

Seventy-two patients (82%) correctly received all treatments, including 90% of 41 patients who received sapropterin and 74% of 47 patients who received placebo. A high percent of patients received the correct dose at each visit (90% sapropterin vs. 74% placebo). Ingestion of treatment at the right time of day was 78% for drug treated patients and 77% for placebo treated patients. These findings are presented in Table 55.

Table 55: Efficacy Study: Compliance with Treatment

Dosing through Week 6	Sapropterin N=41	Placebo N=47	Total N=88
≥ 1 dose administered, n (%)	41 (98)	47 (100)	88 (99)
All doses correctly administered	37 (90)	35 (74)	72 (83)
≥ 1 dose missed, no incorrect doses	2 (5)	9 (19)	11 (13)
≥ 1 incorrect dose, no missed doses	0	2 (4)	2 (2)
At least one incorrect dose and missed dose	2 (5)	1 (2)	3 (3)
Correct study drug dosage taken each day, n (%)			
Throughout all 6 weeks of treatment	37 (90)	35 (74)	72 (83)
Throughout Week 1	40 (98)	43 (91)	83 (94)
Throughout Week 2	40 (98)	44 (94)	84 (95)
Throughout Weeks 3 and 4	38 (93)	42 (89)	80 (91)
Throughout Week 5 and 6	39 (95)	40 (87)	79 (91)
Study drug taken at appropriate time each day, n (%)			
Throughout all 6 weeks of treatment	32 (78)	36 (77)	68 (77)
Throughout Week 1	36 (88)	40 (85)	76 (86)
Throughout Week 2	40 (98)	44 (94)	84 (95)
Throughout Weeks 3 and 4	38 (93)	42 (89)	80 (91)
Throughout Week 5 to Week 6	36 (88)	39 (85)	75 (86)

In sapropterin treated patients mean dose was 10.8 mg/kg/day (SD0.6), (range 9.9 to 12.1), which was close to the desired dose (10 mg/kg/day). This Reviewer concludes there was a high rate of compliance, and the target dose was achieved.

10.1.2.13.4 Protocol Deviations and Violations

There were frequent minor protocol deviations during the study, most of which were out-of-window study visits and procedures which do not affect efficacy or safety analyses. The most commonly reported deviations that could potentially affect efficacy analyses were missed or incorrect doses and changes in dietary Phe intake during the treatment period. Twelve of 47 patients (26%) in the placebo group and seven of 41 patients (17%) in the sapropterin group reported changes in diet during the 6 weeks of treatment.

This majority of patients in both treatment groups maintained dietary Phe restriction. Of 19 patients reporting changes in diet, 14 (9 placebo, 5 sapropterin) patients reported increases in dietary Phe intake. Of these 14 patients, five placebo treated patients and two sapropterin treated patients increased their Phe intake for ≤3 days; therefore, increases in dietary Phe >3days were evenly distributed across treatment groups. Two sapropterin treated patients reported decreased dietary Phe, and three placebo treated patients reported both increases and decreases in dietary Phe at different treatment weeks. Increase in dietary Phe >3 days, and decrease in dietary Phe

were approximately evenly distributed between treatment groups. Diet related protocol deviations are presented in Table 56.

Table 56: Efficacy Study: Self Reported Changes in Diet

Change in Diet	Sapropterin N= 41	Placebo N= 47	Total N= 88
At any time, (n %)	7 (17)	12 (26)	19 (22)
From Screening to Baseline 1	1 (2)	2 (4)	3 (3)
From Baseline 1 to Baseline 2	1 (2)	1 (2)	2 (2)
From Baseline 2 to Week 0	2(5)	1(2)	3 (3)
From Week 0 to Week 1	2 (5)	2 (4)	4 (5)
From Week 1 to Week 2	1 (2)	0 (0)	1 (1)
From Week 2 to Week 4	3 (7)	8 (17)	11 (13)
From Week 4 to Week 6	2 (5)	3 (7)	5 (6)

This Reviewer concludes that protocol deviations were approximately equal between treatment groups and do not preclude inclusion of data from these patients.

10.1.2.13.5 Efficacy Analyses

The efficacy comparisons were change in blood Phe between placebo and sapropterin treated patients at Week 6 from Baseline (primary analysis) and Weeks 1, 2, and 4 (secondary analysis).

10.1.2.13.5.1 Primary Efficacy Analyses

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

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

Table 57 displays the results of the primary efficacy endpoint by mode of analysis. It displays results including results from the single placebo-treated patient with missing Week 6 blood Phe (N=88). It also contains a sensitivity analysis restricted to patients who completed all study procedures (N=87).

Table 57: Efficacy of Sapropterin—Primary Efficacy Analysis; Change in Blood Phe at Week 6 from Baseline

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

Source: FDA statistical review

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

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

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

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

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

Mean Baseline blood Phe in placebo-treated patients (N=47) was 888 uM (SD 323, 95% CI [793, 983]), and mean Week 6 blood Phe was 891 uM (SD 348, 95% CI [789, 993]). Mean change in blood Phe was 3 uM (SD 239), and mean percent change was 3% (SD 33). These findings support the efficacy of sapropterin over placebo in reducing blood Phe in a subset of patients with PKU who are not on controlled diets. These results, summarized in Table 58 below, include a LOCF for one placebo-treated patient with missing Week 6 data.

Table 58: Blood Phe at Baseline and Week 6; Change in Blood Phe, and Percent Change in Blood Phe

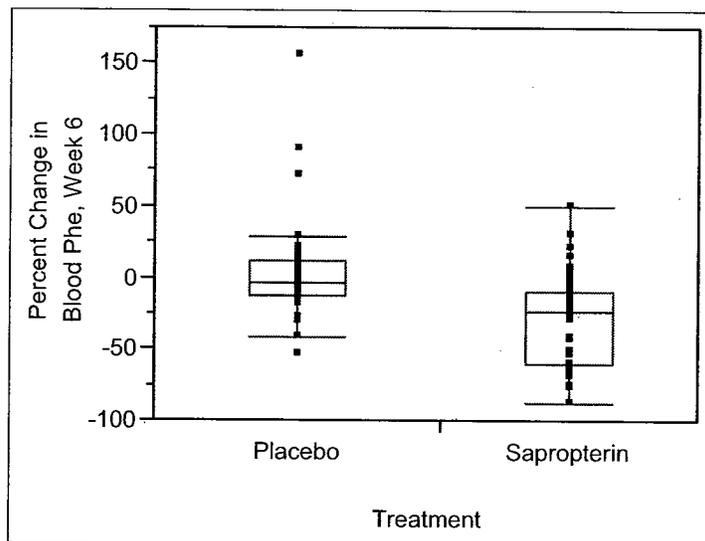
Blood Phe level (uM)	Sapropterin N=41	Placebo N=47
Baseline		
Mean (SD)	843 (300)	888 (323)
95% CI of the Mean	748, 937	793, 983
Median	862	790
Percentiles (25 th , 75 th)	598, 994	618, 1141
Min, max	293, 1643	402, 1745
Week 6		
Mean (SD)	607 (377)	891 (348)
95% CI of the Mean	488, 725	789, 993
Median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

This exploratory analysis supports the primary analysis. Sapropterin treated patients had a greater reduction in blood Phe than placebo treated patients. This Reviewer concludes a reduction of 30% or greater is clinically meaningful. There were no differences in response (change in blood Phe) based age or gender (data not shown).

The result for percent change in blood Phe by individual patient in the sapropterin and placebo groups are displayed graphically in the Figure 9.

Key to Figure 9: Each dot represents one patient's percent change in blood Phe at Week 6. The vertical box encompasses the 25th percentile, median, and 75th percentile of percent change, and the stems delimit the 95% percentiles.

Figure 9: Percent Change in Blood Phe from Baseline to Week 6



In summary, the difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) was -245 uM (SE 53 uM), 95% CI -350, -140; $p < 0.001$. This Reviewer's exploratory analysis of individual patient results shows that mean blood Phe in placebo-treated patients increased 3 uM (SD 33) and blood Phe in sapropterin treated patients decreased 236 uM (SD 257), and the mean percent change in blood Phe in sapropterin-treated patients was approximately 30% greater than in placebo treated patients. This exploratory analysis supports the primary analysis.

In conclusion, the primary analysis provides statistical evidence that sapropterin is more effective than placebo in reducing blood Phe in patients with BH4-responsive PKU. Minimal fluctuations in blood Phe between Baseline Visits 1 and 2 and the Week 0 visit, and review of diet records, suggest diets were stable throughout the study and did not have a noticeable effect on efficacy measures.

10.1.2.13.5.2 Secondary Efficacy Analyses

10.1.2.13.5.2.1 Secondary Efficacy Analysis: Change in blood Phe at Weeks 1, 2, and 4

At the end of all treatment weeks, blood Phe was lower in sapropterin- than in placebo-treated patients. At the end of Week 1, mean blood Phe in sapropterin- and placebo-treated patients was 620 uM (SD 355) and 863 uM (SD 346), respectively. At the end of Week 2, mean blood Phe in

sapropterin- and placebo-treated patients was 639 uM (SD 369) and 863 uM (SD 325), respectively. At the end of Week 4, mean blood Phe in sapropterin- and placebo-treated patients was 587 uM (SD 376) and 906 uM (SD 341), respectively. These results are summarized in Table 59.

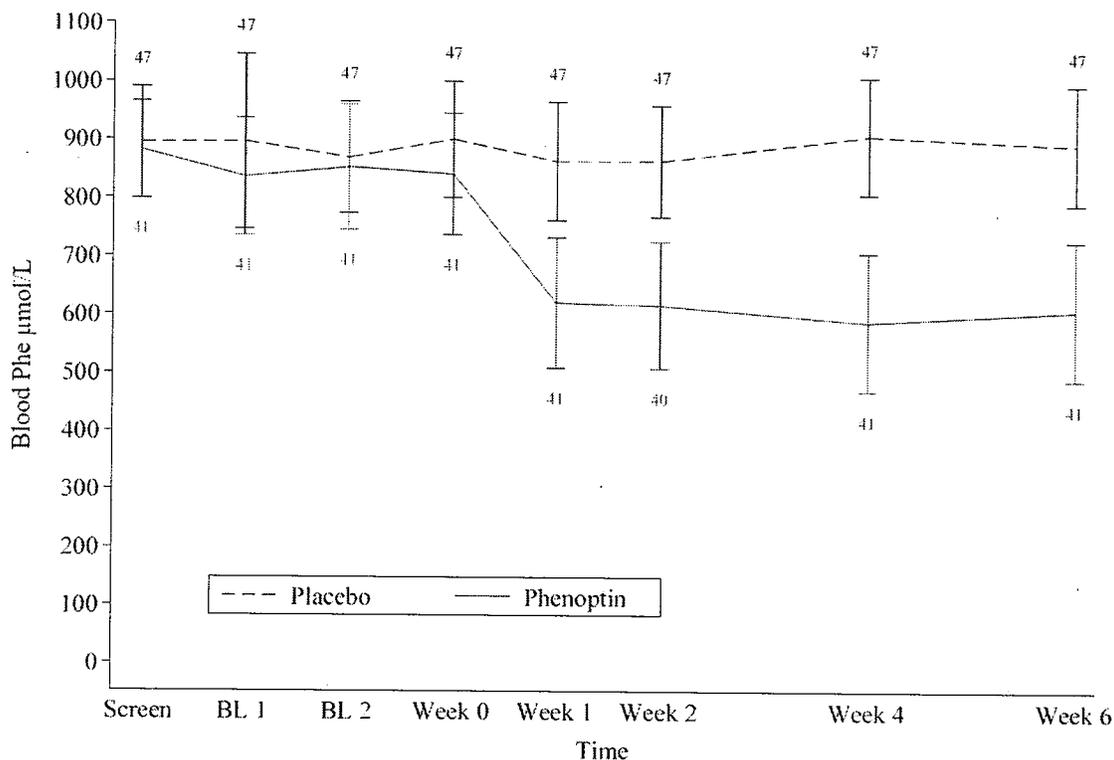
Table 59: Mean Blood Phe at Baseline and Weeks 1, 2, and 4

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

In summary, at the completion of Weeks 1, 2, and 4, blood Phe was lower in sapropterin vs. placebo treated patients. This secondary efficacy analysis supports the primary analysis summarized in Table 56.

Mean blood Phe from Screening through Week 6 are displayed in Figure 10 copied from section 5.3.5.1 of the electronic submission; page 69 of the study report.

Figure 10: Mean Blood Phe Levels from Screening through Week 6



* Phenoptyn: name of sapropterin use in clinical trials

In summary, mean blood Phe in sapropterin- and placebo-treated patients was similar at Baseline, and mean blood Phe at the end of treatment Weeks 1, 2, 4 and 6 was lower in sapropterin-treated than placebo-treated patients.

Change in mean blood Phe from Baseline was greater in sapropterin- than placebo-treated patients.

- At the end of Week 1, mean change blood Phe was -223 uM (SD 192) in sapropterin-treated patients, and -26 uM (SD 232) in placebo treated patients.
- At the end of Week 2, mean change in blood Phe was -203 uM (SD 270) in sapropterin treated patients, and -25 uM (SD 248) in sapropterin treated patients.
- At the end of Week 4 mean change in blood Phe was -255 uM (SD 248) and 19 uM (SD 240) in placebo treated patients.

These results are summarized in Table 60.

Table 60: Efficacy Study: Mean Change in Mean Blood Phe at Weeks 1, 2, and 4

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

In summary, at the completion of Weeks 1, 2, and 4, the mean change (decrease) in blood Phe was always greater in sapropterin- than placebo-treated patients.

This reviewer performed an exploratory analysis to determine the mean percent change in blood Phe at Weeks 1, 2, and 4, compared to Mean Baseline. The net difference in mean percent change in blood Phe between placebo- and sapropterin-treated patients at Week 1 was 27% (-1% minus -28%), at Week 2 was 23% (1% minus -24%), and at Week 4 was 37% (5% minus -32%). These findings are summarized in Table 61.

Table 61: Mean Percent Change Blood Phe at Weeks 1, 2, and 4

Blood Phe level (uM)	Sapropterin N=41	Placebo N=47
Week 1 – Baseline		
Mean (SD)	-28 (25)	-1 (23)
95% CI of the Mean	-36, -20	-8, 6
Median	-32	2
Percentiles (25 th , 75 th)	-48, -9	-11, 11
Min, max	-72, 29	-79, 59
Week 2 – Baseline		
Mean (SD)	-23 (37)	1 (29)
95% CI of the Mean	-35, -11	-8, 10
Median	-22	-3
Percentiles (25 th , 75 th)	-42, -8	-11, 20
Min, max	-91, 95	-87, 88
Week 4 – Baseline		
Mean (SD)	-32 (30)	5 (28)
95% CI of the Mean	-42, -23	-3, 14
Median	-27	4
Percentiles (25 th , 75 th)	-54, -12	-6, 11
Min, max	-92, 41	-67, 127

The mean percent decrease in blood Phe was greater in sapropterin vs. placebo treated patients at the end of treatment Weeks 1, 2, and 4. This exploratory analysis supports the primary analysis.

10.1.2.13.5.2.1 Secondary Efficacy Analysis: Proportion of patients with blood Phe <600 uM at Week 6
 At Screening, nine of 47 placebo-treated patients [19%, 95% CI (10, 32)], and seven of 41 sapropterin-treated patients [17%, 95% CI (9, 31)] had blood Phe <600 uM. At Week 6, 11 of 47 placebo-treated patients 23%, 95% CI (14, 37), and 22 of 41 sapropterin-treated patients [54%, 95% CI (39, 68)] had blood Phe <600 uM. In conclusion, more sapropterin- than placebo-treated patients had decreases in blood Phe to <600 uM from Screening to Week 6. These results are summarized in Table 62.

Table 62: Efficacy Study: Proportion of Patients with Blood Phe Level <600 uM Week 6 vs. Screening

	Sapropterin		Placebo	
	n/N (%)	95% CI, Proportions	n/N (%)	95% CI, Proportions
Blood Phe < 600 uM at Screening	7/41 (17)	(9, 31)	9/47 (19)	(10, 32)
Blood Phe < 600 uM Week 6	22/41 (54)	(39, 68)	11/47 (23)	(14, 37)

In summary, the proportion of patients with Baseline blood Phe <600 uM was similar in sapropterin- and placebo-treated patients. At Week 6, patients treated with sapropterin were more likely than placebo treated patients to have Week 6 Phe to below 600 uM.

10.1.2.13.5.3 Efficacy Summary

Sapropterin lowers blood Phe in patients with BH-4 responsive PKU.

The primary efficacy endpoint was mean change in blood Phe in sapropterin- vs. placebo-treated patients at Week 6 compared to Baseline.

