U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

Statistical Review and Evaluation
CLINICAL STUDIES

NDA/Serial Number:	NDA202810
Drug Name:	Oxcarbazepine (OXC) extended-release tablets (SPN-804O)
Indication(s):	Adjunctive therapy for treating patients with partial onset seizures in adults and children with epilepsy.
Applicant:	Supernus Pharmaceuticals, Inc
Date of Document:	December 19, 2011
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Keywords: *Clinical studies, NDA review, statistical review, endpoint analysi/, multi-center, ANCOVA*

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1. EXECUTIVE SUMMARY

1.1. CONCLUSIONS AND RECOMMENDATIONS

The study drug SPN-804O demonstrated its efficacy as an adjunctive therapy for refractory partial seizures in adults (18 to 65 years old) with 3 or more partial onset seizures (simple or complex, with or without secondary generalization) per 28 days despite treatment with one and up to three other AEDs. The study results showed that adjunctive therapy with SPN-804O at 2400mg, administered once a day, was effective, with a median percentage seizure reduction of 42.9%, a statistically significant difference from placebo, after correction for multiple comparisons (p=0.003). Although the 1200mg/daily dose failed to separate from placebo arm (p=0.078), it helped to decrease in median seizure frequency per 28 days (-38.2%) from baseline compared to the corresponding decrease of (-28.70%) in the placebo arm.

1.2. BRIEF OVERVIEW OF REVIEWED CLINICAL STUDIES

The sponsor submitted efficacy findings of one study to demonstrate the efficacy evidence of SPN-804O in the adjunctive treatment of refractory partial seizures in adults (18 to 65 years old) with 3 or more partial onset seizures (simple or complex, with or without secondary generalization) per 28 days despite treatment with one and up to three other AEDs. It was a multicenter, double-blind, placebo-controlled, parallel-group, three arm (2400 mg, 1200 mg, and placebo), and an 8-week treatment study.

The primary efficacy variable was the percentage change in partial seizure frequency per 28 days during the treatment phase (PCH_T) relative to the total seizures to the baseline period. The primary efficacy endpoint PCH_T was calculated by $PCH_T = 100*(T – B)/B$, where T and B were the partial seizure frequencies per 28 days during the treatment phase and baseline phase, respectively.

Wilcoxon rank-sum test procedure was the primary efficacy analysis method to test the hypothesis of equal median reduction in PCH_T from baseline between SPN-804O 2400mg/day and placebo as well as between SPN-804O 1200 mg/day and placebo. To preserve the overall type I error-rate at 0.050 for the primary efficacy endpoint, a step-up Hochberg's procedure was used for the pair wise comparison of each SPN-804O treatment group against placebo. If both observed p-values from the comparisons were < 0.050 in favor of the SPN-804O treatment groups, then both groups would be declared statistically significantly better than placebo. If the observed p-value was > 0.050 for one SPN-804O treatment group but < 0.025 in favor of the other SPN-804O treatment group, then the latter SPN-804O treatment group would be declared statistically significantly better than placebo.

Several sensitivity/supportive analyses of the primary endpoint including (i) a rank ANCOVA analysis, and (ii) the cumulative distribution of percent reduction in partial seizure frequency per 28 days (i.e., continuous responder curve) were conducted.

Dealings with Dropouts / Missing Data

For the primary efficacy end point, the partial seizures rate per 28 days during the treatment phase was calculated over the number of days with non-missing seizure data in the maintenance period. No explicit imputation of missing data was made, but this approach was implicitly equivalent to using the average seizure rate during the days with non-missing seizure data to impute the seizure rate for days after study discontinuation and days with missing seizure data. As sensitivity analysis of the primary end, the sponsor analyzed the percent reduction in partial seizures per 28 days from baseline to the first 4 weeks, middle 4 weeks, and last 4 weeks of the treatment phase. The findings from this analysis are consistent with the protocol specified analysis findings.

