

Absolute neutrophil counts for these 18 patients are presented in Table 25; drug indicates sapropterin.

Table 25: All Instances of Absolute Neutropenia (ANC < 1,500) in the PKU and Primary BH4 Populations

Patient	Age (y) Gender (M,F)	Baseline	Nadir on Drug	Peak on Drug	Final ANC	Resolved on drug (Y/N)	Occurrence, OL or DB	Double Blind Treatment
Enrichment, Efficacy, Extension Studies								
0121-0011	18, M	960 ¹	500 ¹	1,460 ³	950 ³	N	OL, DB	Drug
0123-0016	41, M	3,970 ¹	570 ¹	5,020 ²	4,380 ²	Y	OL	Drug
0124-0007	41, F	2,890 ¹	970 ¹	—	970 ¹	N	OL	—
0113-0024	10, F	2,390 ¹	1,010 ³	4,170 ³	1,250 ³	N	DB	Drug
0124-0006	20, F	1,470 ¹	1,200 ¹	—	1,200 ¹	N	OL	—
0113-0006	26, M	1,810 ¹	1,350 ¹	—	1,350 ¹	N	OL	—
0124-0001	11, M	5,130 ¹	1,420 ¹	—	1,420 ¹	N	OL	—
0018-0003	9, M	3,690 ¹	1,430 ¹	—	1,430 ¹	N	OL	—
0115-0016	12, F	1,770 ¹	1,480 ³	3,250 ³	3,250 ³	Y	DB	Drug
0109-0024	12, F	2,020 ¹	1,160 ²	2,190 ²	2,500 ³	Y	DB	Placebo
Diet Study								
0184-6045	9, M	3,650	660	660	990	N	OL, DB	Placebo
0135-6071	9, F	1,850	960	2350	960	N	DB	Drug
0015-6054	6, M	1,530	1,190	1,190	1,190	N	OL	—
0109-6013	4, F	1,840	1,450	2,720	1,450	N	DB	Drug
0110-6103	4, F	1,770	1,300	4,660	2,790	Y	DB	Drug
0124-6043	8, M	*	1,090	3,840	3,840	Y	OL, DB	Drug
0109-6084	9, F	3,050	1,480	1,480	1,970	N	OL, DB	Placebo
Primary BH4								
0002-7002	10, F	5,200	200	3,430	2,820	Y	OL	—

¹Enrichment Study; open-label (OL), uncontrolled

²Efficacy Study; randomized, double-blind (DB), placebo-controlled (PC)

³Extension Study; OL, uncontrolled

⁴Diet Study; Part I OL, uncontrolled; Part II randomized, DB, PC

⁵BH4 Study; OL, uncontrolled

* ANC not recorded

— Did not participate in double-blind treatment

Neutropenia is not a recognized characteristic of PKU. Neutropenia is not described in the primary BH4 literature, but the literature base for this condition is small. The mixture of study designs and the small size of the study population prohibits determination of causation. Because neutropenia occurred in approximately 3% (17 of 579) of patients with PKU and 10% (1 of 12) of patients with primary BH4 deficiency, neutropenia should be addressed in labeling.

7.1.4 Other Search Strategies

No other search strategies were used.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse event (AE) collection methods included onsite interviews, review of patient or caregiver diaries, physical examination of the patient, radiological and other procedural test information, and review of clinical laboratory data. AEs were monitored and recorded by investigators or their designees from the time of study entry (signing of the Informed Consent) and at each study visit through the completion of the studies. Clinically significant worsening from Screening in physical examinations, vital signs, and laboratory evaluations were documented as AEs.

Electrocardiograms (ECGs) were performed in two Phase 1 studies with the Sponsor's product. Neither a thorough QT (TQT) study nor a thorough QT assessment (TQA) was performed. Clinical studies that incorporated ECG monitoring are limited to five studies in healthy volunteers: three PK studies of the Biopren, and two studies with Kuvan (PKU-005 and PKU-009), where electrocardiograms (ECG) were collected at Baseline and between one and seven days after dosing. ECGs were not collected at Cmax.

In studies of the Sponsor's product, cardiac related AEs were restricted to the Hypertension Study (Study HTN-001; N=116), which is being investigated under [REDACTED]. In this study one sapropterin-treated patient had a peri-operative myocardial infarction classified as an SAE, which occurred in association with surgery for a gastro-duodenal ulcer. Non-serious cardiac-related AEs were reported in 4 of 77 (5%) of sapropterin-treated patients and 2 of 39 (5%) of placebo-treated patients. Non-serious AEs in sapropterin-treated patients were: ventricular extra-systole in two patients, cardiac murmur in one patient, and T-wave inversion on ECG in one patient. Non-serious AEs in placebo-treated patients were: abnormal ECG in one patient, and ventricular extra-systole in one patient. No cardiac related AEs were reported in healthy volunteers (N=74) or patients with PKU (N=579) treated with sapropterin. In Biopren studies, no cardiac related AEs were reported in healthy volunteers (N=26), or patients with autism (N=451), or Machado-Joseph Disease (N=118).

A consultation by the Interdisciplinary Review Team for QT Studies dated 07-November-2007 (Christine Garnett, PharmD) recommends a TQT study be performed. The opinion of the clinical review team is that a TQT study may be performed as a post-marketing commitment, since cardiac related SAEs were limited to a single report of peri-operative myocardial ischemic event, and non-serious AEs were limited to ECG abnormalities reported in both sapropterin- (4 of 77) and placebo-treated (2 of 39) patients.

A summary of non-clinical/pre-clinical cardiac electrophysiology is located in section 7.1.9.1 of this review.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The Sponsor summarized all AEs using the Medical Dictionary for Regulatory Activities (MedDRA) System, Organ, Class (SOC) and Preferred Term (PT) coding terminology. The MedDRA system contains more than 15,000 AE preferred terms that may result in fragmentation or dilution of AE terms and loss of AE signals. To avoid potential loss of such AE signals, this Reviewer reviewed and compared preferred terms with verbatim investigator terms. This Reviewer re-grouped the following terms under the AE term "rash": rash, rash erythematous, rash macular, rash maculo-papular, and rash papular. This was the only instance where preferred terms were re-grouped.

7.1.5.3 Incidence of common adverse events

7.1.5.3.1 Common AEs in the Enrichment, Efficacy, Extension and Diet Studies

Incidence rates of common AEs reported in the Enrichment, Efficacy, Extension, and Diet Study were determined by this Reviewer from the individual AE datasets located in sections 5.3.5.1 and 5.3.5.2 of the electronic submission. The 120-day safety update, received in the electronic submission on 21-September-2007, contained interim safety data from an Expanded Access Program (EAP; SEAP-001), the Primary BH4 Study (PKU-007), and HTN-001.

The Efficacy Study and Part II of the Diet Study were both randomized, double-blind, placebo-controlled studies in patients with PKU. Safety AE information from these two studies was pooled by this Reviewer and is presented first. This is followed by presentation of AEs from the Enrichment Study, Part I of the Diet Study, and the Extension Study, which are all open-label and uncontrolled.

In the pooled, double-blind, placebo-controlled studies, AEs were more common in placebo-treated patients (70% of patients, N=59) than sapropterin treated patients (64%, N=74); though AEs were lowest in patients receiving sapropterin 10 mg/kg/day (51%, N=41), and highest in patients receiving 20 mg/kg/day (79%, N=33). The most common AEs in patients receiving sapropterin 10 mg/kg/day (N=41) were upper respiratory tract infections (17%), headache (10%), and pharyngo-laryngeal pain (7%). The most common AEs in patients receiving sapropterin 20 mg/kg/day (N=33) were headache and rhinorrhea (21% each), cough (15%), and pharyngo-laryngeal pain, vomiting and diarrhea (12%, each). The most common AEs in placebo-treated patients (N=57) were upper respiratory tract infection (24%), headache (14%), and vomiting, pyrexia and rash (7% each). The AEs reported in sapropterin- and placebo-treated patients were similar in type and severity, and reflect common complaints in the general population. Neurological complaints including headache, dizziness, lethargy, and migraine are as frequent in placebo-treated as sapropterin-treated patients. The small size, short duration, and 3:1 randomization of patients to sapropterin (N=33) and placebo (N=12) in the Part II of the Diet Study may have resulted in wide variation in percentages in that study. These results are summarized in Table 26 in section 7.1.5.4 of this review.

In the open-label, uncontrolled Enrichment Study (N=489), the most commonly reported AEs were headache (10%) diarrhea (5%), abdominal pain (5%), and nausea and upper respiratory tract infections (3% each), which are not distinguishable from common complaints in the general population. However, the study was open-label and determination of causation can not be made. These results are summarized in Table 27 in section 7.1.5.4 of this review.

The laboratory dataset of the Enrichment Study showed increases in ALT, AST, or both in 10 patients, five of whom were also identified in the AE dataset. In eight of these ten patients, the elevated enzyme was present prior to first sapropterin dose. Increases in these liver enzymes may be reported in patients with long-standing, untreated PKU, but it is not commonly reported in patients on modified diets.

In the open-label, uncontrolled portion of the Diet Study (Part I, N=90), the most commonly reported AEs were abdominal pain (6%), headache (4%), and nausea, pharyngeal pain, skin laceration, and rash (2% each). The non-serious AEs represent common complaints in the general population, and otherwise healthy patients with PKU. However, the study was open-label and determination of causation can not be made. These results are summarized in Table 28 in section 7.1.5.4 of this review.

AEs from the Extension Study (N=80) are analyzed by AEs occurring from Week 0 through the Week 6 visit of Part I (fixed-dose), and AEs occurring after the Week 6 visit through completion of Part II (individualized dose). In Part I, from the Week 0 through Week 6 visit, all patients received two weeks of exposure at each of 5, 10, and 20 mg/kg/day dose period (e.g.: 160 patient weeks of exposure per dose). The incidence of non-serious AEs was approximately equal between each two-week dosing period (31% to 34%). The most commonly reported AEs were headache and nasopharyngitis (11%), vomiting (9%), and cough and pharyngeolaryngeal pain (8% each). These non-serious AEs are not readily distinguishable from common complaints in the general population, and a determination of causation is impaired by the open-label nature of the study. These results are summarized in Table 29 in section 7.1.5.4 of this review.

From Week 6 through Week 10 of Part I all patients were treated with sapropterin 10 mg/kg/day. Thereafter, in Part II, patients received individualized dosing at 5 mg/kg/day (N=6), 10 mg/kg/day (n=37), or 20 mg/kg/day (N=37) through the Week 22 visit. AEs were assigned as having occurred in association with the dose administered at the time of occurrence of the AE or the last dose administered for AEs occurring from Week 22 through Week 26. The most common AEs occurring from Week 6 to Week 26 were headache (19%), pharyngeal pain (9%), and diarrhea and vomiting (6% each). During the individualized dose period beginning at Week 10, AEs were more common in patients receiving 20 than 10 mg/kg/day (59 vs. 41%, respectively; N=37 each). The incidence of AEs in patients receiving 5 mg/kg/day was 33%, but too few patients were exposed (N=6) compared to other doses to draw meaningful conclusions. These non-serious AEs reported from Week 6 through Week 22 are not readily distinguishable from common complaints in the general population, and a determination of causation is impaired by the open-label nature of the study. These results are summarized in Table 30 in section 7.1.5.4 of this review.

This Reviewer concludes that AE data from the pooled double-blind, placebo-controlled studies suggest that sapropterin at 10 and 20 mg/kg/day dose is generally safe in patients with PKU, ages four years and older. The most common AEs in patients receiving sapropterin 10 mg/kg/day were upper respiratory tract infections (17%), headache (10%), and pharyngo-laryngeal pain (7%). The most common AEs in patients receiving sapropterin 20 mg/kg/day (N=33) were headache and rhinorrhea (21% each), and vomiting and diarrhea (12% each). The AEs reported in sapropterin- and placebo-treated patients were similar in type and severity, and reflect common complaints in the general population and in patients with PKU.

7.1.5.3.2 Summaries of and Common AEs in the EAP, and the Primary BH4 Deficiency and Chronic Hypertension Studies

At the time of submission of the 120-day safety update, the EAP enrolled 108 patients with PKU who had participated in the Efficacy, Extension, or Diet studies. Patients were treated with sapropterin 5, or 10, or 20 mg/kg/day, under open-label uncontrolled conditions. Mean (SD) duration of exposure was 23 (SD 9) weeks; range 8 to 40 weeks. In the EAP, 64% of patients received 20 mg/kg/day, 32% received 10 mg/kg/day, and 4% received 5 mg/kg/day. No deaths were reported in the EAP. SAEs were reported in two patients and are described in section 7.1.2 of this review.

The most common AEs reported in the EAP were upper respiratory tract infection and pyrexia each occurring in 9% of patients, cough (8%), influenza (6%), and vomiting, nasopharyngitis, and pharyngo-laryngeal pain (5%, each). The incidence and types of AEs reported in the EAP in the 120-day safety update were similar to AEs reported in the Enrichment, Efficacy, Diet, and Extension Studies. This Reviewer concludes that type and incidence of AEs in the EAP are substantially similar to AEs reported in the Enrichment, Efficacy, Extension, and Diet Studies, and reflect common complaints in the general population and in patients with PKU. These findings are summarized in Table 31 in section 7.1.5.4 of this review.

At the time of submission of the 120-day safety update, the primary BH4 deficiency Study (PBH4D Study) enrolled 12 patients. In Part I, patients were followed for two weeks without change in Baseline medications or diet plan. In Parts II and III patients were treated with sapropterin 5 mg/kg/day in two divided doses for four weeks, then started on individual doses at 5, 10, or 20 mg/kg/day for at least seven weeks. Five patients were on BH4 preparations at Baseline; the specific BH4 preparation was not specified (i.e., Kuvan, Biopten, other). Mean age was 13.5 (SD 9.6) years, and age range was 3 to 35 years. No deaths or SAEs were reported. The most commonly reported AEs were diarrhea in 4% of patients, vomiting in 3%, sinusitis in 2%, and nervous system disorders, including dyskinesia or dystonia, in 2% of patients. These neurologic problems were present at Baseline in these patients. One patient experienced severe neutropenia, which resolved while on treatment. With the exception of neurologic findings which were more common in patients with PBH4D, this Reviewer concludes that type and incidence of AEs in the EAP are substantially similar to AEs reported in the Enrichment, Efficacy, Extension, and Diet Studies, and reflect common complaints in the general population and in patients with PKU. These findings are summarized in Table 32 in section 7.1.5.4 of this review.

In the Hypertension Study 116 adult patients with chronic hypertension were randomized (2:1) to receive 8 weeks of treatment with either sapropterin at 5 mg/kg PO BID (10 mg/kg/day; N=77) or placebo (N=39). The type and incidence of non-serious AEs in the Hypertension Study were approximately the same in sapropterin- and placebo-treated patients (56% vs. 58% of 39%). The most common AEs reported in sapropterin-treated patients were headache and peripheral edema (8%, each), arthralgia (6%), and dizziness and upper respiratory tract infection (5%, each). The most common AEs reported in placebo-treated patients were headache (10%), peripheral edema, viral infection, and hypertension (5%, each). Non-serious AEs are summarized in Table 33.

7.1.5.3.3 Summaries of Exposure in Healthy Volunteers

Two pharmacokinetic studies of the Sponsor's product, Kuvan, were performed in healthy volunteers. In PKU-005, 28 healthy adult volunteers were treated with one 10 mg/kg dose once a week for a total of four doses. In PKU-009, 44 healthy adult volunteers were treated with one 10 mg/kg dose once a week for a total of three doses. Since the populations and exposures were similar, AE data were pooled. There were no deaths or SAEs in these two studies. Fourteen of 72 (20%) patients experienced between one and three non-serious AEs. The most common AEs were headache in 4% of patients, and fatigue and rhinitis (2% each). Other notable AEs include dysphoria in one patient, further details not available; and increased AST in two patients, summarized below.

This Reviewer concludes a comparison of incidence rates in healthy volunteers to patients with PKU is not possible due to differences in study design. However, the types of AEs reported in healthy volunteers are substantially similar to AEs reported in the Enrichment, Efficacy, Extension, and Diet Studies, and reflect common non-serious complaints in the general population.

7.1.5.4 Common adverse event tables

The incidence of the most common AEs ($\geq 2\%$ of patients) in the pooled Efficacy and Diet Studies are summarized in Table 26.

Table 26: Incidence of AEs in $\geq 2\%$ Patients in the Efficacy Study and Part II of the Diet Study.

		Total	Dose (mg/kg/day)			
			All Sapropterin	10	20	Placebo
		N=133	N=74	N=41	N=33	N=59
System, Organ, Class	Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	Lymphadenopathy	2 (2)	2 (3)	0	2 (6)	0
Ear and labyrinth disorders	Ear pain	3 (3)	1 (1)	0	1 (3)	2 (3)
Gastrointestinal disorders	Vomiting	10 (8)	6 (8)	2 (5)	4 (12)	4 (7)
	Abdominal pain	9 (7)	4 (5)	1 (2)	3 (9)	5 (8)
	Diarrhea	9 (7)	6 (8)	2 (5)	4 (12)	3 (5)

Table 26: Incidence of AEs in > 2% Patients in the Efficacy Study and Part II of the Diet Study.

		Total	Dose (mg/kg/day)			
			All Sapropterin	10	20	Placebo
System, Organ, Class	Preferred Term	n (%)	n (%)	n (%)	n (%)	n (%)
	Constipation	2 (2)	1 (1)	0	1 (3)	1 (2)
	Dyspepsia	2 (2)	0	0	0	2 (3)
	Toothache	2 (2)	2 (3)	0	2 (6)	0
General disorders and administration site conditions	Pyrexia	9 (7)	5 (7)	2	3 (9)	4 (7)
	Fatigue	5 (4)	2 (3)	1 (2)	1 (3)	3 (5)
	Influenza like illness	3 (3)	1 (1)	1 (2)	0	2 (3)
	Irritability	2 (2)	1 (1)	0	1 (3)	1 (2)
	Malaise	2 (2)	1 (1)	1 (2)	0	1 (2)
Infections and infestations	Upper respiratory tract infection	23 (17)	9 (12)	7 (17)	2 (6)	14 (24)
	Streptococcal infection	4 (3)	1 (1)	0	1 (3)	3 (5)
	Pharyngitis	3 (2)	2 (3)	2 (5)	0	1 (2)
	Rhinitis	3 (2)	1 (1)	1 (2)	0	2 (3)
	Infection	2 (2)	2 (3)	2 (5)	0	0
	Otitis externa	2 (2)	2 (3)	1 (2)	1 (3)	0
	Otitis media	2 (2)	1 (1)	0	1 (3)	1 (2)
	Urinary tract infection	2 (2)	2 (3)	1 (2)	1 (3)	0
Injury, poisoning and procedural complications	Contusion	5 (4)	4 (5)	1 (2)	3 (9)	1 (2)
	Excoriation	2 (2)	2 (3)	0	2 (6)	0
	Joint injury	2 (2)	1 (1)	0	1 (3)	1 (2)
Investigations	Neutrophil count decreased	2 (2)	1 (1)	0	1 (3)	1 (2)
	White blood cell count decreased	2 (2)	1 (1)	0	1 (3)	1 (2)
Metabolism and nutrition disorders	Decreased appetite	2 (2)	2 (3)	0	2 (6)	0
Musculoskeletal and connective tissue	Back pain	5 (4)	2 (3)	1 (2)	1 (3)	3 (5)
	Arthralgia	2 (2)	1 (1)	0	1 (3)	1 (2)
	Pain in extremity	2 (2)	0	0	0	2 (3)
Nervous system disorders	Headache	19 (14)	11 (15)	4 (10)	7 (21)	8 (14)
	Dizziness	2 (2)	0	0	0	2 (3)
	Lethargy	2 (2)	0	0	0	2 (3)
	Migraine	2 (2)	0	0	0	2 (3)
Renal and urinary disorders	Polyuria	2 (2)	0	0	0	2 (3)
Respiratory, thoracic and mediastinal disorders	Cough	8 (6)	5 (7)	0	5 (15)	3 (5)
	Pharyngolaryngeal pain	8 (6)	7 (9)	3 (7)	4 (12)	1 (2)
	Rhinorrhea	8 (6)	8 (11)	1 (2)	7 (21)	0
	Nasal congestion	3 (2)	3 (4)	0	3 (9)	0
Skin and subcutaneous tissue disorders	Rash NOS, maculopapular, erythematous	8 (6)	4 (5)	1 (2)	3 (9)	4 (7)
	Erythema	2 (2)	2 (3)	0	2 (6)	0
Any AE		88 (66)	47 (64)	21 (51)	26 (79)	41 (70)

The incidence of the most common AEs ($\geq 2\%$ of patients) reported in the Enrichment Study are summarized in Table 27.

