
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA SUBMISSION

Brand Name: Kepra

Generic Name: Levetiracetam

Sponsor: UCB Pharma

Indication: Partial Seizures

NDA Number: 21-035

Original Receipt Date: 2/1/99

Clinical Reviewers: Joel Freiman, M.D.

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1 Review Sources

1.1 Materials from NDA

This review was conducted using the electronic versions of the volumes listed below which were submitted on CD-ROM as part of the Levetiracetam New Drug Application on 02/01/99. The Safety Update (Vol. 1-160) submitted on 06/01/99 replaced the original Integrated Summary of Safety (Vol. 452-584) and served as the primary source of the safety review. During the course of the review, additional information was requested from the sponsor and their responses were provided on paper.

Table 1: Review Sources

Volume	Submission Date	Material
Vol. 1, Section 2	02/01/99	Proposed labeling
Vol. 2, Section 3H	02/01/99	Clinical data summary
Vol. 189	02/01/99	Study Report N051
Vol. 155	02/01/99	Study Report N132
Vol. 234	02/01/99	Study Report N138
Vol. 269	02/01/99	Study Report N052
Vol. 452	02/01/99	Integrated Summary of Efficacy
Vol. 1-160	06/01/99	Safety Update
Amendment 18	07/30/99	Re-analyses including titration period
Amendment 20	08/20/99	Listing of discontinuations

2 Background

2.1 Indication

The proposed indication for levetiracetam (Kepra) is:

"Kepra is indicated as adjunctive therapy in the treatment of partial onset seizures with and without secondary generalization in adults with epilepsy." [from "Package Insert", Vol. 1, Section 2, p. 17]

2.2 Administrative History

The NDA sponsor is UCB Pharma, Inc. (UCB), the U.S. subsidiary of UCB S.A. Pharma Sector (Belgium). UCB conducted its U.S. trials under IND

Levetiracetam has been under development for the past 18 years. Most of the studies have taken place outside the U.S. In addition to the treatment of epilepsy levetiracetam has been studied in the treatment of cognition disorders, anxiety disorders, and in patients at risk for deep venous thrombosis.

The Division of Neuropharmacologic Drug Products has held four pre-NDA meetings with UCB. Agreement was made that three adequate and well-controlled studies and one supportive placebo controlled study were adequate to demonstrate efficacy for the proposed indication.

Future development is planned for use in pediatric patients, primary generalized seizure patients, and as monotherapy for partial onset seizure patients.

2.3 Proposed Directions for Use

"The recommended therapeutic dose of Kepra is 500 mg twice daily. According to the patient's response daily doses can be increased by an additional 500 mg twice daily at 2 week intervals up to 1500 mg twice daily. In long-term studies doses up to 2000 mg twice daily were used and well tolerated." [from "Dosage and Administration", Vol. 1, Section 2, p. 28]

In addition the sponsor has provided instructions for patients with impaired renal function accompanied by the following table:

Table 2: Dosing Adjustment Regimen For Patients With Impaired Renal Function

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> 80	500 to 1,500 mg	Every 12 hours
Mild	50 - 79	500 to 1,500 mg	Every 12 hours
Moderate	30 - 59	250 to 750 mg	Every 12 hours
Severe	< 30	250 to 500 mg	Every 12 hours
ESRD patients using dialysis (1)		500 to 1,000 mg	Every 24 hours (2)

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based on sponsor's Table 6 "Dosage and Administration", Vol. 1, Section 2, p. 29

(1) A 750 mg loading dose is recommended on the first day of treatment with Kepra.

(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

2.4 Foreign Marketing

Levetiracetam is not marketed in any country.

3 Chemistry, Manufacturing and Controls

Please see the complete chemistry, manufacturing and controls review .

4 Human Pharmacokinetic Considerations

The sponsor reports that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetics are linear. The bioavailability of levetiracetam is not affected by food. Levetiracetam is not protein bound ($\leq 10\%$ bound) and its volume of distribution is close to the volume of intracellular and extracellular water. In humans 66% of the dose is excreted unchanged in the urine. The major metabolite (ucb L057), accounting for 24% of the dose, is obtained by enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacologic activity and are renally excreted. Plasma half-life of levetiracetam across studies is approximately 6-8 hours.

5 Animal Pharmacology & Toxicology

Please see the complete pharmacology/toxicology review by Jennifer A. Burris, D.V.M., below is a brief summary from Dr. Burris' review.

5.1 Pharmacology

The pharmacologic activity of levetiracetam was evaluated in mice, rats, hamsters and guinea pigs. The mechanism of action of levetiracetam has not been established. Levetiracetam is not active in the classical models of maximal electroshock and pentyleneterazol seizures in mice. Levetiracetam exhibited potential antiepileptogenic activity by its ability to inhibit the development of kindling in both mice and rats. Seizure suppression derives from the parent compound with the major metabolite (ucb L057) displaying no seizure protection.

5.2 Toxicology

Toxicology studies of levetiracetam included single and repeat i.v., and oral dosing in mice, rats, and dogs. Single dose studies indicate low acute toxicity. Repeat dose studies of levetiracetam were well tolerated. Mortality in rats was observed following i.v. administration of 900 mg/kg. In general clinical signs were minimal across studies and species. In the rodent only a reversible increase in liver weight and hypertrophy of centrilobular hepatocytes were observed, without degenerative/necrotic or proliferative changes. The

liver lesions are considered to be adaptive. Kidney lesions consisting of hyaline droplet nephropathy and exacerbation of chronic progressive nephropathy were observed only in male rats. There was no target organ identified in the dog.

Reproductive toxicity studies conducted in rats/or rabbits and mice did not reveal any significant abnormalities. Levetiracetam was not mutagenic and not carcinogenic in lifetime feeding studies in the mouse and rat.

6 Clinical Data Sources

A total of 87 clinical studies were conducted in the levetiracetam development program over the past 18 years.

UCB constructed an integrated structured database referred to as N999 that includes data from 80 studies. Seven studies performed in the early 1980s were not included in the N999 database either because the CRFs were either not available or inadequate to assure reliability (representing 76 subjects). Additionally, 23 patients received levetiracetam in a named patient use program and are also not included in the N999 database. To ensure that each subject was uniquely identified each subject was given a four digit ISS/ISE number.

The N999 database contains data on a total of 4375 subjects, 3340 of who were exposed to levetiracetam. Eight patients were inadvertently double-counted, one of who's CRF was lost. Therefore the tables in the ISS are based on 4382 subjects, 3347 receiving levetiracetam.

The sponsor reported that 364 subjects were exposed in 30 clinical pharmacology studies (271 healthy volunteers, 48 elderly, 16 hepatic impairment, and 29 renal impairment), 1388 subjects were exposed in 30 adult epilepsy studies, 29 subjects were exposed in 2 pediatric epilepsy studies, and 1559 subjects were exposed in 17 studies of other indications. Tables summarizing these trials are included as appendix 1 to this review.

In the sponsor's summary of overall demographics and baseline characteristics on page 57 of the Safety Update (SU), they state that 50.1% (1677/3347) were male and 49.9% (1670/3347) were female. Ethnicity was known for 2455 subjects and 94.6% were Caucasian, 2.1% were Black, and 3.3% were of other ethnic descriptions. The majority of subjects were between 16 and 65 years of age (2963 subjects or 88.5%)

6.1.1 Demographics, Dose, and Duration of Exposure in Adult Epilepsy Studies

Among subjects in all adult epilepsy studies (N = 1393) the mean levetiracetam dose was 2421 mg/day (median 3000 mg/day). The mean duration of exposure was 542 days (median 344 days).

Among the subjects receiving levetiracetam 54.8% were male and 45.2% were female. The mean age was 36.9 years ranging from 13 to 78 years. The majority of subjects in whom ethnicity was known were Caucasian 95.4% (1294/1356).

Dose and duration of exposure are categorized in Table 3. Patients who received more than one dose appear in multiple categories.

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Table 3: Duration of Exposure to Levetiracetam by Dose (All Adult Epilepsy Patients)

ALL ADULT EPILEPSY PATIENTS POOLED								
Dose (mg/day)	Overall N=1393 ^a	Number by Duration of Exposure						
		1d - ≤ 4 wk.	>4wk - ≤ 3 mo.	>3 mo. - ≤ 6 mo.	>6 mo. - ≤ 1 yr.	>1 yr. - ≤ 2 yr.	>2 yr. - ≤ 3 yr.	> 3 yr.
≤ 500	616	541	65	3	3	2	1	1
>500 - ≤ 1500	1053	582	127	291	29	11	2	11
> 1500 - ≤ 2500	1175	557	265	191	66	40	17	39
> 2500 - ≤ 3500	919	92	127	160	199	209	84	48
>3500 - ≤ 4500	416	36	85	52	66	74	84	19
> 4500	3	3	0	0	0	0	0	0

sponsor's Table 17A, ISS Vol. 1, p 79

^a 1393 rather than 1388 due to 5 patients each of whom participated in two epilepsy trials being counted twice

6.1.2 Demographics, Dose, and Duration of Exposure in Well-Controlled Trials of Epilepsy

A total of 769 subjects were exposed to levetiracetam in controlled trials of epilepsy (672 subjects when only considering the first crossover period of study N051).

When considering both double blind periods of Study N051, the mean dose of levetiracetam was 2045 mg/day (median dose 2000 mg/day). The mean duration of exposure was 129 days (median 126 days).

Among the subjects receiving levetiracetam (considering first period of Study N051) 54.5% were male and 45.5% were female. The mean age was 37.4 years ranging from 14 to 70 years. Only 10 patients were greater than or equal to 65 years of age and 3 patients were less than 16 years of age. The majority of subjects in whom ethnicity was known were Caucasian 95.5%.

Dose and duration of exposure are categorized in Table 4. Patients who received more than one dose appear in multiple categories.

Table 4: Duration of Exposure to Levetiracetam by Dose (Well-Controlled Studies of Epilepsy)

ADEQUATE AND WELL CONTROLLED STUDIES IN EPILEPSY								
Dose (mg day)	Overall N=769 ^a	Number by Duration of Exposure						
		1d - ≤ 4 wk.	>4wk - ≤ 3 mo.	>3 mo. - ≤ 6 mo.	>6 mo. - ≤ 1 yr.	>1 yr. - ≤ 2 yr.	>2 yr. - ≤ 3 yr.	> 3 yr.
≤ 500	125	118	7	0				
	104	97	7					
>500 - ≤ 1500	434	141	22	271				
	333	133	16	184				
> 1500 - ≤ 2500	527	231	93	203				
	431	228	83	120				
> 2500 - ≤ 3500	271	12	16	243				
>3500 - ≤ 4500	38	7	2	29				
> 4500								

^a 672 patients when considering only the first period of Study N051

6.1.3 Demographics, Dose, and Duration of Exposure in Pediatric Studies

The mean dose of levetiracetam was 1271 mg/day (median dose 1000 mg/day). When adjusted for body weight the mean pediatric dose was 40 mg/kg/day, comparable to the mean adult dose of 34 mg/kg/day. The mean duration of exposure was 302 days (median 231 days).