1.3. STATISTICAL ISSUES AND FINDINGS

Dealing with missing data in seizure frequency trials is a statistical challenge. The primary efficacy end point is often defined as the average of seizures rate per 28 days during the double-blinded maintenance period, and the rate is calculated over the number of days with non-missing seizure data in the maintenance period. Suppose a subject is dropped out from the trial after 4 days of randomization, his or her rate of seizure frequency per 28 days will be calculated based on the available data for the four days. This approach of dealing with missing data is not different from the last observation carried forward (LOCF) approach. A research on dealing with missing data is necessary to carry out in calculating the rate of seizure frequency per 28 days.

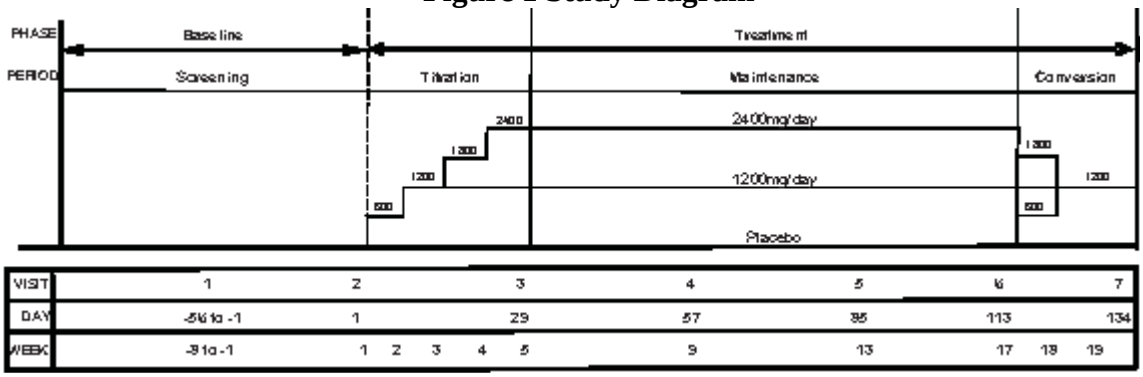
2. INTRODUCTION

2.1 OVERVIEW

The sponsor submitted efficacy findings of one pivotal study to demonstrate the efficacy evidence of SPN-804O as add-on therapy compared to placebo, with SPN-804O administered either as 2 x 600 mg tablets QD or 4 x 600 mg tablets QD. The study was a multicenter, double-blind, randomized (1:1:1), parallel group, placebo-controlled study evaluated add-on therapy with SPN-804O in patients from 18 to 65 years with refractory epilepsy (simple partial seizures, complex partial seizures, or partial seizures evolving to secondarily generalized seizures).

The study consisted of (i) Screening Period, (ii) Titration Period: 4 weeks, and (iii) Maintenance Period: 12 – up to 13 weeks. The study design is illustrated in Figure 1.

Figure 1 Study Diagram



Source: Study Report

The main inclusion criterion for randomization of patients in this study was that patients had at least three countable partial seizures per 28 days on average during the 8-week baseline period. Three hundred sixty-nine subjects were randomized at 88 sites in eight countries (Bulgaria, Canada, Croatia, Mexico, Poland, Romania, Russia, and USA). Among the randomized patients, 366 patients were included in the intent-to-treat (ITT) sample. There were 164 men (44.8%) and 202 women (55.2%) with a mean age of 38.9 years, with no significant height, weight, race or ethnicity differences across treatment groups. The randomized patients took either (i) 2400mg total daily dose of SPN-804O QD, or (ii) 1200mg total daily dose of SPN-804O QD, or (iii) Placebo, QD during the maintenance period. Table 1 summarizes the dosing schedule for each treatment group during the titration, and maintenance periods.

Table 1: Dosing Schedule for Each Treatment Group by Period

Visit #	Study Days	Treatment A (2400mg/d)	Treatment B (1200mg/d)	Treatment C (PLACEBO)
Titration Period				
2	1 - 7	1 X 600mg SPN-804O + 3 X placebo		4 X placebo
	8-14	2 X 600mg SPN-804O + 2 X placebo		4 X placebo
	15 -21	3 X 600mg SPN-804O + 1 X placebo	2 X 600mg SPN-804O + 2 X placebo	4 X placebo
	22 -28	4 X 600mg SPN-804O[a]	2 X 600mg SPN-804O + 2 X placebo	4 X placebo
Maintenance Period				
3	29 (+7)[b] - 56	4 X 600mg SPN-804O[a]	2 X 600mg SPN-804O + 2 X placebo	4 X placebo
4	57 (±7) - 84			
5	85 (±7) - 112			

