CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-285

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	22-285
Drug Name:	Keppra XR™ (levetiracetam)
Indication:	Partial Onset Seizures in Adults and Adolescents
Applicant:	UCB, Inc.
Date of Submission:	11/13/2008
Review Priority:	Standard
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Key Words: Partial onset seizures, Seizure frequency per week, ANCOVA

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study RPCE05M2201/ N01235 shows the benefit of levetiracetam (LEV) as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures, compared with placebo.

1.2 Brief Overview of Clinical Studies

This NDA submission includes one completed pivotal efficacy study, study RPCE05M2201/ N01235. The other pivotal efficacy study, Study N01280, is ongoing.

Study RPCE05M2201/ N01235 was a phase III, placebo-controlled, randomized (1:1), parallel group, double-blind, multi-center, add-on study to evaluate the efficacy, safety and tolerability of LEV XR 2x500 mg/day once daily in refractory epilepsy patients 12 to 70 years of age with partial onset seizures treated with at least one but no more than three concomitant AEDs (Antiepileptic Drug). One hundred and fifty-eight (158) subjects were randomized into the study by 34 investigators in 7 countries, including Brazil, Finland, India, Mexico, Russian Federation, South Africa, and Ukraine. The study duration per subject was approximately 22 weeks: an 8-week Baseline Period followed by a 12-week Treatment Period with a Final Visit occurring within the two weeks after the last investigational drug intake for the subjects discontinuing prematurely or deciding not to convert to LEV IR (Immediate Release).

1.3 Statistical Issues and Findings

For Study N01235, the primary efficacy variable was the partial onset seizure (Type I) frequency per week over the Treatment Period. This variable was logarithmically transformed and was analyzed for ITT population using ANCOVA including treatment as a factor and the log-transformed baseline seizure frequency per week as a covariate. The estimated percent reduction of LEV XR over PBO in seizure frequency per week was 14.4% for ITT population, which was statistically significant at the 2-sided 5% significance level ($p = 0.038$).

However, since log- transformed primary efficacy endpoint was still not normally distributed this reviewer conducted Wilcoxon Rank Sum Test for the original primary efficacy endpoint. The results was statistically significant at two-sided 0.05 level ($p=0.0372$).

Furthermore, due to rapid enrollment at the end of the recruitment, 158 subjects were randomized into the study, instead of originally planned 130 subjects. This reviewer conducted the primary efficacy analysis on the first 130 enrolled subjects and the results were consistent with sponsor's primary efficacy analysis.

2 INTRODUCTION

2.1 Overview

Levetiracetam (LEV) is being developed as therapy for patients with epilepsy. LEV immediate release formulation (LEV IR, Keppra®) has been approved in approximately 60 countries, including United States, as adjunctive treatment of partial onset seizures in adults and children 4 years of age and older with epilepsy.

Several formulations of LEV IR have been approved by both the FDA and the EMEA: 250 mg, 500 mg, 750 mg, and 1000 mg immediate release oral tablets, 10% oral solution (100 mg/mL), and IV injection solution (500 mg/ 5 mL per vial). LEV IR is approved for b.i.d. administration. LEV extended release formulation (LEV XR) is a new formulation under development in order to provide the subjects the convenience of once daily dosing.

This NDA submission includes one completed pivotal efficacy study, study RPCE05M2201/ N01235. The other pivotal efficacy study, Study N01280, is ongoing.

Study RPCE05M2201/ N01235 was a phase III, placebo-controlled, randomized (1:1), parallel group, double-blind, multi-center, add-on study to evaluate the efficacy, safety and tolerability of LEV XR 2x500 mg/day once daily in refractory epilepsy patients 12 to 70 years of age with partial onset seizures treated with at least one but no more than three concomitant AEDs (Antiepileptic Drug). One hundred and fifty-eight (158) subjects were randomized into the study by 34 investigators in 7 countries, including Brazil, Finland, India, Mexico, Russian Federation, South Africa, and Ukraine. The study duration per subject was approximately 22 weeks: an 8-week Baseline Period followed by a 12-week Treatment Period with a Final Visit occurring within the two weeks after the last investigational drug intake for the subjects discontinuing prematurely or deciding not to convert to LEV IR (Immediate Release).