- Mean baseline blood Phe in placebo and sapropterin groups were similar (883 uM (SD 323) and 843 uM (SD 300), respectively). The difference in mean change in blood Phe at Week 6 (sapropterin minus placebo) was -245 uM with a standard error of 53 uM, 95% CI -350, -140; $p < 0.001$, using an ANCOVA model. These findings are statistically significant, and this Reviewer concludes they are clinically meaningful.
- An exploratory analysis performed by this Reviewer showed mean blood Phe decreased 236 uM (SD 257) in sapropterin-treated patients and increased 3 uM (SD 239) in placebo-treated patients. The mean percent change in blood Phe + 3% (SD 33) in placebo treated patients, and -29% (32) in sapropterin treated patients. These results are clinically meaningful and support the primary analysis.

Secondary efficacy analyses

Changes in mean blood Phe at Weeks 1, 2, and 4 are clinically meaningful and support the primary analysis. Changes in mean blood Phe at Weeks 1, 2, and 4 are summarized as follows:

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

The change in the percentage of patients with blood Phe <600 uM at Week 6 compared to Screening are summarized:

- At Screening, 19% (95% CI of proportions 10, 32) of placebo treated patients and 17% (95% CI 9, 31) of sapropterin treated patients had blood Phe < 600 uM. At Week 6, 23% (95% CI 14, 37) of placebo treated patients and 54% (95% CI 39, 68) of sapropterin treated patients had blood Phe < 600 uM. This suggests that sapropterin is more likely than placebo to reduce blood Phe to below 600 uM.

In conclusion, the results of the primary analysis show the sapropterin can produce a statistically significant and clinically meaningful decrease in blood Phe in patients with BH4-responsive

PKU compared to placebo. The results of the secondary analysis of change in blood Phe at Weeks 1, 2, and 4 support these findings.

An important limitation of this study that could have affected efficacy was the lack of dietary control. 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. A review of dietary records indicates the majority of patients in both treatment groups maintained dietary Phe restriction. This Reviewer concludes the study approximated a real-use situation and does not feel these protocol deviations void the primary efficacy analysis. Sapropterin lowers blood Phe in patients with BH-4 responsive PKU.

10.1.2.14 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 Week 10 follow-up. Deaths and Serious AEs were reported from obtaining consent through the Week 10 follow-up. Non-serious AEs were reported from the time of first dose at through completion of the Week 10 follow-up. Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT). Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT). The adverse event, clinical laboratory, and vital sign datasets were reviewed. Significant findings are presented below.

10.1.1.14.1 Exposure

The safety population included 88 patients who received at least one dose of sapropterin or placebo. The last patient completed follow-up on 15-February-2006.

In sapropterin-treated patients mean dose was 10.8 mg/kg/day (SD0.6), (range 9.9 to 12.1), which was close to the desired dose (10 mg/kg/day).

10.1.2.14.2 Adverse Events

AEs are reported from administration of first dose completion of Week 10 study procedures, four weeks after the final dose. Recurrent or continuing AEs were counted only once. AE incidence rates were calculated using all patients who received at ≥ 1 dose of study medication as the denominator (N=88). AEs were tabulated and analyzed using the aedata.xpt dataset (section 5.3.5.1.25.3.1 of the electronic submission).

The most common AEs by MedDRA preferred term in the overall ITT were upper respiratory tract infection (23%), headache (13%), vomiting (7%), abdominal pain and diarrhea (6% each). The most common AEs sapropterin-treated patients were upper respiratory tract infection (17%), headache (10%), and pharyngolaryngeal pain (7%). The most common AEs placebo-treated patients were upper respiratory tract infection (28%), headache (10%), vomiting and abdominal

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pain (9% each). AEs were more common placebo-treated patients (73% of 47 patients) than in the sapropterin-treated patients (51% of 41 patients). Review of the study report does not indicate why the incidence of AEs was more common in the placebo treated group. The types of AEs reported in sapropterin- and placebo-treated patients were similar. AEs occurring in >2% of patients in the ITT are presented in Table 63.

Table 63: Efficacy Study (PKU-003); Adverse Events Occuring in ≥ 2% patients in the ITT

		Total N=88	Sapropterin N=41	Placebo N=47
System, Organ, Class	Preferred Term			
Ear and labyrinth disorders	Ear pain	2 (2)	0	2 (4)
Gastrointestinal disorders	Vomiting	6 (7)	2 (5)	4 (9)
	Abdominal pain	5 (6)	1 (2)	4 (9)
	Diarrhea	5 (6)	2 (5)	3 (6)
	Dyspepsia	2 (2)	0	2 (4)
General disorders and administration site conditions	Pyrexia	4 (5)	2 (5)	2 (4)
	Influenza like illness	3 (3)	1 (2)	2 (4)
	Fatigue	2 (2)	1 (2)	1 (2)
	Malaise	2 (2)	1 (2)	1 (2)
Immune system disorders	Hypersensitivity	1 (1)	0	1 (2)
Infections and infestations	Upper respiratory tract infection	20 (23)	7 (17)	13 (28)
	Pharyngitis	3 (3)	2 (5)	1 (2)
	Infection	2 (2)	2 (5)	0
	Rhinitis	2 (2)	1 (2)	1 (2)
	Bronchitis, Lower Respiratory Tract Infection	2 (2)	1 (2)	1 (2)
Musculoskeletal and connective tissue disorders	Back pain	4 (5)	1 (2)	3 (6)
	Pain in extremity	2 (2)	0	2 (4)
Nervous system disorders	Headache	11 (13)	4 (10)	7 (15)
	Dizziness	2 (2)	0	2 (4)
	Lethargy	2 (2)	0	2 (4)
	Migraine	2 (2)	0	2 (4)
	Tremor	1 (1)	0	1 (2)
Renal and urinary disorders	Polyuria	2 (2)	0	2 (4)
Respiratory, thoracic and mediastinal disorders	Cough	3 (3)	0	3 (6)
	Pharyngolaryngeal pain	3 (3)	3 (7)	0
Skin and subcutaneous tissue disorders	Rash, Maculo-papular Rash	3 (3)	1 (2)	2 (4)
Any AE		55 (63)	21 (51)	34 (73)

Age, gender, and duration of exposure did not appear to affect incidence of AEs.

Three notable severe and moderate AEs are discussed below.

- Patient 0126-0001, a 38 year old male treated with sapropterin, experienced severe abdominal cramping and severe diarrhea during the second week of treatment. Symptoms resolved prior to the third week visit. This patient also had a moderately severe headache during the first week of treatment which resolved prior to the second week visit. The patient completed the study. The abdominal cramping and diarrhea were

reported as possibly related to sapropterin. The CRF was reviewed and this Reviewer concludes the events are possibly related to sapropterin treatment.

- Patient 0113-0015, a 15 year old male treated with sapropterin, experienced a moderately severe maculo-papular exanthem first noted at the end of week four of treatment. The patient was treated with Cetirizine for the rash. The rash persisted through the end of data collection at week ten. The CRF was reviewed and this Reviewer concludes the event is possibly related to sapropterin treatment.
- Patient 0121-1010, a 24 year old male treated with sapropterin, experienced a urinary tract infection during the follow up period, about one week after receipt of the final dose. The patient was treated with Trimethoprim-sulfamethoxazole and the infection resolved. The AE was reported as not related to sapropterin. The CRF was reviewed and this Reviewer concludes the urinary tract infection is not likely related to sapropterin.

The above findings suggest that adverse events associated with sapropterin over a six week period are similar to and not readily distinguishable from common complaints in the general population, including upper respiratory tract infection, headache, and pharyngolaryngeal pain.

10.1.2.14.3 Reports of Deaths and SAEs

No deaths or SAEs occurred during the study.

10.1.2.14.4 Withdrawals

There were two withdrawals, which are described below.

- Patient 0067-0004, a 27 year old female randomized to receive sapropterin withdrew prior to receiving treatment. All Baseline clinical laboratory findings were normal. The patient was treated with sapropterin in the Enrichment Study. This patient received sapropterin during the Enrichment Study (PKU-001). No AEs or notable clinical laboratory findings were reported during prior treatment in the Enrichment Study. The CRF was reviewed and this Reviewer concludes this withdrawal is not related to sapropterin treatment.
- Patient 0021-0008, an 18 year old female randomized to receive placebo, withdrew at after Week 4 due to dysmenorrhea. There were no notable clinical laboratory findings. No AEs or notable clinical laboratory findings were reported during prior treatment in the Enrichment Study. This withdrawal is not related to sapropterin.

10.1.2.14.5 Vital signs

The vital sign datasets were reviewed. Clinically significant vital sign abnormalities that qualified as AEs are included in the AE datasets and are reported in 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, Baseline Visits 1 and 2, and Week 0, 1, 2, 4, and 6 (data not shown). Vital signs assessments at Week 10 were only reported for four patients (0018-0004, 0115-0022, 0119-0002, and 0123-0026). There were no changes from Baseline in these four patients (data not shown).

10.1.2.14.6 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. There were no clinically meaningful changes in mean (SD) values and other measures of central tendencies for any analyte between Week 0 (pre-dose) and Week 6 (treatment dose) within the sapropterin treated group or within the placebo treated group. There were no clinically meaningful differences in mean (SD) values and other measures of central tendencies for any analyte between sapropterin treated patients and placebo treated patients at Week 6. Notable clinical laboratory findings are summarized in Table 64.

Table 64: Efficacy Study: Notable Clinical Laboratory Findings

Patient	Age (years), Gender (M/F)	Lab Finding	Treatment
0121-0011	18 y, F	Low ANC	Sapropterin
0109-0024	12 y, F	Low ANC	Placebo
0129-1004	14 y, M	Increased ALT	Sapropterin
0113-0015	15 y, M	Increased ALT	Sapropterin
0129-0006	32 y, F	Increased ALT	Sapropterin

Two instances of neutropenia, neither severe, were identified.

- Patient 0121-0011, an 18 year old male treated with sapropterin, had moderate neutropenia at Week 0 (ANC= 930) and at Week 6 (ANC=630). This patient's Baseline ANC in the Enrichment Study was 960, and his nadir was 500 during the Enrichment Study. His final ANC during the Extension Study (PKU-004; appendix 10.1.4) was 950.
- Patient 0109-0024, a 12 year old girl treated with placebo was neutropenic (ANC 1,160) at Baseline, but had a normal ANC at Week 6 (ANC 2,190). AEs in this patient around the time of neutropenia included constipation and an upper respiratory tract infection.

Three sapropterin-treated patients and four placebo patients had ALT >50 U/L noted at Week 6. For sapropterin treated patients:

- Patient 0129-1004 was treated with sapropterin and had a Screening ALT value of 32 U/L and a Week 6 ALT of 51 U/L (ULN 45 U/L).
- Patient 0113-0015 was treated with sapropterin and had a Screening ALT value of 22 U/L and a Week 6 ALT of 53 U/L.
- Patient 0129-0006 was treated with sapropterin and had a Screening ALT value of 43 U/L and a Week 6 ALT of 77 U/L, but normal ALT at Week 0.

- No follow up (Week 10) ALT was reported for these three sapropterin treated patients.
- One placebo treated patient (0119-0002) had a normal ALT from Screening through Week 4 (13 to 16 U/L), a Week 6 value of 83, and a Week 10 value of 19. The other three placebo treated patients (0019-0001, 0109-0007, and 0102-0011) had Screening ALT between 52 and 73 U/L, and Week 6 ALT between 58 to 62 U/L.

The incidence of alterations in ALT is approximately equal in sapropterin- and placebo-treated patients, and there were no notable trends in AST or GGT in sapropterin vs. placebo-treated patients in this study. This Reviewer concludes there is no suggestion that sapropterin affects liver enzymes. These findings are limited by the small population and short duration of the study.

10.1.2.14.7 Safety Summary

The safety results from the Enrichment Study show the following:

1. AEs were frequently reported; 51% of sapropterin-treated patients reported at least one AE compared to 73% of placebo-treated patients. 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 incidence rate, the most commonly reported AEs in sapropterin treated patients were upper respiratory tract infection (17%), headache (10%), and pharyngolaryngeal pain (7%).
2. No Deaths or SAEs were reported. Other notable AEs in sapropterin-treated patients include one patient with abdominal cramping and diarrhea, one patient with a moderately severe maculo-papular exanthem, and one patient with a urinary tract infection.
3. Summary clinical laboratory findings include the following:
 - a. Neutropenia was reported in two sapropterin treated patients.
 - b. There were no notable differences in ALT, AST, or GGT between sapropterin- and placebo-treated patients.
4. No notable trends in vital signs were found.

Sapropterin appears to have been well tolerated. Most AEs were mild to moderate in severity, were self-limited, and were consistent with underlying disease or are commonly reported in otherwise healthy individuals. In summary, the short-term safety of sapropterin 10 mg/kg/day in patients with BH4-responsive PKU is established. Important limitations of the study include the short duration (six weeks) and the small study population.

10.1.2.15 Overall Summary of the Efficacy Study (PKU-003)

This was a randomized, double-blind, placebo-controlled, study of 89 patients who qualified for enrollment by demonstrating a $\geq 30\%$ decrease in blood Phe from Day 1 to Day 8 of the Enrichment study. Patients were randomized 1:1 to receive 10 mg/kg/day or placebo. Diet was not controlled, but appeared to be stable throughout the study.

The primary efficacy endpoint was mean change in blood Phe at Week 6 from Baseline. The secondary efficacy analysis was mean change in blood Phe at Weeks 1, 2, and 4. An exploratory analysis of the proportion of patients with blood Phe < 600 uM at Week 6 compared to Screening was performed.

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

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

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

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

Analysis of the proportion of patients with blood Phe < 600 uM at Week 6 compared to Screening suggests that in BH4-responsive patients, sapropterin is more likely than placebo to reduce blood Phe to < 600 uM. These results are summarized below:

- At Screening, 19% (95% CI [10, 32]) of placebo treated patients and 17% (95% CI [9, 31]) of sapropterin treated patients had blood Phe < 600 uM.
- At Week 6, 23% (95% CI [14, 37]) of placebo treated patients and 54% (95% CI [39, 68]) of sapropterin treated patients had blood Phe < 600 uM.

In summary, in patients screened for BH4-responsive PKU, sapropterin is more effective than placebo in reducing blood Phe.

No Deaths or SAEs were reported in the Efficacy Study. Non-serious AEs were common in sapropterin- (51%) and placebo-treated (73%) patients. 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 incidence rate, the most commonly reported AEs in sapropterin treated patients were upper respiratory tract infection, headache, and pharyngolaryngeal pain. Notable laboratory findings include two patients with neutropenia.

In conclusion, the results of the short-term Efficacy Study show that, in patients with BH4-responsive PKU, sapropterin 10 mg/kg/day produces a clinically meaningful and statistically significant reduction in blood Phe compared to placebo. The results also show that short-term administration of sapropterin to patients with BH4-responsive PKU has a reasonable safety profile compared to placebo. A limitation of the study is that while patients and caregivers were instructed not to change the patients' diets throughout the study, unrecorded changes in diet could have affected efficacy results.

10.1.3 Diet Trial (PKU-006)

Title: "A phase 3, multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of Phenoptin™ (sapropterin dihydrochloride) 20 mg/kg/day to increase phenylalanine tolerance in phenylketonuric children on a phenylalanine-restricted diet."

10.1.3.1 Study Design

Study PKU-006, (aka Diet Study), was a two-part, randomized, double-blind, placebo-controlled study enrolled children ages four to 12 years old with phenylketonuria (PKU) who were on prior Phe-restricted diets. After obtaining consent patients completed Screening procedures. Patients with blood Phe level ≤ 480 uM at Screening were eligible for the study. Day 1-Part I procedures were to be completed within 4 weeks of Screening.

In Part I, 90 patients received open-label sapropterin 20 mg/kg/day for 8 days. Patients whose blood Phe levels met the following criteria (sapropterin-responsive) were eligible for Part II:

- A reduction in blood Phe level $\geq 30\%$ between Day 1 prior to treatment and Day 8; and
- Blood Phe level ≤ 300 uM on Day 8.

Patients meeting the above criteria (Responders) underwent a one week non-treatment washout period and were then randomized for Part II. Patients who did not meet the above criteria were withdrawn and were contacted by telephone for follow-up four weeks after the Day 8.

Forty-six patients of 50 Responders were randomized (3:1) to receive sapropterin 20 mg/kg/day (N=34) or a corresponding placebo (N=12) for 10 weeks, and safety assessments were collected for an additional four weeks. Patients were to maintain their previously prescribed low Phe diet without modification for the first three weeks of Part II. After Week 3 laboratory assessments, patients who had blood Phe ≤ 300 uM at the preceding (Week 2) visit had dietary Phe intake (supplement) increased by 5 mg/kg/day by adding a specified quantity of Phe-containing powder

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(in the form of non-fat dry milk or dried egg whites); patients with blood Phe of ≥ 301 uM at the preceding (Week 2) visit were to have no Phe supplement added at that time. Dietary Phe intake could also be modified at Weeks 5, 7, and 9 based on blood Phe levels from Weeks 4, 6, and 8 as outlined in Tables 65 and 66.

