Patients Seizure-Free (All Seizure Types) During the Add - On Evaluation Period

Fourteen of 171 levetiracetam treated patients were seizure free during the complete Evaluation Period and 1 of 102 placebo patients were seizure free in the Evaluation Period.

Partial Onset Seizure Frequency, Absolute and Percentage Reduction From Baseline

The baseline median partial onset seizure frequency was 1.75 and 1.69 for the placebo and levetiracetam 3 g groups, respectively.

The median percentage reduction in seizure frequency from baseline was 7% and 40% for the placebo and levetiracetam 3 g group, respectively (Table 41). Patients in the levetiracetam treatment group had statistically significant ($p<0.001$) reduction in both absolute and percent reduction in seizure frequency compared to the placebo group.

Table 41: Partial Onset (Type I) Seizure Frequencies by Median and Median Absolute Percentage Reduction From Baseline

Period	Placebo (N = 105) Median seizure				Levetiracetam 3 g (N = 181) Median seizure			
	n	freq	ARB[a]	%RB[b]	n	freq	ARB	%RB
Baseline	105	1.75	--[c]	--		1.69	--	--
Evaluation	102	1.75	0.11	7.2	171	1.06	0.53	39.9
p - value[d]							<0.001	<0.001

based on sponsor's Table 11.4.1.2., Vol. 234, p 32685

[a] ARB = Absolute reduction from baseline. Reduction from baseline is for those patients who had both baseline and evaluation period data.

[b] %RB = Percentage reduction from baseline

[c] '-- ' = not applicable

[d] Comparison between placebo and levetiracetam 3 g (Kruskal-Wallis test)

How are numbers obtained for evaluation to arrive at absolute and percent reductions - simple subtraction does not result in correct numbers - assume it has to do with patients who had measurements in both periods. assume patients had more than one seizure type as groups add up to more than ITT

Seizure Frequency by Subtypes

The median absolute reduction in seizure frequency from baseline was greater in the levetiracetam 3 g group compared to the placebo group for all partial seizure subtypes (Table 42).

There were no patients who had type II or III seizures at baseline. There was only one patient who had a type II seizure during the evaluation period

Table 42: Partial Onset Seizure Frequency by Subtype

	Placebo (N = 105)			Levetiracetam 3 g (N = 181)		
	n	median sz frequency	median ARB	n	median sz frequency	median ARB
IA						
Baseline	31	0.56		57	0.46	
Evaluation	28	0.42	-0.05	47	0.50	0.06
IB						
Baseline	102	1.41		178	1.24	
Evaluation	99	1.46	0.20	168	0.76	0.49
IC						
Baseline	36	0.25		60	0.17	
Evaluation	33	0.21	0.08	50	0.06	0.16
IA + IB						
Baseline	103	1.67		181	1.48	
Evaluation	100	1.71	0.13	171	0.93	0.50

7.2.3.5 FDA Summary of Efficacy

The sponsor claims that levetiracetam is effective as adjunctive therapy in the treatment of partial onset seizures in doses ranging from 1000 to 3000 mg daily given twice a day. In support of this claim the sponsor has performed three controlled trials to determine the efficacy of levetiracetam as an antiepileptic drug in patients with partial onset epilepsy.

These studies were double-blind placebo controlled studies. Study N051 was a crossover study, however, only the first period is considered in support of the sponsor's efficacy claim. Study N138 included a monotherapy period which was reviewed by the sponsor but not included in this review as the sponsor intends to file a supplemental NDA for a monotherapy indication.

All of the above studies were designed to evaluate levetiracetam for the treatment of patients with partial onset seizures refractory to treatment with classical antiepileptic drugs. Study N138 further specified that patients have complex partial seizures, whether secondarily generalized or not.

Baseline seizure criteria were similar for studies N051 and N132. Patients had to have been observed to have partial onset seizures for at least the last 2 years prior to study entry in each study. Patients in Study N051 had to have at least 4 partial onset seizures during each 4 weeks of the baseline period. Patients in Study N132 had to 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. In Study 138 patients must have been observed to have partial onset seizures for 1 year prior to study. Patients in Study N138 had to have partial onset seizures with at least two complex partial seizures (CPS) per every 4 weeks during the 12 week baseline period, and at least two CPS during the during the first 4 weeks before the first study visit. All studies had a minimum 8-week baseline period to assess seizure frequency prior to entry into the study. In each of these studies, patients recorded the date, number, duration (except Study N138), and description of their seizures on a daily record card. Investigators then coded the seizures according to the International Classification of Epileptic Seizures.

In Studies N051 and N132 patients were allowed to take between one and two classical AEDs, in Study 138 patients were allowed a single AED. Therefore patients in Study 138 may represent an epilepsy population with less severe disease.

The sponsor attempted to exclude patients with seizure clusters (groupings of seizures in which individual seizures were indistinguishable and could not be quantified) by protocol selection criteria. When a seizure cluster was reported during the course of a study it was handled differently for each study. Clusters were reported as Type IV seizures in study 132 and omitted from the efficacy analysis; in Study N051 were assigned to a seizure subtype and counted as a single seizure; and in Study N138, clusters were recorded as adverse events and no other instructions were given. In Studies N051 and N138 no clusters were reported. In Study 132 there were 4 clusters (3 levetiracetam-treated, 1 placebo-treated patient). Given the rare occurrence of clusters there was no impact on the analyses of these studies.

The majority of patients in the three efficacy trials, 514 of 592 (87%) patients exposed to levetiracetam (86.8%)] and 277 of 312 (89%) placebo patients completed the double blind phase of the study. Reasons for discontinuation were similar for the levetiracetam and placebo groups with the exception a greater frequency of discontinuation for adverse events in the levetiracetam group 53 (9%) compared to placebo 19 (6.1%).

The primary efficacy variable for all three studies was the reduction in the mean weekly seizure frequency from baseline during treatment, as compared to placebo. Only the add-on portions of the above trials for the Inferential ITT population were considered in support of the sponsor's claim (patients with data available both during baseline and during treatment evaluation periods).

The sponsor found levetiracetam statistically significant to placebo for all treatment groups (1 g, 2 g, and 3 g) compared to placebo. Statistical significant differences were not obtained between the levetiracetam treatment groups (1 g vs. 2 g, $p = 0.084$, 1 g vs. 3 g, $p = 0.195$).

The sponsor did not count seizure data from the titration (last 2 weeks of titration period counted in Study N132) period when calculating the mean number of seizures per week for the evaluation period. The sponsor was requested to repeat the statistical analyses including seizure counts from the titration period. The results from the entire treatment period (titration and evaluation period) were nearly identical to the results when the evaluation period was considered alone.

A statistical review and additional analyses of Studies N051, N132, and N138 was conducted by Ohiddul Siddiqui, Ph.D., mathematical statistician. Dr. Siddiqui's findings concur with those of the sponsor.

In conclusion the sponsor has conducted three double-blind, placebo-controlled trials (Studies N051, N132, and N138) demonstrating the efficacy of levetiracetam as adjuvant therapy in patients with partial onset seizures.

8 Integrated Review of Safety

8.1 Background and Methodology

The safety review was conducted using an update of the Integrated Summary of Safety submitted on June 1 1999, as well as study reports and case report forms. The Safety Update (SU) replaced the original Integrated Summary of Safety volumes 463 - 584 and includes all safety data in the N999 clinical database up to November 30, 1998. Serious adverse event data up to February 28, 1999 are included. As of November 30, 1998, treatment was ongoing for 617 patients.

8.2 Deaths

The sponsor begins discussion of deaths on investigational treatment on page 393 of the SU. Deaths occurring up to 30 days after the cessation of treatment were reported to the sites and were included in the N999 database. In addition, death cases were counted if a serious adverse event occurred during that time period (within 30 days after cessation of treatment) that subsequently resulted in death. Therefore, there are cases in which death occurred more than 30 days after the patient discontinued study drug.

8.2.1 Sponsor's Tabulation of Individual Deaths

There were a total of 37 deaths in the levetiracetam treatment program through February 28, 1999. Two deaths occurred during a cognition study (Study N081, not included in the N999 database) conducted in Italy in the late 1980s. This study was not conducted according to Good Clinical Practices and incomplete information is available on these cases. There were 30 levetiracetam and 30 placebo-treated patients in Study N081, both deaths occurred in patients receiving placebo. The sponsor has excluded these two cases from the mortality analysis,

Of the remaining 35 deaths, 4 died during the baseline observation period (2 patients from epilepsy trials, and 2 patients from anxiety studies). Since these patients died prior to randomization to any treatment group the sponsor has reasonably excluded them from any further mortality analysis (person-time excluded). The remaining 31 deaths are summarized by gender, treatment group and type of study (Table 43).

Table 43: Summary of Numbers of Treatment-Emergent Deaths in the Levetiracetam Development Program: by Treatment, Gender, Indication, Etiology, and Geographic Location (February 28. 1999 Cut-off Date)

Category	Subcategory	U.S. Studies	Non-U.S. Studies	Total N
Total Deaths		7	24	31
Gender	Males	3	15	18
	Females	4	9	13
Epilepsy Patients		7	16	23
Gender	Males	3	14	17
	Females	4	2	6
Treatment Group	Levetiracetam	6	15	21
	Placebo	1	1	2
Etiology	SUDEP	5	4	9
	Cancer	0	6	6
	Accidental Injury	0	2	2
	Cardiac	1	1	2
	Pneumonia	0	3	3
	Suicide	0	1	1
Non-epilepsy Patients		0	8	8
Gender	Males	0	1	1
	Females	0	7	7
Treatment Group	Levetiracetam	0	7	7
	Placebo	0	1	1
Etiology	Cancer	0	3	3
	Cardiac	0	1	1
	Pneumonia	0	1	1
	Suicide	0	1	1
	CVA	0	2	2

sponsor's Table 201A, Vol. 2, p.475

8.2.2 Clinical Description of the Deaths

I reviewed the narrative summaries for all deaths and summarized them in Table 44. Among the 31 deaths five occurred in controlled studies of epilepsy (3 levetiracetam and 2 placebo-treated). Nine deaths were attributed to sudden unexplained death in epilepsy (SUDEP), 9 due to cancer, 4 patients died of pneumonia, 3 cardiac events, 2 died in motor vehicle accidents, 2 patients had cerebrovascular accidents, and 2 patients committed suicide. Seventeen of the deaths reported surgical pathology or autopsy findings. Among the 9 SUDEP deaths four had undergone autopsy.