2.2 Data Sources

The sponsor's original electronic submission was stored in the directory of \\Fdswa150\nonectd\N22285\N_000\2007-11-29 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 PROTOCOL RPCE05M2201 / N01235

3.1.1.1 Study Objectives

The objectives of the study were to evaluate the efficacy, safety and tolerability of LEV XR 2x500 mg/day once daily as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures.

3.1.1.2 Study Design

The trial was a phase III, placebo-controlled, randomized (1:1), parallel group, double-blind, multi-center, add-on study in refractory epilepsy patients 12 to 70 years of age with partial onset seizures treated with at least one but no more than three concomitant AEDs (Antiepileptic Drug). One hundred and fifty-eight (158) subjects were randomized into the study by 34 investigators in 7 countries, including Brazil, Finland, India, Mexico, Russian Federation, South Africa, and Ukraine.

The study duration per subject was approximately 22 weeks: an 8-week Baseline Period followed by a 12-week Treatment Period with a Final Visit occurring within the two weeks after the last investigational drug intake for the subjects discontinuing prematurely or deciding not to convert to LEV IR (Immediate Release).

3.1.1.3 Efficacy Measures

The primary efficacy variable was as follows:

- The partial onset seizure (Type I) frequency per week over the Treatment Period.

The secondary efficacy variables were as follows:

- The total seizure (Type I + II + III) frequency per week over the Treatment Period
- The absolute and percentage (%) reduction from baseline in partial onset seizure (Type I) frequency per week over the Treatment Period
- The absolute and percentage (%) reduction from baseline in total seizure (Type I + II + III) frequency per week over the Treatment Period
- The responder rate (the proportion of subjects who have a $\geq$ 50% reduction in seizure frequency per week from baseline) for partial onset seizures (Type I) and for total seizures (Type I + II + III) over the Treatment Period
- The categorical response to treatment: percent reduction from baseline in partial onset seizure (Type I) and in total seizure (Type I + II + III) frequency per week grouped into six categories (< -25%, -25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100% and 100%) over the Treatment Period.

3.1.1.4 Statistical Analysis Plan

Planned Statistical Analyses

The primary efficacy variable was the partial onset seizure (Type I) frequency per week over the Treatment Period. This variable was logarithmically transformed ($\log_e [x+1]$; x being the seizure frequency per week in Baseline or Treatment Periods) and was analyzed for ITT population (please refer to the next section for the definition of ITT) using ANCOVA including treatment as a factor and the log-transformed baseline seizure frequency per week as a covariate. The mean treatment difference adjusted for baseline and its two-sided 95% CI were computed and expressed as a percent reduction over placebo after inverse transformation, *i.e.,* percent reduction over placebo = 100 × (1 - exp [LSMean (LEV) - LSMean (placebo)]), where LSMean was the estimate of the adjusted treatment mean.

If more than 10% of the ITT population is excluded from the PP population, the primary efficacy analysis was to be also performed on the PP population.

Wilcoxon rank-sum test, Hodges-Lehmann method, logistics regression and Mantel-Haenszel chi-square were used to analyze secondary efficacy variables.

Changes in the Planned Analyses (Selected)

The sponsor states that the following changes were made after the protocol approval and documented in the SAP before the unblinding of the database.

The protocol defined the intention-to-treat (ITT) population as "all randomized subjects who received at least one dose of study medication". The sponsor states that since in the current UCB protocol template ITT is defined as "all randomized subjects", this later definition was adopted in data analysis.

A hierarchical testing for secondary endpoints was added to the SAP for controlling the overall type I error. The primary endpoint of partial seizure frequency per week was planned to be tested at the 5% significance level; the following 'label relevant' secondary endpoints were planned to be tested hierarchically:

1. Total seizure (Type I + II + III) frequency per week
2. The responder rate for partial onset seizures (Type I)
3. The responder rate for total seizures (Type I + II + III)
4. The categorized response for partial onset seizures (Type I)
5. The categorized response for total seizures (Type I + II + III)

An endpoint was only tested if all the previous endpoints were found statistically significant in favor of LEV XR. The other secondary endpoints and the exploratory endpoints were tested at the 5% level of significance without any adjustment.

