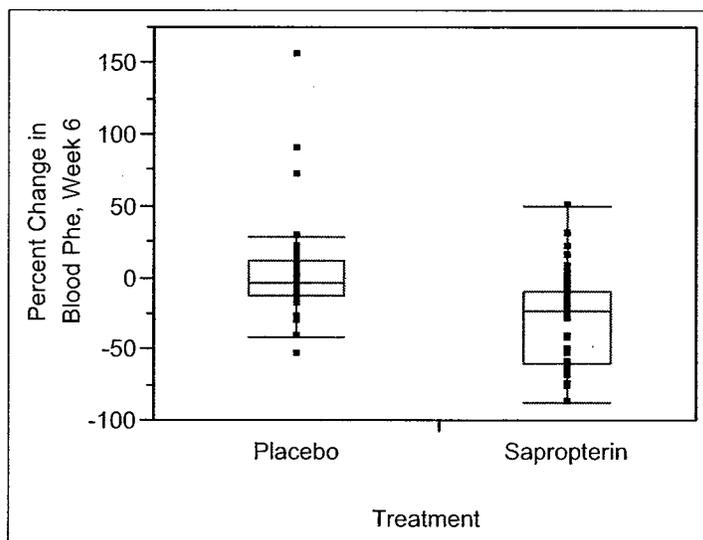
Blood Phe level (uM)	Sapropterin N=41	Placebo N=47
Baseline		
Mean (SD)	843 (300)	888 (323)
95% CI of the Mean	748, 937	793, 983
Median	862	790
Percentiles (25 th , 75 th)	598, 994	618, 1141
Min, max	293, 1643	402, 1745
Week 6		
Mean (SD)	607 (377)	891 (348)
95% CI of the Mean	488, 725	789, 993
Median	526	873
Percentiles (25 th , 75 th)	296, 823	619, 1143
Min, max	110, 1573	313, 1886
Mean Change in Blood Phe, Week 6 – Baseline		
Mean (SD)	- 236 (257)	3 (239)
95% CI of the Mean	-317, -155	-67, 73
Median	-222	-30
Percentiles (25 th , 75 th)	-410, -64	-96, 93
Min, max	-804, 271	-851, 625
Mean Percent Change in Blood, Phe Week 6 – Baseline		
Mean (SD)	- 29 (32)	3 (33)
95% CI of the Mean	-39, -19	-7, 13
Median	-24	-4
Percentiles (25 th , 75 th)	-61, -9	-13, 12
Min, max	-88, 50	-54, 155

Review of diet records and minimal fluctuations in blood Phe between Baseline Visits 1 and 2 and the Week 0 visit suggest diets were stable throughout the study.

The result for percent change in blood Phe by individual patient in the sapropterin and placebo groups are displayed graphically in the Figure 4.

Key to Figure 4: Each dot represents one patient's percent change in blood Phe at Week 6. The vertical box encompasses the 25th percentile, median, and 75th percentile of percent change, and the stems delimit the 95% percentiles.

Figure 4: Percent Change in Blood Phe from Baseline to Week 6



In summary, the primary analysis showed a statistically significant difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) of -245 uM (SE 53), 95% CI [-350, -14]; $p < 0.001$. Mean change for the sapropterin treated group from Baseline was -239 uM (SE 38) compared to the placebo group of 6 uM (SE 36).

This Reviewer's exploratory analysis further supports the clinical relevance of these changes in blood Phe.

- In sapropterin-treated patients, mean blood Phe decreased from 843 uM (SD 300, 95% CI [748, 937]) at Baseline to 607 uM (SD 377, 95% CI [488, 725]) at Week 6. Mean change in blood Phe was -236 uM (SD 257, 95% CI [-317, -155]), and mean percent change was -29% (SD 32, 95% CI [-39, -19]).
- In placebo-treated patients, mean blood Phe increased from 888 uM (SD 323, 95% CI [793, 983]) at Baseline to 891 uM (SD 348, 95% CI [789, 993]) at Week 6. Mean change in blood Phe was 3 uM (SD 239, 95% CI [-73, 67]), and mean percent change was 3% (SD 33, 95% CI [-7, 13]).
- The difference in percent change in blood Phe (sapropterin minus placebo) was 32% which exceeded the >30% reduction in blood Phe used to identify potential responders in the Enrichment Study (PKU-001).

The Reviewer concludes this magnitude of reduction in blood Phe, from approximately 850 to 600 uM is clinically meaningful.

6.1.4.2.3 Secondary Efficacy Analyses

There are two secondary efficacy analyses:

- Change in blood Phe at Weeks 1, 2, and 4
- The proportion of patients with blood Phe <600 uM at Week 6 compared to Screening (rather than Baseline)
-

The protocol does not indicate if these endpoints are to be assessed in a hierarchical order.

6.1.4.2.2.1 Change in blood Phe at Weeks 1, 2, and 4

At the end of all treatment weeks, blood Phe was lower in sapropterin- than in placebo-treated patients. At the end of Week 1, mean blood Phe in sapropterin- and placebo-treated patients was 620 uM (SD 355) and 863 uM (SD 346), respectively. At the end of Week 2, mean blood Phe in sapropterin- and placebo-treated patients was 639 uM (SD 369) and 863 uM (SD 325), respectively. At the end of Week 4, mean blood Phe in sapropterin- and placebo-treated patients was 587 uM (SD 376) and 906 uM (SD 341), respectively. These results are summarized in Table 10.

Table 10: Mean Blood Phe at Baseline and Weeks 1, 2, and 4

Blood Phe level (uM)	Sapropterin N=41	Placebo N=47
Baseline		
Mean (SD)	843 (300)	888 (323)
95% CI of the Mean	748, 937	793, 983
Median	862	790
Percentiles (25 th , 75 th)	598, 994	618, 1141
Min, max	293, 1643	402, 1745
Week 1		
Mean (SD)	620 (355)	863 (346)
95% CI of the Mean	507, 731	761, 964
Median	596	843
Percentiles (25 th , 75 th)	336, 779	549, 1122
Min, max	184, 1603	199, 1766
Week 2		
Mean (SD)	639 (369)	863 (325)
95% CI of the Mean	523, 756	768, 959
Median	603	829
Percentiles (25 th , 75 th)	339, 847	626, 1090
Min, max	67, 1594	125, 1648
Week 4		
Mean (SD)	587 (376)	906 (341)
95% CI of the Mean	469, 706	807, 1007
Median	578	850
Percentiles (25 th , 75 th)	287, 776	640, 1088
Min, max	93, 1534	369, 1732

At all weeks, mean change in mean blood Phe from Baseline was greater in sapropterin- than placebo-treated patients. At the end of Week 1, mean change in blood Phe was -223 uM (SD 192) in sapropterin-treated patients, and was -26 uM (SD232) in placebo-treated patients. At the end of Week 2, mean change in blood Phe was -203 uM (SD 270) in sapropterin-treated patients, and was -25 uM (SD 248) in placebo-treated patients. At the end of Week 4 mean change in blood Phe was -255 uM (SD 248) in sapropterin-treated patients and was 19 uM (SD240) in placebo-treated patients. These results are summarized in Table 11.

Table 11: Change in Mean Blood Phe at Weeks 1, 2, and 4

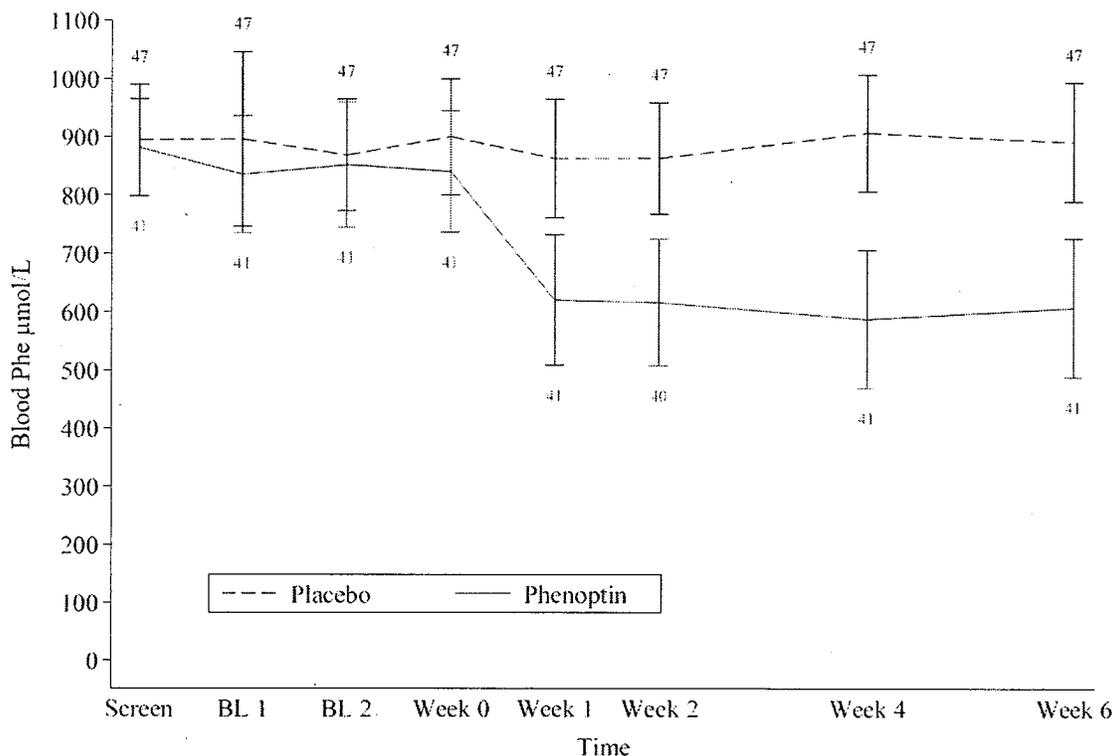
Blood Phe level (uM)	Sapropterin	Placebo
Week 1 – Baseline	N=41	N=47
Mean (SD)	-223 (192)	-26 (232)
95% CI of the Mean	-284, -162	-94, 43
Median	-212,	14
Percentiles (25 th ,75 th)	-387, -74	-98, 14, 90
Min, max	-589, 161	-1035, 409
Week 2 – Baseline		
Mean (SD)	-203 (270)	-25 (261)
95% CI of the Mean	-289, -118	-102, 51
Median	-197	-16
Percentiles (25 th ,75 th)	-307, -64	-109, 113
Min, max	-1029, 389	-1070, 358
Week 4 – Baseline		
Mean (SD)	-255 (248)	19 (240)
95% CI of the Mean	-333, 334	-52, 89
Median	-217	27
Percentiles (25 th ,75 th)	-391, -103	-53, 94
Min, max	-1058, 185	-1044, 729

The difference in mean percent change in placebo- vs. sapropterin-treated patients at each week was also analyzed. At Week 1 the difference in mean percent change (placebo minus sapropterin) was 27% (-1% minus -28%). At Week 2 the difference was 23% (1% minus -24%). At Week 4 was 37% (5% minus -32%). These results are summarized in Table 61 in section 10.1.2.13.5.2.1 of this review.