Table 44: Death Listing (through February 28, 1999)

Study	Patient ISS #	Age (yrs)	Sex	Dose (mg)	Time (days)	Pathology	Description
Cognition Studies							
N012	4832	76	F	1000	15		cystic astrocytoma
N013	4331	64	M	1500	6	Autopsy	cerebrovascular event
N022	3504	87	F	500	29	Pathology	gastric carcinoma
Anxiety Studies							
N045	728	45	F	1000	4		suicide
N122	1648	93	F	500	7		cardiac arrest
N045	965	62	F	1000	33	Pathology	metastatic adenoca
N042	1683	86	F	PBO	21		pneumonia/sepsis
Anti-thrombic Study							
N099	4643	79	F	250	1		CVA post AAA repair
Epilepsy Studies (non-controlled)							
N035	174	65	M	2000	372	Pathology	gliobastoma multiforme
N035	163	68	F	500	469	Pathology	hepatoma
N129	165	64	M	500	1355	Pathology	glioblastoma multiforme
N129	2141	47	M	2000	585	Autopsy	SUDEP
N140	2553	37	F	3000	204	Autopsy	SUDEP
N147	2330	56	F	3000	86	Autopsy	ruptured left ventricle
N129	1739	43	M	3000	791		SUDEP
N141	2091	22	M	4000	845		pneumonia
N133	2275	45	M	3000	728	Pathology	lung cancer
N147	2641	40	M	3000	373	Autopsy	SUDEP
N129	2875	53	M	3000	535	Pathology	astrocytic glioblastoma
N141	2061	62	M	4000	1168		pneumonia
N129	2776	46	M	3000	755	Autopsy	heart failure
N147	2475	59	M	2000	616		SUDEP
N147	2392	62	M	4000	545	Autopsy	SUDEP
N147	2432	25	F	4000	570	Autopsy	gastric adenoca
N153	4913	28	M	3000	91	Autopsy	SUDEP
N129	179	84	M	2000	2400	Autopsy	pneumonia
Epilepsy Studies (controlled)							
N051	1952	37	M	PBO	5		accident
N051	1987	26	F	2000	63		accident
N052	2073	62	M	2000	140		SUDEP
N132	2365	25	F	PBO	2		SUDEP
N138	2940	44	M	3000	128		suicide

8.2.3 Sponsor's Death Rate Analysis

The sponsor's approach to analyzing deaths in the levetiracetam development program involved the computation of the Standardized Mortality Ratio (SMR). This ratio represents the number of deaths observed in the levetiracetam development program to the number of deaths expected in the program if it had the same rate structure as a standard population. The sponsor has chosen to use the U.S. mortality from all causes in 1998 as the standard rate recognizing that this rate may not be ideally suited for the standardization of European studies. This is because mortality rates in European countries may be higher than in the United States.

Person-time was estimated from the exposure data in the N999 database through November 30, 1998. Additional person-time from ongoing studies (N147, N129, and N157) was included from November 30, 1998 through February 28, 1999. The sponsor has categorized person-time exposure in Table 45.

Table 45: Summary of Exposure (Person-years)

	Subcategory	Additional Subcategory	Exposure (Person-years)
All Patients			2692.4
	By Treatment	Levetiracetam	2449.0
		Placebo	243
Epilepsy Patients			2409.7
	By Gender	Male	1392.2
		Female	1017.5
	By Treatment	Levetiracetam	2257.6
		Placebo	152.1
	U.S. Patients	Levetiracetam	761.0
		Placebo	33.1
	Placebo-Control	Levetiracetam	278.9
		Placebo	143.8
Non-Epilepsy Patients			254.3
	By Treatment	Levetiracetam	163.1
		Placebo	91.2
	By Gender	Male	106.2
		Female	148.1

based on sponsor's Table 202A, Vol. 2, p. 484

The overall mortality rate in the levetiracetam program was 11.5 per 1000 person-years (31 deaths/ 2694 person-years) with a resulting SMR of 1.3. For all epilepsy patients the mortality rate was 9.5 per 1000 person-years [23 deaths/2410 person-years (SMR 1.8)] with a rate of 9.3 per 1000 person-years [21 deaths/2252 person-years (SMR 1.7)] for levetiracetam-treated patients and 13.1per 1000 person-years [2 deaths/ 152.1 person-years (SMR 2.5)] for placebo-treated patients (Table 46).

The finding of an elevated SMR is not unexpected in an epilepsy population, however comparisons of SMRs between the levetiracetam development program and other drug development programs or epilepsy populations must be interpreted cautiously as the underlying populations being compared are not identical.

Most importantly, in controlled studies in epilepsy patients there were 3 deaths in the levetiracetam and 2 deaths in the placebo-treated patients, with correspondingly similar mortality rates of 10.7 per 1000 person-years and 13.9 per 1000 person-years for levetiracetam and placebo-treated patients, respectively.

In contrast, in controlled studies in non-epilepsy patients there were 7 deaths among 1561 levetiracetam-treated patients and 1 death among 869 placebo-treated patients, with corresponding mortality rates of 42.9 per 1000 person-years and 11 per 1000 person-years for levetiracetam and placebo-treated patients, respectively. However, 3 of the deaths in the levetiracetam-treated patients were due to advanced cancer. All 3 cancer patients had an adverse event leading to discontinuation within 30 days of levetiracetam-treatment. In all 3 patients the event leading to discontinuation appears to be related to the underlying cancer, and all 3 patients died more than 30 days after the cessation of levetiracetam treatment. I have summarized the 3 cancer deaths below.

4832 This 76 y/o female with a history of CVA was receiving levetiracetam 1000 mg/day for 15 days when she was noted to be confused and disoriented (3/22/89). Levetiracetam was discontinued the same day. On 5/3/89 the patient underwent a CT scan demonstrating a large cystic astrocytoma in the left hemisphere, with mid-line shift, dilated right ventricle and evidence of slow coning over. The patient died on 5/18/99, approximately 2 months after the discontinuation of levetiracetam.

3504 This 87 y/o female was receiving levetiracetam 500 mg/day for 29 days when she was hospitalized for gastric carcinoma. Levetiracetam was discontinued at the time of hospitalization. An exploratory laparotomy was performed and the cancer was found to be inoperable. The patient died approximately 6 weeks later.

965 This 62 y/o female was receiving levetiracetam 1000 mg/day for 33 days when she stopped treatment because of increasing dyspnea. Further evaluation revealed a large left pleural effusion. One month later a pleurectomy was performed at which time numerous nodules were discovered on the surface of the parietal pleura and the surface of the lungs. Histopathology was consistent with pleural metastasis from adenocarcinoma. She subsequently underwent a left lung resection followed by chemotherapy. The patient died approximately 7 months after discontinuing levetiracetam.

Given the circumstances of these 3 deaths I feel it is reasonable to exclude them from the mortality analysis since these deaths are unlikely to be associated with short-term exposure to study drug. The mortality rate difference is reduced and the mortality signal diminished with the exclusion of these 3 cases (levetiracetam 25.4 per 1000 person-years, placebo 11 per 1000 person-years).

Table 46: Observed, Expected Deaths and Standardized Mortality Rates Levetiracetam Program (February 28, 1999 Cut-Off date)

Category	Person-years Exposure	U.S. Standard Death Rate[c]	Levetiracetam Mortality Rate[d]	Observed Deaths	Expected U.S. Deaths	SMR
Total Levetiracetam Program[a]	2692.4	8.73	11.5	31	23.5	1.3
Levetiracetam	2449.0	8.73	11.4	28	21.4	1.3
Placebo	243.4	8.73	12.3	3	2.1	1.4
Epileptic Patients (Adults)[a]	2409.7	5.36	9.5	23	12.9	1.8
Men	1392.2	6.61	12.2	17	9.2	1.8
Women	1017.5	4.15	5.9	6	6.1	1.0
On Levetiracetam	2257.6	5.36	9.3	21	12.1	1.7
Men	1313.2	6.61	12.1	16	8.7	1.8
Women	944.4	4.15	5.3	5	4.4	1.1
On Placebo	152.1	5.36	13.1	2	0.8	2.5
Men	79.0	6.61	12.6	1	0.5	2
Women	73.1	4.15	13.6	1	0.3	3.3
Non Epileptic Patients[b]	254.3	10.94	31.4	8	2.8	2.8
Men	106.2	11.36	9.4	1	1.2	0.83
Women	148.1	10.56	47.2	7	1.6	4.4
On Levetiracetam	163.1	10.94	42.9	7	1.8	3.9
On Placebo	91.2	10.94	11	1	1.0	1.0

based on Sponsor's Table 203A and 204A, Vol. 2, pp. 485-6
[a] 15-74 years
[b] 15-85 years
[c] U.S. Standard Death Rate per 1000 person-years
[d] Levetiracetam mortality rate per 1000 peson-years

8.2.4 Sudden and Unexpected Death in Epilepsy

The sponsor provided a cause specific analysis of SUDEP. Using previously developed criteria the sponsor defined SUDEP as follows:

- The victim suffered from epilepsy, defined as recurrent unprovoked seizures.
- The victim died unexpectedly while in a reasonable state of health.
- The death occurred "suddenly" (in minutes), when known.

- The death occurred during normal activities, *e.g.*, in or around bed, at home, at work and benign circumstances.
- An obvious medical cause of death was not found.
- The death was not the direct result of status epilepticus or direct trauma due to seizure.