Among the pediatric subjects 65.5% were male and 34.5% were female. The mean age was 8.7 years ranging from 5 to 12 years. The majority of subjects were Caucasian 89.7%

Dose and duration of exposure are categorized in Table 5. Patients who received more than one dose appear in multiple categories.

Table 5: Duration of Exposure to Levetiracetam by Dose (Pediatric Studies)

ALL PEDIATRIC EPILEPSY PATIENTS								
Dose (mg/day)	Overall N=29	Number by Duration of Exposure						
		1d - ≤ 4 wk.	>4wk - ≤ 3 mo.	>3 mo. - ≤ 6 mo.	>6 mo. - ≤ 1 yr.	>1 yr. - ≤ 2 yr.	>2 yr. - ≤ 3 yr.	> 3 yr.
≤ 500	29	10	18	1	0	0	0	0
>500 - ≤ 1500	29	3	8	12	3	1	0	2
> 1500 - ≤ 2500	16	1	9	4	2	0	0	0
> 2500 - ≤ 3500	6	3	2	0	1	0	0	0
>3500 - ≤ 4500	3	2	1	0	0	0	0	0
>4500	1	0	1	0	0	0	0	0

6.1.4 Demographics, Dose, and Duration of Exposure in Studies of Other Indications

Prior to the initiation of the levetiracetam development program in epilepsy, 2526 patients participated in clinical trials with levetiracetam in other indications. Among subjects included in the N999 database 394 were exposed in 8 studies of cognition. The mean age of patients participating in the cognition studies was 60 years, ranging from 17 to 94 years. In 8 studies of anxiety (7 controlled, 1 open-label) 1084 subjects were exposed to levetiracetam. The mean age in the controlled studies was 45.5 years, ranging from 18 to 101 years. Approximately two thirds of patients were female. Three subjects were exposed in a study for the prevention of deep venous thrombosis.

By design, patients in studies of other indications received lower doses for shorter periods of time. Dose and duration of exposure are categorized in Table 6.

Table 6: Duration of Exposure to Levetiracetam by Dose (Studies in Other Indications)

STUDIES IN OTHER INDICATIONS				
Dose (mg/day)	Overall N=1558 ^a	Number by Duration of Exposure		
		1 day - ≤ 4 wk.	> 4 wk. - ≤ 3 mo.	≥ 3 months
≤ 500	1087	335	731	1
>500 - ≤ 1500	528	188	339	1

based on sponsor's Table 25, SU, Vol. 1 p. 89

^a 1558 rather than 1559 due to one anxiety patient with a lost CRF

In summary, 990 patients were exposed to levetiracetam for more than 6 months, 677 for more than 1 year and 430 for more than 2 years. As can be seen from Table 7, nearly all the long-term exposure derives from the uncontrolled adult epilepsy studies.

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Table 7: Duration of Exposure to Levetiracetam by Study Category

Group	Number by Duration of Exposure						
	> 1d	> 4wk	> 3 mo.	> 6 mo.	>1 yr.	> 2 yr.	> 3 yr.
All Studies	3347	2403	1216	990	677	430	262
Adult Epilepsy	1393	1284	1186	971	674	428	260
Controlled Epilepsy	769	732	679	90	0	0	0
Pediatric Epilepsy	29	29	27	19	3	2	2
Other Indications	1558	1090	3	0	0	0	0
Clinical Pharm.	364	0	0	0	0	0	0

based on sponsor's Tables 5.7a-d, 5.7i, and 5.8c-g

7 Integrated Review of Efficacy

7.1 Overview of Clinical Studies

Three adequate and well-controlled clinical trials have been submitted to this NDA in support of the sponsor's claim for efficacy of levetiracetam as adjunctive therapy in the treatment of partial onset seizures. Study N132 was conducted in the U.S.

1. Study N132, a randomized, placebo-controlled, parallel group, double-blind, multi-center trial in which patients were treated with one of two doses of levetiracetam or placebo.
2. Study N051, a randomized, placebo-controlled, cross-over, double-blind, multi-center trial in which patients were treated with one of two doses of levetiracetam or placebo. Only data from the first portion of the study was included in the efficacy analyses.
3. Study N138, a randomized, placebo-controlled, parallel group, double-blind, multi-center trial in which patients were treated with levetiracetam or placebo (in a 2:1 randomization).

The protocol specified primary efficacy variable for these studies was the reduction in the mean weekly seizure frequency from baseline during treatment, compared to placebo.

In addition, the sponsor submitted a fourth placebo-controlled, parallel-group study (N052) as supportive of product safety.

7.2 Summary of Studies Pertinent to Efficacy

7.2.1 Study N051

7.2.1.1 Protocol Synopsis

Title:

Evaluation of the Efficacy and Tolerability of ucb L059 (500 and 1000 mg b.i.d, tablets) Add-On Treatment in Refractory Epileptic Patients with Partial Onset Seizures: A 32 Week Double-Blind, Placebo-Controlled Crossover Multicenter Trial

Objectives:

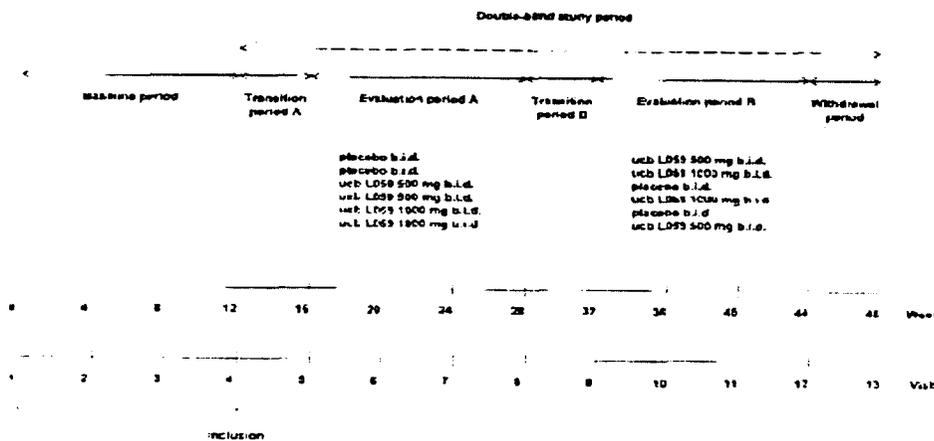
The primary objective was to evaluate the efficacy and tolerability of two fixed doses of L059 as add-on treatment in refractory partial onset epilepsy through a double-blind, placebo-controlled, crossover multicenter trial (86 investigators at 62 centers).

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Study Design:

The trial was designed as a double-blind, two-period (A&B) and three treatment crossover of levetiracetam in patients with treatment-resistant partial onset epileptic seizures. However, for comparison with the other two pivotal trials the first period was considered and analyzed as a parallel group study. The protocol calls for 78 patients in each two-treatment and two-period crossover.

Figure 1: Study Schematic:



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From sponsor's figure 9.1, Vol. 189, p 17316

Study Schedule

Patients were enrolled at a selection visit followed by a baseline period to verify all inclusion and exclusion criteria. Study treatment began after a 4-week transition period during which study drug was titrated to the dose required for the 12-week evaluation period.

The study drug was taken as add-on therapy to the baseline antiepileptic drug (AED) treatment. Patients were randomized to placebo, 1 g or 2 g levetiracetam given in equal doses before breakfast and before dinner.

Enrollment Criteria

Eligible patients were male or female in-patients or out-patients between 16 and 65 years-old. Women of childbearing potential could only be included if they were surgically sterile, two years postmenopausal, or if of childbearing potential, using an acceptable method of contraception. Patients must have refractory epilepsy, experiencing only or predominately partial onset seizures classifiable according to the International Classification of Epileptic Seizures and be on a stable dosage regimen of a maximum of 2 AEDs. Patients must have been observed to have partial onset seizures for at least the last two years despite taking at least 2 AEDs and have at least 4 partial onset seizures during each 4 weeks of the baseline period. Eligible patients must be free of any serious medical conditions and not be taking any medications influencing the central nervous system (e.g. neuroleptics, antidepressants, anxiolytics, stimulants, anticholinergics, tranquilizers, hypnotics, narcotic analgesics, and other compounds with intrinsic central nervous system activity) except for medication taken as epileptic treatment. Patients with seizures that were uncountable due to clustering during the baseline period were excluded.

Efficacy

Patients maintained a seizure diary to record the date, duration and description of each seizure. Based on the patient diary the investigator classified and recorded the seizures according to the International League Against Epilepsy criteria. If a diary was completed by the patient's caregiver, it was emphasized that it should be the same person throughout the study who observed the seizures and recorded the details in the diary.

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The following types of seizures were categorized in this study:

- partial onset (I)
 - simple partial (IA)
 - complex partial (IB)
 - partial onset and secondarily generalized (IC)
 - simple partial + complex partial (IA + IB)
- primary generalized (II)
- unclassifiable (III)
- combination of all seizure types (I + II + III)

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Primary Efficacy Variable

The primary efficacy variable described for this study was the mean number of partial onset seizures per week over evaluation periods A and B compared to baseline and computed as follows:

[number of seizures over evaluation period/number of days in evaluation period] * 7

Investigators were instructed to report clusters of seizures of a specific type within the corresponding seizure category. Counting of seizures within a cluster and reporting would depend on the information obtained from the patient. No specific rules were applied for reporting of clusters.

Descriptive and inferential statistical analyses were performed on log-transformed seizure frequency data, using the transformation $Y = \ln(X + 1)$ when the seizure frequency was measured by least squares means and percentage reduction from placebo.

Secondary Efficacy Variables

Secondary efficacy variables for this study were:

1. responder rate, the proportion of patients experiencing a $\geq 50\%$ reduction in partial onset seizure frequency during the evaluation period compared to the baseline period
2. response to treatment, the percentage reduction in partial onset seizure frequency during the evaluation period compared to the baseline period expressed in six improvement classes
3. incidence of seizure free patients
4. absolute and percent reduction in partial onset seizure frequency from baseline
5. seizure frequency by seizure subtype
6. quality of life assessments

7.2.1.2 Protocol Amendments

Amendment 1:

This amendment was dated 3/1/94. Significant changes include:

- shortening the duration of the baseline period from 12 to 8 weeks
- requirement that adverse events be reported in baseline period
- pregnancy would lead to removal from the study

Amendment 2:

This amendment was dated 6/20/94. Significant changes include:

- an EEG recording was not required at the inclusion visit
- breaking of the study code would lead to patient removal from the study

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7.2.1.3 Study Conduct

Patient Populations

The sponsor defined four patient populations:

1. **All Patients:** This population consisted of all patients who entered the study at the selection visit (includes those found ineligible and not randomized).
2. **Intent-To-Treat (ITT) Population:** This population included all patients randomized and had taken at least one dose of study medication.
3. **Inferential Intent-To-Treat Population:** This population included all patients from the ITT population who had efficacy data for the relevant treatment periods. For the parallel group analysis of evaluation period A, a patient had to have data for at least one visit in evaluation period A to be included in the inferential ITT population.
4. **Per-Protocol (PP) Population:** This population included all patients of the ITT population who had no major protocol violations during the baseline period or period A.