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Mean blood Phe from Screening through Week 6 are displayed in Figure 5 copied from section 5.3.5.1 of the electronic submission; page 69 of the study report.

Figure 5: Mean Blood Phe Levels from Screening through Week 6



* Phenoptin: name of sapropterin use in clinical trials

These findings show that in BH4-responsive patients, reduction in blood Phe is seen as early as the first week of treatment and effect is sustained through six weeks of treatment. Also, the magnitude of reduction appears sustained over six weeks. The Reviewer concludes these findings support the primary efficacy analysis and show that in patients with BH4-responsive PKU, sapropterin is more effective than placebo in reducing blood Phe, and a reduction of blood Phe of approximately 25 to 35% seen from Weeks 1 through 6 is clinically meaningful.

6.1.4.2.2.2 Proportion of patients with blood Phe <600 µM at Week 6

At Screening, nine of 47 placebo-treated patients [19%, 95% CI (10, 32)], and seven of 41 sapropterin-treated patients [17%, 95% CI (9, 31)] had blood Phe <600 µM. At Week 6, 11 of 47 placebo-treated patients 23%, 95% CI (14, 37), and 22 of 41 sapropterin-treated patients [54%, 95% CI (39, 68)] had blood Phe <600 µM. In conclusion, more sapropterin- than placebo-treated patients had decreases in blood Phe to <600 µM from Screening to Week 6.

6.1.4.2.4 Conclusions

The primary efficacy endpoint of this randomized, double-blind, placebo-controlled study was mean change in blood Phe from Baseline to Week 6. Secondary endpoints included mean change in blood Phe at Weeks 1, 2, and 4; and the proportion of patients with blood Phe <600 uM at Week 6 compared to Screening.

For the primary efficacy endpoint, sapropterin-treated patients had a greater mean decrease in blood Phe than placebo-treated patients.

- The difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) for the ITT was -245 uM with a standard error of 53 uM, 95% CI [-350, -140]; p<0.001.

For the secondary efficacy endpoint of change in blood Phe at Weeks 1, 2, and 4, sapropterin-treated patients had a greater mean change in blood Phe than placebo-treated patients.

- At Week 1, mean change in blood Phe in placebo- vs. sapropterin-treated patients was -26 uM (SD 232) vs. -223 uM (SD 192), respectively; and the difference in mean percent change (placebo minus sapropterin) was 27% (-1% minus -28%).
- At Week 2, mean change in blood Phe in placebo- vs. sapropterin-treated patients was -25 uM (SD 248) vs. -203 uM (SD 270), respectively; and the difference in mean percent change (placebo minus sapropterin) was 23% (1% minus -24%).
- At Week 4 mean change in blood Phe in placebo- vs. sapropterin-treated patients was 19 uM (SD 240) vs. -255 uM (SD 248), respectively; and the difference in mean percent change (placebo minus sapropterin) was 37% (5% minus -32%).

The proportion of patients with blood Phe <600 uM was similar at Screening in sapropterin- and placebo-treated patients (17% and 19%, respectively). At Week 6, a greater percentage of sapropterin- than placebo-treated patients had blood Phe <600 uM (54% vs. 23%, respectively) suggesting that sapropterin is more likely than placebo to reduce blood Phe to below 600 uM.

In conclusion, the results provide strong statistical evidence that the study drug, sapropterin, decreased blood Phe in a subset of patients with PKU who underwent prior screening to determine potential response. The Reviewer concludes the magnitude of decrease (23 to 32%) is clinically significant, appears rapidly (at Week 1), and is durable through six weeks of treatment.

6.1.4.3 Diet Study (PKU-006)

6.1.4.3.1 Demographics and Disposition

Eighty-nine patients received ≥ 1 dose of OL sapropterin (20 mg/kg) in Part I (Part I ITT=89). Gender composition was 57% male and 43% female. The mean (SD) age was 7.3 ± 2.5 years. Eighty-five (94%) of the subjects were Caucasian.

Fifty patients responded to OL sapropterin treatment in Part I, and 46 of these patients were randomized to DB treatment with either placebo or sapropterin in Part II. Mean (SD) daily dose

in Responders and Non-Responders was the same; 19.5 mg/kg/day (SD 1.8). Forty-five of 46 patients randomized to Part II received ≥ 1 dose (Part II ITT=45). Gender composition for the placebo group was equal and gender composition for sapropterin group were 61% male and 39% female. The mean age of placebo-treated patients (N=12) was 7.5 years (SD 2.6), and the mean age of sapropterin-treated patients (N=33) was 7.7 (SD 2.8) years. Thirty-two sapropterin- and nine placebo-treated patients completed Part II (Completers).

6.1.4.3.2 Primary Efficacy Analysis Part I

The primary efficacy endpoint of Part I was a $\geq 30\%$ reduction in blood Phe from Baseline to Day 8 and Day 8 blood Phe ≤ 300 uM at Day 8, during open-label, uncontrolled treatment with sapropterin, under diet controlled conditions and without Phe supplement. Ninety patients enrolled, 89 patients received ≥ 1 dose and completed Day 1 and Day 8 study procedures. Fifty patients (56%) were Responders.

From Day 1 to Day 8, mean blood Phe in Responders decreased from 317 uM (SD 173) to 108 uM (SD 70), mean percent change was -64% (SD 18), and median percent change was -66 uM. From Day 1 to Day 8, mean blood Phe in Non-Responders increased from 234 uM (SD 186) to 264 uM (SD 171), mean percent change was 131% (SD 389), and median percent change was 11%. Five patients with percent increases of 236, 321, 533, 1300, and 2050% caused the mean percent change of Non-Responders to increase. These results are summarized in Table 12.

Table 12: Mean Blood Phe at Day 1 and Day 8, and Mean Percent Change in Blood Phe at Day 8

Blood Phe level (uM)	Responders N=50	Non-Responders N=39
Day 1		
Mean (SD)	317 (173)	234 (186)
95% CI of the Mean	267, 366	174, 295
Median	311	170
Percentiles (25 th , 75 th)	180, 438	72, 440
Min, max	49, 824	4, 572
Day 8		
Mean (SD)	108 (70)	264 (171)
95% CI of the Mean	88, 128	208, 319
Median	102	236
Percentiles (25 th , 75 th)	41, 159	144, 342
Min, max	6, 270	30, 832
Mean Percent Change in Blood Phe, Day 8 – Day 1		
Mean (SD)	-64 (18)	131 (389)
95% CI of the Mean	-69, -59	5, 257
Median	-66	11
Percentiles (25 th , 75 th)	-78, -51	-12, 73
Min, max	-99, -30	-39, 2050

This Reviewer concludes the Sponsor successfully identified 50 patients with a $\geq 30\%$ decrease in blood Phe from Day 1 to Day 8, who also had Day 8 blood Phe < 300 uM. These patients qualified for further study under controlled conditions in Part II of this study.

6.1.4.3.3 Primary Efficacy Analysis Part II

Forty-six of 50 Responders from Part I were randomized, and 45 patients received ≥ 1 dose of sapropterin (N=33) or placebo (N=12) in Part II.

The primary efficacy endpoint of Part II was the amount of Phe supplement tolerated at Week 10. This was defined as the net amount of Phe supplement (maximum 50 mg/kg/day) tolerated while maintaining blood Phe level < 360 uM. Diet was to remain unchanged except for protocol directed changes in supplement.

Phe supplement tolerated at Week 10 by sapropterin-treated patients was 21 mg/kg/day (SD 15) ($p < 0.001$; FDA statistical review; Stella Grosser, PhD). Phe supplement tolerated by placebo-treated patients was 3 mg/kg/day (SD 4) ($p = 0.03$; FDA statistical review; Stella Grosser, PhD), which was statistically different from zero supplement. The Sponsor performed an analysis of supplement tolerated by blood Phe stratum (average blood Phe < 300 vs. ≥ 300 uM in the six months preceding Screening). Sapropterin-treated patients in the < 300 uM stratum tolerated more supplementary Phe than patients in the ≥ 300 uM stratum [25 (SD 16) vs. 17 (SD 15) mg/kg/day]. The small size of the strata limits statistical inferences of analysis by strata. These findings are summarized in Table 13 below.