The overall rate of SUDEP (includes definite, probable, and possible SUDEPs) in the levetiracetam epilepsy treatment program was 3.7 per 1000 person-years with a rate of 3.54 per 1000 person-years and 6.58 per 1000 person-years for levetiracetam and placebo-treated patients, respectively (Table 47). In the controlled epilepsy studies there was one SUDEP in each the levetiracetam and placebo-treated patients with a corresponding rate of 3.5 per 1000 person-years for levetiracetam and 7.0 per 1000 person-years for placebo.

Table 47: Observed SUDEP Rates in Epilepsy Studies

Category	Person-years Exposure	Observed Deaths	Observed Rate[a]
SUDEP Overall	2409.7	9	3.7
Men	1392.2	7	5.0
Women	1017.5	2	1.97
By Treatment			
Levetiracetam	2257.6	8	3.54
Placebo	152.1	1	6.58
By Treatment and Gender			
Levetiracetam Men	1313.2	7	5.33
Levetiracetam Women	944.4	1	1.06
Placebo Men	79.0	0	-
Placebo women	73.1	1	13.68

based on Sponsor's Table 205A, Vol. 2, p 487

[a] Observed Rate per 1000 person years

8.3 Dropouts and "Other Significant Adverse Events"

The sponsor discuses the method for assessing premature discontinuations on page 32 of the Safety Update. Summary tables showing the number and percentage of subjects who completed and the reason for premature termination were produced. In addition, for epilepsy studies tables showing reasons for termination categorized by cumulative duration of exposure were produced.

The sponsor responded to a request for additional data and clarification of issues related to discontinuations on August 20, 1999 (Amendment 20). The issues were as follows:

1 Clarification of discontinuations due to adverse events

In the SU specific adverse events leading discontinuation were listed along with adverse events leading to dose reduction. In Amendment 20, a complete listing of adverse events leading to discontinuation alone is provided. The adverse events were based on the CRF termination page rather than the Adverse Event page of the CRF.

2 What method was used to assure that there were not hidden AEs in those patients in whom discontinuation was due to reasons other than an adverse event?

The sponsor states that special attention was paid to such cases in order to detect any potential "hidden" adverse events.

3 What is the difference between a discontinuation due to "lack of efficacy" vs. an adverse event such as "increase in convulsions"?

Lack of efficacy was considered the reason for termination when there was not an increase in the overall seizure frequency compared to baseline. Where there was an increase over baseline in the overall seizure frequency, discontinuation was attributed to an adverse event. The investigator made this determination and the sponsor did not attempt to reclassify patients.

In addition the sponsor points out that for the adequate and well controlled studies in epilepsy there are more discontinuations than dose reductions and the reverse is true for the other adult epilepsy studies. The reason for this is that dose reduction was generally not allowed in the controlled studies and therefore investigators had to opt to discontinue patients. In the other adult epilepsy studies, investigators were allowed to adjust the dose downward.

8.3.1 Discontinuations Due to Adverse Events for Controlled Epilepsy Trials

The sponsor begins discussion of discontinuations from treatment on p. 80 of the SU. Among patients participating in the placebo-controlled clinical trials, 571 of the 672 (85%) of the levetiracetam-treated patients and 306 of 351 (87%) of placebo-treated patients completed the first double blind portion of the study. The most common reason for discontinuation was an adverse event occurring in 10.3% and 7.1 % of the levetiracetam and placebo-treated patients, respectively. When considering both double blind periods of Study N051 the proportion of patients discontinuing due to an adverse event was similar to that when only the first period is considered. The reasons for discontinuation are presented in Table 48.

Table 48: Classification and Enumeration of Discontinuation in Adult Epilepsy Patients

	Placebo-Controlled Studies				
	First Period of N051 Only		Both Periods of N051		Overall
Status	Levetiracetam	Placebo	Levetiracetam	Placebo	Levetiracetam
Exposed	672	351	769	439	1393
Completed	571 (85%)	306 (87%)	638 (83%)	378 (86%)	237 (17%)
Ongoing	0	0	0	0	556 (40%)
Reason for Discontinuation					
AE	69 (10%)	25 (7%)	86 (11%)	35 (8%)	219 (16%)
Lack of efficacy	5 (0.7%)	2 (0.6%)	9 (1%)	4 (0.9%)	219 (16%)
Withdrawal of consent	17 (3%)	9 (3%)	22 (3%)	11 (3%)	79 (6%)
Protocol violation	2 (0.3%)	5 (1%)	6 (0.8%)	7 (2%)	33 (2%)
Other	8 (1%)	4 (1%)	8 (1%)	3 (0.7%)	59 (4%)

based on sponsor's Table 18A SU Vol. 1 p 81

I used sponsor's Table 5.9 from Amendment 20 to summarize adverse events leading to discontinuation of at least 0.4% of levetiracetam exposed epilepsy patients enrolled in placebo-controlled trials (Table 49).

Table 49: Adverse Events Causing Discontinuation in ≥ 0.4% of Levetiracetam Treated Patients in Placebo-Controlled Studies

Body System/ Preferred Term	Levetiracetam (N = 769) AEs (N = 86)[a]	Placebo (N = 439) AEs (N = 35)	Overall (N = 1023) AEs (N = 121)
Body As A Whole			
Accidental Injury	4 (0.5%)	0	4 (0.4%)
Asthenia	6 (0.8%)	2 (0.5%)	8 (0.8%)
Headache	7 (0.9%)	1 (0.2%)	8 (0.8%)
Hostility	3 (0.4%)	0	3 (0.3%)
Nervous System			
Ataxia	4 (0.5%)	0	4 (0.4%)
Convulsion	17 (2.2%)	17 (3.9%)	34 (3.3%)
Dizziness	4 (0.5%)	0	4 (0.4%)
Emotional Lability	3 (0.4%)	0	3 (0.3%
Insomnia	3 (0.4%)	0	3 (0.3%)
Nervousness	3 (0.4%)	1 (0.2%)	4 (0.4%)
Personality Dis.	4 (0.4%	0	4 0.4%)
Somnolence	23 (3.0%)	4 (0.9%)	27 (2.6%)
Thinking Abnormal	4 (0.4%)	1 (0.2%)	5 (0.4%)

based on sponsors Table 5.9, Amendment 20, pp. 25 - 28
[a] An individual patient can have multiple AEs (maximum 4) related to discontinuation

I reviewed the narrative summaries of all discontinuations. The majority of discontinuations were related to epilepsy (convulsions) or from a known and common side effect of the drug (somnolence). There were no discontinuations for aplastic anemia, liver failure, renal failure or rhabdomyolysis among levetiracetam-treated patients. Four patients discontinued for rash, 3 of whom received placebo and 1 of whom received levetiracetam (patients are identified by their unique ISS/ISE number). The levetiracetam-treated patient with rash is summarized below:

3016 This 62 y/o female was receiving levetiracetam 1000 mg/day for 1 day when she developed a maculopapular rash of the feet and trunk. Levetiracetam was withdrawn over 3 days while lamictal 400 mg day was continued. The patient was seen by a dermatologist who reports that the rash had diminished within 3-4 days, though the rash was still minimally apparent approximately 2 months after discontinuation.

Of note several levetiracetam-treated patients discontinued due to adverse behavioral events. COSTART terms applied to such patients included hostility, psychosis, personality disorder and emotional lability. These cases are summarized below:

1715 This 37 y/o male was receiving levetiracetam 1000 mg/day for 6 days when he reported suffering from irritability. The patient also reported agitation while on placebo. Irritability, agitation, and drowsiness resolved 15 days after levetiracetam withdrawal.

1809 This 38 y/o female was receiving levetiracetam 1000 mg/day for 12 days when she began to suffer from mood swings which resolved 7 days after levetiracetam withdrawal.

1817 This 31 y/o male with a history of drug induced psychosis (phenytoin in '84 and tiagabin in '93) was receiving levetiracetam 2000 mg/day for 7 days when he developed progressive behavioral symptoms

(inappropriate laughing, odd ideas) leading to psychosis. His symptoms abated the same day that levetiracetam therapy was withdrawn.

1830 This 38 y/o female was receiving levetiracetam 1000 mg/day for 7 days when she became increasingly depressed and suffered from auditory hallucinations suggesting morbid and suicidal ideas. Levetiracetam was tapered and withdrawn with a gradual resolution of her symptoms over 2 weeks.

1865 This 39 y/o female was receiving levetiracetam 2000 mg/day for 10 days she began to suffer from "behavioral disturbance and aggression" and requested withdrawal from the study. The symptoms resolved over 18 days.

1984 This 14 y/o female was receiving levetiracetam 1000 mg/day for 13 days when she began to suffer from worsening seizures and character problems. The symptoms resolved over 17 days.

2009 This 57 y/o male with a history of a major aggressive episode 20 years prior was receiving levetiracetam 2000 mg/day for 42 days when increasingly aggressive behavior was noted. The patient threatened to kill his wife and was committed to a psychiatric hospital. The patient was treated with loxapine, trihexyphenidyl, tinaptine and zolpidem. His symptoms abated over nine days.

2106 This 27 y/o male was receiving levetiracetam 2000 mg/day for 22 days when study medication was discontinued because of asthenia, headache and moderate emotional labiltiy. The symptoms were still present at his final visit 2 weeks after discontinuation.

2402 This 34 y/o male with a history of organic personality disorder was receiving levetiracetam 666 mg day for 27 days when he displayed intermittent aggressive behavioral outbursts. The patient remained on levetiracetam at a dose of 1000 mg day for several more weeks with a worsening in the severity of his behavioral problem. The symptoms abated 9 days after complete withdrawal of therapy.

2805 This 45 y/o female was receiving levetiracetam 3000 mg/day for 28 days when she experienced intermittent aggression of moderate severity. She was continued on levetiracetam for several more weeks at gradually reduced dosages and finally withdrawn. The patient is reported to have recovered approximately 2 months following discontinuation of levetiracetam.

2842 This 24 y/o female was being titrated to levetiracetam 2000 mg/day for 7 days when she experienced mood swings and somnolence of moderate severity. The patient recovered 18 days after levetiracetam discontinuation.