Enrollment

A total of 392 patients were screened and 324 were randomized from 62 centers (112 placebo, 106 levetiracetam 1g, and 106 levetiracetam 2g). A total of 46 (14%) of patients dropped out in period A, leaving 278 patients completing this period. The table below summarizes overall patient discontinuations. Fifteen (13%) patients were receiving placebo, 12 (11%) were receiving levetiracetam 1g, and 19 (18%) were receiving levetiracetam 2g. Of the 46 dropouts, 29 (9%) were discontinued because of adverse events, 10 (3%) withdrew consent, and 7 (2%) discontinued for other reasons (Table 8).

Table 8: Patient Disposition for Premature Termination During Evaluation Period A

(ITT Population)

Disposition	Placebo n (%)	Levetiracetam		Total n (%)
		1 gram n (%)	2 gram n (%)	
Randomized	112	106	106	324
Completed Study	97 (87)	94 (89)	87 (82)	278 (86)
Total Prematurely Discontinued	15 (13)	12 (11)	19 (18)	46 (14)
Reason for Discontinuation				
AE	6 (5)	8 (8)	15 (14)	29 (9)
Withdrew Consent	5 (5)	2 (2)	3 (3)	10 (3)
Other	4 (4)	2 (2)	1 (1)	7 (2)

From sponsor's Table 10.1, Vol. 189, p 17353

Demographic and Baseline Characteristics

The mean age for all patients was 37 years (range=14-69). Forty-eight percent (157) were males. Most patients (99% (321/324)) were Caucasian. The patients were diagnosed with epilepsy for a mean of 23.6 years (median 22.7, range=0.8 - 59.8). Table 9 summarizes patient demographics for all randomized patients by treatment group. The treatment groups were similar with respect to these baseline characteristics.

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Table 9: Summary of Patient Demographics and Baseline Characteristics

	Placebo	Levetiracetam		Overall
		1 g	2 g	
N	112	106	106	324
Gender				
Male	55 (49%)	51 (48%)	51 (48%)	157 (48%)
Female	57 (51%)	55 (52%)	55 (52%)	167 (52%)
Age (mean)	37	36	37	37
min-max	16 - 69	16 - 68	14 - 65	14 - 69
Race				
Caucasian	109 (97%)	106 (100%)	106 (100%)	321 (99%)
Black	2 (2%)	0	0	2 (0.8%)
Other	1 (1%)	0	0	1 (0.3%)
Median years with epilepsy	22.4	22.6	22.9	22.7
min-max	2 - 52	1 - 55	2 - 60	1 - 60

For more than half the patients (56% (183/324)) the etiology of epilepsy was unknown and was similar across treatment groups. The most common etiologies when known were encephalitis (4.6%), birth injury (3.7%), febrile convulsion and birth asphyxia (both 2.2%), congenital malformation and meningitis (both 1.9%).

Comparisons of concomitant AEDs used by patients during the titration and evaluation period A showed similar usage (Table 10).

Table 10: Summary of Concomitant Antiepileptic Drug Usage During The Titration and Evaluation Period A

Concomitant AED	Placebo N = 112	Levetiracetam	
		1 g N = 106	2 g N = 106
Carbamazepine	79 (71%)	75 (71%)	80 (75%)
Clobazam	9 (8%)	10 (9%)	12 (11%)
Clonazepam	4 (4%)	7 (7%)	3 (3%)
Diazepam	7 (6%)	6 (6%)	10 (9%)
Lamotrigine	14 (13%)	13 (12%)	11 (10%)
Phenobarbital	14 (13%)	11 (10%)	8 (8%)
Phenytoin	30 (27%)	21 (20%)	21 (20%)
Primidone	7 (6%)	7 (7%)	6 (6%)
Valproic Acid	21 (19%)	25 (24%)	21 (20%)

based on sponsor's Table 4.2, Vol. 190, pp. 17652 - 5

Baseline Phase Comparability of Weekly Seizure Rates

During the baseline period all patients had partial onset seizures with a mean and median of 5.92 and 2.62 seizures per week, respectively. During the baseline period 31% (101) patients had simple partial seizures (IA), 83% had complex partial seizures (IB) and 25.6% of patients had secondarily generalized seizures (IC). Only a few patients had generalized seizures or unclassifiable seizures, 6.7% and 1.5%, respectively.

The seizure frequency distribution is positively skewed. Fifty-six percent of patients had up to 3 seizures per week, 39% had 3 - 9 seizures per week and 15% had more than 9 seizures per week. Among the patients having more than 9 seizures per week 4 patients had more than 50 seizures per week.

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The baseline frequency of partial onset seizures was generally comparable by treatment group with the exception of a higher frequency of type IB seizures among the levetiracetam 2 g group (Table 11).

Table 11: Seizure Frequencies During the Baseline Period

Seizure Type	Placebo N = 112	Levetiracetam	
		1 g N = 106	2 g N = 106
Partial Onset (I)			
Mean	5.39	5.51	6.88
Max			
Simple Partial (IA)			
Mean	2.02	2.19	2.16
Max			
Complex Partial (IB)			
Mean	3.21	2.91	4.48
Max			
Secondarily Generalized (IC)			
Mean	0.16	0.33	0.26
Max			

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based on sponsor's Table 3.4, Vol. 190, pp. 17618 - 33

Protocol Violations

A total of 120 (37%) patient's had a major protocol violation, 39 (33%), 31(29%), and 50 (47%) in the placebo, levetiracetam 1 g and 2 g groups, respectively. An additional 25 patients were partially excluded from the PP analysis because of a protocol deviation, 13 (12%), 6 (6%), and 6 (6%) in the placebo, levetiracetam 1 g and 2 g groups, respectively (Table 12).

Table 12: Numbers of Protocol Deviations per Deviation Category, Leading to Complete Exclusion of Patients from the Per Protocol Efficacy Analysis

Protocol Deviation Category	Placebo N ^a 112 n ^b = 39	Levetiracetam		Total N = 324 n = 120
		1 g N = 106 n = 31	2 g N = 106 n = 50	
AED intake, including BZD	18	14	27	59
Intake of CNS active drugs	15	16	16	47
Early drop-outs	8	5	15	28
Study drug compliance	6	3	5	14
Baseline seizure frequency	3	4	5	12
Investigational center 137 ^c	2	2	1	5
Concomitant disorders	1	1	1	3

based on sponsor's Table 10.2, Vol. 189, p 17355

^a number of patients ITT population

^b number of observations

^c study site closed because of unreliable data

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Patients Who Had the Study Blind Broken

Three patients had the study blind broken all occurring during evaluation period A.

1. Patient: 067/077, levetiracetam 1 g; patient became pregnant
2. Patient 069/032, placebo; patient had a generalized seizure requiring hospitalization
3. Patient 069/052, levetiracetam 1 g; patient had a generalized seizure

7.2.1.4 Sponsor's Efficacy Results

This trial was designed as a two-period, three-treatment crossover design. However for comparison with the other pivotal trials a parallel group analysis was conducted with data from evaluation period A only.

For efficacy, a patient was considered to be evaluable in the parallel group analysis if there was a seizure count for at least one visit in evaluation period A. Two patient populations were examined in the parallel group analysis (Table 13):

1. **Inferential Intent-To-Treat Population:** This population included all patients from the ITT population who had efficacy data for evaluation period A.
2. **Per-Protocol (PP) Population:** This population included all patients from the ITT population who had no major protocol violations during the baseline period or evaluation period A.

Table 13: Number of Evaluable Patients In Parallel Group Analysis (Period A)

	Placebo	Levetiracetam		Total
		1 gram	2 gram	
Randomized	112	106	106	324
Evaluation Period A Inferential ITT	106	101	95	302
Evaluation Period A Per-Protocol	73	75	56	204

based on sponsor's Table 11.1, Vol. 189, p 17356

Partial Onset Seizure Frequency Over Evaluation Period A. LSM Analysis. Inferential ITT Population

"A covariance analysis was carried out on the log-transformed seizure frequency over the evaluation period A with the log-transformed seizure frequency over the baseline period as covariate."

Levetiracetam was statistically superior to placebo in lowering partial onset seizure frequency (1 g group p = 0.006, 2 g group p = 0.003). The percentage reduction in partial onset seizure frequency for levetiracetam over placebo was 16.4% (98% CI: 2.7; 28.1) and 17.7% (98%CI: 4.1; 29.4) in the 1 g and 2 g groups, respectively (Table 14). There was no statistically significant difference between the two doses of levetiracetam.

A per-protocol analysis (exclusion of 120 patients with major protocol deviations) yielded results consistent with the inferential ITT analysis.

Table 14: Partial Onset Seizure Frequency by LSM and Percent Reduction for the Evaluation Period A (Inferential ITT Population - Log-Transformed Data)

Placebo n = 106	Levetiracetam 1 g n = 101			Levetiracetam 2 g n = 95			p - val. 1g vs. 2g	p - val. ^c overall
	LSM ^a (SE)	%red ^b (98% CI)	p - val. ^c	LSM (SE)	%red (98% CI)	p - val.	p - val. ^d	p - val.
1.455 (0.045)	1.274 (0.046)	16.4 (2.7;28.1)	0.006	1.258 (0.048)	17.7 (4.1;29.4)	0.003	0.804	0.004

based on sponsor's Table 11.4.1.1.A, Vol. 189, p 17373

^a LSM = least squares mean (Adjusted mean)

^b Percentage reduction over placebo = 100 [1 - exp (LSM treatment - LSM placebo)]

^c Pairwise comparison with placebo

^d Pairwise comparison of levetiracetam 1 g vs. 2 g

^e Overall ANCOVA or ANOVA treatment effect

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Examination of seizure frequency by visit during evaluation period A revealed a statistically significant lower mean partial onset seizure frequency in the levetiracetam 2 g group compared to placebo at each visit (Table 15). In the levetiracetam 1g group a statistically significant lower mean partial onset seizure frequency was seen only at visit 6.