Table 13: Phe Supplement Tolerated at Week 10, ITT

Maximum Phe Supplement tolerated (mg/kg/day)	Sapropterin N=33	Placebo N=12
ITT (n)	33	12
Mean (SD)	21 (15)	3 (4)
95% CI of the Mean	16, 26	0.5, 5
Percentiles (25 th , median, 75 th)	7.5, 20, 35	0, 0, 5
Min, Max	0, 50	0, 10
p-value (one-sample t-test) ¹	$p < 0.001$	$p = 0.03$
Blood Phe Stratum < 300 uM (n)	16	5
Mean (SD)	25 (16)	2 (5)
95% CI of the Mean	16, 33	-4, 8
Percentiles (25 th , median, 75 th)	11, 20, 35	*, *, 5
Min, Max	0, 50	0, 10
Blood Phe Stratum ≥ 300 uM (n)	17	7
Mean (SD)	17 (15)	4 (4)
95% CI of the Mean	10, 25	< 1 , 7
Percentiles (25 th , median, 75 th)	3, 15, 35	*, 5, 5
Min, Max	0, 40	0, 10

¹Source; FDA Statistician's Review

* Population of group is too small for meaningful analysis

This Reviewer performed a sensitivity analysis of the nine placebo- and 32 sapropterin-treated patients who completed Part II. Phe supplement tolerated at Week 10 by sapropterin treated patients was 22 mg/kg/day (SD 15). Phe supplement tolerated by placebo treated patients at Week 10 was 3 mg/kg/day (SD 4). Sapropterin-treated patients in the < 300 uM stratum tolerated more supplementary Phe than patients in ≥ 300 uM stratum [25 (SD 16) vs. 18 (SD 14) mg/kg/day]. These results are similar to the results of the ITT analysis. These results are

summarized in Table 14 below. Table 14 also displays Phe tolerated by 10 mg/kg/day categories for illustrative purposes. Of Completers, 65% of sapropterin-treated patients tolerated >10 mg/kg/day of supplement compared to 0% of placebo-treated patients.

Table 14: Phe Supplement Tolerated at Week 10; Completers

Maximum Phe Supplement tolerated (mg/kg/day)	Sapropterin N=33	Placebo N=12
Completers (n)	32	9
Mean (SD)	22 (15)	3 (4)
95% CI of the Mean	16, 27	0, 6
Percentiles (25 th , median, 75 th)	10, 20, 35	0, 0, 5
Min, Max	0, 50	0, 10
Blood Phe Stratum < 300 uM (n)	16	3
Mean (SD)	25 (16)	0
95% CI of the Mean	16, 33	n/a
Percentiles (25 th , median, 75 th)	11, 20, 35	n/a
Min, Max	0, 50	n/a
Blood Phe Stratum ≥ 300 uM (n)	16	6
Mean (SD)	18 (14)	4 (4)
95% CI of the Mean	10, 26	n/a
Percentiles (25 th , median, 75 th)	6, 18, 35	*, 5, 6
Min, Max	0, 40	0, 10
Groupings of tolerated Phe supplement, n (%)		
0 mg/kg/day	4 (13)	5 (56)
1-10 mg/kg/day	7 (22)	4 (44)
11-20 mg/kg/day	8 (25)	0
21-30 mg/kg/day	2 (6)	0
31-40 mg/kg/day	8 (25)	0
41-50 mg/kg/day	3 (9)	0

* Population of strata are too small for meaningful analysis

In conclusion, patients treated with sapropterin tolerated more supplemental Phe than placebo treated patients during this ten week study.

This Reviewer's overall conclusion of primary efficacy analysis and the sensitivity analysis is that these findings are not clinically meaningful because the amount of tolerated dietary Phe supplement is not a recognized clinical endpoint. For tolerated dietary Phe supplement to be considered as a clinical endpoint, the results would have to be tied to neurocognitive outcomes such as neurocognitive development in long-term studies of at least five to ten years duration.

6.1.4.3.4 Secondary Efficacy Analysis Part II

The secondary efficacy endpoint of Part II was comparison of mean change in blood Phe from non-treatment Baseline to blood Phe at completion of three weeks of double-blind, placebo-controlled therapy, under diet controlled conditions, prior to Phe-supplementation. The Sponsor specified that this assessment was to be done for sapropterin-treated patients; however, an assessment was performed for placebo-treated patients as well.

From Week 0 to Week 3, mean blood Phe in sapropterin-treated patients changed from 276 uM (SD 135) to 127 uM (SD 90), mean change was -149 uM (SD 134), mean percent change was -32% (SD 111), and median percent change was -55%. In placebo-treated patients, mean blood Phe changed from 326 uM (SD 235) to 230 uM (SD 116), mean change was -97 uM (SD 244), mean percent change was 31% (SD 149), and median percent change was -17%. These findings are summarized in Table 15.

Table 15: Mean Change and Mean Percent Change in Blood Phe at Weeks 0 and 3

Blood Phe level (uM)	Sapropterin N=33	Placebo N=12
Week 0 (n)		
Mean (SD)	276 (135)	326 (235)
95% CI of the Mean	228, 324	177, 476
Median	283	301
Percentiles (25 th , 75 th)	180, 352	141, 376
Min, max	30, 570	53, 802
Week 3 (n)		
Mean (SD)	127 (90)	230 (116)
95% CI of the Mean	95, 159	156, 302
Median	100	218
Percentiles (25 th , 75 th)	60, 168	113, 320
Min, max	19, 366	91, 428
Mean Change in Blood Phe: Week 3 – Week 0		
Mean (SD)	-149 (134)	-97 (244)
95% CI of the Mean	-196, -101	-251, 58
Median	-150	-58
Percentiles (25 th , 75 th)	-220, -74	-230, 75
Min, max	-372, 266	-642, 276
Mean Percent Change in Blood Phe: Week 3 – Week 0		
Mean (SD)	-32 (111)	31 (149)
95% CI of the Mean	-72, 7	-63, 126
Median	-55	-17
Percentiles (25 th , 75 th)	-72, -40	-58, 34
Min, max	-93, 532	-86, 388

Under conditions of dietary Phe restriction, sapropterin 20 mg/kg/day is more effective than placebo in reducing blood Phe. The small size of the placebo group may have affected results.

6.1.4.3.5 Conclusions

In Part I, 50 of 89 patients (56%) were Responders. Mean percent change in Responders was -64% (SD 18). This Reviewer concludes that the Sponsor succeeded in identifying a subset of patients who qualified for Part II of the study. These patients had a decrease in blood Phe of $\geq 30\%$ at Day 8 and a blood Phe < 300 uM at Day 8.

In Part II, for the primary efficacy endpoint of Phe supplement tolerated at Week 10, sapropterin-treated patients tolerated a mean of 21 mg/kg/day (SD 15) ($p < 0.001$) and placebo-treated patients tolerated a mean of 3 mg/kg/day (SD 4) ($p = 0.03$). Sapropterin-treated patients in the < 300 uM

stratum tolerated more supplementary Phe than patients in ≥ 300 uM stratum [25 (SD 16) vs. 17 (SD 15) mg/kg/day]. These data indicate more supplemental Phe was tolerated by patients treated with sapropterin than placebo.

In Part II, for the secondary efficacy endpoint, prior to any dietary Phe supplement, sapropterin-treated patients had a decrease in mean blood Phe at Week 3 compared to Baseline. Changes in blood Phe in sapropterin- and placebo-treated patients at Week 3 compared to Baseline are as follows:

- Mean changes in blood Phe for sapropterin and placebo patients were -149 uM (SD 134) and -97 uM (SD 244), respectively.
- Mean percent changes in sapropterin and placebo patients were -32% (SD 111) and 31% (SD 149), respectively.
- Median percent changes in sapropterin and placebo patients were -55% and -17%, respectively.

The data suggest that under diet controlled conditions, sapropterin is more likely to reduce blood Phe than placebo.

The findings in Part II do not eliminate the need for long-term studies with neurocognitive outcomes _____

This Reviewer recommends _____ that the primary efficacy endpoints of Part II be confirmed with long-term studies that incorporate neurocognitive outcomes. These studies may be conducted post-approval.

6.1.4.4 Extension Study (PKU-004)

Per the protocol, the primary objective of the Extension Study was safety, and all efficacy objectives were secondary.

Efficacy endpoints included:

- Mean change in blood Phe from Week 0 at the end of each two-week dose period of 5, then 20, then 10 mg/kg/day); Part I.
- Estimation of dose effect by comparing the change at each dose to each other (5 vs. 10, 5 vs. 20, and 10 vs. 20 mg/kg/day); Part I.
- Mean change in blood Phe from Week 0 during Part II (Individualized dose; Weeks 12 to 22).

No patients were treated with placebo in the Extension Study. For the purposes of this analysis the following terminology is used:

- Prior Placebo Population (PPbo): Patients who received placebo in the Efficacy Study
- Prior Sapropterin Population (SP): Patients who received sapropterin in the Efficacy Study

6.1.4.4.1 Demographics and Disposition

The ITT consists of 80 patients who received ≥ 1 dose. All patients completed Part I of the Extension Study and 79 patients completed Part II. Diet was not controlled from Screening through completion of all study procedures. The SP and PPbo sub-groups were similar in age and gender. Patient gender was 59% male and 41% female, and mean age was 20.4 (SD 9.6) years.

6.1.4.4.2 Efficacy Analyses

The efficacy variable in Parts I and II was change in blood Phe from Week 0. Results are presented as mean blood Phe and mean change in blood Phe for the ITT.

6.1.4.4.2.1 Change in blood Phe at Weeks 2, 4, and 6

The efficacy analysis of Part I was mean change in blood Phe from Week 0 at the end of each Week 2, 4, and 6 (5, then 20, then 10 mg/kg/day). The efficacy analysis and conclusions are based on the ITT; however, because seven patients were on treatment (10 mg/kg/day) at Week 0, results are also presented by PPbo and SP sub-groups.

In the Efficacy Study, mean Baseline blood levels for the PPbo, SP, and ITT were 889 uM (SD 337), 828 uM (SD 297), and 860 uM (SD 318), respectively (data not shown). At Week 0 of the Extension Study mean blood Phe for the PPbo, SP, and ITT were 915 uM (SD 391), 769 uM (SD 396), and 844 uM (SD 398), respectively. The lower Baseline blood Phe in the SP group is due, in part, to the seven patients in this group who were on sapropterin (10 mg/kg/day) at Week 0.

At the end of Week 2 (5 mg/kg/day), mean blood Phe levels for the PPbo, SP, and ITT were 755 (SD 417), 733 (SD 352), and 744 uM (SD 384), respectively.

