11/01/99

Statistical Review and Evaluation

NDA# 21-035
Sponsor: UCB Pharma, Inc.
Name of Drug: Levetiracetam (1000 to 3000 mg/day- Kepra ™ Tablets 250 mg, 500 mg, and 750 mg)
Indication: Add-on treatment in refractory epileptic patients with partial onset seizures.
Documents Reviewed: Statistical methods for analyzing the primary and secondary efficacy measures and the findings from the analyses.
Studies Reviewed: Three Pivotal studies (Protocols N051, N132, and N138), and one supportive study (Protocol N052).

Introduction:

Results of three double blind, placebo controlled studies (Studies N051, N132, and N138) were submitted to demonstrate the efficacy of levetiracetam as an add-on therapy in a dose range of 1000 mg/day to 3000 mg/day in the treatment of partial onset seizure. One study (Study N051) was a crossover design trial, and the other two studies were parallel group design trials. One study (Study N132) was conducted in the United States, while the other two studies (Studies N051 and N138) were conducted in multiple European centers. In the three studies, a total of 904 patients were randomized to placebo (n=312), levetiracetam 100 mg/day (n=204), 2000 mg/day (n=106), and 3000 mg/day (n=282). Table 1 lists an overview of designs of the three primary placebo controlled epilepsy studies.

Table 1. Overview of Design of the Three Primary Placebo Controlled Epilepsy Studies.

Study No.	Design	Treatment Groups	N	Ethnicity	Mean Age (years) [Range]	Planned Dose and Duration (mg)/(mg/day)
N051[a]	Placebo controlled, crossover, add-on therapy	Placebo (N=112)[†]	55 male 57 female	109 Caucasian 2 black 1 other	37 [16-69]	500, 1000 b.i.d. 2 x 16 weeks
		1000 mg/day (N=106)[†]	51 male 55 female	106 Caucasian	36 [16-68]	
		2000 mg/day (N=106)[†]	51 male 55 female	106 Caucasian	37 [14-65]	
N132[a]	Placebo controlled parallel group, add-on therapy	Placebo (N=95)	50 male 45 female	81 Caucasian 7 black 7 other	38 [20-65]	500, 1500 b.i.d. X 18 weeks
		1000 mg/day (N=98)	62 male 36 female	82 Caucasian 10 black 6 other	38 [16-70]	
		3000 mg/day (N=101)	66 male 35 female	88 Caucasian 9 black 4 other	38 [16-66]	
N138[b]	Placebo controlled, parallel group, add-on study	Placebo (N=105)	51 male 54 female	105 Caucasian	36 [17-69]	1500 b.i.d. X 18 weeks
		3000 mg/day (N=181)	87 male 94 female	181 Caucasian	37 [17-70]	

[a] Patients enrolled in studies N051 and N132 had refractory partial onset seizures for at least 2 years and had taken two or more classical AEDs.
[b] Patients enrolled in study N138 had refractory partial onset seizures with or without secondary generalization and had taken only one concomitant AED
[†] First period (Period A)
Source of Table 1: Table 9, Integrated Summary of Efficacy (Vol 452).

The sponsor also submitted results of another study (Study N052) and considered it as a supportive study. This study was not powered to demonstrate efficacy but was mainly intended to assess safety of high-doses of levetiracetam. Safety and efficacy of two dose levels of levetiracetam (2000 mg/day and 4000 mg/day) were compared with placebo. The primary outcome measure of the supportive study was also different from the primary outcome measures in the three pivotal studies.

Next, the findings of each of the three pivotal studies submitted by the sponsor will be reviewed and the primary and secondary outcome measures of each of the studies will be reanalyzed according to the statistical models specified in the protocols. Subgroup (i.e., by gender) analyses will be done on the primary outcome measures of the three pivotal studies. As the primary outcome measure of the supportive study (Study N052) was different from the primary outcome measures of the pivotal studies, and the study was not powered to demonstrate efficacy, the reported results of the supportive study will be reviewed here only. Finally, the efficacy and safety[1] of the levetiracetam doses will be evaluated by pooling the three pivotal studies' data sets.

Study N051:

Study N051 was a 32-week crossover multi-center trial. Patients with refractory epilepsy experiencing only or predominantly partial onset seizures for at least 2 years, and having taken in the past at least two classical AEDs were included in the study. The other inclusion criteria were (a) male and female patients with age between 16 to 65; (b) women of childbearing potential could only be included if they were using a medically accepted safe method of contraception or if they had been surgically sterilized; (c) absence of major concomitant disorders; and (d) patients had at least four partial onset seizures per each four weeks during the baseline period. During the study period, the randomized patients had to take at least one AED, and could take a maximum of two AEDs [2].

The main objectives of this study were to evaluate the efficacy and safety of two dose levels (1000 mg/day and 2000 mg/day) of levetiracetam in adults with partial onset seizures that were refractory to classical AED drug treatment.

It was a two-period crossover study. Each treatment period was of 12 weeks, with an intervening 4-week transition period. During the consecutive treatment periods (Periods A and B), patients received two out of the three possible treatments. Patients received either (1) placebo and levetiracetam 1000 mg/day; or (2) placebo and

[1] In evaluating safety, the supportive study N052 will be pooled with the three pivotal studies.
[2] The most frequently prescribed AEDs were carbanazepine(234 patients(72%)), phenytoin(72 patients (22%)), and valproic acid derivatives (67 patients (21%)). Phenobarbital or primidone were taken by 33 and 20 patients, respectively (16%). There were 58 patients (18%) who took vigabatrin and 39 patients took lamotrigine (12%). Majority of patients (247 patient, 76.2%) were on regimens that included two AEDs. Sixty patients (18.5%) received one AED in addition to double blind treatment, 14 patients (4.3%) received three AEDs, and 3 patients (0.9%) received more than three AEDs.

levetiracetam 2000 mg/day; or (3) levetiracetam 1000 mg/day and levetiracetam 2000 mg/day. There were six possible treatment sequences.

Three hundred twenty four (324) patients were randomized to the study. There were 112 patients in the placebo group (58 patients randomized to the placebo/levetiracetam 1000 mg/day sequence and 54 patients who were randomized to the placebo/levetiracetam 2000 mg/day sequence), 106 patients in the levetiracetam 1000 mg/day group (53 patients randomized to the levetiracetam 1000 mg/day/placebo sequence and 53 patients randomized to the levetiracetam 1000 mg/day/levetiracetam 2000 mg/day sequence), and 106 patients in the levetiracetam 2000 mg/day group (54 patients randomized to the levetiracetam 2000 mg/day / placebo sequence and 52 patients randomized to the levetiracetam 2000 mg/day / levetiracetam 1000 mg/day sequence).

Two hundred seventy eight (86%) patients completed the evaluation period A. During period A, 18%, 11%, and 13% patients were prematurely terminated from the levetiracetam 2000 mg/day, 1000 mg/day, and placebo groups, respectively. Among the 278 completers in period A, 232 (83%) patients completed evaluation period B. The termination rates during period B were 18%, 14%, and 18% for the levetiracetam 2000 mg/day, 1000 mg/day, and placebo groups, respectively. The reasons for dropout were adverse events (AEs), withdrew consent, and others (includes ineligibility, protocol violation, lack of efficacy, decision of UCB Pharma, Inc.). Table 1.1 lists the percentages of dropouts by reasons.

Table 1.1: Reason for dropout during Evaluation period A and period B (ITT Population)

	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day
Period A	N=112	N=106	N=106
Completers	97 (86.6%)	94 (88.7%)	87 (82.1%)
Dropouts	15 (13.4%)	12 (11.3%)	19 (17.9%)
Reasons for Dropout			
AE	6 (5.4%)	8 (7.5%)	15 (14.2%)
Withdrew consent	5 (4.5%)	2 (1.9%)	3 (2.8%)
Other [a]	4 (3.6%)	2 (1.9%)	1 (0.9%)
Period B	N=88	N=94	N=96
Completers	72 (81.8%)	81(86.2%)	79 (82.3%)
Dropouts	16 (18.2%)	13 (13.8%)	17 (17.7%)
Reasons for Dropout			
AE	10 (11.4%)	6 (6.4%)	11 (11.5%)
Withdrew consent	2 (2.3%)	2 (2.1%)	3 (3.1%)
Other [a]	4 (4.6%)	5 (5.3%)	3 (3.1%)

[a] includes ineligibility, protocol violation, lack of efficacy, decision of UCB

The intent-to-treat [3] (ITT) sample consisted of the 324 patients randomized in period A. Data from 204 patients were used for per-protocol [4](PP) analyses and data from

[3] This sample included all patients who were randomized to study treatment and had taken at least one dose of study medication.

[4] This sample consisted of patients from the ITT population who had no major protocol violation during the

265 patients were used for the Inferential ITT[5] sample in the crossover analysis. No interim analysis was planned and performed.

Patients (or their caretakers) recorded their seizures in personal diaries. The investigators classified the recorded seizures according to the International League Against Epilepsy (ILAE) criteria. For each seizure type, the total number of seizures that occurred since the previous study visit was recorded as seizure count.

Per protocol, the primary efficacy parameter was the mean number of partial onset seizure frequency per week over the evaluation periods A and B. The secondary efficacy parameters were: (1) the absolute and percent reduction in weekly partial onset seizure frequency from baseline, (2) the seizure frequency by seizure subtypes, (3) the responder rate, (4) the categorical response to treatment, (5) the incidence of seizure-free patients, and (6) the ESI-55 as a measure of QOL.