Table 65: Change in Dietary Phe Supplementation Based on Blood Phe

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

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

Two examples of change in dietary Phe supplement based on blood Phe levels are provided in Table 66 below.

Table 66: Examples of Change in Supplement by Blood Phe

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

Recommendations for Phe supplementation were performed by study personnel blinded to sapropterin/placebo treatment. Dietary reviews were performed by an independent nutritionist, blinded to treatment group, to verify the accuracy of the records and to document any discrepancies.

Patients were evaluated weekly either at the study site or at the patient's home by qualified staff. Blood Phe analysis was performed weekly using local laboratories. Compliance with Phe-restricted diets during Part II were assessed by review of weekly, three-day diet diaries that reported the weighed or measured amounts of all foods and beverages ingested, including medical foods and Phe-free formulas.

Consent for the first patient was signed on 09-February-2006 and the final assessment was performed on 06-November-2006.

10.1.3.2 Study Objectives

Part I: To identify patients with PKU with PKU under dietary Phe control and moderately elevated blood Phe (<480 uM) who had a $\geq 30\%$ reduction in blood Phe from Baseline to Day 8 when treated with sapropterin treatment (20 mg/kg/day) in order to qualify for randomization into Part II.

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

Part II had three secondary efficacy objectives were:

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

Safety measures included baseline and interval physical, history, and clinical laboratory studies, vital signs, and collection of AEs. Safety assessments collected during treatment were compared with baseline.

Blood Phe is an appropriate efficacy endpoint. The Division does not accept and will not consider dietary Phe supplementation as an efficacy endpoint at this time because:

- Increased dietary Phe is not an established independent clinical endpoint.
- The study was not designed to link increased dietary Phe (e.g., Phe supplement) to preservation of normal neurocognitive development.

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

Cost reduction of treatment of any disease is a desired outcome, but such economic issues do not fall under FDA's regulatory authority. Explorations of cost reduction will not be assessed.

10.1.3.3 Eligibility Criteria

To be eligible for the study, patients must have been 4 to 12 years old, diagnosed with PKU, with hyper-Phe documented by at least one blood Phe measurement ≥ 360 μM (6 mg/dL). Patient must also have had blood Phe level ≤ 480 μM at Screening. Adherence to a Phe-restricted diet on entry was required, and was demonstrated by at least 6 months of blood Phe control (mean level of ≤ 480 μM) prior to Screening, while daily Phe consumption was ≤ 1000 mg/day.

Notable exclusion criteria included: diagnosis of primary BH4 deficiency, concomitant use of folate inhibitors or levodopa, blood alanine amino-transferase (ALT) >2 times the upper limit of normal (ULN), any serious illness not under medical control, or history of liver transplant. The method of exclusion of primary BH4 deficiency was not stated.

Notable differences in exclusion criteria from the Enrichment, Efficacy, and Diet Studies are reduction of upper limit of ALT from >5 times to >2 time the ULN, and exclusion of patients with liver transplants. The reason for reduction of the ULN of ALT was not stated, but this Reviewer concludes that it increases the safety of the study. The reason for excluding patients with liver transplants was not stated, but liver transplantation cures the metabolic defect in patients with PKU, and including such patients would affect efficacy comparisons. Exclusion of patients with PKU who have had liver transplants is appropriate.

10.1.3.4 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 (Part II, Week 14) were recorded in the CRFs.

Investigators could prescribe any required non-prohibited medication. In an emergency, any needed medications could be prescribed without prior approval, but the medical monitor was to be notified of the use of any contraindicated medications immediately thereafter.

10.1.3.5 Study Visits and Procedures

The Day 8 visit was to be performed within one day, and Part II visits were to take place within two days of the scheduled visit. All procedures for Weeks 0 through 10 were to take place before the daily dose of sapropterin or placebo. Week 10 procedures were performed in case of early withdrawal. Clinical laboratory tests included blood Phe analyses, hematology, chemistry, and urine tests. Day 1 and 8, and Week 0, 2, 4, 8, and 10 procedures were to be performed at clinic sites. Week 1, 3, 5, 7, and 9 procedures could be performed at home. Study procedures are summarized in Table 67.

Table 67: Diet Study: Study Procedures

Procedure	Part I Open-label Sapropterin Response Phase			Part II Randomized, Double-blind, Placebo-controlled Phase													
	Screen ^a	Day		Wash ^a	WEEK											F/U ^a	
		1	8		0	1	2	3	4	5	6	7	8	9	10		14
Informed consent	X																
Diet history	X																
Medical history	X																
Vital signs & weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X		X		X				X				X		X
Laboratory tests ^b	X	X	X		X		X				X				X		X
Blood Phe	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Diet Review					X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug		X			X	X	X	X	X	X	X	X	X	X	X	X	
Phe Supplement Modification	No Diet Change							X		X		X		X			

^a Screen=Screening visit; Wash=Washout Period; F/U=Follow-Up visit.

^b No patient was of childbearing potential, and no pregnancy tests were performed.

Blood for blood Phe analyses were to be collected two and one half to five hours after meals; around the same time of day.

10.1.3.6 Randomization, Blinding and Controls

Treatment in Part I was open-label sapropterin 20 mg/kg/day for eight days.

Part II: Prior to the Week 0 visit of the DB treatment period (Part II), patients were randomized 3:1 to receive Sapropterin (N=34) or placebo (N=12). Randomization was stratified by the average blood Phe level in the six months prior to Screening (<300 vs. ≥300 uM). Patients and investigators were blinded to treatments.

- The Reviewer concludes the small size of the placebo group in Part II was too small to permit meaningful analysis by strata of tolerated Phe supplement by strata, but was

meaningful in assuring an approximately even distribution of entry blood Phe between sapropterin and placebo treatment groups.

Sapropterin treatments were labeled with a lot numbers, the re-test date, the study number, and unique identifiers. In the event of a medical emergency, the investigator was to contact the medical monitor or authorized representative to discuss the necessity of unblinding the patient's treatment assignment. Treatment assignments were to be made accessible to the investigator if unblinding were required due to a medical emergency. If unblinding occurred, the reason for unblinding and the date and time of the event were documented in the CRFs.

10.1.3.7 Study Medication Dose Selection, Dispensing, and Compliance

Pre-clinical/non-clinical studies support the safety and tolerability of the 20 mg/kg/day sapropterin dosage for human use. Clinical data from other studies including the Enrichment study (PKU-001) and the Efficacy study (PKU-003), indicate that daily Sapropterin doses of 5 mg/kg, 10 mg/kg, or 20 mg/kg demonstrate efficacy and are tolerated.

In Part I of the current study, patients received sapropterin (20 mg/kg/day) as tablets dissolved in four to eight ounces of water or apple juice. Each tablet contains 100 mg of sapropterin dihydrochloride. The first dose was taken under direct observation. All other doses were to be taken daily at home in the morning. For Part I, drug treatments were dispensed in 45-tablet per bottle units, with the number of units sufficient for eight days of therapy.

In Part II of the study, a placebo was provided as tablets similar to sapropterin. Placebo was administered orally once daily in the morning dissolved in four to eight ounces of water or apple juice. The number of tablets equivalent to sapropterin 20 mg/kg/day were provided. Weekly sapropterin and placebo treatments were dispensed in 45-tablet per bottle units. Treatments were dispensed weekly through Week 10. The following batch numbers of study drug were used: T140604, T140601, and T140602 (45-tablet bottles); T140509 (blister cards).

Unused treatments at the end of each week were to be returned at the next visit with delivery of the following week's treatments. Compliance with the dosing regimen was assessed by reconciliation of the used and unused study drug. The quantity dispensed, returned, used, or lost was recorded on the dispensing log provided for the study.

10.1.3.8 Diet

To enroll, patients must have been maintaining a low-Phe diet for six months prior to Screening. Screening blood Phe levels were to be ≤ 480 μM . Patients were to maintain their low-Phe diet throughout the study, with the exception of the Phe supplements prescribed according to the protocol during Part II.

Starting at Week 3 of Part II, dietary Phe supplement could increased by adding a specified quantity of either non-fat dry milk (~~_____~~)

The amount of Phe added was equivalent to the prescribed increase in milligrams per day, based on ideal body weight for age and gender, and was divided into two doses.

10.1.3.9 Efficacy and Endpoint Measures

10.1.3.9.1 Primary Efficacy Endpoint

The primary efficacy endpoint was $\geq 30\%$ reduction in blood Phe from Baseline to Day 8 and Day 8 blood Phe ≤ 300 μM at Day 8, during OL treatment, under diet controlled conditions, and without Phe-supplementation.

The primary efficacy endpoint of Part II was the amount of dietary Phe tolerated at Week 10 of sapropterin treatment compared with pre-treatment Phe intake in Part II of the study while maintaining adequate blood Phe control.

10.1.3.9.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint of Part II was comparison of change in blood Phe in the sapropterin group from non-treatment baseline to blood Phe at completion of three weeks of DB, PC therapy, under diet controlled conditions and without Phe-supplementation.

- This Reviewer also assessed change in blood Phe in the placebo group from Baseline to Week 3 for illustrative purposes.

Supplemental secondary analyses include:

- The mean change in daily dietary Phe intake in Part II.
- The mean difference in the amount of supplemental Phe prescribed minus ingested; Weeks 3 through 10 in Part II.
- The mean Phe supplement tolerated at each Week from first supplement to Week 10. These were not to be assessed in a hierarchical order.

10.1.3.9.3 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. The reporting period ended with the conclusion of the Week 14 follow-up visit. If AEs were not resolved at the end of Week 14, 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 PI and Medical Monitor were to make a clinical assessment as to whether continued follow-up was warranted, and to document results.

10.1.3.9.4 PK and PD Measures

Pharmacokinetic analyses were not part of this trial.

Blood Phe is a pharmacodynamic measure and was used as the sole efficacy measure in Part I, and a component of determining Phe supplement tolerated in Part II.

10.1.3.10 Additional Statistical Considerations

The Sponsor proposes a Phe supplement 17.5 mg/kg/day may be tolerated based on a review of the literature.

The Sponsor proposes that with a mean Phe supplement of 0 mg/kg/day at Week 0 and presumption of a mean Phe supplement tolerated of 17.5 mg/kg/day (SD 16) at Week 10 in the sapropterin group, and a 2-sided type I error rate=0.05, then a sample size of 30 subjects receiving sapropterin would provide over 99% power to detect the specified increase in total daily Phe supplement tolerated. If the observed total daily Phe supplement tolerated were 17.5 mg/kg/day (SD16), the 95% CI for Phe supplement tolerated would be (11.7, 23.3) mg/kg/day.

The primary efficacy analysis was evaluated using an ANOVA model. The results of the primary efficacy analysis, supplemental Phe tolerated at Week 10 (sapropterin group minus placebo group) are presented as least squared means and standard error or means. The draft FDA statistical review, Stella Grosser PhD, indicates the statistical design is acceptable.

10.1.3.11 Protocol Amendments

No protocol amendments were submitted.

The Sponsor's statistical plan was modified. The original statistical plan specified a 1-way ANOVA comparison without blood Phe as covariate for comparison. The Sponsor states the lack of inclusion of blood Phe as a covariate for the ANOVA analysis was an oversight because randomization was performed within blood Phe stratum.

The preliminary review from the FDA statistician (Stella Grosser, Ph D) states the modified statistical plan is acceptable.

10.1.3.12 Study Conduct

The Sponsor states the study was conducted in accordance with Good Clinical Practices and E6 ICH guidelines and in accordance with the Declaration of Helsinki in accordance with clarifications as of October 2000 (sic 2002).

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 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.

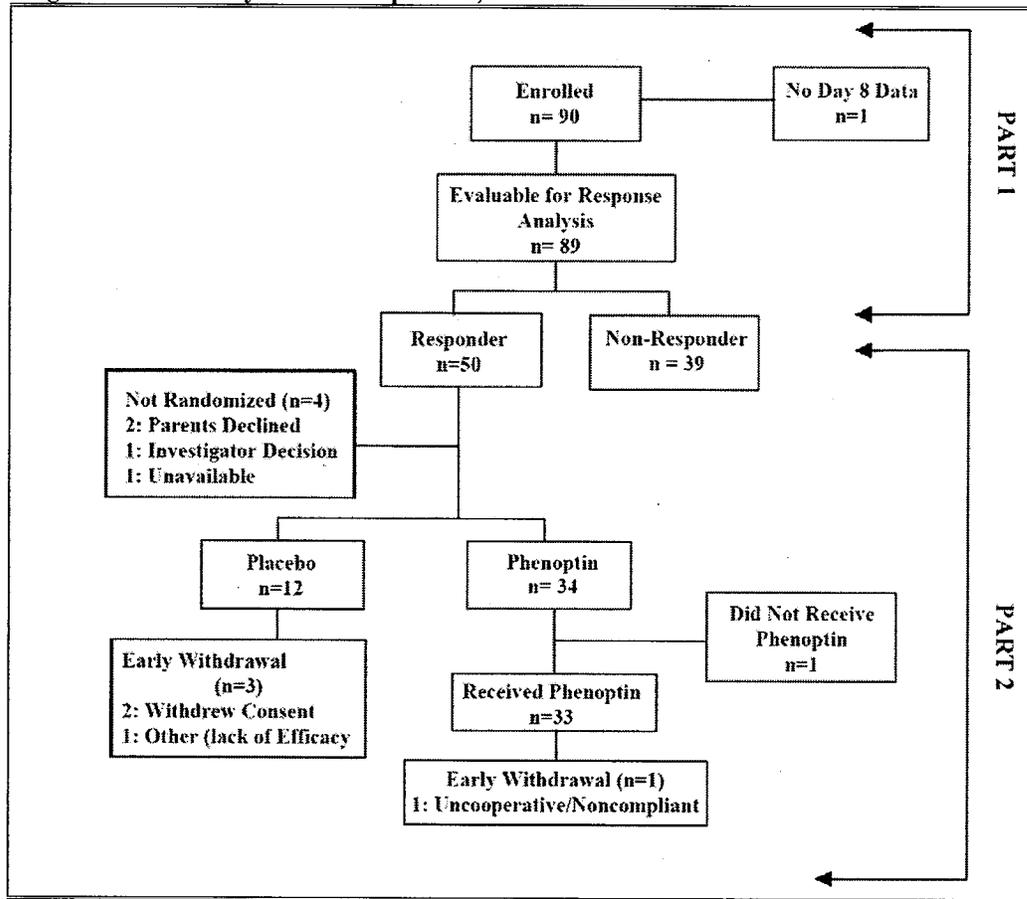
Three sites were selected for inspection because of their high enrollment. The overall observation noted by the DSI Inspector (Khairy Malek, MD) is that inspection of the “sites reveals that the data from these sites are acceptable and can be used in support of the NDA.”

10.1.3.13 Study Results

10.1.3.13.1 Patient Disposition

Of 90 patients who met screening criteria and received ≥ 1 dose in Part I, 89 had Day 1 and Day 8 blood Phe available for analysis (Analysis Population Part I, N=89). Forty-six of the 50 patients who were Responders in Part I were randomized to receive sapropterin (N=34) or placebo (N=12) in Part II. Forty-five randomized patients received ≥ 1 dose of sapropterin or placebo (ITT Part II, N=45). This information is summarized in Figure 11, copied page 67 of the study report (PKU-006); located in section 5.3.5.1.3 of the electronic submission.

Figure 11: Diet Study: Patient Disposition, Parts I and II



* Phenoptin = Previous name for Sapropterin.

10.1.3.13.2 Patient Population and Demographics

In Part I, more males (57%) than females (43%) enrolled. The mean (SD) age was 7.3 (SD 2.5) years. Eighty-five (94%) of the subjects were Caucasian. Demographic characteristics of patients in Part I are summarized by Baseline Phe stratum in the prior six month period in Table 68.

Table 68: Diet Study: Demographic Characteristics Diet Study Part I by Baseline Phe Stratum, ITT

Trait	Blood Phe Stratum uM		ITT N=90
	< 300 N=47	≥ 300 N=43	
Gender, n (%)			
Male	28 (60)	23 (53)	51 (57)
Female	19 (40)	20 (47)	39 (43)
Age (years)			
mean (SD)	6.8 (2.5)	7.8 (2.5)	7.3 (2.5)
25 th , med, 75 th percentile	5, 6, 9,	6, 7, 10	5, 7, 10
Min, max	4, 11	4, 12	4, 12
Race, n (%)			
Caucasian	44 (94)	41 (95)	85 (94)
Hispanic	1 (2)	0	1(1)
Native American	1 (2)	0	1 (1)
Other	1 (2)	2 (5)	3 (3)
Weight (kg)			
mean (SD)	26.7 (8.5)	29.9 (9.6)	28.2 (9.1)
25 th , med, 75 th percentile	19, 25, 35	23, 26, 37	21, 26, 36
Min, max	14, 47	16, 51	14, 51

This Reviewer concludes that in Part I demographic differences between Baseline blood Phe strata were minor. The small number of non-Caucasian patients precludes analysis by race. There were no notable differences in age, gender or weight between Responders and Non-Responders in Part I (data not shown).