Table 15: Summary of Partial Onset Seizure Frequency by LSM and Percent Reduction by Visit for the Evaluation Period A (Inferential ITT Population - Log-Transformed Data, Repeated Measures Analysis)

Placebo n = 106	Levetiracetam 1 g n = 101			Levetiracetam 2 g n = 95			p - val. 1g vs. 2g	p - val. ^c overall
LSM ^a (SE)	LSM (SE)	%red ^b (98% CI)	p - val. ^c	LSM (SE)	%red (98% CI)	p - val.	p - val. ^d	p - val.
Visit 6 (Week 20)								
1.445 (0.051)	1.194 (0.046)	22.2 (7.8;34.4)	<0.001	1.205 (0.054)	21.4 (6.5;33.9)	0.001	0.882	<0.001
Visit 7 (Week 24)								
1.426 (0.051)	1.282 (0.053)	13.4 (-2.8;26.4)	0.051	1.247 (0.055)	16.4 (0.4;29.9)	0.017	0.642	0.039
Visit 8 (Week 28)								
1.400 (0.052)	1.268 (0.053)	12.4 (-4.2;26.4)	0.075	1.218 (0.055)	16.7 (0.6;30.2)	0.017	0.510	0.044

based on sponsor's Table 11.4.1.1.B, Vol. 189, p 17374

^a LSM = least squares mean (Adjusted mean)

^b Percentage reduction over placebo = 100 [1 - exp (LSM treatment - LSM placebo)]

^c Pairwise comparison with placebo

^d Pairwise comparison of levetiracetam 1 g vs. 2 g

^e Overall ANCOVA or ANOVA treatment effect

Responder Rate Over Evaluation Period A, Inferential ITT Population, Untransformed Data

Levetiracetam was statistically superior to placebo in increasing the proportion of patients with a reduction of partial onset seizures of 50% or more during evaluation period A (Table 16). The responder rate was 10.4%, 22.8% and 31.6% in the placebo, 1 g and 2 g groups, respectively. There was no statistically significant difference in responder rate between the two doses of levetiracetam (p = 0.167).

Table 16: Partial Onset Seizure Responder Rate by Study Period (Inferential ITT Population)

Treatment	Proportion (%)	P - Value
Placebo	11/106 (10.4%)	
Levetiracetam 1 g	23/101 (22.8%)	0.019
Levetiracetam 2 g	30/95 (31.6%)	<0.001

based on sponsor's Table 11.4.1.2, Vol. 189, p 17377

Response to Treatment Over Evaluation Period A, Inferential ITT Population, Untransformed Data

Continuing to focus on response rates the sponsor has categorized the proportion of patients with a reduction in partial onset seizure from < - 25% (a 25% or greater increase in the percent of seizures in the evaluation period) to 100% (seizure free in the evaluation period).

Seventy-five percent of patients in the placebo group, 57% of patients in the levetiracetam 1g group and 49% of patients in the levetiracetam 2g group had a < 25% reduction to 25% increase in response (Table 17). The sponsor notes that such a small change in seizure frequency (<25% reduction to 25% increase) could be explained by fluctuations in the seizure pattern that is regularly observed in patients with epilepsy and is not necessarily treatment-related.

Levetiracetam was statistically superior to placebo in increasing the proportion of patients with a reduction of partial onset seizures, p = 0.002 and p < 0.001 for the 1 g and 2 g groups, respectively.

There was no statistically significant difference in response between the two doses of levetiracetam (p = 0.454).

Table 17: Summary of Partial Onset Seizures Response to Treatment During Evaluation Period A (Inferential ITT Population)

	Placebo		Levetiracetam 1 g		Levetiracetam 2 g	
	n	(%)	n	(%)	n	(%)
Total	106	(100.0)	101	(100.0)	95	(100.0)
< - 25 %	31	(29.2)	14	(13.9)	18	(19.0)
- 25 % to < 25 %	49	(46.2)	44	(43.6)	29	(30.5)
25 % to < 50 %	15	(14.2)	20	(19.8)	18	(19.0)
50 % to < 75 %	8	(7.6)	12	(11.9)	14	(14.7)
75 % to < 100 %	2	(1.9)	6	(5.9)	14	(14.7)
100 % (seizure-free)	1	(0.9)	5	(4.9)	2	(2.1)

based on sponsor's Table 11.4.1.3, Vol. 189, p 17379

Patients Seizure-Free (All Seizure Types) During Evaluation Period A (Inferential ITT Population)

Seven levetiracetam patients were seizure free during the complete evaluation period A and 1 placebo patient did not report any seizures until dropout at day 29 of treatment. The reliability of the diagnosis and treatment of epilepsy in this placebo patient (patient 069/117, center 137) is raised by the sponsor.

Partial Onset Seizure Frequency, Absolute and Percentage Reduction From Baseline Over Evaluation Period A (Inferential ITT population, Untransformed Data)

The baseline median partial onset seizure frequency was 2.5, 2.8, and 2.5 for the placebo, levetiracetam 1 g and 2 g groups, respectively.

The median percentage reduction in seizure frequency from baseline was 6.1%, 17.7% and 26.5% for the placebo, levetiracetam 1 g and 2 g groups, respectively (Table 18).

Table 18: Summary of Partial Onset (Type I) Seizure Frequencies by Median and Median Absolute Percentage Reduction From Baseline (ITT and Inferential ITT Population)

Period	Placebo (N ^a = 112) Median seizure				Levetiracetam 1 g (N = 106) Median seizure				Levetiracetam 2 g (N = 106) Median seizure			
	n	freq	ARB ^b	%RB ^c	n	freq	ARB	%RB	n	freq	ARB	%RB
Baseline ^e	112	2.50	-- ^d	--	106	2.82	--	--	106	2.58	--	--
Evaluation A ^f	106	2.58	0.08	6.1	101	2.00	0.37	17.7	95	1.85	0.61	26.5

based on sponsor's Table 11.4.1.5.1, Vol. 189, p 17382

^a N = Total number of ITT patients within a treatment group, n = number of patients who had a seizure evaluation

^b ARB = Absolute reduction from baseline. Reduction from baseline is for those patients who had both baseline and evaluation period data.

^c %RB = Percentage reduction from baseline

^d -- = not applicable

^e ITT population

^f Inferential ITT population

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Seizure Frequency by Partial Onset Subtypes

Continuing to focus on median seizure frequencies of untransformed data the sponsor stratified partial onset seizures by subtype (Table 19). There were generally larger reductions in seizure frequency in the levetiracetam treatment groups than placebo. The sponsor does not provide any inferential statistics upon these subgroups.

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A covariance analysis was carried out on the log-transformed frequency of partial onset seizure subtypes over the evaluation period A with log-transformed seizure frequency over the baseline period as a covariate.

Levetiracetam was statistically significant to placebo for seizure frequency reductions in IA (p = 0.023) and IA + IB (p = 0.009) subgroups for levetiracetam 2 g and in IA (p = 0.032) and IA + IB (p = 0.016) subgroups for levetiracetam 1 g.

Table 19: Summary of Partial Onset Seizure Frequencies, by Subtypes, by Median and Absolute Reduction from Baseline (Subgroups from ITT population, Untransformed Data)

Seizure type Period	Placebo (N ^a = 112) Median Seizure			Levetiracetam 1 g (N = 106) Median Seizure			Levetiracetam 2 g (N = 106) Median Seizure		
	n	freq	ARB ^b	n	freq	ARB	n	freq	ARB
Simple partial (IA)									
Baseline ^d	53	1.17	-- ^c	37	1.25	--	44	1.21	--
Evaluation A	47	1.50	- 0.08	34	0.66	0.69	32	0.98	1.00
Complex partial (IB)									
Baseline ^d	95	1.70	--	87	2.07	--	94	1.96	--
Evaluation A	89	1.33	0.14	83	1.58	0.21	83	1.54	0.37
Partial secondarily generalized (IC)									
Baseline ^d	38	0.13	--	35	0.38	--	37	0.38	--
Evaluation A	32	0.39	- 0.20	31	0.31	0.09	25	0.50	0.08
Simple complex partial (IA + IB)									
Baseline ^d	112	2.11	--	100	2.46	--	105	2.50	--
Evaluation A	106	2.12	0.09	96	1.92	0.37	94	1.71	0.56

based on sponsor's Table 11.4.1.5.2A, Vol. 189, p 17383

^aN = Total number of ITT patients within a treatment group, n = number of patients who had a seizure evaluation

^bARB = Absolute reduction from baseline. Reduction from baseline is for those patients who had both baseline and evaluation period data.

^c-- = not applicable

^dITT population

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Seizure Frequency by All Subtypes (Types I, II and III)

Seventeen patients had type II or III seizures at baseline. Among patients with type II seizures 5, 4, and 8 patients were in the placebo, levetiracetam 1 g and 2 g groups, respectively. Among patients with type III seizures 3 patients were in the placebo group and 2 in the levetiracetam 2 g group. Changes from baseline were not presented for patients with type II or III seizures.

Median percentage changes in seizure frequency from baseline for all seizure types (I, II and III) was nearly identical to the changes described for partial onset seizures alone.

A covariance analysis was carried out on the log-transformed frequency of all seizure types over the evaluation period A with log-transformed seizure frequency over the baseline period as a covariate.

Levetiracetam was statistically superior to placebo in lowering all seizure types (1 g group p = 0.008, 2 g group p = 0.005).

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7.2.2 Study N132

7.2.2.1 Protocol Synopsis

Title:

Evaluation of the Efficacy and Tolerability of ucb L059 (500 and 1500 mg b.i.d, tablets) Add-On Treatment in Epileptic Patients with Partial Onset Seizures: A 38-Week Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Trial

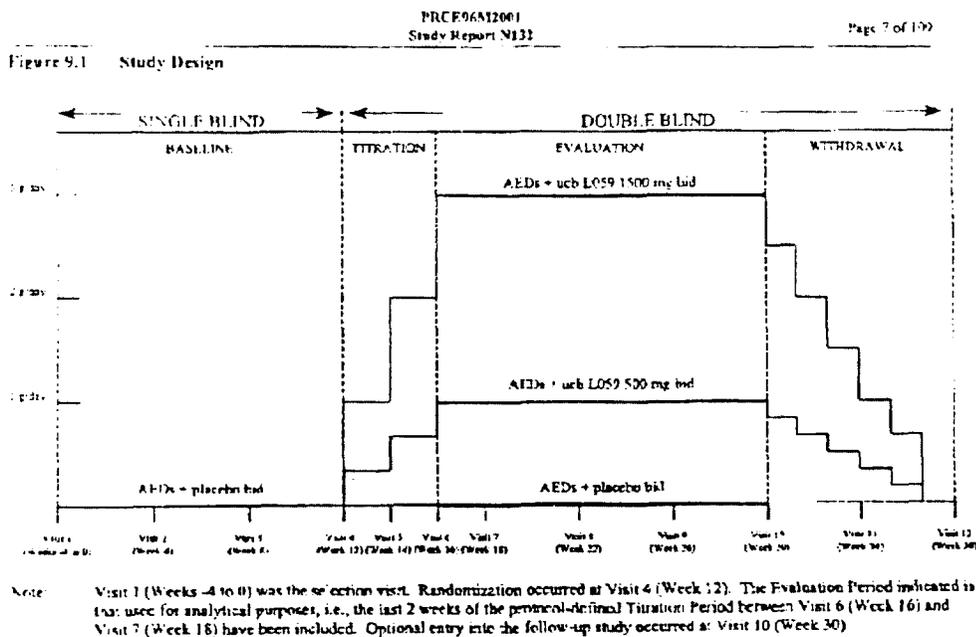
Objectives:

The primary objective was to evaluate the efficacy and tolerability of two fixed doses of L059 as add-on treatment in refractory partial onset epilepsy through a double-blind, placebo-controlled, crossover multicenter trial.