Changes in the Analysis after Database Lock and Not Documented in SAP (Selected)

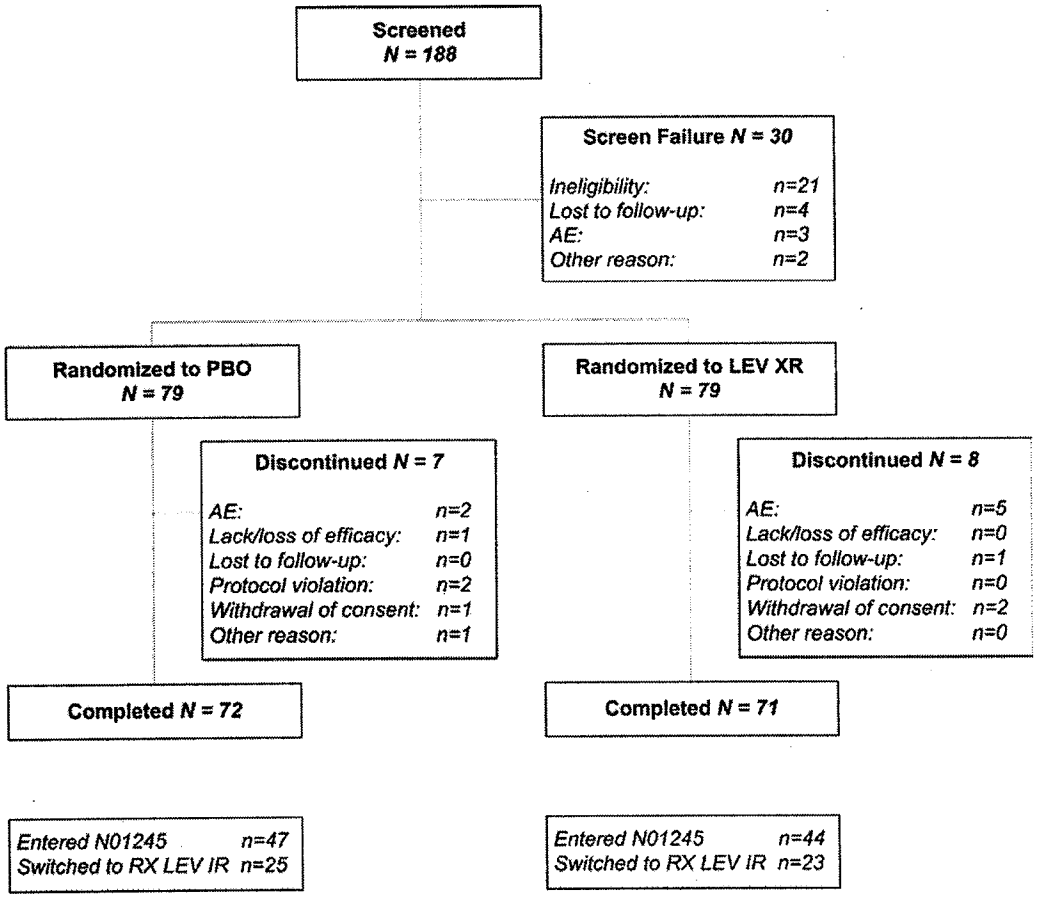
The protocol did not foresee adjustment for multiple comparisons among the secondary endpoints. This was added later at the SAP level to control the type I error for several 'label relevant' secondary endpoints. Since the secondary efficacy variables are all related to the primary endpoint (seizure frequency per week), the secondary analyses were supportive to the primary efficacy analysis and supported the same claim. In that context, a hierarchical testing was not relevant and all the secondary analyses were performed as planned in the protocol for a better understanding and interpretation of the primary efficacy variable, and for explanatory purposes.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

It was planned to randomize 130 subjects into the study. One hundred eighty-eight (188) subjects were screened, 158 were randomized and 143 completed the study. The disposition of the subjects in the study is displayed in Figure 1.