Of the 45 patients who received ≥1 dose in Part II, gender composition for the placebo group was equal and gender composition for the sapropterin group were 61% male and 39% female. The mean age of placebo-treated patients (N=12) was 7.5 (SD 2.6) years, and the mean age of sapropterin-treated patients (N=33) was 7.7 (SD 2.8) years. Thirty-two sapropterin- and nine placebo-treated patients completed Part II (Completers). These findings are summarized in Table 69.

Table 69: Diet Study: Demographic Characteristics, Diet Study Part II

Trait	Sapropterin N=33	Placebo N=12	ITT N=45
Gender, n (%)			
Male	20 (61)	6 (50)	26 (58)
Female	13 (39)	6 (50)	19 (42)
Age (years)			
mean (SD)	7.7 (2.8)	7.1 (2.0)	7.5 (2.6)
25 th , med, 75 th percentile	5, 8, 10	7	6, 7, 10
Min, max	4, 12	4, 11	4, 12
Race, n (%)			
Caucasian	33 (100)	11 (92)	44 (98)
Hispanic	0	1 (8)	1 (2)
Weight (kg)			
mean (SD)	17.9 (2.3)	17.3 (2.2)	17.8 (2.3)
25 th , med, 75 th percentile	16, 18, 19	17	16, 17, 19
Min, max	14, 24	15, 22	14, 24

Demographic characteristics appear evenly distributed across treatment groups; however, efficacy and safety comparisons by demographic characteristics between treatment groups is limited by the small population size of Part II, and 3:1 randomization of sapropterin to placebo.

10.1.3.13.3 Concomitant Medication

Concomitant medications were listed in the cm.xpt dataset, but the data presentation was not amenable to review.

10.1.3.13.4 Compliance with Study Medication

A high rate of compliance was achieved during Parts I and II.

Of 90 patients enrolled in Part I, all patients received ≥ 1 dose (20 mg/kg/day). Seventy-four patients (82%) took all the correct doses at the correct times through study Day 8; 12 patients (13%) missed ≥ 1 dose, but took no incorrect dose; and one patient (1%) received an incorrect dose, but missed no dose. Three patients (3%) had missing dosing data for portions of Part I. Most patients (86 of the 87) took their dose at the appropriate time of day. The mean number of missed doses was 0.2. Treatment compliance was comparable between the two blood Phe strata. These data are summarized in Table 70.

Table 70: Diet Study: Compliance Part I

Doses	Blood Phe Stratum (uM)		Total N=90
	< 300 N=47	> 300 N=43	
≥ 1 dose Administered, n (%)	47 (100)	43 (100)	90 (100)
All doses taken correctly	37 (79)	37 (86)	74 (82)
≥ 1 missed dose; none incorrect	8 (17)	4 (9)	12 (13)
≥ 1 incorrect dose; none missed	1 (2)	0	1 (1)
≥ 1 missed and ≥ 1 incorrect dose	0	0	0
Missing data for Part I	1 (2)	2 (5)	3 (3)
Drug taken at correct time, n (%)	46 (100)	40 (98)	86 (99)
Missed doses (n)	46	41	87
Mean (SD)	0.2 (0.6)	0.1 (0.3)	0.2 (0.5)
Range (min, max)	0, 3	0, 1	0, 3
Incorrect doses (n)	46	41	87
Mean (SD)	0 (0.1)	0	0 (0.1)
Range (min, max)	0, 1	0	0, 1

One patient withdrew from Part II prior to receiving sapropterin. Of the remaining 45 patients received ≥ 1 dose of either placebo or sapropterin (20 mg/kg/day). In Part II, 80% of patients who received ≥ 1 dose received all their doses in the prescribed amounts throughout Part II (67% of placebo patients, 85% of sapropterin patients). In both groups, missed doses were more common than incorrect doses. These findings are summarized in Table 71.

Table 71: Diet Study: Compliance, Part II

Doses	Sapropterin	Placebo	Total
Randomized	N=34	N=12	N=46
≥ 1 dose Administered, n (%)	33 (97)	12 (100)	45 (98)
All doses taken correctly	28 (85)	8 (67)	36 (80)
≥ 1 missed dose; none incorrect	2 (6)	4 (33)	6 (13)
≥ 1 incorrect dose; none missed	2 (6)	0	2 (1)
≥ 1 missed and ≥ 1 incorrect dose	1 (3)	0	1 (2)
Drug taken at correct time, n (%)	27 (82)	12 (100)	39 (87)

In Part I, mean (SD) daily dose was 19.6 mg/kg/day. There was no difference in mean daily dose for Responders or Non-Responders. The target dose for Part I was achieved.

In Part II, mean (SD) daily dose for sapropterin-treated patients was 19.9 mg/kg/day (SD 1.2). This Reviewer concludes the target dose for Part II was achieved.

10.1.3.13.5 Protocol Deviations and Violations

Protocol exemptions were granted for one patient who was not in diet control (blood Phe 483 uM) prior to the study, and for three patients with blood Phe >480 uM at Screening (486, 605, and 616 uM).

- This reviewer concludes granting exemptions for these patients should not affect the determination of safety or efficacy for Part I.

The most common protocol deviations in Parts I and II were procedure deviations. In Part I, protocol deviations were more common in the <300 uM blood Phe stratum (77% of 47 patients) than in the ≥300 uM blood Phe stratum (58% of 43 patients). In Part II, 83% of 12 placebo- and 88% of 33 sapropterin-treated patients had one or more protocol deviations. These findings are summarized in Table 72.

Table 72: Diet Study: Most Common Protocol Deviations

	Blood Draw	Off Schedule Visits	Dose Deviations	Compliance
Part I, n (%)	20 (22)	20 (22)	6 (14)	2 (2)
<300 Strata	8 (17)	11 (23)	12 (26)	1 (2)
≥300 Strata	12 (28)	9 (21)	6 (14)	1 (2)
Part II, n (%)	9 (20)	14 (31)	13 (29)	6 (13)
Sapropterin	7 (21)	11 (33)	10 (30)	3 (9)
Placebo	2 (17)	3 (25)	3 (25)	3 (25)

This Reviewer feels the most potentially meaningful deviations are dose and compliance deviations. Compliance with sapropterin administration in Part II was high, and 85% of patients took all doses correctly (see section 10.1.3.13.3 of this review). Therefore, this Reviewer concludes these deviations are not likely to affect analyses.

10.1.3.13.6 Efficacy Analyses

10.1.3.13.6.1 Efficacy Analyses Part I

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

At Screening, mean (SD) blood Phe for Responders and Non-Responders was similar [245 uM (SD 119) vs. 236 uM (SD 142), respectively]. Mean blood Phe for Non-Responders was stable from Screening to Day 1 [236 uM (SD 142) vs. 234 uM (SD 186), respectively]. Mean blood Phe for Responders increased from 245 uM (SD 119) to 317 uM (SD 173) from Screening to Day 1. This may be due to increased in dietary Phe between Screening and Day 1.

From Day 1 to Day 8, mean blood Phe in Responders decreased from 317 uM (SD 173) to 108 uM (SD 70), mean percent change was -64% (SD 18), and median percent change was -66 uM. From Day 1 to Day 8, mean blood Phe in Non-Responders increased from 234 uM (SD 186) to 264 uM (SD 171), mean percent change was 131% (SD 389), and median percent change was 11%. Five patients with percent increases of 236, 321, 533, 1300, and 2050% caused the mean percent change of Non-Responders to increase. These results are summarized in Table 73.

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Table 73: Diet Study: Mean Blood Phe Part I and Mean Percent Change in Blood Phe from Day 1 to Day 8

Blood Phe level (uM)	Responders	Non-Responders
	N=50	N=39
Screening		
Mean (SD)	245 (119)	236 (142)
95% CI of the Mean	212, 279	190, 281
Median	231	231
Percentiles (25 th , 75 th)	182, 330	126, 348
Min, max	12, 616	18, 605
Day 1		
Mean (SD)	317 (173)	234 (186)
95% CI of the Mean	267, 366	174, 295
Median	311	170
Percentiles (25 th , 75 th)	180, 438	72, 440
Min, max	49, 824	4, 572
Day 8		
Mean (SD)	108 (70)	264 (171)
95% CI of the Mean	88, 128	208, 319
Median	102	236
Percentiles (25 th , 75 th)	41, 159	144, 342
Min, max	6, 270	30, 832
Mean Change in Blood Phe, Day 8 – Day 1		
Mean (SD)	-209 (139)	30 (117)
95% CI of the Mean	-248, -170	-9, 68
Median	-184	12
Percentiles (25 th , 75 th)	-298, -104	-30, 82
Min, max	-656, -18	-215, 484
Mean Percent Change in Blood Phe, Day 8 – Day 1		
Mean (SD)	-64 (18)	131 (389)
95% CI of the Mean	-69, -59	5, 257
Median	-66	11
Percentiles (25 th , 75 th)	-78, -51	-12, 73
Min, max)	-99, -30	-39, 2050

The percent of Responders in the two strata, <300 and ≥300 uM, were similar (53% vs. 60%, respectively (data not shown). The mean percent change in blood Phe from Day 1 to Day 8 in Responders in the two strata, <300 and ≥300 uM, was similar -60% (SD 19) vs. -67% (SD 15), respectively (data not shown).

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

10.1.3.13.6.2 Part II, Primary Efficacy Analysis

The primary efficacy endpoint of Part II was the amount of Phe supplement tolerated at Week 10. This was defined as the net amount of Phe supplement tolerated while maintaining blood Phe level <360 uM. Diet was to remain unchanged except for protocol directed Phe supplement.

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

Phe supplement tolerated at Week 10 by sapropterin-treated patients was 21 mg/kg/day (SD 15) ($p < 0.001$; FDA statistical review; Stella Grosser, PhD). Phe supplement tolerated by placebo-treated patients was 3 mg/kg/day (SD 4) ($p = 0.03$; FDA statistical review; Stella Grosser, PhD), which was statistically different from zero supplement. The Sponsor performed an analysis of supplement tolerated by blood Phe stratum (average blood Phe < 300 vs. ≥ 300 uM in the six months preceding Screening). Sapropterin-treated patients in the < 300 uM stratum tolerated more supplementary Phe than patients in the ≥ 300 uM stratum [25 (SD 16) vs. 17 (SD 15) mg/kg/day]. The small size of the strata limits statistical inferences of analysis by strata. These findings are summarized in Table 74, which also displays Phe tolerated by 10 mg/kg/day categories for illustrative purposes. Of Completers, 63% of sapropterin-treated patients tolerated > 10 mg/kg/day of supplement compared to 0% of placebo-treated patients.

Table 74: Diet Study: Phe Supplement Tolerated at Week 10, ITT

Maximum Phe Supplement tolerated (mg/kg/day)	Sapropterin N=33	Placebo N=12
ITT (n)	33	12
Mean (SD)	21 (15)	3 (4)
95% CI of the Mean	16, 26	0.5, 5
Percentiles (25 th , median, 75 th)	7.5, 20, 35	0, 0, 5
Min, Max	0, 50	0, 10
p-value (one-sample t-test) ¹	$p < 0.001$	$p = 0.03$
Blood Phe Stratum < 300 uM (n)	16	5
Mean (SD)	25 (16)	2 (5)
95% CI of the Mean	16, 33	-4, 8
Percentiles (25 th , median, 75 th)	11, 20, 35	*, *, 5
Min, Max	0, 50	0, 10
Blood Phe Stratum ≥ 300 uM (n)	17	7
Mean (SD)	17 (15)	4 (4)
95% CI of the Mean	10, 25	$< 1, 7$
Percentiles (25 th , median, 75 th)	3, 15, 35	*, 5, 5
Min, Max	0, 40	0, 10
Groupings of tolerated Phe supplement, n (%)		
0 mg/kg/day	5 (15)	7 (58)
1-10 mg/kg/day	7 (21)	5 (42)
11-20 mg/kg/day	8 (24)	0
21-30 mg/kg/day	2 (6)	0
31-40 mg/kg/day	8 (24)	0
41-50 mg/kg/day	3 (9)	0

¹Source; FDA Statistician's Review

* Population of strata is too small for meaningful analysis

This Reviewer concludes that patients treated with sapropterin tolerated a statistically greater amount of dietary Phe supplement at Week 10.

This Reviewer performed an exploratory analysis on the 9 of 12 (75%) of placebo-treated patients and 32 of 33 (97%) of sapropterin-treated patients who completed the Part II. At Week

10, Phe supplement tolerated by sapropterin treated patients was 22 mg/kg/day (SD 15) and Phe supplement tolerated by placebo treated patients was 3 mg/kg/day (SD 4). Sapropterin-treated patients in the <300 uM stratum tolerated more supplementary Phe than patients in the >300 uM stratum [25 (SD 16) vs. 18 (SD 14) mg/kg/day]. The small size of the strata limits statistical inferences of comparison by strata. The small sizes of the strata of placebo treated patients who completed the study, precludes accurate determination of percentiles and confidence intervals. These findings are summarized in Table 75.

Table 75: Phe Supplement Tolerated at Week 10; Completers

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

* Population of strata is too small for meaningful analysis

This exploratory analysis supports the primary analysis; patients treated with sapropterin tolerated a statistically greater amount of dietary Phe supplement at Week 10. Table 76 also displays Phe tolerated by 10 mg/kg/day categories for illustrative purposes. Of Completers, 65% of sapropterin-treated patients tolerated >10 mg/kg/day of supplement compared to 0% of placebo-treated patients.

This Reviewer also assessed mean daily dietary Phe, excluding supplement, from Week 0 through 10 to determine if diet was stable. Dietary Phe, excluding supplement, at Week 0 was similar in sapropterin- and placebo-treated patients; 16.8 vs. 16.3 mg/kg/day, respectively. In sapropterin-treated patients, dietary Phe varied from 19.6 to 21.7 mg/kg/day from Week 1 to Week 10. In placebo-treated patients dietary Phe varied from 19.0 to 23.5 mg/kg/day from Week 1 to Week 10. These data are presented in Table 76.

Table 76: Mean (SD) Dietary Phe, Excluding Supplement, by Treatment Group

Dietary Phe (mg/kg/day)	Sapropterin N=34			Placebo N=12		
	n	Mean	SD	n	Mean	SD
Week 0	30	16.8	7.6	9	16.3	8.4
Week 1	33	20.5	13.4	12	21.6	10.2
Week 2	33	19.6	11.6	12	20.1	9.5
Week 3	33	20.3	11.3	12	19.4	8.1
Week 4	32	20.4	12.8	11	21.0	7.0
Week 5	32	20.9	13.0	10	21.8	9.0
Week 6	32	21.0	15.0	10	23.5	9.9
Week 7	32	19.7	11.8	10	22.2	11.6
Week 8	31	20.7	10.9	9	21.1	8.6
Week 9	31	21.0	16.4	9	20.8	12.1
Week 10	31	21.7	15.6	9	19.0	11.2

Source: Clinical Reviewer's Analysis

These findings indicate that dietary compliance, excluding Phe supplement, was well-controlled during Part II of the study.

In summary, this Reviewer concludes amount of Phe supplement tolerated at Week 10 was statistically greater in sapropterin [21 mg/kg/day (SD 15) (p<0.001)] than placebo [3 mg/kg/day (SD 4) (p=0.03)] treated patients. Daily dietary Phe intake, exclusive of supplement, did not affect analysis.

10.1.3.13.6.3 Part II, Secondary Efficacy Analyses

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

Forty-five patients who were randomized received either placebo (N=12) or sapropterin (N=33) completed treatment through Week 3.

From Week 0 to Week 3, mean blood Phe in sapropterin treated patients changed from 276 uM (SD 135) to 127 uM (SD 90), mean change was -149 uM (SD 134), mean percent change was -32% (SD 111), and median percent change was -55%. In placebo treated patients, mean blood Phe changed from 326 uM (SD 235) to 230 uM (SD 116), mean change was -97 uM (SD 244), mean percent change was 31% (SD 149), and median percent change was -17%. These findings are summarized in Table 77.

Table 77: Mean Change and Mean Percent Change in Blood Phe at Weeks 0 and 3

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

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

These findings suggest that sapropterin is more effective than placebo in reducing blood Phe in patients with BH-4 responsive PKU. Results at Weeks 1 and 2 were similar (data not shown).