Source: Study Report

The primary efficacy endpoint PCH_T was calculated by $PCH_T = 100*(T – B)/B$, where T and B were the partial seizure frequencies per 28 days during the treatment phase and baseline phase, respectively. The partial seizure frequency per 28 days was defined as (S/D) x 28, where S was the sum of the partial seizures reported in the subject seizure diary, and D was the number of days with non-missing seizure frequency data in the subject seizure diary. No explicit imputation of missing data was made, but the above approach in calculating PCH_T was implicitly equivalent to using the average partial seizure rate during the days with non-missing seizure data to impute the seizure rate for days after study discontinuation and days with missing seizure data.

The primary efficacy endpoint analysis was done on the intent-to-treat (ITT) population- all partial seizures up to the point of subject discontinuation before the end of treatment phase were included. Each subject recorded the date and number of partial seizures in his or her seizure diary.

The sample size was determined from a consideration of Wilcoxon rank sum test. Based on the following Table 2, an intermediate sample size of 120 per treatment group (for a total of 360 subjects) provided over 80% power to detect the difference of 24-32% between placebo and 1200mg/day and over 95% power to detect the difference of 31-42% between placebo and 2400mg/day, each at the two-sided 0.025 level (for an overall type I error rate of 0.050).

Table 2: Sample Size Calculations for the Study.

Sample Size per treatment group	(Δ_1 , Δ_2)	SD	(p_1, p_2)	Power
110	(32%, 42%)	70%	(0.6267, 0.6643)	(84%, 97%)
130	(24%, 31%)	60%	(0.6114, 0.6426)	(80%, 95%)

Source: Study report

where p1 = probability that the PCH_T is higher for placebo than for 1200mg/day; p2 = probability that the PCH_T is higher for placebo than for 2400mgday; $\Delta 1$ = the median PCH_T difference between placebo and 1200mg/day, and $\Delta 2$ = the median PCH_T difference between placebo and 2400mg/day with an estimated common standard deviation (SD) of approximately 60% to 70%.

Wilcoxon rank-sum test procedure was the primary efficacy analysis method to test the hypothesis of equal median reduction in PCHT from baseline between SPN-804O 2400mg/day and placebo as well as between SPN-804O 1200 mg/day and placebo. To preserve the overall type I error-rate at 0.050 for the primary efficacy endpoint, a step-up Hochberg's procedure was used for the pair wise comparison of each SPN-804O treatment group against placebo. If both observed p-values from the comparisons were < 0.050 in favor of the SPN-804O treatment groups, then both groups would be declared statistically significantly better than placebo. If the observed p-value was > 0.050 for one SPN-804O treatment group but < 0.025 in favor of the other PN-804O treatment group, then the latter PN-804O treatment group would be declared statistically significantly better than the placebo group.

Several sensitivity analyses were done to evaluate the impact of dropouts on the primary efficacy results. The main sensitivity analyses were (i) the primary efficacy analysis was carried out on the completers; and (ii) Mixed Model Repeated Measures (MMRM) analysis was carried out on the ranks of PCH_T for the ITT population. The completer population included all randomized subjects that completed at least part of the double-blind combined titration and maintenance periods. The MMRM analysis was carried out on the ranks of PCH_T for the ITT population. The dependent variable was the rank of PCH_T. The model included treatment, protocol-specified visit, treatment-by-visit interaction, and country as fixed effects; the rank of B (the partial seizure frequency per 28 days during the baseline phase) as a covariate; and visit as a repeated measure. The model included an unstructured covariance matrix.