At the end of Week 4 (20 mg/kg/day), mean blood Phe levels for the PPbo, SP, and ITT were 619 uM (SD 424), 540 uM (372), and 581 uM (SD 399), respectively.

At the end of Week 6 (10 mg/kg/day), mean blood Phe levels for the PPbo, SP, and ITT were 687 uM (SD 426), 591 uM (328), and 640 uM (SD 382), respectively. Week 10 blood Phe results (10 mg/kg/day) were similar to Week 6 results (data not shown).

These findings are summarizing in Table 16.

Table 16: Mean Blood Phe Weeks 0, 2, 4, and 6 by Prior Treatment Group

Part I	Prior Treatment Group in the Efficacy Study		
	Placebo N=41	Sapropterin N=39	ITT N=80
Week 0			
Mean (SD)	915 (391)	769 (396)	844 (398)
95% CI of the Mean	792, 1039	641, 898	756, 933
Median	828	744	801
Percentiles (25 th , 75 th)	639, 112	427, 1042	564, 1099
Min, max	396, 2190	53, 1573	53, 2190
Week 2 (5 mg/kg/day)			
Mean (SD)	755 (417)	733 (352)	744 (384)
95% CI of the Mean	623, 886	619, 847	658, 829
Median	587	711	701
Percentiles (25 th , 75 th)	441, 1091	424, 931	433, 966
Min, max	217, 1828	107, 1513	107, 1828
Week 4 (20 mg/kg/day)			
Mean (SD)	619 (424)	540 (372)	581 (399)
95% CI of the Mean	486, 753	420, 661	492, 670
Median	494	362	492
Percentiles (25 th , 75 th)	288, 910	261, 706	277, 767
Min, max	65, 1935	47, 1520	47, 1935
Week 6 (10 mg/kg/day)			
Mean (SD)	687 (426)	591 (328)	640 (382)
95% CI of the Mean	552, 821	485, 697	555, 725
Median	641	498	522
Percentiles (25 th , 75 th)	318, 1018	351, 769	337, 842
Min, max	163, 2106	135, 1493	135, 2106

PPbo and SP patients had similar results from Week 2 to Week 6; however, mean blood Phe was higher in PPbo patients at all weeks. The reason for this is not clear; however, as noted above mean Baseline blood Phe was higher in PP patients at the beginning of the Efficacy Study. Possible reasons for the difference between the groups include differences in mean residual enzyme activity levels between the groups, and differences in diet or compliance that were not recorded in the datasets.

Mean change in blood Phe from Baseline was calculated at Weeks 2, 4, and 6. Mean changes in blood Phe from Baseline at Week 2 (5 mg/kg/day) for the PPbo, SP, and ITT were -161 uM (SD 284), -37 uM (297), and -100 uM (SD 295), respectively. Mean changes from Baseline at Week 4 (20 mg/kg/day) for the PPbo, SP, and ITT were -296 uM (SD 295), -229 uM (SD 341), and -263 uM (SD 318), respectively. Mean changes from Baseline at Week 6 (10 mg/kg/day) for the PPbo, SP, and ITT were -241 uM (SD 302), -154 uM (SD 324), and -199 uM (SD 314), respectively. These results are summarized in Table 17.

Table 17: Mean Change in Blood Phe from Baseline at Weeks 2, 4, and 6 by Prior Treatment Group.

Part I	Prior Treatment Group in the Efficacy Study		
	Placebo N=41	Sapropterin N=39	ITT N=80
Week 2 – Week 0			
Mean (SD)	-161 (284)	-37 (297)	-100 (295)
95% CI of the Mean	-251, 71	-133, 60	-166, -34
Median	-151	-47	-100
Percentiles (25 th , 75 th)	-298, -23	-187, 89	-226, -40
Min, max	-1424, 586	-687, 739	-1424, 739
Week 4 – Week 0			
Mean (SD)	-296 (295)	-229 (341)	-263 (318)
95% CI of the Mean	-389, -203	-340, -119	-334, -192
Median	284	-202	-270
Percentiles (25 th , 75 th)	-439, -134	-506, -42	472, -61
Min, max	-1336, 237	-960, 540	-1336, 540
Week 6 – Week 0			
Mean (SD)	-229 (274)	-178 (332)	-204 (303)
95% CI of the Mean	-315, -142	-286, -71	-272, -137
Median	-222	-131	-205
Percentiles (25 th , 75 th)	-346, -45	-424, 15	-380, -13
Min, max	-1474, 332	-751, 843	-1474, 843

The results show that, in patients with BH4-responsive PKU, reduction in blood Phe is greatest at 20 mg/kg/day doses and least with 5 mg/kg/day doses.

6.1.4.4.2.2 Comparison of Dose Effect at Weeks 5, 10, and 20 mg/kg/day

Pair-wise comparisons of the dose groups were performed and statistical significance was demonstrated for the difference in mean (\pm SE) change from Week 0 in blood Phe between 5, 10, and 20 mg/kg/day administered in Part I. The mean (\pm SE) change (decrease) in blood Phe was greater with increasing dose. Treatment with 10 mg/kg/day resulted in a 104 μ M (SE 19) greater decrease than treatment with 5 mg/kg/day. Treatment with 20 mg/kg/day resulted in a 163 μ M (SE 24) greater decrease than treatment with 5 mg/kg/day. Treatment with 20 mg/kg/day resulted in a 59 μ M (SE 23) greater decrease than treatment with 10 mg/kg/day. These results are summarized in Table 18.

Table 18: Pair-wise Comparison of Dose: Decrease in Blood Phe from Week 0 at Each Dose in Part I; ITT

	Mean (SE)	95% CI
Change at 5 v. 10 mg/kg/day	104 (19)	65, 142
Change at 5 v. 20 mg/kg/day	163 (24)	115, 211
Change at 10 v. 20 mg/kg/day	59 (23)	14, 105

These findings show that in patients with BH4-responsive PKU, as sapropterin dose increases from 5 to 20 mg/kg/day, blood Phe decreases. This suggests response increases as dose increases from 5 to 20 mg/kg/day.

6.1.4.4.2.3 Change in blood Phe from Week 0 through completion of dosing at Week 22

The efficacy endpoint of Part II was change in blood Phe from Week 0 at Weeks 12 to 22 (Individualized dose). As in Part I, the PPbo and SP groups behaved similarly at all weeks and the PPbo group had higher mean blood Phe at all weeks. At Week 22, however, mean blood Phe increased in the PPbo group. The datasets indicate this is likely due decreased compliance with medication in the PPbo group. Discussion of mean blood Phe is hereafter restricted to the ITT. Mean blood Phe for the SP and PPbo are included in the tables for illustrative purposes only.

Of the 80 patients who entered Part II, six (8%) were assigned 5 mg/kg/day, 37 (46%) were assigned 10 mg/kg/day, and 37 (46%) were assigned 20 mg/kg/day during the fixed-dose period. No patient increased dose during the fixed-dose period. Blood Phe remained below Week 0 at Weeks 12, 16, 20, and 22.

At Week 12 mean blood Phe for the ITT was 620 uM (SD 371), and mean change in blood Phe from Week 0 was -224 uM (SD 326). At Week 16 mean blood Phe for the ITT was 632 uM (SD 369), and mean change in blood Phe from Week 0 was -206 uM (SD 380). At Week 20 mean blood Phe for the ITT was 626 uM (SD 379), and mean change in blood Phe from Week 0 was -220 uM (SD 352). At Week 22 mean blood Phe for the ITT was 652 uM (SD 382), and mean change in blood Phe from Week 0 was -190 uM (SD 356). Mean change in blood Phe from Baseline was persistent from Weeks 12 through 22. These data are summarized in Tables 19 and 20.

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Table 19: Extension Study: Mean Blood Phe Weeks 12 through 22 by Prior Treatment Group

Part II	Prior Treatment Group in the Efficacy Study		
	Placebo N=41	Sapropterin N=39	ITT N=80
Week 12 (n)	41	39	80
Mean (SD)	658 (402)	579 (336)	620 (371)
95% CI of the Mean	531, 785	471, 688	537, 702
Median	530	496	514
Percentiles (25 th , 75 th)	351, 975	328, 726	336, 839
Min, max	192, 2064	149, 1403	149, 2064
Week 16 (n)	40	39	79
Mean (SD)	652 (402)	610 (312)	632 (369)
95% CI of the Mean	518, 787	509, 712	549, 715
Median	519	541	541
Percentiles (25 th , 75 th)	354, 858	322, 769	348, 796
Min, max	185, 2074	133, 1403	133, 2074
Week 20 (n)	40	38	78
Mean (SD)	656 (398)	593 (360)	626 (379)
95% CI of the Mean	529, 783	475, 712	540, 711
Median	505	467	493
Percentiles (25 th , 75 th)	380, 900	344, 825	364, 855
Min, max	127, 2162	115, 1528	115, 2162
Week 22 (n)	40	39	79
Mean (SD)	715 (400)	588 (357)	652 (382)
95% CI of the Mean	587, 843	472, 703	567, 738
Median	638	469	580
Percentiles (25 th , 75 th)	401, 970	316, 763	366, 869
Min, max	108, 2042	176, 1710	108, 2042

Mean blood Phe was stable from Week 12 to Week 22.

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Table 20 summarized mean change in blood Phe from Baseline at Weeks 12 through 22.