10.1.3.13.6.4 Part II, Supplementary Efficacy Analyses

10.1.3.13.6.4.1 Mean Change in Daily Phe Intake

The mean (95% CI) changes in total daily Phe intake for sapropterin- and placebo-treated patients were 20.7 (95% CI 15.3, 26.1) and 7.4 (95% CI -1.1, 16.0) mg/kg/day, respectively. Since diet was stable (section 10.1.3.13.6.2; Table 77) this finding supports the primary efficacy findings.

The mean (SD) total daily Phe intake for both treatment groups is presented for illustrative purposes. For sapropterin-treated patients, mean (SD) total daily Phe intake increased from 16.8 mg/kg/day (SD 7.6) at Week 0 (prior to Phe supplementation) to 43.8 mg/kg/day (SD 24.6) at Week 10. For placebo-treated patients, mean (SD) total daily Phe intake increased from 16.3

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mg/kg/day (SD 8.4) Week 0 to 28.0 mg/kg/day (SD 11.3) at Week 6, and was 23.5 mg/kg/day (SD 12.6). These data are presented in Table 78.

Table 78: Mean (SD) Total Daily Phe, by Treatment Group

Dietary Phe (mg/kg/day)	Sapropterin N=33			Placebo N=12		
	n	Mean	SD	n	Mean	SD
Week 0	30	16.8	7.6	9	16.3	8.4
Week 1	33	20.5	13.4	12	21.6	10.2
Week 2	33	19.6	11.6	12	20.1	9.5
Week 3	33	20.7	11.4	12	19.4	8.1
Week 4	32	20.7	12.7	11	24.2	6.4
Week 5	32	25.7	12.9	10	24.3	9.1
Week 6	32	35.7	16.7	10	28.0	11.2
Week 7	32	34.8	13.6	10	26.0	13.7
Week 8	31	41.3	16.7	9	25.6	12.4
Week 9	31	41.2	21.6	9	22.8	15.0
Week 10	31	43.8	24.6	9	23.5	12.6

Source: Clinical Reviewer's Analysis

More Phe supplement was tolerated in sapropterin- than placebo-treated patients.

10.1.3.13.6.4.2 Difference in Mean Supplemental Phe Prescribed minus Ingested; Weeks 3 through 10

The difference mean Phe supplement (prescribed minus ingested) from Weeks 3 to 5 in sapropterin- and placebo treated patients was similar (-0.4 to 0.3 mg/kg/day and 0 to 1.4 mg/kg/day, respectively). From Week 6 to Week 10 the difference in mean supplemental (prescribed minus ingested) was higher in placebo- vs. sapropterin-treated patients (0.5 to 3.2 vs. 0.1 to 0.4 mg/kg/day, respectively). The mean Phe supplement taken by placebo-treated patients remained less than 5 mg/kg/day throughout the study. These findings are presented in Table 79.

Table 79: Diet Study: Mean Daily Phe Supplement Prescribed minus Ingested

Dietary Phe (mg/kg/day)	Sapropterin N=33				Placebo N=12			
	n	Mean	SD	95% CI	n	Mean	SD	95% CI
Week 3	33	-0.4	1.9	-1.0, 0.3	12	0	0	0
Week 4	32	0.3	1.4	-0.2, 0.9	11	0.4	1.5	-0.6, 1.5
Week 5	32	-0.1	0.9	-0.4, 0.2	10	1.4	2.0	0, 2.9
Week 6	32	0.4	1.9	-0.3, 1.1	10	2.5	6.3	-2.0, 7.0
Week 7	32	0.1	1.4	-0.4, 0.7	10	3.2	6.7	-1.6, 8.0
Week 8	31	0.1	2.0	-0.7, 0.8	9	0.5	1.7	-0.8, 1.8
Week 9	31	0.1	2.1	-0.7, 0.9	9	3.0	6.6	-2.1, 8.1
Week 10	31	0.4	2.9	-0.7, 1.4	9	0.6	1.7	-0.7, 1.9

Source: Clinical Reviewer's Analysis

These findings suggest that compliance with prescribed supplement was lower in placebo-treated patients; however, due to the uneven randomization (12 placebo vs. 33 sapropterin) the clinical relevance of these findings are unclear. This Reviewer concludes the effect on efficacy can not be determined.

10.1.3.13.6.4.3 Mean Phe Supplement Tolerated at Each Week (Weeks 3 through 10)

Per the study protocol, dietary Phe adjustments could only be made at odd numbered weeks, and assessments of tolerance could only be made at even number weeks.

- At Week 4 Phe supplement tolerated in sapropterin- and placebo-treated patients were 4.2 (SD 1.8) and 2.7 (SD 2.6) mg/kg/day.
- At Week 6 Phe supplement tolerated in sapropterin- and placebo-treated patients were 12.0 (SD 7.5) and 3.5 (SD 4.1) mg/kg/day.
- At Week 8 Phe supplement tolerated in sapropterin- and placebo-treated patients were 16.3 (SD 11.8) and 2.2 (SD 3.6) mg/kg/day.
- At Week 10 Phe supplement tolerated in sapropterin- and placebo-treated patients were 21.8 (SD 15.4) and 2.8 (SD 3.6) mg/kg/day.

At all Weeks where supplemental Phe tolerance was assessed, sapropterin-treated patients tolerated more dietary Phe than placebo-treated patients. These results are summarized in Table 80.

Table 80: Diet Study: Tolerated Supplemental Phe at Weeks 4, 6, 8, and 10

Dietary Phe (mg/kg/day)	Sapropterin N=33				Placebo N=12			
	n	Mean	SD	95% CI	n	Mean	SD	95% CI
Week 4	32	4.2	1.8	3.6, 4.9	11	2.7	2.6	1.0, 4.5
Week 6	32	12.0	7.5	9.3, 14.7	10	3.5	4.1	0.6, 6.4
Week 8	31	16.3	11.8	12.0, 20.5	9	2.2	3.6	-0.6, 5.0
Week 10	31	21.8	15.4	16.1, 27.4	9	2.8	3.6	0, 5.6

Source: Clinical Reviewer's Analysis

These results support the primary efficacy finding of Part II, but should not be used to suggest that the effect of sapropterin increases with duration of treatment.

10.1.3.13.6.4 Efficacy Summary

The efficacy goal of Part I was to identify patients with PKU on Phe-restricted diets with moderately elevated blood Phe (≤ 460 uM) who responded to an eight day course of treatment with sapropterin (20 mg/kg/day). Response was defined as a $>30\%$ decrease in blood Phe from Day 1 (Baseline) to Day 8, and blood Phe ≤ 300 uM at Day 8. Of 90 patients enrolled in the study, 89 patients (99%) completed Part I.

- In Part I, 50 patients had a mean change from Day 1 blood Phe level to Day 8 of -209 uM (SD 139), and mean percent change (decrease) of -64% (SD 18) and were eligible for entry into Part II (e.g., Responders).

In conclusion, the Sponsor successfully identified 50 patients (56%) who qualified for enrollment in Part II.

The primary efficacy endpoint of Part II was the amount of Phe supplement tolerated at Week 10. This was defined as the net amount of Phe supplement (maximum 50 mg/kg/day) tolerated

while maintaining blood Phe level <360 uM. Diet was to remain unchanged except for protocol directed changes in supplement.

- For the ITT of Part II, Phe supplement tolerated at Week 10 by patients treated with sapropterin was 21 ± 15 mg/kg/day ($p < 0.001$) and Phe supplement tolerated by placebo treated patients was 3 ± 4 mg/kg/day ($p = 0.03$).
 - For patients in the < 300 uM stratum, mean Phe supplement tolerated at Week 10 was 25 ± 16.0 mg/kg/day.
 - For patients in the > 300 uM stratum, mean Phe supplement tolerated at Week 10 was in 17 ± 15 mg/kg/day.
 - Mean dietary Phe, without supplement, was similar in placebo- and sapropterin-treated patients, and did not affect primary efficacy analysis.

In summary, the amount of Phe supplement tolerated at Week 10 was statistically greater in sapropterin [21 mg/kg/day (SD 15; $p < 0.001$)] than placebo [3 mg/kg/day (SD 4); $p = 0.03$] treated patients, and variability in daily Phe intake, excluding supplement, did not affect analysis.

The secondary efficacy endpoint of Part II was to compare change in blood Phe from pre-treatment (Week 0) to Week 3 of treatment, sapropterin-treated patients.

- In sapropterin-treated patients, the mean (SD) change in blood Phe from Week 0 to Week 3 was -149 uM (SD 134), the mean percent change was -32% (SD 111), and the median percent change was -55% .

The results of the secondary efficacy analysis suggest that when diet is controlled, sapropterin 20 mg/kg/day reduces blood Phe in patients with BH-4 responsive PKU.

The therapeutic goal for patients with PKU is reduction in blood Phe, which is correlated with improved long-term neurologic outcome. Tolerated dietary Phe supplement has not been correlated with long-term neurologic outcomes and is, therefore, not an established clinical endpoint.

_____ | long-term studies with neurocognitive outcomes are required in order to establish safety and efficacy of dietary Phe supplementation.

10.1.3.14 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. Deaths and serious AEs were collected from the signing of informed consent through completion of the Week 14 follow-up. Non-serious AEs were reported from the time of first dose through completion of the Week 14 follow-up. Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT). The adverse event, clinical laboratory, and vital sign datasets were reviewed. Notable findings are presented below.

10.1.3.14.1 Exposure

The safety population included 90 patients received at least one dose of sapropterin. The first consent was signed on 9-February-2006 and the final safety assessment was performed on 6-November-2006.

In Part I, the mean dose was 19.6 mg/kg/day (SD 1.6), and 75 of 90 patients (83%) took at least 8 doses. In Part II, mean dose in sapropterin treated patients (N=33) was 19.6 mg/kg/day (SD 1.2). In Part II, 85% of sapropterin treated patients and 67% of placebo treated patients received all their doses.

10.1.3.14.2 Adverse Events

AEs are reported from administration of first dose completion of Week 14 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 sapropterin as the denominator (N=90). AEs were tabulated and analyzed using the aadata.xpt dataset (section 5.3.5.1.25.3.1 of the electronic submission).

Part I: The most common non-serious AEs in Part I 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. These findings are summarized in Table 81.

Table 81: Diet Study Part I; Non-Serious AEs in ≥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)

Additionally, one patient had moderate neutropenia (ANC 660) documented as an AE at Day 8. This patient's ANC remained between 850 and 990 during double blind treatment with placebo in Part II. Neutropenia is discussed in section 10.1.3.15.6, below.

Part II: In this randomized, double-blind, placebo controlled portion of the study the incidence of non-serious AEs was higher in sapropterin- than placebo-treated patients (79% vs. 58%, respectively).

Non-serious AEs occurred in 26 (79%) of sapropterin-treated patients and in 7 (58%) of placebo-treated patients. The most common AEs in sapropterin-treated patients were headache and rhinorrhea (21% each), cough (15%), and diarrhea and vomiting (12%, each). The most common AEs in placebo-treated patients were pyrexia, fatigue, streptococcal infection, and rash, (17%, each). Additionally, one patient in each treatment group had moderate neutropenia during Part II. The majority of these AEs represent common non-serious complaints in the general population and patients in clinical trials. Neutropenia is discussed in section 10.1.3.15.6. AEs occurring in ≥ 2 patients are listed in Table 82.

Table 82: Diet Study Part II: Non-Serious AEs in ≥ 2 patients

		Total N=45	Sapropterin N=33	Placebo N=12
System, Organ, Class Term	Preferred Term	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	Lymphadenopathy	2 (4)	2 (6)	0
Gastrointestinal disorders	Diarrhea	4 (9)	4 (12)	0
	Vomiting	4 (9)	4 (12)	0
	Abdominal pain	4 (9)	3 (9)	1 (8)
	Toothache	2 (4)	2 (6)	0
	Aphthous stomatitis	1 (2)	0	1 (8)
General disorders and administration site conditions	Pyrexia	5 (11)	3 (9)	2 (17)
	Fatigue	3 (7)	1 (3)	2 (17)
Infections and infestations	Upper respiratory tract infection	3 (7)	2 (6)	1 (8)
	Streptococcal infection	3 (7)	1 (3)	2 (17)
Injury, poisoning and procedural complications	Contusion	4 (9)	3 (9)	1 (8)
	Excoriation	2 (4)	2 (6)	0
Investigations	Neutrophil count decreased	2 (4)	1 (3)	1 (8)
	White blood cell count decreased	2 (4)	1 (3)	1 (8)
Metabolism and nutrition disorders	Decreased appetite	2 (4)	2 (6)	0
Nervous system disorders	Headache	8 (18)	7 (21)	1 (8)
Respiratory, thoracic and mediastinal disorders	Rhinorrhea	7 (16)	7 (21)	0
	Cough	5 (11)	5 (15)	0
	Pharyngolaryngeal pain	5 (11)	4 (12)	1 (8)
	Nasal congestion	3 (7)	3 (9)	0
Skin and subcutaneous tissue disorders	Erythema	2 (4)	2 (6)	0
	Rash not otherwise specified; erythematous, pruritis	5 (11)	3 (9)	2 (17)
Any AE		33 (73)	26 (79)	7 (58)

The significance of the higher incidence of AEs in sapropterin treated patients is uncertain due to unequal randomization (3:1), short duration of treatment, and small study size.

10.1.3.14.3 Deaths and SAEs

No deaths were reported. No SAEs were reported in Part I. Two SAEs were reported in Part II.

- Patient 0110-6103, four year old female, had streptococcal pharyngitis during sapropterin treatment in Part II. Hospitalization and antibiotic treatment was required. The CRF was reviewed and this Reviewer concludes the AE was not related to sapropterin treatment.
- Patient 0114-6044, a seven year old girl, treated with placebo in Part II, had appendicitis. The CRF was reviewed and this Reviewer concludes this AE was not related was not related to sapropterin treatment.

10.1.3.14.4 Withdrawals

Five patients withdrew due to compliance (N=4) or increase in blood Phe (N=1). See Table 83.

Table 83: Diet Study, Withdrawals

Patient	Part of Study	Treatment	Dose	Comment
0109-6008	Part I	Sapropterin	Unknown	No Day 8 procedures
0110-6029	Part II	Sapropterin	Not given	No Week 0 Visit; No AE
0109-6001	Part II	Placebo	n/a	Withdrew consent; Skin Rash; Strep
0113-6027	Part II	Placebo	n/a	Withdrew consent; No AE
0185-6065	Part II	Placebo	n/a	Withdrew consent; Increase in blood Phe; rhinitis and prurigo

The CRFs were reviewed for these patients, and this Reviewer concludes these five withdrawals were not related to receipt of sapropterin.

10.1.3.14.5 Vital signs

The vital sign dataset was reviewed and there were no notable differences in mean, median, and 25th and 75th percentiles between non-treatment baseline and Day 8 of treatment in Part I, or between placebo and sapropterin treated patients in Part II of the study.

10.1.3.14.6 Laboratory Analyses

The entire laboratory dataset was reviewed. Notable findings are presented.

Of seven patients with neutropenia identified in the Diet Study, two patients had moderate neutropenia and five patients had mild neutropenia. These findings are summarized in Table 84.

Table 84: Diet Study, Neutropenia

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
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

— Did not participate in double-blind treatment

- Patient 0184-6045, a nine year old male, developed moderate neutropenia in Part I and remained moderately neutropenic through Part II during double-blind placebo treatment. The maximum post-sapropterin ANC in this patient was at Week 14 follow-up (ANC 1,210). AEs in Part I included abdominal pain, ear infection, and decreased WBC count (2,600). AEs in Part II included abdominal pain, pharyngolaryngeal pain, thermal burn, and decreased WBC count (2,800). The patient's WBC count increased to 3,900 by the end of the study. This Reviewer concludes potential contributing factors were present.
- Patient 0015-6054, six year old male, had moderate neutropenia in Part I but did not continue in Part II. A single AE was reported in Part I, an excoriated elbow and knee. This patient's WBC count was normal.
- Patient 0135-6071, a nine year old female, became moderately neutropenic at Week 0 of double-blind phenoptin treatment. This patient's ANC increased to 2350 at Week 6 and decreased to 960 at Week 10. No AEs were reported in Part I. AEs reported in Part II included two arthropod bites or stings, confusion, headache, rash, and decreased WBC count (3,000).
- Patient 0110-6103, a four year old female, had moderate neutropenia that increase to 2.790 at Week 10 of double blind sapropterin treatment. Part I AEs included cervical lymphadenopathy, nausea, and pharyngolaryngeal pain. Part II AEs included cough, diarrhea, headache, irritability, pyrexia, rhinorrhea, and streptococcal infection. This patient's WBC count was normal. This Reviewer concludes potential contributing factors were present.
- Patient 0109-6084, a nine year old female, had mild neutropenia during Part I, which returned to normal during the washout period. No AEs were reported during Part I. AEs reported during Part II include pyrexia, upper respiratory tract infection, and rash. This patient's WBC count was normal.
- Patient 0109-6013, a four year old female, had mild neutropenia that resolved while on double blind sapropterin treatment. No AEs were reported during Part I. AEs reported during Part II include abdominal pain, confusion, decreased appetite, diarrhea,

rhinorrhea, streptococcal infection, and vomiting. This patient's WBC count was normal. This Reviewer concludes potential contributing factors were present.