Table 3: Subject Disposition

Category	SPN-8040 2400mg/d (N=123)	SPN-8040 1200mg/d (N=122)	Placebo (N=121)	Total (N=366)[a]
Completed, n (%)	71 (57.7)	82 (67.2)	95 (78.5)	248 (67.8)
Discontinued, n (%)	52 (42.3)	40 (32.8)	26 (21.5)	118 (32.2)
Adverse Event [b]	37 (30.1)	18 (14.8)	10 (8.3)	65 (17.8)
Subject Withdrew Consent	11 (8.9)	10 (8.2)	6 (5.0)	27 (7.4)
Non-compliance	1 (0.8)	6 (4.9)	4 (3.3)	11 (3.0)
Lost to Follow-up	1 (0.8)	5 (4.1)	2 (1.7)	8 (2.2)
Other	2 (1.6)	0	2 (1.7)	4 (1.1)
Protocol Violation	0	1 (0.8)	1 (0.8)	2 (0.5)
Investigator decision	0	0	1 (0.8)	1 (0.3)

Source: Study Report

Disposition of Subjects

The patient disposition of the study is listed in table 3. In the study, a total of 366 randomized subjects (i.e., ITT sample) were analyzed by treatment group. The percentage of subjects who discontinued was higher in active treatment groups (42.3% in the SPN-804O 2400mg/d

group and 32.8% in the SPN-804O 1200mg/d group) than among the subjects in the placebo group (21.5%). Higher dropouts in both treatment groups are likely due to the higher incidence of AEs.

2.2 DATA SOURCES

The study reports and SAS data sets are available at
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3. STATISTICAL EVALUATION

3.1 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Table 4 lists the demographic characteristics of the randomized subjects. The demographics for all subjects were comparable across the treatment groups. Table 5 lists epilepsy history by treatment group. Epilepsy history was also similar with the exception of the baseline mean seizure frequency (number of episodes/28 days), which was higher in the SPN-804O 2400mg/d group (37.4 seizures) than in the SPN-804O 1200mg/d (18.5 seizures) and placebo (13.0 seizures) groups. In the SPN-804O 2400mg/d group, two subjects had more than 612 baseline seizure frequency per 28 days. After excluding these two subjects' baseline data, the baseline mean seizure frequency per 28 days for the SPN-804O 2400mg/d group is 16.42, and it is comparable to the means for the other groups. Since the primary efficacy analysis is based on a nonparametric approach, these two subjects' data do not have any impact on the efficacy decision of the study drug.

Table 4: Baseline Demographic Characteristics of Subjects

Characteristic (N=366)	SPN-8040 2400mg/d (N=123)	SPN-804O 1200mg/d (N=122)	Placebo (N=121)	Total
Sex, n (%)				
Male	59 (48.0)	51 (41.8)	54 (44.6)	164 (44.8)
Female	64 (52.0)	71 (58.2)	67 (55.4)	202 (55.2)
Race, n (%)				
White	105 (85.4)	104 (85.2)	107 (88.4)	316 (86.3)
Black	1 (0.8)	5 (4.1)	1 (0.8)	7 (1.9)
Asian	1 (0.8)	1 (0.8)	0	2 (0.5)
American Indian or Alaska Native	1 (0.8)	0	0	1 (0.3)
Other	15 (12.2)	12 (9.8)	13 (10.7)	40 (10.9)
Age (years)				
Mean (SD)	38.5 (11.58)	39.1 (11.51)	39.1 (12.49)	38.9 (11.84)
Median	40.0	39.0	39.0	39.0
Min, Max	18, 64	18, 64	18, 66	18, 66