Table 20: Extension Study: Mean Change in Blood Phe Weeks 12 through 22 by Prior Treatment Group

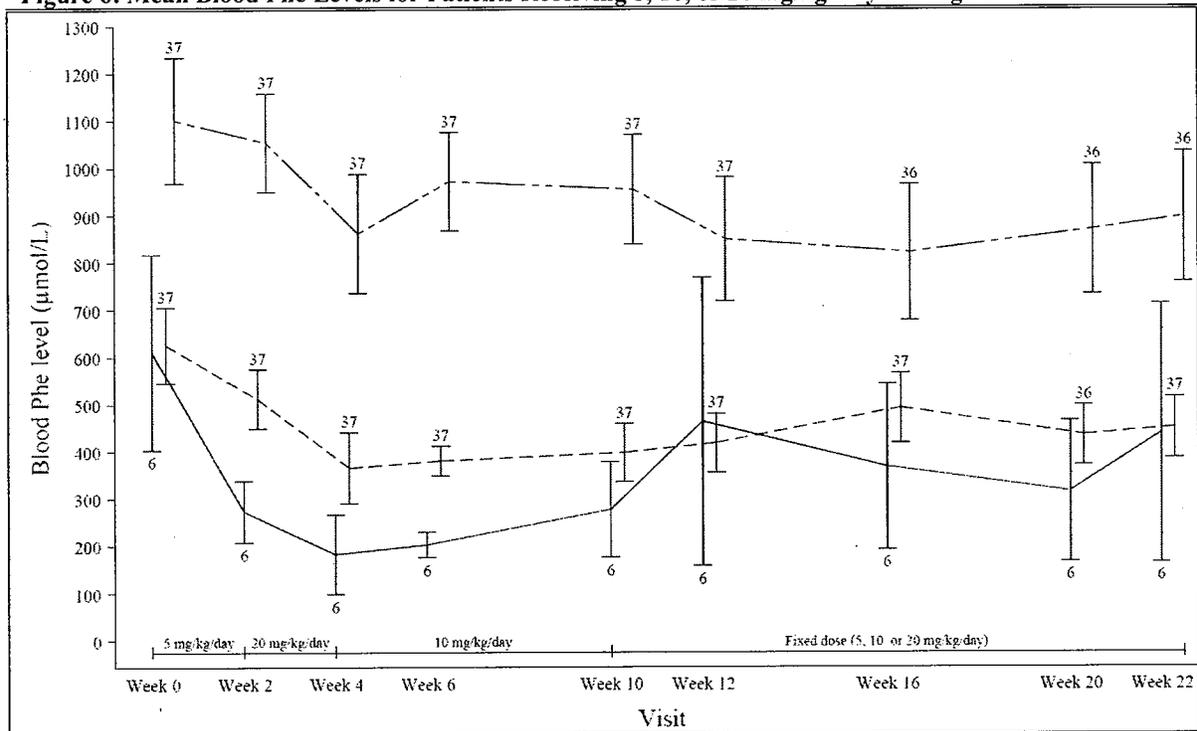
Part II: Individualized Dose	Prior Treatment Group in the Efficacy Study		
	Placebo N=41	Sapropterin N=39	ITT N=80
Week 12 –Week 0 (n)	41	39	80
Mean (SD)	-257 (303)	-190 (350)	-224 (326)
95% CI of the Mean	-352, -161	-303, -77	-297, -151
Median	-216	-164	-212
Percentiles (25 th , 75 th)	-386, -92	-467, 46	-401, -22
Min, max	-1645, 290	-796, 662	-1645, 662
Week 16 –Week 0 (n)	40	39	79
Mean (SD)	-252 (354)	-159 (405)	-206 (380)
95% CI of the Mean	-365, -139	-290, -28	-291, -121
Median	-163	-140	-151
Percentiles (25 th , 75 th)	-385, -38	-430, 140	-408, -1
Min, max	-1533, 300	-1069, 759	-1533, 759
Week 20 –Week 0 (n)	40	38	78
Mean (SD)	-258 (344)	-179 (360)	-220 (352)
95% CI of the Mean	-369, -148	-297, -61	-299, -140
Median	-226	-123	-200
Percentiles (25 th , 75 th)	-423, -65	-506, 44	-431, -41
Min, max	-1714, 388	-733, 663	-1714, 663
Week 22 –Week 0 (n)	40	39	79
Mean (SD)	-199 (366)	-182 (349)	-190 (356)
95% CI of the Mean	-316, -82	-295, -68	-270, -111
Median	-206	-216	-216
Percentiles (25 th , 75 th)	-402, 78	-373, 88	-373, 79
Min, max	-1317, 78	-796, 652	-1317, 802

Mean change in blood Phe from Week 0 was stable from Weeks 12 through 22.

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Figure 6 displays mean blood Phe by dose level in Part II. Patients treated with a fixed dose of 5 mg/kg/day had more variability in mean blood Phe than patients treated with 10 or 20 mg/kg/day. This may be due to the smaller number of patients treated with 5 mg/kg/day (n = 6) compared to patients treated with 10 and 20 mg/kg/day (n = 37, each). This figure represents the minimum dose required to maintain blood Phe at a given level; that is, patients treated with 5 mg/kg/day had lower blood Phe than patients treated with 20 mg/kg/day, therefore they were assigned a lower dose (copied from page 71 of the study report located in section 5.2.5.2.3 of the electronic submission).

Figure 6: Mean Blood Phe Levels for Patients Receiving 5, 10, or 20 mg/kg/Day During Part II

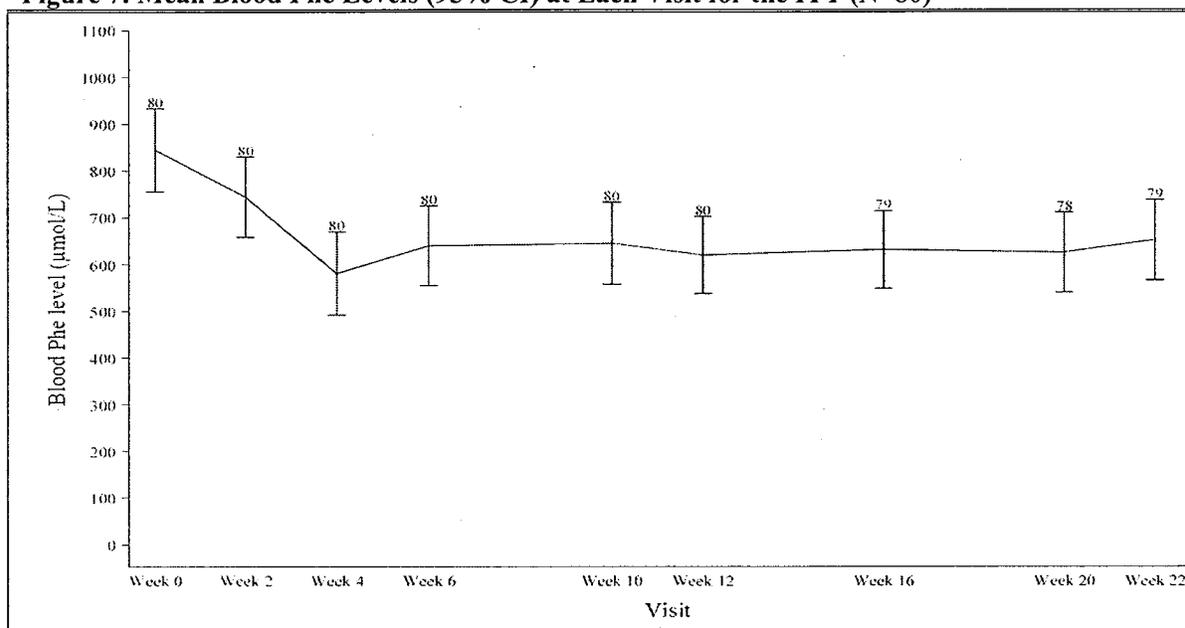


The vertical brackets indicate 95% CI of blood Phe for each dose group at each visit week

- 5 mg/kg/day
- - - 10 mg/kg/day
- - - 20 mg/kg/day

As discussed in section 6.1.4.4.2.1 above, seven patients were receiving sapropterin 10 mg/kg/day at Week 0, which may have reduced mean blood Phe at Week 0. At Week 2, when all patients had been treated with sapropterin 5 mg/kg/day, mean blood Phe was similar in the two groups and remained similar through completion of the fixed dose period. Thereafter, blood Phe remained reduced through Week 20, and increased moderately at Week 22 associated with decreased compliance. These findings are displayed in Figure 7 (copied from page 66 of the study report located in section 5.2.5.2.3 of the electronic submission).

Figure 7: Mean Blood Phe Levels (95% CI) at Each Visit for the ITT (N=80)



The numbers above each 95% CI bar indicate the number of patients at each visit.

6.1.4.4.3 Conclusions

Part I: The efficacy endpoint of Part I was change in blood Phe at the end of each two-week dose period (5, then 20, then 10 mg/kg/day) compared to Week 0 (Baseline), and comparison of dose effect between 5, 10, and 20 mg/kg/day. Mean blood Phe at Week 0 was 844 (398), but was probably affected by seven patients (9%) who were on treatment (10 mg/kg/day) at Week 0.

- At the end of treatment with 5 mg/kg/day, mean change in blood Phe was -100 uM (SD 295).
- At the end of treatment with 10 mg/kg/day, mean change in blood Phe was -204 uM (SD 303).
- At the end of treatment with 20 mg/kg/day, mean change in blood Phe was -263 uM (SD 318).

In patients with BH4-responsive PKU, mean blood Phe level decreased as the dose of sapropterin increased when diet is not controlled.

A comparison of dose effect in Part I showed:

- 10 mg/kg/day resulted in a 104 uM (SE 19) greater decrease in mean blood Phe than treatment with 5 mg/kg/day; 95% CI (65, 142).
- 20 mg/kg/day resulted in a 163 uM (SE 24) greater decrease in mean blood Phe than treatment with 5 mg/kg/day; 95% CI (65, 142).
- 20 mg/kg/day resulted in a 59 uM (SE 23) greater decrease in mean blood Phe than treatment with 10 mg/kg/day; 95% CI (65, 142).

In patients with BH4-responsive PKU, 20 mg/kg/day had a greater effect than 5 or 10 mg/kg/day, and 10 mg/kg/day has a greater effect than 5 mg/kg/day.

In Part II, the reduction in mean blood Phe for the ITT established in Part I was maintained with individualized dosing.