Table 27: Non-Serious AEs in $\geq 2\%$ of Patients in the Enrichment Study

System, Organ, Class Term	Preferred Term	N=489 n (%)
Gastrointestinal disorders	Abdominal pain, upper, lower, not specified	28 (6)
	Diarrhea	24 (5)
	Nausea	16 (3)
	Flatulence	11 (2)
	Vomiting	9 (2)
General disorders and administration site conditions	Fatigue	14 (3)
Infections and infestations	Upper respiratory tract infection	17 (3)
Metabolism and nutrition disorders	Decreased appetite or Anorexia	12 (3)
Nervous system disorders	Headache	50 (10)
	Hyperreflexia	10 (2)
	Tremor	9 (2)
Skin and subcutaneous tissue disorders	Rash	8 (2)
Any AE		233 (48)

The incidence of the most common AEs ($\geq 2\%$ of patients) reported in Part I of the Diet Study are summarized in Table 28.

Table 28: Diet Study Part I; Non-Serious AEs in $\geq 2\%$ of Patients

		Sapropterin N=90
System, Organ, Class	Preferred Term	n (%)
Gastrointestinal disorders	Abdominal pain	5 (6)
	Nausea	2 (2)
Nervous system disorders	Headache	4 (4)
Injury, poisoning and procedural complications	Skin laceration	2 (2)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	2 (2)
	Rhinorrhea	2 (2)
Skin and subcutaneous tissue disorders	Rash	2 (2)
Any AE, Part I		28 (31)

The incidence of the most common AEs ($\geq 2\%$ of patients) reported in Weeks 0 through 6 of the Extension Study are summarized in Table 29.

Table 29: Non-Serious AEs in ≥ 2 Patients Week 0 through Week 6 of the Extension Study (N=80)

System, Organ, Class	Preferred Term	Total	Dose (mg/kg/day)		
		N=80	5	10	20
		n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	Lymphadenopathy	2 (3)	1 (1)	0	1 (1)
Gastrointestinal disorders	Vomiting	7 (9)	2 (3)	2 (3)	3 (4)
	Diarrhea	5 (6)	4 (5)	0	1 (1)
	Nausea	3 (4)	0	1 (1)	1 (1)
	Abdominal pain	2 (3)	2 (3)	0	1 (1)
General disorders and administration site conditions	Pyrexia	2 (3)	1 (1)	1 (1)	1 (1)
Infections and infestations	Nasopharyngitis	9 (11)	3 (4)	4 (5)	2 (3)
	Upper respiratory tract infection	5 (6)	1 (1)	0	4 (5)
	Influenza	2 (3)	1 (1)	0	1 (1)
	Pharyngitis	2 (3)	1 (1)	1 (1)	0
Investigations	Alanine aminotransferase increased	3 (4)	1 (1)	2 (3)	0
Nervous system disorders	Headache	9 (11)	4 (5)	1 (1)	4 (5)
	Migraine	4 (5)	1 (1)	0	3 (4)
Respiratory, thoracic and mediastinal disorders	Cough	6 (8)	2 (3)	2 (3)	2 (3)
	Pharyngolaryngeal pain	6 (8)	3 (4)	1 (1)	2 (3)
Any AE		54 (68)	27 (34)	25 (31)	26 (33)

The incidence of the most common AEs ($\geq 2\%$ of patients) reported from Week 6 through 22 of the Extension Study are summarized in Table 30. The Total column is AEs occurring in $\geq 2\%$ of patients who received at least one dose of sapropterin (5, 10, or 20 mg/kg/day).

Table 30: Non-Serious AEs Occurring in $\geq 2\%$ Patients, Week 6 to Week 22 of the Extension Study

Dose (mg/kg/day)		Total	Weeks 6 to 10	Weeks 10 to 22		
		Any N=80 n (%)	10 N=80 n (%)	5 N=6 n (%)	10 N=37 n (%)	20 N=37 n (%)
System, Organ, Class	Preferred Term					
Gastrointestinal disorders	Diarrhea	5 (6)	1 (1)	0	2 (5)	2 (5)
	Vomiting	5 (6)	0	1 (17)	2 (5)	2 (5)
	Abdominal pain upper	3 (4)	1 (1)	0	1 (3)	1 (3)
	Abdominal pain	2 (3)	1 (1)	0	0	1 (3)
General disorders and administration site conditions	Fatigue	2 (3)	1 (1)	0	0	1 (3)
Immune system disorders	Seasonal allergy	2 (3)	1 (1)	0	1 (3)	0
Infections and infestations	Nasopharyngitis	4 (5)	2 (3)	0	1 (3)	1 (3)
	Gastroenteritis	3 (4)	1 (1)	0	0	2 (5)
	Upper respiratory tract infection	3 (4)	3 (4)	0	0	0
	Influenza	2 (3)	0	0	2 (5)	0
	Otitis media	2 (3)	0	0	1 (3)	1 (3)
	Rhinitis	2 (3)	1 (1)	0	1 (3)	0
	Streptococcal infection	2 (3)	0	0	0	2 (5)
	Tonsillitis	2 (3)	0	0	0	2 (5)
Tooth abscess	2 (3)	0	0	0	2 (5)	
Injury, poisoning and procedural complications	Contusion	2 (3)	1 (1)	0	1 (3)	0
Investigations	Blood amino acid level increased	2 (3)	0	1 (17)	1 (3)	0
Musculoskeletal and connective tissue disorders	Back pain	3 (4)	2 (3)	0	0	1 (3)
Nervous system disorders	Headache	15 (19)	7 (9)	0	3 (8)	5 (14)
	Migraine	4 (5)	2 (3)	0	1 (3)	1 (3)
	Dizziness	3 (4)	0	0	0	3 (8)
Reproductive system and breast disorders	Dysmenorrhoea	2 (3)	0	0	0	2 (5)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	7 (9)	2 (3)	1 (17)	2 (5)	2 (5)
	Cough	2 (3)	1 (1)	0	0	1 (3)
Skin and subcutaneous tissue disorders	Eczema	2 (3)	0	0	1 (3)	1 (3)
Any AE		67 (84)	29 (36)	2 (33)	15 (41)	22 (59)

The incidence of the most common AEs ($\geq 2\%$ of patients) reported in the EAP are summarized in Table 31.

Table 31 AEs occurring in $\geq 2\%$ of Patients in the EAP; N=108

		N=108
System, Organ, Class	Preferred Term	n (%)
General disorders and administration site conditions	Pyrexia	10 (9)
Infections and infestations	Upper respiratory tract infection	10 (9)
	Influenza	7 (6)
	Nasopharyngitis	6 (6)
	Gastroenteritis viral	5 (5)
	Bronchitis	4 (4)
	Sinusitis	3 (3)
	Pharyngitis	2 (2)
	Urinary tract infection	2 (2)
Respiratory, thoracic and mediastinal disorders	Viral infection	2 (2)
	Cough	9 (8)
	Pharyngolaryngeal pain	6 (6)
	Nasal congestion	4 (4)
Gastrointestinal disorders	Rhinorrhea	3 (3)
	Vomiting	6 (6)
	Abdominal pain upper	2 (2)
	Nausea	2 (2)
	Headache	5 (5)
Metabolism and nutrition disorders	Hypersensitivity	2 (2)
	Decreased appetite	2 (2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Skin papilloma	2 (2)
Any AE		63 (58%)

Table 32 summarizes all AEs reported in the PBH4D Study.

Table 32: All Non-Serious AEs in the Primary BH4 Deficiency Study; N=12

System, Organ, Class	Preferred Term	N=12
		n (%)
Gastrointestinal disorders	Diarrhea	4 (33)
	Vomiting	3 (25)
	Abdominal pain upper	1 (8)
	Dyspepsia	1 (8)
Infections and infestations	Sinusitis	2 (17)
	Respiratory tract infection	1 (8)
	Upper respiratory tract infection	1 (8)
Blood and lymphatic system disorders	Neutropenia	1 (8)
Ear and labyrinth disorders	Vertigo	1 (8)
General disorders and administration site conditions	Fatigue	1 (8)
Injury, poisoning and procedural complications	Contusion	1 (8)
Investigations	Blood creatine increased	1 (8)
Nervous system disorders	Dyskinesia	1 (8)
	Dystonia	1 (8)
Respiratory, thoracic and mediastinal disorders	Cough	1 (8)
	Rhinorrhea	1 (8)
	Tonsillar hypertrophy	1 (8)
Skin and subcutaneous tissue disorders	Hyperhidrosis	1 (8)
	Rash	1 (8)
Any AE		9 (75)

Table 33 summarizes all AEs reported in the PBH4D Study.

Table 33: AEs in > 3% patients in HTN-001

		Sapropterin N=77	Placebo N=39
System, Organ, Class	Preferred Term	n (%)	n (%)
Nervous system disorders	Headache	6 (8)	4 (10)
	Dizziness	4 (5)	1 (3)
General disorders and administration site conditions	Edema peripheral	6 (8)	2 (5)
Musculoskeletal and connective tissue disorders	Arthralgia	5 (6)	1 (3)
	Back pain	3 (4)	1 (3)
Infections and infestations	Upper respiratory tract infection	4 (5)	1 (3)
	Bronchitis	2 (3)	1 (3)
	Viral infection	1 (1)	2 (5)
	Blood potassium decreased	2 (3)	1 (3)
	Urine albumin/creatinine ratio increased	2 (3)	1 (3)
Gastrointestinal disorders	Nausea	3 (4)	1 (3)
	Diarrhea	2 (3)	1 (3)
Cardiac disorders	Ventricular extra-systoles	2 (3)	1 (3)
Vascular disorders	Hypertension	1 (1)	2 (5)
Respiratory, thoracic and mediastinal disorders	Cough	2 (3)	1 (3)
Any AE		43 (56)	19 (58)

7.1.5.5 Identifying common and drug-related adverse events

The methods for determining AEs, SAEs, withdrawals, and deaths is described in sections 7.1, and 7.1.5.1 through 7.1.5.3 of this review. Events were designated AEs if they occurred any time from the first administration of drug or placebo (complete or partial dose) through the end of the safety monitoring period. AEs were classified as having occurred during the concurrent dose (sapropterin or placebo). For AEs occurring during the follow-up period, this Reviewer designated them as having occurred in association with the last dose (sapropterin or placebo) preceding the AE.

7.1.5.6 Additional analyses and explorations

This Reviewer found that gender and age did not appear to affect occurrence of AEs (data not shown).

In Weeks 0 through 6 of the open-label Extension Study, the incidence of AEs at 5, 10, and 20 mg/kg/day were 34, 33, and 31%, respectively. The types of AEs in the three dose groups were similar, but accurate comparison between the three doses is limited by the short exposure to each dose (two weeks). In patients receiving 5 mg/kg/day, AEs occurring in $\geq 5\%$ of patients were diarrhea and headache (5% each). In patients receiving 10 mg/kg/day, the only AE occurring in $\geq 5\%$ of patients was nasopharyngitis (5%). In patients receiving 20 mg/kg/day, AEs occurring in $\geq 5\%$ of patients were upper respiratory tract infection and headache (5% each). In Weeks 10 to 22 of the Extension Study AEs were more common in patients receiving 20 mg/kg/day than 10 mg/kg/day (59% vs. 41%; N=37 of 80 patients each dose).

This Reviewer concludes the types of AEs reported at 10 and 20 mg/kg/day in controlled studies of six to ten weeks are similar to, and not readily distinguishable from the general population and otherwise healthy patients with PKU. Similarly, the types of AEs reported at 10 and 20 mg/kg/day in a single, uncontrolled, 22-week study are similar to, and not readily distinguishable from the general population and otherwise healthy patients with PKU. The safety experience with 5 mg/kg/day is limited to two weeks in 80 patients; six of whom were treated for an additional 12 weeks. Therefore, accurate comparison of incidence of 5 to 10 and 20 mg/kg/day for longer than two weeks is not possible.

7.1.6 Less Common Adverse Events

Exposure to sapropterin in patients with PKU was limited: 579 patients were treated for one week; 42 of whom were treated for an additional six weeks, 33 of whom were treated for an additional 10 weeks, and 80 of whom were treated for an additional 22 weeks. Therefore, the longest exposure in patients enrolled in more than one trial was 29 weeks in 80 patients. This limited exposure may not have been adequate for detection of less common adverse events.

Events occurring in the non-PKU study population are discussed in section 7.2 of this Review.

7.1.7 Laboratory Findings

Laboratory datasets for the Enrichment, Efficacy, Extension, and Diet Studies, and the EAP were individually reviewed. There were no consistent findings across studies, and there were no changes in measures of central tendency for any analyte. Reference values for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) varied by laboratory site.

- In the Enrichment Study, ten patients had elevated AST, ALT or both at anytime from Baseline through completion of follow-up. In approximately 80% of these patients, elevations in these parameters were present prior to first treatment with sapropterin. Additionally, one patient with normal Screening and Baseline GGT had an increase in GGT at Day 8, which returned to normal by Day 36. Age and gender of patients with liver enzyme abnormalities were approximately evenly distributed. The clinical significance of these findings is unclear due to the lack of a placebo control and the prevalence of pre-treatment elevation of these enzymes. A discussion of the clinical laboratory findings in the Enrichment Study is found in section 10.1.1.14.7 of this Review.
- In the Efficacy Study, five patients had elevated ALT noted at Week 6; three sapropterin-treated patients, and two placebo-treated patients. Two of the three sapropterin-treated patients with elevated ALT had normal ALT at Screening and Week 0, and one of the sapropterin-treated patients with elevated ALT had elevated ALT at Screening, but normal ALT at Week 0. No follow up (Week 10) ALT was reported for these three sapropterin-treated patients. There were no notable changes in AST in this study. A discussion of the clinical laboratory findings in the Efficacy Study is found in section 10.1.2.14.6 of this review.
- In the Extension Study, notable laboratory findings included increased GGT in four patients. GGT in these patients was elevated at Baseline and remained elevated through completion of follow-up. One patient had an increase in AST from 41 at Week 0 to 71 U/L at Week 4 (ULN 31 U/L), which remained between 47 and 63 U/L through completion of the study. Six patients had Baseline ALT ≥ 50 IU/L (ULN 29 to 45 U/L at different sites), including three patients with prior exposure to placebo and three patients with prior exposure to sapropterin. Of seven patients with ALT ≥ 50 at Week 22, three had baseline ALT between 28 and 47 IU/L, and four patients had Baseline ALT ≥ 50 IU/L. A discussion of the clinical laboratory findings in the Enrichment Study is found in section 10.1.4.14.5 of this review.
- In the Diet Study, there were no abnormalities in ALT or GGT. A single patient (0110-6018) had an increase in AST from 33 to 50 in Part I, which fell to 36 (normal) at

Screening for Part II; however, the patient was not randomized to Part II and was not re-challenged with sapropterin. A discussion of the clinical laboratory findings in the Enrichment Study is found in section 10.1.3.14.6 of this review.

This Reviewer concludes the abnormalities in AST, ALT, and GGT and ALT in the Enrichment, Efficacy, Diet, and Extension Studies not be clinically meaningful for the following reasons. Increases in ALT prior to first exposure in the Enrichment Study were common (about 10%), no consistent pattern of liver enzyme abnormalities (AST, ALT, or GGT) was seen in placebo controlled trials, and decreases in these enzymes were as common as increases.

- Laboratory findings in the EAP were notable for one instance of neutropenia reported in one patient which resolved while still on treatment. There were no other notable findings in the laboratory dataset.
- In the Hypertension Study, four sapropterin-treated patients (5%) had increased GGT reported as an AE.
 - Patient 0215-001 had a Baseline GGT of 33, a Week 8 GGT of 32 while on treatment, and a Week 12 GGT of 41. This Reviewer concludes GGT was not elevated in this patient.
 - Patient 0216-004 had a Baseline GGT of 80, a Week 8 GGT of 61 while on treatment, and a Week 12 GGT of 53 four weeks after sapropterin treatment ended. This Reviewer concludes GGT there was no clinically meaningful change in GGT in this patient.
 - Patient 0208-003 had a Baseline of GGT of 165 (ULN 48 U/L), a GGT of 255 at Week 8 of treatment, and a Week 12 GGT of 133 four weeks after sapropterin treatment ended.
 - Patient 0215-006 had a Baseline GGT of 17, a Week 4 GGT of 18, a Week 8 GGT of 59 while on treatment, and a Week 12 GGT of 19, four weeks after sapropterin treatment ended.
 - On review of the clinical laboratory dataset, three placebo-treated patients (8%) had similarly elevated GGT identified on review of the laboratory dataset that were not recorded as AEs. Two of these patients had slightly elevated GGT at Baseline (59 and 71) that remained unchanged during placebo treatment. A third placebo treated patient had a Baseline GGT of 181, a Week 4 GGT of 215, and 301 at Week 12 GGT of 301, four weeks after placebo-treatment ended.

This Reviewer concludes the classification of elevated GGT as AEs in this study was inconsistent and was therefore not clinically meaningful. Review of the laboratory dataset indicates the incidence of changes in GGT in sapropterin- and placebo-treated patients was approximately the same (3% each).

- Two sapropterin-treated patients experienced neutropenia.
 - Patient 0217-005's ANC dropped from 2,240 at Baseline to 390 at Week 4 of sapropterin treatment, and increased to 2,380 by Week 8 of sapropterin treatment.
 - Patient 0207-010's ANC dropped from 1,630 at Baseline to 1,400 at Week 4 of sapropterin-treatment, and increased to 1,910 at Week 8 of sapropterin treatment,

- There were no trends in ALT, AST, or GGT, or bilirubin in sapropterin-treated patients in this study.
- Laboratory findings in PKU-005 and PKU-009 were notable for two healthy volunteers with increases in ALT, AST, or LDH described below.
 - Patient 0138-0020, a 34-year old male, had elevated ALT, AST, and LDH during the follow-up period. At Week 1 and Week 5 (one week after the final dose) these enzymes were within normal limits. The patient was evaluated one month later for an unidentified complaint, and enzyme levels were: ALT of 140 U/L (ULN 40 U/L), AST of 331 U/L (ULN 40 U/L), and LDH of 391 IU/L (ULN 250 U/L). The next day, the enzyme levels were: ALT of 108 U/L, AST of 149 U/L, and LDH of 171 U/L. The patient tested negative for hepatitis C at the Week 5 visit. The clinical summary states these enzymes were within normal limits approximately six weeks later; however, the CRF and laboratory values from that follow-up visit not available for review. This Reviewer concludes a relationship to sapropterin is unlikely.
 - Patient 0138-0023, a 38 year old male, had normal ALT at Screening (33 U/L) and ALT of 50 U/L at Week 5. One month later the ALT was 52 U/L. AST, LDH and total bilirubin were normal from Screening through follow-up. The CRF was not provided, and no further clinical information is available. The Reviewer concludes a relationship of this mild elevation in ALT to sapropterin is unlikely but possible.

As discussed in sections 7.1.3.3 and 7.1.5.3 above, neutropenia ($ANC \leq 1500$) occurred one or more times in 17 of 579 PKU patients (3%), 15 of whom had $ANC > 1500$ Baseline. 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 Reviewer concludes the risk of neutropenia is to be addressed prominently in labeling.