Figure 1 Subject disposition



Source: Figure 10:1 of sponsor's Clinical Study Report

Demographic Characteristics

Summary statistics of the demographic characteristics for the ITT population are displayed in Table 1. It appears that Demographic characteristics for the ITT population were similar between treatment groups.

Table 1: Demographic Characteristics (ITT Population)

Characteristics	Statistics	PBO N=79	LEV XR N=79
Age (years)	Mean (SD)	32.38 (12.60)	33.97 (13.41)
	Min - Max	13.3 - 67.9	12.2 - 67.9
Gender			
Male	n (%)	47 (59.5)	52 (65.8)
Female	n (%)	32 (40.5)	27 (34.2)
Race			
White	n (%)	35 (44.3)	37 (46.8)
Asian / Pacific Islander	n (%)	1 (1.3)	0
Hispanic	n (%)	15 (19.0)	15 (19.0)
Indian / Pakistani	n (%)	27 (34.2)	27 (34.2)
Other	n (%)	1 (1.3)[a]	0
Weight (kg)	Mean (SD)	67.80 (15.55)	70.21 (15.66)
	Min - Max	48.0 - 134.0	50.0 - 118.0
Height (cm)	Mean (SD)	165.7 (9.8)	168.1 (10.3)
	Min - Max	138 - 189	150 - 188
BMI (kg/m^2)	Mean (SD)	24.60 (4.55)	24.76 (4.71)
	Min - Max	16.8 - 38.6	17.6 - 47.1

[a] The race for subject 4003/0006 reported as "mixture of Mexican and Hispanic" was assimilated to the race category "Other".
Source: Table 14.1.2:1

Source: Table 11:1 of sponsor's Clinical Study Report

Baseline Characteristics – History of Epilepsy

History of epilepsy was summarized in Table 2. It seems that the duration of epilepsy was shorter in the LEV XR group while the age at onset of first diagnosis was younger in the PBO group.

Table 2: History of Epilepsy (ITT Population)

	Statistics	PBO N=79	LEV XR N=79
Epilepsy duration at Randomization Visit (yr)	Mean (SD)	16.43 (11.93)	13.11 (10.87)
	Min - Max	0.7 - 53.5	0.8 - 42.6
Age at the Epilepsy Diagnosis (year)	Mean (SD)	15.95 (11.51)	20.86 (15.18)
	Min - Max	0.1 - 47.9	0.3 - 61.5

Source: Table 14.1.3:1

Source: Table 11:2 of sponsor's Clinical Study Report

Baseline Characteristics – Epileptic Seizures

The classification of the epileptic seizures at Screening Visit was summarized in Table 3 and it seems that it was similar between treatment groups.

Table 3: Classification of Epileptic Seizures at Screening Visit (ITT Population)

Seizure Type (ILAE Classification) Seizure Subtype	PBO N=79 n (%)	LEV XR N=79 n (%)
Partial Seizures (I)	79 (100.0)	79 (100.0)
Simple Partial Seizures (IA)	33 (41.8)	36 (45.6)
Complex Partial Seizures (IB)	53 (67.1)	52 (65.8)
Partial Seizures Secondarily Generalized (IC)	66 (83.5)	56 (70.9)
Generalized Seizures (II)	1 (1.3)	2 (2.5)
Absence Seizures (IIA1)	1 (1.3)	1 (1.3)
Tonic-Clonic Seizures (IIE)	1 (1.3)	1 (1.3)

Source: Table 14.1.3:4

Source: Table 11:5 of sponsor's Clinical Study Report

3.1.1.6 Sponsor's Primary Efficacy Results

The primary efficacy variable was the partial onset seizure (Type I) frequency per week over the Treatment Period. Table 4 presents the summary statistics of partial onset seizure frequency for Baseline and Treatment Periods for ITT population.