1754 This 19 y/o female participant in the N051 crossover trial was receiving levetiracetam 1000 mg/day for 109 days (corresponding with the end of Period A) when she reported drowsiness, irritation, depressed mood, and trembling. Withdrawal took place over three weeks and her symptoms were resolved 1 week after complete discontinuation of levetiracetam.

I classified the above case as a treatment related event even though the sponsor lists the case as being on placebo at the time of the event. This is because by convention the sponsor decided that only one treatment would be assigned to the up-titration period or transition periods. The treatment assigned is the one from the following evaluation period. Since this patient's event occurred at the end of Period A beginning of Transition Period the patient was assigned to placebo even though she was in the beginning of down-titration to placebo.

In addition one patient receiving levetiracetam had suicidal ideation and another successfully completed suicide.

2385 This 47 y/o female with a history of situational depression was receiving levetiracetam 3000 mg/day for 56 days when she experienced an episode of suicidal tendency. Levetiracetam tapering was initiated 14 days later because of persistent symptoms. No follow-up information is available.

2940 This 43 y/o male was receiving levetiracetam 3000 mg/day for 128 days when he successfully committed suicide. Additional details are not provided in the narrative. Review of the CRF notes the patient cut his forearm veins and that symptoms of depression were not observed during administration of study medication. However, mention is made that the patient was having marital and financial problems.

Only one similar discontinuation for a behavioral event was found among placebo-treated patients.

2804 This 55 y/o male was receiving placebo for 55 days when he experienced a single episode of severe mood swing and severe confusional state. Study medication was withdrawn and the patient was fully recovered by the next day.

The sponsor has taken note of the disproportionate occurrence of discontinuations due to behavioral adverse events among levetiracetam-treated patients and has conducted additional analyses and explorations of these events, which are reviewed in section 8.9.2.

8.3.2 Discontinuations by Time from Treatment for Adult Patients in Controlled Clinical Trials

The proportion of patients discontinuing treatment by time interval (≤ 4wk, >4 wk.-≤ 3 mo., >3 mo.- ≤6 mo.) was similar across time intervals and among treatment groups (Table 50). When considering both double blind periods of Study N051 the proportion of patients discontinuing treatment by time interval and treatment group was similar to when only the first period of Study N051 was considered.

Table 50: Time Course of Discontinuation from Treatment: Placebo-Controlled Clinical Trials

(First period of Study N051 Only)

	Total	≤ 4 wk.	> 4 wk. - ≤3 mo.	> 3 mo. - ≤6 mo.	> 6 mo. - ≤ 1 yr.
Levetiracetam-Treated Group					
Exposed	672	672	639	595	1
Completed	571	0	1	569	1
Discontinued	101	33 (5%)	43 (7%)	25 (4%)	0
Reason for Discontinuation					
Adverse Event	69	28 (4%)	28 (4%)	13 (2%)	0
Lack of Efficacy	6	0	1 (0.2%)	5 (0.7%)	0
Withdrawal of Consent	20	2 (0.3%)	8 (1%)	10 (2%)	0
Protocol Violation	4	1 (1%)	0	3 (0.4%)	0
Other	8	2 (0.3%)	6 (0.8%)	0	0
Placebo-Treated Group					
Exposed	351	351	341	318	1
Completed	306	0	0	305	1
Discontinued	45	10 (3%)	23 (7%)	12 (4%)	0
Reason for Discontinuation					
Adverse Event	25	7 (2%)	15 (4%)	3 (1%)	0
Lack of Efficacy	3	0	1 (0.3%)	2 (0.8%)	0
Withdrawal of Consent	9	2 (0.6%)	4 (1%)	3 (0.9%)	0
Protocol Violation	5	0	1 (0.3%)	4 (1%)	0
Other	4	1 (0.3%)	3 (0.6%)	0	0

based on sponsors Table 19A, SU, Vol. 1, p 82

8.3.3 Discontinuations Due to Adverse Events for All Adult Epilepsy Patients

The sponsor did not provide a separate listing of discontinuations which occurred while patients where receiving levetiracetam in phase 2 studies and long-term extension studies. Among the 1393 levetiracetam exposed patients 556 were continuing in long term extension studies as of the data cut off date. Of the remaining 837 patients 237 (37%) were categorized as having completed all study participation. Six hundred nine patients discontinued. Adverse events and lack of efficacy each accounted for 219 (16%) of discontinuations.

I reviewed the narrative summaries from all discontinuations. Additional patients with behaviorally related adverse events were identified and reviewed (ISS Numbers: 133, 148,153, 217, 1948, 2134, 2231, 2242, 2471, 2479, 2485, 2533, 2582, 2684, 2807, 4901,4911, 4927, 5046, 5049, 5053, and 5082). These case were similar to the behavioral adverse events leading to discontinuation in the controlled epilepsy studies.

Other discontinuation in all adult epilepsy studies of interest (liver, hematologic, renal or hypersensitivity events) included:

1582 This 44 y/o male with a baseline GGT of 731 IU/L was receiving levetiracetam 2500 mg/day for 577 days when GGT peaked at 1827 IU/L. At this time other liver enzymes were AST 78 IU/L, ALT 105 IU/l , total bilirubin 1.1 mg/dl and alkaline phosphatase 378 IU/L. Levetiracetam was discontinued and at the last post-treatment visit GGT was 780 IU/L, AST 49 IU/L, ALT 73 IU/L, and alkaline phosphatase 295 IU/L.

2321 This 52 y/o male was receiving levetiracetam 3000 mg/day for 268 days when routine blood sampling revealed a GGT of 641 U/L, AST 121 U/L, ALT 182 U/L and total bilirubin of 1.4 mg/dl. Levetiracetam and valproic acid were both withdrawn. His ALT and AST normalized, total bilirubin decreased and GGT was still mildly elevated (179 U/L) at 4 months after discontinuation. Representative laboratory values are charted below.

Date	Levetiracetam mg/day	Total Bilirubin mg/dl (normal 0.2-1.)	GGT IU/L (normal 9-50)	Alkaline Phos. IU/L (normal 53-128)	AST IU/L (normal 10-30)	ALT IU/l (normal 10-30)
04/12/95	baseline	0.5	46	76	24	18
07/24/95	1000	0.4	58	80	25	18
10/09/95	3000	0.4	73	76	23	21
01/03/96	3000	1.4	641	150	121	182
04/10/96	post-treatment	0.6	179	167	33	23

2791 This 37 y/o female was receiving levetiracetam for 182 days when she was noted to have a significant rise in liver enzymes (ALT 256 U/L, AST 116 U/L, GGT 126 U/L, and Alk Phos. 259 U/L). The patient was hospitalized on 06/19/96 for further investigation of elevated liver enzymes. Levetiracetam dosage was decreased to 1000 mg/day and an ultrasound of the abdomen was reported as normal. Levetiracetam was discontinued and enzymes returned towards baseline. Concomitant antiepileptic medication at the time of the event was carbamazipine 600 mg/day, which the patient had taken since 1993.

Date	Levetiracetam mg/day	Total Bilirubin mg/dl (normal 0.2-2.0)	Alkaline Pnos. U/L (normal 73-207)	GGT U/L (normal 5-25)	AST U/L (normal 0-21)	ALT U/L (normal 0-21)
09/06/95	baseline	0.8	188	40	20	32
04/10/96	3000	0.3	222	51	46	95
05/17/96	3000	0.6	259	126	116	256
07/01/96	levetiracetam discontinued					
07/15/96		0.8	190	47	26	48

2617 This 51 y/o male with a history of alcohol abuse was noted to have an elevated GGT level when he initially entered into study N132 (level not specified). On entry into Study N147 his GGT level was 497 U/L. While receiving levetiracetam 4000 mg/day for 622 days the patient was discontinued because of reported excessive alcohol intake with a persistently elevated GGT.

2426 This 53 y/o black female was receiving levetiracetam 1500 mg/day for 247 days when routine blood sampling revealed a WBC of 4.2 x 10^3/L and a neutrophil count of 1.79 x 10^3/L. Study medication was withdrawn and a final neutrophil count 2 months later was 1.94 x 10^3/L.

2439 This 30 y/o male with a history of glioma, food allergies and intermittent eosinophila since the screening visit of a prior study was receiving levetiracetam 4000 mg/day for 113 days when the eosinophil level was 18.4%. At the time of the eosinophil elevation he was also receiving chemotherapy. The eosinophil level was still elevated 2 weeks after discontinuation of levetiracetam and decreased to 7.7% several months later after resection of his glioma.

2551 This 57 y/o black female with a history of low WBC and low neutrophil counts was receiving levetiracetam 1000 mg/day for 15 days when routine lab revealed a WBC of 3.1 x 10^3/L and a neutrophil count of 1.17 x 10^3/L. These values were lower than baseline and she was discontinued from the study. The event was considered resolved at her final visit 2 weeks later.

1850 This 47 y/o male patient was receiving levetiracetam 2000 mg/day for 34 weeks when he was hospitalized because of "fits". Rhabdomyolysis developed and led to acute renal failure. Levetiracetam as well as gabapentin were discontinued. Carbamazepine dosage was reduced and phenytoin added to his regimen The patient is reported to have recovered after a 20 day hospitalization.

2734 This 40 y/o female was receiving levetiracetam 500 mg day for 181 days when she developed a rash (not further described) which reportedly resolved after 6 months.

8.3.4 Discontinuations Due to Adverse Events in Trials for Other Indications

Among the 1558 levetiracetam exposed patients participating in trials for other indications 1292 (83%) completed study participation. Adverse events were the most frequent reason for termination and were greater among levetiracetam treated patients in controlled trials of cognition and anxiety. The general reasons for termination are listed in Table 51. For purposes of comparison it should be noted that patients in studies for other indications received treatment for shorter periods of time and at lower doses than in the epilepsy studies.

