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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21035 /Sup 040/ N21-505/S-007
Drug Name:	Levetiracetam (Keppra®) tablets
Indication(s):	Add-On Treatment in Refractory Pediatric Patients With Partial Onset Seizures
Applicant:	UCB Pharma, Inc.
Date of Document:	December 20, 2004
Review Priority:	Standard
Biometrics Division:	Division 1 (HFD-710)
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Keywords: NDA review, endpoint analysis/LOCF, multi-center, partial onset seizures, ANCOVA analysis

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1. EXECUTIVE SUMMARY

The sponsor has submitted the efficacy findings of one adequate and well-controlled study (study # N159) to demonstrate efficacy and tolerability of levetiracetam as add-on treatment in refractory pediatric patients (age 4 to 16 years) with refractory partial onset seizures. A total of 198 patients (of which only 50 patients were 12 to 16 years older) enrolled in the study. The study was conducted at 49 study centers in the United States and 11 study centers in Canada.

1.1 Conclusions and Recommendations

The statistical findings of the study N159 demonstrate that levetiracetam as adjunctive therapy at total daily dose levels from 20-60 mg/kg/day was effective in children 4-16 years old with refractory partial onset seizures.

1.2 Brief Overview of Clinical Studies

Study # N159 was a randomized, double-blind, placebo-controlled, multi-center study in pediatric epilepsy patients (4 to 16 years old) with refractory partial onset seizures. A total of 198 patients (of which only 50 patients were 12 to 16 years older) enrolled in the study. The study was conducted at 49 study centers in the United States and 11 study centers in Canada.

The patients were randomized to placebo or levetiracetam groups after following an 8-week baseline period. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day. Patients remained at the 60 mg/kg/day dose for a total of 10 weeks.

The primary efficacy parameter in the study was the partial onset (Type I; Type IC included) seizure frequency per week during the entire up-titration and evaluation period. The primary efficacy variable was analyzed using analysis of covariance (ANCOVA).

1.3 Statistical Issues and Findings

The ANCOVA analysis results of Partial Onset (Type I) Seizure Frequency per Week demonstrated that the least squares mean partial onset seizure frequency per week was significantly ($p=0.0002$) smaller for levetiracetam (1.57) than for placebo (1.88) in the treatment period. For levetiracetam, the percent reduction over placebo was 26.8%. When the study periods were analyzed separately, levetiracetam significantly reduced the partial onset seizure frequency over placebo by 31.2% and 22.4% in the Titration and Evaluation Periods, respectively.

No statistical issues were found in the study design and in the submitted efficacy findings.

2. INTRODUCTION

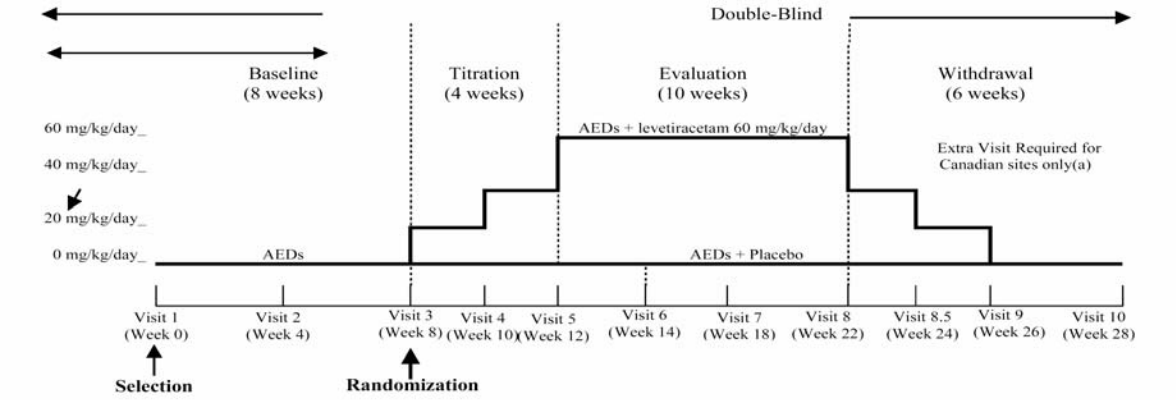
2.1 Overview

The sponsor has submitted the efficacy findings of one adequate and well-controlled study (study # N159) to demonstrate efficacy and tolerability of levetiracetam as add-on treatment in refractory pediatric patients (age 4 to 16 years) with refractory partial onset seizures. Study N159 was a randomized, double-blind, placebo-controlled, multi-center study in pediatric epilepsy patients (4 to 16 years old) with refractory partial onset seizures. A total of 198 patients (of which only 50 patients were 12 to 16 years older) enrolled in the study. The study was conducted at 49 study centers in the United States and 11 study centers in Canada.