Table 4: Partial Onset Seizure (Type I) Frequency per Week (ITT Population)

Period	Statistics	PBO N=79	LEV XR N=79
Baseline Period	n	79	79
	Mean (SD)	3.73 (6.57)	4.87 (8.23)
	Median	2.11	1.80
	Q1 - Q3	1.33 - 3.26	1.13 - 4.13
	Min - Max	1.0 - 53.5	0.0 - 47.3
Treatment Period	n	78	75
	Mean (SD)	2.77 (4.64)	3.27 (5.98)
	Median	1.36	0.99
	Q1 - Q3	0.92 - 2.85	0.33 - 2.70
	Min - Max	0.0 - 33.9	0.0 - 29.1
% Reduction from Baseline Period	n	78	74
	Mean (SD)	19.33 (51.75)	42.65 (48.54)
	Median	33.40	46.07
	Q1 - Q3	-6.63 - 51.81	22.95 - 76.86
	Min - Max	-199.0 - 100.0	-210.5 - 100.0

Source: Table 14.2.1:1

Source: Table 11:15 of sponsor's Clinical Study Report

There was one subject in the PBO group and three subjects in the LEV XR group with no DRC (Diary Record Card) information during the Treatment Period. In the PBO group, subject 4006/0002 was given the drug, then withdrew her consent, and the sponsor could not determine whether or not she took the drug; in the LEV XR group, two subjects (4003/0005, 5006/0001) did not receive study drug, and one subject (3010/0007) took the drug but did not return his DRC for the Treatment Period. In addition to those subjects, there was one subject (4001/0006) in the

LEV XR group who returned his DRC but the seizure count was recorded as unknown. Percent reduction from baseline was computed for 74 subjects in the LEV XR group since one subject (4003/0002) in this group had no partial onset seizure count at baseline.

The primary efficacy variable was logarithmically transformed ($\log_e [x+1]$; x being the seizure frequency per week in Baseline or Treatment Periods) and was analyzed for ITT population using ANCOVA including treatment as a factor and the log-transformed baseline seizure frequency per week as a covariate. The results were presented in Table 5.

Table 5: Partial Onset Seizure Frequency per Week over the Treatment Period (ITT Population)

Partial onset seizure (Type I) frequency per week	**PBO N=79**	**LEV XR N=79**
n	78	75
Log- transformed value		
LS Mean (SE)	1.067 (0.052)	0.912 (0.053)
2-sided 95% CI (LEV XR – PBO)		0.009 - 0.301
Inverse-transformed value		
Percentage of reduction of LEV XR over PBO		14.4%
2-sided 95% confidence interval of the % reduction		0.9% - 26.0%
p-value		0.038

ANCOVA model with treatment as factor and the transformed baseline seizure frequency per week as covariate.
Source: Table 14.2.1:2

Source: Table 11:16 of sponsor's Clinical Study Report

The estimated percent of reduction of LEV XR over PBO in seizure frequency per week was 14.4% for ITT population, which was statistically significant at the 2-sided 5% significance level ($p = 0.038$).

As planned in the SAP, if more than 10% of subjects from the ITT population were excluded to the PP population due to major protocol deviation, the primary efficacy analysis was also performed on the PP Population. Results on the PP population were consistent with those obtained on the ITT population. The results were presented in Table 6 and Table 7.

Table 6: Partial Onset Seizure Frequency per Week over the Treatment Period (PP Population)

Period	Statistics	PBO N=69	LEV XR N=68
Baseline Period	n	69	68
	Mean (SD)	3.79 (6.98)	5.22 (8.78)
	Median	2.04	1.81
	Q1 - Q3	1.27 - 3.11	1.13 - 3.97
	Min - Max	1.0 - 53.5	0.9 - 47.3
Treatment Period	n	69	67
	Mean (SD)	2.93 (4.90)	3.29 (5.84)
	Median	1.40	1.07
	Q1 - Q3	0.93 - 2.85	0.41 - 2.74
	Min - Max	0.0 - 33.9	0.0 - 29.1
% Reduction from Baseline Period	n	69	67
	Mean (SD)	17.39 (50.54)	44.30 (38.54)
	Median	28.05	44.77
	Q1 - Q3	-6.63 - 51.52	22.95 - 73.90
	Min - Max	-199.0 - 100.0	-51.7 - 100.0