- At Week 12 mean change in blood Phe from Week 0 was -224 uM (SD 326).
- At Week 16 mean change in blood Phe from Week 0 was -206 uM (SD 380).
- At Week 20 mean change in blood Phe from Week 0 was -220 uM (SD 352).
- At Week 22 mean change in blood Phe from Week 0 was -190 uM (SD 356).

Reduction in blood Phe was maintained for 22 weeks.

6.1.5 Clinical Microbiology

Sapropterin is not intended for use as an anti-microbial, anti-fungal, or anti-viral product and clinical microbiology studies were not part of the development plan.

6.1.6 Efficacy Conclusions

The BH4-responsive PKU development plan included four safety and efficacy studies. The Enrichment Study (PKU-001) and Part I of the Diet Study (PKU-006) were each one-week, open-label, uncontrolled studies used to screen patients for potential BH4-responsiveness. The Efficacy Study (PKU-003) and Part II of the Diet Study were randomized, double-blind (DB), placebo-controlled, safety and efficacy studies of six and ten weeks, respectively. The Extension Study was a 22-week, open-label, uncontrolled, safety and efficacy study; Part I compared change in blood Phe at three different doses, and Part II assessed durability of change in blood Phe.

Enrollment in the Efficacy and Extension Studies was limited to patients who showed a $\geq 30\%$ reduction in blood Phe during the Enrichment Study. These studies, therefore, represent a continuum of investigation of one group of patients. Diet was not controlled in these studies.

The Enrichment Study (PKU-001) was an open-label, uncontrolled study of 489 patients with PKU ages 8 to 48 years, all of whom received sapropterin 10 mg/kg/day for eight days. For the primary analysis, 20% of patients [95% CI (16, 23)] were Responders; defined as a $\geq 30\%$ decrease in blood Phe from Day 1 (pre-treatment) to Day 8. This Reviewer concludes the Efficacy study identified a subset of potentially BH4-responsive PKU patients for further study under placebo controlled conditions. These results support the efficacy of sapropterin in reducing blood Phe in a subset of patients with PKU, as demonstrated in the Efficacy Study.

The Efficacy Study (PKU-003) was a randomized, double-blind, placebo-controlled, study of 88 patients who demonstrated a $\geq 30\%$ decrease in blood Phe from Day 1 to Day 8 in the Enrichment study. Patients were randomized 1:1 to receive 10 mg/kg/day or placebo. The primary endpoint was mean change in blood Phe from Baseline at Week 6. The secondary efficacy endpoint was mean change in blood Phe from Baseline at Weeks 1, 2, and 4. An additional exploratory analysis of the proportion of patients with blood Phe < 600 uM at Week 6 compared to Screening was performed.

- For the primary efficacy endpoint, sapropterin-treated patients had a greater mean change in blood Phe than placebo treated patients. The difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) for the ITT was -245 uM with a standard error of 53 uM, 95% CI [-350, -140]; $p < 0.001$.
- For the secondary efficacy endpoint of changes in blood Phe from Baseline at Weeks 1, 2, and 4, sapropterin-treated patients had a greater mean change in blood Phe than placebo-treated patients at all weeks. In sapropterin-treated patients, mean change in blood Phe at Weeks 1, 2, and 4 varied from -203 to -255 uM, and mean percent change varied from -24% to -32%. In placebo-treated patients, mean change in blood Phe at Weeks 1, 2, and 4 varied from -26 to 25 uM, and mean percent change varied from -1% to 5%.
- The analysis of the proportion of patients with blood Phe < 600 uM at Week 6 compared to Screening showed that the proportion of patients with blood Phe < 600 uM at Screening was approximately equal (17% sapropterin vs. 19% placebo, respectively); whereas, at Week 6, more sapropterin- than placebo-treated patients had blood Phe < 600 uM (54% vs. 23%, respectively).

This Reviewer concludes the result of the primary endpoint analysis demonstrates that sapropterin produces a clinically meaningful and statistically significant reduction in blood Phe in patients with BH4-responsive PKU. This Reviewer concludes the results of the secondary endpoint analyses support these findings. The additional exploratory analysis suggests that in patients with BH4-responsive PKU, sapropterin is more likely than placebo to reduce blood Phe to < 600 uM.

Part I of the Diet Study was an open-label, uncontrolled study of sapropterin (20 mg/kg/day) in 89 patients with PKU, ages 4 to 12 years. The efficacy endpoint of Part I was a $\geq 30\%$ decrease in blood Phe from Baseline to Day 8 and blood Phe < 300 uM at Day 8. Fifty of 89 patients (56%)

had a $\geq 30\%$ decrease in blood Phe from Baseline to Day 8 and had Day 8 blood Phe < 300 uM, which qualified them for randomization in Part II.

Part II of the Diet Study was a randomized, double-blind, placebo-controlled study in 45 Responders identified in Part I. Patients were randomized 3:1 to receive either sapropterin or placebo for ten weeks. After Week 3 laboratory assessments, supplemental dietary Phe could be added as specified in the protocol.

- The primary efficacy endpoint of Part II was Phe supplement tolerated at Week 10. Phe supplement tolerated by sapropterin-treated patients was 21 mg/kg/day (SD 15); $p < 0.001$. Phe supplement tolerated by placebo-treated patients was 3 mg/kg/day (SD 4); $p = 0.03$. Sapropterin-treated patients tolerated a statistically greater amount of Phe supplement than placebo-treated patients at Week 10.
- The secondary efficacy endpoint of Part II of the Diet Study was change in blood Phe of sapropterin-treated patients from Week 0 to Week 3 (prior to dietary Phe supplementation). In sapropterin-treated patients mean change in blood Phe from Week 0 to Week 3 was -149 uM (SD 134), mean percent change was -32% (SD 111), and median percent change was -55%. By comparison, in placebo-treated patients, mean change in blood Phe from Week 0 to Week 3 was -97 uM (SD 244), mean percent change in blood Phe was 31% (SD 149), and median percent change was -17%. These results show that under diet-controlled conditions, sapropterin is more likely to reduce blood Phe than placebo. These results support the primary and secondary efficacy findings in the Efficacy Study (PKU-003).

As discussed in section 6.1.2 above, the primary efficacy variable, dietary supplement tolerated at Week 10, was not suitable to establish efficacy. The Division is not willing to allow this endpoint ~~_____~~ due to the following:

- Increased dietary Phe is not an established clinical endpoint.
- Current treatment with dietary Phe reduction is intended to prevent neurological sequelae.
- Long-term neurocognitive endpoints were not evaluated in this study.

~~_____~~

The Extension Study (PKU-004) was a two-part, open-label study of 80 patients who received $\geq 80\%$ of doses (sapropterin or placebo) in the Efficacy Study.

Part I: The efficacy endpoints of Part I were change in blood Phe at the end of each two-week dose period (5, then 20, then 10 mg/kg/day) compared to Week 0 (Baseline), and comparison of dose effect between 5, 10, and 20 mg/kg/day. Mean blood Phe at Week 0 was 844 (398), but was probably affected by seven patients (9%) who were on treatment (10 mg/kg/day) at Week 0.

- For the efficacy endpoint of change in blood Phe from Baseline at 5, 20, and 10 mg/kg/day, results showed the following: At Week 2 (5 mg/kg/day), mean change in blood Phe was -100 uM (SD 295). At Week 4 (20 mg/kg/day), mean change in blood Phe was -263 uM (SD 318). At Week 6 (10 mg/kg/day), mean change in blood Phe was -204 uM (SD 303).
- For the efficacy endpoint of comparison of dose effect of 5, 10, and 20 mg/kg/day, the results showed the following: 10 mg/kg/day resulted in a 104 uM (SE 19) greater decrease in mean blood Phe than 5 mg/kg/day dose; 95% CI (65, 142); 20 mg/kg/day resulted in a 163 uM (SE 24) greater decrease in mean blood Phe than 5 mg/kg/day; 95% CI (65, 142); and 20 mg/kg/day dose resulted in a 59 uM (SE 23) greater decrease in mean blood Phe than 10 mg/kg/day; 95% CI (65, 142).
- Results from Part II showed that the following: At Week 12 mean change in blood Phe from Week 0 was -224 uM (SD 326). At Week 16 mean change in blood Phe from Week 0 was -206 uM (SD 380). At Week 20 mean change in blood Phe from Week 0 was -220 uM (SD 352). At Week 22 mean change in blood Phe from Week 0 was -190 uM (SD 356). In Part II, the reduction in mean blood Phe for the ITT established in Part I was maintained.

This Reviewer concludes that in patients with BH4-responsive PKU, the efficacy data of this open-label, uncontrolled study shows that sapropterin 20 mg/kg/day reduces blood Phe more than 10 mg/kg/day and 5 mg/kg/day doses, sapropterin 10 mg/kg/day reduces blood Phe more than 5 mg/kg/day doses, and reduction in blood Phe appears to be durable to 22 weeks of treatment.

Overall Conclusion

This Reviewer concludes the results of the Enrichment, Efficacy, Extension, and Diet Studies supports the following indication:

Kuvan is a phenylalanine hydroxylase-directed cofactor, indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4) responsive Phenylketonuria (PKU). Kuvan is to be used in conjunction with a Phe restricted diet.

The following are not suitable indications at this time:

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This original NDA includes clinical safety data from four completed clinical studies in patients with PKU, and two completed studies in healthy volunteers. Additionally, the 120-day safety update included interim safety data from one study in patients with chronic hypertension, another study in patients with primary BH4 deficiency, and the Expanded Access Program (EAP; SEAP-001) in patients with BH4-responsive PKU.

Four clinical studies were completed in patients with PKU; the Enrichment Study (PKU-001), the Efficacy Study (PKU-003), the Extension Study (PKU-004), and the Diet Study (PKU-006). The safety analysis of sapropterin in patients with PKU focuses on exposures in these four studies, and the ongoing EAP. In these studies, 579 patients received at least one dose of sapropterin in uncontrolled studies; 74 of 579 patients also received at least one dose of sapropterin in placebo-controlled studies, and 59 of 579 patients also received placebo in placebo-controlled studies. The Efficacy Study and Part II of the Diet Study were both randomized, double-blind, and placebo-controlled and safety data were pooled. The Enrichment Study, Part I of the Diet Study, the Extension Study, and the EAP were open-label, uncontrolled, and varied in length from one week to approximately six months; therefore these data were not amenable to pooling. Descriptions of the Enrichment Study (PKU-001), the Efficacy Study (PKU-003), the Extension Study (PKU-004), and the Diet Study (PKU-006) are found in section 6.1.3 of this review.