Table 51: Classification and Enumeration of Discontinuations from Treatment: Other Indications

Reason for Discontinuing	Cognition		Anxiety			DVT	Total
	Levetir-acetam	Placebo	Levetir-acetam	Placebo	Open Label		
Exposed	394	344	1084	525	77	3	1558
Completed	346 (88%)	307 (89%)	891 (82%)	453 (86%)	53 (69%)	2 (67%)	1292 (83%)
Reason for Discontinuation							
Adverse Event	38 (9.6%)	16 (4.7%)	86 (7.9%)	29 (5.5%)	7 (9.1%)	1 (33.3%)	132 (8.5%)
Lack of Efficacy	1 (0.3%)	0	28 (2.6%)	13 (2.5%)	0	0	29 (1.9%)
Withdrawal Consent	2 (0.5%)	9 (2.6%)	28 (2.6%)	7 (1.3%)	13 (17%)	0	43 (2.8%)
Protocol Violation	5 (1.3%)	10 (2.9%)	33 (3.0%)	14 (2.7%)	4 (5.2%)	0	42 (2.7%)
Loss of Follow-up	2 (0.5%)	1 (0.3%)	13 (1.2%)	4 (0.8%)	0	0	15 (1.0%)
Other	0	1 (0.3%)	5 (0.5%)	5 (1.0%)	0	0	5 (0.3%)

based on sponsor's Table 26, SU, Vol. 1, p 90

I used the sponsor's Table 5.10 from Amendment 20 to summarize AEs leading to discontinuation of at least 0.4% of levetiracetam exposed epilepsy patients enrolled in studies of other indications. (Table 52).

Table 52: Adverse Events Causing Discontinuation in ≥0.4% of Levetiracetam Treated Patients in Studies of Other Indications

Body System/ Preferred Term	Levetiracetam (N =1558) AEs (N = 132)[a]	Placebo (N = 869) AEs (N = 45)
Body as a Whole		
Asthenia	10 (0.6%)	2 (0.2%)
Headache	11 (0.7%)	5 (0.6%)
Digestive System		
Nausea	19 (1.2%)	5 (0.6%)
Nervous System		
Depression	9 (0.6%)	3 (0.3%)
Dizziness	17 (1.1%)	5 (0.6%)
Somnolence	26 (1.7%)	2 (0.2%)
Vertigo	7 (0.4%)	2 (0.2%)

based on sponsor's Table 5.10, Amendment 20, pp. 29 - 36

[a] An individual patient can have multiple AEs (maximum 4) related

8.4 Adverse Event Incidence Tables

8.4.1 Approach to Eliciting Adverse Events

Adverse Experiences (AEs) were defined by the sponsor as "... any undesirable experience concerning the health of the study participant whether or not considered related to investigational treatment... Adverse events could include intercurrent illnesses, hypersensitivity reactions, toxicity, injury, clinically relevant laboratory abnormalities, overdose, or pregnancy."

Investigators obtained adverse event information at each study visit from spontaneous reports by the subject, through standard questioning by the investigator, and by laboratory and other safety assessments.

8.4.2 Adverse Events Categorization and Preferred Terms

All AEs were classified according to Version 5.0 of the COSTART dictionary for International Monitoring of Adverse Reactions to Drugs.

The sponsor's method for ensuring consistency and accuracy of adverse event coding primarily involved medical data validation and review of each individual study. Two additional verifications of adverse event coding were conducted. The sponsor reviewed all verbatim terms coded to a particular COSTART term in order to identify instances where an inappropriate COSTART term was chosen. A total of 169 (0.6% of all adverse event occurrences) were found to be inaccurately coded by this method. The second method involved the review of similar adverse event verbatim terms in order to evaluate consistency of associated COSTART codes. The sponsor reports that this review did not indicate the existence of major inconsistencies in adverse event coding.

In addition to reporting adverse experiences by the COSTART body system categories, the sponsor created 61 groupings of COSTART preferred terms that were felt to be more clinically meaningful.

The sponsor's tabulation of adverse events is based on the premise that a given adverse event is counted only once within a subject in its worst severity, attribution to treatment, and outcome.

8.4.3 Treatment Emergent Adverse Events in Adult Patients with Epilepsy

The sponsor presented treatment emergent adverse events separately for the four adequate and well-controlled studies and for the entire epilepsy patient group exposed to levetiracetam. There was no separate

presentation of the extension studies (i.e., treatment emergent adverse events excluding those from the controlled epilepsy studies).

8.4.3.1 Adequate and Well-Controlled Studies

The sponsor summarized treatment emergent adverse events in two versions. In one version only the first double blind period of Study N051 (crossover study) is included (672 levetiracetam patients, 351 placebo patients); in the second version both double blind periods of Study N051 are included (769 levetiracetam patients, 439 placebo patients).

Table 53 provides the incidence of treatment emergent adverse events that occurred in at least 3% of patients in either treatment group. The incidence of adverse events is similar whether one or both double blind periods of Study N051 are considered. The most common adverse events (in at least 10%) among levetiracetam treated patients were somnolence (14.8%), asthenia (14.7%), headache (13.7%), infection (13.4%) and accidental injury (10.7%).

Review of sponsor's Table 7.2.c.1 providing the number and percentage of any treatment-emergent adverse events revealed only one event which occurred using a more restrictive criteria of occurring in at least 2% of the levetiracetam-treated patients and twice as frequent compared to placebo-treated patients. This event was hostility reported in 2.3% of levetiracetam-treated patients and 0.9% of placebo patients.

Table 53: Incidence of Adverse Events by Body System Reported in ≥ 3.0% of Patients in the Placebo-Controlled Studies in Patients with Epilepsy

Body System/ Preferred Term	First Period of N051 Only		Both Periods of N051	
	Levetiracetam (N = 672)	Placebo (N = 351)	Levetiracetam (N = 769)	Placebo (N = 439)
Body as a Whole				
abdominal pain	25 (3.7%)	18 (5.1%)	30 (3.9%)	20 (4.6%)
Accidental Injury [a]	69 (10.3%)	58 (16.5%)	82 (10.7%)	68 (15.5%)
Asthenia [a]	95 (14.1%)	34 (9.7%)	113 (14.7%)	40 (9.1%)
Back pain	27 (4.0%)	16 (4.6%)	30 (3.9%)	21 (4.8%)
Flu syndrome	28 (4.2%)	21 (6.0%)	31 (4.0%)	24 (5.5%)
Headache	88 (13.1%)	48 (13.7%)	105 (13.7%)	59 (13.4%)
Infection [a]	89 (13.2%)	26 (7.4%)	103 (13.4%)	33 (7.5%)
Pain	44 (6.5%)	23 (6.6%)	52 (6.8%)	26 (5.9%)
Digestive System				
Diarrhea	28 (4.2%)	18 (5.1%)	33 (4.3%)	21 (4.8%)
Dyspepsia	20 (3.0%)	12 (3.4%)	20 (2.6%)	12 (2.7%)
Nausea	28 (4.2%)	16 (4.6%)	34 (4.4%)	19 (4.3%)
Nervous System				
Convulsion	40 (6.0%)	24 (6.8%)	53 (6.9%)	35 (8.0%)
Depression	27 (4.0%)	8 (2.3%)	31 (4.0%)	10 (2.3%)
Dizziness [a]	62 (9.2%)	15 (4.3%)	68 (8.8%)	18 (4.1%)
Insomnia	20 (3.0%)	10(2.8%)	24 (3.1%)	11 (2.5%)
Nervousness [a]	26 (3.9%)	6 (1.7%)	30 (3.9%)	8 (1.8%)
Somnolence [a]	100 (14.9%)	34 (9.7%)	114 (14.8%)	37 (8.4%)
Respiratory System				
Pharyngitis	38 (5.7%)	13 (3.7%)	47 (6.1%)	17 (3.9%)
Rhinnitis	29 (4.3%)	9 (2.6%)	34 (4.4%)	11 (2.5%)
Skin and Appendages				
Rash	19 (2.8%)	14 (4.0%)	24 (3.1%)	14 (3.2%)
Urogenital System				
UTI	13 (1.9%)	12 (3.4%)	18 (2.3%)	13 (3.0%)

based on sponsor's Table 40A , SU p. 127

[a] 95% CI of the difference does not include zero

The sponsor examined the time to onset of treatment emergent adverse events (Table 54) Among the most frequently reported adverse events (at least 5% overall and more frequent in the levetiracetam treatment group) asthenia somnolence and dizziness appeared to occur early in treatment.

Table 54: Incidence of Adverse Events by Onset (events in ≥ 5.0% of Levetiracetam Patients Overall and More than in the Placebo group, (both crossover periods of Study N051)

Body System/ Preferred Term	1d - ≤ 4wks (N = 769)	>4wk-≤3mo (N = 732)	>3mo-≤6mo (N = 679)	>6mo-≤1yr (N =90)	Overall (N = 769)
Body as a Whole					
Asthenia	69 (9.0%)	28 (3.8%)	21 (3.1%)	2 (2.2%)	113 (14.7%)
Headache	58 (7.5%)	38 (5.2%)	29 (4.3%)	5 (5.6%)	105 (13.7%)
Infection	26 (3.4%)	46 (6.3%)	37 (5.4%)	4 (4.4%)	103 (13.4%)
Pain	14 (1.8%)	23 (3.1%)	17 (2.5%)	2 (2.2%)	52 (6.8%)
Nervous System					
Dizziness	37 (4.8%)	32 (4.4%)	8 (1.2%)	1 (1.1%)	68 (8.8%)
Somnolence	90 (11.7%)	19 (2.6%)	9 (1.3%)	4 (4.4%)	114 (14.8%)
Respiratory System					
Pharyngitis	12 (1.6%)	21 (2.9%)	14 (2.1%)	2 (2.2%)	47 (6.1%)

based on sponsors Table 42A, SU, p. 130

The sponsor examined the effect of randomized dose on treatment emergent adverse events (Table 55). Somnolence was increased at the 4000 mg/day dose. The sponsor noted several other adverse events that were greater in the highest dose group but not greater among levetiracetam patients overall compared to placebo patients. These adverse events include nausea (13.2% 4000 mg/day vs. 4.2% all levetiracetam), vomiting (7.9% 4000 mg/day vs. 2.8% all levetiracetam, and dyspepsia (7.9% 4000 mg/day vs. 3.0% all levetiracetam).