The primary efficacy variable (i.e., logarithm-transformed of mean number of partial onset seizure frequency per week during the evaluation periods A and B) was analyzed using analysis of variance (ANOVA) for the crossover data. For the evaluation period A data, the primary efficacy variable (i.e., logarithm-transformed of mean number of partial onset seizure frequency per week during the evaluation period A) was analyzed using analysis of covariance (ANCOVA). The mean number (in logarithm-transformed) of partial onset seizure frequency per week during the baseline period was included in the model as a covariate. The analyses used least-square mean (LSMs) logarithm-transformed[6] data in calculating the percent reduction over placebo. The primary analyses were performed on the ITT sample. The analyses were also done on the PP sample.

The secondary efficacy outcome measures (the responder rate, response to treatment, and number of seizure-free patients) were analyzed using logistic regression with estimation of odds ratio. For subgroup analyses on the subtypes of seizures and the quality of life (QOL) assessments, the same methods as for the primary efficacy variable were applied. A Bonferroni procedure was used to adjust for multiple comparisons; each of the three pairwise comparisons between treatments was carried out at $\alpha = 0.02$ ($\approx \alpha / 3$). The analyses of the secondary measures were also performed on the ITT sample.

Sponsor's Results:

There were 48.5% males among the 324 randomized patients. All (except 3 patients) were Caucasians. The mean age of the patients was 37 (range from 14-69 years) years. The three treatment groups were comparable at baseline with respect to their demographic characteristics.

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baseline period or period A.

[5] This sample included all patients from the ITT population who had efficacy data for the relevant treatment periods.

[6] 100 X [1- Exp(LSM Treatment –LSM Placebo)]

The mean duration of epilepsy for the 324 patients was 23.6 years, and the mean age of epilepsy onset was 13.7 years. The etiology of epilepsy was unknown for about 56.5% patients. About 10.5% patients had a history of status epilepticus and 7.4% had a history of withdrawal seizures. The three treatment groups were comparable with respect to the epilepsy histories at baseline.

At baseline period (8 to 12 weeks), all patients had partial onset seizures, with a median of 2.62 seizures per week (range 0.3 to 102.7); 55% of the patients had <=3 seizures per week; 30% patients had from 3 to 9 seizures per week; and 15% patients had >9 seizures per week. Complex partial seizures were the most common (present in 270 patients or 83.3%). The median seizure frequencies at baseline period were comparable among the three treatment groups.

The statistical analyses of the primary efficacy measures during the evaluation periods A and B (considering as a two-period crossover design), as well as during the evaluation period A alone (considering as an independent parallel group design) demonstrated a statistically significantly lower partial onset seizure frequencies for the levetiracetam groups, as compared to the placebo group. The estimated least square means (LSMs) for the levetiracetam groups were statistically significant (p<.006), as compared to the estimated mean for the placebo group. However, there was no statistical significant difference between the levetiracetam dose groups. Percent reductions of partial onset seizure frequency per week for the levetiracetam 1000 mg/day and 2000 mg/day groups over the placebo group (calculation based on the LSMs) were 16.4% and 17.7% in period A, and 16.9% and 18.5% in period A+B. Table 1.2 lists all of the results including the p-values.

Statistically significantly lower partial onset seizure frequencies were also seen in the levetiracetam groups, as compared to the placebo group in the analyses based on the PP sample (results are not shown here).

Percent reductions in partial onset seizure frequency from baseline (median) during the evaluation periods A and B together were greater in the levetiracetam 1000mg /day (22.9%) and levetiracetam 2000 mg/day (23.9%) groups, as compared to the placebo (7%) group. During the evaluation period A alone, the percent reductions were also greater for the levetiracetam groups, as compared to the placebo group. The percentages were 17.7%, 26.5%, and 6.1% for the levetiracetam 1000, 2000 mg/day, and placebo groups, respectively.

The levetiracetam groups had statistically significantly (p<=.019) more responders (i.e., >=50% reduction from baseline), as compared to the placebo group. Furthermore, the responder rate in the levetiracetam 2000 mg/day group was statistically significantly greater, as compared to the rate in the levetiracetam 1000 mg/day group (p=0.018, not shown in Table 1.2). During the evaluation period A and B together, the odds of obtaining a reduction in partial onset seizure frequency of at least 50% in the levetiracetam 1000 mg/day and 2000 mg/day groups over the placebo group were 5.6 and

12.1, respectively. The corresponding odds ratios during the evaluation period A were 2.6 and 4.0. The summarized results including the p-values are listed in Table 1.2.

Table 1.2: Summary of Partial Onset Seizure Frequency Data (ITT Population) -logarithmic transform analysis

Weekly seizure Frequency	Placebo (N=112)	Levetiracetam 1000 mg/day (N=106)	Levetiracetam 2000 mg/day (N=106)
Baseline			
N	112	106	106
Mean [b] (S.D)	1.44 (0.79)	1.49 (0.73)	1.56 (0.86)
Median	1.25	1.34	1.28
Range			
Period A + B			
N	172	183	175
Mean [b] (S.D)	1.37 (0.80)	1.24 (0.90)	1.22 (0.92)
Median [b]	1.17	1.07	1.04
LSM [c] (S.E)	1.41 (0.025)	1.22 (0.024)	1.20 (0.025)
% reduction over placebo [d]	--	16.9%	18.5%
(98% CI)		(9.6, 23.6)	(11.2, 25.2)
p-value (Versus placebo)	--	<.001	<.001
% reduction in seizure frequency from baseline (median)	7.0	22.9	23.9
>=50% reduction from baseline (%)	12.2%	26.2%	34.3%
odds ratio (98% CI)		5.6 (1.4, 22.5)	12.1 (2.0, 74.3)
p-value (Versus placebo)		.004	.001
Period A only			
N	106	101	95
Mean [b] (S.D)	1.40 (0.81)	1.28 (0.88)	1.31 (0.91)
Median [b]	1.28	1.10	1.05
LSM [c] (S.E)	1.45 (0.045)	1.27 (0.046)	1.25 (0.048)
% reduction over placebo [d]		16.4%	17.7%
(98% CI)	--	(2.7, 28.1)	(4.1, 29.4)
p-value (Versus placebo)	--	0.006	0.003
% reduction in seizure frequency from baseline (median)	6.1	17.7	26.5
>=50% reduction from baseline (%)	10.4%	22.8%	31.6%
odds ratio (98% CI)		2.6 (1.0,6.4)	4.0 (1.6, 9.8)
p-value (Versus placebo)		.019	<.001

Source of Table 2: Tables 19 & 20 of Integrated Summary of Efficacy (Vol 452) and table 8.2.2.1 (Vol. 622).

[a] Seizure frequency=7 X Total number of Seizures during Evaluation Period/ Number of Days during the Evaluation Period.

[b] Ln (X+1)

[c] Least square mean derived from analysis of variance for crossover design (evaluation periods A and B together) or analysis of covariance for (for evaluation period A) on ln(X+1)

[d] 100 X [1-Exp(LSM Treatment -LSM Placebo)]

The percent reductions in the seizure frequency from baseline by seizure subtypes were greater in the levetiracetam groups than the percent reduction in the placebo group. The LMS analyses by subtype also demonstrated statistically significantly lower seizure frequency during treatment period for the levetiracetam 1000 mg/day and 2000 mg/day groups, as compared to placebo group ($p<0.001$). The results obtained from the analyses of all seizure frequencies (Type I+II+III) were nearly identical to the results obtained from the analyses of partial onset seizure frequencies (Type I: Partial onset seizure). It was due to the occurrence of only a small fraction of seizures that were not partial onset seizures.

Table 1.3: Percentages of patients experienced Treatment-Emergent AE / SAE (ITT Population)

	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day
Period A	N=112	N=106	N=106
Treatment-Emergent AE	82 (73.2%)	75 (70.8%)	80 (75.5%)
Treatment-Related AE	40 (35.7%)	42 (39.6%)	50 (47.2%)
Treatment-Emergent SAE	10 (8.9%)	11 (10.4%)	17 (16.0%)
Treatment-Related SAE	3 (2.7%)	2 (1.9%)	8 (7.5%)
Period B	N=88	N=94	N=96
Treatment-Emergent AE	62 (70.5%)	60 (63.8%)	72 (75.0%)
Treatment-Related AE	31 (35.2%)	33 (35.1%)	41 (42.7%)
Treatment-Emergent SAE	13 (14.8%)	12 (12.8%)	8 (8.3%)
Treatment-Related SAE	2 (2.3%)	3 (3.2%)	4 (4.2%)

Source: Vol621 Table 12.2.1

No changes in quality of life scores were seen in the levetiracetam groups, as compared to the placebo group. The incidences of treatment-emergent adverse events were comparable between the levetiracetam and placebo groups. Table 1.3 displays the percentages of patients experienced treatment-emergent AE/SAE. Two patients died (belonging to levetiracetam 1000 mg/day group) during the study. The investigators reported that the deaths were due to car accidents, and not related with drug medication.

Reviewer's Analyses:

The primary efficacy measures, mean number of partial onset seizure frequency per week during the evaluation periods A and B were recalculated by this reviewer according to the formula given in the protocol and the values were matched with the sponsor's calculated values. The ANCOVA model for analyzing the period A data and ANOVA model for analyzing the periods A and B data, as mentioned in the protocol, were fitted. The analyses were based on the ITT sample. For Period A (i.e., considering as a parallel group design) data, the two levetiracetam dose groups were statistically significantly ($p<0.006$) different from the placebo group in reducing the mean number of partial onset seizure frequency at evaluation period from baseline. No statistically significant differences between the levetiracetam groups were detected.

Similarly, for the periods A and B (i.e., considering as a crossover design) data, the two treatment groups were statistically significantly ($p<0.0001$) different from the placebo group in reducing the mean number of partial onset seizure frequency at evaluation period from baseline. The two treatment groups were not found statistically significantly different from each other. The treatment sequence was not statistically significant.

All of the statistics reported in Table 1.2 for the primary and secondary outcome measures were recalculated from the ITT sample and found to be consistent with the sponsor's calculations.