In studies of the Sponsor's product, safety was assessed by types and incidence of Adverse Events (AEs), discontinuations due to AEs; drug-related, serious and severe AEs; and changes from Baseline in physical examinations (exams), vital signs, and clinical laboratory assessments, including clinical chemistry, hematology, and urinalyses. Safety information was collected from Screening through completion of all study procedures at final follow-up for each study, which was four weeks after the last dose of drug or placebo in all studies. Deaths and Serious AEs were reported from signing of informed consent through the final follow-up. Non-serious AEs were reported from the time of first dose through completion of follow-up. Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT).

Table 21 summarizes studies with the Sponsor's product. The table indicates which studies are reviewed and which studies are briefly summarized in this review.

Table 21: Studies with Kuvan

Study	Full Review or Summary	Comment
Phenylketonuria		
Enrichment Study (PKU-001)	Full	One-week, open-label (OL) study in patients with PKU, 8 to 49 years old; sapropterin 10 mg/kg/day; N=489
Efficacy Study (PKU-003)	Full	Six-week, 1:1 randomized (R), DB, PC study in patients with PKU, 8 to 49 years old; Sapropterin 10 mg/kg/day, N=41; Placebo, N=47
Extension Study (PKU-004)	Full	OL extension study of patients 80 patients who participated in PKU-003; Part I: 5, 10, and 20 mg/kg/day x two weeks at each dose; then 10 mg/kg/day for four more weeks Part II: 12 weeks of 5 (N=6), or 10 (N=37) or 20 (N=37) mg/kg/day
Diet Study (PKU-006)	Full	Part I: One-week, OL, study of patients with PKU, 4 to 12 years old: sapropterin 20 mg/kg/day; N=90 Part II: 10-week R, DB, PC; Sapropterin 20 mg/kg/day, N=33; Placebo, N=12. After Week 3, possible dietary Phe supplemented added per protocol
EAP (SEAP-001)	Summary	OL; expanded access with 5, 10, or 20 mg/kg/day until market approval; N=108
Healthy Volunteers		
PKU-005	Summary	OL, bioavailability (BA) study in healthy volunteers, 19 to 50 years old; sapropterin 10 mg/kg/day once per week x four weeks; N=28
PKU-009	Summary	OL, BA-study in healthy volunteers, 19 to 50 years old; sapropterin 10 mg/kg/day once per week x three weeks; N=44
Other		
BH4 Deficiency (PKU-007)	Summary	OL, uncontrolled study in 12 patients with primary BH4 deficiency; not completed at 120-day safety update. Part I observation; Part II 5 mg/kg/day x six weeks then two weeks of individualized dose; Part III 20 mg/kg/day x seven weeks.
Hypertension Study (HTN-001)	Summary	Eight-week, R, DB, PC study of 116 patients, 31 to 81 years old, with hypertension. Sapropterin 10 mg/kg/day, N=77; Placebo N=39.

The above studies represent the entire safety experience of Kuvan.

The Sponsor also submitted primary data from three Phase 1 studies of a different formulation of the same active ingredient, sapropterin dihydrochloride, in healthy subjects [Daiichi Suntory Pharma; Biopten Granules] and summary data from 11 clinical studies and a single post-marketing safety report for Biopten in the treatment of diseases other than PKU. Clinical studies with Biopten are summarized in Table 22.

Table 22: Studies with Biopten

Study	Full Review or Summary	Comment
Controlled		
FB1602 Healthy Volunteers	Summary	One-week single-blind (SB), pharmacokinetic (PK) study; Sapropterin 200 mg PO TID (10.1 - 11.2 mg/kg/day) or placebo x 7 days; Biopten, N=6; Placebo, N=2
D261 Autism	Summary	DB, PC 12-week study; 1 to 5 mg/kg/day PO x 5 to; Biopten, N=42; Placebo, N=42
ZD2201 Autism	Summary	R, DB, PC 12-week study in patients with autism; 0 to 3 mg/kg/day PO x 12 weeks; Biopten, N=149; Placebo, N=73
FB3701 Machado-Joseph Disease (MJD)	Summary	R, DB, PC, eight-week study, 200 mg PO TID; Biopten, N=84; Placebo, N=89
Uncontrolled		
FB1701 Healthy Volunteers	Summary	One-week OL treatment; 200 mg TID; N=6 (9.0 - 10.6 mg/kg/day)
P1501 Healthy Volunteers	Summary	One-week OL, PK study; 100 or 200 mg PO/week (1.4 - 3.3 mg/kg) x two weeks; N=6 vs. 100 mg PO TID (4.2 - 4.9 mg/kg/d) x seven days; N=6
D271 and D271b Autism	Summary	OL, 1-3 mg/kg/day; 12 to 24 weeks; N=99
D381 Autism	Summary	OL, 1-3 mg/kg/day x 12 to 24 weeks; N=138
D383 Autism	Summary	OL, 1-3 mg/kg/day x 3 months; N=7
D384 Autism	Summary	OL, 2.1-3.3 mg/kg/day x 12 to 20 weeks; N=9
D272 BH4 Deficiency	Summary	OL, 1.5 to 10 mg/kg/day x 10 to 12 months; 3 months to 29 years old; N=16
Post market report BH4 Deficiency	Summary	5 to 20 mg/kg/day x 10 years
FB2501 MJD	Summary	OL, 1.0 to 5.0 mg/kg/day x four weeks; N=7
FB2601 MJD	Summary	OL, 100 or 200 mg PO TID x four weeks; N=16
FB2602 MJD	Summary	OL, 100 to 200 mg PO TID x 24 to 48 weeks; N=13

The above studies represent the entire safety experience of Biopten.

In this review, sapropterin refers to the Sponsor's product (i.e., Kuvan) and Biopten refers to the Daiichi Suntary product. Safety data from Biopten studies are summarized in section 7.2.2 (Secondary Clinical Data Sources) of this review.

This Reviewer concludes sufficient data were submitted to allow substantive review of safety of sapropterin in the treatment of patients with hyper-Phe due to BH4 responsive PKU.

7.1.1 Deaths

No deaths were reported in the PKU clinical studies, the EAP, the Hypertension Study, or the Biopten clinical studies or post-market report. This represents the entire known exposure to sapropterin.

7.1.2 Other Serious Adverse Events

In the PKU studies, eight patients experienced one SAE each. SAEs occurred in seven of 579 (1%) patients exposed to sapropterin and one of 59 patients (2%) during placebo treatment. SAEs were reported in 3 of 116 patients (3%) in the Hypertension Study (HTN-001), and 2 of 108 of patients (2%) in the EAP. There were no SAEs in the Efficacy Study, or interim study report of patients with Primary BH4 deficiency.

All SAEs occurring in studies of sapropterin or Biopten are summarized in Table 3. Discussion of the SAEs follows the table.

Table 23: SAEs in PKU Studies, the EAP and HTN-001

Study	Patient	Age (y), Gender (M/F)	SAE	Treatment	During/After Treatment
Enrichment¹	0132-0007	14 y, F	Acute appendicitis	10 mg/kg/day	After
Extension¹	0115-0016	12 y, F	Urinary Tract Infection	5 mg/kg/day	During
	0119-0003	13 y, M	Fractured Tibia	20 mg/kg/day	After
	0118-0015	14 y, M	Spinal Cord Injury	5 mg/kg/day	During
Diet^{1,2}	0110-6103	4 y, M	Streptococcal pharyngitis	20 mg/kg/day	During
	0114-6044	7 y, M	Acute appendicitis	Placebo	After
EAP¹	0102-0011	50 y, M	Testicular carcinoma	20 mg/kg/day	During
	0131-0013	15 y, F	Gastritis	5 mg/kg	During
Hypertension Study¹	0217-011	67 y, M	Gastro-intestinal bleeding, myocardial infarction, respiratory failure	10 mg/kg/day	During
	0235-001	64 y, M	Post-procedural bleeding following prostate biopsy	10 mg/kg/day	During
	0207-020	81 y, M	Transient ischemic attack	Placebo	During

¹ Open Label

² Randomized, double-blind, placebo controlled

One SAE was reported in the Enrichment Study (PKU-001).

- Patient 0132-0007, 14 year old female, developed acute appendicitis 15 days after administration of the final dose of sapropterin (10 mg/kg/day). The CRF was reviewed. This Reviewer concludes this SAE was not related to administration of sapropterin.

One SAE was reported in each of three patients in the Extension Study (PKU-004).

Clinical Review

Ethan D. Hausman, MD

NDA 22-181

Kuvan™ (sapropterin, 6R-BH4)

- Patient 0115-0016, 12 year old female had a urinary tract infection (UTI) during Week 18 while receiving 5 mg/kg/day of sapropterin. She was treated with intravenous Cefuroxime for one day and oral Cefalexin for one week and the UTI resolved. The CRF was reviewed. The patient continued to receive sapropterin. This Reviewer concludes this SAE was not related to administration of sapropterin.
- Patient 0119-0003, a 13 year old male, suffered a fractured tibia at Week 23, one week after the final 20 mg/kg/day dose. The CRF was reviewed. The patient continued to receive sapropterin. This Reviewer concludes this SAE was not related to administration of sapropterin.
- Patient 0118-0015, a 14 year old male, suffered a spinal cord injury at Week 15 while on fixed 5 mg/kg/day dosing. The CRF was reviewed. The mechanism of the injury (other than trauma) was not stated. The patient continued to receive sapropterin. This Reviewer concludes this SAE was not related to administration of sapropterin.

One SAE was reported in each of two patients in the Diet Study (PKU-006).