Study Design:

The trial was designed as a multicenter (39 investigators at 41 centers, double-blind, placebo-controlled, parallel group, add-on AED trial with two dose groups. The protocol calls for 80 patients in each treatment group.

Figure 2: Study Design



Study Schedule

Patients were enrolled at a selection visit followed by a 12-week single-blind placebo Baseline Period to verify all inclusion and exclusion criteria. The Double-Blind Phase started with a 6-week Titration Period during which study drug was titrated to the dose required for the 12-week Evaluation Period. On completion of the Evaluation Period patients entered an 8-week Withdrawal Period. The study drug was taken as add-on therapy to the baseline antiepileptic drug (AED) treatment. Patients were randomized to placebo, 1 g or 3 g of levetiracetam.

Enrollment Criteria

Eligible patients were male or female in-patients or out-patients between 16 and 70 years-old. Women of childbearing potential could only be included if they were surgically sterile, two years

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postmenopausal, or if of childbearing potential, using an acceptable method of contraception. Patients must have uncontrolled epilepsy, experiencing simple and/or complex partial onset seizures with or without secondary generalization classifiable according to the "Proposal for revised clinical and electroencephalographic classification of epileptic seizures" and be on a stable dosage regimen of a maximum of 2 allowed AEDs. Patients must have been observed to have partial onset seizures for at least the last two years prior to study entry and have at least 12 partial onset seizures in 12 weeks with a minimum of 2 partial onset seizures in 4 weeks during the 3 months prior to the selection visit and during the baseline period. Eligible patients must be free of any serious medical conditions and not be taking any medications influencing the central nervous system (e.g. neuroleptics, antidepressants, anxiolytics, stimulants, anticholinergics, tranquilizers, hypnotics, narcotic analgesics, and other compounds with intrinsic central nervous system activity) except for medication taken as epileptic treatment. Patients with partial onset seizures that were uncountable due to clustering (including status epilepticus) during the 3 months prior to study entry were excluded.

Efficacy

Patients maintained a daily record card to record the date, number, duration and description of each seizure. Based on the daily record card the investigator classified and recorded the seizures according to the International League Against Epilepsy criteria.

Seizure clusters were defined as groupings of seizures in which individual seizures were indistinguishable and unquantifiable. Clusters were recorded as Type IV.

The following types of seizures were categorized in this study:

- partial onset (I)
 - simple partial (IA)
 - complex partial (IB)
 - partial onset and secondarily generalized (IC)
 - simple partial + complex partial (IA + IB)
- primary generalized (II)
- unclassifiable (III)
- clusters (IV)

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Primary Efficacy Variable

The primary efficacy variable described for this study was the mean number of partial onset seizures per week computed for the Evaluation Period as a single time point. The weekly mean number of seizures is calculated as follows:

$$[\text{number of seizures over time period} / \text{number of days in time period}] * 7$$

Investigators were instructed to report clusters of seizures of a specific type within the corresponding seizure category. Counting of seizures within a cluster and reporting would depend on the information obtained from the patient. No specific rules were applied for reporting of clusters.

Descriptive and inferential statistical analyses were performed on log-transformed seizure frequency data, using the transformation $Y = \ln(X + 1)$ when the seizure frequency was measured by least squares means and percentage reduction from placebo.

Secondary Efficacy Variables

Secondary efficacy variables for this study were:

1. responder rate, the proportion of patients experiencing a $\geq 50\%$ reduction in partial onset seizure frequency during the evaluation period compared to the baseline period
2. response to treatment, the percentage reduction in partial onset seizure frequency during the evaluation period compared to the baseline period expressed in six improvement classes
3. incidence of seizure free patients

4. absolute and percent reduction in partial onset seizure frequency from baseline
5. seizure frequency by seizure subtype
6. quality of life assessments

7.2.2.2 Protocol Amendments

Amendment 1:

This amendment was dated 6/20/94. Significant changes include:

- the dosage of levetiracetam was decreased from 1000 and 2000 mg bid to 500 and 1500 mg bid (change made prior to start of study).

Amendment 2:

This amendment was dated 9/20/94. Significant changes include:

- inclusion of women of childbearing potential using adequate birth control

Amendment 3:

This amendment was dated 1/27/95. Significant changes include:

- an exploratory analysis for age and gender effects
- the definition of an unexpected AE was broadened

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7.2.2.3 Study Conduct

Patient Populations

The sponsor defined three patient populations:

1. **All Patients:** This population consisted of all patients who entered the study at the selection visit (includes those found ineligible and not randomized).
2. **Intent-To-Treat (ITT) Population:** This population included all randomized patients who were dispensed randomized treatment, regardless of whether actual dosing could be confirmed.
3. **Per-Protocol (PP) Population:** This population included all patients of the ITT population who had no major protocol violations.

Enrollment

A total of 385 patients were screened and 294 were randomized from 41 centers (95 placebo, 98 levetiracetam 1g, and 101 levetiracetam 3g). A total of 268 (91%) patients completed the Evaluation Period through week 30. Table 20 summarizes overall patient discontinuations. Six (6%) patients were receiving placebo, 12 (12%) were receiving levetiracetam 1g, and 8 (8%) were receiving levetiracetam 3g. Of the 26 patients who discontinued, 18 (6%) were discontinued because of adverse events, 4 (1%) withdrew consent, and 4 (1%) discontinued for other reasons (Table 20).

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**Table 20: Patient Disposition for Premature Termination Through Evaluation Period Week 30
(ITT Population)**

Disposition	Placebo n (%)	Levetiracetam		Total n (%)
		1 gram n (%)	3 gram n (%)	
Randomized	95	98	101	294
Completed Study	89 (94)	86 (88)	93 (92)	278 (86)
Total Prematurely Discontinued	6 (6)	12 (12)	8 (8)	26 (9)
Reason for Discontinuation				
AE	5 (5)	6 (6)	7 (7)	18 (6)
Withdrew Consent	1 (1)	2 (2)	1 (1)	4 (1)
Other	0 (0)	4 (4)	0 (0)	4 (1)

From sponsor's Figure 10.1, Vol. 155, p 5719

Demographic and Baseline Characteristics

The mean age for all patients was 38 years (range=16-70). Sixty-percent (178) were males. Most patients (85% (251/294) were Caucasian. The patients were diagnosed with epilepsy for a mean of 23.6 years (median 22.7, range=0.8 - 59.8). Table 21 summarizes patient demographics for all randomized patients by treatment group. The treatment groups were similar with respect to these baseline characteristics.

Table 21: Summary of Patient Demographics and Baseline Characteristics

	Placebo	Levetiracetam		Overall
		1 g	3 g	
N	95	98	101	294
Gender				
Male	50 (53%)	62 (63%)	66 (65%)	178 (60%)
Female	45 (47%)	36 (37%)	35 (35%)	116 (40%)
Age (mean)	38	38	38	38
min-max	20 - 65	16 - 70	16 - 66	16 - 70
Race				
Caucasian	81 (85%)	82 (84%)	88 (87%)	251 (85%)
Black	7 (7%)	10 (10%)	9 (9%)	26 (9%)
Other	7 (7%)	6 (6%)	4 (4%)	17 (6%)
Median years with epilepsy	24	22	23	23
min-max				

From sponsor's Table 11.2.1, vol. 155, p 5723

For approximately half the patients (49% (145/294) the etiology of epilepsy was unknown and was similar across treatment groups. The most common etiologies when known were head injury (16%), encephalitis (4%), fever (4%), febrile convulsion (3%), birth injury, meningitis, and birth injury (each 2%).

Comparisons of concomitant AEDs used by patients during the titration and evaluation period showed similar usage (Table 22) with the exception of higher gabapentin usage and lower primidone usage among the levetiracetam 1 g group.

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Table 22: Summary of Concomitant Antiepileptic Drug Usage During The Titration and Evaluation Period

Concomitant AED	Placebo N = 95	Levetiracetam	
		1 g N = 98	3 g N = 101
Carbamazepine	59 (62%)	53 (53%)	56 (55%)
Clonazepam	3 (3%)	1 (1%)	2 (2%)
Gabapentin	24 (25%)	35 (36%)	24 (24%)
Phenobarbital	7 (7%)	9 (9%)	10 (10%)
Phenytoin	29 (30%)	37 (38%)	36 (36%)
Primidone	9 (9%)	2 (2%)	9 (9%)
Valproic Acid	28 (29%)	24 (24%)	26 (26%)

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based on sponsor's Table 4.2, Vol.155, pp. 5878-5882

Baseline Phase Comparability of Weekly Seizure Rates

During the baseline period all patients had partial onset seizures with a median of 2.13 seizures per week (Table 23). During the baseline period 50% (148) patients had simple partial seizures (IA), 95% (280) had complex partial seizures (IB) and 36% (106) of patients had secondarily generalized seizures (IC). Only a few patients had generalized seizures or unclassifiable seizures, 4% and 7%, respectively.

The baseline overall frequency of partial onset seizures was elevated in the levetiracetam 1 g group.

Table 23: Seizure Frequencies During the Baseline Period

Seizure Type	Placebo N = 95	Levetiracetam	
		1 g N = 98	3 g N = 101
Partial Onset (I)			
Mean	5.05	6.87	5.50
Max			
Simple Partial (IA)			
Mean	4.26	5.68	5.84
Max			
Complex Partial (IB)			
Mean	2.76	3.66	2.53
Max			
Secondarily Generalized (IC)			
Mean	0.13	0.59	0.35
Max			

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based on sponsor's Table 8.2.2, Vol.155, pp. 5948-5953 and Table 8.2.7, Vol.155 pp. 5981-6022

Protocol Violations

A total of 51 (17%) patient's had a major protocol violation, 13 (14%), 21 (21%), and 17 (17%) in the placebo, levetiracetam 1 g and 3 g groups, respectively (Table 36). An additional 28 patients were partially excluded from the Per Protocol analysis because of a protocol deviation, 12 (13%), 8 (8%), and 8 (8%) in the placebo, levetiracetam 1 g and 3 g groups, respectively.