Source: Study Report

Table 5: Baseline Epilepsy History

Characteristic	SPN-8040 2400mg/d (N=123)	SPN-804O 1200mg/d (N=122)	Placebo (N=121)	Total (N=366)
Epilepsy History (years)				
n	121	121	121	363
Mean (SD)	19.8 (12.96)	21.3 (14.47)	21.2 (13.91)	20.8 (13.77)
Median	19.1	19.8	19.7	19.5
Min, Max	0.3, 55.1	0.2, 55.4	0.3, 52.2	0.2, 55.4
Number (%) of subjects with				
Simple partial seizures	44 (35.8)	37 (30.3)	45 (37.2)	126 (34.4)
Complex partial seizures	93 (75.6)	90 (73.8)	94 (77.7)	277 (75.7)
Secondarily generalized seizures	62 (50.4)	60 (49.2)	58 (47.9)	180 (49.2)
Other	7 (5.7)	9 (7.4)	10 (8.3)	26 (7.1)
Number (%) of subjects receiving				
1 AED	40 (32.5)	36 (29.5)	43 (35.5)	119 (32.5)
2 AEDs	67 (54.5)	68 (55.7)	61 (50.4)	196 (53.6)
3 AEDs	15 (12.2)	18 (14.8)	17 (14.0)	50 (13.7)
4 AEDs	1 (0.8)	0	0	1 (0.3)
Number (%) of subjects receiving				
Carbamazepine	49 (39.8)	53 (43.4)	44 (36.4)	146 (39.9)
Valproate[a]	62 (50.4)	55 (45.1)	49 (37.2)	166 (45.4)
Phenytoin	2 (1.6)	3 (2.5)	4 (3.3)	9 (2.4)
Lamotrigine	34 (27.6)	31 (25.4)	37 (30.6)	102 (27.9)
Levetiracetam[b]	28 (22.8)	20 (16.4)	27 (22.3)	75 (20.5)
Topiramate[b]	23 (18.7)	23 (18.8)	21 (17.3)	67 (18.3)
Other[b]	18 (14.6)	29 (23.8)	26 (21.5)	73 (19.9)
Baseline seizure frequency (number of episodes/28 days)				
Mean (SD)	37.4 (190.24)	18.5 (48.41)	13.0 (27.55)	23.1 (115.04)
Median	6.0	6.0	7.0	6.5
Min, Max	1.5, 2005.8	1.5, 462.2	2.2, 284.5	1.5, 2005.8

Source: Study report

3.2 EFFICACY EVALUATION

Sponsor's Reported Analyses Results

Table 6 lists the primary efficacy results of the primary endpoint PCH_T. Superiority of SPN-804O 2400mg/d relative to placebo with a p-value ≤ 0.003 and a median PCHT of -42.90 was demonstrated in the study. While the median percentage change in partial seizure rate was higher with SPN-804O 1200mg/d than placebo, the difference was not statistically

significant (-38.20 versus -28.70; p=0.078). Figure 2 also supported the findings listed in table 6.