The sponsor calculated the mean number of partial onset seizure frequency per week during the evaluation periods based on the information collected at visits 6,7, and 8 for period A, and the information collected at visits 10, 11, and 12 for period B. The

titration periods of the sequences A and B (i.e. during the periods [visit 5 & 9], the patients were on the target dose of levetiracetam) seem to be clinically important to consider as parts of evaluation periods. FDA (letter dated April 26, 1995) also suggested the sponsor to do so, but the sponsor did not consider the titration period as a part of evaluation period. This reviewer recalculated mean number of partial onset seizure frequency per week based on the information at visits 5,6,7 and 8 for evaluation period A and visits 9, 10, 11, and 12 for evaluation period B. The ANCOVA model for analyzing the period A data and ANOVA mode for analyzing the periods A and B data, as mentioned in the protocol, were fitted. The conclusions remained same (although p-values were changed) to the conclusions obtained in the sponsor's analyses. The results are not reported here.

Subgroup Analysis:

Table 1.4 lists the summary statistics of the primary efficacy measure, mean number (in logarithm transformed) of partial onset seizure frequency per week, by gender and treatment groups. The subgroup analyses (least square means from ANOVA/ANCOVA models) indicated that the levetiracetam doses were effective in reducing the partial onset of seizure frequencies for both the male and female patients. The percent reductions in seizure frequency due to treatment were also similar between the male and female patients. This was true for both period A and Period A+B data. Since all (except 3 patients) were Caucasians, no subgroup analysis had been done with respect to ethnicity.

Table 1.4 Summary of Partial Onset Seizure Frequency Data by Gender (ITT Population) -logarithmic transform analysis

Weekly seizure Frequency	Female			Male		
Baseline	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day
N	57	55	55	55	51	51
Mean [b] (S.D)	1.36 (.72)	1.59 (.74)	1.52 (.77)	1.52 (.85)	1.38 (.70)	1.59 (.94)
Median	1.17	1.39	1.31	1.28	1.22	1.25
Range						
Period A only						
N	53	53	48	53	48	47
Mean [b] (S.D)	1.33 (.73)	1.45 (.94)	1.24 (.82)	1.46 (.87)	1.09 (.76)	1.37 (.99)
Median [b]	1.23	1.22	1.04	1.27	97	1.04
Range						
LSM [c]	**1.39**	**1.32**	**1.21**	**1.50**	**1.27**	**1.28**
% reduction over placebo [d]	**–**	**7.04**	**17.14**	**–**	**20.46**	**19.74**
% reduction in seizure frequency from baseline (median)	9.84	9.74	22.99	2.85	24.35	27.47
>=50% reduction from baseline (%)	13.2	15.1	29.2	7.5	31.3	34.0
Period A + B						
N	84	87	91	88	96	84
Mean [b] (S.D)	1.31 (.70)	1.31 (.87)	1.25 (.90)	1.41 (.87)	1.17 (.92)	1.18 (.94)
Median [b]	1.14	1.17	1.06	1.24	92	96
Range						
LSM [c]	**1.43**	**1.24**	**1.22**	**1.39**	**1.21**	**1.19**
% reduction over placebo [d]	**–**	**16.72**	**18.77**	**–**	**16.80**	**18.20**
% reduction in seizure frequency from baseline (median)	9.30	20.0	20.83	1.98	28.12	27.69
>=50% reduction from baseline (%)	13.1	20.7	34.1	11.4	31.3	34.5

[b] Ln (X+1)

[c] Least square mean derived from analysis of variance for crossover design (evaluation periods A and B together) or analysis of covariance for (for evaluation period A) on ln(X+1)

[d] 100 X [1-Exp(LSM Treatment –LSM Placebo)]

Study N132:

Study N132 was designed as a multicenter, randomized, add-on, double-blind, parallel group, 38-week study (12-weeks baseline, 6-week titration, 12-week evaluation, and 8-week withdrawal). Patients who had experienced uncontrolled simple and/or complex partial seizures with or without secondary generalization for at least 2 years prior to entry and who had been exposed to at least two classical AEDs, either simultaneously or consecutively, were included in the study. The other inclusion criteria were (a) male and female patients with age between 16 to 70; (b) women of childbearing potential could only be included if they were nonchildbearing potential; and (c) patients whose daily intake of AEDs remained unchanged for at least the 4 weeks prior to the selection visit and during the 12-week baseline period.

The main objectives of this study were to evaluate the efficacy and tolerability of two dose levels (1000 and 3000 mg/day) of levetiracetam in adults with partial onset seizures that were refractory to classical AED drug treatment.

Two hundred ninety four (294) patients were randomized to three treatment groups, 98 patients to levetiracetam 1000 mg/day, 101 patients to levetiracetam 3000 mg/day, and 95 patients to placebo. During the study period, the randomized patients had to take at least one AED, and could take a maximum of two AEDs [7].

Two hundred sixty eight (91%) patients completed the evaluation period. There were 6.31%, 12.24%, and 7.92% patients were prematurely terminated from the placebo, levetiracetam 1000 mg/day, and 3000 mg/day groups, respectively. The main reasons for termination were adverse events (AEs). Table 2.1 lists the percentages of dropouts from the study by reasons. The percentages of dropouts by reasons were comparable among the three treatment groups.

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Table 2.1: Reason for dropout during Evaluation period (ITT Population)

	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 3000 mg/day
	N=95	N=98	N=101
Completers	89 (93.7%)	86 (87.8%)	93 (92.1%)
Dropouts	6 (6.3%)	12 (12.2%)	8 (7.9%)
Reasons for Dropout			
AE	5 (5.3%)	6 (6.1%)	7 (6.9%)
Withdrew consent	1 (1.1%)	2 (2.0%)	1 (1.0%)
Other [a]	0 (0.0%)	4 (4.1%)	0 (0.0%)

[a] includes ineligibility, protocol violation, lack of efficacy, decision of UCB
Source of table: Vol 587, table 1.4

[7] The most frequently prescribed AEDs were carbanazepine(234 patients(72%)), phenytoin(72 patients (22%)), and valproic acid derivatives (67 patients (21%)). Phenobarbital or primidone were taken by 33 and 20 patients, respectively (16%). There were 58 patients (18%) who took vigabatrin and 39 patients took lamotrigine (12%). Majority of patients (247 patient, 76.2%) were on regimens that included two AEDs. Sixty patients (18.5%) received one AED in addition to double blind treatment, 14 patients (4.3%) received three AEDs, and 3 patients (0.9%) received more than three AEDs.

The intent-to-treat [8](ITT) sample included 294 patients and Per-Protocol[9] (PP) sample included 243 patients.

Per protocol, the primary efficacy variable was defined as the mean number of partial onset seizure frequency per week over the evaluation period.

The secondary efficacy parameters were (1) seizure frequency measures [10], (2) the mean number of seizures according to the seizure type [11], (3) the responder rate[12], (4) the categorical treatment response[13], (5) the incidence of seizure-free patients, and (6) the QOLLIE-31 as QOL assessment.

The primary analyses were done on the ITT sample. No interim analysis was planned and performed.

The primary efficacy variable (in logarithm transformed) was analyzed using ANCOVA with the baseline mean number (in logarithm transformed) of partial onset seizure frequency per week as a covariate. The analyses used least square means (LSMs) log-transformed data and an estimation of the percent reduction over placebo by back transformation of the LSMs data. Bonferroni adjustment (Hochberg procedure) was used for multiple comparisons.

A logistic regression model was used to analyze the responder rates. The Cochran-Mantel-Haenzel (CMH) test was used for the categorical response to treatment. All of the above analyses were performed on the ITT and PP patient samples.

Sponsor's Results:

Among the 294 randomized patients, 60.5% patients were males; 85.4% patients were Caucasians, 8.8% were Blacks, and the remaining 5.8% were Asians/other. Baseline demographic characteristics were comparable among the three treatment groups. The three treatment groups were also balanced with respect to patients' medical history and concurrent disorders. All patients were receiving AEDs [14].

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[8] This sample included all randomized patients who were dispensed randomized treatment, regardless of whether actual dosing could be confirmed.

[9] This sample included those who were not excluded from the study due to major protocol violations.

[10] The absolute and percentage change in the mean number of partial onset seizures during the evaluation period, as compared to the baseline period, and the mean number of partial onset seizures per week by study visit.

[11] Simple partial, complex partial, partial secondary generalized, simple+complex partial, and generalized.

[12] The incidence of patients with >=50% reduction from baseline in the frequency of partial onset seizures.

[13] The percent reduction in partial onset seizure frequency based on six categories (<-25%, -25% to 24.9%, 25 to 49.9%, 50 to 74.9%, 75 to 99.9%, and 100% or seizure free) of response.

[14] The most commonly used AEDs were carbanazepine, phenytoin, gabapentin, and valproic acid.

At baseline, the patients experienced a median of 2.13 partial seizures per week. The most common seizure type was complex partial experienced by 280 patients out of the 294 randomized patients.

There was a statistically significantly (ANCOVA, $p<0.001$) lower mean partial onset seizure frequency per week during the evaluation period in the levetiracetam-treated groups, as compared to the placebo group. There was no statistically significantly difference between the levetiracetam 1000 mg/day and 3000 mg/day groups. The LSM percent reductions over placebo were 20.9% and 27.7% for the levetiracetam 1000 and 3000 mg/day groups, respectively. The median percent reductions in partial onset seizure frequency from baseline were 32.5%, and 37.1% for the levetiracetam 1000 mg/day and 3000 mg/day groups, respectively, and were higher as compared to the percent reduction (6.8%) for the placebo group. The proportions of patients who were responders (defined as >=50% reduction in partial seizure frequency from baseline) also were higher in the levetiracetam-treated groups (33.0% and 39.8% for levetiracetam 1000 mg/day and 3000 mg/day groups, respectively), as compared to the placebo-treated group (10.8%). All of these differences were statistically significantly ($p<0.001$) different from zero. The above results were obtained from the ITT sample and summarized in Table 2.2.