- Patient 0110-6103, a four year old female treated with sapropterin in Parts I and II of the study developed streptococcal pharyngitis, which required hospitalization and antibiotic treatment. The CRF was reviewed. This Reviewer concludes this SAE was not related to administration of sapropterin.
- Patient 0114-6044, a seven year old female treated with sapropterin in Part I and placebo in Part II of the study had appendicitis during the follow up period. The CRF was reviewed. This Reviewer concludes this SAE was not related to administration of sapropterin.

SAEs in the EAP

- Patient 0102-0011, a 50 year old man, developed a testicular neoplasm during participation in the EAP. He received sapropterin during the Enrichment Study, placebo during the Efficacy Study, and he received doses of 5, 10, and 20 mg/kg/day during the Extension Study. On completion of the Extension Study, he continued treatment with 20 mg/kg/day in the EAP for approximately 14 months until the time of the event. Past medical history was non-contributory.

Three years prior to the event the patient discovered a lump in his testicle and he was treated for epididymitis-orchitis. He received treatment (not-specified), and pain and other complaints resolved. A painless mass remained in his scrotum. The mass increased in size and became harder in texture (elapsed time not reported) and an ultrasound performed during the EAP showed an irregular testicular mass. At that time he also had an elevated β -hCG. On _____ he underwent a left radical orchiectomy, and histopathology revealed a mixed germ cell tumor; 50% teratoma, 50% seminoma. Operative staging was T1, and no evidence of metastasis was reported on lymph node

dissection. No further details are available. The CRF was reviewed. This Reviewer concludes this SAE was not related to administration of sapropterin.

- Patient 0131-0013, a 15 year old female, developed gastritis or gastric reflux during the EAP. She received sapropterin during the Enrichment Study, placebo during the Efficacy Study, and she completed the Extension study at doses of 5, 10, and 20 mg/kg/day. Approximately six months after completion of the Extension Study, she enrolled in the EAP and received sapropterin 5 mg/kg/day for eight days until the time of the event. Concomitant medications included “high-dose” ibuprofen for menstrual pain.

On the second day of treatment in the EAP, she began self-treatment with ibuprofen 600 mg per day for menstrual pain. The next day she experienced epigastric pain, nausea and vomiting, which were treated with metoclopramide. Two days later she had a second event which was treated with ranitidine and aluminum hydroxide, and the dose of sapropterin was omitted. Two days later she experienced a third event. On the sixth day of symptoms she was admitted to the hospital with acute epigastric pain. An upper gastrointestinal endoscopy was performed. Results are not reported in the clinical synopsis; however, at follow-up approximately eight weeks after the event occurred, the event resolved and the clinician classified the event as gastro-esophageal reflux. This Reviewer concludes that a causal relationship of this AE with sapropterin is unlikely, and high dose ibuprofen was a contributing factor.

SAEs in the Hypertension Study

- Patient 0217-011, a 67-year-old male, receiving sapropterin experienced a duodenal ulcer, post-operative respiratory failure, pneumonia, and myocardial infarction. On treatment day 20 he had fever and was treated with Reglan, Bactrim DS, and Flagyl, and he discontinued sapropterin. Two days later he had a fever > 102 F, and he developed loose stools. Five days later he returned to the clinic complaining of nausea, dull back pain, abdominal bloating and a temperature of 102.0 °F. Gastrointestinal hemorrhage and duodenal ulcer were identified on endoscopy, and he underwent a laparotomy and duodenotomy with over-sewing of a bleeding duodenal ulcer. He was hypotensive prior surgery, which was presumed to be secondary to bleeding. He received fluid and blood resuscitation and was returned to the intensive care while still intubated. Postoperative respiratory failure was diagnosed and reported as an SAE. The patient remained intubated, ventilated, and “in acute respiratory failure” for an undetermined period of time. Mechanical ventilation was discontinued (date not reported), but the patient continued to have difficulty breathing and developed pneumonia, which was treated with antibiotics.

The investigator concluded the relationship of the gastrointestinal hemorrhage SAE was “possibly related” to sapropterin “due to acidity of the product”, and the myocardial infarct and pneumonia SAEs were not related. This Reviewer agrees.

- Patient 0235-001, a 64-year-old male, experienced “uncontrolled bleeding” following a prostate biopsy at day 55 of sapropterin treatment. Sapropterin had been stopped two

days prior to surgery. The patient was admitted to the hospital and catheterization, clot irrigation, and continuous bladder irrigation were performed. There were no transfusions. Concomitant medications prior to the event were aspirin and clopidogrel bisulfate. Treatment with Ciprofloxacin was given. The SAE resolved within two days of onset. The investigator classified the event as not related to study drug. This patient also had gout and subconjunctival hemorrhage, both classified as non-serious. Platelet counts, ALT, and AST were normal from Screening through the end of the reporting period. The investigator classified the event as not related to study drug. This Reviewer concludes the bleeding event was probably unrelated to sapropterin treatment.

- One patient receiving placebo, patient 0207-020, experienced a transient ischemic attack on study day 39. The CRF indicates the patient never received sapropterin. This reviewer concludes the SAE was not related to sapropterin treatment.

This Reviewer concludes that the SAEs reported in the PKU development program and in the Hypertension Study were not related to sapropterin administration.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Discussion of withdrawals is limited to patients in the PKU development program. Seven patients withdrew. Reasons listed for withdrawal included non-compliance (N=4), and AEs (N=2), and pregnancy (N=1). More females withdrew than males. There was no other demographic pattern associated with withdrawal. Withdrawals reported in the PKU development program are summarized in Table 24 below.

Table 24: Withdrawals from PKU Studies and the EAP

Study	Patient	Age (yr) Gender (M/F)	Reason	Dose mg/kg/day	Relation to Treatment
Enrichment ¹	0118-0009	21 y, F	Pregnancy	10	During
	0119-0001	15 y, F	Non-Compliance	--	Unknown
Efficacy ²	0067-0004	27 y, F	Non-compliance	Not applicable	Before first dose; exposure 10 mg/kg/day in the Enrichment Study
	0021-0008	18 y, F	Dysmenorrhea	Placebo	During; exposure 10 mg/kg/day in the Enrichment Study
Extension ¹	0113-0001	18 y, M	Non-compliance	10	During
Diet ^{1,2}	0109-6008	5 y, F	Non-compliance	10	During
EAP ¹	0102-0011	50 y, M	Testicular Neoplasm	20	During

¹ Open Label

² Randomized, double-blind, placebo controlled

A second pregnancy, not leading to withdrawal, was reported and is discussed in section 7.1.3.3. These are the only two pregnancies reported in patients treated with Kuvan. This Reviewer concludes the withdrawals described above are not related to administration of sapropterin. One of two SAEs in the EAP, testicular carcinoma, led to patient withdrawal but symptoms pre-dated sapropterin exposure.

7.1.3.2 Adverse events associated with dropouts

Enrichment Study

- Patient 0118-0009, a 21 year old woman, withdrew from the Enrichment Study due to pregnancy after receiving one dose of sapropterin. The CRF states the pregnancy occurred during use of birth control and the pregnancy was electively terminated for reasons unrelated to the study (not otherwise specified). This Reviewer concludes the relationship of the pregnancy termination and withdrawal to receipt of sapropterin is not known and can not be determined.

Efficacy Study

- Patient 0021-0008, an 18 year old female randomized to receive placebo, withdrew after Week 4 due to dysmenorrhea. The patient was treated with sapropterin in the Enrichment Study. No AEs or notable clinical laboratory findings were reported during prior treatment in the Enrichment Study. The CRF was reviewed and this Reviewer concludes this withdrawal is not related to sapropterin treatment.

EAP

- Patient 0102-0011, a 50 year old man receiving sapropterin during the EAP withdrew due to testicular carcinoma. This patient is discussed in section 7.1.2, and 7.1.3.2 above. Symptoms pre-dated sapropterin exposure and the withdrawal is not related to sapropterin treatment.

No other withdrawals were reported in studies of PKU patients. This Reviewer concludes these withdrawals were not apparently related to administration of sapropterin.

7.1.3.3 Other significant adverse events

Other significant adverse events include one pregnancy and one case of erythema multiforme reported during the Enrichment Study, and neutropenia occurring in multiple patients in multiple studies.

- Patient 0115-0006, a 31 year old woman, developed moderately severe erythema multiforme approximately three weeks after receiving her eighth and final dose of sapropterin 10 mg/kg/day during the Enrichment study. The event was contemporaneous with a urinary tract infection and administration of trimethoprim-sulfamethoxazole. The

erythema multiforme remitted within five days. The incidence of erythema multiforme may be 0.01 to 1% of the population (lifetime risk), and exposure to trimethoprim is associated with erythema multiforme in approximately 1 in 35,000 exposures. The Reviewer feels that the relationship of erythema multiforme in this patient is more likely to be related to trimethoprim than sapropterin exposure, and more definitive statements about causation or association can not be made.

- Patient 0121-0021, a 24 year old woman in the Enrichment study became pregnant during the study. She had been amenorrheic for one year prior to enrollment. All doses of sapropterin were administered and the pregnancy was reported at the 36 day follow up. The original pregnancy screen result was judged false negative. The pregnancy continued. No further details are available.

Absolute neutropenia ($ANC \leq 1,500 \times 10^9/mL$) was documented in 18 patients; 17 with PKU (N=579), and one with primary BH4 deficiency (N=12). One patient had moderate neutropenia and one patient had mild neutropenia prior to first sapropterin exposure. In three patients, neutropenia occurred or re-occurred while patients received placebo, and in seven patients neutropenia occurred or reoccurred while patients were receiving sapropterin under double-blind conditions. In four patients who experienced neutropenia while receiving sapropterin, neutropenia resolved by the conclusion of the safety monitoring period. Neutropenia was also reported in one of ten patients in the primary BH4 deficiency study (PKU-007). The combination of open-label and blinded studies precludes attribution of causation; however, the risk neutropenia is to be addressed prominently in labeling.

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