Table 24: Numbers of Protocol Deviations per Deviation Category, Leading to the Partial or Total Exclusion of Their Data, Per Treatment Group (ITT Population)

Protocol Deviation Category	Placebo N ^a = 95 n ^b = (%)	Levetiracetam		Total N = 294 n = (%)
		1 g N = 98 n = (%)	3 g N = 101 n = (%)	
Total Exclusions from PP Population				
Change in AED dose > 20%	4 (4)	4 (4)	5 (5)	13 (4)
Seizure info not available	2 (2)	7 (7)	4 (4)	13 (4)
Baseline seizure frequency	2 (2)	5 (5)	3 (3)	10 (3)
Intake of CNS active drugs	2 (2)	1 (1)	2 (2)	5 (2)
BZD use for > 2 days	1 (1)	1 (1)	2 (2)	4 (1)
Medication intake < 80%	0 (0)	1 (1)	1 (1)	2 (1)
≥ concomitant AEDs	1 (1)	1 (1)	0 (0)	2 (1)
Baseline sz clustering	1 (1)	0 (0)	0 (0)	1 (0.3)
Improper sz counting	0 (0)	1 (1)	0 (0)	1 (0.3)
Partial Exclusions from PP Population				
Medication intake < 80%	2 (2)	6 (6)	4 (4)	12 (4)
Change in AED dose > 20%	5 (5)	2 (2)	1 (1)	8 (3)
Premature termination	2 (2)	0 (0)	1 (1)	3 (1)
Intake of CNS active drugs	0 (0)	0 (0)	2 (2)	2 (1)
Errors in titration	2 (2)	0 (0)	0 (0)	2 (1)
Seizure info not available	1 (1)	0 (0)	0 (0)	1 (0.3)

Based on sponsor's Table 10.2, Vol. 155, p 5721

^a number of patients ITT population

^b number of observations

Patients Who Had the Study Blind Broken

The sponsor did not identify any patients who had the study blind broken.

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7.2.2.4 Sponsor's Efficacy Results

The primary efficacy variable was the mean number of partial onset seizures per week computed for the Evaluation Period. As suggested by FDA, the Evaluation Period included the last 2 weeks of the Titration Period for analytic purposes.

Analyses were performed on three patient populations:

1. All Patients: This population consists of all patients who entered the study at the selection visit.
2. Intent-to-Treat Population (ITT): This population includes all patients who were randomized to study treatment and took study treatment at least once.
3. Per-Protocol Population: This population is a subset of the ITT Population who were fully evaluable and have no major protocol violations.

In addition the ITT population was analyzed with reference to a single time point (i.e., seizure frequency over the entire Evaluation Period), by visit, and by last observation carried forward. The focus of this review will be on the ITT Population analyzed over the entire Evaluation Period and by visit.

Partial Onset Seizure Frequency as a Single Time Point During the Evaluation Period. LSM Analysis, ITT Population

A covariance analysis was carried out on the log-transformed seizure frequency over the Evaluation Period (weeks 18, 22, 26, and 30) with the log-transformed seizure frequency over the baseline period as covariate.

Levetiracetam was statistically superior to placebo in lowering partial onset seizure frequency (1 g group p = 0.001, 3 g group p < 0.001). The percentage reduction in partial onset seizure frequency for levetiracetam over placebo was 20.9% (98% CI: 6.8; 32.9) and 27.7% (98% CI: 15.1; 38.5) in the 1 g and 3 g groups, respectively (Table 25). The overall treatment effect was statistically significant p < 0.001. There was no statistically significant difference between the two doses of levetiracetam.

Table 25: Partial Onset Seizure Frequency by LSM and Percent Reduction as a Single Time Point for the Evaluation Period (ITT Population - Log-Transformed Data)

Placebo n = 95	Levetiracetam 1 g n = 98			Levetiracetam 3 g n = 101			p - val. 1g vs. 3g	p - val. ^c overall
	LSM ^a (SE)	LSM (SE)	%red ^b (98% CI)	p - val. ^c	LSM (SE)	%red (98% CI)	p - val.	p - val. ^d
1.366 (0.053)	1.131 (0.050)	20.9 (6.8;32.9)	0.001	1.0411 (0.049)	27.7 (15.1;38.5)	<.001	0.195	<0.001

based on sponsor's Table 11.4.1.1.1, Vol. 155. p 5733

^a LSM = least squares mean (Adjusted mean)

^b Percentage reduction over placebo = 100 [1 - exp (LSM treatment - LSM placebo)]

^c Pairwise comparison with placebo

^d Pairwise comparison of levetiracetam 1 g vs. 3 g

^e Overall ANCOVA or ANOVA treatment effect

Examination of seizure frequency by visit during the Evaluation Period revealed a statistically significant lower mean partial onset seizure frequency overall and in each levetiracetam treatment group compared to placebo at each visit (Table 26). There were no statistically significant differences between the levetiracetam 1g and 3g groups except at visit 7.

An analysis of the ITT population with the last observation carried forward (LCOF) showed an overall statistically significant treatment effect. An analysis of the Per Protocol Population showed an overall statistically significant treatment effect with the exception of Visit 9, p = 0.098.

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Table 26: Summary of Partial Onset Seizure Frequency by LSM and Percent Reduction by Visit for the Evaluation Period (ITT Population - Log-Transformed Data, Repeated Measures Analysis)

Placebo n = 95	Levetiracetam 1 g n = 98			Levetiracetam 3 g n = 101			p - val. 1g vs. 3g	p - val. ^c overall
	LSM ^a (SE)	LSM (SE)	%red ^b (98% CI)	p - val. ^c	LSM (SE)	%red (98% CI)	p - val.	p - val.
Visit 7 (Week 18)								
1.406 (0.061)	1.120 (0.059)	24.9	<0.001	0.918 (0.057)	38.6	<0.001	0.014	<0.001
Visit 8 (Week 22)								
1.327 (0.061)	1.066 (0.059)	22.9	0.002	0.956 (0.057)	31.0	<0.001	0.181	<0.001
Visit 9 (Week 26)								
1.295 (0.062)	1.066 (0.060)	20.5	0.008	1.085 (0.058)	19.0	0.013	0.821	0.012
Visit 10 (Week 30)								
1.289 (0.062)	1.079 (0.061)	18.9	0.016	0.983	26.4	<0.001	0.253	0.001

based on sponsor's Table 11.4.1.1.2.1, Vol. 155, p 5734

^a LSM = least squares mean (Adjusted mean)

^b Percentage reduction over placebo = 100 [1 - exp (LSM treatment - LSM placebo)]

^c Pairwise comparison with placebo

^d Pairwise comparison of levetiracetam 1 g vs. 3 g

^e Overall ANCOVA or ANOVA treatment effect

Responder Rate During the Evaluation Period. ITT Population. Untransformed Data

Levetiracetam was statistically superior to placebo in increasing the proportion of patients with a reduction of partial onset seizures of 50% or more during the Evaluation Period (Table 27). The responder rate was 10.8%, 33% and 39.8% in the placebo, 1 g and 3 g groups, respectively. There was no statistically significant difference in responder rate between the two doses of levetiracetam (p = 0.326).

Table 27: Partial Onset Seizure Responder Rate by Study Period (ITT Population)

Treatment	Proportion (%)	P - Value
Placebo	10/93 (10.8%)	
Levetiracetam 1 g	31/94 (33%)	<0.001
Levetiracetam 2 g	39/98 (39.8%)	<0.001

based on sponsor's Table 11.4.1.2, Vol. 155, p 5738

Response to Treatment During the Evaluation Period. ITT Population. Untransformed Data

Continuing to focus on response rates the sponsor has categorized the proportion of patients with a reduction in partial onset seizure from < - 25% (a 25% or greater increase in the percent of seizures in the evaluation period) to 100% (seizure free in the evaluation period).

Fifty-nine percent of patients in the placebo group, 40% of patients in the levetiracetam 1g group and 39% of patients in the levetiracetam 3g group had a < 25% reduction to 25% increase in response (Table 28).

Levetiracetam was statistically superior to placebo in increasing the proportion of patients with a reduction of partial onset seizures, p = 0.001 and p < 0.001 for the 1 g and 3 g groups, respectively. There was no statistically significant difference in response between the two doses of levetiracetam (p = 0.812).

Table 28: Summary of Partial Onset Seizures Response to Treatment During the Evaluation Period (ITT Population)

	Placebo		Levetiracetam 1 g		Levetiracetam 3 g	
	n	(%)	n	(%)	n	(%)
Total	95	(100.0)	98	(100.0)	101	(100.0)
< - 25 %	24	(25.8)	13	(13.8)	12	(12.2)
- 25 % to < 25 %	31	(33.3)	25	(26.6)	26	(26.5)
25 % to < 50 %	28	(30.1)	25	(26.6)	21	(21.4)
50 % to < 75 %	9	(9.7)	19	(20.2)	19	(19.4)
75 % to < 100 %	1	(1.1)	9	(9.6)	11	(11.2)
100 % (seizure-free)	0	(-)	3	(3.2)	9	(9.2)

based on sponsor's Table 11.4.1.3, Vol. 155, p 5740

Patients Seizure-Free (All Seizure Types) During the Evaluation Period (ITT Population)

Eleven levetiracetam treated patients (3 in the 1 g group and 8 in the 3 g group) were seizure free during the complete Evaluation Period. None of the placebo patients were seizure free in the Evaluation Period.

Partial Onset Seizure Frequency, Absolute and Percentage Reduction From Baseline Over Evaluation Period A (Inferential ITT population, Untransformed Data)

The baseline median partial onset seizure frequency was 1.77, 2.53, and 2.08 for the placebo, levetiracetam 1 g and 3 g groups, respectively.

The median percentage reduction in seizure frequency from baseline was 6.8%, 32.4% and 37.1% for the placebo, levetiracetam 1 g and 3 g groups, respectively (Table 29). Patients in both levetiracetam treatment groups had statistically significant ($p < 0.001$) with-in treatment median percent decreases from baseline in partial onset seizure frequency.

Table 29: Summary of Partial Onset (Type I) Seizure Frequencies by Median and Median Absolute Percentage Reduction From Baseline (ITT and Inferential ITT Population)

Period	Placebo (N ^a = 95) Median seizure				Levetiracetam 1 g (N = 98) Median seizure				Levetiracetam 3 g (N = 101) Median seizure			
	n	freq	ARB ^b	%RB ^c	n	freq	ARB	%RB	n	freq	ARB	%RB
Baseline	95	1.77	-- ^d	--	98	2.53	--	--	101	2.08	--	--
Evaluation	93	1.73	0.13	6.83	94	1.77	0.81	32.45	98	1.29	0.98	37.08

based on sponsor's Table 11.4.1.5, Vol. 155, p 5744

^a N = Total number of ITT patients within a treatment group, n = number of patients who had a seizure evaluation

^b ARB = Absolute reduction from baseline. Reduction from baseline is for those patients who had both baseline and evaluation period data.

^c %RB = Percentage reduction from baseline

^d -- = not applicable

Seizure Frequency by Partial Onset Subtypes

Continuing to focus on median seizure frequencies of untransformed data the sponsor stratified partial onset seizures by subtype (Table 30) There were larger reductions in seizure frequency in the levetiracetam treatment groups than in the placebo group.