7.1.8 Vital Signs

The vital sign datasets for the Enrichment, Efficacy, Extension, and Diet Studies, the EAP, PKU-005 and PKU-009, and the PBH4D Study were reviewed. There were no notable changes in individuals, and no notable trends or changes in measures of central tendency.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Thorough QT studies and thorough QT assessments were not performed. Limitations in cardiac assessments in the PKU development program are discussed in section 7.1.5.1 of this review. A TQT study is recommended as a post-marketing commitment. Non-clinical electrophysiologic evaluations are summarized below.

- A hERG channel assay study (0162-06-005) was negative. The results of this study showed that the IC₅₀ for the effect of sapropterin on hERG potassium current was not determined, but was estimated to be >680 uM (terfenadine control was positive at 60 nM).
- An electrophysiologic/telemetry study (Study 0166-06-015) in eight conscious dogs at doses of 20, 50 or 100 mg/kg on Days 1, 4, 8 and 11 did not show abnormal findings by the cardiovascular parameters of ECG analysis, hemodynamic data (diastolic, systolic, and mean arterial pressures), inotropic state, and heart rate (NOEL 100 mg/kg).
- A second cardiovascular safety study (Study 0166-06-020) was performed in eight beagle dogs. Oral sapropterin (at doses up to 100 mg/kg) was administered in combination with sildenafil citrate. Results showed that sildenafil alone or in combination with sapropterin decreased diastolic pressure. No effect of sapropterin alone was noted on any of the cardiovascular parameters, but there was an indication the sapropterin may attenuate or augment the observed sildenafil-induced increase in pulse pressure.

Clinical studies that incorporated ECG monitoring include three studies with Biopten, and two Phase 1 studies with the Sponsor's product (PKU-005, and -009). These studies are summarized in Table 34 as the descriptions following Table 34.

Table 34: Table of PK and Bioavailability Studies in Healthy Volunteers

Name/Treatment	Study Design
PKU-005 ¹ Kuvan	Open-Label (OL), Randomized (R), Cross-over (CO), bioavailability (BA) study in healthy volunteers 19 to 50 years old; Sapropterin 10 mg/kg/day once per week x four weeks under Fed or Fasted conditions; N=28
PKU-009 ¹ Kuvan	OL, R, CO, BA study in healthy volunteers 19 to 50 years old; Sapropterin 10 mg/kg/day once per week x three weeks; intact vs. dissolved tabs under Fed or Fasted conditions; N=44
P1501 Biopten	One-week, OL, pharmacokinetic (PK) study; 100 or 200 mg PO/week x two weeks (1.4 - 3.3 mg/kg/dose); N=6; or 100 mg PO TID x seven days (4.2 - 4.9 mg/kg/day); N=6
FB1602 Biopten	One-week single-blind (SB), PK study; 200 mg PO TID (10.1 - 11.2 mg/kg/day) or placebo x 7 days; Biopten, N=6; Placebo, N=2
FB1701 Biopten	One-week OL, PK study; 200 mg PO, TID (9.0 - 10.6 mg/kg/day) x 7 days; N=6

¹Electrocardiograms were not performed at Cmax

- Studies PKU-005 and PKU-009, both performed with the Sponsor's product, were single daily dose studies of sapropterin 10 mg/kg in healthy volunteers (N=72). Four and three doses, respectively, were administered seven days apart. ECGs were performed at Baseline and one week after the last dose. No electrophysiological abnormalities or cardiac-associated AEs were reported. ECGs were not collected at Cmax, and the applicability of the information is limited.

The three studies below were performed with Biopten.

- Study P1501 was a Phase 1 study in 12 healthy adults. All patients received sapropterin. In six patients treated with single dose on Day 1 and a second dose on Day 7, ECGs were performed at pre-dose, two hours after dose, and 24 hours after the Day 7 dose. In six patients treated with TID dosing for seven days, ECGs were performed at pre-dose, two hours after each morning dose, and 24 hours after the final dose.
 - No abnormalities in ECG were observed.
 - No AEs were reported in the Cardiovascular System Organ Class.
- FB1602 was a Phase 1 multi-dose study in healthy adult males (N=6 sapropterin; N=2 placebo). Study subjects received their daily study drug treatment as three divided doses for seven days. ECGs were performed prior to each daily dose, two hours after each daily dose, and 24 hours after the final dose.
 - No abnormalities in ECGs were observed.
 - No AEs were reported in the Cardiovascular System Organ Class.
- FB1701 was a Phase 1 multi-dose study in six healthy adult volunteers. Study subjects received their daily study drug treatment as three divided doses for seven days. ECGs were performed on Day 7 after completion of study. The study report does not clearly indicate if Baseline ECGs were performed.
 - No abnormalities in ECGs were observed.
 - The study report does not provide or discuss objective ECG findings.

Study HTN-001, a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study (N=39 placebo; N=77 sapropterin) was performed to evaluate the effects of sapropterin on blood pressure in patients with poorly controlled systemic hypertension. Sapropterin was administered as a 10 mg/kg/day dose, divided into two 5 mg/kg doses, for eight weeks. ECGs were performed at Screening, prior to dosing at the Week 8 visit, and at the Week 12 visit (four weeks after the final dose). The Sponsor reports that the mean values for ECG parameters, including QT interval, were similar between placebo- and sapropterin-treated groups. Mean changes in ECGs from Baseline were negligible in sapropterin-treated patients, and there were no adverse event reports that were suggestive of pro-arrhythmogenic effects of sapropterin.

Clinical Review
Ethan D. Hausman, MD
NDA 22-181
Kuvan™ (sapropterin, 6R-BH4)

A consultation by the Interdisciplinary Review Team for QT Studies was requested, 12-October-2007. The consultation dated 07-November-2007 (Christine Garnett, PharmD) recommends a TQT study be performed. The opinion of the clinical review team is that a TQT study may be performed as a post-marketing commitment, since cardiac related SAEs were limited to a single report of peri-operative myocardial ischemic event, and non-serious AEs were limited to ECG abnormalities reported in both sapropterin- (4 of 77) and placebo-treated (2 of 39) patients.

7.1.10 Immunogenicity

Sapropterin is a small molecule rather than a therapeutic protein or enzyme, and immunogenicity studies were not part of the Kuvan development plan.

7.1.11 Human Carcinogenicity

Human carcinogenicity studies were not performed.

One patient developed a testicular neoplasm during the EAP. This SAE was not felt to be related to administration of sapropterin. This event is discussed in sections 7.1.2 and 7.2.2.1 of this review.

Animal carcinogenicity is discussed in the Pharmacology-Toxicology review (Fang Cai, PhD).

7.1.12 Special Safety Studies

No special safety studies were performed.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No withdrawal or abuse potential has been identified.

7.1.14 Human Reproduction and Pregnancy Data

No adequate and well-controlled clinical trials enrolling pregnant women were performed.

Two women in the PKU development program were exposed to sapropterin around the time of conception. A 21-year old woman received one dose of sapropterin then electively terminated her pregnancy. A 24-year old woman with a negative pregnancy test on entry received all eight doses of sapropterin. Pregnancy was reported at the 36-day follow up. Further evaluation gave an estimated date of conception of two weeks prior to entering the study, and the original

negative test was considered a false negative. The pregnancy continued. No further information is available.

If sapropterin is approved, it is likely that it will be used by pregnant women and women of reproductive potential. Future labeling should address safety in pregnancy. The Reviewer recommends Pregnancy “Category C”; studies not conducted. The Clinical Review team is also requesting a pregnancy registry as post-marketing commitment.

7.1.15 Assessment of Effect on Growth

Height and weight were part of Baseline and periodic assessments in all PKU studies, but growth was not assessed as a safety or efficacy endpoint in the PKU development plan. This Reviewer feels that treatments in controlled studies (six to ten weeks) were of insufficient duration to adequately assess differences in growth between sapropterin- and placebo-treated patients.

Since it is expected that sapropterin will be used from infancy through adulthood, long-term studies in infants and children that incorporate growth assessments should be performed. These studies should enroll patients from birth through approximately ten years of age. Growth parameters to be assessed are height, weight, and BMI. Measurements should be performed at quarterly intervals for infants less than two years of age, and yearly thereafter through completion of Tanner Stage IV or approximately 15 years, whichever occurs later. These assessments may be studied independently, or as a component of other post-marketing studies.

7.1.16 Overdose Experience

There was one reported overdose, which occurred in a patient in the Extension study. The patient received a single dose of 4,500 mg (36 mg/kg) instead of 2,600 mg (20 mg/kg) in Week 16 of the 26-week study. He reported a mild headache and dizziness immediately after taking the dose which resolved within one hour without intervention. Laboratory tests to monitor liver function were obtained immediately following the event and all the results were within normal limits. Sapropterin treatment was suspended for 24 hours. No abnormal signs or symptoms were reported on resumption of treatment.

7.1.17 Postmarketing Experience

Sapropterin is not a marketed product. There is no post-marketing experience with Sapropterin.

Biopten, marketed by Daichii Suntory Pharma, is marketed in Japan for “lowering of serum phenylalanine level in hyperphenylalaninemia based on the deficiency of dihydrobiopterin synthase or dihydropteridine reductase (atypical hyperphenylalaninemia).” Post-marketing experience with Biopten is discussed in section 7.2.2.2 of this review.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The Kuvan clinical development program, patient exposure, and assessments are described in detail in the following sections: 1) Section 4 Data Sources, Review Strategy, and Data Integrity (including subsections 4.1 Sources of Clinical Data, 4.2 Tables of Clinical Studies, and 4.3 Review Strategy); 2) Section 6 Integrated Review of Efficacy (including subsections 6.1.1 Methods and 6.1.3 Study Design); and 3) Section 7 Integrated Review of Safety (including subsection 7.1 Methods and Findings). Please refer to these sections for additional information.

The total PKU patient exposure is limited to patients in the clinical program for NDA 22-181, which was conducted in 579 male and female patients from 4 to 49 years old with hyper-Phe due to PKU. The Sponsor provided primary source safety data in patients with PKU from four completed BioMarin-sponsored clinical studies and the ongoing Expanded Access Program (EAP) in patients with PKU. Safety assessments included Baseline and periodic history, physical examination, and clinical laboratory assessments, including serum chemistry, hematology, and urine tests, and collection of AEs from Screening through completion of follow-up periods, from four weeks after the final study dose or at resolution of unresolved AEs. As described in sections 7.1, and 7.2.1.1 through 7.2.1.3 of this review duration of exposure and dose were adequate to assess short-term safety. Specific deficiencies noted in those sections are include:

- No TQT study or TQT assessment was performed
- Studies did not enroll patients younger than four years of age
- Duration of exposure was inadequate to make an assessment of long-term safety
- No studies incorporated neurocognitive outcomes
- No studies assessed growth and development

Based on the safety information summarized in section 7.1, and sections 7.2.2.1 and 7.2.2.2 of this review, this Reviewer concludes that short-term safety (up to 22 weeks in a single study and up to 29 weeks in combined studies) is supported; therefore, the above deficiencies may be addressed in post-marketing commitment studies as outlined in section 1.2.2 of this review.

Additional limited safety information was submitted from referenced sources of another sponsor's formulation of the same active ingredient (i.e., Biopten Granules). This product is currently marketed outside the US for treatment of dihydropteridine reductase deficiency and dihydropteridine synthase deficiency. This product is not marketed for treatment of PKU or BH4-responsive PKU. Clinical information of Biopten is discussed in sections 7.2.2.1.4 and 7.2.2.2 of this review. No additional safety concerns were noted in these studies.

7.2.1.1 Study Type and Design/Patient Enumeration

The PKU development program consisted of four clinical studies (Enrichment, Efficacy, Extension, and Diet) and the EAP. Five-hundred-seventy-nine patients with PKU were assessed for BH4-responsiveness in one-week, open-label trials of 10 (N=489) and 20 (N=90) mg/kg/day. Eighty patients were treated with 5, 10 or 20 mg/kg/day for a cumulative exposure of 22 weeks in the open-label, uncontrolled Extension Study. Forty-one of 88 patients with BH4-responsive PKU were treated with 10 mg/kg/day for six weeks in one controlled trial, and 33 of 45 patients were treated with 20 mg/kg/day for 10 weeks in a second controlled trial. This represents the entire sapropterin-PKU clinical experience. Exposure by clinical trial is summarized in Table 35.

Table 35: Clinical Studies in Patients With PKU

Study	Design	Population; Regimen	Treatment	
			Drug	Placebo
Controlled Clinical Studies in patients with PKU				
Efficacy Study¹ (PKU-003)	Randomized (R), DB, PC study to evaluate safety and efficacy in patients with BH4-responsive PKU and hyper-Phe; Diet not Phe restricted	8 to 49 years 10 mg/kg/day PO x 6 weeks	41	47
Diet Study Part II (PKU-006)	R, DB, PC study to study to evaluate safety and efficacy of Kuvan in patients with BH4-responsive PKU and hyper-Phe (Part I), and dietary Phe tolerance; Diet Phe-restricted	4 to 12 years 20 mg/kg/day PO x 10 weeks	33	12
Patients Exposed in Controlled Studies			74	59
Non- Controlled Clinical Studies in Patients with PKU				
Enrichment Study (PKU-001)	OL, uncontrolled study in patients with hyper-Phe due to PKU to identify patients with $\geq 30\%$ reduction in blood Phe with Kuvan treatment to qualify for the Efficacy Study. Diet not Phe restricted	8 to 48 years old 10 mg/kg/day x 8 days	489	n/a
Extension Study² (PKU-004)	OL, uncontrolled extension study evaluating safety and efficacy of Kuvan in patients with hyper-Phe due to PKU. Diet not Phe restricted.	8 to 49 years old 5, 10, and 20 mg/kg/day x 2 weeks; then 10 mg/kg/day x 4 weeks; then 5, or 10, or 20 mg/kg/day x 12 weeks	80	n/a
Diet Study Part I (PKU-006)	OL, uncontrolled study in patients with hyper-Phe due to PKU to identify patients with $\geq 30\%$ reduction in blood Phe for study in Part II. Diet Phe restricted	4 to 12 years old 20 mg/kg/day x 8 days	90	n/a
Patients Exposed in Uncontrolled Studies			579	n/a
All Patients Exposed			579	59

¹Prior participation in Enrichment Study

²Prior participation in Enrichment and Efficacy Studies

This Reviewer concludes that the Efficacy Study and Part II of the Diet Study were appropriately designed to assess short-term (six to ten weeks) safety in patients with BH4-responsive PKU. The studies were of insufficient duration to assess long-term safety.

This Reviewer concludes these studies were not adequately designed to assess long-term safety of 5 mg/kg/day. The maximum cumulative exposure to 10 and 20 mg/kg/day under controlled and uncontrolled studies was approximately 30 weeks. Safety data from studies of at least two years are needed to adequately assess long-term safety of sapropterin in patients with BH4-responsive PKU. These studies may be performed as a post-marketing commitment.

7.2.1.1 Demographics

Gender composition was approximately equal in all clinical trials. In controlled trials (i.e., the Enrichment Study and Part II of the Diet Study) gender distribution was 58% male and 42% female. In uncontrolled studies gender distribution varied between 48% to 59% male and 52% to 41% female. These findings are consistent with the autosomal transmission of PKU. The short duration of these studies and the small size of the studies may limit the ability to detect long-term differences in AEs by gender. Approximately equal gender representation in long-term post-marketing studies is recommended.

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. Post-marketing studies should include non-Caucasians.

Studies included 579 patients between 4 and 49 years of age at first treatment. Fifty children between 4 and ≤ 12 years old were treated for up to 11 weeks in the Diet Study and 104 children between the ages of 8 and ≤ 12 years were treated for up to six weeks in the Efficacy Study. Fifteen children 8 to ≤ 12 years were treated for an additional 22 weeks in the Extension Study. No patients over 50 years of age were studied. These findings are summarized in Table 36.

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Table 36: Demographic Features of Patients in PKU Studies

Trait	Studies					All Exposed N=579
	Open-label Uncontrolled			Double-Blind Placebo Controlled		
	Enrichment Study PKU-001 N=489	Diet Study Part I PKU-006 N=90	Extension Study PKU-004 N=80	Efficacy Study PKU-003 N=88	Diet Study Part II PKU-006 N=45	
Gender, n (%)						
Male	236 (48)	51 (57)	47 (59)	51 (58)	26 (58)	287 (50)
Female	253 (52)	39 (43)	33 (41)	37 (42)	19 (42)	292 (50)
Age (n)						
Mean (SD)	22 (9)	7 (3)	20 (10)	20 (10)	8 (3)	20 (10)
Percentiles (25 th , med, 75 th)	15, 20, 28	5, 7, 10	14, 18, 25	14, 18, 25	6, 7, 10	12, 18, 26
Min, Max	8, 48	4, 12	8, 49	8, 49	4, 12	4, 49
Category, n (%)						
4 < Age ≤ 8	--	50 (56)	--	--	24 (53)	50 (9)
8 ≤ Age ≤ 12	64 (13)	40 (44)	15 (19)	17 (19)	21 (47)	104 (18)
Age > 12	425 (87)	--	65 (81)	71 (81)	--	425 (73)
Race						
Caucasian	468 (96)	85 (94)	78 (98)	86 (98)	44 (98)	553 (96)
African-American/Black	1 (<1)	0	0	0	0	1 (<1)
Hispanic	11 (2)	1 (1)	0	0	1 (2)	12 (2)
Asian-Pacific Islander	4 (1)	0	1 (1)	1 (1)	0	4 (1)
Native American	0	1 (1)	0	0	0	1 (<1)
Other	5 (1)	3 (3)	1 (1)	1 (1)	0	8 (1)

In summary, the longest exposure in children in controlled trials was 10 weeks and the longest exposure in uncontrolled trials was 23 weeks. No patients younger than four years old were enrolled in clinical trials.

This Reviewer concludes that the safety Kuvan in patients with BH4-responsive PKU less than four years of age was not assessed, and as discussed in section 7.2.1.1, long-term safety in children four years of age and older was inadequate. Based on short-term safety information summarized in section 7.1, and sections 7.2.2.1 and 7.2.2.2 of this review, this Reviewer recommends that post-marketing studies enroll children less than four years of age. Since PKU is diagnosed through newborn screening programs in infants as young as several weeks of age, these post-marketing studies must enroll patients from time of first diagnosis.

7.2.1.2 Extent of Exposure (dose/duration)

In the Sponsor's studies patients with BH4-responsive PKU were treated with sapropterin at daily doses of 5 mg/kg, 10 mg/kg, and 20 mg/kg for periods from eight days to approximately six months. The longest exposure in controlled clinical trials was between six weeks (10

mg/kg/day) and ten weeks (20 mg/kg/day). The longest exposure in uncontrolled trials was 22 weeks in the Extension Study. These findings are summarized in Table 37.

Table 37 Exposure to Sapropterin in PKU Patients

	Controlled Studies		Controlled and Non-Controlled Studies
	Placebo	Sapropterin	Sapropterin
Exposure (days), n	58	74	576
Mean (SD)	46 (12)	54 (14)	35 (60)
Median	43	44	8
Min, max	10, 73	22, 765	1, 210
Dosing Regimen (mg/kg/day), n	59	74	579
1 to 5, n (%)	0	0	80 (14)
5 to 10, n (%)	47 (80)	41 (55)	409 (71)
11 to 15, n (%)	0	0	0
16 to 20, n (%)	12 (20)	33 (46)	90 (15)

Additionally, mean exposure during the EAP was 23 (SD 9) weeks (range 9½ to 69 weeks). Duration of exposure was from one to 210 days.

This Reviewer concludes the doses explored are consistent with proposed labeling, but that duration of exposure was insufficient to support long-term safety. This Reviewer recommends long-term studies of at least two years duration, or per minimum ICH-E1A guidelines. Long-term studies that incorporate neurocognitive outcomes should be required. These studies may be performed as a post-marketing commitment and may be a component of a long-term registry.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Additional limited safety data from ten studies of another manufacturer's product, Biopten, in patients with autism, Machado-Joseph Disease (MJD), and primary BH4 deficiency are discussed in section 7.2.2.1 of this review.

