CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21710
Drug Name:	SPD417 (Carbamazepine extended release capsules)
Indication(s):	Bipolar disorder (manic or mixed subtype)
Applicant:	Shire Pharmaceutical
Date(s):	Feb 13, 2004 (received the NDA application)
Review Priority:	
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Keywords: NDA review, endpoint analysis/LOCF, multi-center

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1. EXECUTIVE SUMMARY

The sponsor submitted two short-term (3-week study) randomized double-blind, placebo-controlled, parallel-group, multicenter clinical trials to claim the efficacy of SPD417 (carbamazepine extended release capsules) in the treatment of bipolar disorder (mania or mixed). One study (Study #105.301) was conducted in the United States (24 sites), and another study (Study #417.304) was conducted in the United States (19 sites) and India (6 sites). The two studies were identical in all aspects of study design.

1.1 Conclusions and Recommendations

The two short-term studies demonstrated the efficacy of SPD417 (carbamazepine extended release capsules) in the treatment of bipolar disorder (mania or mixed).

1.2 Brief Overview of Clinical Studies

The two short-term studies were three-week, randomized, double-blind, placebo-controlled, parallel group multicenter study in subjects with bipolar I disorder (manic or mixed). The study consisted of a screening/lead-in phase (Day -5 to -2) followed by 3 weeks of double-blind treatment. At baseline (Day -1), subjects were randomized in a 1:1 ratio to receive either SPD417 or placebo. All subjects were hospitalized during the screening/lead-in phase and for at least the first seven days of double-blind treatment. Subjects randomized to receive SPD417 began treatment on Day 1 at 400mg/day. The total dosage was increased in increments of 200 mg/day to a maximum total daily dosage of 1600mg based on the subject's tolerability of the medication. Efficacy assessments were conducted at screening, baseline, and Visits 3 [Day 7], 4 [Day 14] and/or 5 [Day 21]) of the double-blind treatment period.

In each of the studies, the acute efficacy of extended-release carbamazepine (over-encapsulated SPD417) compared to placebo in the treatment of manic symptoms in subjects with bipolar I disorder was evaluated using the Young Mania Rating Scale (YMRS) as the primary efficacy measure.

In each study, the primary efficacy measure was analyzed using an ANCOVA model that included the effects of treatment, center as factors and the baseline score of YMRS as covariate.

1.3 Statistical Issues and Findings

No statistical issue was found in these two short-term studies.

2. INTRODUCTION

2.1 Overview

The sponsor submitted two short-term (3-week study) randomized double-blind, placebo-controlled, parallel-group, multicenter clinical trials to demonstrate the efficacy of SPD417 (carbamazepine extended release capsules) in the treatment of bipolar disorder (mania or mixed). One study (Study #105.301) was conducted in the United States (24 sites), and another study (Study #417.304) was conducted in the United States (19 sites) and India (6 sites). The two studies were identical in all aspects of study design.

2.2 Data Sources

SAS data sets of each of the studies are available at \\Cdsesub1\N21710\N_000\2004-02-13\crt\datasets. The study reports are available at\\Cdsesub1\N21710\N_000\2004-02-13\clinstat\bipolar.

3. STATISTICAL EVALUATION

3.1 Study reviewed

The sponsor claimed the effectiveness of SPD417 (carbamazepine extended release capsules) in the treatment of bipolar disorder (mania or mixed) based on the findings of two positive studies ((Studies #105.301, and #417.304). In this review, the findings of both studies are reviewed.

3.1.2 Study Design - Studies #105.301 and #417.304

Both studies were three-week, randomized, double-blind, placebo-controlled, parallel group, multi-center study in subjects with bipolar I disorder (manic or mixed). Eligible subjects were randomized to receive either SPD417 or placebo. Subjects randomized to receive SPD417 began treatment on Day 1 at 400mg/day. The total dosage was increased in increments of 200mg/day to a maximum total daily dosage of 1600mg based on the subject's tolerability of the medication. All subjects remained in-hospital during the screening and lead- in phase and for at least the first 7 days of double-blind treatment period.

3.1.3 Patient Population - Studies #105.301 and #417.304

The patients were inpatient/outpatients and from both gender. Patients were $\geq$ 18 years old and met DSM-IV criteria for bipolar disorder. Patients also had a history of at least one previous manic or mixed episode, had a minimum pre-study and baseline (Day -1) total score of 20 on the YMRS.