Patients being treated with a maximum of two other AEDs were included in the trial. To participate in the trial, the patients were required to have at least four partial onset seizures per each 4-week period during the 8-week baseline.

Patients were randomized to placebo or levetiracetam groups after following an 8-week baseline period. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day. The randomized patients remained at the 60 mg/kg/day dose for a total of 10 weeks. Dosing could be adjusted as needed for tolerability.

Figure 1: Study Design



The dose of double-blind study medication was gradually increased during the Titration Period by administering a dose level of 20 mg/kg/day of levetiracetam or placebo for the first 2 weeks, followed by a dose level of 40 mg/kg/day of levetiracetam or placebo for 2 weeks. The dose level was then increased to 60 mg/kg/day of levetiracetam or placebo for the remaining 2 weeks; however, the dose level could be reduced if necessary.

The primary efficacy parameter in this study was the partial onset (Type I; Type IC included) seizure frequency per week during the entire up-titration and evaluation period. While on treatment, patients were seen every 2 weeks for the first 6 weeks and then once every 4 weeks. Patients who discontinued or who decided not to enter the long-term extension study were to be down-titrated in 20-mg/kg/day decrements every 2 weeks. They were to be seen every 2 weeks for a total of 4 weeks following discontinuation.

The partial onset seizure frequency per week was computed as follows:

$$\text{Seizure frequency per week} = \frac{7 \text{ x number of seizures in the period}}{\text{number of days with seizure count} \geq 0 \text{ in the period}}$$

The patients who took at least one dose of levetiracetam or placebo were included in the ITT population. One Site#55 having 16 randomized patients was excluded from the ITT population due to unreliability of the data.

The primary efficacy variable was analyzed using analysis of covariance (ANCOVA). A $\log_e (x+1)$ transformation was applied to the primary efficacy measure- Seizure frequency per week data. An ANCOVA model was applied on the $\log_e (x+1)$ transformed data (seizure frequency per week), including treatment as a factor and the $\log_e (x+1)$ transformed baseline seizure frequency per week as a covariate.

2.2 Data Sources

SAS data sets of the study are available at \\Cdsesub1\N21035\S_040\2004-12-20\Analysis Datasets. The study report is available at \\Cdsesub1\N21035\S_040\2004-12-20\clinstat.

3. STATISTICAL EVALUATION

3.1 Patient Population

A total of 198 patients (101 levetiracetam, 97 placebo) were included in the ITT population. The randomized patients were 3 to 17 years of age. About 50.0% of the patients were males and 70% of the patients were Caucasians. The treatment groups were comparable for demographic characteristics.

Table 1 list the demographic characteristics of the ITT population.

Characteristic		Levetiracetam (N=101)	Placebo (N=97)
Age (Years)	Mean (SD)	10.2 (3.2)	9.8 (3.4)
	Median	10.4	9.7
	Min-Max	4.1 - 17.0	3.3 - 17.2
Age Class (Years)			
<4	n (%)[a]	0 (0.0%)	2 (2.1%)
≥4 to <8	n (%)	25 (24.8%)	30 (30.9%)
≥8 to <12	n (%)	46 (45.5%)	42 (43.3%)
≥12 to <17	n (%)	30 (29.7%)	20 (20.6%)
≥17	n (%)	0 (0.0%)	3 (3.1%)
Gender			
Female	n (%)	47 (46.5%)	51 (52.6%)
Male	n (%)	54 (53.5%)	46 (47.4%)
Race			
White/Caucasian	n (%)	74 (73.3%)	65 (67.0%)
Black/African-American	n (%)	13(12.9%)	12 (12.4%)
Hispanic	n (%)	9 (8.9%)	11 (11.3%)
Asian/Pacific Islander	n (%)	2 (2.0%)	1 (1.0%)
American Indian / Alaska Native	n (%)	0 (0.0%)	2 (2.1%)
Indian/Pakistani	n (%)	1 (1.0%)	0 (0.0%)
Other/Mixed Race	n (%)	2 (2.0%)	6 (6.2%)

Ref: Table 11.1 in the study report.