PK and PD data from three studies of Biopten in healthy volunteers were submitted in support of the PKU indication. These studies were reviewed by the Clinical Pharmacology reviewer and are discussed in section 5 of this review. The safety information in clinical study reports, and AE, vital signs, and laboratory datasets from these three studies were reviewed and no additional safety concerns were found (data not shown).

7.2.2.1 Other studies

7.2.2.1.1 Biopten Studies

Additional limited safety data were submitted from 14 studies of Biopten in healthy volunteers, and patients with autism, Machado-Joseph Disease (MJD), and primary BH4 deficiency. These studies are summarized in Table 21 in section 7.1 of this review.

Exposure of healthy volunteers (N=24), and patients with autism (N=451), primary BH4 deficiency (N=16), and MJD (N=118) are summarized in Table 38.

Table 38: Summary of Population Exposure; Biopten Granules

Population	N	Age range	Dose (mg/kg/day)	Exposure
Healthy	24	20 to 49 years	1.0 to 10.0	1 to 7 days
Autism	451	2 to 17 years	0.6 to 6.0	12 to 105 weeks
BH4 Deficiency	16	3 months to 29 years	1.5 to 10.0	10 to 12 months
Machado Joseph Disease	118	> 20 to 63 years	1.0 to 5.0	1 to 12 months

The safety summaries, and the AE, laboratory, and vital sign datasets for studies using Biopten were reviewed. The safety profile is substantially similar to the safety profile of sapropterin in patients with PKU. The only notable difference in controlled trials occurred in patients with autism where polyuria was noted in 9% of 191 sapropterin-treated patients and 3% of 115 placebo-treated patients. Since polyuria in these patients was not associated with other AEs or clinical laboratory abnormalities, and since polyuria was not noted in studies with Kuvan, this Reviewer concludes this clinical relevance to the PKU population is unclear. ~~_____~~

7.2.2.2 Postmarketing experience

Biopten Granules produced by Daiichi Suntary Pharma, is marketed outside the US for lowering of serum phenylalanine level in patients with dihydrobiopterin synthase or dihydropteridine reductase deficiencies. Biopten was marketed based on studies of 16 patients with these disorders. There is ten years of post-marketing follow-up of 30 patients treated with Biopten, and it is believed these are the only 30 patients exposed to Biopten during that time period. Dose was individualized in all patients; most commonly between 2 and 5 mg/kg/day.

Datasets are not available for review. The summary text and tables below are taken from section 5.3.6 of the electronic submission, "Reports of Post-marketing Experience." The text does not indicate what AE terminology system (for example MedDRA or COSTART) was used.

Patients were treated with Biopten for: dihydrobiopterin synthase deficiency (DHBS deficiency; N=22); dihydropteridine reductase deficiency (DHPR deficiency; N=5); and BH4-responsive hyper-Phe (N=3; off-label use). Age at first exposure was <1 year in 14 (47%) patients, ≥1 to ≤7 years in five patients (17%) patients, >7 to ≤16 years in five (17%) patients, and >16 years in six (20%) patients. Twenty-five patients (83%) received concurrent treatment with Biopten and levodopa.

No deaths or SAEs were reported. Non-serious AEs were reported in 11 of 30 patients (37%). The summary did not indicate which AEs occurred in which patients. The incidence of any AE in patients with and without concurrent levodopa exposure was approximately equal (36% of 25 patients vs. 40% of 5 patients, respectively). The most common AEs by incidence were

convulsions or exacerbation of convulsion (10% of patients) followed by increased GGT (7%). The remaining AEs were reported in one patient each. These findings are summarized in Table 39, which lists AEs by verbatim term for all 30 patients and by concomitant levodopa exposure.

Table 39: AEs by Concurrent Exposure to Levodopa

Adverse Event Verbatim Term	Levodopa N=25	No Levodopa N=5	Total N=30
Neurologic	4 (16)	1 (20)	5 (17)
Convulsion or Exacerbation of Convulsion	2 (8)	1 (20)	3 (10)
Disturbance of Consciousness	1 (4)	0	1 (3)
Involuntary Movement of Lips	1 (4)	0	1 (3)
Stammering	1 (4)	0	1 (3)
Inarticulateness	1 (4)	0	1 (3)
Myoclonus	0	1 (20)	1 (3)
Hypertonia	1 (4)	0	1 (3)
Other	3 (12)	0	3 (10)
Ocular Displacement	1 (4)	0	1 (3)
Psychiatric Morose and Euphoria	1 (4)	0	1 (3)
Psychiatric Euphoria	0	1 (20)	1 (3)
Heterotropia (sic)	1 (4)	0	1 (3)
Salivation	1 (4)	0	1 (3)
Loose Stools	1 (4)	0	1 (3)
Hepatic Function Disorder	3 (12)	1 (2)	4 (13)
Not Specified	1 (4)	0	0
Increased GGT	2 (8)	0	2 (7)
AST and ALT Increased	0	1 (20)	1 (3)
Any AE	9 (36)	2 (40)	11 (37)

Neurological impairment and seizures are reported in patients with DHPR and DHBS deficiency. Neurologic-related AEs were reported in patients with and without concomitant levodopa exposure. The small population size, the uneven distribution of patients with and without levodopa exposure (5:1), and the common finding of neurologic-related findings in patients at Baseline with DHPR and DHBS deficiency preclude further determination of attribution. The translated label for Biopten received with the NDA contains language addressing “increased excitability” when Biopten is co-administered with levodopa. Kuvan studies excluded patients with concomitant levodopa exposure and safety of co-administration was not investigated.

In summary, review of the Biopten post-marketing information was limited by lack of access to primary data and unspecified AE terminology, and the above summary was taken from the Sponsor’s summary in section 5.3.6.32 of the electronic submission. The most common AEs were neurological, similar to common complaints in these rare disorders. This Reviewer concludes that Kuvan labeling should include language indicating “increased excitability” has been reported in patients treated concomitantly with another manufacturer’s product and levodopa,

7.2.3 Adequacy of Overall Clinical Experience

As discussed in sections 7.2.1 and 7.2.2.1 through 7.2.1.3 of this review, it is the conclusion of this Reviewer that the overall clinical experience of sapropterin 10 and 20 mg/kg/day in patients with BH4-responsive PKU is adequate to support short-term safety in patients 4 to 50 years old.

Per ICH guidelines, treatments in controlled trials (six to ten weeks, 74 of 133 patients) was not adequate to assess long-term safety (≥ 100 patients ≥ 1 year) or to determine rare events ($\leq 1/1000$). Longer exposures in uncontrolled trials were limited to 80 patients treated for 22 weeks. Since BH4-responsive PKU patients will probably be on Kuvan treatment for years, or for life, this Reviewer concludes exposure was inadequate to assess long-term safety.

Therefore, long-term safety studies of adequate duration must be a component of post-marketing safety evaluations. Exposure and safety assessments in such studies should last for one to two years for general safety assessments including, but not limited to, collection of clinical laboratory data and AEs. Assessments for neurocognitive outcomes and for growth should be incorporated in studies lasting at least seven years.

Other specific deficiencies include the lack of TQT study and failure to enroll patients younger than four years of age, both of which must be evaluated in post-marketing studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Animal testing was performed as part of the non-clinical/pre-clinical development program. Refer to section 3.2 of this review for a summary of animal testing data. For complete discussion of animal studies, see the pharmacology-toxicology review by Fang Cai, PhD.

No additional special animal testing or *in vitro* testing was performed.

7.2.5 Adequacy of Routine Clinical Testing

Sapropterin was administered to 579 patients with PKU. Routine clinical testing in the PKU development plan consisted of Baseline medical, surgical, and medication histories; Baseline biochemical and hematological evaluations including pre-treatment blood Phe; Baseline vital sign assessments; and periodic reassessments of these assessments at daily or weekly intervals through the treatment period for each study. Clinical studies in PKU patients included follow-up approximately four weeks after the final dose of sapropterin or placebo, which included interval medical, surgical, and medication histories, and follow-up clinical laboratory tests for any biochemical or hematological tests that were abnormal at the end of dosing.

Cardiac related AEs were only reported in patients with chronic hypertension being investigated under a separate [REDACTED] one post-operative myocardial infarction was reported in one sapropterin-treated patient and non-serious cardiac-related AEs were reported in 5% of 77

sapropterin-treated patients and in 5% of 39 placebo-treated patients. As discussed in section 7.1.5.1 of this review, neither a thorough TQT study nor a TQT assessment was performed, and a TQT study is required as a post-marketing commitment.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Naturally occurring and synthetic BH4 are involved in multiple metabolic interactions primarily in the liver. Metabolic and clearance evaluations were limited to PK and PD studies in healthy volunteers and in patients with PKU. To date, animal studies have not identified the metabolic pathway for elimination of sapropterin.

Drug-drug interaction studies were not part of the PKU development program. Labeling of another manufacturer's product (Biopten) with the same active ingredient, sapropterin dihydrochloride, suggests an increase risk (not defined) of hyper-excitability in patients with diseases other than PKU including primary BH4 deficiency, when sapropterin is administered with levodopa. ~~_____~~

Theoretical drug-drug interactions with nitric oxide mediated vaso-relaxants and folate inhibitors are possible. Labeling should prominently describe theoretical drug-drug interactions with inhibitors of nitric oxide mediated vaso-relaxants and folate inhibitors. Labeling should state that the safety of co-administration of Kuvan with folate inhibitors, and Kuvan with nitric oxide mediated vaso-relaxants have not been assessed in clinical trials. For details of the risk of co-administration of sildenafil and sapropterin in animals, please see the Pharmacology-Toxicology review (Fang Cai, PhD).

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Drug-drug interaction studies were not performed. The clinical protocols collected information on concomitant medications in use at the beginning of all studies, or first used during the studies. No adverse drug-drug interactions were identified.

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

Recommendations for further studies are discussed and summarized in sections 1.2.3, 7.2.1 and 7.2.3 of this review.

7.2.8 Assessment of Quality and Completeness of Data

The study reports and AE, vital signs, clinical laboratory, concomitant medication, medical-surgical history, dosing, and compliance datasets for the Enrichment, Efficacy, Extension, and Diet Studies were complete and presented in a reviewable format. The interim safety report for the EAP and the datasets for the EAP were substantially complete and presented in a reviewable format. This Reviewer concludes the data submitted from BioMarin sponsored studies of Kuvan were adequate for review and support the safety and efficacy of Kuvan for the treatment of patients with BH4-responsive PKU.

Summary safety reports and secondary datasets for Biopten Granules, including a 10 year post-marketing experience for patients with DHPR and DHBS deficiency, were substantially complete and reviewable; however, primary datasets and CRFs were not available for review and limitations of the datasets are discussed in section 4 of this review. No clinical trials of efficacy of Biopten in patients with PKU were submitted in support of Kuvan for the treatment of BH4-responsive PKU. This Reviewer concludes that since the determination of safety and efficacy of sapropterin for the treatment of BH4-responsive PKU was based solely on data submitted from clinical trials of Kuvan, the safety data from the Biopten studies supports the overall safety of Kuvan.

7.2.9 Additional Submission, Including Safety Update

Additional pertinent sources of clinical information received in support of safety are limited to information received in the 120-day safety update. These include interim study reports from three studies: the expanded access protocol (SEAP-001) discussed in section 7.1 of this review; the Hypertension Study (HTN-001) discussed in section 7.2.2.1.3 of this review; and the primary BH4 Study (PKU-007) discussed in section 7.2.2.1.4 of this review.

There were no other pertinent sources of clinical information.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The safety results from the Kuvan clinical development program are notable for the following safety signals and concerns that are to appear prominently in the product labeling:

- Neutropenia was noted in 17 of 579 (3%) of patients treated with sapropterin. The small size of the studies, their short duration (as short as eight in approximately 420 patients), and the lack of an opportunity for a challenge-rechallenge, limits assessments of causation. Neutropenia was also noted in one patient in the primary BH4 study. The risk of neutropenia is to be noted in labeling.

- Definite or probably gastritis was noted in two patients, and both events were classified as SAEs. Sapropterin and _____, an inactive ingredient in the product formulation, may both increase gastric acidity, and the risk of gastritis is to be noted in labeling.

Safety results are otherwise summarized as follows:

- No deaths were reported in clinical studies in patients with PKU, or diseases other than PKU.
- SAEs, other than gastritis, occurring in patients with PKU during Kuvan treatment included: acute appendicitis, urinary tract infection, fractured tibia, spinal cord injury, streptococcal pharyngitis, testicular and carcinoma; none of which were related to sapropterin treatment. SAEs in two patients receiving Kuvan in the Hypertension Study included myocardial infarction and respiratory failure in one patient and post-procedural bleeding after a prostate biopsy in another patient. None of these SAEs were assessed as being related to sapropterin treatment.
- The most common AEs reported in sapropterin-treated patients in pooled controlled clinical trials were headache, upper respiratory tract infection, rhinorrhea, and pharyngolaryngeal pain. The most common AEs in placebo-treated patients in pooled controlled trials were upper respiratory tract infection, headache, and abdominal pain. The types of non-serious AEs in sapropterin- and placebo-treated patients were similar to common non-serious complaints in the general population or in otherwise healthy patients with PKU.

In summary, this Reviewer concludes that short-term safety of Kuvan for reducing blood Phe in patients with BH4-responsive PKU has been demonstrated. Common non-serious AEs were similar in sapropterin- and placebo-treated patients are similar to common complaints in the general population and in otherwise healthy patients with PKU and no notable differences were seen between placebo- and sapropterin-treated patients. The occurrence of gastritis and neutropenia are to be addressed in labeling. The occurrence of testicular carcinoma and myocardial infarction are probably not be attributable to sapropterin treatment, but should be included in Kuvan labeling as a list of SAEs occurring in clinical trials. Long-term post-marketing studies should be conducted to demonstrate long-term safety of Kuvan in patients with BH4-responsive PKU.

7.4 General Methodology

A discussion of methods used to assess safety is located in section 7.1 of this review.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The methodology of the Efficacy Study (PKU-003) and Part II of the Diet Study (PKU-006) allowed for pooling of the safety data from these two randomized, double-blind, placebo-controlled studies (see section 7.1.2.3 of this review).

The Enrichment Study (PKU-001), Part I of the Diet Study, the Extension Study (PKU-004), and the EAP were open label and uncontrolled. These safety data were discussed individually. Data from open-label, uncontrolled trials were not pooled with each other, or with the randomized, double-blind, placebo-controlled studies because of differences in study design, doses, length of treatment, and patient age.

A comparison on AEs, laboratory results, vital signs, and concomitant medicines between the pooled data from controlled studies and the non-pooled studies was performed. The types and incidences of AEs and abnormal clinical laboratory findings were similar across the groups.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

In the range of 5 to 20 mg/kg/day, the occurrence of AEs or laboratory abnormalities was not apparently related to daily dose. The only substantial exposure to 5 mg/kg/day (80 patients treated for two weeks) occurred in Part I of the Extension Study. The most accurate comparison of safety of the 5 mg/kg/day dose was to the other two doses administered during Part I of the study so that time of exposure to each dose was as closely matched as possible. The types and incidences of AEs and laboratory abnormalities were similar across the dose groups.

7.4.2.2 Explorations for time dependency for adverse findings

Exposure in randomized, double-blind, placebo-controlled trials was six weeks for 41 patients treated with 10 mg/kg/day, and ten weeks for 33 patients treated with 20 mg/kg/day. The longest exposure in completed open label trials was 22 weeks for 80 patients at doses of 5, 10, and 20 mg/kg/day. The occurrence of AEs and laboratory abnormalities were not apparently related to duration of exposure to Kuvan.

7.4.2.3 Explorations for drug-demographic interactions

In patients treated with Kuvan for hyper-Phe due to PKU, the occurrence of AEs was not apparently related to gender or age. Patients with PKU treated with Kuvan were from 4 to 49 years of age at first exposure, and genders were represented in approximately equal proportions.

7.4.2.4 Explorations for drug-disease interactions

Drug-disease interactions were not formally explored. Long term safety and efficacy trials with neurocognitive outcomes are being developed.

7.4.2.5 Explorations for drug-drug interactions

Drug-drug interaction studies were not performed. The clinical protocols collected information on concomitant medications in use at the beginning of all studies, or first used during the studies. No adverse drug-drug interactions were identified.

8 ADDITIONAL CLINICAL ISSUES

8.1 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.

No dose related safety concerns were noted. Please see section 7 of this review for a discussion the safety of Kuvan.

Patients with liver function abnormalities were not systematically studied and patients with alanine aminotransferase levels from two to five times the upper limit of normal were excluded from clinical studies. Patients with liver impairment should be carefully monitored when receiving Kuvan because hepatic damage has been associated with impaired Phe metabolism.

8.2 Drug-Drug Interactions

Potential drug-drug interactions include co-administration of Kuvan with folate inhibitors, nitric oxide mediated vaso-relaxants, and with levodopa. Labeling should state that specific drug-drug interaction studies with these drugs were not performed.

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.

8.3 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. Therefore, it is expected that Kuvan will be prescribed for infants as young as one month of age and 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)

8.4 Pediatrics

The PKU clinical program did not enroll patients younger than four years of age. 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 the time of diagnosis.

Labeling should state that children less than four years of age were not studied in clinical trials.

Patients treated for one week in open-label uncontrolled studies included 50 patients who were four to eight years old, and 104 patients who were 8 to 12 years old. Patients treated for six to ten weeks in randomized, double-blind, placebo-controlled trials included 24 patients who were 4 to 8 years old, and 38 patients who were 8 to 12 years old. Fifteen patients who were 8 to 12 years old were treated for 22 weeks in open-label, uncontrolled clinical trials.

This Reviewer concludes that short-term efficacy and safety have been demonstrated in pediatric patients four years and older. However, since Kuvan will likely be used for extended periods of time in patients with BH4-responsive PKU, this Reviewer concludes that long-term safety in children has not been evaluated. Long-term evaluations of efficacy and safety, including such parameters as neurocognitive assessments, will be required as a condition of approval (i.e., post-marketing commitment). Children with PKU younger than four years old should be studied patients in the post-approval period (i.e., as a post-marketing commitment).

8.5 Advisory Committee Meeting

No Advisory Committee meeting was convened.

8.6 Literature Review

Reviews and discussions of PKU and efficacy endpoints are provided in sections 2.6 and 6.1.2, respectively. Citations for references in those discussions are provided in Appendix 10.3 of this review.

8.7 Postmarketing Risk Management Plan

No post-marketing risk management plan is recommended at this time.

8.8 Other Relevant Materials

No other relevant materials were reviewed.

9 OVERALL ASSESSMENT

9.1 Conclusions

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.”

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.

Dietary Phe tolerance was studied in a single short-term clinical trial. The long-term safety and efficacy of dietary Phe tolerance were not established by the evaluation of neuro-cognitive outcomes. [REDACTED]

[REDACTED] the eight-day efficacy results from the Diet Study (PKU-006) should be included in labeling at this time (e.g., Responder analysis).
[REDACTED]

9.1.1 Efficacy

This Reviewer's recommendation for approval is based on a clinically meaningful reduction in blood Phe in sapropterin- vs. placebo-treated patients demonstrated in the Efficacy Study (PKU-003). Efficacy results from the Enrichment Study (PKU-001) and the Extension Study (PKU-004) are supportive of efficacy. The primary efficacy endpoint of the Diet Study (PKU-006),

dietary Phe tolerance [REDACTED] The results of this Reviewers efficacy analyses were substantially similar to the Sponsor's results.

Efficacy results from these studies are summarized below:

Enrichment Study (PKU-001): In this open-label, 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. 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 from Baseline. 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.

In conclusion, this study supports the short-term clinical effectiveness of Kuvan treatment in the reduction of blood Phe in patients with BH4-responsive PKU.

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 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 and were 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.

Diet Study (PKU-006): This was a two part study. Results and conclusions for Parts I and II are discussed separately.

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.

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.