In Study #105.301, a total of 204 patients were randomized (101 patients to SPD417 treatment and 103 patients to placebo treatment), and 192 patients were included in the ITT population (94 patients were treated with SPD417 and 98 patients were treated with placebo) who received at lease 1 dose of randomized study medication in the double-blind treatment phase. Twelve patients were excluded from the primary efficacy analysis because they did not have a post-randomization YMRS score.

In Study#417.304, a total of 239 patients were randomized (122 patients to SPD417 treatment and 117 patients to placebo treatment) and 235 patients were included in the ITT population (120 SPD417-treated patients and 115 placebo-treated patients) who received at lease 1 dose of randomized study medication in the double-blind treatment phase. Four patients were excluded from the primary analysis because they did not have a post-randomization YMRS score.

3.1.4 Efficacy Parameters - Studies #105.301 and #417.304

The primary efficacy variable was the Young Mania Rating Scale (YMRS) total score. The primary efficacy endpoint was the YMRS total score at the end of double- blind treatment period (i. e., study endpoint).

Secondary efficacy variables were the Clinical Global Impression (CGI) severity and improvement scores for overall bipolar illness, Hamilton Rating Scale for Depression (HAM- D) total score, HAM- D depressed mood item score, and YMRS number of responders and sustained responders. On the YMRS scale, a subject whose total score decreased by 50% or more from the baseline total score was considered a responder.

3.1.5 Statistical Analyses - Studies #105.301 and #417.304

The primary efficacy endpoint was the YMRS total score at the end of double-blind treatment period and analyzed for the LOCF data of ITT population using the analysis of covariance (ANCOVA) model. The model included treatment group, the corresponding baseline score (the covariate), and site. In an exploratory analysis, the site by treatment effect was examined by including the site- by- treatment interaction in the ANCOVA model.

The YMRS total score was set to missing if more than two of the 11 individual items were invalid. If there were only one or two missing individual items, the items with missing scores were imputed based on the mean of the non- missing item scores, then the YMRS total score was derived by adding up the imputed missing item scores and non- missing item scores. If the score from the baseline visit was missing, the last available score from the screening visit was used in the analyses as the "baseline" score.

The primary efficacy endpoint was also analyzed based on the subgroup populations: gender (Males vs. Females), subjects of various age groups, and ethnic origin.

The secondary outcome measures HAM-D total score, HAM-D depressed mood item score, and CGI severity score at the endpoint were analyzed using a two-way analysis of covariance (ANCOVA) model with treatment and site as the main factors and the baseline value as the covariate for the ITT population. The CGI improvement score was analyzed using the Chi-square test with continuity adjustment.

3.1.6 Sponsor's Results - Studies #105.301 and #417.304

3.1.6.1. Patient Characteristics - Studies #105.301 and #417.304

In study #105.301 (the US study), majority of randomized patients (72.5%) were Caucasian. In Study #417.304 (conducted in US and India), 61% of patients were enrolled in US. A total of 47.3% were Caucasian, 13.5% were Black, and 39.2% were other races including those subjects from India. Among the randomized patients, 52.5% and 70.5% patients were male in the study #105.301 and study#417.304, respectively.

Across the two studies and treatment groups, the patient population was similar with respect to gender, race, mean age (ranging from approximately 37 to 38 years), and mean weight (ranging from approximately 167 to 195 lbs).

Table 1 lists the patient disposition of the two studies. In study# 105.301, 50 (49.5%) Carbatrol patients and 46 (44.7%) placebo patients completed the study duration. In each group, more than 50% randomized patients dropped out from the study. The most frequent reason for discontinuation was subject choice for Carbatrol patients and lack of efficacy for placebo patients. The second most frequent reason for discontinuation was lack of efficacy for Carbatrol patients and subject choice for placebo patients.

In study# 417.304, 80 (65.6%) SPD417 subjects and 64 (54.7%) placebo subjects completed the study duration. For SPD417 subjects, the most frequent reasons for discontinuation were adverse events and subject choice, and protocol violation. For the placebo subjects, the most frequent reasons for discontinuation were lack of efficacy, and subject choice.