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Table 30: Summary of Partial Onset Seizure Frequencies, by Subtypes, by Median and Median Absolute Reduction from Baseline (Subgroups from ITT population, Untransformed Data)

Seizure type Period	Placebo (N ^a = 95) Median Seizure			Levetiracetam 1 g (N = 98) Median Seizure			Levetiracetam 3 g (N = 101) Median Seizure		
	n	freq	ARB ^b	n	freq	ARB	n	freq	ARB
Simple partial (IA)									
Baseline	46	0.52	-- ^c	52	0.96	--	50	1.07	--
Evaluation	44	0.51	0.12	52	0.55	0.35	49	0.57	0.42
Complex partial (IB)									
Baseline	92	1.41	--	94	1.80	--	94	1.29	--
Evaluation	90	1.43	0.12	90	1.18	0.44	91	0.79	0.45
Partial secondarily generalized (IC)									
Baseline	33	0.50	--	39	0.36	--	34	0.31	--
Evaluation	33	0.27	0.08	35	0.07	0.16	34	0.13	0.24
Simple complex partial (IA + IB)									
Baseline	95	1.60	--	96	2.39	--	101	1.95	--
Evaluation	93	1.57	0.27	92	1.68	0.70	98	1.21	0.93

based on sponsor's Table 11.4.1.5, Vol. 155, p 5644-5746

^aN = Total number of ITT patients within a treatment group, n = number of patients who had a seizure evaluation

^bARB = Absolute reduction from baseline. Reduction from baseline is for those patients who had both baseline and evaluation period data.

^c-- = not applicable

Seizure Clusters

Partial onset seizure clusters occurred in 1 patient in the levetiracetam 1 g group and in 2 patients in the levetiracetam 3 g group. Generalized seizure clusters occurred in 1 patient in the placebo group.

7.2.3 Study N138

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7.2.3.1 Protocol Synopsis

Title:

Evaluation of the Efficacy and Tolerability of ucb L059 (1500 mg b.i.d, 500 mg tablets) monotherapy in epileptic patients with complex partial onset seizures, having experienced improved seizure control under add-on treatment. A 60 - week (maximum), double-blind, multicenter, responder-selected trial.

Objectives:

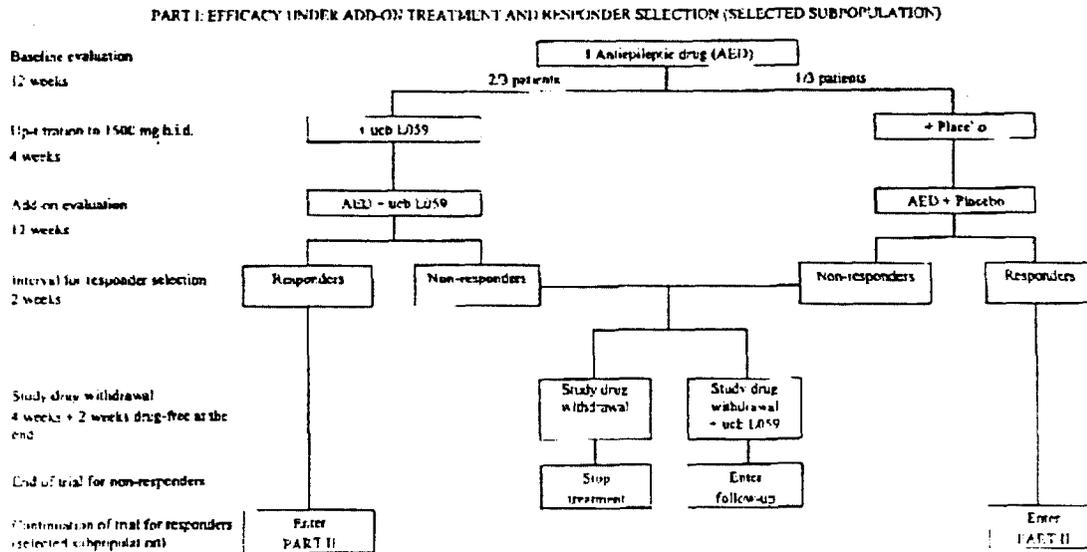
The primary objective was to show that levetiracetam 1500 mg b.i.d is safe and efficacious when administered as monotherapy.

Study Design:

The trial was designed as a multicenter (51 investigators at 51 centers, unbalanced (2 active: 1 placebo), double-blind, placebo-controlled, parallel group, responder selected study (part I: add-on AED trial; part II: monotherapy).

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Figure 3: Study Design



sponsor's Figure 9.1.A, Vol. 234, p 32609

Study Schedule. Part I: Efficacy Under Add-on Treatment

Patients were enrolled at a selection visit followed by a 12-week Baseline Period to verify all inclusion and exclusion criteria. The Double-Blind Phase started with a 4-week Titration Period during which study drug was titrated to the dose required for the 12-week Evaluation Period. On completion of the Evaluation Period patients entered a 2-week Responder Selection Period. During the Responder Selection Period a central evaluator used the seizure profiles to determine which patients fulfilled the criteria to enter the monotherapy part of the study. Patients not fulfilling the criteria as a responder entered an Add-on Withdrawal Period and either stopped study drug treatment or entered an open-label study (N129).

The study drug was taken as add-on therapy to the baseline antiepileptic drug (AED) treatment. Patients were randomized to one of two treatments (1/3 of patients to placebo, 2/3 of patients to 3 g of levetiracetam a day). The responder criteria were defined as:

- Significant reduction in seizure frequency during the 12-week Evaluation Period which corresponded to :
 1. $\geq 50\%$ reduction in total number of partial seizures compared to Baseline, or
 2. $\geq 35\%$ reduction in the total number of partial seizures compared to Baseline provided that the total number of complex partial seizures (including partial seizures secondarily generalized) has been reduced by $\geq 50\%$ compared to baseline, and the total number of partial seizures secondarily generalized has not exceeded the total number during Baseline;
 3. The total number of partial seizures secondarily generalized has not doubled compared to the total number at Baseline;
 4. No partial seizures secondarily generalized or primarily generalized seizures during the Evaluation Period, if absent during Baseline.

Enrollment Criteria

Eligible patients were male or female in-patients or out-patients between 16 and 70 years-old. Women of childbearing potential could only be included if they were surgically sterile, two years postmenopausal, or if of childbearing potential, using an acceptable method of contraception. Patients

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must have clinical observation of partial onset epileptic seizures present at least for 1 year before study entry and be on a stable dosage regimen of a maximum of 1 allowed AED. Patients must have partial onset seizures with at least two complex partial seizures (CPS) (whether or not they were secondarily generalized) per every 4 weeks during the 12 week Baseline Period and at least two CPS during the 4 weeks before the first study visit. Eligible patients must be free of any serious medical conditions and not be taking any medications influencing the central nervous system (e.g. neuroleptics, antidepressants, anxiolytics, stimulants, anticholinergics, tranquilizers, hypnotics, narcotic analgesics, and other compounds with intrinsic central nervous system activity) except for medication taken as epileptic treatment. Patients with partial onset seizures that were uncountable due to clustering (including all forms of convulsive or non-convulsive status epilepticus) during the 12-week Baseline Period and the 5 years preceding inclusion in the study.

Efficacy

Patients maintained a daily record card to record the date, number, duration and description of each seizure. Based on the daily record card the investigator classified and recorded the seizures according to the International League Against Epilepsy criteria.

Seizure clusters were not counted as a separate subtype, but were documented by the investigator as adverse events.

The following types of seizures were categorized in this study:

- partial onset (I)
 - simple partial (IA)
 - complex partial (IB)
 - partial onset and secondarily generalized (IC)
 - simple partial + complex partial (IA + IB)
- primary generalized (II)
- unclassifiable (III)
- all seizure types (I + II + III)

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Study Schedule. Part I: Efficacy Under Add-on Treatment

Primary Efficacy Variable (whole study)

The primary efficacy variable for the whole study was the proportion of patients who completed the monotherapy period compared to the number of patients randomized to Part I (ITT Population).

Primary Efficacy Variable (Part I)

The primary efficacy variable described for this study was the mean number of partial onset seizures per week computed for the Evaluation Period. The weekly mean number of seizures is calculated as follows:

[number of seizures over time period/number of days in time period] * 7

Descriptive and inferential statistical analyses were performed on log-transformed seizure frequency data, using the transformation $Y = \ln(X + 1)$ when the seizure frequency was measured by least squares means and percentage reduction from placebo.

Secondary Efficacy Variables (Part I)

Secondary efficacy variables for this study were:

1. Seizure frequency per week for each seizure subtype;
2. Type IC seizure frequency compared to type I seizure frequency;
3. Responder rate, the proportion of patients experiencing a $\geq 50\%$ reduction in partial onset seizure frequency during the evaluation period compared to the baseline period;

4. Response to treatment, the percentage reduction in partial onset seizure frequency during the evaluation period compared to the baseline period expressed in six improvement classes;
5. Incidence of seizure free patients;
6. Absolute and percent reduction in partial onset seizure frequency from baseline, for each seizure subtype;
7. Quality of life assessments.

7.2.3.2 Protocol Amendments

The protocol was amended on 7/7/95 (amendment I) and 2/12/96 (amendment II) prior to unblinding of the study. The amendments did not substantively alter the protocol and for the most part dealt with minor changes in the collection of laboratory data, treatment withdrawal schedules and reporting of adverse events. Protocol Amendment III (9/21/98) was issued after unblinding and required that only one investigator sign-off on the study report. In addition, country specific amendments were made for Norway, Denmark and Sweden concerning local labeling and drug dispensing requirements.

7.2.3.3 Study Conduct

Patient Populations

The sponsor defined five patient populations:

1. **All Patients:** This population consisted of all patients who entered the study at the selection visit (includes those found ineligible and not randomized).
2. **Intent-To-Treat (ITT) Population:** This population included all randomized patients who were dispensed randomized treatment.
3. **Per-Protocol (PP) Population (Part I: add-on part of study):** This population included all patients of the ITT population who had no major protocol violations.
4. **Selected-Patients:** This population included all patients from the ITT population who were selected at the end of the add-on evaluation period by the central evaluator to enter Part II of the study.
5. **PP population (whole study: add-on and monotherapy):** This population included all patients from the ITT population who had no major protocol violations during Part I and Part II of the study.

Enrollment

A total of 343 patients were screened and 286 were randomized from 47 centers (105 placebo, 181 levetiracetam 3g). A total of 239 (83.6%) patients completed the Evaluation Period through week 14. The table below summarizes overall patient discontinuations. Fifteen (14%) patients were receiving placebo and 32 (18%) were receiving levetiracetam 3g. Of the 47 patients who discontinued, 26 (9%) were discontinued because of adverse events, 7 (2%) withdrew consent, 4 (1%) discontinued for loss or lack of efficacy, and 10 (4%) withdrew for other reasons (Table 31).

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Table 31: Patient Disposition for Premature Termination - Part I

	Placebo	Levetiracetam 3 gram n (%)	Total n (%)
Randomized	105	181	286
Completed Part I	90 (86)	149 (82)	239 (84)
Total Prematurely Discontinued	15 (14)	32 (18)	47 (16)
Reason for Discontinuation			
AE	9 (9)	17 (9)	26 (9)
Lack of Efficacy	1 (1)	3 (2)	4 (1)
Withdrew Consent	1 (1)	6 (2)	7 (2)
Other	4 (4)	6 (3)	10 (4)

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From sponsor's Figure 10.1.B, Vol. 234, p 32661

Demographic and Baseline Characteristics

The mean age for all patients was 36 years (range=17-70). Forty-eight percent (138) were males. All of the patients were Caucasian. The patients were diagnosed with epilepsy for a median of 17 years (range 1-53). Table 32 summarizes patient demographics for all randomized patients by treatment group. The treatment groups were similar with respect to these baseline characteristics.