9.1.2 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 chronic hypertension/cardiovascular disease is to be included in labeling, and includes: myocardial infarction, respiratory failure, and post-procedural bleeding following prostate biopsy
- 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.
 - Since dietary Phe tolerance was not assessed in long-term studies with neurocognitive outcomes, the safety of dietary Phe tolerance has not been established. ~~_____~~
 - 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;

9.1.3 Conclusion

It is the overall assessment of this Reviewer that data from one short-term clinical safety and efficacy study (the Efficacy Study) conducted in pediatric and adult patients with PKU who were not on dietary Phe restriction, supports the effectiveness of sapropterin (e.g., Kuvan) 10 mg/kg/day for the reduction of blood Phe in patients with BH4-responsive PKU, ages 8 years and older. Data from a second short-term clinical safety and efficacy study (the Diet Study) conducted in pediatric patients with PKU who were on dietary Phe restriction, supports the effectiveness of Kuvan 20 mg/kg/day for the reduction of blood Phe in patients with BH4-responsive PKU, ages four to twelve years. Data from the Enrichment Study and Part I of the Diet Study suggest that patients with PKU can be screened for BH4-responsiveness with a one week trial of sapropterin 10 or 20 mg/kg/day, optimally when dietary Phe intake is held stable. Data from the Extension Study demonstrates that reduction in blood Phe in patients with BH4-responsive PKU can be maintained for 22 weeks.

The short-term safety of Kuvan in patients with BH4-responsive PKU has been demonstrated in these four short-term clinical trials and the EAP.

Neutropenia was noted in 3% of 579 patients exposed to Kuvan and should be addressed in labeling.

Review of clinical safety information of Biopten Granules was notable for seizures or convulsions noted in patients with primary BH4 deficiency. While the incidence of seizures at Baseline in these patients is not known, the risk of seizure or convulsions in patients receiving concomitant Biopten Granules and levodopa therapy is addressed in labeling for Biopten Granules. Since no seizures were reported in studies of Kuvan, and since the safety of concomitant administration of Kuvan and levodopa was not evaluated, this Reviewer recommends that the Kuvan label state that in clinical studies of another manufacturer's product containing the same active ingredient in patients with diseases other than PKU, seizures were noted in some patients with concomitant levodopa exposure.

9.2 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.”

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No risk management activities are recommended at this time.

9.3.2 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.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are recommended at this time.

9.4 Labeling Review

The labeling underwent extensive negotiations between the Sponsor and FDA. Please refer to the final negotiated labeling.

9.5 Comments to Applicant

The Sponsor should receive an Approval Letter. Additional requirements for post-marketing commitments should be included in the letter. Please refer to section 1.2.2 and 9.3.2 of this review for a discussion of post-marketing commitments and to the final version of the Approval letter for exact wording of these post-marketing commitments.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Enrichment Study (PKU-001)

Study Title: “A phase 2, multi-center, 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”

10.1.1.1 Study Design

The Enrichment Study (PKU-001), was a Phase 2, multi-center, open-label (OL) study to evaluate the efficacy and safety of sapropterin treatment in patients with phenylketonuria (PKU), ages eight years and older, who had elevated blood phenylalanine (Phe) levels ≥ 450 μM at screening. Patients received eight days of OL sapropterin 10 mg/kg/day in a single dose. Blood Phe levels were obtained at Screening, on Day 1 prior to first dose, and on Day 8 of treatment. Efficacy was change in blood Phe from Baseline (Day 1) to Day 8. Responders were defined as having a $\geq 30\%$ reduction in blood Phe from Baseline to Day 8. This study was designed to identify a population of sapropterin-responsive patients for enrollment in the Efficacy Study (PKU-003; discussed in Appendix section 10.1.2 of this review).

A sub-study of the Enrichment Study (PKU-001 Sub-study 01) was conducted at one study site, which evaluated the affect of a single daily dose of sapropterin on blood Phe over 24-hours. Important findings from the Clinical Pharmacology Review by Hae-Young Ahn, PhD are found in her review and are summarized in section 5 of this review.

An important limitation of this study that could have affected the overall study results was the lack of dietary control during the study. Although patients/caregivers were instructed not to change their diet from Screening through completion of the study, blood Phe in patients with PKU is dependant on dietary protein load, and blood Phe in these patients changes rapidly due to meal-to-meal and day-to-day changes in dietary protein load. Therefore, changes in dietary protein load (up or down) could have resulted in the incorrect identification of both responders and non-responders that were due to diet, not study drug.

The first patient was enrolled 4-December-2004, and the last follow-up visit was 4-November-2005.

10.1.1.2 Study Objectives

The primary objective of Study PKU-001 was to evaluate the short-term (eight day) safety and efficacy of sapropterin in patients with PKU in order to identify patients for study in PKU-003 (Efficacy Study). Efficacy was assessed by the pharmacodynamic effect of sapropterin on blood Phe levels. Response was defined as patients who demonstrated a $\geq 30\%$ decrease in blood Phe on treatment baseline (Day 1 pretreatment) to Day 8.

In conclusion the objective of the study was to identify responders with a $\geq 30\%$ reduction in blood Phe with sapropterin treatment for enrollment in PKU-003.

10.1.1.3 Eligibility 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. Notable exclusion criteria included: from study participation if they had any of the following exclusion criteria: diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, blood alanine amino-transferase (ALT) > 5 times the upper limit of normal (ULN), or serious illness not under medical control.

The method of excluding primary BH4 deficiency was not stated.

10.1.1.4 Prior, 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).

10.1.1.5 Study Visits and Procedures

It is noted that the blood samples obtained for phenylalanine hydroxylase (PAH) mutation analysis was for exploratory purposes, and the results were not part of the study report. Day 1 blood Phe was measured prior to the first dose. Day 8 blood Phe was measured 2 ½ to 5 hours

after the daily dose which was to be taken five to ten minutes before the morning meal. Study visits and procedures are summarized in Table 40.

Table 40: Enrichment Study: Schedule of Events

Procedure	Screening	Day 1 Baseline	Day 4 (± 1 day) Phone visit	Day 8 (± 1 day)	Day 36 (± 3 days); Final Study Visit
Informed consent	X				
Medical history	X				
Vital signs and weight	X	X		X	
Physical examination	X			X	
Clinical laboratory tests	X	X		X	X ¹
Thyroid Panel (T4 and TSH)		X		X	
Urine pregnancy test	X	X			
Concomitant medications	X	X		X	X
Adverse events	X	X	X	X	X
Blood Phe	X	X		X	
<i>PAH</i> gene mutation analysis	X				
Dispense study drug		X			
Study termination assessments					X

¹ If previous results revealed clinically significant abnormalities.

10.1.1.6 Randomization, Blinding and Controls

This was an open-label, uncontrolled study. All patients received treatment with sapropterin 10mg/kg/day in one daily dose. No blinding of patients, families or study personnel was performed.

10.1.1.7 Study Medication Dose Selection, Dispensing, and Compliance

The study drug (sapropterin) was supplied as 300 mg tablets for oral administration. Each tablet contained 100 mg of the active ingredient sapropterin. Sapropterin was administered after dissolution of the sapropterin tablets in four to eight ounces of water, orange juice, or apple juice. Patients were to ingest the solution within 10 to 15 minutes of dissolution. The first dose was to be taken 3 to 5 hours after any meal; all other doses were to be taken 5 to 10 minutes before the morning meal. All patients received sapropterin at a dose of 10 mg/kg/day in one daily dose for eight days. Doses were calculated using whole tablets (100 mg drug/tablet). This was done by multiplying patient weight in kilograms by 10 mg/kg and rounding up to the next 100 mg. For example, if a patient weighed 42 kg, the weight was multiplied by 10 mg/kg, resulting in 420 mg, which was rounded up to a dose of 500 mg, or five tablets, to be taken once daily.

The Sponsor cites two references for the dose selected for study. The first reference is a published trial of sapropterin (source Daiichi Suntory, Japan) in 12 patients with BH4-responsive

hyperphenylalaninemia (hyper-Phe).¹⁷ The second reference is a published retrospective review where sapropterin was used as a diagnostic test for BH4-responsive hyper-Phe syndromes, including patients with BH4-responsive PKU.¹⁸

Compliance was assessed by comparing used vs. unused sapropterin tablets. The quantity dispensed, returned, used, or lost was recorded in a dispensing log.

10.1.1.8 Diet

Diet was not controlled. The study enrolled patients with PKU who were not following Phe restricted diets. Patients and caregivers were instructed that diet was not to be modified from Screening through completion of all study procedures; however, diet was not controlled through the provision of quantified meals; therefore, dietary Phe could have increased or decreased.

Blood Phe in patients with PKU is dependant on dietary protein load, and blood Phe changes rapidly in these patients due to meal-to-meal and day-to-day changes in dietary protein load. Thus, the lack of a dietary control was noted by this Reviewer to be a limitation of the study, which could have affected the study results. Patients may have been incorrectly identified as either sapropterin responders or non-responders when the measured changes in blood Phe were due to changes in diet. However, since one of the objectives of this study was to identify responders for further study in a randomized, double-blind study (the Efficacy Study), this Reviewer concludes that the lack of dietary control did not prevent the identification of a potentially responsive population for further study in the Efficacy Study.

10.1.1.9 Efficacy and Endpoint Measures

10.1.1.9.1 Primary Efficacy Endpoint

The primary efficacy 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:

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

10.1.1.9.2 Secondary Efficacy Endpoints

Secondary endpoints included the following assessments.

The Sponsor specified an exploratory analysis of change in blood Phe by Day 1 blood Phe strata (<600 uM vs. ≥ 600 uM).

The Sponsor specified an exploratory analysis to determine the percentage of Responders by pre-treatment Day 1 blood Phe strata (<600 uM vs. ≥600 uM).

This Reviewer performed an analysis of net change in blood Phe for the analysis population and by Day 1 blood Phe strata (<600 vs. ≥600 uM) for illustrative purposes.

10.1.1.9.3 Safety Assessments

Safety assessments included the collection of adverse events during sapropterin treatment, and the change from Baseline in clinical laboratory assessments (blood chemistry, urinalysis, and hematology), physical examinations, and vital sign measurements. Safety assessments were performed according to the schedule of events shown in Table 40 in section 10.1.1.5 of this review.

10.1.1.9.4 PK and PD Measures

Pharmacokinetic assessments were not performed in this study.

Twenty-four hour PD assessments were performed in sub-study 01 and are discussed in the Clinical Pharmacology review (Hae-Young Ahn, PhD).

10.1.1.9.5 Exploratory Endpoints

Blood was collected for Phe hydroxylase mutation analysis for correlation of response with genotype. The results of that mutation analysis were not included in this study report and will be submitted at a later date.

10.1.1.10 Additional Statistical Considerations

The Sponsor based the original target sample size on a desired response rate of 30%, with a 95% confidence interval of 26% to 35%. The Sponsor estimated that 490 patients were needed to identify 80 to 100 patients who would demonstrate a ≥30% reduction in blood Phe at Day 8 compared to Baseline. The proportion of Responders was calculated as the number of Responders divided by the number of patients who enrolled and had both Day 1 and Day 8 blood Phe levels (Analysis Population, AP).

The Sponsor's sub-analysis of the percentage of patients with blood Phe <600 vs. ≥600 uM at Day 8 compared to Screening was not pre-specified.

10.1.1.11 Protocol Amendments

The first patient was enrolled 4-December-2004, and the last follow-up visit was 4-November-2005.

There were two protocol amendments.

Amendment 1, dated 8-October-2004, prior to first patient enrollment was notable for the following:

- Apple juice was added as an option for dissolving study drug tablets.
- Other minor administrative changes and the addition of physical examinations to Day 8 study procedures.

Amendment 2, dated 17-June-2005, submitted during the study period after patient enrollment commenced was notable for the following:

- The inclusion criteria were changed so that patients were eligible for inclusion in the study if they had a Screening blood Phe levels of ≥ 450 uM (had been ≥ 600 uM in the original protocol).
 - The Sponsor states this was done to allow patients with screening blood Phe as low as 450 uM to enroll. No other rationale was provided. The effect on efficacy measures is not quantifiable because the correlation of baseline blood Phe with BH4-responsiveness is unknown.
- Increased the number of patients to be enrolled and treated in the study to 700 (was 490 patients in the original protocol)
 - This was done to increase enrollment, and should not affect efficacy analyses.
- Changed the window between the Screening visit and Day 1 from 4 weeks to 6 weeks
 - This was done to allow time for completion of screening blood Phe. This should not affect efficacy analyses, which are defined as changes in blood Phe from Baseline (Day 1) pre-treatment to Day 8 of treatment.
- Increased the number of study centers from 20 to 25, to 30 to 35 to increase enrollment.
 - This should not affect efficacy analyses.
- Changed the definition of “response” to a $\geq 30\%$ reduction in blood Phe between Baseline (now defined as Day 1, prior to first dose) and Day 8 for all patients
 - Response was originally defined as a reduction in blood Phe level of $\geq 30\%$ from baseline in patients with a baseline Phe of < 1200 uM or a reduction of ≥ 50 in patients with a baseline Phe of ≥ 1200 uM.
 - The Sponsor states this was done because researchers and physicians who treat PKU patients consider a reduction in blood Phe of $\geq 30\%$ to be clinically meaningful (references not provided); and
 - To be consistent with the definition of a response to sapropterin in the PKU-003 study.

Correlations between baseline blood Phe and BH4-responsiveness are unknown and it is uncertain if reducing the lower limit of Screening blood Phe from ≥ 600 to ≥ 450 uM would affect efficacy analyses. This protocol change allowed enrollment of an additional 22 patients (5% of 490).

Changing the definition of response could affect efficacy analyses. However, while treatment goals for blood Phe are not uniform, NIH treatment guidelines from 2000 call for a target blood Phe of ≤ 600 uM.³ Further, communications between the Sponsor and the Division of Metabolic and Endocrine drug product indicate that a $\geq 30\%$ decrease in blood Phe in was negotiated as an acceptable goal for the Efficacy Study, discussed in section 10.1.2 of this review. Therefore, because the primary goal of the current open-label study was to identify patients for further study in controlled clinical trials, this Reviewer concludes this amendment should not affect efficacy measures.

10.1.1.12 Study Conduct

The Sponsor states that the study was conducted in accordance with International Conference on Harmonisation (ICH) guidelines, Good Clinical Practices, and the Declaration of Helsinki.

The Sponsor certifies that no debarred investigators participated in this study, and that each investigator provided an FDA Form 1572 and a Financial Disclosure Form. Sub-investigators were listed on FDA Form 1572. No financial interests were reported.

The study was administered and monitored by employees or representatives of BioMarin. Clinical research associates (CRAs) monitored each site periodically and performed verification of source documentation for each subject. CRF data were entered in duplicate into a validated study database by _____ the designee for Clinical Data Management at BioMarin. Data quality control and analysis were performed by BioMarin or a designee, based on a predefined data management and Statistical Analysis Plan (SAP).

10.1.1.13 Study Results

10.1.1.13.1 Patient Population and Demographics, and Disposition

Of the 571 patients who were screened, 59 patients failed to meet inclusion or exclusion criteria. Of these 59 patients, 56 patients had blood Phe below the cut-off (600 uM prior to amendment 2, and 450 uM after Amendment 2 criteria). The reason for failure to qualify for three patients was not stated. Of the 512 patients who met entry criteria, 22 patients elected to withdraw prior to the first dose (reasons not provided).

Of the 490 patients who completed screening procedures, one patient never received sapropterin. The remaining 489 patients who received ≥ 1 dose of sapropterin (ITT population) were included in the safety analysis. Day 8 blood Phe values were only available in 485 patients (Analysis

Population; AP). Since the goal was to identify individual patients with a decrease of $\geq 30\%$, the Reviewer presents efficacy results from the AP.

Demographic characteristics of the ITT included 64 patients ages 8 to ≤ 12 years, 127 patients ages 13 to ≤ 17 years, and 294 adults ages 18 to 48 years. Gender distribution was 52% female and 48% male, which is consistent with autosomal transmission of PKU. Age distribution for each gender was approximately equivalent to age distribution across the ITT. Racial composition was 96% Caucasian, 2% Hispanic, 1% Asian/Pacific, and 1% Other (including one self reported Italian and three self reported Arab patients). This imbalance is due to differences in incidence among different racial groups (about 1 in 8,000 in US Caucasians to about 1 in 70,000 in US African-Americans). Demographic characteristics of the ITT population, by Day 1 (Baseline) blood Phe, are summarized in Table 41.

Table 41: Enrichment Study: Demographic Characteristics, ITT Population by Day-1 Blood Phe

Demographic Trait	Baseline Blood Phenylalanine		Total N=489
	<600 N=57	≥ 600 N=432	
Gender, n (%)			
Male	32 (56)	204 (47)	236 (48)
Female	25 (44)	228 (53)	253 (52)
Age (years), n (%)	57	432	490
Mean (SD)	17.6 (7.6)	22.4 (8.9)	21.8 (8.9)
Percentiles (25, median, 75)	13, 15, 20	16, 20, 29	15, 20, 28
Minimum, Maximum	9, 42	8, 48	8, 48
Age Group n (%)			
8 to ≤ 12 years	14 (25)	50 (12)	64 (13)
> 12 years	43 (75)	382 (88)	425 (87)
Race, n (%)			
Caucasian	56 (98)	412 (95)	469 (96)
Black	0	1 (<1)	1 (<1)
Hispanic	0	11 (3)	11 (2)
Asian/Pacific Islander	1 (2)	3 (1)	4 (1)
Other	0	5 (1)	5 (1)
Weight (kg), n	57	431	489
Mean (SD)	64 (22)	70 (22)	69 (22)
Percentiles (25, median, 75)	48, 63, 75	55, 68, 82	55, 67, 81
Minimum, Maximum	26, 149	21, 166	21, 166

10.1.1.13.2 Concomitant Medication

Prior medications were defined as medicines taken by the patient from thirty days prior to Screening up to immediately prior to receipt of first dose. Twenty-two percent (22%) of patients had one or more prior medications listed. By incidence, the most common prior medicines used were pain relievers, including ibuprofen (6%), paracetamol (3%), dextromethorphan containing cough medicines (2%) and salicylates (1%). Other common prior medicines at entry included antibiotics (3%), including amoxicillin/amoxicillin-clavulanate (1%), azithromycin (1%), and cephalexin (1%). These medicines were used for a variety of complaints including headache, sore throat, menstrual cramps, and upper respiratory tract infection (data not shown). The most

commonly reported prior medications (used by $\geq 1\%$ of patients in the study) are summarized in Table 42.

Table 42: Enrichment Study: Prior Medicine Used by $\geq 1\%$ of Patients

Prior Medicines	N=490 n (%)
Ibuprofen	27 (6)
Paracetamol	16 (3)
Dextromethorphan hydrobromide with or without Guaifenesin, Paracetamol, Ephedrine or Pseudoephedrine, Doxylamine, or Ethanol	8 (2)
Amoxicillin, Amoxicillin-Clavulanate	7 (1)
Acetylsalicylic acid	6 (1)
Azithromycin	4 (1)
Cefalexin	4 (1)
Salbutamol sulfate	3 (1)
Xylometazoline hydrochloride	3 (1)

Concomitant medications were defined as medicines ingested after the administration of the first dose on Day 1 through the final dose on Day 8. Fifty-four percent (54%) of patients (269 of 489) received at least one concomitant medication. The most common concomitant medicines were pain relievers, including ibuprofen (12%) and paracetamol (8%), vitamins (8%), and calcium supplements (4%); followed by vitamins and minerals (11%). These medicines were most commonly administered for general health maintenance (e.g. vitamins), headache, and treatment of pre-existing disorders, including asthma and environmental allergies. This study was uncontrolled, and the adverse events associated with use the concomitant medicines described above are general in nature. Therefore, no relationship to sapropterin administration to AEs related to use of these concomitant medicines can be inferred. It is noted that Vitamins and The most commonly reported concomitant medications (used by $\geq 2\%$ of patients in the study) are summarized in Table 43.