- Patient 0124-6043, an eight year old male, had mild neutropenia that resolved that while on double blind sapropterin treatment. This patient had a WBC count of 5,100 at Screening, 2,800 at Week 0, and 6,100 at Week 10.

Seven patients in the Diet Study had neutropenia. Neutropenia was also noted in the Enrichment Study, the Diet Study, and the Extension Study (appendix 10.1.4). The combination of open-label non-placebo-controlled and randomized double-blind, placebo controlled studies, and the presence of potential contributing factors in several patients makes determination of causation difficult. This Reviewer recommends that neutropenia be addressed in labeling.

There were no notable abnormalities in alanine amino transferase or gamma-glutamyl transferase. 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. This patient did participate in Part II.

There were no other notable clinical laboratory findings.

10.1.3.14.7 Safety Summary

The safety results from the Diet Study show the following:

1. 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). In Part I, non-serious AEs including abdominal pain, headache, and nausea were common. In Part II, non-serious AEs were more common in sapropterin- than placebo-treated patients (79% vs. 58%, respectively). The most common AEs in sapropterin-treated patients were headache and rhinorrhea (21% each), and cough (15%). The most common AEs in placebo-treated patients were pyrexia, fatigue, streptococcal infection, and rash, (17%, each).
2. No Deaths were reported. Two SAEs were reported in Part II, including one report of streptococcal pharyngitis in a sapropterin-treated patient, and one report of appendicitis in a placebo-treated patient.
3. Summary clinical laboratory findings include the following:
 - a. Seven patients had mild to moderate neutropenia, four of whom first experienced neutropenia during open-label treatment. Six patients had neutropenia during Part II, two of whom were receiving placebo; neutropenia was documented in these two patients in Part I.
4. No notable trends in vital signs were found.

Sapropterin appears to have been well tolerated. Most AEs were mild to moderate in severity, were self-limited, and were consistent with underlying disease or commonly reported illnesses in otherwise healthy individuals. In summary, the short-term safety of sapropterin 10 mg/kg/day in patients with BH4-responsive PKU is established. Important limitations of the study include the short duration (ten weeks), the small study population, and 3:1 randomization. Though the incidence of mild to moderate neutropenia in Part II in sapropterin- and placebo-treated patients was similar (12% vs. 17%), all patients had prior exposure to sapropterin, and challenge/re-challenge assessments were not possible. This Reviewer, therefore, recommends that neutropenia be addressed in labeling

10.1.3.16 Overall Summary of the Diet Study (PKU-006)

The efficacy endpoint of Part I was a $\geq 30\%$ decrease in blood Phe from Baseline to Day 8 and blood Phe < 300 uM at Day 8.

- Fifty of 89 patients (56%) had a $\geq 30\%$ decrease in blood Phe from Baseline to Day 8 and had Day 8 blood Phe < 300 uM.

The primary efficacy endpoint of Part II was Phe supplement tolerated at Week 10 (mg/kg/day).

- Phe supplement tolerated by sapropterin treated patients was 21 mg/kg/day (SD 15); $p < 0.001$.
- Phe supplement tolerated by placebo treated patients was 3 mg/kg/day (SD 4); $p = 0.03$.

In summary, sapropterin treated patients tolerated a statistically greater amount of Phe supplement than placebo treated patients at Week 10.

The secondary efficacy endpoint was comparison of the change in blood Phe of sapropterin-treated patients from Week 0 to Week 3 (prior to dietary Phe supplementation).

- In sapropterin-treated patients, the mean (SD) change in blood Phe from Week 0 to Week 3 was -149 uM (SD 134), the mean percent change was -32% (SD 111), and the median percent change was -55% .
- In contrast, in placebo-treated patients, the mean (SD) change in blood Phe from Week 0 to Week 3 was -97 uM (SD 244), the mean percent change was 31% (SD 149), and the median percent change was -17% .

Under diet controlled conditions, sapropterin reduces blood Phe in patients with BH4-responsive PKU. These results support the primary efficacy findings in the Efficacy Study (PKU-003).

The primary efficacy variable, dietary supplement tolerated at Week 10, was not a suitable efficacy endpoint. The Division is not willing to allow this endpoint ~~_____~~ at the current time due to the following:

10.1.4.1 Study Design

The Extension Study (PKU-004) was a 26 week, multi-national, open-label (OL), safety, efficacy, and dose-titration study of 80 patients with PKU who completed the Efficacy Study and received $\geq 80\%$ of doses in the Efficacy Study. The Extension study was designed to evaluate the long-term safety and efficacy of three different doses of sapropterin in 80 patients with PKU. The study was conducted in two parts. Part I was a six-week forced dose-titration study of three different doses of sapropterin (5, 10, and 20 mg/kg/day) for two weeks each. Part II was a fixed-dose study where patients were treated with a dose selected based on blood Phe during Part I.

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

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

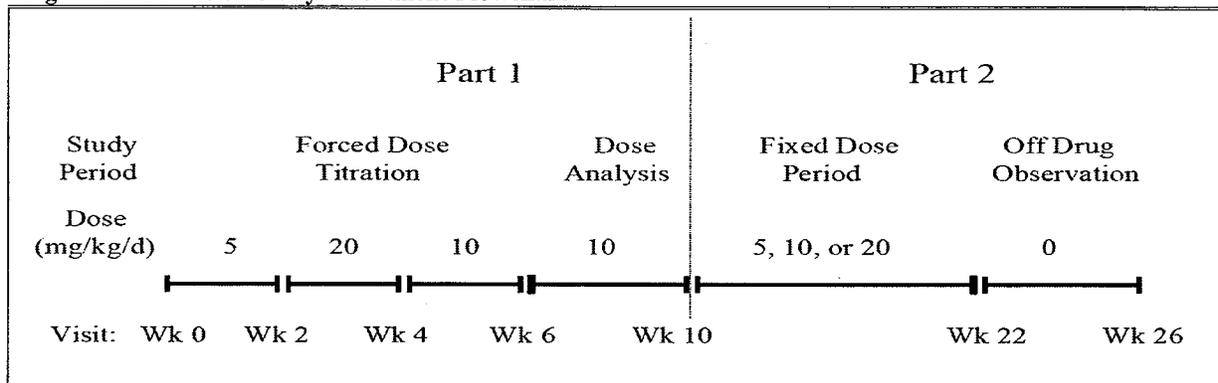
- If blood Phe was < 240 uM at the Week 6 visit and < 600 uM at the Week 2 visit, then provide a fixed dose of 5 mg/kg/day.
- If blood Phe was < 240 uM at the Week 6 visit and ≥ 600 uM at the Week 2 visit, then provide a fixed dose 10 mg/kg/day.
- If blood Phe at Week 6 was ≥ 240 uM and < 600 uM, provide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

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

Diet was not controlled, but patients were instructed to continue their usual diet without modification throughout the study.

The study design is presented in Figure 12.

Figure 12: Extension Study: Treatment Flowchart



Plasma samples for tetrahydrobiopterin (BH4) analysis were obtained at Weeks 16, 20 and 22 in order to perform population PK analyses. A subset of patients was offered participation in a sub-study to evaluate potential changes in blood Phe over a 24-hour period (PD) during Week 6 to Week 10 of the study. The PK and PD results are presented in a separate report and are discussed in the Clinical Pharmacology review (Hae-Young Ahn, PhD).

10.1.4.2 Study Objectives

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

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

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

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

10.1.4.3 Eligibility Criteria

To be eligible for the study, patients must have been diagnosed with BH4-responsive PKU and must have received $\geq 80\%$ of the scheduled doses in the Efficacy Study (PKU-003). Patients must have been willing to continue current diet unchanged during in the study.

Patients were excluded from study participation if they had primary BH4 deficiency, or recent or current use of folate inhibitors or levodopa; or if they failed to complete the Efficacy Study, except for patients who were removed from the Efficacy study because their blood Phe exceeded the alert level, or if they had any serious illness not under medical control.

The method of excluding primary BH4 deficiency was not provided.

10.1.4.4 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 (Week 26) were recorded in the CRFs.

10.1.4.5 Study Visits and Procedures

Study visits and procedures are summarized in the following table. All procedures were to be performed within two days of scheduled visit. The first dose of sapropterin was taken at home, the day after the Week 0 visit. If a patient's Week 6 visit in the Efficacy Study coincided with Week 0 of the current study, blood Phe analysis at Week 0 remained blinded to within the Efficacy Study datasets. Patients who were to receive a fixed dose of 5 mg/kg/day who had a Week 12 blood Phe \geq 600 uM were instructed to increase the dose to 10 mg/kg/day. Study procedures are summarized in Table 85.

Table 85: Extension Study: Table of Events

Procedure	Open-Label Treatment									
	Part I				Dose Analysis	Part II				F/U
	Forced Dose Titration Period					Fixed Dose Period				
Events	Wk 0	Wk 2	Wk 4	Wk 6	Wk 10	Wk 12	Wk 16	Wk 20	Wk 22	Wk 26
Consent	X									
History	X									
Vital signs	X	X	X	X	X	X	X	X	X	X
Physical Exam	X					X			X	X
Lab Tests	X		X		X		X	X	X	X
Blood Phe	X	X	X	X	X	X	X	X	X	X
PK assessments							X	X	X	X
Pregnancy Test	X		X		X		X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X
Dispense Drug	X	X	X	X	X	X	X	X	X	
Diet Query	X	X	X	X	X	X	X	X	X	
Dose mg/kg/day	5	20	10	10		5, 10, or 20, based on Week 2, 6, and 12 Blood Phe				None

10.1.4.6 Randomization, Blinding and Controls

This was an open-label study. There was no randomization, blinding, or control. Diet was not controlled.

10.1.4.7 Study Medication Dose Selection, Dispensing, and Compliance

Drug was provided in tablets containing 100 mg of sapropterin. At each scheduled dose, patients or their caregivers dissolved the prescribed number of sapropterin tablets in four to eight ounces of water, apple juice, or orange juice by mixing gently. The number of tablets per dose was calculated for the patient. Drug was to be ingested as solution within 15 minutes of dissolution. No instructions were given regarding the administration of drug in relationship to meals. Drug was dispensed by study qualified staff.

Drug product packaging was stamped with the lot number and retest date and was provided in a bottle or card labeled with the study number. For the bottled tablets, lot numbers T140503, T140504, T140507, T140508, T140601, T140602, T140604, and T140505 were used, and lot number T140511 was used for blister card tablets.

Drug was supplied as 300 mg tablets, each containing 100 mg of sapropterin dihydrochloride. Drug was packaged in bottles containing 45 tablets per bottle or in blister cards containing 28 tablets.

10.1.4.8 Diet

Low Phe diets were abandoned prior to entering, but not as a condition of entering, this study. Patients were instructed to not modify their diet from enrollment through completion of all study procedures. Patients were counseled on the benefits of dietary control as standard of care. In summary, dietary Phe intake was not controlled during this study.

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 particularly during Part I (forced dose titration).

10.1.4.9 Efficacy and Endpoint Measures

The efficacy variable was blood Phe.

10.1.4.9.1 Primary Efficacy Endpoint

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

Efficacy endpoints included:

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

10.1.4.9.3 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 outlined in Table 86 in section 10.1.4.5 of this review. SAEs were reported from Screening through completion of Week 26 follow-up. Non-serious AEs were reported from time of first dose through completion of Week 26 follow-up. AEs or clinical laboratory abnormalities that persisted through the end of the study were to be followed until resolution or stabilization, or determination that the AE was not reasonably caused by the study drug.

10.1.4.9.4 PK and PD Measures

Population PK analyses were performed on blood samples collected on selected patients during the Week 16, 20, and 22 visits (Sub-study 01) and results are discussed in the Clinical Pharmacology review (Hae-Young Ahn, PhD).

10.1.4.10 Additional Statistical Considerations

No formal calculation was conducted to determine the sample size for this study. Patients who participated in the Efficacy Study (PKU-003) were eligible to enroll the current Extension Study (PKU-004). This provided a potential sample size of 88 subjects if all patients enrolled in the Enrichment Study were to receive $\geq 80\%$ of treatments in that study. The sponsor assumed 80 patients would enroll.

There was no imputation for missing data.

10.1.4.11 Protocol Amendments

One amendment dated 24-January-2006 allowed for an interim analysis at the end of Week 6. The purpose of this interim analysis was to compare the safety, tolerability, and effect on blood Phe of the three doses.

It is not apparent how the study could have proceeded to Part II without an interim analysis of effect (change in blood Phe) during Part I. This Reviewer concludes the interim analysis was necessary to determine fixed doses during Part II. The lack of blinding to treatment or blood Phe may affect determination of “optimum dose” in Part I.

10.1.4.12 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.

10.1.4.13 Study Results

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

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

Eighty patients enrolled, including 41 patients who received placebo and 39 patients who received sapropterin in the Efficacy Study (PKU-003). Of the 39 patients who received sapropterin during the Efficacy Study, seven transitioned directly into the Extension study with no gap in treatment. The remaining 32 patients with prior exposure in the Efficacy Study had a mean gap in treatment of 63.2 days (SD23; range 14 to 133) between the last dose in the Efficacy Study and the first dose in the Extension Study. Prior to receipt of the first dose in the Extension Study, the most recent exposure to sapropterin for patients who received placebo during the Efficacy Study was >30 days (i.e., the last dose during the Enrichment Study).

10.1.4.13.1 Patient Population and Demographics

Gender distribution in the ITT was approximately even and age was 20.4 years (SD 9.6). The SP and PPbo sub-groups were similar in age and gender. Demographic characteristics are summarized in Table 86.

Table 86: Subject Characteristics at Baseline by Study PKU-003 Treatment Group

Trait	PKU-003 Treatment Group		Total N=80
	Placebo N=41	Sapropterin N=39	
Gender			
Male, n (%)	21 (51)	26 (67)	47 (59)
Female, n (%)	20 (49)	13 (33)	33 (41)
Age (y)			
Mean (\pm SD)	19.5 (9.9)	21.3 (9.3)	20.4 (9.6)
25 th , median 75 th percentile	13, 17, 22	14, 18, 29	14, 18, 25
8 to \leq 12 years	10 (24)	5 (13)	15 (19)
12 years and older	31 (76)	34 (87)	65 (81)
Race, n (%)			
Caucasian	41 (100%)	37 (95)	78 (98)
Asian/Pacific Islander	0	1 (3)	1 (1)
Other	0	1 (3)	1 (1)
Weight (kg)			
Mean (\pm SD)	69.8 (26)	64.8 (16)	67.3 (22)
25 th , median 75 th percentile	51, 68, 78	55, 60, 76	54, 67, 76
Min, max	28, 144	36, 101	28, 144

10.1.4.13.2 Concomitant Medication

One hundred thirty five different types of concomitant medicines or combination preparations were taken during the study. Sixty-seven patients were exposed to concomitant medications during the study. One patient received measles, mumps, rubella vaccine, and one patient received meningococcal vaccine during the study. The most commonly administered concomitant medications were non-prescription pain relievers including paracetamol (31%) and ibuprofen (25%), followed by vitamin preparations (17%). Table 87 summarized concomitant medications used in \geq 4% of patients in the Extensions Study.

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Table 87: Extension Study: Concomitant Medications used in ≥4% of Patients.

Medicine	N=80 n (%)
Paracetamol	25 (31)
Ibuprofen	20 (25)
Vitamins nos, Vitamins/Minerals	13 (17)
Acetylsalicylic acid	5 (6)
Diphenhydramine hydrochloride	5 (6)
Loratadine	5 (6)
Pseudoephedrine hydrochloride	5 (6)
Cefalexin	4 (5)
Paroxetine	4 (5)
Oral Contraceptives	4 (5)
Ethinylestradiol/Gestodene	2 (3)
Ethinylestradiol/Norgestimate	2 (3)
Amoxicillin	3 (4)
Cetirizine hydrochloride	3 (4)
Choline salicylate	3 (4)
Clarithromycin	3 (4)
Codeine phosphate/Paracetamol	3 (4)
Cough and cold preparations	3 (4)
Dextromethorphan hydrobromide/Doxylamine succinate/Ephedrine sulfate/Ethanol/Paracetamol	3 (4)
Loperamide hydrochloride	3 (4)
Salbutamol sulfate	3 (4)

10.1.4.13.3 Compliance with Study Medication

Sixty percent of patients took all doses correctly. In the current study, 69% of patients who had received sapropterin in the Efficacy Study and (51%) of patients who had received placebo in the Efficacy Study received all doses correctly. Eighteen percent of patients missed ≥1 dose, 9% of patients had ≥1 incorrect dose, and 14% of patients had ≥1 missed dose and ≥1 incorrect dose. These findings are summarized in Table 88.