Source: Table 14.2.1:8

Source: Table 11:17 of sponsor's Clinical Study Report

Table 7: Partial Onset Seizure Frequency per Week over the Treatment Period (PP Population)

Partial onset seizure (Type I) frequency per week	PBO N=69	LEV XR N=68
n	69	67
Log- transformed value		
LS Mean (SE)	1.119 (0.048)	0.914 (0.049)
2-sided 95% CI (LEV XR – PBO)		0.070 - 0.341
Inverse-transformed value		
Percentage of reduction of LEV XR over PBO		18.6%
2-sided 95% confidence interval of the % reduction		6.7% - 28.9%
p-value		0.003

ANCOVA model with treatment as factor and the transformed baseline seizure frequency per week as covariate.
Source: Table 14.2.1:6

Source: Table 11:18 of sponsor's Clinical Study Report

3.1.1.7 Sponsor's Secondary Efficacy Results (Selected)

Total Seizure (Type I + II + III) Frequency per Week over the Treatment Period

Since only one subject in the PBO group and six subjects in the LEV XR group had Type II seizures, and since only one subject in the LEV XR group had Type III seizures, the results obtained for total seizures (Type I + II + III) were very similar to those obtained for partial seizures. The estimated difference between LEX XR and PBO in percent reduction in total seizure (Type I + II + III) frequency per week was 14.7% for ITT population.

Responder Rates

A responder was defined as a subject having at least 50% reduction in seizure frequency per week from baseline in partial onset (Type I) [total (Type I + II + III)] seizures over the Treatment Period. Subjects with missing or unknown count during the Treatment Period were considered as non-responder in the analyses on responder rate.

Responder rates in seizure frequency per week over the Treatment Period were provided in Table 8 (Type I) and in Table 9 (Type I + II + III).

Table 8: Responder Rate in Seizure Frequency per Week for Partial (Type I) Seizures – ITT Population

	PBO (N=79) n (%)	LEV XR (N=79) n (%)
Evaluable Subjects	79	79
Responder (a)	23 (29.1%)	34 (43.0%)
Non-Responder	56 (70.9%)	45 (57.0%)

Source: Excerpt from Table 14.2.2:4 of sponsor's Clinical Study Report

Table 9: Responder Rate in Seizure Frequency per Week for All (Type I+II+III) Seizures – ITT Population

	PBO (N=79) n (%)	LEV XR (N=79) n (%)
Evaluable Subjects	79	79
Responder (a)	24 (30.4%)	34 (43.0%)
Non-Responder	55 (69.6%)	45 (57.0%)

Source: Excerpt from Table 14.2.2:6 of sponsor's Clinical Study Report

The proportion of responders in partial onset seizure (Type I) frequency per week over the Treatment Period was numerically higher for LEV XR group (43.0%), as compared to PBO group (29.1%).

Similarly, the proportion of responders in total seizure (Type I + II + III) frequency per week over the Treatment Period was numerically higher for LEV XR group (43.0%), as compared to PBO group (30.4%).

Categorized Response

Percent reductions from baseline over the Treatment Period in partial onset (Type I) and in total (Type I + II + III) seizures frequency per week were grouped into five categories (< -25%, -25% to < 25%, 25% to < 75%, 75% to < 100% and 100%). Subjects with missing or unknown counts during the Treatment Period were considered as worsening (< -25%) in the analyses on categorical response.

Categorized responses in seizure frequency per week over the Treatment Period were provided in Table 10 (Type I) and in Table 11 (Type I + II + III).