Table 2.2: Partial Onset Seizure Frequency and Responder Rate (ITT population)- logarithmic transform analysis

	Placebo (N=95)	Levetiracetam 1000 mg/day (N=98)	Levetiracetam 3000 mg/day (N=101)
Baseline			
N	95	98	101
Mean [a] (S.D.)	1.26 (0.70)	1.56 (0.85)	1.38 (0.75)
Median	1.77	2.53	2.08
Range			
Evaluation Period			
N	93	94	98
Mean [a] (S.D.)	1.23(0.75)	1.28 (0.89)	1.03 (0.86)
Median	1.73	1.77	1.29
Range			
LSM [b]	1.366	1.131	1.041
% reduction over placebo [c]		20.9%	27.7%
(98% CI)		(6.8, 32.9)	(15.1, 38.5)
p-value (Versus placebo)		<0.001	<0.001
% reduction in seizure frequency from baseline (median)	6.8	32.5	37.1
>=50% reduction from baseline (%)	10.8%	33.0%	39.8%
odds ratio (98% CI)		4.08 (1.7, 10.6)	5.49 (2.4, 14.1)
p-value (Versus placebo)		<0.001	<0.001

Source of table 3: Table 23 in integrated summary of efficacy (Vol 452)
[a] x=7 X Total number of Seizures during Evaluation Period/ Number of Days during the Evaluation Period.
[b] ln (X+1)
[c] 100 X [1-Exp(LSM Treatment –LSM Placebo)]

The analyses based on the PP sample also yielded similar results with a statistically significantly fewer partial onset seizure frequency per week and higher incidence of responders in the levetiracetam groups, as compared to the placebo group.

Mean reductions in the seizure frequency for all categories of seizures[15] were seen for the levetiracetam groups, as compared to the placebo group. The absolute change in

[15] Simple partial (Type IA), complex partial (Type IB), partial secondary generalized

the median frequency from baseline of seizure Types IA, IB, and IC showed greater reductions for both levetiracetam groups, as compared to the placebo group. The difference (for levetiracetam 3000 mg/day vs. placebo group) for seizure Type IB was statistically significant ($p<0.018$,), but it was not statistically significant for seizure Types IA and IC. The absolute reduction in mean seizure frequency for seizure Type IA+IB showed statistically significant ($p<0.018$) in the levetiracetam groups, as compared to the placebo group.

Mean changes from baseline in the subscales of the quality-of-life in epilepsy (QOLIE-31) were small. The levetiracetam 3000 mg/day group showed a statistically significant improvements in the overall QOL score ($p=0.03$) from the baseline score. Both of the levetiracetam treated groups showed statistically significant ($p<0.001$) improvements in seizure worry, as compared to the placebo group.

Table 2.3 lists the percentages of patients experienced treatment-emergent AE/SAE. There was a total of 20 treatment-emergent Serious Adverse Events (SAEs) reported in this study. One patient died before randomization and another patient died from the placebo group during the study period.

Table 2.3: Percentages of patients experienced Treatment-Emergent AE / SAE (ITT Population)

	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 3000 mg/day
	N=95	N=98	N=101
Treatment-Emergent AE	84 (88.4%)	87 (88.8%)	90 (89.1%)
Treatment-Related AE	47 (49.5%)	50 (51.0%)	59 (58.4%)
Treatment-Emergent SAE	11[a] (11.5%)	7 (7.1%)	2 (2.0%)
Treatment-Related SAE	1 (1.1%)	2 (2.0%)	0 (0.0%)

Source: Vol587. table 12.2.1
[a] including one death

Reviewer's Analyses:

The primary efficacy measure, the mean number of partial onset seizure frequency per week over the evaluation period was recalculated according to the formula stated in the study protocol and the values were matched with the sponsor's calculated values. The ANCOVA model for analyzing the data, as mentioned in the protocol, was fitted. This reviewer's analyses were based on the ITT sample. The two levetiracetam dose group were statistically significantly ($p<0.001$) different from the placebo group in reducing partial onset seizure frequency from baseline. No significant difference between the levetiracetam doses was detected.

All of the statistics reported in Table 2.2 for the primary and secondary outcome measures were recalculated from the ITT sample and found to be consistent with the sponsor's calculations.

The sponsor calculated the mean number of partial onset seizure frequency per week during the evaluation period based on the information collected at visits 7,8,9, and

(Type IC), and simple+complex partial(Type IA+IB).

10. This reviewer recalculated the mean number of partial onset seizure frequency per week during the evaluation period (including titration period) based on the information collected at visits 6, 7, 8, 9, and 10. The ANCOVA model, as mentioned in the protocol, was fitted. The conclusions remained same (although p-values were changed) to the conclusions obtained in the sponsor's analyses. The results are not reported here.

Subgroup Analysis:

Table 2.4 lists the summary statistics of the primary efficacy measure, the mean number (in logarithm transformed) of partial onset seizure frequency per week, by gender and treatment groups. The subgroup analyses (least square means from ANCOVA model) indicated that the levetiracetam doses were effective in reducing the partial onset of seizure frequencies for both the male and female patients. The percent reductions in seizure frequency due to treatment were also similar between the male and female patients. Since there were more than 85% Caucasians in the sample, no subgroup analysis had been done with respect to ethnicity.

Table 2.4: Summary of Partial Onset Seizure Frequency Data by Gender (ITT Population) -logarithmic transform analysis

Weekly seizure Frequency	Female			Male		
Baseline	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 3000 mg/day	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 3000 mg/day
N	45	36	35	50	62	66
Mean[a] (S.D)	1.27 (.80)	1.35 (.57)	1.36 (.78)	1.24 (.60)	1.68 (.97)	1.39 (.73)
Median	1.05	1.30	1.11	1.01	1.21	1.14
Range	[redacted]					
Evaluation Period						
N	44	34	34	49	60	64
Mean[a] (S.D)	1.26 (.85)	1.16 (.71)	1.01 (.89)	1.19 (.64)	1.34 (.97)	1.04 (.84)
Median[a]	1.00	97	80	1.00	1.05	87
Range	[redacted]					
LSM	1.32	1.12	0.96	1.37	1.09	1.12
% reduction over placebo[b]	--	17.79	29.74	--	24.27	21.88
% reduction in seizure frequency from baseline (median)	6.76	33.24	41.21	20.15	31.15	35.94
>=50% reduction from baseline (%)	6.8	32.4	40.60	14.3	33.3	38.20

[a] Ln(X+1)
[b] 100 X [1-Exp(LSM Treatment -LSM Placebo)]

Study N0138:

Study N138 was designed as a 60-week multicenter, randomized, double-blinded, parallel group, placebo controlled, two-part (add-on therapy and monotherapy) study that evaluated the efficacy and safety of levetiracetam 3000 mg/day in treating the adult patients with complex partial seizures. The epileptic patients who had experienced uncontrolled partial onset seizures, and were using one standard AED at optimal dose were eligible for this study. The other inclusion criteria were (a) male and female patients with age between 16 to 70; (b) women of childbearing potential could only be included if they were nonchildbearing potential; and (c) patients had at least two complex partial seizures (whether or not they were secondarily generalized) per every 4 weeks during the

12-week baseline. The selected patients had to be taking one standard AED at stable, optimal dose for at least 4 weeks preceding study entry.

Study N138 consisted of two parts. In part I, the patients were followed for 30 weeks (12 weeks baseline, 4 weeks up-titration, 12 weeks add-on evaluation, and 2 weeks responder selection). In this part, a parallel group comparison of levetiracetam 3000 mg/day versus placebo (in a 2:1 randomization) was done for the efficacy assessment. At the end of this part, the patients were grouped into responders[16] or non-responders.

The responded patients in part I were enrolled in part II and followed for 30 weeks maximum [12 weeks (maximum) therapy shift, 12 weeks monotherapy, and 6 weeks for drug withdrawal]. The efficacy of levetiracetam 3000 mg/day was assessed during their 12-week monotherapy period.

The sponsor submitted this NDA to demonstrate the efficacy of levetiracetam as an add-on therapy in treating the patients with partial onset seizures with or without secondary generalization. To accomplish the main objectives of this NDA, the add-on part (i.e., part 1) of the study N138 will be reviewed and reanalyzed here.

Table 3.1. Reason for dropout during add-on therapy Evaluation period (ITT Population)

	Placebo	Levetiracetam 3000 mg/day
	N=105	N=181
Completers	90 (85.7%)	149 (82.3%)
Dropouts	15 (14.3%)	32 (17.7%)
Reasons for Dropout		
AE	9 (8.6%)	17 (9.4%)
Withdrew consent	1 (1.0%)	6 (3.3%)
Other [a]	5 (4.9%)	9 (5.0%)

[a] includes ineligibility, protocol violation, lack of efficacy

Source of table: Vol 666, table 1.2

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A total of 286 patients (105 patients in the placebo group and 181 patients in the levetiracetam 3000 mg/day group) were randomized to receive double-blinded treatment. Among the 286 randomized patients, 239 (83.6%) completed the add-on part of the study (90 patients in the placebo group and 149 patients in the levetiracetam 3000 mg/day group). Forty-seven (16.4%) patients discontinued the add-on part of the study (15 patients in the placebo group and 32 patients in levetiracetam 3000 mg/day group). Table 3.1 lists the percentages of dropouts by reasons.

Per protocol, the primary efficacy variable was defined as the partial onset seizure frequency per week during the evaluation period of part I.

The secondary efficacy variables were a) seizure frequency of other seizure types, subtypes, and combinations, b) type 1C seizure frequency compared to type I seizure

[16] The responder was defined as the proportion of ITT patients who had a reduction in type I seizure frequency of at least 50% during the add-on evaluation period compared to baseline period.

frequency, c) responder rate and response to treatment[17], d) number of seizure-free patients, e) seizure severity scale (NHS3), f) Visual analogue scale, and g) global clinical evaluation.