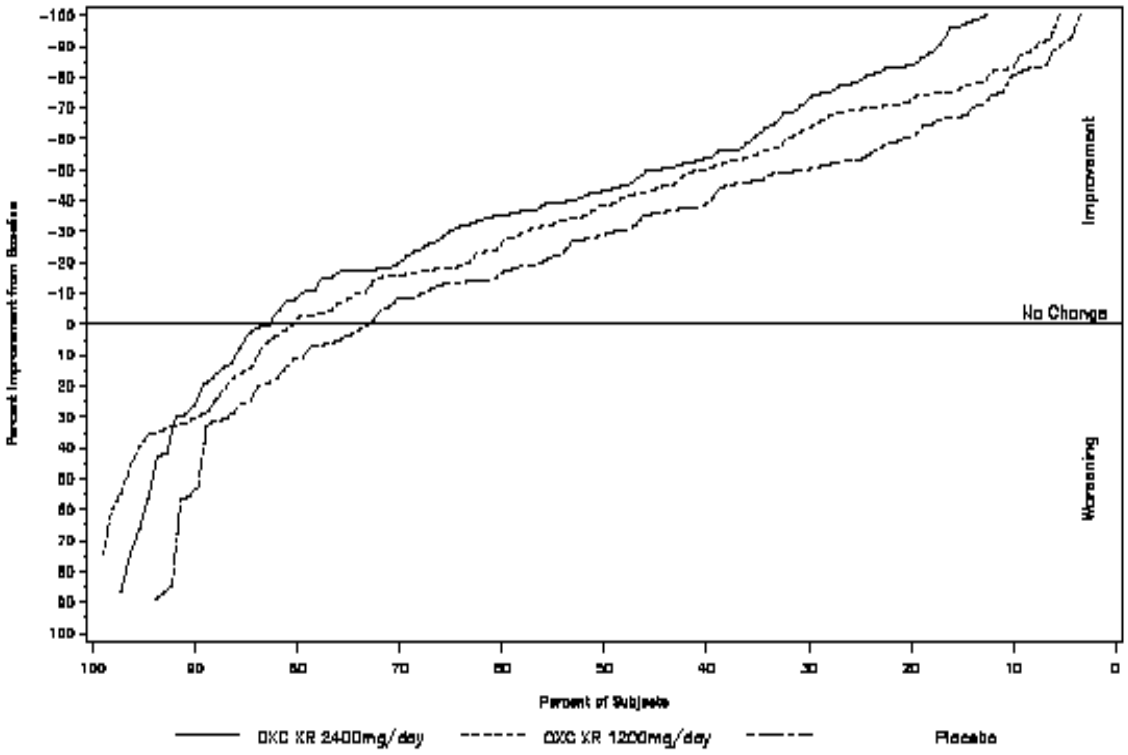
Table 6: Primary Efficacy Results

Statistic	SPN-8040 2400mg/d (N=123)	SPN-804O 1200mg/d (N=122)	Placebo (N=121)
N	111	109	117
Mean (SD)	-38.03 (53.11)	-29.14 (69.84)	-15.43 (67.34)
Median	-42.90	-38.20	-28.70
Min, Max	-100.0, 212.8	-100.0, 556.1	-100.0, 333.6
p-value versus placebo[a]	0.003	0.078	
Hodges-Lehmann Estimate	-18.30	-10.30	
95% Confidence Interval	(-30.40, -5.80)	(-22.30, 1.20)	

Source: Study report

[a] *Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 16-week Treatment Phase (Titration + Maintenance Periods) relative to the 8-week Baseline Phase.*

Figure 2. Continuous Responder Curves Based on PCH (T) – TT Population



Source: Study report.

Table 7: Secondary Efficacy Results

Statistic	SPN-804O 2400mg (N=123)	SPN-804O 1200mg (N=122)	Placebo (N=121)
ITT Population			
PCH – Maintenance Period Only			
n	123	122	121
Median	-49.15	-35.30	-32.90
p-value versus placebo [a]	0.003	0.589	
Responder Rate – Treatment Phase			
n	123	122	121
Responder, n (%)	50 (40.7)	44 (36.1)	34 (28.1)
Non-responder, n (%)	61 (49.6)	65 (53.3)	83 (68.6)
p-value versus placebo [b]	0.018	0.075	
Seizure-Free Rates - Treatment Phase			
N	123	122	121
Subjects with valid diary data	111	109	117
Number (%) seizure free	14 (11.4)	6 (4.9)	4 (3.3)
p-value versus placebo [c]	0.013	0.528	
Seizure-Free Rates - Maintenance Period Only			
N	123	122	121
Number (%) seizure free	17 (13.8)	4 (3.3)	7 (5.8)
p-value versus placebo [c]	0.008	0.546	

Source: Study report

[a] *Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 8-week Maintenance Period relative to the 8-week Baseline Phase*

[b] *P-value from logistic regression model with treatment group as a factor and country (or cluster), age, sex, and baseline seizure frequency per 28 days as explanatory variables.*

[c] *P-value from Fisher's exact test*

Table 7 lists the findings of the secondary efficacy measures on the ITT population. Each of the included secondary measures supported those of the primary efficacy analysis, with SPN-804O 2400mg/d being superior to placebo ($p<=0.018$). The SPN-804O 1200mg/d was numerically more effective than placebo for all but seizure-free rates during the maintenance period; the difference between groups was not statistically significant ($p >=0.075$).

In the changes of the clinical global impression for the ITT population, both SPN-804O treatment groups were not statistically significant ($p>0.087$) from the placebo group at the end of the maintenance period.

As a sensitivity analysis, the primary efficacy analysis was also carried out on the completers. The completers include all randomized subjects who complete at least part of the double-blind combined titration and maintenance period. Table 8 lists the findings of the analysis. The sensitivity analysis also supported the results of the overall primary efficacy analysis: 2400mg/d was superior to placebo, but 1200 mg/day was not different from placebo.