Table 10: Categorized Response in Partial (Type I) Seizure Frequency per Week – ITT Population

Percentage reduction from baseline	PBO (N=79) n (%)	LEV XR (N=79) n (%)
Evaluable Subjects	79	79
< -25%	13 (16.5%)	11 (13.9%)
-25% to < 25%	23 (29.1%)	14 (17.7%)
25% to < 75%	34 (43.0%)	35 (44.3%)
75% to <100%	7 (8.9%)	11 (13.9%)
100%	2 (2.5%)	8 (10.1%)

Source: Excerpt from Table 14.2.2:8 of sponsor's Clinical Study Report

Table 11: Categorized Response in All (Type I+II+III) Seizure Frequency per Week – ITT Population

Percentage reduction from baseline	PBO (N=79) n (%)	LEV XR (N=79) n (%)
Evaluable Subjects	79	79
< -25%	13 (16.5%)	10 (12.7%)
-25% to < 25%	23 (29.1%)	14 (17.7%)
25% to < 75%	34 (43.0%)	37 (46.8%)
75% to <100%	7 (8.9%)	11 (13.9%)
100%	2 (2.5%)	7 (8.9%)

Source: Excerpt from Table 14.2.2:9 of sponsor's Clinical Study Report

The categorized responses in both partial onset seizure (Type I) and all seizure (Type I+II+III) frequency per week over the Treatment Period showed that a larger number of subjects had a very positive response (≥ 75%) for LEV XR group than for PBO group.

3.1.2 Reviewer's Analysis/Comments for Study RPCE05M2201 / N01235

This reviewer confirmed sponsor's efficacy analyses results presented in this review.

3.1.2.1 Sensitivity Analysis for Primary Efficacy Endpoint

The primary efficacy variable was the partial onset seizure (Type I) frequency per week over the Treatment Period, which was logarithmically transformed ($\log_e[x+1]$) and was analyzed for ITT population using ANCOVA. However, since log- transformed primary efficacy endpoint was still not normally distributed this reviewer conducted Wilcoxon Rank Sum Test for the original primary efficacy endpoint. The results was statistically significant at two-sided 0.05 level ($p=0.0372$).

3.1.2.2 Baseline Partial Onset Seizure (Type I) Frequency per Week

At Baseline Period, the median partial onset seizure frequency per week was 2.04 and 1.81 for PBO group and LEV group, respectively. This difference was not statistically significant ($p=0.42$), based on Wilcoxon Rank Sum test.

3.1.2.3 Number of Subjects Planned vs Number of Subjects Randomized

In the Clinical Study Report, the sponsor states that, with an estimated screen failure rate of approximately 20%, it was planned to screen 162 subjects in order to randomize 130 into the study. The enrollment was slow at the beginning but very fast at the end of enrollment. By 01-Dec-2006, a total of 88 subjects had been screened and of those, only 16 subjects were randomized while 68 subjects remained in the screening phase. When the sponsor was notified on 27-Dec-2007 that the targeted number of subjects screened had been reached on 26-Dec-2007 (when 12 subjects had been recruited, resulting in a total of 166 subjects), it took until the end of the next day on 28-Dec-2007 to have the enrollment stopped. During these 2 days, an additional 22 subjects were enrolled and started their Baseline Period. Thus, 188 subjects were screened and 158 were randomized, the final screen failure rate being 16% and not 20% as anticipated.

Since 158 subjects were randomized into the study, instead of originally planned 130 subjects, this reviewer conducted the primary efficacy analysis on the first enrolled 130 subjects and the results are consistent with sponsor's primary efficacy analysis.

3.2 Evaluation of Safety

Please read Dr. Martin Rusinowitz's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group for Study RPCE05M2201/ N01235

Partial Onset Seizure Frequency per Week over the Treatment Period (log-transformed) by Subgroup and Treatment Group for ITT Population is summarized in Table 12.