Table 1: Summary of Patient Disposition

	Study #105.301		**Study #417.304**	
	Carbatrol N (%)	Placebo N (%)	Carbatrol N (%)	Placebo N (%)
Randomized	101 (100%)	103 (100.0%)	122 (100.0%)	117 (100.0%)
Completed Study	50 (49.5%)	46 (44.7%)	80 (65.6%)	64 (54.7%)
Discontinued Study	51 (50.5%)	57 (55.3%)	42 (34.4%)	53 (45.3%)
Lost to Follow-up	3 (3.0%)	3 (2.9%)	2 (1.6%)	2 (1.7%)
Adverse Event(s)	13 (12.9%)	6 (5.8%)	11 (9.0%)	6 (5.1%)
Subject Choice	17 (16.8%)	19 (18.4%)	11 (9.0%)	11 (9.4%)
Lack of Efficacy	14 (13.9%)	22 (21.4%)	8 (6.5%)	27 (23.1%)
Protocol Violation	1 (1.0%)	2 (1.9%)	9 (7.4%)	4 (3.4%)
Other	3 (3.0%)	5 (4.9%)	1 (0.8%)	3 (2.5%)

Source: Table 2 in the study reports.

3.1.6.2. Primary Efficacy Analyses- Studies #105.301 and #417.304

Table 2 lists the primary efficacy results of the studies #105.301 and #417.304 based on the primary efficacy measure-the change from baseline to endpoint in YMRS total score. In both studies, a statistically significant difference in YMRS total scores at endpoint between the treatment groups in favor of SPD417 was noted. In Study #105.301, the least square mean changes from baseline to endpoint in YMRS scores were -7.82 in the SPD417 treatment group, and -4.77 in the placebo group (difference of -3.05, p-value=0.033). In Study #417.304, the least square mean changes from baseline to endpoint in YMRS score were -14.83 in the SPD417 treatment group and -6.96 in the placebo group (difference of -7.87, p-value<0.0001).

Table 2: LOCF Analyses of Covariance on the change Scores of YMRS Total Scores from the baseline scores at end point (ITT Population)

	Least Squares			
	Mean Change	SE	Mean Difference from placebo	P-value
Study #105.301				
Placebo (n=98)	-4.77	1.19		
Carbatrol (n=94)	-7.82	1.18	-3.05	0.033
Study #417.304				
Placebo (n=115)	-6.96	1.09		
Carbatrol (n=120)	-14.83	1.05	-7.87	<0.001

LS mean and P-values are based on ANCOVA model with baseline (covariate), site, and treatment group in the model for post-randomization visits.

*Sponsor did not report the least square means. This reviewer produced the LS means using the above ANCOVA model. Sponsor's reported P-values are matched with this reviewer's calculated P-values.

Table 3 lists the primary efficacy results of the studies #105.301 and #417.304 based on the primary efficacy measure-the change from baseline of mean change in YMRS total score from baseline to each double-blind treatment week based on observed cases. Individual study results revealed that in Study #417.304, these differences between the two group with respect to YMRS total scores were statistically significant at all time points (p<0.0001); in Study #105.301, statistically significant differences between the groups were observed at Day 21 using the observed case analysis (p=0.016).

Table 3: Mean Change in Weekly YMRS Total Scores in the Subjects with Mixed or Manic Bipolar Disorder in General - ITT Population (Observed Case)

	Study #105.301					Study# 417.304					
Treatment Group	N	Least Square Means	SE	LS Mean Difference from Placebo	p-value	Treatment Group	N	Least Square Means	SE	LS Mean Difference from Placebo	p-value
Day 7						**Day 7**					
Placebo	98	-4.90	.93			Placebo	114	-5.55	.79		
SPD417	94	-6.07	.93	-1.17	0.294	SPD417	120	-9.89	.82	-4.34	<.0001
Day 14						**Day 14**					
Placebo	72	-5.51	1.33			Placebo	95	-8.60	1.09		
SPD417	74	-8.43	1.35	-2.92	0.071	SPD417	103	-14.28	1.05	-5.66	<.0001
Day 21						**Day 21**					
Placebo	51	-7.29	1.46			Placebo	75	-10.36	1.20		
SPD417	52	-11.94	1.57	-4.65	0.016	SPD417	89	-17.14	1.15	-6.78	<.0001

3.1.6.3. Secondary Efficacy Analyses - Studies #105.301 and #417.304

Table 4 summarizes the LOCF endpoint efficacy results of the secondary efficacy measures CGI-severity and HAM-D total scores. A statistically significant difference at endpoint between the treatment groups in favor of SPD417 was observed in CGI-severity scores in each of the studies.