The efficacy analyses (i.e., primary analyses) were conducted on the ITT sample. Analyses based on PP[18] sample were also conducted for the primary and secondary efficacy variables. No interim analysis was planned and performed.

The primary efficacy variable (in logarithm transformed) was analyzed using ANCOVA with the baseline mean number (in logarithm transformed) of partial onset seizure frequency per week as a covariate. The analyses used least square means (LSMs) log-transformed data and an estimation of the percent reduction over placebo by back transformation of the LSMs data. The secondary efficacy variables were analyzed using parametric and nonparametric procedures (including ANOVA, logistic regression, Wilcoxon rank-sum test, etc.), as appropriate.

Sponsor's Results:

There were 48.3% males among the 286 randomized patients. All patients were Caucasians. The mean age of the patients was 36, ranging from 17 to 70 years. The two groups were comparable with respect to their demographic characteristics.

The overall mean duration of epilepsy for the 286 patients was 19 years, and the mean age of epilepsy onset was 18 years. The etiology of epilepsy was unknown for about 55.9% patients. About 1.0% patients had a history of status epilepticus and 1.4% had a history of withdrawal seizures. Patients had been exposed to approximately four AEDs prior to this study. The two treatment groups were comparable at baseline with respect to their epilepsy histories and use of antiepileptic medications.

At baseline period (12 weeks), all patients had partial seizures, with a median of 1.7 seizures per week (range 0.13 to 170); 23.1% patients had simple partial seizures, 96.9% patients had complex partial seizures, and 26.6% patients had secondarily generalized seizures. The median seizure frequencies and the proportion of seizure types at baseline were also comparable between the two treatment groups.

The protocol allowed a maximum of only one concomitant AED during the up-titration and add-on evaluation periods. Patients took the following classic AEDs during the study period: carbamazepine (74%); lamotrigine (9%); valproate (8%); phenytoin (6%); vigabatrin (2%); and oxcarbazepine (1%). The percentages by treatment groups were comparable.

[17] Response to treatment was defined as a decrease in the partial seizure frequency during the evaluation period compared to the baseline period.

[18] Consisted of patients from the ITT sample who were fully evaluable and who reported no major protocol deviations during the study.

The statistical analyses (based on ITT sample) on the primary efficacy variable, the logarithm-transformed of mean number of partial onset seizure frequency per week during the part I evaluation period demonstrated statistically significantly greater reduction in partial onset seizure frequency from baseline for the levetiracetam group, as compared to the reduction for the placebo group ($p<0.001$). The LSM percent reduction in partial onset seizure frequency in the levetiracetam group over the placebo group was 22.2%. Statistically significantly greater median percent reduction in seizure frequency from baseline was also found in the levetiracetam group (39.9%), as compared to the placebo group (7.2%). Table 3.2 lists all of the results including the p-values.

Table 3.2: Partial Onset Seizure Frequency and Responder Rate (ITT population)-logarithmic transform analysis

	Placebo (N=105)	Levetiracetam 3000 mg/day (N=181)
Baseline		
N	102	171
Mean [b] (S.D.)	1.24 (0.86)	1.18 (0.77)
Median [b]	1.01	0.99
Range [b]	[redacted]	
Add-on Evaluation Period		
N	102	171
Mean [b] (S.D.)	1.17 (0.91)	0.90 (0.83)
Median [b]	1.01	0.72
Range [b]	[redacted]	
LSM [c]	1.15	0.899
% reduction over placebo [c]	--	22.2
(95% CI)		14.3, 29.4
p-value (Versus placebo)		<0.001
% reduction in seizure frequency from baseline (median)	7.2	39.9
>=50% reduction from baseline (%)	16.7%	42.1%
odds ratio (98% CI)	--	3.6 (2.0, 6.7)
p-value (Versus placebo)	--	<0.001

Source of table 3: Table 8.1(vol. 666) .28 & 29 in integrated summary of efficacy (Vol 452)
[a] y=7 X Total number of Seizures during Evaluation Period/ Number of Days during the Evaluation Period.
[b] ln (X+1)
[c] 100 X [1-Exp(LSM Treatment -LSM Placebo)]

The analyses based on PP sample also demonstrated a statistically significant reduction in partial onset seizure frequency in the levetiracetam group, as compared to the placebo group (results are not shown here).

The responder rate in the levetiracetam group (42.1%) was statistically significantly ($p<0.001$) higher than the rate in the placebo group (16.7%). During the part I evaluation period, 8.2% patients in the levetiracetam group, and 1.1% patients in the placebo group were reported as seizure-free. From baseline to add-on evaluation period, the NHS3 scores were improved for 28.6% patients in the levetiracetam group and 5.9% patients in the placebo group. The mean absolute changes in visual analog score for everyday life from baseline to add-on evaluation period were .72 for the levetiracetam group and .30 for the placebo group and the corresponding changes for seizure control were 1.69 and .76 for the levetiracetam and placebo groups, respectively. About 54.7% in the levetiracetam group and 37.1% in the placebo group experienced an improvement in global clinical evaluation from baseline to the add-on evaluation period. About 4.4% in the levetiracetam group and 10.5% in the placebo group worsened.

Table 3.3: Percentages of patients experienced Treatment-Emergent AE / SAE in Add-on treatment period (ITT Population)

	Placebo	Levetiracetam 3000 mg/day
	N=105	N=181
Treatment-Emergent AE	56 (53.3%)	100 (55.2%)
Treatment-Related AE	35 (33.3%)	57 (31.5%)
Treatment-Emergent SAE	1 (1.0%)	10 (5.5%)
Treatment-Related SAE	1 (1.0%)	4 (2.2%)

Source: Vol587, table 12.2.1.1

Table 3.3 lists the percentages of patients experienced treatment-emergent AE/SAE. During add-on therapy period, one patient in the placebo group and 10 patients in the levetiracetam group reported at least one treatment-emergent SAEs during the add-on therapy period. The majority of these SAEs was related to convulsions. One patient (in the levetiracetam group) died at the end of add-on evaluation period; and this death (suicide) was considered by the investigator not to be related to the study medication.

Reviewer's Analyses:

The primary efficacy measure in part I, the mean number of partial onset seizure frequency per week over the add-on evaluation period was recalculated according to the formula stated in the study protocol and the values were matched with the sponsor's calculated values. The ANCOVA model for analyzing the data, as mentioned in the protocol, was fitted. This reviewer's analyses were based on the ITT sample. Levetiracetam 3000 mg/day was statistically significantly ($p<0.001$) different from placebo in reducing the number of partial onset seizure frequency.

All of the statistics reported in Table 3.2 for the primary and secondary outcome measures at baseline and evaluation period were recalculated from the ITT sample and found to be consistent with the sponsor's calculations.

The sponsor calculated the mean number of partial onset seizure frequency per week during the add-on evaluation period based on the information collected at visits 6,7,8, and 9. This reviewer recalculated the mean number of partial onset seizure frequency per week during the evaluation period (including titration period) based on the information collected at visits 5, 6, 7, 8, and 9. The ANCOVA model, as mentioned in the protocol, was fitted. The conclusions remained same (although p-values were changed) to the conclusions obtained in the previous analyses. The results are not reported here.

Subgroup Analysis:

Table 3.4 lists the summary statistics of the primary efficacy measure, the mean number (in logarithm transformed) of partial onset seizure frequency per week, by gender and treatment group. The subgroup analyses indicated that the levetiracetam 3000 mg/day was effective in reducing the partial onset of seizure frequencies for both the male and female patients. The percent reductions in partial seizure frequency were also similar between the males and females patients.

Table 3.4: Summary of Partial Onset Seizure Frequency Data by Gender (ITT Population) -logarithmic transform analysis

Weekly seizure Frequency	Female		Male	
Baseline	Placebo	Levetiracetam 3000 mg/day	Placebo	Levetiracetam 3000 mg/day
N	54	94	51	87
Mean [b] (S.D)	1.43 (1.02)	1.26 (.84)	1.04 (.58)	1.09 (.67)
Median	1.11	1.04	.88	.85
Range				
Evaluation Period				
N	51	87	51	84
Mean [b] (S.D)	1.30 (1.10)	1.02 (.86)	1.03 (.63)	.75 (.76)
Median [b]	1.07	87	88	53
Range				
LSM [c]	**1.28**	**1.07**	**1.07**	**0.76**
% reduction over placebo [c]	–	**19.18**	–	**26.65**
% reduction in seizure frequency from baseline (median)	7.04	32.57	7.26	50.21
>=50% reduction from baseline (%)	23.50	33.3	9.80	51.2

[b] Ln (X+1)
[c] 100 X [1-Exp(LSM Treatment –LSM Placebo)]

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Diagnostics of the ANOVA/ANCOVA Model fitting:

Diagnostics of the model fittings in each of the three pivotal studies were done by this reviewer through a normal probability plot (Q-Q plot) of the residuals, a plot of residuals vs. fitted values of the response measure, and a plot of Cook's distance. The Q-Q plots of the residuals of the ANCOVA/ANOVA models were close to a 45 degree straight lines. From the values of the Cook's distance statistics, several subjects were found to be influential to the model parameter estimates and it was true in each of the studies. However, after dropping the influential subjects from the analyses, the conclusion (i.e. significance levels) remained almost same as before. Therefore, the ANCOVA/ANOVA models fitted the data well in each of the three studies.

Study N052:

Study N052 was a 24 week multicentered, double-blinded, parallel-group, add-on study to compare the efficacy and tolerability of two doses of levetiracetam (2000 mg/day and 4000 mg/day) with placebo in patients with refractory epilepsy, followed by a 24-week open-label active treatment. The patients who continued to have seizures during the first 24-week segment (i.e., in the double blind period) of the study were included in the open label treatment with levetiracetam 4000 mg/day. The study was conducted at 37 centers (34 sites in Belgium and 3 sites in the United Kingdom).