Table 32: Summary of Patient Demographics and Baseline Characteristics

	Placebo	Levetiracetam 3 g	Overall
N	95	181	286
Gender			
Male	51 (49%)	87 (48%)	138 (48%)
Female	54 (51%)	94 (52%)	148 (52%)
Age (mean) min-max	36 17 - 69	37 17 - 70	36 17 - 70
Race			
Caucasian	105 (100%)	181 (100%)	286 (100%)
Median years with epilepsy min-max	17	17	17

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From sponsor's Table 11.2.1, vol. 234, p 32677

For slightly more than half the patients (56% (160/286) the etiology of epilepsy was unknown and was similar across treatment groups. The most common etiologies when known were head injury (11%), cerebral infection (9%), perinatal events (8%), congenital malformation (6%), and familial epilepsy (4%).

Comparisons of concomitant AEDs used by patients during the titration and evaluation period showed similar usage (Table 33) with the exception of higher valproate usage and lower phenytoin usage among the levetiracetam 3 g group. A total of seven patients recorded intermittent short-term usage of benzodiazepines.

Table 33: Summary of Concomitant Antiepileptic Drug Usage During The Titration and Add-On Evaluation Period

Concomitant AED	Placebo N = 105	Levetiracetam 3 g N = 181	Total N = 286
Carbamazepine	80 (76%)	132 (73%)	212 (74%)
Lamotrigine	10 (10%)	15 (8%)	25 (9%)
Oxcarbazepine	0 (0%)	3 (2%)	3 (1%)
Phenytoin	9 (9%)	8 (4%)	17 (6%)
Valproate	4 (4%)	20 (11%)	24 (8%)
Vigabatrin	2 (2%)	3 (2%)	5 (2%)
Clonazepam	1 (1%)	0 (0%)	1 (0%)
Diazepam	5 (5%)	2 (1%)	7 (2%)

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based on sponsor's Table 11.2.6, Vol.234, p 32671

Baseline Phase Comparability of Weekly Seizure Rates

During the baseline period all patients had partial onset seizures with a median of 1.7 seizures per week. At baseline period 23% (66) patients had simple partial seizures (IA), 97% (277) had complex partial seizures (IB) and 27% (77) of patients had secondarily generalized seizures (IC). There were no patients who had generalized seizures or unclassifiable seizures during the baseline period.

The baseline overall frequency of partial onset seizures was elevated in the placebo group (Table34).

Table 34: Seizure Frequencies During the Baseline Period

Seizure Type	Placebo N = 105	Levetiracetam 3 g N = 181	Total N = 286
Partial Onset (I)			
Mean	5.83	4.49	4.89
Max			
Simple Partial (IA)			
Mean	0.99	1.43	1.23
Max			
Complex Partial (IB)			
Mean	4.73	2.93	3.59
Max			
Secondarily Generalized (IC)			
Mean	0.21	0.13	0.16
Max			

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based on sponsor's Table 11.2.5, Vol. 234 , p 32670
and Table 3.4, Vol.234 pp. 32828 - 32843

Protocol Violations

A total of 110 (38.5%) of the 286 randomized patients had at least one protocol deviation, 30 (10.5%) were considered major protocol violations (Table 35) the protocol violations were generally similar by treatment group with the exception of inadequate compliance, 17% and 8% in the placebo and levetiracetam group, respectively.

Table 35: Protocol Deviations - Part I

Protocol Deviation Category	Placebo N ^a = 105 n ^b = (%)	Levetiracetam 3 g N = 181 n = (%)	Total N = 286 n = (%)
Min required szs not reached at baseline	2 (2)	7 (4)	9 (3)
Instability of AED daily dose	2 (2)	8 (4)	10 (4)
Intake of second concomitant AED	6 (6)	2 (1)	8 (3)
Intake of barbiturates or benzodiazepines	7 (7)	8 (4)	15 (5)
Inadequate compliance	18 (17)	14 (8)	32 (11)
Duration of baseline too short		1 (1)	1 (0)
Instability of study drug dose	6 (6)	10 (6)	16 (6)
Intake of forbidden medication	9 (9)	17 (9)	26 (9)
Placebo patients with plasma values for levetiracetam	3 (3)		
Clusters-status-primarily generalized szs	1 (1)	3 (2)	4 (1)
Selection criteria for randomization not met	6 (6)	12 (7)	18 (6)

based on sponsor's Table 10.2.A, Vol. 234, p 32664

^a number of patients ITT population

^b number of observations

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Patients Who Had the Study Blind Broken

The sponsor did not note any patients who had study blind broken.

7.2.3.4 Sponsor's Efficacy Results

The focus of this review will be on part 1 of the study, which provides clinical trial data to support the claim of adjunctive therapy in partial onset seizures.

The primary efficacy variable for part 1 was the mean number of partial onset seizures per week computed for the Evaluation Period. The data from the 12- week Evaluation Period and 2 week Responder Period were combined for analytic purposes.

Analyses were performed on the following populations:

Intent-to-Treat Population (ITT): This population includes all patients who were randomized to study treatment and took study treatment at least once.

Per-Protocol Population: This population is a subset of the ITT Population who were fully evaluable and have no major protocol violations.

Partial Onset Seizure Frequency Over the Add - On Evaluation Period. LSM Analysis. ITT Population

A covariance analysis was carried out on the log-transformed seizure frequency over the Evaluation Period with the log-transformed seizure frequency over the baseline period as covariate.

Levetiracetam was statistically superior to placebo in lowering partial onset seizure frequency ($p < 0.001$). The percentage reduction in partial onset seizure frequency for levetiracetam over placebo was 22.9% (98% CI: 14.3; 29.4).

Table 36: Partial Onset Seizure Frequency Add-On Evaluation

(ITT Population - Log-Transformed Data)

Placebo N = 105	Levetiracetam N = 181		
LSM ^a (SE)	LSM (SE)	%red ^b (98% CI)	p - val. ^c
1.150 (0.039)	0.899 (0.031)	22.9 (14.3;29.4)	<0.001

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based on sponsor's Table 11.4.1.2.A. Vol. 234, p 32680

^aLSM = least squares mean (Adjusted mean:ANCOVA, with baseline as a covariate and country as a factor)

^bPercentage reduction over placebo = 100 [1- exp (LSM treatment - LSM placebo)]

^c Comparison between placebo and levetiracetam 3 g

Seizure Frequency, by Type, During the Add-On Evaluation Period

Levetiracetam was statistically superior to placebo in lowering partial onset seizure subtypes IB and IA + IB (p < 0.001). The percentage reduction in partial onset seizure frequency for levetiracetam over placebo was 22.9% (98% CI: 14.3; 29.4).

Table 37: Seizure Frequency by Subgroups of Seizure Type Add-On Evaluation

Seizure type	Placebo (N = 105)			Levetiracetam 3 g (N = 181)			%red ^b (95% CI)	p-value ^c
	n	mean ^a (SD)	LSM (SE)	n	mean (SD)	LSM (SE)		
IA	28	0.55 (0.56)	0.656 (0.108)	28	0.78 (1.02)	0.708 (0.084)	-0.053 (-22.0; 32.4)	0.705
IB	99	1.03 (0.93)	0.986 (0.040)	168	0.73 (0.73)	0.750 (0.032)	21.0 (12.8;28.4)	<0.001
IA + IB	100	1.12 (0.93)	1.102 (0.040)	171	0.86 (0.84)	0.864 (0.032)	21.2 (13.1;28.6)	<0.001
I + II + III	102	1.17 (0.91)	1.150 (0.040)	171	0.90 (0.83)	0.901 (0.032)	22.1 (14.1;29.3)	<0.001

based on sponsor's Table 11.4.1.2, Vol. 234, p 32681

^a ln (x+1)

^b percent reduction over placebo = 100* [1-exp (LSM treatment - LSM placebo)]

^c comparison between placebo and levetiracetam 3 g

Type IC Seizure Frequency compared to Type I Seizure Frequency

The ratio of the frequency of type IC seizures over the frequency of type I seizures was determined for the baseline and evaluation period for each patient. Levetiracetam was not statistically superior (p = 0.141) to placebo in increasing the ratio of patients with a reduction of type IC partial onset seizures of 50% or more during the Evaluation Period (Table 38).

Table 38: Type IC Success Rate - Add-On Evaluation

	Placebo (N = 105)	Levetiracetam 3 g (N = 181)
Type IC Success %	16/33 (48.5%)	34/50 (68%)
Odds Ratio (95% CI)		2.02 (0.79;5.17)
p - value ^a		0.141

based on sponsor's Table 11.4.1.2.C, Vol. 234, p 32682

^a Logistic regression with country as a factor

Responder Rate

Seventeen percent of patients in the placebo group and 42% of patients in the levetiracetam group (p = <0.001) had a ≥ 50% reduction in partial onset seizure frequency during the evaluation period compared to the baseline period (Table 39).

Table 39: Responder Rate - Add - On Evaluation

≥50% reduction from baseline ^a	Placebo (N = 105)	Levetiracetam 3 g (N = 181)
n (n%)	17/102 (16.7%)	72/171 (42.1%)
Odds ratio (95% CI)		3.6 (2.0;6.7)
p - value ^b		< 0.001

based on sponsor's Table 11.4.1.2.D, Vol. 234, p 32682

^a reduction in partial onset seizure frequency defined as follows:

sz frequency at baseline - sz frequency at specified period / sz frequency at baseline * 100

^b Logistic regression analysis with country as a factor

Response to Treatment

Continuing to focus on response rates the sponsor has categorized the proportion of patients with a reduction in partial onset seizure from < - 25% (a 25% or greater increase in the percent of seizures in the evaluation period) to 100% (seizure free in the evaluation period).

Sixty-six percent of patients in the placebo group and 39% of patients in the levetiracetam 3 g group had a < 25% reduction to 25% increase in response (Table 40).

Levetiracetam was statistically superior to placebo in increasing the proportion of patients with a reduction of partial onset seizures, p < 0.001.

Table 40: Summary of Partial Onset Seizures Response to Treatment During the Evaluation Period

	Placebo (N = 105)		Levetiracetam 3 g (N = 181)	
	n	(%)	n	(%)
< - 25 %	22	(21.6)	22	(12.9)
- 25 % to < 25 %	45	(44.1)	45	(26.3)
25 % to < 50 %	18	(17.6)	32	(18.7)
50 % to < 75 %	11	(10.8)	32	(18.7)
75 % to < 100 %	5	(4.9)	26	(15.2)
100 % (seizure-free)	1	(1.0)	14	(8.2)
Total	102		171	

based on sponsor's Table 11.4.1.2.E, Vol. 234, p 32683

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