Table 8: Median PCH_T in the Completers Population

SPN-804O		Placebo	p value vs. Placebo [a]	
2400mg	1200mg		2400mg	1200mg
N= 71	N= 82	N=95		
-50.4	-37.4	-30.3	0.001	0.233

[a] *Wilcoxon rank-sum test*

Another sensitivity analysis: Mixed MMRM analysis was performed on the ranks of PCH_T for the ITT population. The dependent variable was the rank of PCH_T. The model included treatment, protocol-specified visit, treatment-by-visit interaction, and country as fixed effects; the rank of B (the partial seizure frequency per 28 days during the baseline phase) as a covariate; and visit as a repeated measure. The model included an unstructured covariance matrix. The findings from MMRM analysis are not different from the findings obtained from the protocol specified primary statistical method, but only the relative p values: for the 2400mg/d group vs. placebo p = 0.005 (vs. p=0.003) and for the 1200mg/d group, p=0.161 (vs. p=0.078).

As requested by this reviewer, the sponsor also submitted following two additional sensitivity analysis results. An ANCOVA analysis was done on log transformed of total partial seizures per 28 days during the treatment phase including the log transformed total partial seizures per 28 days during the baseline phase, treatment, and country as covariates. The findings of this analysis did not change the primary statistical outcome, but only the relative p values: for the 2400mg/d group vs. placebo p = <0.001 (vs. p=0.003) and for the 1200mg/d group, p=0.109 (vs. p=0.078).

In the second analysis, the sponsor reported results of an ANCOVA on rank of the primary endpoint PCHT including baseline (rank of total partial seizures per 28 days during the baseline phase), treatment, and country as covariates. In the rank ANCOVA analysis, the findings of this analysis did not change the primary statistical outcome, but only the relative p values: for the 2400mg/d group vs. placebo p = <0.004 (vs. p=0.003) and for the 1200mg/d group, p=0.281 (vs. p=0.078).

Dealings with Dropouts or Missing Data

To evaluate the impact of missing data, analyses on the primary efficacy endpoint - percent reduction in partial seizure frequency per 28 days were conducted considering (i) baseline compared to first, (ii) baseline compared middle, and (iii) baseline compared last 4 weeks of the maintenance period of ITT Population. The seizure rate during the treatment phase was calculated over the number of days with non-missing seizure data in the treatment phase. SPN-804O 2400mg/d was statistically significantly superior to the placebo group for the percent reduction in partial seizures from baseline to the first 4 weeks (Weeks 5-8) and last 4 weeks (Weeks 13-16) of the treatment phase (Table 8). While the median percentage change in partial seizure rate was higher with SPN-804O 1200mg/d than placebo, the difference was

not statistically significant. These findings support that the missing data has no major impact on the findings based on the primary analysis in the study.

Table 9. Percent Reduction in Partial Seizures Frequency per 28 days (PCH) (Baseline Compared to First, Middle, and Last 4 Weeks of Treatment Period) – ITT Population

Interval of Treatment Period		Dose Level	
	Placebo N = 121	2400 mg N=123	1200 mg N=122
First 4 weeks (Weeks 5-8)	N = 109	N = 88	N = 97
Baseline median seizure rate	7.00	5.93	6.50
Treatment phase median seizure rate	5.33	2.24	4.00
Median percent reduction in seizure rate	-32.20	-55.60	-38.90
p-value: comparison to placebo [1]		<.001	0.189
Middle 4 weeks (Weeks 9-12)	N = 108	N = 76	N = 90
Baseline median seizure rate	7.00	5.25	6.50
Treatment phase median seizure rate	4.67	3.00	4.41
Median percent reduction in seizure rate	-42.55	-48.85	-34.70
p-value: comparison to placebo [1]		0.189	0.397
Last 4 weeks (Weeks 13-16)	N = 107	N = 74	N = 87
Baseline median seizure rate	7.00	5.25	6.50
Treatment phase median seizure rate	4.67	2.90	3.61
Median percent reduction in seizure rate	-41.2	-54.60	-45.50
p-value: comparison to placebo [1]		0.026	0.4375

[1] Wilcoxon rank-sum test

3.3. FDA Reviewer's Data Analyses and Comment

This reviewer re-analyzed the efficacy data of this study according to the protocol specified statistical analysis plan and found that the efficacy findings are consistent with the sponsor's reported efficacy findings. The missing data had no impact on the efficacy conclusions of the study. The findings from a completer analysis are also consistent with the findings from the ITT population. This reviewer also did two sensitivity analyses (ANCOVA on log-transformed data; and ANCOVA on the rank-transformed data). The findings from these two types of analyses are also consistent with the primary endpoint analysis findings. As requested from this reviewer, the sponsor also submitted the findings of these two types of analyses.