The main reasons of considering this study as supportive study were (1) the enrollment in the study was open to a heterogeneous patient population with a variety of seizure types; and (2) no stringent minimal baseline seizure frequency was defined as a requirement. This study also was not powered to demonstrate efficacy but was mainly intended to assess safety of high-dose, immediate and long-term exposure.

One hundred nineteen patients (39 in placebo, 42 in 2000mg/day, and 38 in 4000 mg/day) of aged 16 to 67, diagnosed with any type of refractory epilepsy, having at least

four seizures during the 24 weeks prior to entry into the study were randomized. Patients who entered the study must had taken from one to three AED(s) at a stable dose during the 3 months prior to entry into the study.

Eighty-six patients continued treatment during the open label period with levetiracetam 4000 mg/day. Approximately half of the patients had partial onset seizures during the baseline period, while other half had generalized seizures.

The primary efficacy parameter was the responder rate and it was defined as the proportion of patients who experienced a >=50% weekly reduction in their seizures (Type I+II+III) from the baseline measures up to the end of the 24-week treatment double blind period.

Nine secondary efficacy measures were defined in the protocol. They were (1) the responder rates over the entire double-blind period, 4 weeks of treatment, and 12 weeks of treatment; (2) the efficacy for the onset of action during the first 4 weeks of treatment; (3) the seizure frequency by seizure type; (4) the recorded seizure-free intervals; (5) as subjective patient-rated QOL evaluation; and (6) the investigator-rated CGI severity of illness score.

The seizure frequency per week was analyzed from the inferential ITT sample using ANOVA. The analysis was not adjusted for the baseline seizure frequency. The sponsor did not mention any justification of not including the baseline seizure frequency as a covariate. The country variable was added as a factor into the analysis.

Sponsor's Results:

Levetiracetam-treated patients had a slightly greater mean age (39 and 40 years) compared to the placebo-treated patients (35 years). A slightly fewer percentage of males were in levetiracetam 4000 mg/day (52.6%), as compared to the percentage in the levetiracetam 2000 mg/day (69%) or in the placebo group (61.5%). All patients were Caucasians.

Patients within the three treatment groups had a similar histories of epilepsy (mean duration is 23.8 years). Patients in the placebo group experienced an earlier median onset of their seizures (9.48 years) compared to the patients in the levetiracetam 2000 mg/day (13.79 years) group or the patients in the levetiracetam 4000 mg/day (12.47 years) group. Patients in the placebo group also had a lower incidence of status epilepticus (7.7%), as compared to the levetiracetam 2000 mg/day (11.9%), and 4000 mg/day (18.8%) groups. During baseline, 58 patients (48.7%) had partial onset seizures, 50 patients (42.0%) had generalized seizures (Type II).

The most frequently used AEDs were crabamazepine (69 patients or 57.9%), valproic acid derivates (38 patients, 31.9%), phenytoin (37 patients or 30.1%), phenobarbital (25 patients or 21.0%), lamotrigine (29 patients or 16.8%), and clobazam (20 patients or 16.8%).

Table 4.1: Reason for dropout during add-on therapy Evaluation period (ITT Population)

	Placebo	Levetiracetam2000 mg/day	Levetiracetam4000 mg/day
	N=39	N=42	N=38
Completers	29 (74.4%)	28 (66.4%)	29 (76.3%)
Dropouts	10 (25.6%)	14 (33.3%)	9 (23.7%)
Reasons for Dropout			
AE	6 (15.4%)	11 (26.2%)	5 (13.2%)
Withdrew consent	2 (5.1%)	1 (2.4%)	2 (5.3%)
Other [a]	2 (5.1%)	2 (4.8%)	2 (5.3%)

[a] includes ineligibility, protocol violation, lack of efficacy

Fifty-seven of 80 levetiracetam-treated patients (71.3%) and 29 of 39 placebo-treated patients (74.4%) entered the second 24-week open level segment. The primary reason for discontinuation was adverse events (Table 4.1). Overall incidences of treatment-emergent serious adverse events (SAEs) during double-blind period were 7.7%, 7.1%, and 10.5% for placebo, levetiracetam 2000 mg/day, and 4000 mg/day groups (Table 4.2). One patient died from the levetiracetam 2000 mg/day group during the study period. The investigator reported that the death was not related to the study medication. Another patient died before randomization.

Table 4.2: Percentages of patients experienced Treatment-Emergent AE / SAE (ITT Population, Double-Blind Period)

	Placebo	Levetiracetam 2000 mg/day	Levetiracetam 4000 mg/day
	N=39	N=42	N=38
Treatment-Emergent AE	33 (84.6%)	35 (83.3%)	32 (84.2%)
Treatment-Related AE	19 (48.7%)	31 (73.8%)	25 (65.8%)
Treatment-Emergent SAE	3 (7.7%)	3 (7.1%)	4 (10.5%)
Treatment-Related SAE	1 (2.6%)	1[a] (2.4%)	--

[a] Died during the study period

Data from 86 patients who completed the entire 24-week treatment segment had been used in calculating the responder rate (>=50% reduction from baseline) in their seizure frequency. There was a statistically significantly (p=0.011) greater number of responders in the levetiracetam 2000 mg/day group (48.1%), as compared to the placebo group (16.1%). Although the levetiracetam 4000 mg/day group showed a greater number of responders (28.6%) as compared to the placebo group (16.1%), this difference was not statistically significantly (p=0.271) different from zero.

The ANOVA analysis (LSMs in Table 4.3) indicated that the reductions in seizure frequency up to the end of the first 24-week treatment period were numerically greater in the levetiracetam 2000 and 4000 mg/day groups, as compared to the placebo group. However, these percent reductions over placebo were not statistically significant.

Table 4.3: Weekly Seizure Frequency (type I+II+III) and percent reduction of LSM (inferential ITT population)-logarithmic transform analysis

	Placebo (N=39)	Levetiracetam 2000 mg/day (N=42)	Levetiracetam 4000 mg/day (N=38)
Baseline			
N	38	38	38
Mean [b] (S.D.)	1.09(1.16)	1.15(1.10)	1.10(1.05)
Median [b]	0.71	0.70	0.85
Range [b]			
Evaluation Period			
N	37	36	36
Mean [b] (S.D.)	1.11 (1.24)	0.81 (0.98)	0.93 (0.97)
Median [b]	0.87	0.48	0.46
LSM [c]	1.127	0.843	0.948
% reduction over placebo [c]	–	24.7%	16.4%
(95% CI)	–	-22.4, 53.6	-35.9, 48.6
p-value (Versus placebo)	–	0.250	0.239
Responder rate (>=50% reduction in total seizure frequency from baseline)			
Responder [d] (after 24 weeks)	5/31 (16.1%)	13/27 (48.1%)	8/28 (28.6%)
Odds-ratio (95% CI)		4.9 (1.4;16.8)	2.0 (0.6;7.2)
P-value [e]		0.011	0.271
Responder [f] (overall double-blind period)	6/36 (16.7%)	14/34 (41.2%)	10/36 (27.8%)
Odds-ratio (95% CI)		3.5 (1.2;10.8)	1.9 (0.6;6.1)
P-Value [e]		0.027	0.259
Responder [g] (up to week 4)	7/36 (19.4%	15/34 (44.1%)	12/36 (33.3%)
Odds-ratio (95% CI)		3.3 (1.1;9.5)	2.1 (0.7;6.1)
P-Value [e]		0.029	0.185

Source of table 5: Table 8.1(vol. 702) .11.4.1.4 in study report (Vol 701)
[a] y=7 X Total number of Seizures during Evaluation Period/ Number of Days during the Evaluation Period.
[b] ln (X+1)
[c] 100 X [1-Exp(LSM Treatment –LSM Placebo)]
[d] Based the number of patients who completed 24 weeks of treatment.
[e] From logistic regression
[f] Based on number of patients with adequate efficacy data at baseline and at least at visit 3.
[g] Based on number of patients with adequate efficacy data at baseline and at visit 3.

The responder rate (secondary measure) over entire double-blinded period for the levetiracetam 2000 mg/day group (41.2%) was statistically significant (p=0.027) as compared to the rate for the placebo group (16.7%). Responder rate up to 4 weeks for the levetiracetam 2000 mg/day group (44.1%) was also statistically significant (p=0.029) as compared to the rate for placebo group (19.4%). Although the levetiracetam 4000 mg/day showed improvement over the entire double-blinded period and over the 4 weeks period as compared to the placebo group, but these improvements were not statistically significantly different from zero. Table 4.3 lists all of the above results. For the other secondary measures, the three groups were not statistically significantly different among themselves.

The N052 study was not powered to demonstrate efficacy, and the primary outcome measure of this study was different from the primary outcome measures in the pivotal studies. Therefore, this reviewer has not reanalyzed the data set to evaluate the efficacy of levetiracetam. The study was mainly intended to assess safety of high-dose, immediate and long-term exposure and hence the efficacy analysis was considered as descriptive. The sponsor's analyses indicated that the high dose (levetiracetam 4000 mg/day) group was not statistically significantly different from the placebo group with

respect to the primary outcome measure and the secondary outcome measures. Reasons of the insignificance might be that the study was not powered to demonstrate the efficacy, or the effect of levetiracetam was diminished at the high dose level. The levetiracetam 2000 mg/day group was statistically significantly different from the placebo group with respect to the responder rate. However, with respect to the percent reduction over placebo (calculation based on LSMs from ANOVA analysis), neither of the levetiracetam 2000mg/day or 4000 mg/day groups were statistically significantly different from the placebo group.