Table 12: Percent Reduction from Baseline in Partial Onset Seizure Frequency per Week by Subgroup and Treatment Group (ITT Population)

Subgroup	Treatment Group	n	Mean	SD	Median	Min	Max
<= 16 years	LEV XR	6	14.59	125.06	74.91	-210.53	100
	PBO	4	30.59	32.29	34.76	-12.67	65.52
> 16 years	LEV XR	68	45.13	36.37	42.92	-44.44	100
	PBO	74	18.72	52.68	30.63	-199.04	100
<=31.66 years*	LEV XR	32	30.55	61.87	42.92	-210.53	100
	PBO	41	20.54	47.72	33.68	-79.51	100
>31.66 years	LEV XR	42	51.88	33.15	57.18	-25.93	100
	PBO	37	17.99	56.52	33.21	-199.04	96.3
Female	LEV XR	24	41.56	43.86	33.73	-51.72	100
	PBO	31	15.81	65.17	34.25	-199.04	100
Male	LEV XR	50	43.18	51.05	49.1	-210.53	100
	PBO	47	21.65	41.22	27.62	-79.51	94.25
White	LEV XR	36	45.8	34.73	44.22	-44.44	100
	PBO	35	22.56	48.12	33.21	-73.54	100
Indian/Pakistani	LEV XR	26	33.82	61.78	39.73	-210.53	100
	PBO	27	18.43	58.89	34.79	-199.04	100
other	LEV XR	12	52.38	52.94	69.62	-51.72	100
	PBO	16	13.78	49.29	28.85	-102.37	82.41

*The median age is 31.66.
Source: Reviewer's Analysis

It appears that the point estimates of percent reduction from Baseline were in the same direction across the patient subgroups investigated, except for patients less than 16 years of age.

4.2 Other Subgroup Populations

The percent reduction from baseline in partial onset seizure frequency per week by pooled countries was summarized in Table 13.

Table 13: Percent Reduction from Baseline in Partial Onset Seizure Frequency per Week by Pooled Countries (ITT Population)

Pooled Countries	Statistics	PBO N=79	LEV XR N=79
India	n	26	24
	Mean (SD)	19.44 (59.81)	31.76 (63.10)
	Median	35.31	39.73
	Q1 - Q3	-6.63 - 54.17	7.15 - 75.38
	Min - Max	-199 - 100	-210.5 - 100.0
Brazil, Mexico, South Africa	n	19	17
	Mean (SD)	18.71 (49.37)	53.28 (46.79)
	Median	33.60	67.18
	Q1 - Q3	-4.54 - 51.81	23.81 - 93.94
	Min - Max	-102.4 - 91.0	-51.7 - 100.0
Russian Federation	n	19	18
	Mean (SD)	9.74 (52.65)	43.29 (30.44)
	Median	26.74	33.73
	Q1 - Q3	-46.41 - 51.81	27.87 - 64.04
	Min - Max	-73.5 - 82.0	-26.3 - 100.0
Ukraine, Finland	n	14	15
	Mean (SD)	32.98 (37.88)	47.28 (41.85)
	Median	30.41	55.54
	Q1 - Q3	-0.38 - 51.78	15.30 - 70.01
	Min - Max	-22.2 - 100.0	-44.4 - 100.0

Source: Table 14.2.1:4

Source: Table 11:22 of sponsor's Clinical Study Report

It appears that the point estimates of percent reduction from Baseline were in the same direction for pooled countries.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For Study N01235, the primary efficacy variable was the partial onset seizure (Type I) frequency per week over the Treatment Period. This variable was logarithmically transformed and was analyzed for ITT population using ANCOVA including treatment as a factor and the log-transformed baseline seizure frequency per week as a covariate. The estimated percent reduction of LEV XR over PBO in seizure frequency per week was 14.4% for ITT population, which was statistically significant at the 2-sided 5% significance level ($p = 0.038$).

However, since log- transformed primary efficacy endpoint was still not normally distributed this reviewer conducted Wilcoxon Rank Sum Test for the original primary efficacy endpoint. The results was statistically significant at two-sided 0.05 level ($p=0.0372$).

Furthermore, due to rapid enrollment at the end of the recruitment, 158 subjects were randomized into the study, instead of originally planned 130 subjects. This reviewer conducted the primary efficacy analysis on the first 130 enrolled subjects and the results were consistent with sponsor's primary efficacy analysis.

5.2 Conclusions and Recommendations

Study RPCE05M2201/ N01235 shows the benefit of levetiracetam (LEV) as adjunctive therapy in the treatment of refractory epilepsy patients 12 to 70 years of age with partial onset seizures, compared with placebo.

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