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Table 43: Enrichment Study: Concomitant Used by $\geq 2\%$ of Patients

Concomitant Medicines	490 n (%)
Ibuprofen	59 (12)
Vitamins, Vitamins not otherwise specified (NOS), and Minerals NOS	56 (11)
Paracetamol	38 (8)
Calcium	20 (4)
Ethinylestradiol/Levonorgestrel	17 (3)
Salbutamol sulfate	17 (3)
Calcium carbonate	14 (3)
Loratadine	14 (3)
Ascorbic acid	12 (3)
Ethinylestradiol/Norgestimate	11 (2)
Desogestrel/Ethinylestradiol	9 (2)
Omeprazole	9 (2)
Amoxicillin	9 (2)
Fluticasone propionate/Salmeterol xinafoate	8 (2)
Paracetamol/Pseudoephedrine hydrochloride	8 (2)

The most common concomitant medications that were administered in association with documented AEs were ibuprofen (6%) and paracetamol (5%) and the most commonly reported verbatim terms associated with concomitant medications included headaches (11%), followed by general health general health (6%), and allergies and birth control (5% each); (data not shown).

10.1.1.13.3 Compliance with Study Medication

Compliance with study medication was very high, with 480 patients (98%) receiving ≥ 8 doses of sapropterin. Of 489 patients in the ITT, seven patients received seven doses, and one patient did not turn in their dosing diary and compliance could not be assessed. Sixteen patients received more than eight doses of study medication: fourteen patients received nine doses, and two patients received 11 doses. The study report does not indicate why these patients ingested additional dose of medication.

The mean daily dose of sapropterin received by patients in the study was 10.8 mg/kg (minimum 7.8 mg/kg; maximum 13.1 mg/kg). The protocol explains why some patients may have received doses above 10 mg/kg/day. Review of the datasets and the study report does not indicate why some patients were received less than 10 mg/kg/day.

10.1.1.13.4 Protocol Deviations and Violations

Four patients in the Analysis Population received ≥ 1 dose of sapropterin, and completed Day 8 but not Day 36 procedures. This did not affect efficacy analyses. The Reviewer concludes there was minimal affect on safety analyses; see discussion in section 10.1.1.14.5 below.

Deviations in sapropterin administration include 16 patients who took an extra dose of sapropterin on Day 9, two of whom also took doses on Days 10 and 11; and 19 patients who either missed a dose or took an incorrect dose of sapropterin between Days 1 and 8. Missed Day 1 doses and extra doses at any time can not affect efficacy results. Missed Day 2 through 6 doses are not likely to affect Day 8 blood Phe. It is unlikely that missed Day 7 (n=2) results would affect blood Phe because the half-life is approximately 4 to 6 hours and there would have been little if any continued drug effect at Day 8. Of four patients who missed Day 8 dosing but who had blood Phe measured on that day, blood Phe decreased 5% in one patient and 20% in a second patient. Blood Phe increased 15% in a third patient and was unchanged in a fourth patient. Therefore, these deviations do not affect blood Phe in the AP.

Protocol violations include four patients with a screening blood Phe of ≥ 590 uM but < 600 uM enrolled prior to Amendment 2 (Amendment 2 allowed for enrollment of patients with blood Phe ≥ 450 uM); and two patients who were screened 30 days rather than 28 days prior to Day 1 of drug administration. These violations do not affect blood Phe analysis.

This Reviewer concludes these deviations and violations do not affect efficacy or safety analyses.

10.1.1.13.5 Efficacy Analyses

10.1.1.13.5.1 Primary Efficacy Analyses

The primary efficacy endpoint was to identify individual patients with a decrease in blood Phe of $\geq 30\%$ from Day 1 Baseline to Day 8 for enrollment in the Efficacy Study.

Each patient's percentage change in blood Phe level at Day 8 was calculated as:

$$\frac{[(\text{Day 8 blood Phe} - \text{Day 1 blood Phe})]}{\text{Day 1 blood Phe}} \times 100\%$$

Only patients with Day 1 and Day 8 blood Phe are analyzed (Analysis Population). Blood Phe results for all Responders (primary efficacy analysis) and for Responders by Day 1 blood Phe (< 600 or ≥ 600 uM) are presented.

In Responders, blood Phe was stable from Screening to Day 1 [796 uM (SD 207) vs. 806 uM (SD 315), respectively]. Overall, 96 of 485 of patients (20%; 95% CI [16%, 23%]) in the Analysis Population (AP) were Responders. From Day 1 to Day 8, Responders' mean blood Phe decreased from 806 uM (SD 315) to 415 uM (SD 235). The mean change for Responders was -392 uM (SD 185), and the mean percent change of -50% (SD 16).

For the exploratory (secondary) analysis of change in blood Phe from Day 1 to Day 8 by Day 1 (Baseline) blood Phe strata, the results showed:

- In patients with Baseline blood Phe < 600 uM, mean blood Phe decreased from 524 uM (SD 67) on Day 1 to 237 uM on Day 8. The mean change for Responders with Day 1

blood Phe <600 uM was -286 uM (SD 84) and the mean percent change was -55% (SD 17).

- In patients with Baseline blood Phe ≥ 600 uM, mean blood Phe decreased from 941 uM (SD 296) on Day 1 to 499 uM on Day 8. The mean change in blood Phe for Responders with Day 1 blood Phe ≥ 600 uM was -442 uM (SD 199), and mean percent change was -48% (SD 17).

These results are summarized in Table 44.

Table 44: Enrichment Study: Mean Blood Phe at Day 1, and Day 8; Responders Only

Blood Phe (uM)	Baseline blood Phe level (uM)		All
	<600	≥ 600	
Analysis Population, N=	57	428	485
Responders, n=	31	65	96
Day 1 Blood Phe (uM)			
Mean (SD)	524 (67)	941 (296)	806 (315)
Median	537	843	705
Percentiles (25 th , 75 th)	493, 576	702, 1089	577, 953
Min, max	345, 599	607, 1689	345, 1689
Day 8 Blood Phe (uM)			
Mean (SD)	237 (97)	499 (235)	415 (235)
Median	245	453	378
Percentiles (25 th , 75 th)	181, 309	318, 631	246, 526
Min, max	17, 395	71, 1177	17, 1177
Mean Change in Blood Phe from Baseline at Day 8 (uM)			
Mean (SD)	-286 (84)	-442 (199)	-392 (185)
Median	-271	-410	-356
Percentiles (25 th , 75 th)	-333, -215	-500, -306	-456, -273
Min, max	-480, -164	-1312, -187	-1312, -164
Mean Percent Change in Blood Phe from Baseline at Day 8 (%)			
Mean (SD)	-55 (17)	-48 (15)	-50 (16)
Median	-51	-42	-45
Percentiles (25 th , 75 th)	-66, -44	-57, -35	-59, -36
Min, max	-95, -32	-94, -30	-95, -30

Blood Phe results at Screening (not show in Table 44) are summarized as follows: The mean blood Phe in Responders (N=96) was 796 uM (SD 207), which was similar to Day 1 blood Phe 806 uM (SD 315). In Responders with Day 1 blood Phe ≥ 600 uM, mean blood Phe increased 10% from Screening to Day 1 [857 uM (SD 210) vs. 941 uM (SD 296)], respectively. For Responders with Day 1 blood Phe <600 uM, mean blood Phe decreased 21% from Screening to Day 1 [667 uM (SD 129) vs. 524 uM (SD 67)], respectively. These findings suggest that factors other than treatment with sapropterin, such as diet, affected blood Phe prior to treatment. Since the goal of this open-label, uncontrolled study was to identify individual patients for future study these changes in blood Phe from Screening to Day 1 do not invalidate Day 1 to Day 8 comparisons.

In summary, 20% (95% CI 16, 23) of patients were Responders. In Responders, mean percent change in blood Phe was -50% (SD 16, 95% CI [-47, -53]). Lack of treatment and diet control

restricts efficacy conclusions to qualification for further study in the Efficacy Study (PKU-003). In conclusion, the study succeeded in identifying a sub-population of 96 patients for further study.

10.1.1.13.5.2 Secondary Efficacy Analysis; Percentage of Patients with Day 8 blood Phe <600. 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 Table 45.

Table 45: Enrichment Study: Responders by Day 1 blood Phe <600 uM vs. ≥600 uM

Analysis Population	Day 1 Blood Phe <600 uM	Day 1 Blood Phe ≥600 uM
	n =57	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. These findings would need to be corroborated in controlled trial.

10.1.1.13.5.3 Secondary Efficacy; Change in blood Phe for the AP, and Non-Responders

This Reviewer performed an analysis of change in blood Phe from Baseline to Day 8 for the entire Analysis Population and for Non-Responders. This was done for illustrative purposes only.

Screening and Baseline blood Phe results for the ITT (N=489) and for the Analysis populations (N=485) are compared.

- Mean blood Phe at Screening for the ITT (N=489) and for Completers (N=485) were similar; 999 uM (SD 312) and 1,000 uM (SD 313), respectively.
- The four patients from the ITT who did not have Day 8 blood Phe levels all had Day 1 blood Phe ≥600 uM.
- Mean blood at Screening in the sub-population with Day 1 (Baseline) blood Phe >600 uM was similar for the ITT and the AP [1038 uM (SD 308) vs. 1040 uM SD 308); respectively].

This Reviewer concludes mean blood Phe between the ITT (N=489) and the Analysis Population (N=485) was similar. These results are summarized in Table 46.

Table 46: Enrichment Study: Mean Blood Phe at Screening; ITT and Analysis Population (AP)

Entry Blood Phe (uM)	Baseline blood Phe level (uM)		Population
	<600	≥ 600	
ITT at Screening, N	57	432	489
Mean (SD)	701 (134)	1038 (308)	999 (312)
Median	686	995	951
Percentiles (25 th , 75 th)	617, 805	791, 1238	749, 1198
Min, max	454, 1054	504, 2204	454, 2204
Analysis Population (AP) at Screening, n	57	428	485
Mean (SD)	701 (134)	1040 (308)	1000 (313)
Median	686	1002	954
Percentiles (25 th , 75 th)	617, 805	794, 1240	749, 1200
Min, max	454, 1054	504, 2204	454, 2204

Since mean blood Phe for the ITT and AP are similar, further discussions are restricted to the Analysis Population.

For the Analysis Population (N=485), Screening and Day 1 blood Phe were similar [1000 uM (SD 313) vs. 1005 uM (SD 346), respectively], and mean blood Phe decreased 10% from Day 1 to Day 8 [1005 uM (SD 346) vs. 905 uM (SD 412), respectively]. For patients with Day 1 blood Phe ≥ 600 uM, Screening and Day 1 blood Phe were similar [1040 uM (SD 308) vs. 1067 uM (SD 314), respectively], and mean blood Phe decreased 9% from Day 1 to Day 8 [1067 uM (SD 315) vs. 975 uM (SD 381), respectively]. For patients with Day 1 blood Phe < 600 uM, mean blood Phe decreased 26% from Screening to Day 1 [(701 uM (SD 134) vs. 517 (SD 84)], and mean blood Phe decreased another 26% from Day 1 to Day 8 [517 uM (SD 84) vs. 382 uM (SD 206), respectively]. These results are summarized in Table 47.

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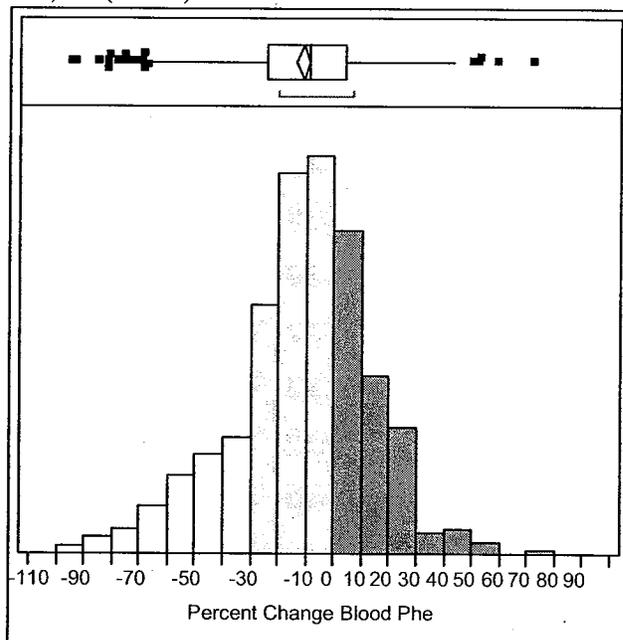
Table 47: Enrichment Study: Mean Blood Phe at Screening, Day 1, and Day 8; Analysis Population

Entry Blood Phe (uM)	Baseline blood Phe level (uM)		AP
	<600	≥600	
Analysis Population, n=	57	428	485
Screening Blood Phe (uM)			
Mean (SD)	701 (134)	1040 (308)	1000 (313)
Median	686	1002	954
Percentiles (25 th , 75 th)	617, 805	794, 1240	749, 1200
Min, max	454, 1054	504, 2204	454, 2204
Day 1 Blood Phe (uM)			
Mean (SD)	517 (84)	1067 (314)	1005 (346)
Median	537	1012	963
Percentiles (25 th , 75 th)	489, 576	821, 1286	740, 1244
Min, max	148, 599	604, 2104	148, 2104
Day 8 Blood Phe (uM)			
Mean (SD)	382 (206)	975 (381)	905 (412)
Median	332	964	897
Percentiles (25 th , 75 th)	226, 561	696, 1224	613, 1192
Min, max	17, 863	71, 2184	17, 2184
Mean Change in Blood Phe from Baseline at Day 8 (uM)			
Mean (SD)	-134 (200)	-94 (222)	-99 (220)
Median	-184	-83	-94
Percentiles (25 th , 75 th)	-289, 50	-210, 46	-215, 46
Min, max	-480, 287	-1312, 521	-1312, 521
Mean Percent Change in Blood Phe from Baseline at Day 8 (%)			
Mean (SD)	-25 (39)	-10 (23)	-11 (26)
Median	-35	-8	-9
Percentiles (25 th , 75 th)	-52, 13	-21, 4	-24, 4
Min, max	-95, 59	-94, 72	-95, 72

The changes in mean blood Phe for patients with Day 1 blood Phe <600 uM suggest that environmental changes, such as diet, may affect blood Phe. Therefore, changes in mean blood Phe in Responders described in section 10.1.1.13.5.1 may not be solely attributable to administration of sapropterin.

The changes in blood Phe for the AP are presented in Figure 8 below. The horizontal axis displays mean percent change in blood Phe from Day 1 to Day 8. Open vertical bars are Responders. Non-Responders are displayed as patients with increase in blood Phe (dark shaded bars) and patients with decrease in blood Phe <30% (light shaded bars). 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.

Figure 8: Enrichment Study: Mean Percent Change Blood Phe; AP (N=485)



This figure demonstrates that of 485 patients who completed the study, 20% (96) were Responders, 47% (230) were non-Responders with a decrease in blood Phe < 30% represented by the light shaded bars, and 33% (159) were non-Responders with an increase in blood Phe. Twelve percent (58) of patients had a decrease between 20% and 29%, 18% (87) had a decrease between 10% and 19%, and 18% (85) had a decrease in between > 0 and 9%. Fifteen percent of patients (71) had an increase in blood Phe between > 0 and 9%, 9% (42) had an increase between 10 and 19%, 6% (29) had an increase between 20 and 29%, and 4% (17) had an increase \geq 30%.

Changes in blood Phe for Non-Responders are presented below. Lack of response was defined as an increase in blood Phe, or a <30% decrease in blood Phe from Day 1 to Day 8.

For Non-Responders, Screening, Day 1 (Baseline), and Day 8 blood Phe were similar; 1,051 uM (SD 314), 1054 uM (SD 336), and 1,027 uM (SD 352), respectively. In non-Responders with Baseline blood Phe \geq 600 uM, mean blood Phe at Screening, Day 1 and Day 8 were 1073 uM (SD312), 1093 uM (SD 312), and 1061 uM (SD 337), respectively. In non-Responders with Baseline blood Phe <600 uM, mean blood Phe at Screening, Day 1 and Day 8 were 741 uM (SD 130), 508 uM (SD 101), and 555 uM (SD 164), respectively. Changes in blood Phe from Screening to Day 1 in patients with blood Phe < 600 uM at Day 1 are likely due to environmental factors such as diet. These findings are summarized in Table 48.

Table 48: Enrichment Study: Mean Blood Phe at Day 1, and Day 8; Non-Responders

Entry Blood Phe (uM)	Baseline blood Phe level (uM)		AP
	<600	≥600	
Analysis Population, n=	57	428	485
Non-Responders, n=	26	363	389
Screening Blood Phe (uM)			
Mean (SD)	741 (130)	1073 (312)	1051 (314)
Median	743	1038	1016
Percentiles (25 th , 75 th)	651, 848	828, 1264	800, 1248
Min, max	454, 1054	504, 2204	454, 2204
Day 1 Blood Phe (uM)			
Mean (SD)	508 (101)	1093 (312)	1054 (336)
Median	543	1046	1009
Percentiles (25 th , 75 th)	442, 577	846, 1330	807, 1290
Min, max	148, 594	604, 2104	148, 2104
Day 8 Blood Phe (uM)			
Mean (SD)	555 (164)	1061 (337)	1027 (352)
Median	573	1034	1009
Percentiles (25 th , 75 th)	439, 674	788, 1272	765, 1246
Min, max	184, 863	442, 2184	184, 2184
Mean Change in Blood Phe from Baseline at Day 8 (uM)			
Day 8 - Day 1 (n)			
Mean (SD)	47 (135)	-32 (160)	-27 (159)
Median	70	-52	46
Percentiles (25 th , 75 th)	-73, 146	-150, 65	-147, 77
Min, max	-163, 287	-387, 521	-387, 521
Mean Percent Change in Blood Phe from Baseline at Day 8 (%)			
Day 8 - Day 1 (n)			
Mean (SD)	10 (27)	-3 (16)	-2 (17)
Median	15	-5	-4
Percentiles (25 th , 75 th)	-16, 26	-15, 6	-15, 7
Min, max	-29, 59	-29, 72	-29, 72

In summary, there was no meaningful change mean in blood Phe from Screening to Day 1, from Screening to Day 8, or from Day 1 to Day 8 for all Non-Responders or for patients with Day 1 blood Phe ≥ 600 uM. For patients with Day 1 blood Phe < 600 uM, blood Phe increased 10% (SD 27) between Day 1 and Day 8. In conclusion, 389 patients (80% of 485) failed to achieve a greater than 30% decrease in blood Phe from Baseline to Day 8 and were classified as non-Responders. Lack of diet control may have affected results.

10.1.1.13.5.4 Efficacy Summary

This was an open-label, uncontrolled study of patients with PKU ages 8 to 48 years, treated with sapropterin 10 mg/kg/day for eight days. The Analysis Populations was comprised of 485 patients who receive ≥ 1 dose and had Day 1 and Day 8 blood Phe levels.

- 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

- Mean percent change in Responders was -50% (SD 16, 95% CI [-47, -53]).
- Mean change in blood Phe in Responders was -392 uM (SD 185).
- Noteworthy secondary (exploratory) analyses are summarize as follows:
 - Fifty-four percent (95% CI [41, 68]) of patients with Day 1 blood Phe <600 uM were Responders compared to 15% (95% CI 12, 19)] of patients with Day 1 blood Phe ≥600 uM. This suggests the likelihood of response may be related to pre-treatment blood Phe level.

These data suggest a subset of patients with PKU may respond to sapropterin. Changes in blood Phe between screening and Baseline suggest dietary effect can not be ruled out, and since diet and drug treatment were not controlled, these data should not be relied upon to demonstrate efficacy. Controlled studies are required confirm these findings.

This Reviewer concludes the Sponsor successfully identified patients for study in the Efficacy Study.

10.1.1.14 Review of Safety

Safety was assessed by types and incidence of Adverse Events (AEs), discontinuations due to AEs, and drug-related, serious and severe AEs, and changes from baseline in physical exams, vital signs, clinical laboratory assessments including clinical chemistry, hematology, and urinalyses. Safety information was collected from screening through completion of all study procedures at the Day 36 follow up. Deaths and Serious AEs were reported from obtaining consent through the Day 36 follow-up. Non-serious AEs were reported from the time of first dose at Day 1 through completion of the Day 36 follow-up. Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT).