4. SUBGROUP ANALYSIS

Subgroup Analyses

Table 8 lists subgroup analysis results for the primary efficacy endpoint PCHT of partial seizure by gender, region, and for the PCHT of different seizure types: simple partial seizures, complex partial seizures, simple and complex partial seizures, secondarily generalized seizures. The subgroup analyses of PCHT were conducted on the ITT population. In each gender group, the median percentage changes in partial seizure rate were higher in the SPN-804O doses as compared to the change in the placebo group. In the ITT sample, more than 85% randomized subjects were Whites, and hence no subgroup analysis was done by race.

Within each subgroup, all SPN-804O dose groups had numerically greater median percent reductions in PCH_T as compared to the reductions in the placebo group. That is, subgroup analyses of the percentage reduction in partial seizure frequency per 28 days during the PCH_T also supported the efficacy of the SPN-804O doses.

Table 8: Percentage Reduction in Partial Seizure Frequency per 28 days during the PCH_T by Demographic Characteristics and Seizure Types-ITT Population

Age Category	OXC XR 2400 mg/day	OXC XR 1200 mg/day	Placebo
Gender			
Female	N =64	N = 71	*N = 67*
Median percent reduction in seizure rate	-50.40	-34.50	*-27.30*
Male	N = 59	N = 51	*N = 54*
Median percent reduction in seizure rate	-39.10	-41.25	*-29.50*
Race			
White or Caucasian	N = 105	N = 104	*N = 107*
Median percent reduction in seizure rate	-40.60	-36.20	*-28.70*
Region			
North America (US /Canada, Mexico)	N = 35	N = 40	*N = 41*
Median percent reduction in seizure rate	-52.0	-34.5	*-13.3*
Other Region (Poland, Romania, Russia)	N = 88	N = 82	*N = 80*
Median percent reduction in seizure rate	-41.2	-38.4	*-33.2*
Seizure Type:			
Seizure Type: Simple partial seizure with motor component	N=27	N=27	*N=29*
Median percent reduction in partial seizure frequency per 28 days during treatment phase	-40.70	-33.70	*-25.30*
Seizure Type: Complex partial seizure	N=71	N=65	*N=68*
Median percent reduction in partial seizure frequency per 28 days during treatment phase	-40.70	-40.70	*-34.20*
Seizure Type: Secondarily generalized seizures	N=21	N=28	*N=21*
Median percent reduction in partial seizure frequency per 28 days during treatment phase	-74.6	-50.0	*-39.0*
Seizure Type: Sum of simple and complex partial seizures	N=93	N=88	*N=95*
	-38.90	*-34.35*	*-28.8*

Source: study report

5. SUMMARY AND CONCLUSIONS

SPN-804O 2400mg/day demonstrated its efficacy in reducing the partial seizure frequency per 28 days, with a median percentage seizure reduction of 42.9% from baseline (vs. the reduction of 28.70% in the placebo group). The difference in reduction between SPN-804O 2400mg/day and placebo group was statistically significant (p=0.003). The 1200mg/daily dose also demonstrated a decrease (-38.2%) in median seizure frequency per 28 days, but it

failed to be statistically significantly different from the placebo arm (p=0.078). SPN-804O 2400mg/day also demonstrated its efficacy regardless of gender, race, and region.

Sensitivity analyses supported the efficacy results of the primary endpoint. SPN-804O 2400mg/day medium-dose was statistically significantly superior to the placebo group in all sensitivity analyses. Results of secondary endpoints were consistent with the results of the primary endpoint.

The cumulative distribution of frequency curves based on percent reduction from baseline in partial seizures also supported the primary efficacy of SPN-804O 2400mg/day and 1200mg/day.

In conclusion, 2400mg SPN-804O administered QD demonstrated an effective treatment for refractory partial epilepsy, and 1200mg QD demonstrated numerically better than placebo in reducing the partial seizure frequency.

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/s/

OHIDUL I SIDDIQUI
09/13/2012

KUN JIN
09/13/2012
I concur with this review.

HSIEN MING J HUNG
09/14/2012