Pooled Data Analyses:

Data from studies N051 (only Period A data), N132, and N138 were pooled together. The statistical tests based on the pooled data (as more patients are available in each group) will have higher power to detect the significance of the treatment effects. However, in interpreting the results from the pooled data, it is important to remember that there was some difference in the baseline severity of epilepsy among the populations of the three studies. The number of AEDs at baseline also differed between the studies. In study N138, patients took only one AED, while in Studies N051, and N132, the patients were to take one to two AEDs.

Figures 1 and 2 list the observed mean number[19] of partial onset of seizure frequency per week by treatment groups. Both figures indicate that at each dose level of levetiracetam, the mean number of partial onset seizure frequency per week at evaluation period was smaller, as compared to the baseline mean. As expected, the means at baseline and evaluation periods for the placebo group were remained almost same.

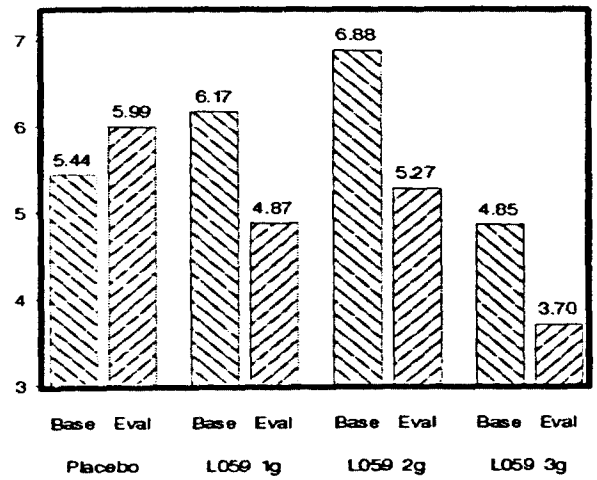

Figure 1: Mean number of Seizue Frequency per Week at Baseline and Evaluation period by Treatment Group

[19] Titration period was included in calculating the mean number seizures per week during evaluation period

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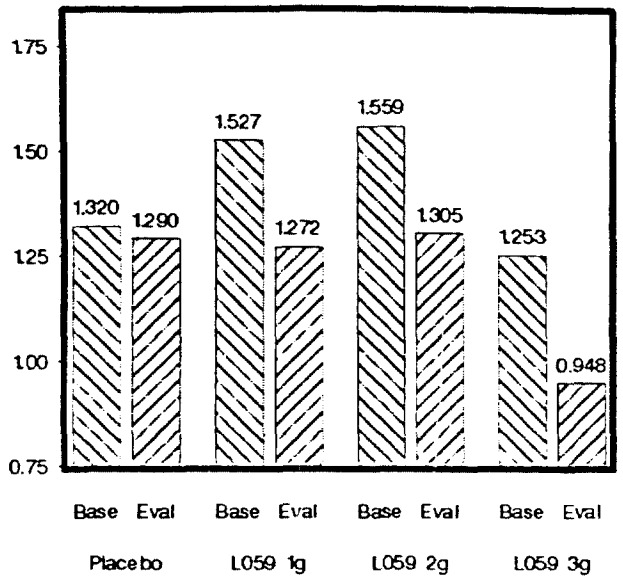

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Figure 2: Mean number (in log) of Seizue Frequency per Week at Baseline and Evaluation period by Treatment Group

An ANCOVA model was also fitted to the pooled data set considering the logarithm transformed of the mean number of partial onset seizure frequency per week during evaluation period as dependent measure, and treatment group (Placebo, levetiracetam 1000 mg/day, 2000 mg/day, and 3000 mg/day) as factor. The logarithm transformed of the mean number of partial onset seizure frequency per week at baseline was considered as a covariate. The analyses indicated that each of the dose levels of levetiracetam was statistically significant ($p <= 0.001$) in reducing the partial onset of seizure frequency during evaluation period, as compared to the placebo group. The three dose levels of levetiracetam were not statistically significantly different with respect to their effects in reducing the partial onset seizure frequency. The diagnostics of the model fittings indicated that the models fitted the data well.

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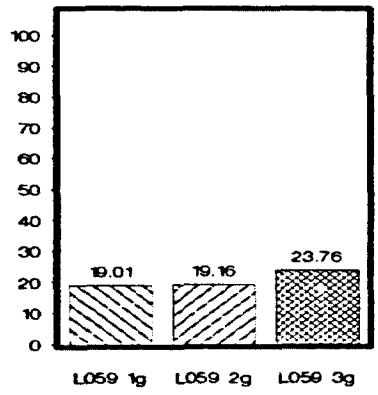

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Figure 3: Percent Reduction of Partial onset Seizures over Placebo (based on Least Square Means) by Treatment Group

Figure 3 lists the percentages of reduction[20] over placebo based on the estimated least square means obtained from the fitted ANCOVA model. The highest reduction (23.76%) of mean number of partial onset seizure frequency over the placebo group was in the levetiracetam 3000 mg/day group.

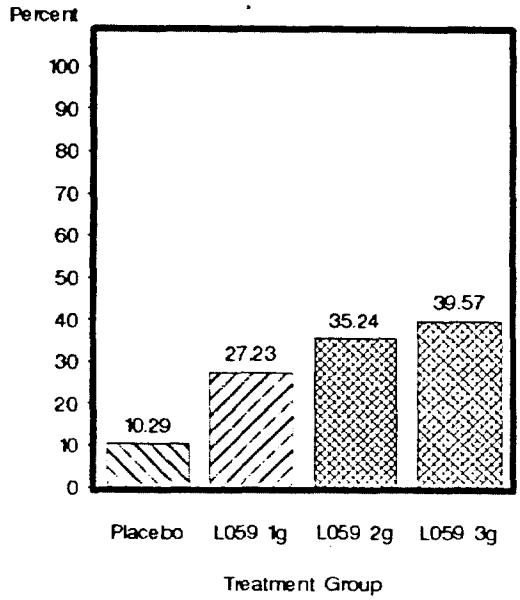

Figure 4: Percentages of Patients Responded (> = 50% reduction from Baseline) by Treatment Group

Figure 4 lists the percentages of responders (i.e. >=50% reduction from baseline) during the evaluation period by treatment groups. The figure indicated that the percentage of responders the levetiracetam groups increased as the dose levels increased.

All of the analyses were replicated on the pooled data set by gender. The findings were very similar with respect to gender, and hence the results were not reported here.

The table 5 lists the percentages of patients who dropped out from the studies due AEs or suffered from treatment related AEs/SAEs, based on the pooled data set (AEs data from the N052 study were included in table 5). In the levetiracetam 2000 mg/day and 4000 mg/day groups, higher percentages of patients dropped out due to AEs. In the levetiracetam 2000 mg/day group, a higher percentage of patients also suffered from treatment related SAEs. In the remaining groups, the percentages were very similar to each other. There were five deaths during the study periods (Table 6). The sponsor reported that none of these deaths were related to the study medication.

[20] 100 X [1-Exp(LSM Treatment –LSM Placebo)]

Table 5: Percentages of patients dropped out due to Aes/SAEs ,or experienced Treatment-Emergent AE / SAE

	Placebo	Levetiracetam 1000 mg/day	Levetiracetam 2000 mg/day	Levetiracetam 3000 mg/day	Levetiracetam 4000 mg/day
	N=351	N=204	N=148	N=282	N=38
Dropped out from study due to AEs	26 (7.40%)	14 (6.86%)	26 (17.56%)	24 (8.51%)	5 (13.15%)
Treatment-Related AE	141(40.17%)	92 (45.01%)	81 (54.73%)	116(40.42%)	25 (65.79%)
Treatment-Related SAE	6 (1.71%)	4 (1.96%)	9 (6.08%)	4 (1.42%)	0 (0%)

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Table 6: Number of Deaths by study and reason of death.

Study	No. of Death	Treatment Group	Reason of Death (Reported by the sponsor)
N051	2	Levetiracetam 1000 mg/day	Died due to car accidents during the evaluation period. Not related to study medication
N132 [a]	1	Placebo	Died suddenly and unexpectedly during the evaluation period. Not related to study medication
N138	1	Levetiracetam 3000 mg/day	Died at the end of the add-on evaluation period. This death is due to suicide. Not related to study medication.
N052 [b]	1	Levetiracetam 2000 mg/day	Died suddenly during the evaluation period. Not related to study medication

[a] One patient died before randomization.
[b] One patient died before randomization
Source: Study Reports.

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Reviewer's Overall Conclusion:

This reviewer reanalyzed the primary and secondary outcome measures of each of the three pivotal studies using ANCOVA/ANOVA models (as specified in the protocols). The findings were consistent with the findings provided by the sponsor. Levetiracetam was significantly efficacious in reducing the partial onset seizure frequency, as compared to placebo. There was no evidence of treatment-by-center interaction in any of the studies. The subgroup analyses also indicated that levetiracetam was efficacious as compared to placebo for males and females separately.

The statistical analyses based on the pooled data also indicated that each of the levetiracetam doses were statistically significantly efficacious in reducing the partial onset seizure frequency, as compared to placebo. The levetiracetam dose groups were not statistically significantly different among themselves with respect to efficacy. However, figures 1- 4 showed an increasing trend of efficacy with increasing the dose level of levetiracetam.

It can also be concluded that Levetiracetam doses were significantly efficacious in reducing the partial onset of seizure frequency with respect to the responder rates.

Only in one study (Study N132), the overall quality of life (QOL) scores were statistically significantly improved in the levetiracetam treated patients, as compared to their baseline QOL score (p-value=0.03). This significant evidence was not strong enough to conclude that levetiracetam had significant effect in improving the overall QOL of epileptic patients.

Levetiracetam doses and placebo had a similar safety profiles with respect to the incidences of AEs /SAEs and reasons for dropout from the studies.