10.1.1.14.1 Exposure

The safety population included 489 patients who received ≥1 doses of sapropterin. The last patient completed follow-up on 31-October-2005.

Mean daily dose was 10.8 (SD 0.6) mg/kg/day, and mean exposure was 8 (SD 0.5) days. Fifteen patients received nine days, and two additional patients received treatment for eleven days. The study report does not indicate why 17 patients had greater than eight days of exposure.

10.1.1.14.2 Adverse Events

AEs are reported from administration of first dose on Day 1 through completion of Day 36 study procedures. Recurrent or continuing AEs were counted only once. AE incidence rates were calculated using all patients who received at least one dose of study medication as the denominator (n=489). AEs were tabulated and analyzed using the aedata.xpt dataset (section 5.3.5.2.25.3.1 of the electronic submission).

Forty-eight percent (233 of 489) patients reported from 1 to 14 AEs. The most commonly reported AEs by MedDRA System, Organ, Class term were Gastrointestinal Disorders, Nervous System Disorders, and Infections and Infestations. The most common AEs by MedDRA preferred term were headache (10%) diarrhea (5%), abdominal pain (5%), and nausea, upper respiratory tract infections and fatigue (3% each). These AEs represent common complaints in the general population and in otherwise healthy patients with PKU. AEs occurring in >2% of patients are summarized in Table 49.

Table 49: Enrichment Study: Non-Serious AEs in > 2% of Patients

System, Organ, Class Term	Preferred Term	N = 489 n (%)
Gastrointestinal disorders	Abdominal pain, upper, lower, not specified	28 (6)
	Diarrhea	24 (5)
	Nausea	16 (3)
	Flatulence	11 (2)
	Vomiting	9 (2)
General disorders and administration site conditions	Fatigue	14 (3)
Infections and infestations	Upper respiratory tract infection	17 (3)
Metabolism and nutrition disorders	Decreased appetite	8 (2)
Nervous system disorders	Headache	50 (10)
	Hyperreflexia	10 (2)
	Tremor	9 (2)
Respiratory, Thoracic, and Mediastinal Disorders System	Pharyngolaryngeal pain	9 (2)
Skin and subcutaneous tissue disorders	Rash ¹	8 (2)
Any AE		233 (48)

¹ Includes one patient with erythema multiforme.

The above findings suggest that adverse events associated with sapropterin over an eight day period is similar to and not readily distinguishable from common complaints in the general population. The findings are limited by open-label dosing non-placebo-controlled dosing, and a short study period.

A discussion of neutropenia, which occurred in seven (1%) of patients, follows in section 10.1.1.14.7 of this review.

10.1.1.14.3 Reports of Deaths and SAEs

No deaths were reported.

One SAE occurred during the study. Patient 0132-0007, a 14 year old female, developed acute appendicitis 15 days after administration of the final dose of study drug. The event was judged as not causally related to administration of the study drug. The CRF was reviewed in this Reviewer agrees.

Patient 0121-0021, a 24 year old woman who had been amenorrheic, for one year conceived during the study. The CRF states all doses of the study drug were administered. The patient had a documented negative urine pregnancy screen on [REDACTED] (initial screening) and on [REDACTED] (day one of drug administration). The pregnancy was reported on 36-day follow-up. The estimated date of conception was [REDACTED]. The pregnancy screen result of [REDACTED] was judged false negative. The pregnancy continued. No further information is available.

10.1.1.14.4 Withdrawals

Five patients withdrew after receiving ≥ 1 dose of sapropterin. One patient withdrew on Day 1 after receiving one dose. One patient did not complete Day 8 study procedures and the number of doses received is unknown. Three patients received eight daily doses and completed Day 8 study procedures but did not complete Day 36 follow-up procedures. These findings are summarized in Table 50.

Table 50: Withdrawals; Enrichment Study

Patient	Age years Gender (M/F)	Reason	Dose	Comment
0118-0009	23 y, F	Pregnancy diagnosed Day 1	1	Major protocol violation; not included in ITT or Analysis Population
0119-0001	27 y F	No Day 8 Visit	Unknown	Non-compliant; No AE, laboratory, or vital sign abnormality
0120-0009	35 y, M	No Day 36 Visit	8	No AE, laboratory, or vital sign abnormality
0120-0011	23 y, F	No Day 36 Visit	8	No AE, laboratory, or vital sign abnormality
0123-0023	33 y, F	No Day 36 Visit	8	No AE, laboratory, or vital sign abnormality

Patient 0118-0009, 23 year old woman withdrew due to pregnancy diagnosed on the first day. The AE dataset indicates the patient did not receive sapropterin. The study report, the CRF, and the ex.xpt dataset indicate the patient received one dose of sapropterin. This Reviewer concludes this patient received one dose. The CRF states the pregnancy occurred during use of birth control and the pregnancy was electively terminated. The Reviewer concludes the relationship of the pregnancy termination and withdrawal to receipt of sapropterin is undetermined.

10.1.1.14.5 Other Notable Adverse Events

Patient 0112-0017, a 13 year old boy, had angina pectoris reported two days prior to the Day 36 follow-up. The event was judged non-serious and of moderate severity. No details other than angina and treatment with “effergan” were documented on the case report form. The CRF was reviewed and no other information is available. This Reviewer can not determine the nature of the complaint or the relationship to sapropterin.

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. The event was contemporaneous with a urinary tract infection and administration of trimethoprim-sulfamethoxazole, which has a known association with erythema multiforme. The erythema

multiforme remitted within five days. Trimethoprim and other sulfa-based antibiotics are a recognized cause of erythema multiforme. This Reviewer concludes the event was possibly related to administration of the study drug.

Clinically meaningful laboratory findings, including seven patients with neutropenia are discussed in section 10.1.1.14.7.

10.1.1.14.6 Vital signs

Vital signs were reviewed. Clinically meaningful vital sign abnormalities that qualified as AEs are included in the AE datasets and are reported in the AE tables. There were no notable changes in means, percentiles, and ranges for vital signs (weight, sitting systolic blood pressure, sitting diastolic blood pressure, heart rate, respiratory rate, and oral temperature) between Screening, Day 1, Day 8, and Day 36 (data not shown).

10.1.1.14.7 Laboratory Analyses

The entire clinical laboratory dataset was reviewed including all hematological, biochemical, and urinary parameters. Additionally, the AE dataset was reviewed for clinical and laboratory abnormalities that qualified as AEs; discussion of which are included AE tables. Notable findings are summarized below.

Seven patients had absolute neutropenia (ANC <1,500), one instance of which was reported in the AE dataset. The remaining six patients with neutropenia were found on analysis of the clinical laboratory dataset.

Patients with neutropenia are described in table 51 below. The table also includes patients with neutropenia reported in Efficacy Study and Extension Study, which enrolled patients from the Enrichment Study. The table identifies each patient with neutropenia, their Baseline ANC, their lowest ANC, their highest ANC, their final ANC, and the relationship of the ANC to sapropterin (sapropterin or placebo in the Efficacy Study), and if neutropenia resolved while the patient was still receiving sapropterin. Drug indicates sapropterin.

Table 51: All Instances of Absolute Neutropenia (ANC ≤ 1,500) in the PKU Population								
Patient	Age, Gender	Baseline	Nadir on Drug	Peak on Drug	Final ANC	Resolved on Drug (Y/N)	Occurrence, OL or DB	If DB Drug or Placebo
Enrichment, Efficacy, Extension Studies								
0121-0011	18, M	960 ¹	500 ¹	1,460 ³	950 ³	N	OL, DB	Drug
0123-0016	41, M	3,970 ¹	570 ¹	5,020 ²	4,380 ²	Y	OL	Drug
0124-0007	41, F	2,890 ¹	970 ¹	—	970 ¹	N	OL	—
0113-0024	10, F	2,390 ¹	1,010 ³	4,170 ³	1,250 ³	N	DB	Drug
0124-0006	20, F	1,470 ¹	1,200 ¹	—	1,200 ¹	N	OL	—
0113-0006	26, M	1,810 ¹	1,350 ¹	—	1,350 ¹	N	OL	—
0124-0001	11, M	5,130 ¹	1,420 ¹	—	1,420 ¹	N	OL	—
0018-0003	9, M	3,690 ¹	1,430 ¹	—	1,430 ¹	N	OL	—
0115-0016	12, F	1,770 ¹	1,480 ³	3,250 ³	3,250 ³	Y	DB	Drug
0109-0024	12, F	2,020 ¹	1,160 ²	2,190 ²	2,500 ³	Y	DB	Placebo
¹ Enrichment Study; open-label (OL), uncontrolled ² Efficacy Study; randomized, double-blind (DB), placebo-controlled (PC) ³ Extension Study; OL, uncontrolled ⁴ Diet Study; Part I OL, uncontrolled; Part II randomized, DB, PC * ANC not recorded — Did not participate in double-blind treatment								

For the purposes of the descriptions below, neutropenia is classified as severe (ANC ≤500), moderate (ANC >500 and ≤1,000) or mild (ANC >1,000 and ≤1,500).

- Patient 0121-0011, an 18 year old male, had an absolute neutrophil count (ANC) of 1,090 (x10⁹/L) at Screening, 960 at Baseline, 500 at Day 8 (severe neutropenia), and no result at Day 36. The ANC increased to 1,460 during drug treatment in the Extension study, but decreased again to 950 at the end of the Extension Study. This patient had a white blood cell (WBC) count of 3.1 at Screening, 2.8 at Baseline, and 2.1 at Day 8. There were no other hematological abnormalities. No concomitant AEs were reported.
- Patient 0123-0016, a 41 year old male, had an ANC of 4,270 (x10⁹/L) at Screening, 3,970 at Baseline, 570 at Day 8, and 3,750 at Day 36. This is the only instant of neutropenia reported in the AE dataset. This patient had a WBC count of 5.8 at Screening, 5.5 at Baseline, 2.3 at Day 8, and 2.3 at Day 36. No concomitant hematological abnormalities or AEs were reported.
- Patient 0124-0007, a 41 year old woman, had an ANC of 2,890 (x10⁹/L) at Screening, no result listed at Baseline, and an ANC of 970 Day 8. This patient had a WBC count of 5.4 at Screening, 4.3 at Baseline, and 3.3 at Day 8. There were no other hematological abnormalities and no AEs were reported.
- Patient 0124-0001, an 11 year old male, had an ANC of 2,150 (x10⁹/L) at Screening, 5,310 at Day 1, and 1,420 at Day 8. This patient had a WBC count of 4.1 at Screening, 7 at Baseline, and 3.6 at Day 8. There were no other hematological abnormalities.

Concomitant AEs include recurrent bronchitis, otitis media, respiratory symptoms and heartburn.

- Patient 0124-0006, a 20 year old female, had an ANC of 2,770 ($\times 10^9/L$) at Screening, 1,470 at Baseline, and 1,200 at Day 8. This patient had a WBC count of 5 at Screening, 2.5 at Baseline, and 3.2 at Day 8. No concomitant hematological abnormalities or AEs were reported.
- Patient 0113-0006, a 26 year old male, had an ANC of 2,390 ($\times 10^9/L$) at Screening, 1,810 at Baseline, and 1,350 at Day 8. This patient had low normal lymphocytes at Screening and at Baseline ($990 \times 10^9/L$), and had lymphopenia at Day 8 with an absolute lymphocyte count of $540 \times 10^9/L$. This patient had a WBC count of 3.7 at Screening, 3.1 at Baseline, and 2.3 at Day 8. There were no other hematological abnormalities. Concomitant AEs include loss of appetite, increase temperature to around 100 F, and shivering. This patient did not participate in any other study.
- Patient 0018-0003, a nine year old male, had an ANC of 7,070 ($\times 10^9/L$) at Screening, 3,690 at Baseline, and 1,430 at Day 8 (mild neutropenia). There were no concomitant hematological abnormalities or AEs. The patient did not participate in subsequent studies.
- Of three patients who had neutropenia in the Efficacy or Extension Study, patients 0109-0024, 0113-0024, and 0115-0016 had a normal ANCs (>1500) in the Enrichment Study, but had ANCs between 1,010 to 1,480 in the Efficacy and Extension Study. Final ANCs for these patients at the end of the Extension Study was between 1,250 and 3,250. AEs in patient 0109-0024 around the time of neutropenia included constipation and an upper respiratory tract infection. AEs in patient 0113-0024 around the time of neutropenia included Fifth disease and exanthema. AEs in patient 0115-0016 around the time of neutropenia included: abdominal pain, vomiting, dysmenorrhea, lower respiratory tract infection, lymphadenopathy, pharyngo-laryngeal pain, urinary tract infection, vomiting and decreased white blood cell count.

The clinical significance of neutropenia is unclear. Although concomitant AEs were described in several patients with neutropenia, a causal relationship between administration of sapropterin and neutropenia can not be dismissed. As shown in Table 51, neutropenia occurred in 14 patients during treatment with open-label or double-blind treatment with sapropterin. This Reviewer recommends neutropenia be addressed in labeling.

Two patients had thrombocytopenia. Each instance of thrombocytopenia was documented in the AE dataset and the clinical laboratory dataset.

- Patient 0015-011, a 15 year old female, had platelet counts of 184 ($\times 10^9/L$) at Screening, 139 at Baseline, 80 at Day 8, and 158 at Day 36. No other clinically relevant hematological abnormalities were found. This patient participated in both the Efficacy and Extension Studies. Her platelet count was 101 at the start of the Efficacy Study and

increased to 150 during the Extension Study. One other AE, upper respiratory tract infection, was reported. This Reviewer does not believe the low platelet count in the Enrichment Study was due to sapropterin treatment.

- Patient 0102-0007, a 44 year old female, had platelet counts of 342 ($\times 10^9/L$) at Screening, 315 at Baseline, 307 \times at Day 8, 40 \times at Day 36, and 321 \times 1 six months later. The Day 36 sample was documented as clotted. AEs reported in this patient include thrombocytopenia, increased blood cholesterol, and a thermal. The Reviewer concludes this finding is an artifact, and not due to sapropterin.

A central lab was not used for chemistry and hematological tests and reference values varied by laboratory site. There were no clinically meaningful changes in mean, standard deviation, coefficient of variation, and 95th percentile distribution. Review of the individual patient laboratory data was notable for the following:

- Ten patients had clinically significant increases in AST, ALT, or both. In 80% of patients with elevations in AST, ALT, or both, these enzymes were above the ULN at Baseline.
 - Patients (0125-0022, 0130-0022, 0013-0022, 0113-0024, 0123-0020, 0019-0004, 0116-0006, 0010-0015, 0102-0017, and 0010-003) had clinically meaningful changes in AST.
 - Patients (0123-0020, 0123-0024, and 0130-0022) had clinically significant increases in ALT that were not present at Screening or Day 1.
- One patient with normal Screening and Baseline GGT had an increase in GGT at Day 8, which returned to normal by Day 36.

Age and gender of patients with liver function abnormalities were approximately evenly distributed. The clinical significance of these findings is unclear due to the lack of a placebo control, the frequency of Screening and Baseline alterations in liver function, and the common finding of altered liver function in patients with PKU. There were no notable trends or abnormalities identified in liver enzymes in controlled trials (i.e., the Efficacy or Diet Trials).

10.1.1.14.8 Safety Summary

The safety results from the Enrichment Study show the following:

1. AEs were frequently reported, and 48% of patients reported at least one AE. Most AEs were mild to moderate in severity, were self-limited, and were consistent with common complaints reported in otherwise healthy individuals (such as headache). By AE preferred term, the most commonly reported AEs by incidence rate were headache (10%), diarrhea (5%), and abdominal pain (5%).
2. No Deaths were reported. One SAE, appendicitis, occurred 15 days after exposure ended. Other notable AEs in this study included one report of erythema multiforme in a patient with a UTI treated with trimethoprim-sulfamethoxazole.

3. Summary clinical laboratory findings include the following:
 - a. Neutropenia was reported in 1% of patients (one severe, two moderate, and four mild cases). Six of the patients with neutropenia also had mild to moderate leucopenia with or without associated lymphopenia. In two of these patients fever or infections were documented.
 - b. Increased ALT, or AST, or both, in 1% of patients, 80% of whom had elevations at Baseline.
 - c. One patient with mild to moderate thrombocytopenia who had normal platelet counts in subsequent studies.
4. No notable trends in vital signs were found.

While most AEs were mild to moderate in severity, self-limited, and were representative of common complaints in otherwise healthy individuals, important limitations of the study include the short duration (eight days), the lack of placebo control, and the open-label study design. The placebo controlled studies (PKU-003 and PKU-006) will be reviewed with special attention to liver function abnormalities, neutropenia, and erythema multiforme.

10.1.1.15 Overall Summary of the Enrichment Study (PKU-001)

The primary efficacy goal was achieved.

- Ninety-six patients (20%, 95% CI 16%, 23%) treated with sapropterin had a greater than 30% decrease in blood Phe at Day 8 from Baseline, and qualified for enrollment in the Efficacy Study (PKU-003).
- In Responders, mean change in blood Phe was -50% (SD 16, 95% CI -47, -53).

These data suggest a subset of patients with PKU and elevated blood Phe may respond to Sapropterin.

Secondary analyses show that 54% of 57 patients with Day 1 blood <600 uM, were Responders (95% CI 41, 68) and 15% of 428 patients with Day 1 blood Phe \geq 600 uM were Responders (95% CI 12, 19). Responder status may be related to pre-treatment blood Phe.

Diet effect can not be ruled out. Confirmatory studies incorporating placebo are required. Confirmatory studies incorporating some form of dietary control are required.

The safety results from the Enrichment Study show the following:

- AEs were frequently reported, and 48% of patients reported at least one AE. Most AEs were mild to moderate in severity, were self-limited, and were consistent with common complaints reported in otherwise healthy individuals (such as headache). By AE

preferred term, the most commonly reported AEs by incidence rate were headache (10%), diarrhea (5%), and abdominal pain (5%).

- No Deaths were reported. One SAE, appendicitis, occurred 15 days after exposure ended. Other notable AEs in this study included one report of erythema multiforme in a patient with a UTI treated with trimethoprim-sulfamethoxazole.
- Clinical laboratory abnormalities included:
 - Increased ALT, or AST, or both, in 1% of patients, 80% of whom had elevations at Baseline.
 - Neutropenia was reported in 1% of patients (one severe, two moderate, and four mild cases). Six of the patients with neutropenia also had mild to moderate leucopenia with or without associated lymphopenia. In two of these patients, fever or infections were documented.
- No notable trends in vital signs were found.

While most AEs were mild to moderate in severity, self-limited, and were representative of common complaints in otherwise healthy individuals, important limitations to the study include short duration (eight days), lack of placebo control, and open-label study design.

The placebo controlled Efficacy and Diet Studies were reviewed with special attention to erythema multiforme, liver function abnormalities, and neutropenia. There were no other reports of erythema multiforme, and there were no notable trends in liver enzymes (AST, ALT, or GGT). Neutropenia was noted in 3% of 579 patients in the Enrichment, Efficacy, Extension and Diet Studies. These patients represent the entire PKU population exposed to sapropterin. The risk of neutropenia is to be addressed prominently in labeling.

10.1.2 Efficacy Study (PKU-003)

Study Title: “A Phase 3, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Phenoptin (sapropterin dihydrochloride) in subjects with Phenylketonuria who have elevated phenylalanine levels.”

10.1.2.1 Study Design

The Efficacy Study (PKU-003), was a Phase 3, 10 week, multi-center, randomized, double-blind (DB), placebo-controlled (PC) trial 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. Treatments were oral sapropterin (10 mg/kg/day) or placebo for six weeks. Patients must have been Responders in the Enrichment Study (PKU-001). Response in the Enrichment Study was defined as a $\geq 30\%$ in decrease in blood Phe from Day 1 (Baseline) to Day

8 of open-label, uncontrolled, sapropterin treatment. The Enrichment Study is discussed in Appendix 10.1 of this review.