In Study #105.301 at the LOCF endpoint analysis, the difference between the treatment groups was not statistically significant. In Study #417.304, the difference between the treatment groups was statistically significant (LS mean difference of -1.639, p=0.005).

Table 4: LOCF Analyses of Covariance on the Change Scores of the Secondary measures(ITT Population)

Secondary Measures		Least Squares			
		Mean Change	SE	Mean Difference from placebo	P-value
CGI severity	**Study #105.301**				
	Placebo (n=98)	-0.241	.137		
	Carbatrol (n=94)	-0.638	.137	-0.397	0.017
	Study #417.304				
	Placebo (n=115)	-0.468	.137		
	Carbatrol (n=120)	-1.355	.132	-0.887	<.0001
HAM-D Total Scores	**Study #105.301**				
	Placebo (n=98)	-1.005	.695		
	Carbatrol (n=94)	-1.831	.697	-0.826	0.325
	Study #417.304				
	Placebo (n=115)	0.391	.542		
	Carbatrol (n=120)	-1.248	.527	-1.639	0.005

LS mean and P-values are based on ANCOVA model with baseline (covariate), site, and treatment group in the model for post-randomization visits.
*Sponsor did not report the least square means. This reviewer produced the LS means using the above ANCOVA model. Sponsor's reported P-values are matched with this reviewer's calculated P-values.

With respect to the percentages of YMRS responders (YMRS total score decreased 50% or more from baseline) and CGI-Improvement at the LOCF endpoint analyses, SPD417 was statistically significant different from placebo in both studies [Table 5].

Table 5. Percentage of Responders in Secondary Measures (ITT LOCF Population)

Secondary Measure	Study	Carbatrol		Placebo		P-value
		N	Responders (%)	N	Responders (%)	
YMRS total score decreased 50% or more from baseline.	#105.301	94	39 (41.5)	98	22 (22.4)	0.007
	#417.304	120	73 (60.8)	115	33 (28.7)	<0.001
CGI-Improvement Score	#105.301	94	41 (43.6)	96	23 (24.0)	0.006
	#417.304	120	78 (65.0)	115	37 (32.2)	<0.001

3.1.6.4. FDA Reviewer's Data Analyses and Comment - Studies #105.301 and #417.304

This reviewer re-analyzed the data sets of the Studies #105.301 and #417.304 according to the protocol specified statistical analysis plans. The findings for the primary and secondary efficacy measures matched with the findings submitted by the sponsor.

4. Subgroup Analyses

4.1 Subgroup Analyses - Studies #105.301 and #417.304

In both of the studies (#105.301 and #417.304), subgroup analyses on the primary efficacy endpoint, YMRS total scores were performed to evaluate the uniformity of treatment effect within patient subgroups (gender, age: 18-39 years age Vs. ≥40 years age, race: Caucasian Vs. Non-Caucasian, and national origin in study#417.304: US Population Vs. Indian Population). An ANCOVA model that included the subgroup characteristic, treatment group, baseline YMRS total scores, and a treatment-by-characteristic interaction term was used to test at $\alpha < 0.05$, for evidence of a difference in the treatment effect across levels of the subgroup characteristic. No significant interaction effect of treatment group by any of the subgroup characteristics was found. The lack of significant interaction indicates that the treatment effect is similar irrespective of the patients' characteristics.

The FDA reviewer also did the subgroup analyses on both studies. The reviewer's conclusions based on the subgroup analysis findings were similar to the sponsor's conclusions.

5. SUMMARY AND CONCLUSIONS

5.1 Collective Evidence of Efficacy in Studies #105.301 and #417.304

Using the LOCF analyses, a positive response to Carbatrol was observed at Day 21 (the endpoint) for the ITT population in both studies. That is, the patients treated with Carbatrol were benefited in improving their acute manic symptoms as measured by the mean change from baseline in YMRS total score.

Both studies also demonstrated a significant Carbatrol response with respect to the percentage of patients considered responders (having a 50% reduction from baseline to endpoint for the YMRS total score),CGI severity, and CGI-Improvement Score.

5.2 Conclusions and Recommendations

Studies #105.301 and #417.304 demonstrated that Carbatiol was an effective drug for the treatment of manic symptoms in bipolar patients (manic or mixed) for up to 21 days at a titrated dose of between 200 mg/day and 1600 mg/day, given twice daily.

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