From the analyses of the individual study data sets and the pooled data set, it could be concluded that levetiracetam 3000 mg/day might be an optimal dose as an add-on therapy to treat patients with partial onset seizures that are refractory to classical AED treatment. Since there were some evidences (although not statistically significant) that a trend for a greater response with the increase of levetiracetam dose level, patients might be treated first with lower doses of levetiracetam, and if the patient fails to respond, then higher doses of levetiracetam might be prescribed.

/S/

Ohidul Siddiqui, Ph.D
Mathematical Statistician

Concur: Dr. Kun Jin /S/

Dr. George Chi /S/

CC:
Arch NDA # 21-035
HFD-120/Dr. Katz
HFD-120/Dr. Freiman
HFD-120/Ms. Malandrucco
HFD-344/Dr. Barton
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HFD-710/Dr. Jin
HFD-710/Dr. Siddiqui
HFD-710/Chron

COMPLETED OCT 0 5 1999

OCT 4 1999

Statistical Review and Evaluation

Review of Carcinogenicity Data

NDA#: 21-035

Applicant: UCB PHARMA, Inc.

Name of Drug: Kepra (Levetiracetam) Tablets

Documents Reviewed: Volume 1.53 Containing the Mouse Study Report and Pages 15131-15275 from Volume 1.57 Containing the Rat Study Report. Data Diskettes were also Provided by the Sponsor.

Pharmacology Reviewer: Jennifer Burris, D.V.M. (HFD-120)

I. Background

The Division of Biometrics 1 was requested to evaluate the two oncogenicity studies. The results were discussed with the reviewing pharmacologist, Dr. J. Burris.

II. The Rat Study

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II.1 Sponsor's Findings

In this study, 50 CRL:CD(SD)BR rats per group per sex received the drug at doses of 0, 0, 50, 300, and 1800 mg/kg/day as admixture in the diet for 104 weeks. Survival was not affected by treatment and no increases in tumor incidence were attributed to the drug. Body weight gains of the mid and high dose groups of either sex were substantially lower than the controls during the first year. During the second year the body weight gains were similar to that of the controls.

II.2 Reviewer's Findings

The sponsor's number of animals surviving till terminal sacrifice and the tumor incidence frequencies were identical to this reviewer's. The two control groups were identical and combined in all analyses.

Male Rats:
Survival was better than fifty percent at the end of the study, with the high dose animals experiencing the (numerically) best survival (Tables 1-2, Figure 1). The tissues of all decedents and the tissues of the terminally sacrificed controls and high dose animals were microscopically examined. Therefore, only pairwise comparisons of the incidence rates of (combined) controls with high dose are appropriate. None of these comparisons reached statistical significance (Table 3).

Female Rats:
Survival of the (combined) controls and high dose animals was very similar (Tables 4-5, Figure2). The statistically significant departure from linear trend and lack of homogeneity is mostly due to the mid dose experiencing the best survival. Survival was good for all groups with the poorest showing (46 %) being the controls. Pairwise comparisons of tumor incidence rates did not reach statistical significance for any tumor/tissue combination (Table 6).

As neither the male nor the female rats showed any statistically significant tumor findings, the validity of this study needs to be evaluated.

II.3 Validity of the Rat Study

As there were no statistically significant differences in control and high dose tumor incidences, the validity of the study needs to be evaluated. Two questions need to be answered (1):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?

(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

The following rules of thumb are suggested by experts in the field. Haseman (2) had found that in his experience on the average, approximately 50 % of the animals in the high dose group survived a two-year study. In a personal communication with Dr. Karl Lin (HFD-720), he suggested that 50 % survival of the usual 50 initial animals in the high dose group between weeks 80-90 would be considered a sufficient number and adequate exposure. Chu, Cueto, and Ward (3) proposed that 'To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50 % survival at one year'. From these sources, it appears that the proportions of survival at weeks 52, 80-90, and at two years are of interest in determining the adequacy of exposure and number of animals at risk.

In determining the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD. Chu, Cueto, and Ward (1981) suggest:

(i) 'A dose is considered adequate if there is a detectable weight loss of up to 10% in a dosed group relative to the controls'.

(ii) 'The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical'.

(iii) 'In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls'.

In another paper, Bart, Chu and Tarone (4) stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, 'Usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD.'

It is clear that in this study there were sufficient numbers of animals surviving a sufficient length of time. Survival of the high dose animals

was not reduced when compared to the controls. Figure 3 taken from the sponsor's submission, shows that average body weights of the mid- and high dose animals were strongly affected. The effects appeared early in the study and were maintained throughout. For the males, the 10% criterion was exceeded after week 4 and for the females after week 6. It appears from these considerations that the high dose was beyond the MTD. The evaluation of clinical signs and severe histopathologic toxic findings is left to the expertise of the reviewing pharmacologist.

III. The Mouse Study

III.1 Sponsor's Findings

In this study 52 Crl:CD-1(ICR)BR mice per group per sex were treated with 0, 0, 60, 240, and 960 mg/kg/day of the drug in the diet for 80 weeks. The two control groups were combined for analysis. The sponsor reported no adverse effect of the treatment on survival. Body weight gains among the high dose males were up to 21% lower than the controls during the first 26 weeks, but regained parity during the later phase of the study. No major changes were seen among the females. There was no increased incidence for any particular tumor type nor for the overall number of tumors.

III.2 Reviewer's Findings

This appears to be a well controlled and well executed study except it is not clear to this reviewer why it lasted only 80 weeks.

Other than liver, most tissues were examined for all control and HD animals and for decedents of the low and mid doses. This design requires pairwise comparisons between HD and controls and trend tests are applicable only to liver tumors. This reviewer reproduced the sponsor's table of end mortality as well as tumor incidences. The two control groups were combined in all analyses. The results of the statistical analyses are as follows:

Male Mice:
Survival was not affected by treatment (Tables 7-8, Figure 4). All groups had better than 50 percent survival at the end of the study. Investigating tumor incidence rates showed no statistically significant findings (Table 9).

Female Mice:
There was no treatment effect on survival (Tables 10-11, Figure 5). The controls had numerically the highest mortality, which reached 21% at the end of the study. No tumor incidence comparisons approached statistical significance (Table 12).

As no tumor findings reached statistical significance the validity of both the male and female portions of the study needs to be examined.

III.3 Validity of the Mouse Study

Following the criteria outlined above for the rats, it is obvious that there were sufficient numbers of animals surviving till the end of the study. However, whether the length of exposure was sufficient is not clear. When survival is excellent there appear no good design reasons for conducting a carcinogenicity study of only 80 weeks. When evaluating

whether the high dose was close to the MTD, it can be seen from the sponsor's figure (Figure 6) that the male HD animals experienced lower average bodyweights early in the study. The differential was largest around week 20 when it reached 7 percent. Among the females, all average bodyweight curves were close together and no consistent pattern emerged. From these findings it appears that the MTD was reached for the HD males, but not for the HD females. The evaluation of clinical findings and severe histopathologic toxic effects is left to the expertise of the pharmacologist.

IV. Summary

IV.1 The Rat Study

This appears to be a well controlled study in which 50 animals per treatment group per sex received the drug as admixture in the diet. The dose levels were 0 mg/kg/day for the two controls groups, and 50, 300, and 1800 mg/kg/day for the treated groups. Survival was not negatively affected by the treatment and no increases in tumor incidence rates were observed. Exploring whether this study was valid, it was clear that there were sufficient numbers of animals treated long enough (104 weeks). However, based on the strong effect of the treatment on reducing average bodyweight, it appears that the high dose was beyond the MTD for either sex.

IV.2 The Mouse Study

This also appears to be a well controlled study in which 52 mice per treatment group per sex received the drug as admixture in the diet at doses of 0, 0, 60, 240 and 960 mg/kg/day. All groups of both sexes experienced better than 50 percent survival at the end of the study and it is not clear to this reviewer why the study was conducted for only 80 weeks. No increases in tumor incidence rates were observed for either sex. Exploring the validity of the study, it is not clear whether the length of study was sufficient. Average body weights of the male mice were suppressed early in the study and did not exceed the 10 percent criterion, suggesting that for these animals the high dose may have been close to the MTD. However, for the female mice none of the criteria used to establish the MTD was met and from a statistical point of view, the validity of this portion of the study is questionable. Again, from a statistical point of view the length of the study may have been insufficient for the manifestation of late developing tumors.

References:

(1) Haseman: Statistical Issues in the Design, Analysis and Interpretation of Animal Carcinogenicity Studies, Environmental Health Perspectives, Vol 58, pp 385-392, 1984

(2) Haseman: Issues in Carcinogenicity Testing: Dose Selection, Fundamental and Applied Toxicology, Vol5, pp 66-78, 19985

(3) Chu, Cueto, and Ward: Factors in the Evaluation of 200 National Cancer Institute Carcinogen Bioassays, Journal of Toxicology and Environmental Health, Vol 8, pp 251-280, 1981

(4) Bart, Chu and Tarone: Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity, Journal of the National Cancer Institute 62, pp 957-974, 1979

/S/
Roswitha Kelly, M.S.
Mathematical Statistician

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/S/
Kun Jin, Ph.D.
Team Leader

/S/ for George Chi
George Chi, Ph.D.
Director, Division of Biometrics I

To: Archival NDA 21-035, Kepra (levetiracetam) Tablets, UCB Pharma, Inc
CARCINOGENICITY

HFD-120/Ms. Mallandrucco, CSO
HFD-120/Dr. Burris
HFD-120/Dr. Fitzgerald
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HFD-710/Dr. Jin
HFD-710/Ms. Kelly
HFD-710/Chron.
This review consists of 5 pages, 12 tables, 6 figures.
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Table 1: NUMBER OF ANIMALS

MALE RATS

Week	Treatment Groups Comb. Ctrl	Low	Med	High	Total
0-52	3		2		5
53-78	13		4		32
79-91	17		1		25
92-104	13		4		30
105-107	54		39		158
Total	100		50		250

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