Table 55: Incidence of Adverse Events by Randomized Dose (events in ≥3.0% of levetiracetam patients overall and more than in the placebo group, first period of Study N051)

Body System/ Preferred Term	By Dose (mg/day)				Overall	
	1000 (N = 204)	2000 (N = 148)	3000 (N = 282)	4000 (N = 38)	Leve. (N = 672)	PBO (N =351)
Body as a Whole						
Asthenia	25(12.3%)	27(18.2%)	38(13.5%)	5 (13.2%)	95(14.1%)	34(9.7%)
Infection	36(17.6%)	8 (5.4%)	39(13.8%)	6 (15.8%)	89(13.2%)	26(7.4%)
Nervous System						
Depression	8 (3.9%)	8 (5.4%)	8 (2.8%)	3 (7.9%)	27 (4.0%)	8 (2.3%)
Dizziness	22(10.8%)	9 (6.1%)	27(9.6%)	4 (10.5%)	62 (9.2%)	15 (4.3%)
Insomnia	5 (2.5%)	2 (1.4%)	11 (3.9%)	2 (5.3%)	20 (3.0%)	10 (2.8%)
Nervousness	7 (3.4%)	6 (4.1%)	11 (3.9%)	2 (5.3%)	26 (3.9%)	6 (1.7%)
Somnolence	30(14.7%)	23(15.5%)	30(10.6%)	17(44.7%)	100 (15%)	34 (9.7%)
Respiratory System						
Pharyngitis	16(17.8%)	10 (6.8%)	10 (3.5%)	2 (5.3%)	38 (5.7%)	13 (3.7%)
Rhinitis	18 (8.8%)	1 (0.7%)	9 (3.2%)	1 (2.6%)	29 (4.3%)	9 (2.6%)

based on sponsor's Table 44A, SU, p. 133

8.4.3.2 All Epilepsy Studies

The sponsor begins discussion of adverse events in all adult epilepsy patients on page 152 of the SU. Among 1393 adult patients in studies of epilepsy 1243 (89%) had at least one treatment-emergent adverse event. The most commonly reported events were accidental injury (25%), headache (25%), infection (23%), asthenia (22%), somnolence (22%), and convulsion (22%). Table 56 provides the incidence of adverse events that occurred in at least 5% of patients exposed to levetiracetam.

Table 56: Incidence of Adverse Experiences by Body System Reported in ≥ 5.0% of Adult Epilepsy Patients Exposed to Levetiracetam (through November 30, 1998)

Body System/ Preferred Term	(N =1393)	Body System/ Preferred Term	(N = 1393)
Body as a Whole		**Nervous System (cont.)**	
Abdominal Pain	129 (9.3%)	Convulsion	313 (22.5%)
Accidental Injury	349 (25.1%)	Depression	136 (9.8%)
Asthenia	309 (22.2%)	Dizziness	249 (17.9%)
Back Pain	112 (8.0%)	Insomnia	97 (7.0%)
Flu Syndrome	141 (10.1%)	Nervousness	103 (7.4%)
Headache	344 (24.7%)	Somnolence	308 (22.1%)
Infection	323 (23.2%)	Tremor	96 (6.9%)
Pain	202 (14.5%)	**Respiratory System**	
Digestive System		Bronchitis	67 (4.8%)
Diarrhea	129 (9.3%)	Pharyngitis	154 (11.1%)
Dyspepsia	72 (5.2%)	Rhinitis	129 (9.3%)
Nausea	120 (8.6%)	**Skin and Appendages**	
Nervous System		Rash	107 (7.7%)
Anxiety	80 (5.7%)	**Urogenital System**	
Ataxia	86 (6.2%)	Urinary Tract Infection	96 (6.9%)

based on sponsor's Table 55A, SU Vol. 2, p 154

8.4.3.3 Non-Epilepsy Indications

The sponsor begins discussion of adverse experiences in non-epilepsy indications on page 172 of the SU. Among 1558 patients randomized to levetiracetam 864 (56%) experienced at least one treatment-emergent adverse event and among 869 placebo-treated patients 422 (49%) experienced at least one treatment-emergent adverse event. Table 57 provides the incidence of adverse events that occurred in at least 1% of patients exposed to levetiracetam.

Table 57: Incidence of Adverse Experiences by Body System Reported in ≥ 1.0% of Patients Levetiracetam in Non-Epilepsy Indications

Body System/ Preferred Term	Levetiracetam	Placebo
Body as a Whole		
Asthenia	122 (7.8%)	57 (6.6%)
Back Pain	38 (2.4%)	16 (1.8%)
Flu Syndrome	32 (2.1%)	16 (1.8%)
Infection	39 (2.5%)	17 (2.0%)
Digestive System		
Anorexia	16 (1.0%)	7 (0.8%)
Dry Mouth	18 (1.2%)	3 (0.3%)
Dyspepsia	28 (1.8%)	10 (1.2%)
GGT Increased	17 (1.1%)	9 (1.0%)
Nausea	56 (3.6%)	21 (2.4%)
Hemic and Lymphatic System		
Leukopenia	28 (1.8%)	5 (0.6%)
Nervous System		
Depression	25 (1.6%)	10 (1.2%)
Dizziness	82 (5.3%)	29 (3.3%)
Nervousness	23 (1.5%)	11 (1.3%)
Somnolence	129 (8.3%)	31 (3.6%)
Thinking Abnormal	15 (1.0%)	1 (0.1%)
Respiratory System		
Bronchitis	27 (1.7%)	13 (1.5%)
Pharynitis	37 (2.4%)	19 (2.2%)
Rhinitis	29 (1.9%)	12 (1.4%)
Skin and Appendages		
Pruitus	16 (1.0%)	7 (0.8%)
Urogenital System		
Urinary Tract Infection	27 (1.7%)	12 (1.4%)

based on sponsor's Table 64, Su Vol. 2, p 173

8.5 Serious Adverse Events

The sponsor defined serious adverse events (SAEs) as "... an adverse experience of such seriousness (as defined by the Code of Federal Regulations) that it had to be reported immediately to UCB or its representatives." The following events were considered SAEs:

- Death
- Inpatient hospitalization
- Permanent or significant disability/incapacity
- Prolongation of an existing stay in the hospital
- Any life-threatening condition (immediate risk of dying)
- Congenital abnormality/birth defect
- Diagnosis of cancer in subject or offspring
- Overdose
- Any adverse event reported to any Health Authorities by an investigator
- Physical or psychic dependence on the investigational treatment
- An adverse event which may indicate that a serious adverse event was developing

SAEs occurring up to 30 days after cessation of investigational treatment had to be reported.

8.5.1.1 Adequate and Well Controlled Studies

The sponsor begins discussion of serious treatment-emergent adverse events in controlled studies on page 146 of the SU. When considering only the first period of Study N051, 58 (8.6%) of levetiracetam-treated patients and 25 (7.1%) of placebo treated patients experienced one or more serious adverse events. Serious adverse events occurring in 2 or more patients in either treatment group are summarized by the sponsor in Table 58.

Table 58: Incidence of Serious Adverse Events by Body System That Occurred in 2 or More Patients in Either Treatment Group, Controlled Studies in Epilepsy Patients

Body System/ Preferred Term	First Period of N051 Only		Both Periods of N051	
	Levetiracetam (N = 672)	Placebo (N = 351)	Levetiracetam (N = 769)	Placebo (N = 439)
Body as a Whole				
Abscess	2 (0.3%)	0	2 (0.3%)	0
Accidental Injury	10 (1.5%)	6 (1.7%)	12 (1.6%)	7 (1.6%)
Headache	3 (0.4%)	0	3 (0.4%)	0
Suicide Attempt	3 (0.4%)	0	4 (0.5%)	0
Nervous System				
Confusion	0	1 (0.3%)	0	2 (0.5%)
Convulsion	10 (1.5%)	6 (1.7%)	14 (1.8%)	6 (1.4%)
Grand Mal Convul.	4 (0.6%)	3 (0.9%)	8 (1.0%)	6 (1.4%)
Personality Dis.	3 (0.4%)	0	3 (0.4%)	0
Psychosis	2 (0.3%)	0	2 (0.3%)	0
Somnolence	2 (0.3%)	0	2 (0.3%)	0
Status Epi Partial	3 (0.4%)	1 (0.3%)	3 (0.4%)	4 (0.9%)

Sponsor's Table 52A, SU, p.148

I reviewed all the case narratives for serious adverse events in controlled trials of epilepsy. Events which are noteworthy and not already included as either a death or discontinuation include the following:

1854 This 32 y/o male with a history of depression and automutilation was receiving levetiracetam 2000 mg/day for 47 days when he was hospitalized for attempted suicide and depression. He was treated medically without interruption or change in his levetiracetam dose.

1945 This 40 y/o male was receiving placebo for 14 days when he was hospitalized for anxiety, depression and insomnia felt to be related to recent deaths of friends. The study medication was not altered.

2034 This 30 y/o female was receiving levetiracetam 2000 mg/day for 17 weeks when she attempted suicide by drinking a glass of alcohol, 2 tablets of carbamazipine, and one tablet of phenobarbital. While on levetiracetam therapy the patient was perceived to be more emotionally labile and occasionally aggressive which was unusual for her. The patient continued in the trial as planned.

2102 This 44 y/o female with a history of depressive symptoms was receiving levetiracetam 4000 mg/day for 83 days took an overdose of Dipiperon. No action was taken and the patient recovered the same day.

8.5.1.2 Serious Adverse Events All Adult Epilepsy Studies

Among all adult epilepsy patients 334 (24%) experienced one or more serious adverse events. The most frequently reported SAEs were convulsion (5.6%), accidental injury (4.2%), grand mal convulsion (1.0%), and status epilepticus not otherwise specified (1.0%). Serious adverse events occurring in 3 or more patients are summarized by the sponsor in Table 59.