Table 88: Extension Study: Treatment Compliance

	Prior Treatment in Efficacy Study (PKU-003)		Total (N=80)
	Placebo (N=41)	Sapropterin (N=39)	
≥ 1 dose administered, n (%)	41 (100)	39 (100)	80 (100)
All doses correctly administered	21 (51)	27 (69)	48 (60)
≥ 1 missed dose; no incorrect dose	9 (22)	5 (13)	14 (18)
≥ 1 incorrect dose; no missed dose	4 (10)	3 (8)	7 (9)
≥ 1 missed dose; ≥ 1 incorrect dose	7 (17)	4 (10)	11 (14)

This Reviewer concludes that blood Phe results could be affected; however, because diet was not controlled, the effect of missed or incorrect doses on blood Phe can not be determined.

10.1.4.13.4 Protocol Deviations and Violations

Dosing deviations are discussed in Compliance (section 10.1.4.14.3, above). One patient received placebo for three days which had been labeled for use in the Efficacy Study.

Nineteen patients reported diet changes which were evenly distributed between patients with prior placebo treatment and prior sapropterin treatment in the Efficacy Study. Protocol deviations are summarized in Table 89.

Table 89: Extension Study: Protocol Deviations

Violation Type	Prior Treatment in Efficacy Study (PKU-003)		Total (N=80)
	Placebo (N=41)	Sapropterin (N=39)	
≥ 1 of the following; n (%)	24 (59)	15 (38)	39 (49)
Eligibility criteria	1 (2)	0	1 (1)
Dosing	20 (49)	12 (31)	32 (40)
Diet	10 (24)	9 (23)	19 (24)

This Reviewer concludes that blood Phe results could be affected; however, because diet was not controlled, the effect of missed or incorrect doses on blood Phe can not be determined.

Additionally an exemption was made for one patient who received mumps.

10.1.4.13.5 Efficacy Analyses

During forced dose titration, patients received sapropterin 5 mg/kg/day for two weeks, followed by 20 mg/kg/day for two weeks, followed by 10 mg/kg/day for two weeks (ending at the Week 6 visit). Patients then continued on 10 mg/kg/day treatment for four more weeks ending at the Week 10 visit. All patients in the current study had a $\geq 30\%$ decrease in blood Phe compared to non-treatment Baseline in the Efficacy Study (PKU-003).

The primary efficacy analysis in the Extension Study was change in blood Phe from Baseline at the end of each two week at dosing period (Weeks 2, 4, and 6).

Baseline for the Extension Study was defined as the Week 0 blood Phe level. If patients did not enroll directly from the Efficacy Study (e.g. there was an interruption in placebo or drug treatment), the Baseline blood Phe for the Extension Study was measured at the Week 0 visit of the Extension Study. If the patient enrolled immediately from the Efficacy Study (e.g., no interruption in treatment) the Week 6 blood Phe measurement from the Efficacy Study was used as the Baseline blood Phe value for the Extension Study.

10.1.4.13.5.1 Efficacy Analyses Part I

10.1.4.13.5.1.1 Primary Efficacy Analysis

The primary efficacy endpoint of Part I was change in blood Phe at the end of Week 2 (5 mg/kg/day), Week 4 (20 mg/kg/day), and Week 6 (10 mg/kg/day) compared to Week 0. All 80 patients completed Part I visits and procedures. The efficacy analysis and conclusions are based

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on the ITT; however, because seven patients were on sapropterin treatment (10 mg/kg/day) at Week 0, results are also presented by PPbo and SP sub-groups.

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

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

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

At the end of Week 6 (10 mg/kg/day), mean blood Phe levels for the PPbo, SP, and ITT were 687 uM (SD 426), 591 uM (328), and 640 uM (SD 382), respectively.

At the end of Week 10 (10 mg/kg/day), mean blood Phe levels for the PPbo, SP, and ITT were 674 uM (SD 397), 615 uM (SD 392), and 645 uM (SD 393); similar to Week 6.

Blood Phe results from Week 0 through Week 6 are summarized in Table 90.

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Table 90: Mean Blood Phe Weeks 0, 2, 4, and 6 by Prior Treatment Group

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

Mean blood Phe at Week 10 blood Phe is not shown

Mean blood Phe for the ITT decreased with first exposure during Week 2 (5 mg/kg/day). PPbo and SP patients behaved similarly from Week 2 to Week 6; however, the decrease in blood Phe for SP patients was less than PPbo patients at Week 2 which is likely because 18% of these 39 patients were already on treatment (10 mg/kg/day) at Week 0. Possible reasons for the difference between the groups include differences in mean residual enzyme activity levels between the groups, and differences in diet or compliance that were not recorded in the datasets.

Mean change in blood Phe from Baseline was calculated at Weeks 2, 4, and 6. Mean changes in blood Phe from Baseline at Week 2 (5 mg/kg/day) for the PPbo, SP, and ITT were -161 uM (SD 284), -37 uM (SD 297), and -100 uM (SD 295), respectively. Mean changes from Baseline at Week 4 (20 mg/kg/day) for the PPbo, SP, and ITT were -296 uM (SD 295), -229 uM (SD 341), and -263 uM (SD 318). Mean changes from Baseline at Week 6 (10 mg/kg/day) for the PPbo, SP, and ITT were -241 uM (SD 302), -154 uM (SD 324), and -199 uM (SD 314). These results are summarized in Table 91.

Table 91: Mean Change in Blood Phe from Baseline at Weeks 2, 4, and 6 by Prior Treatment Group.

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

Change in mean blood Phe from Week 0 to Week 10 is not shown.

The results show that, in patients with BH4-responsive PKU, reduction in blood Phe is greatest at 20 mg/kg/day doses and least with 5 mg/kg/day doses. The datasets indicate that compliance for the prior placebo treated group was lower throughout the study which may partly explain higher blood Phe in this group at those visits.

10.1.4.13.5.1.2 Secondary Efficacy Analysis

A secondary efficacy analysis compared the difference in mean (\pm SE) change from Week 0 (Baseline) in blood Phe between 5, 10, and 20 mg/kg/day from Baseline. The mean (\pm SE) change (decrease) in blood Phe was greater with increasing dose. Treatment with 10 mg/kg/day resulted in a 104 μ M (SE 19) greater decrease than treatment with 5 mg/kg/day. Treatment with 20 mg/kg/day resulted in a 163 μ M (SE 24) greater decrease than treatment with 5 mg/kg/day. Treatment with 20 mg/kg/day resulted in a 59 μ M (SE 23) greater decrease than treatment with 10 mg/kg/day. These findings are summarized in Table 92.

Table 92: Pair-wise Comparison of Dose: Decrease in Blood Phe from Week 0 at Each Dose in Part I; ITT

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

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

10.1.4.13.5.2 Efficacy Analyses Part II; Change in Blood Phe, Weeks 12 Through 22

In Part II, each patient's daily dose of drug was set at 5, or 10, or 20 mg/kg/day on the basis of the patient's Week 6 (Part I) blood Phe levels according to the following:

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

Using the above protocol, six patients received 5 mg/kg/day, 37 patients received 10 mg/kg/day, 37 patients and received 20 mg/kg/day. Seventy-nine of 80 patients completed Part II visits and procedures. One prior placebo treated patient assigned to receive 20 mg/kg/day did not complete Part II procedures and withdrew after the Week 12 visit.

10.1.4.13.5.2.1 Primary Efficacy Analyses

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

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

At Week 12 mean blood Phe for the ITT was 620 uM (SD 371), and mean change in blood Phe from Week 0 was -224 uM (SD 326). At Week 16 mean blood Phe for the ITT was 632 uM (SD 369), and mean change in blood Phe from Week 0 was -206 uM (SD 380). At Week 20 mean blood Phe for the ITT was 626 uM (SD 379); and mean change in blood Phe from Week 0 was -220 uM (SD 352). At Week 22 mean blood Phe for the ITT was 652 uM (SD 382), and mean change in blood Phe from Week 0 was -190 uM (SD 356). Mean change in blood Phe from baseline was persistent from Weeks 12 through 22. These data are summarized in Tables 93 and 94.

Table 93 summarizes mean blood Phe from Weeks 12 through 22.

Table 93: Extension Study: Mean Blood Phe for Weeks 12 through 22 by Prior Treatment Group

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

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

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Table 94 summarizes mean change in blood Phe from Baseline at Weeks 12 through 22.

Table 94: Extension Study: Mean Change in Blood Phe for Weeks 12 through 22 by Prior Treatment Group

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

Mean change in blood Phe from Week 0 was stable from Weeks 12 through 22. At all visits in Part II, blood Phe was higher in the prior placebo treated group and mean change in blood Phe was therefore lower in this group. As noted for Part I, datasets indicate that compliance for the prior placebo treated group was lower throughout the study which may partly explain higher blood Phe in this group.

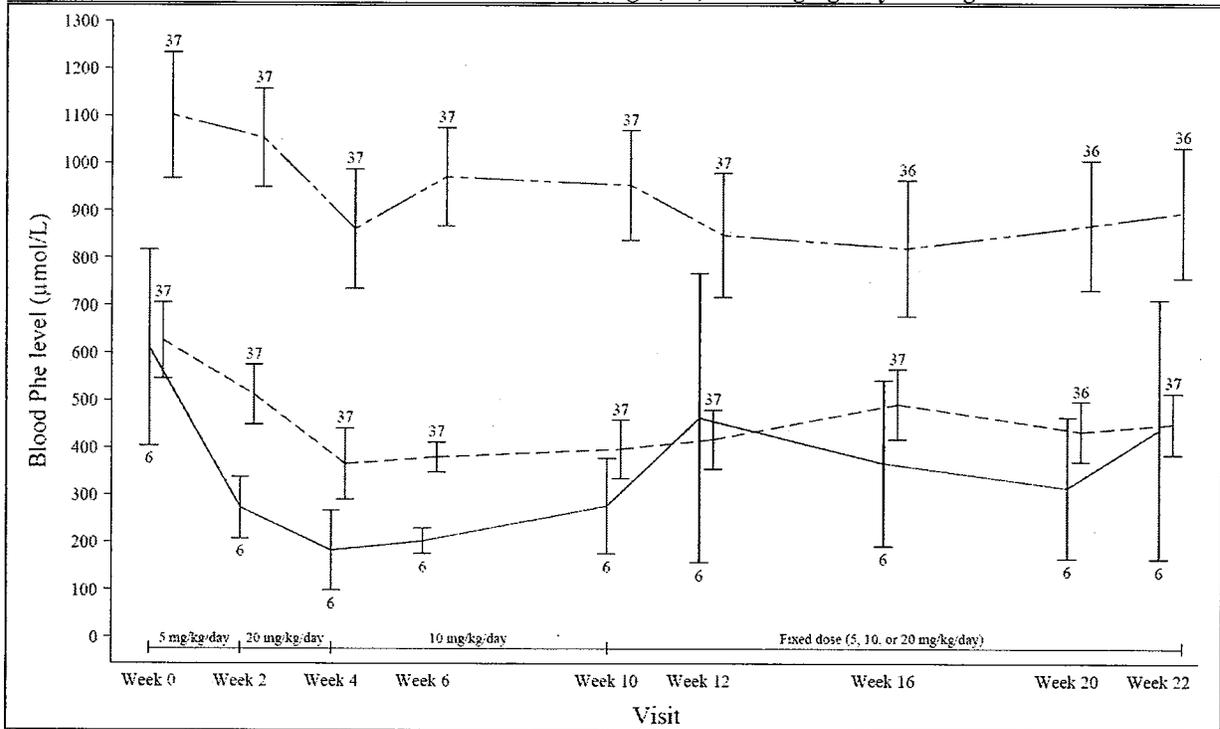
10.1.4.13.5.2.2 Efficacy Analysis Figures

Figure 13 displays mean blood Phe by dose level in Part II. Patients treated with a fixed dose of 5 mg/kg/day had more variability in mean blood Phe than patients treated with 10 or 20 mg/kg/day. This may be due to the smaller number of patients treated with 5 mg/kg/day (n = 6) compared to patients treated with 10 and 20 mg/kg/day (n = 37, each). This figure represents the minimum dose required to maintain blood Phe at a given level; that is, patients treated with 5 mg/kg/day had lower blood Phe than patients treated with 20 mg/kg/day, therefore they were

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assigned a lower dose (copied from page 71 of the study report located in section 5.2.5.2.3 of the electronic submission).

Figure 13: Mean Blood Phe Levels for Patients Receiving 5, 10, or 20 mg/kg/Day During Part II



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

— 5 mg/kg/day

- - - 10 mg/kg/day

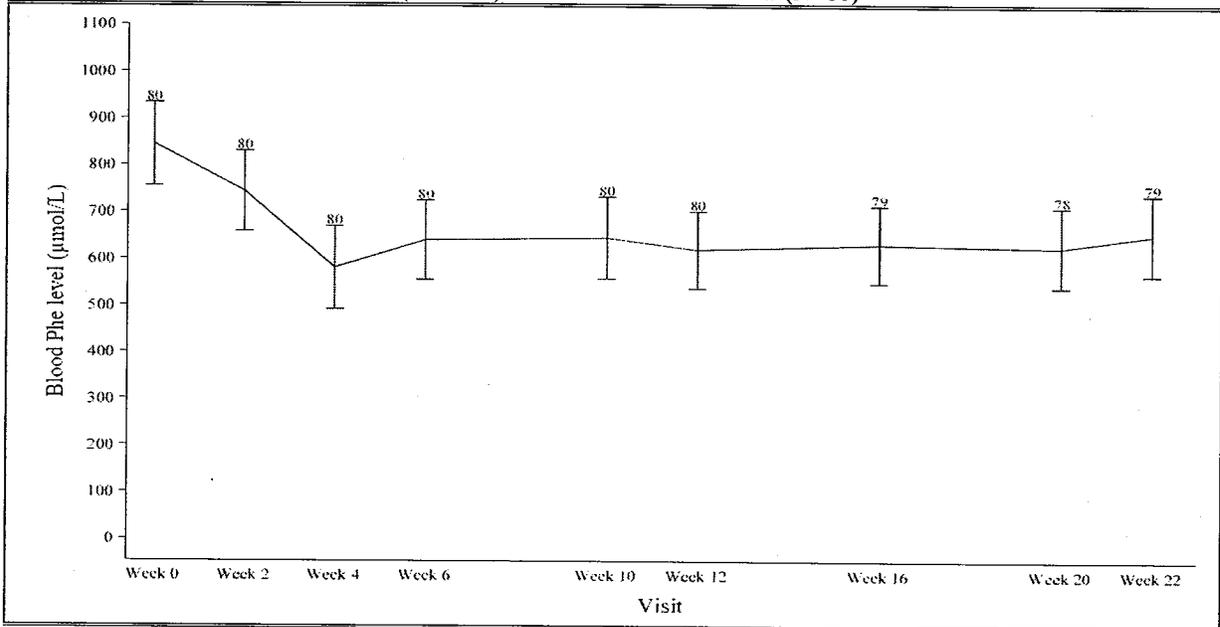
- · - · 20 mg/kg/day

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As discussed in section 10.1.4.13.5.1.1, seven patients were receiving sapropterin 10 mg/kg/day at Week 0, which may have reduced mean blood Phe at Week 0. At Week 2, when all patients had been treated with sapropterin 5 mg/kg/day, mean blood Phe was similar in the two groups and remained similar through completion of the fixed dose period. Thereafter, blood Phe remained reduced through Week 20, and increased moderately at Week 22 associated with decreased compliance. These findings are displayed in Figures 14 and 15 (copied from pages 66 and 71, respectively, of the study report located in section 5.2.5.2.3 of the electronic submission).

Figure 14 summarizes the mean blood Phe for the ITT from Week 0 through Week 22.