Majority of the patients completed the double-blind trial. The retention was higher amongst the patients randomized to levetiracetam (94 patients or 93.1%) as compared to the patients randomized to placebo (83 patients or 85.6%). A total of 21 patients discontinued early; 14 due to AEs, 3 were lost to follow-up, 2 for lack of efficacy, and 2 for other reasons. More placebo patients (9, 9.3%) than levetiracetam patients (5, 5.0%) discontinued due to AEs. Table 2 lists the patients' disposition.

Table 2: Patients Disposition (ITT Population)

	Levetiracetam		Placebo	
	N	%	N	%
Number Randomized	101		97	
Completed Treatment	94	(93.1%)	83	(85.6%)
Reasons Discontinued				
Adverse Event	5	(5.0%)	9	(9.3%)
Lack of efficacy	0	(0.0%)	2	(2.1%)
Lost to follow-up	1	(1.0%)	2	(2.1%)
Other	1	(1.0%)	1	(1.0%)

Ref: Table 10.1 in the study report.

3.2 Efficacy Results

Primary Efficacy Analysis:

The primary efficacy variable was the partial onset (Type I) seizure frequency per week during the Treatment Period. The primary efficacy analysis performed on the ITT population was an ANCOVA model. The model included treatment and baseline terms. Log $_e$ (x+1) transformed data was used in the analysis.

Table 3: Partial Onset (Type I) Seizure Frequency per Week and Percent Reduction Over Placebo (Log-Transformed Data, ITT Population)

	Seizure Frequency per Week Least Square Means[a]				
	Levetiracetam (N=101)	Placebo (N=97)	Difference (95% CI)	*p*-value[b]	Percent Reduction[c] (95% CI)
Partial Onset Seizures[d]					
Titration Period	1.55	1.92	0.37 (0.20, 0.55)	< 0.0001	31.2% (18.0 - 42.3%)
Evaluation Period	1.55	1.81	0.26 (0.07, 0.44)	0.0067	22.4% (6.9 – 35.4%)
Treatment Period	1.57	1.88	0.31 (0.15, 0.47)	0.0002	26.8% (14.0 – 37.6%)

(a)Seizure frequency per week = 7 X (total number of seizures during the time period / number of days with seizure count ≥ 0 during the time period)
(b) From ANCOVA model using loge (partial seizure frequency per week + 1) as the response variable and the loge (baseline seizure frequency per week + 1) as a covariate.
(c) % Reduction over placebo = 100 x [1-exp (LSM levetiracetam-LSM placebo)]
(d) Type I seizures.
Source: table 11:8 in the study report.

Table 3 lists the ANCOVA analysis results of Partial Onset (Type I) Seizure Frequency per Week and Percent Reduction. The least squares mean partial onset seizure frequency per week was significantly (p=0.0002) smaller for levetiracetam (1.57) than for placebo (1.88) in the treatment period. For levetiracetam, the percent reduction over placebo was 26.8%. When the study periods were analyzed separately, levetiracetam significantly reduced the partial onset seizure frequency over placebo by 31.2% and 22.4% in the Titration and Evaluation Periods, respectively.

Table 4: Number (%) of Patients with Reduction in Seizure Frequency per Week of at Least 50% from Baseline (ITT Population)

Percent Reduction[a]	Levetiracetam (N=101)	Placebo (N=97)	Odds Ratio[b] 95% CI	*p*-value[b]
Partial Onset Seizures (Type I)				
<50% Reduction	56 (55.4%)	78 (80.4%)	3.30	0.0002
≥50% Reduction	45 (44.6%)	19 (19.6%)	1.75 - 6.24	
Total Seizures (Types I, II, III)				
<50% Reduction	56 (55.4%)	79 (81.4%)	3.53	0.0001
≥50% Reduction	45 (44.6%)	18 (18.6%)	1.85 - 6.72	

(a) Reduction = 100 X [(seizure frequency over the Treatment Period - seizure frequency during the Baseline Period) / seizure frequency during the Baseline Period].
(b) From logistic regression analysis.
Source of the table: Table 11.9 in the study report.