Table 59: Incidence of Serious Adverse Events by Body System That Occurred in 3 or More Levetiracetam-Treated Patients, All Adult Epilepsy Patients (Through November 30, 1998)

Body System/ Preferred Term	(N =1393)	Body System/ Preferred Term	(N = 1393)
Body as a Whole		**Nervous System**	
Abdominal Pain	4 (0.3%)	Ataxia	3 (0.2%)
Accidental Injury	58 (4.2%)	CNS neoplasia	5 (0.4%)
Accidental overdose	5 (0.4%)	Confusion	6 (0.4%)
Back Pain	4 (0.3%)	Convulsion	78 (5.6%)
Cellulitis	3 (0.2%)	Depression	5 (0.4%)
Death	3 (0.2%)	Grand mal convulsion	14 (1.0%)
Headache	4 (0.3%)	Hostility	4 (0.3%)
Infection	5 (0.4%)	Personality disorder	7 (0.5%)
Intentional overdose	4 (0.3%)	Psychosis	4 (0.3%)
Neoplasm	3 (0.2%)	Somnolence	6 (0.4%)
Overdose	3 (0.2%)	Status epilep gen. conv.	3 (0.2%)
Pain	3 (0.2%)	Status epilepticus NOS	14 (1.0%)
SUDEP	5 (0.4%)	Status epilepticus partial	8 (0.6%)
Suicide attempt	8 (0.6%)	**Respiratory System**	
Cardiovascular System		Pharyngitis	5 (0.4%)
Cerebral hemorrhage	4 (0.3%)	Pneumonia	6 (0.4%)
Cerebral ischemia	3 (0.2%)	**Urogenital System**	
Varicose vein	3 (0.2%)	Metorrhagia	4 (0.3%)
Digestive System		Unintended pregnancy	1 (0.1%)
Cholelithiasis	4 (0.3%)		

based on sponsor's Table 60A, SU, Vol. 2 p 166

Events which are noteworthy and not already included as either a death or discontinuation include the following:

176 This 24 y/o female was receiving levetiracetam 2000 mg/day for 1411 days when leukopenia (3400 leukocytes per mm^3) was noted. The patient was continued on therapy and the leuckocytes eventually returned above 4000 per mm^3.

2135 This 21 y/o female was receiving levetiracetam 500 mg/day with a total exposure of 491 days when neutropenia, thrombocytopenia and lymphopenia were noted (04/27/95). The patient was continued on levetiracetam at a reduced dose of 250 mg/day with improvement in her indices. Concomitant medications included carbamazepine 1200 mg/day, lamotrigine 250 mg/day and sodium valproate 1500 mg/day. Levetiracetam was discontinued on 05/08/95 and on 05/25/5 values from blood tests were reported as still "low".

Date	Levetiracetam mg/day	WBC x 10^9/L (Normal	Neutophils x 10^9/L	Lymphocytes x10^9/L	Platelets x 10^9/L
12 23 93	baseline	3.8	1.6	1.6	169
04 27 95	500 mg	2.5	0.6	1.3	81
05 01 95	250 mg	3.5	1.6	1.3	164
05 04 95	250 mg	2.7	1.1	1.3	166

8.5.2 Serious Adverse Events in Studies of Other Indications

Overall 36 (2.3%) levetiracetam-treated patients and 18 (2.1%) of placebo-treated patients reported serious adverse events in studies of other indications.

In studies of cognitive impairment 16 levetiracetam-treated patients reported serious adverse events. Of note one patient had an elevation of liver enzymes that resolved with discontinuation of levetiracetam and is summarized below.

Patient **4257** was receiving levetiracetam 1000 mg/day for 2 days when total bilirubin and alkaline phosphatase were noted to be elevated. Concomitant medication consisted of bromocriptine 40 mg/day for the past 2 years. The patient had slightly elevated values of total bilirubin and alkaline phosphatase at baseline. There was no evidence of hemolysis. The patient continued to have intermittent elevations of total bilrubin and alkaline phosphatase following discontinuation of levetiracetam.

In studies of anxiety 19 levetiracetam-treated patients reported serious adverse events. Events reported in two or more levetiracetam-treated patients included accidental injury (0.3%) and suicide attempt 2 (0.2%). Of note one patient with thrombocytopenia was reported, however the event was most likely due to concomitant heparin therapy.

1667 This 91 y/o female was receiving levetiracetam 250 mg/day for 30 days when she was hospitalized for right iliac phlebitis. The patient was treated with heparin and the platelet count decreased from 600.000 x 10^6/L to 40,000 x 10^6/L within 48 hours. Heparin was discontinued and the thrombocytopenia resolved.

8.6 Named Patient Use

In total 69 patients received levetiracetam on a Named Patient Use basis Forty-six of these patients had participated in a UCB study and were awaiting entry into an extension protocol. Due to regulatory requirements 6 patients enrolled in Denmark were not allowed to participate in any further studies and continued to receive levetiracetam on a Named Patient Use basis. There were no adverse events of significance among the forty-six patients during the time of participation in the Named Patient Use program.

Twenty-three patients received levetiracetam only on a Named Patient Use basis. Adverse events were reported for six patients and include vestibular reaction/nystagmus, low neutrophil count, skin rash, hospitalization for frequent seizures, and behavior problems. Three adverse events deserve further discussion.

001/009 This a 42 y/o female was receiving levetiracetam 500 mg/day for 20 days when her WBC and neutrophil counts had fallen to 1.99 x 10^9/L and 0.82 x 10^9/L, respectively. Baseline values for WBCs and neutrophils were 3.5 x 10^9/L and 1.9 x 10^9/L, respectively. Five days following discontinuation of levetiracetam her WBC was 1.8 x 10^9/L, and neutrophils 0.66 x 10^9/L.

A report from her physician notes that the patient has a history of cycling neutrophil counts prior to receiving any antiepeleptic medications. The patient also had low neutrophil counts while treated with felbamte in the past. A bone marrow examination was preformed after discontinuation of levetiracetam indicating normal neutrophil production. The patient's local hematologist attributes the low neutrophil counts to increased peripheral consumption.

005/002 This 34 y/o male was receiving levetiracetam 500 mg/day for a few days when he developed a rash. Reportedly the patient has a history of intermittent skin rashes. No follow-up information is provided.

002/026 This 19 y/o female started receiving levetiracetam in August of 1997 at an unknown dose. She discontinued therapy in April of 1998 because of behavioral problems. Even though her seizure frequency was reduced she felt that her behavior had become more aggressive.

8.7 Laboratory Findings

The sponsor discusses the methods used to evaluate laboratory data on page 41 of the SU. The protocols for the studies included in the N999 database required laboratory monitoring. In general the required tests included hematology, blood chemistry, and urinalysis. Urinalysis was typically performed using a dipstick test. Several laboratories were used in the analysis of blood and urine data, therefore multiple normal

reference ranges existed for each laboratory parameter. Normal ranges were established and applied to blood parameters for which normal ranges were not provided with the data. Criteria for identifying adult subjects with treatment-emergent possibly clinically significant (PCS) abnormal values were defined according to FDA Division of Neuropharmacologic Products guidelines with some UCB modifications (p 44 of SU).

All statistical comparisons were for descriptive purposes only. For each continuous parameter, within treatment group changes from baseline at the final visit were compared using a Wilcoxon Signed-Rank test. The change from baseline at the final visit was compared between treatment groups using a Wilcoxon Rank-Sum test.

Patients who met the criteria for a possibly clinically significant laboratory abnormality but were not classified as a death, discontinuation, or serious adverse event have no narrative summary or CRF provided. However the sponsor provided a listing of laboratory data for patients who met the criteria for a possibly clinically significant laboratory value. The listing includes all laboratory values by study period, daily dose, and treatment date.

The sponsor begins discussion of the laboratory evaluation from the levetiracetam development program on page 183 of the SU. Patients with treatment-emergent laboratory abnormalities that were not possibly clinically significant and that were not classified as a death, discontinuation, or serious adverse event were not reviewed further other than for those comments provided by the sponsor related to specific cases.

8.7.1 Tests Reflective of Liver Function

8.7.1.1 Controlled Trials: Mean Change From Baseline Analysis

The following table summarizes the results from the mean change from baseline analysis for liver enzyme data for controlled epilepsy studies (both crossover periods of Study N051). The mean changes from baseline are small and tend to be in the same direction for levetiracetam and placebo. Findings are similar when only the first period of Study N051 is considered.

Table 60: Summary of Mean Change from Baseline to Final Visit by Treatment Group: Liver Function Tests in Adequate and Well Controlled Studies (both crossover periods of Study N051)

Parameter (units)	Levetiracetam Mean change from baseline (n)	Placebo Mean change from baseline (n)
AST (IU/L)	-0.39 (762)	-0.10 (435)
ALT (IU/L)	-0.60 (762)	-0.05 (435)
GGT (IU/L)	-0.01 (762)	0.05 (435)
Total bilirubin (mg/dL)	0.01 (762)	0 (434)
Alkaline phosphatase IU/L	-1.67 (761)	-0.08 (435)

based on sponsor's Table 74A, SU Vol. 2 p 186

8.7.1.2 Controlled Trials: Patients with Possibly Clinically Significant Abnormalities

The sponsor identified all patients with a first occurrence of a clinically significant liver enzyme parameter ($\geq$3 times upper limit of normal for AST, ALT, GGT, Alkaline phosphatase, and $\geq$ 2.0 mg/dL for total bilirubin). Among levetiracetam-treated patients 11 (1.4%) were identified and among placebo-treated patients 6 (1.4%) were identified (Table 61).