Figure 14: Mean Blood Phe Levels (95% CI) at Each Visit for the ITT (N=80)

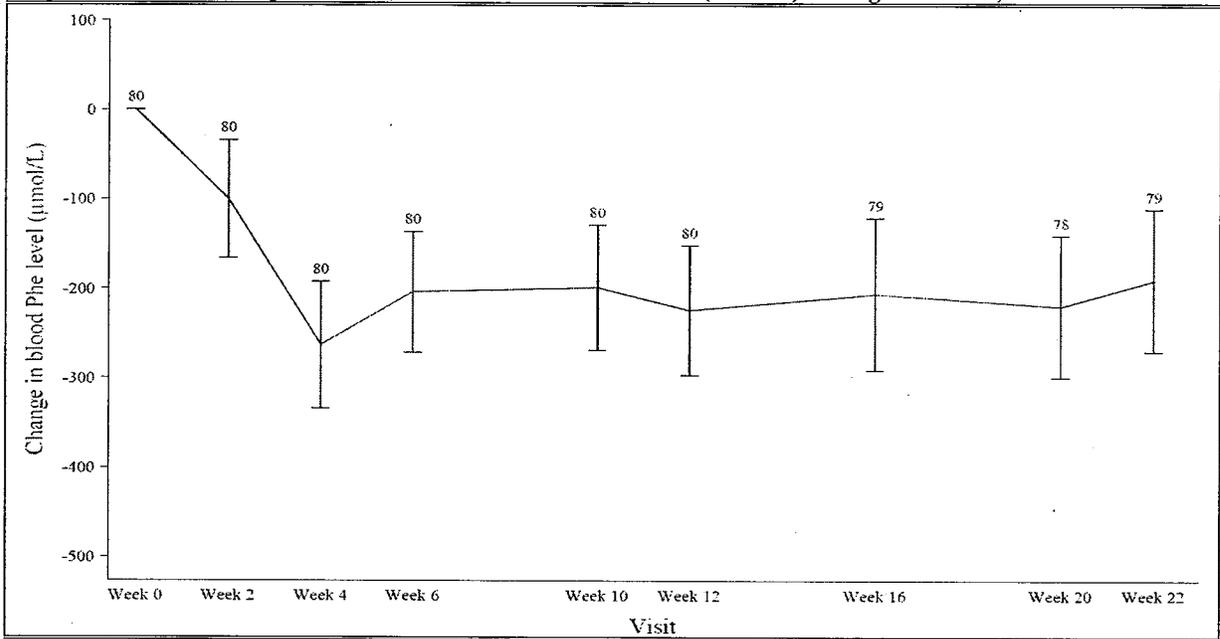


The numbers above each 95% CI bar indicate the number of patients at each visit.

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Figure 15 summarizes the mean change in blood Phe for the ITT from Week 0 through Week 22.

Figure 15: Mean Change (95% CI) in blood Phe from Baseline (Week 0) through Week 22; ITT



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

10.1.4.13.6 Efficacy Summary

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

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

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

A comparison of dose effect in Part I showed:

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

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

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

Part II: The first efficacy analysis of the Part II was change in blood Phe from Week 0 (Baseline) at Weeks 12, 16, 20, and 22. In Part II, the reduction in mean blood Phe for the ITT established in Part I was maintained with individualized dosing.

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

Reduction in blood Phe was maintained for 22 weeks.

This Reviewer concludes the efficacy data of this open-label, uncontrolled study support that sapropterin 20 mg/kg/day reduces blood Phe more than 10 mg/kg/day or 5 mg/kg/day doses, and that sapropterin 10 mg/kg/day reduces blood Phe more than 5 mg/kg/day doses. Effect appears to be durable to 22 weeks of treatment.

10.1.4.14 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 Week 26 follow-up. Deaths and Serious AEs were reported from obtaining consent through the Week 26 follow-up. Non-serious AEs were reported from the time of first dose at through completion of the Week 26 follow-up. Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT). Adverse events were classified according to MedDRA system, organ, class (SOC) and preferred term (PT). The adverse event, clinical laboratory, and vital sign datasets were reviewed.

10.1.4.14.1 Exposure

The safety population included 80 patients who received ≥ 1 dose of sapropterin. The last patient completed follow-up on 10-October-2006.

Mean dose in Part I was 5.7 (SD 0.6), 20.8 (SD 0.7), then 10.7 (SD 0.6) mg/kg/day, for two weeks each; followed by four weeks of 10.7 (SD 0.6) prior to the beginning of Part II.

In Part II, patients in the 5 mg/kg/day group (N=6) received 6.6 (SD 0.6) mg/kg/day; patients in the 10 mg/kg/day group (N=37) received 10.7 (SD 0.6) mg/kg/day; and patients in the and 20 mg/kg/day group (N=37) received 20.5 (SD 0.9) mg/kg/day.

Combined exposure to any dose (5, or 10, or 20 mg/kg/day) in Parts I and II was 180 (SD 11) days; range 105 to 191 days.

Table 95 summarizes sapropterin exposure in Parts I and II of the Extension Study.

Table 95: Extensions Study: Exposure to Sapropterin

Dose	Study Week							
	Study Part I Visit Week				Study Part II Visit Week			
	2	4	6	10	12	16	20	22
5 mg, n =	80	0	0	0	6	6	6	6
10 mg, n =	0	0	80	80	37	37	36	37
20 mg, n =	0	80	0	0	37	36	36	36
Total patients, n =	80	80	80	80	80	79	78	79

10.1.4.14.2 Adverse Events

AEs are reported from administration of first dose at Week 0 through completion of Week 26 follow-up 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=80). AEs were tabulated and analyzed using the aedata.xpt dataset (section 5.3.5.2.25.3.1 of the electronic submission).

In Part I, from the Week 0 through Week 6 visit, all 80 patients received two weeks of exposure at each of 5, 10, and 20 mg/kg/day (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 96.

Table 96: Non-Serious AEs in ≥ 2 Patients Week 0 through Week 6 of the Extension Study (N=80)

		Total	Dose (mg/kg/day)		
			5	10	20
		N=80	N=80	N=80	N=80
System, Organ, Class	Preferred Term	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)

From Week 6 through Week 10 of Part I all patients were treated with sapropterin 10 mg/kg/day and are discussed with AEs occurring in Part II. 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 clinical 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 97.

Table 97: Non-Serious AEs Occurring in ≥ 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	10	5	10	20
		N=80	N=80	N=6	N=37	N=37
System, Organ, Class	Preferred Term	n (%)				
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 above findings suggest that sapropterin in doses of 5, 10, and 20 mg/kg/day is well tolerated over 22 weeks in patients with BH4-responsive PKU.

10.1.4.14.3 Reports of Deaths and SAEs

No deaths were reported.

One patient withdrew due to noncompliance. Three serious AEs and one severe but non-serious AE were reported; none of which led to withdrawal. These findings are summarized in Table 98.

Table 98: Withdrawals, Serious and Severe AEs

Patient	Age years Gender (M/F)	Reason	Dose mg/kg/day	Comment
0113-0001	18 y, M	Compliance	Unknown	Failed to complete Week 12 through 22 visits; Increased ALT Part I, resolved
0119-0003	13 y, M	Fractured Tibia	20	Trauma witnessed; not related to sapropterin
0118-0015	14 y, M	Spinal cord injury	5	Trauma witnessed; not related to sapropterin
0115-0016	12 y, F	UTI	5	Hospitalization and IV antibiotics
0128-0013	29 y, M	Tooth abscess	20	Severe, not serious.

- Patient 0119-0003, a 13 year old male, suffered a fractured tibia at Week 23, one week after the final 20 mg/kg/day dose. The patient completed the study. The CRF was reviewed and this Reviewer concludes this AE is not related administration of sapropterin.
- Patient 0118-0015, a 14 year old male, suffered a spinal cord injury at Week 15 while on fixed 5 mg/kg/day dosing. The patient completed the study. The CRF was reviewed and this Reviewer concludes this AE is not related administration of sapropterin.
- Patient 0115-0016, a 12 year old female, had a urinary tract infection (UTI) during Week 18 while receiving 5 mg/kg/day of sapropterin. She was treated with intravenous Cefuroxime for one day and oral Cefalexin for one week and the UTI resolved. The investigator concluded the AE was not related to administration of sapropterin. The patient completed the study. The CRF was reviewed and this Reviewer concludes a temporal relationship to sapropterin is established. A causative relationship is possible; however, UTIs are common in women. This Reviewer feels this AE was not related to administration of sapropterin.
- Patient 0128-0013, a 29 year old male, experienced at tooth abscess that was classified as severe and non-serious. The event occurred during Week 15 while receiving 20 mg/kg/day. The patient completed the study. The CRF was reviewed and this Reviewer concludes this AE was not related to administration of sapropterin.
- One patient withdrew. Patient 0113-0001, an 18 year old male, failed to return for Week 16 and subsequent visits. He was to receive sapropterin 10 mg/kg/day during Part II. He had increased AST at Week 4 (69 U/L) which resolved by Week 10 (32 U/L). This Reviewer concludes the relationship of this withdrawal to sapropterin can not be determined.

10.1.4.14.4 Vital signs

The vital sign dataset for Parts I and II were reviewed. There were no meaningful differences in mean, median, and 25th and 75th percentiles between prior placebo (N=41) and prior sapropterin (N=39) treated patients at Week 0. During Part I, there were no notable differences in vital signs between 5, 10, and 20 mg/kg/day dosing periods (data not shown). There were no notable findings in vital signs in Part II (data not shown).

10.1.4.14.5 Laboratory Analyses

The entire laboratory dataset was reviewed and there were no clinically meaningful differences in mean, median, and 25th and 75th percentiles for any laboratory analytes between prior placebo (N=41) and prior sapropterin (N=39) treated patients at Week 0. For the ITT (N=80), there were no clinically meaningful differences in vital sign parameters between 5, 10, and 20 mg/kg/day dosing periods. Notable findings are described.

One patient had neutropenia, four patients had increase gamma-glutamyl transferase (GGT) and one patient had increased ALT. These findings are summarized in Table 99.

Table 99: Extension Study:

Abnormality	N	Comment
Neutropenia	1	Reported in this patient in the Enrichment and Efficacy studies
Increased GGT	4	Present at Baseline; 3 prior sapropterin, 1 prior placebo
Increased ALT	7	6 elevated at Baseline; 3 prior sapropterin, 3 prior placebo
Increased AST	1	Normal at Baseline, elevated at end of study

- Patient 0121-0011 had a fixed-dose of 20 mg/kg/day in Part II. This patient had an ANC of 1,460 at Week 0, which increased to 1,660 at Week 10, and decreased to 950 by Week 22. This patient had moderate neutropenia prior to drug exposure in the Enrichment Study, and continued neutropenia in the Efficacy Study (placebo).
- Four patients had elevated gamma-glutamyl transferase levels throughout the study (0118-0028, 0124-0005, 0127-1022, and 0018-0017) from Week 0 through Week 22; three of whom had elevated GGT at Baseline in the current study (ULN 29 to 39 U/L).
 - Patient 0018-0017 (fixed dose 20 mg/kg/day) had a GGT of 111 prior to first exposure in the Enrichment Study and between 100 and 115 in the in the Extension Study.
 - Patient 0118-0028 (fixed dose 20 mg/kg/day) had a GGT of 32 prior to first exposure in the Enrichment Study and between 39 and 47 in the Extension Study.
 - Patient 0124-0005 (fixed dose 10 mg/kg/day) had a GGT of 38 prior to first exposure in the Enrichment Study and between 46 and 63 in the Extension Study.
 - Patient 0127-1022 (fixed dose 10 mg/kg/day) had a GGT of 40 prior to first exposure in the Enrichment Study and between 51 and 85 in the Extension Study.
- Six patients had baseline ALT \geq 50 IU/L including three patients treated with placebo in the Efficacy Study and three patients treated with sapropterin in the Efficacy Study. Of

seven patients with ALT \geq 50 at Week 22, three had Baseline ALT between 28 and 47 IU/L, and four patients had Baseline ALT \geq 50 IU/L.

- Three of seven patients with ALT > 50 U/L at Week 22 had normal ALT prior to first exposure in the Enrichment Study. Two patients had elevations between 15 and 28 U/L, and one patient had an increase from 44 U/L to 125 U/L.
- Patient 0124-0005 had a significant increase in AST from 41 to 71 IU/L which remained elevated for the duration of the study.

In summary, neutropenia was noted in one patient, and in 3% of patients in clinical trials of sapropterin in PKU patients. The risk of neutropenia is to be addressed in labeling.

The abnormalities in GGT and ALT in this study may not be clinically meaningful because 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 (data not shown).

10.1.4.14.6 Safety Summary

The safety results from the Extension Study show the following:

1. AEs were frequently reported; 68% of patients reported at least one AE in Part I, 68% of patients reported at least one AE in Part II, and overall 82% of patients reported at least one AE in either Part I or Part II. 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).
 - a. In Part I, the incidence of non-serious AEs was approximately equal between 5, 10, and 20 mg/kg/day dose periods. By preferred term, the most commonly reported AEs in Part I were headache and nasopharyngitis each in 11% of patients (9), vomiting 9% of patients (N=7), and cough and pharyngeolaryngeal pain (8% each). There was no difference in incidence of AEs at 5, 10, or 20 mg/kg/day in Part I.
 - b. From Weeks 6 to 10 and for Part II, the most common AEs by incidence were headache in 19% of patients (N=15), pharyngeal pain (9%), and diarrhea and vomiting (6% each).
2. No deaths were reported. Three SAEs were reported including two trauma associated long bone fractures and a urinary tract infection; none of which were related to sapropterin treatment.
3. There were no apparent trends in vital signs in Parts I or II
4. Notable clinical laboratory findings include a single patient with neutropenia. This patient had moderate neutropenia prior to drug exposure in the Enrichment Study, and continued neutropenia in the Efficacy Study (placebo).

In conclusion, 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, lack of placebo control, and open-label study design.

10.1.4.16 Overall Summary of the Long Term Study (PKU-004)

Part I: During Part I, mean blood Phe level decreased as the dose of sapropterin increased. Mean (SD) blood Phe at Baseline for the ITT (N=80) was 844 uM (SD 398).

1. At the end of treatment with 5 mg/kg/day, mean blood Phe was 744 uM (SD 384). At the end of treatment with 20 mg/kg/day, mean blood Phe was 581 uM (SD 399). At the end of treatment with 10 mg/kg/day of, mean blood Phe was 640 uM (SD 382). These data suggest that in patients with hyper-Phe due to PKU, mean blood Phe level decreases as the dose of sapropterin increases when diet is not controlled.
2. Comparison of dose effect
 - a. Treatment with 10 mg/kg/day resulted in a 104 uM (SE 19) greater decrease than treatment with 5 mg/kg/day; (95% CI 65, 142).
 - b. Treatment with 20 mg/kg/day resulted in a 163 uM (SE 24) greater decrease than treatment with 5 mg/kg/day; (95% CI 115, 211).
 - c. Treatment with 20 mg/kg/day resulted in a 59 uM (SE 23) greater decrease than treatment with 10 mg/kg/day; (95% CI 14, 105)

Part II: The first efficacy analysis of the Part II was change in blood Phe from Week 0 (Baseline) at Weeks 12, 16, 20, and 22.

1. Mean (SD) blood Phe was stable from Weeks 12 through 22. For the ITT mean (SD) blood Phe ranged from 620 uM (SD 371) to 652 uM (SD 382).
2. Mean change from Week 0 was consistent between visits and ranged from -190 uM (SD 356) to -224 uM (SD 326).

This Reviewer concludes the efficacy data of this open-label, uncontrolled study support that sapropterin 20 mg/kg/day reduces blood Phe more than 10 mg/kg/day or 5 mg/kg/day doses, and that sapropterin 10 mg/kg/day reduces blood Phe more than 5 mg/kg/day doses. Effect appears to be durable to 22 weeks of treatment.

Safety results from the Extension Study show the following:

1. AEs were frequently reported; 68% of patients reported at least one AE in Part I, 68% of patients reported at least one AE in Part II, and overall 82% of patients reported at least one AE in either Part I or Part II. 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).

- a. In Part I, the incidence of non-serious AEs was approximately equal between 5, 10, and 20 mg/kg/day dose periods. By preferred term, the most commonly reported AEs in Part I were headache and nasopharyngitis each in 11% of patients (9), vomiting 9% of patients (N=7), and cough and pharyngeolaryngeal pain (8% each). There was no difference in incidence of AEs at 5, 10, or 20 mg/kg/day in Part I.
 - b. From Weeks 6 through 22, the most common AEs by incidence were headache in 19% of patients (N=15), pharyngeal pain (9%), and diarrhea and vomiting (6% each). There were no notable differences in the types of AEs between patients receiving 10 or 20 mg/kg/day in Part II.
2. No deaths were reported. Three SAEs were reported including two trauma associated long bone fractures and a urinary tract infection.
 3. Notable clinical laboratory findings include a single patient with neutropenia. This patient had moderate neutropenia prior to drug exposure in the Enrichment Study, and continued neutropenia in the Efficacy Study (placebo).

In conclusion, 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, lack of placebo control, and open-label study design. It is this Reviewer's conclusion that in patients with BH4-responsive PKU, substantive data support safety and durability in reduction of blood Phe (efficacy) of sapropterin for up to 22 weeks in patients eight to 49 years old.

10.2 Line-by-Line Labeling Review

Labeling underwent extensive negotiations between FDA and the Sponsor. Please see the final labeling. Notable

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