Secondary Efficacy Analyses

A patient was considered a responder if the reduction from baseline in the seizure frequency

per week was at least 50% over the entire Treatment Period. Table 4 lists the responder rates of the ITT patients. The response rate for partial onset seizure frequency per week was 44.6% for levetiracetam and 19.6% for placebo. The difference between treatments was statistically significant (p-value=0.0002). Levetiracetam was also statistically significantly (p-value=0.0001) from placebo with respect to the response rate for total seizure frequency.

Interim Analysis

A blinded review of variability was carried out when 64 evaluable patients were available for analysis. This review was carried out solely to determine if planning assumptions for the sample size estimation were accurate. This analysis resulted in an increase in the number of randomized patients. The sponsor met with the Division of Neuropharmacological Drug Products (FDA) to discuss the increase in sample size. It was agreed that the sample size would be increased without adjustment for Type 1 error. Additionally increasing the number of sites, including Canadian sites, was an acceptable means to increase study enrollment.

3.2.1 FDA Reviewer's Data analyses and Comments:

This reviewer re-analyzed the data sets of the study according to the protocol specified statistical analysis plan. The findings for the primary and key secondary efficacy measures matched with the findings submitted by the sponsor.

As a secondary analysis, this reviewer included the 16 randomized patients from Site#55 (16 patients were excluded from the ITT population due to unreliability of the data) in the analysis. Levetiracetam group still remained statistically significantly superior (p-value=.0003) compared to placebo in reducing partial onset seizure frequency per week.

4. Subgroup Analyses

Subgroup analyses were conducted on the primary efficacy measure- partial onset seizure frequency per week by gender, race and age group (<8 years, $\geq$ 8 to < 12 years, and $\geq$12 years).

Table 5 lists the means of Partial Onset (Type I) Seizure Frequency per Week by Gender, Race, and Age Group for the baseline and treatment period. As expected, the means are smaller at the treatment period as compared to the baseline period in each subgroup. In addition, none of the subgroups had significant interaction effect with the treatment group in the ANCOVA model. So, the treatment groups had no differential effect across gender, race, and age groups.

Table 5: Mean of Partial Onset (Type I) Seizure Frequency per Week (Log-Transformed Data, ITT Population) by Gender, Race, and Age Group.

	BASELINE		TREATMENT PERIOD	
	Levetiracetam	Placebo	Levetiracetam	Placebo
SubGroups	Mean (N)	Mean (N)	Mean (N)	Mean (N)
Gender: Female	1.96 (47)	2.06 (51)	1.45 (47)	1.81 (51)
Male	2.09 (54)	2.07 (46)	1.64 (54)	2.00 (46)
Race: White	2.05(74)	2.04 (65)	1.55 (74)	1.88 (65)
Black	1.97 (27)	2.12 (32)	1.56(27)	1.94 (32)
Age: <12 years	2.12 (71)	2.01 (74)	1.64 (71)	1.80 (74)
>=12 Years	1.81 (30)	2.26 (23)	1.35 (30)	2.20 (23)

N=# of Subjects in the group.

5. SUMMARY AND CONCLUSIONS

5.1 Collective Evidence of Efficacy

The treatment groups were comparable for the demographic and baseline characteristics of the randomized patients. A high percentage of randomized patients (93.1% levetiracetam, 85.6% placebo) completed the Treatment Period.

The efficacy results demonstrated that Levetiracetam provided a statistically significant (p=0.0002) reduction in partial onset seizure frequency per week over placebo.

5.2 Conclusions and Recommendations

The statistical findings of the study N159 demonstrate that levetiracetam as adjunctive therapy at total daily dose levels from 20-60 mg/kg/day was effective in children 4-16 years old with refractory partial onset seizures.

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