In the Efficacy Study, the efficacy measure was the change in blood Phe level from Baseline to Week 6. Baseline blood Phe levels were calculated as the mean of the pre-treatment measurements taken at three pre-treatment visits: Visit 1, Visit 2, and Week 0. The Week 0 blood Phe sample was collected immediately prior to 1:1 randomization and first dose of sapropterin (10 mg/kg/day in one daily dose). Eighty-nine patients were screened and 88 patients entered the randomized phase (ITT, N=88).

Treatment period Blood Phe samples were collected at Weeks 1, 2, 4, and 6 or upon early withdrawal. Change in blood Phe for each patient was defined as [Week X blood Phe – Baseline blood Phe], where X is Week 1, 2, 4, or 6.

An important limitation of this study that could have affected the overall study results was the lack of dietary control during the study. Although patients/caregivers were instructed not to change their diet from Screening through completion of the study, blood Phe in patients with PKU is dependant on dietary protein load, and blood Phe in these patients changes rapidly due to meal-to-meal and day-to-day changes in dietary protein load. Therefore, changes in dietary protein load (up or down) could have resulted in the incorrect identification of both responders and non-responders that were due to diet, rather than sapropterin.

After six weeks of treatment, patients who took $\geq 80\%$ of scheduled doses were eligible for enrollment in an open-label, long-term study [PKU-004]. Patients who did not transition into PKU-004 were followed for four additional weeks.

Consent for the first patient was signed on 26-March-2005, and the final safety assessment was performed on 15-February-2006.

10.1.2.2 Study Objectives

The objectives were 1) to evaluate the efficacy, reduction of blood Phe, over six weeks of treatment and 2) to evaluate safety over six weeks of treatment with an additional safety assessment at the end of week ten.

Safety objectives included collection of deaths, SAEs from first Screening visit through the four week follow-up period at Week 10. AEs, changes in vitals signs, and changes in clinical laboratory parameters were monitored from first dose through final study visit at week 10.

10.1.2.3 Eligibility Criteria

To be eligible for the study, patients must have had PKU, had a Screening blood Phe ≥ 600 μM (initial protocol inclusion criterion) or ≥ 450 μM (after protocol Amendment 2), and must have been eight years or older. Patients must have received seven of eight doses during the

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Kuvan™ (sapropterin, 6R-BH4)

Enrichment Study, 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.

Notable exclusion criteria included: diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, blood alanine amino-transferase (ALT) > 5 times the upper limit of normal (ULN), or any serious illness not under medical control.

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

10.1.2.4 Prior, 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.

10.1.2.5 Study Visits and Procedures

All visits and procedures occurred within two days of the scheduled visit. Baseline 1 and 2 blood Phe samples were to be drawn at least one week apart, and within one month of the Week 0 blood Phe sample. Blood samples for Blood Phe at Week 0 were collected prior to the first dose of sapropterin or placebo. Clinical laboratory tests, including general chemistry and hematology tests, urinalyses, and blood Phe at subsequent visits, were collected 2½ to five hours after breakfast, preferably around the same time of day. Breakfast was defined as any food and/or beverage normally eaten before 12:00 noon. At Week 6, patients who ingested $\geq 80\%$ (or ≥ 7 of 8 doses) of treatment doses were eligible for enrollment in the Extension Study (PKU-004). Study procedures for the Efficacy Study are described in Table 52.

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Table 52: Efficacy Study: Schedule of Events

Procedure	Screening	Baseline (Bsl)		Double-Blind Treatment					Follow-up ¹
		Bsl 1 [Wk-2]	Bsl 2 [Wk-1]	Wk 0	Wk 1	Wk 2	Wk 4	Wk 6	Wk 10
Informed consent	X								
History	X								
Randomization				X					
Vitals	X	X	X	X	X	X	X	X	X
Physical Exam	X			X				X	X
General Lab Tests	X			X				X	X
ALT, AST, total Bilirubin							X		X
T4 and TSH				X				X	X
Pregnancy test	X			X				X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	
Blood Phe	X	X	X	X	X	X	X	X	
Dispense drug/placebo				X	X	X	X		

^a Follow-up by phone. If there were abnormal vital signs, physical exam, or clinical laboratory tests at Wk 6, then clinic visit.

10.1.2.6 Randomization, Blinding and Controls

This was a randomized, double-blind, placebo-controlled trial.

Blinding was achieved by designing the placebo to be similar in appearance, solubility, and labeling, and by third party randomization assignment. Interim or emergency unblinding was not required.

Randomization was stratified by study site and screening visit blood Phe level, initially <1200 versus ≥1200 uM, and after Protocol Amendment 2, <600 versus ≥600 uM. The Sponsor states this change was made because tests of executive and higher cognitive function show improvement when blood Phe is ≤600 uM. The lower blood Phe level is in concert with NIH treatment guidelines for PKU published in 2000.³

A third party statistical consultant used a computer program to generate randomization lists. BioMarin and individual investigators were blinded to treatment assignment. Patients enrolled from prior study PKU-001 retained their unique subject identification numbers from that study.

Diet was not controlled; see section 10.1.2.8 below.

10.1.2.7 Study Medication Dose Selection, Dispensing, and Compliance

Patients were randomly assigned to receive either 10 mg/kg/day of sapropterin or placebo. Dose was fixed and was calculated by multiplying each patient's weight in kilograms by 10 and rounding up to the next 100 mg unit dose tablet. For example, a 50 kg patient would take 500 mg/day = 5 x 100 mg unit dose tablets/day = 10 mg/kg/day; a 37 kg patient would take 400 mg/day = 4 x 100 mg unit dose tablets/day = 11 mg/kg/day.

Patients received once daily doses of either sapropterin, as tablets containing 100 mg of the active ingredient, or similar appearing placebo. The first dose was taken under direct observation at the completion of the Week 0 visit. Subsequent doses were taken in the morning as the number of tablets equivalent to 10 mg/kg body weight. If patients missed a scheduled morning dose, it could be taken later up until 12 hours before the next scheduled morning dose. Patients were allowed to take the study drug in the fed or fasted state. Patients were to dissolve study drug tablets in four to eight ounces of water, apple juice, or orange juice and gently mix. They were instructed to ingest the entire solution within 15 minutes of dissolving the tablets.

Compliance was assessed by reconciliation of the used and unused sapropterin tablets. The quantity dispensed, returned, used, or lost was recorded in a dispensing log.

10.1.2.8 Diet

Diet was not controlled. The study enrolled patients with PKU who had a >30% reduction in blood Phe in the Enrichment Study who were not following Phe restricted diets. Diet was not Phe-restricted in the Enrichment Study. Patients and caregivers were instructed not to alter dietary Phe intake in the current study from Screening through completion of all study procedure. Diet was monitored by review of patients/caregiver diaries. However, diet was not controlled through the provision of quantified meals; therefore, dietary Phe could have increased or decreased.

Results may be affected. The use of the mean of three blood Phe levels, at least one week apart and within four weeks of the start of treatment, to establish baseline may minimize day to day fluctuations in dietary and blood Phe. This Reviewer concludes this approach is reasonable.

10.1.2.9 Efficacy and Endpoint Measures

10.1.2.9.1 Primary Efficacy Measures

The primary efficacy endpoint is the mean change in blood Phe from Baseline to Week 6 Phe in the sapropterin vs. placebo treated groups. Each patient's Baseline blood Phe is defined as the mean of available blood Phe values at Visits -1, -2, and Week 0 prior to administration of first dose.

10.1.2.9.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint was to evaluate mean change in blood Phe levels over six weeks of treatment, and to determine the proportion of patients with blood Phe levels <600 uM at Weeks 1, 2, and 4.

10.1.2.9.3 Safety Assessments

Safety assessments included Baseline and interval medical history and physical, vital sign and clinical laboratory assessments.

AEs were defined as any untoward medical occurrence in a patient irrespective of causal relationship between the events and the study treatment. This definition included intercurrent illnesses or injuries, and exacerbation (increase in frequency, severity or specificity) of pre-existing conditions.

The reporting period for SAEs began with time of consent. The reporting period for AEs began with the first administration of study drug. If AEs were not resolved at the end of week 10, they were monitored until resolution (i.e., upper respiratory tract infection or laboratory abnormalities). In the case of suspected chronic AEs, AEs were monitored until a cause was identified. If AEs were unresolved at the conclusion of the study, the clinical investigator and Medical Monitor were to make a clinical assessment as to whether continued follow-up was warranted, and to document results.

For patients continuing into the open-label long-term Extension study (PKU-004), the safety reporting period ended with the signing of informed consent for PKU-004. The safety reporting period ended at the Week 10 visit.

Patients could be removed during for the following blood Phe elevations:

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

10.1.2.9.4 PK and PD Measures

Pharmacokinetic analyses were not part of this trial.

Blood Phe is a pharmacodynamic measure and was measured as a primary efficacy endpoint.

10.1.2.10 Additional Statistical Considerations

The sponsor states an assumption of a mean difference between placebo and Sapropterin of 150 uM, with two-sided Type I error rate of 0.05 and a sample size of 80 randomized patients (40 in each group) would provide > 95% power to detect a difference in mean blood Phe level between placebo and sapropterin groups.

The primary efficacy analysis was evaluated using ANCOVA. The results of the primary efficacy analysis, (sapropterin group minus placebo group) mean change at Week 6 from Baseline, are presented as least squared means and standard error or means. Missing values were accounted for using a Last Observation Carried Forward (LCOF method). Personal communication with the FDA statistician, Stella Grosser PhD, indicates the statistical design is acceptable. Therefore, the ITT includes 88 patients who had a Baseline Phe recorder, who received one or more doses and who had at least one blood Phe measurement reported at Visit 1, 2, 4, 5, or 6.

10.1.2.11 Protocol Amendment

Consent for the first patient was signed on 26 March 2005 and the final dose was given on 19 January 2006.

There were two protocol amendments.

Amendment 1, dated 8-December-2004, prior to first patient enrollment was notable for the following:

- Changed the statistical analysis for the primary endpoint from a longitudinal model to an analysis of covariance model using the LOCF approach.
 - This method of handling of missing data is acceptable.
- Added age-specific details to the criteria for removal of patients from the study due to elevated Phe levels, discussed in section 10.1.2.9.3 of this review.
 - This modification increases patient safety but should not affect efficacy analyses.
- The study was shortened from twelve to six weeks and the statistical plan was modified from being able to detect a 200 uM difference in mean change between groups at Week 12 to detecting a 200 uM difference in mean change at Week 6 between sapropterin- and placebo-treated groups. The statistical modification also changed the secondary endpoint from “evaluating sustained reduction in Phe levels” to assessing the mean change in weekly blood Phe levels during the 6 weeks of treatment. This modification is acceptable.
- New secondary efficacy endpoint added: proportion of subjects with blood Phe <600uM at Week 6; prior endpoint was the proportion of patients with blood Phe <600 uM at five of seven visits for Weeks 1, 2, 4, 6, 8, 10, and 12.

- The Clinical Pharmacology review (Hae-Young Ahn, PhD) indicates the half-life of sapropterin is approximately four to six hours, and the biological effect is approximately 24 hours. Therefore, shortening treatment period from twelve to six weeks and the modification of the statistical plan should not affect determination of the primary efficacy endpoint. The modification of the secondary efficacy outcomes but should not affect the new primary efficacy endpoint.
- Miscellaneous administrative changes, including increased number of study sites to accelerate patient accrual.

This Reviewer concludes for the reasons stated above, these changes should not invalidate primary affect efficacy analyses. The new secondary endpoints are reasonable short term efficacy goals.

Amendment 2, 28-June-2005, was notable for the following:

- Reduced the blood Phe level for entry from ≥ 600 uM to ≥ 450 uM.
 - The Sponsor states this was done to allow patients with screening blood Phe as low as 450 uM to enroll, in order to enroll patients more likely to respond.
 - Literature is conflicted regarding potential correlations between BH4-responsiveness and non-treatment blood Phe level. The inclusion of patients with lower Baseline Phe should not affect primary or secondary efficacy analyses, and study of these patients is reasonable.
- Changed the planned number of patients in the study from 100, to a range of 80 to 100, and changed the efficacy goal of detecting a 200 uM difference in mean change in blood Phe between sapropterin- and placebo-treated groups to detecting a difference in mean change in blood Phe between sapropterin- and placebo-treated patients.
 - Review of the statistical plan indicated that 80 patients would not be sufficient to detect a difference in mean change of blood Phe of 200 uM between groups.
 - The change in study population is acceptable.
 - Changing the efficacy goal to simply detecting a difference in mean change in blood Phe between groups was inappropriate. The study may not be invalidated if the difference in mean change in blood Phe between groups is clinically meaningful.
- Changed the stratification for randomization from blood Phe levels of < 1200 uM and ≥ 1200 uM to blood Phe levels of < 600 /L and ≥ 600 uM.
 - This is in concert with NIH treatment guidelines for PKU published in 2000 and is clinically acceptable.³
- Miscellaneous administrative changes.

For the reasons stated above, this Reviewer feels these amendments should not invalidate primary affect efficacy analyses. The new secondary endpoints are reasonable.

10.1.2.12 Study Conduct

Section 5.2 of the study report states the study was conducted in accordance with US Code of Federal Regulations (CFR) sections that address clinical research studies, and/or other national and local regulations, as applicable; E6 International Conference on Harmonization [E6 ICH] Guideline for Good Clinical Practice (May 1996); and the Declaration of Helsinki (52nd WMA General Assembly, Edinburgh, October 2000, with clarification on Paragraph 29 by 53rd WMA General Assembly, Washington, October 2000).

The Sponsor certifies that no debarred investigators participated in this study, and that each investigator provided an FDA Form 1572 and a Financial Disclosure Form. Sub-investigators were listed on FDA Form 1572. No financial interests were reported.

Section 9.3.3 of the study report indicates a Data Safety Monitoring Board (DSMB) acted in an advisory capacity to monitor patient safety. DSMB responsibilities included: review of the protocol, consent/assent documents, evaluation of subject accrual and retention, and recommendations for patient continuation or withdrawal. The DSMB could also conduct interim efficacy and safety analyses, neither of which was required.

Section 9.6 of the study report states the study was conducted according to the principles of Good Clinical Practice.

Two 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 “sites reveals that the data from these sites are acceptable and can be used in support of the NDA.”

10.1.2.13 Study Results

10.1.2.13.1 Patient Population and Demographics

Of 89 patients randomized patients, 88 patients received ≥ 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 ≥ 600 uM was similar in the two groups (81% placebo; 83% sapropterin). These findings are summarized in Table 53.

Table 53: Efficacy Trial: Demographic Characteristics, ITT

Demographic Characteristic	Sapropterin N=41	Placebo N=47	ITT N=88
Gender, n (%)			
Male	27 (66)	24 (51)	51 (58)
Female	14 (34)	23 (49)	37 (42)
Age (years)			
n	41	47	88
Mean (SD)	21.5 (9.5)	19.5 (9.8)	20.4 (9.7)
Percentiles (25, median, 75)	15, 18, 29	13, 17, 23	14, 18, 25
Minimum, Maximum	8, 42	8, 49	8, 49
8 ≤ to ≤12 years	6 (15)	11 (23)	17 (19)
≥ 12 years	35 (85)	36 (77)	71 (81)
Race, n (%)			
Caucasian	39 (95)	47 (100)	86 (98)
Asian/Pacific Islander	1 (2)	0	1 (1)
Other	1 (2)	0	1 (1)
Screening Blood Phe, n (%)			
Phe >450 and <600 uM	7 (17)	9 (19)	16 (18)
Phe ≥ 600 uM	34 (83)	38 (81)	72 (82)

In conclusion, the randomization groups were demographically similar.

10.1.2.13.2 Concomitant Medication

Sixty-seven of 88 patients in the ITT (75%) took at least one concomitant medication during the study. Forty of 47 (85%) of patients who received placebo and 27 of 41 (64%) of patients receiving sapropterin took at least one concomitant medication. The most common medicines taken by patients receiving sapropterin were pain relievers including ibuprofen (62%) and paracetamol (17%); vitamins and minerals (40%); antibiotics/antivirals/anti-infectives (29%); and cough and cold remedies (21%). The most common medicines taken by patients receiving placebo were pain relievers including paracetamol (34%) and ibuprofen (28%); antibiotics/antivirals/anti-infectives (30%); and cough and cold remedies (26%). In summary, the types of concomitant medications used in sapropterin- and placebo-treated patients were similar. Table 54 summarizes concomitant medications by general category (i.e., pain relievers, vitamins/minerals, etc.) used in ≥10% of patients in either treatment group.

Table 54: Efficacy Study: Concomitant Medications

Medicines ¹	Sapropterin N=42	Placebo N=47
Pain Relievers, n (%)	26 (62)	35 (74)
Ibuprofen	13 (31)	13 (28)
Paracetamol	7 (17)	16 (34)
Naproxen	0	2 (4)
Other: [Ibuprofen/Pseudoephedrine hydrochloride, Paracetamol/Caffeine/Mepyramine maleate, Diclofenac, Acetylsalicylic acid, Oxycodone hydrochloride/Paracetamol, Piroxicam] [#] and [Codeine Phosphate (PO4), Codeine PO4 with Promethazine, Dihydrocodeine/Paracetamol, Mefenamic Acid] [*]	1 (2) each [#]	1 (2) each [*]
Vitamins/Minerals, n (%)	17 (40)	8 (17)
Minerals NOS ² /Vitamins NOS/Citric Acid/Folate/Iron	13 (31)	7 (15)
Calcium NOS/Calcium Carbonate/Calcium Citrate	4 (10)	1 (2)
Antibiotics/Antivirals/Anti-Infectives NOS, n (%)	12 (29)	14 (30)
Amoxicillin/Amoxicillin-Clavulanate	4 (10)	3 (6)
Cephalosporins and related substances	3 (7)	3 (6)
Clotrimazole	0	2 (4)
Other: [Acyclovir, Clarithromycin, Trimethoprim, Minocycline hydrochloride, Chlorquinaldol] [#] , and [Azithromycin, Clarithromycin, Flucloxacillin, Fosfomycin Trometamol, Ketoconazole, Trimethoprim] [*]	1 (2) each [#]	1 (2) each [*]
Cough and Cold Remedies, n (%)	9 (21)	12 (26)
Dextromethorphan hydrobromide/Doxylamine succinate/Ephedrine sulfate/Ethanol/Paracetamol	4 (10)	3 (6)
Dextromethorphan hydrobromide/Guaifenesin/Paracetamol/Pseudoephedrine hydrochloride	2 (5)	2 (4)
Pseudoephedrine hydrochloride, Guaifenesin/Pseudoephedrine hydrochloride	3 (7)	2 (4)
Other: Cough and Cold NOS and Dextromethorphan	0	3 (6)
Oral Contraceptives, n (%)	5 (12)	7 (15)
Ethinylestradiol/Levonorgestrel	1 (2)	2 (4)
Ethinylestradiol/Norgestimate	1 (2)	2 (4)
Ethinylestradiol/Gestodene, Progesterone, Desogestrel	1 (2) each	1 (2) each
Antihistamines, n (%)	4 (10)	10 (21)
Loratadine	2 (5)	2 (4)
Cetirizine [*] , Cetirizine-Diphenhydramine [^] , Cetirizine-Pseudoephedrine [#]	1 (2) each ^{**}	1 (2) each ^{**}
Diphenhydramine	0	2 (4)
Xylometazoline hydrochloride	0	2 (4)
Other: Brompheniramine/Pseudoephedrine hydrochloride, Famotidine	0	1 (2) each

¹ NOS=not otherwise specified

The types of events associated with concomitant medications (i.e., headache, otitis media, upper respiratory infections, and general health) were similar between drug and placebo treatment groups. Review of the study report, data listings, and CRFs does not provide an explanation why the patients exposed to placebo had a higher rate of concomitant medication use.

10.1.2.13.3 Compliance with Study Medication