Table 61: Patients with a Possibly Clinically Significant Liver Function Test Abnormalities

Summary of Epilepsy Patients with Possibly Clinically Significant Liver Function Test Abnormalities by Treatment Group (First Occurrence) in Adequate and Well-controlled Studies in Epilepsy

Patient No.	Parameter	Baseline Value	Time on Drug (days)	On-treatment Value	Final Value	Time post-observation (days)
FIRST PERIOD ONLY						
Levetiracetam Treatment Group						
2265	ALT	193 IU/L	29	151 IU/L	164 IU/L	6 mo
2412	ALT	62 IU/L	15	108 IU/L	56 IU/L	3 mo
2459	ALT	145 IU/L	26	88 IU/L	98 IU/L	77 days
2791	ALT	44 IU/L	28	121 IU/L	95 IU/L	3 mo
3002	ALT	40 IU/L	88	80 IU/L	79 IU/L	50 days
2974	GGT	20 IU/L	78	104 IU/L	31 IU/L	35 days
3069	GGT	18 IU/L	113	77 IU/L	77 IU/L	30 days
2097	Total bilirubin	1 mg/dl	44	2 mg/dl	2.2 mg/dl	4 mo
2686	Alk. phosphatase	1175 IU/L	16	1213 IU/L	1202 IU/L	3 mo
Placebo Treatment Group						
2194	AST	24 IU/L	106	118 IU/L	39 IU/L	21 days
1867	ALT	122 IU/L	58	176 IU/L	125 IU/L	50 days
2397	ALT	201 IU/L	15	146 IU/L	178 IU/L	82 days
2509	ALT	32 IU/L	28	305 IU/L	44 IU/L	70 days
2880	ALT	86 IU/L	29	110 IU/L	132 IU/L	54 days
3096	ALT	16 IU/L	85	73 IU/L	103 IU/L	28 days
	GGT	25 IU/L	85	80 IU/L	93 IU/L	28 days
SECOND PERIOD OF STUDY N051						
Levetiracetam Treatment Group						
2273	ALT	115 IU/L	134	163 IU/L	57 IU/L	56 days
1951	GGT	45 IU/L	140	170 IU/L	129 IU/L	4 mo

This patient also subsequently met criteria while participating in Period B of Study N051 while on levetiracetam: the first occurrence value was 168 IU/L after 59 days of treatment and the final value was 157 IU/L 33 days later.

Among the 11 levetiracetam-treated patients identified with a PCS liver function test two were reported as an adverse event. Patient 2791 has already been discussed with serious adverse events. Patient number 2974 had an elevation of GGT judged to be of mild severity and transient in nature. The patients GGT returned to normal one month later without change in levetiracetam dose (3000 mg/day). Among the 6 levetiracetam-treated patients with a PCS elevated ALT all had elevated ALT values at baseline. One levetiracetam-treated patient (2097) had a PCS elevated total bilirubin of 2.2 mg/dl after receiving levetiracetam 2000 mg/day for 97 days. After 288 days of levetiracetam 2000 mg/day total bilirubin was 1.8 mg/dl. The final total bilirubin (3 months after the previous value) for this patient during down-titration and while on placebo was 2.0 mg/dl. None of the levetiracetam-treated patients had a PCS elevated AST value.

8.7.1.3 Controlled Trials: Patients with Treatment-Emergent Adverse Event Reflective of Liver Function

There were 9 (1.2%) levetiracetam-treated patients and 8 (1.8%) placebo-treated patients with a treatment-emergent adverse event reflective of liver function abnormality. Only two of the patients (2791 and 2974)

met the criteria for a possibly clinically significant liver function abnormality and have already been discussed. Table 62 summarizes the treatment-emergent adverse events reflective of liver function.

Table 62: Treatment-Emergent Adverse Events Reflective of Liver Function (Controlled Epilepsy Studies)

UCB Adverse Event Grouping Term / Preferred Term	Baseline (N = 1023)	Levetiracetam (N = 769)	Placebo (N = 439)
Hepatobiliary Symptoms	24 (2.3%)	9 (1.2%)	8 (1.8%)
Alkaline phosphatase increased	1 (0.1%)	1 (0.1%)	2 (0.6%)
Bilirubinemia	0	0	0
Cholecystitis	1 (0.1%)	0	1 (0.2%)
Cholelithiasis	2 (0.2%)	0	1 (0.2%)
GGT increased	20 (2.0%)	4 (0.5%)	5 (1.1%)
Hepatitis	0	0	0
Hepatomegaly	0	0	0
Liver damage	0	1 (0.1%)	0
Liver function tests abnormal	1 (0.1%)	3 (0.4%)	1 (0.2%)
SGOT increased	1(0.1%)	0	0
SGPT increased	2 (0.2%)	0	0

based on sponsor's Table 182A, SU, Vol. 2. p. 355

The sponsor notes that 4 levetiracetam-treated patients had increased GGT (**2328**, **1731**, **2752**, and **2909**), and 1 levetiracetam-treated patient (**3016**) had increased liver enzymes that subsided while the patient remained on levetiracetam.

8.7.1.4 All Adult Epilepsy Patients: Mean Change from Baseline Analysis

To evaluate long-term trends in parameters reflective of liver function the sponsor evaluated mean values over time for all adult epilepsy patients treated with levetiracetam (Table 63). There are limitations that must be kept in mind when examining only the levetiracetam group. No comparator group is available and patients dropping out over time may be for reasons related to an elevated liver enzyme being reported.

That said the sponsor reports that 1361 patients had on-treatment values. Overall there was a slight decrease in mean AST (18.83 IU/L to 17.66 IU/L) and ALT (20.75 IU/L to 19.45 IU/L) from baseline to the final visit. Mean Alkaline phosphatase decreased from 154.76 IU/L at baseline to 136.73 IU/L at the final visit. The range of on-treatment values for AST, ALT and Alkaline phosphatase were 4 to 93 IU/L, 2 to 151 IU/L and 26 to 847 IU/L, respectively.

Mean baseline and final values for GGT were 65.83 IU/L and 63.90 IU/L respectively. GGT values ranged from 4 to 780 IU/L. Mean baseline and final values for total bilirubin were 0.39 and 0.40 mg/dL, respectively. Total bilirubin ranged from 0.1 to 2.3 mg/dL.

The sponsor examined the subset of patients (967) who remained on treatment with levetiracetam for at least 6 months (sponsor's Table 78A, SU Vol. 2 p 192). Keeping in mind that patients treated for more than 6 months may differ from those treated for less time there is no clinically significant trend in mean values for tests reflective of liver function.

Table 63: Liver Function Tests for Patients on Levetiracetam for more than 6 Months

Mean (S.D.) Laboratory Parameter Values for Patients on Levetiracetam for More Than 6 Months: Liver Function Tests (Adult Epilepsy Patients) (through 30 November 1998)

Parameter (unit)	Baseline	Time on Treatment						
		1 - ≤ 4 wk	>4 wk - ≤ 3 mo	>3 - ≤ 6 mo	>6 mo - ≤ 1yrs	>1 - ≤ 2yrs	>2 - ≤ 3yrs	> 3 yrs
N	964	671	956	941	887	656	408	242
AST (IU/L)	19.0 (9.13)	20.3 (9.20)	19.4 (10.26)	19.7 (11.63)	19.0 (11.44)	20.6 (17.13)	19.6 (11.80)	19.0 (9.13)
N	967	669	957	946	893	658	409	241
ALT (IU/L)	21.5 (15.89)	22.6 (15.45)	21.7 (17.15)	21.8 (20.11)	21.5 (18.29)	21.8 (15.82)	21.7 (19.10)	20.0 (12.10)
N	965	670	955	944	889	656	407	240
GGT (IU/L)	65.6 (63.13)	69.0 (67.65)	70.5 (73.01)	71.3 (66.92)	72.6 (75.05)	77.7 (100.7)	76.5 (75.14)	71.4 (70.46)
N	965	668	955	944	889	656	408	239
Total bilirubin (mg/dL)	0.4 (0.15)	0.2 (0.16)	0.4 (0.19)	0.4 (0.20)	0.4 (0.22)	0.4 (0.23)	0.4 (0.20)	0.5 (0.21)
N	967	669	958	946	893	658	409	242
Alkaline phosphatase (IU/L)	157.5 (79.20)	167.4 (88.84)	159.5 (85.17)	157.7 (84.85)	156.1 (85.06)	154.6 (81.86)	126.2 (59.82)	129.8 (61.57)

Please refer to Table 8.2.a for complete tabulation

8.7.1.5 All Adult Epilepsy Patients: Possibly Clinically Significant Abnormalities

The sponsor identified 9 additional patients (not already identified in the controlled trials) who met the criteria for a possibly clinical significant AST level, 15 with a PCS ALT, 4 with a PCS GGT, 3 with a PCS total bilirubin and 2 with a PCS alkaline phosphatase. I reviewed the laboratory listing (Listing 6.b.2) for each of these patients. None of the patients with a PCS ALT, AST, GGT, or alkaline phosphatase had a concomitant elevation of total bilirubin. Among the 3 patients with a PCS elevated total bilirubin patients 2138 and 2600 had isolated elevations of 2.6 mg/dl and 2.3 mg/dl, respectively. Patient 3112 had persistent elevations of total bilirubin while receiving levetiracetam 3000 mg/day from 12/11/97 (2.3 mg/dl) through the last reported value on 7/30/98 (2.3 mg/dl). None of the patients with elevated total bilirubin had concomitant elevations of other liver enzymes.

8.7.1.6 All Adult Epilepsy Patients: Treatment-Emergent Adverse Events Reflective of Liver Function

In addition to the possibly clinically significant abnormalities the sponsor identified 64 additional treatment-emergent adverse events related to a liver parameter: 6 patients with increased alkaline phosphatase; 31 patients with GGT increased; 1 patient with hepatitis; 1 patient with hepatoma; 6 patients with hepatomegaly; 1 patient with a bladder tumor and liver lesions; 5 patients with liver function abnormal; 9 patients with SGOT increased; and 7 patients with SGPT increased.

Nine patients had a treatment emergent adverse event with a possibly clinically significant liver function test. Among these nine patients 2 were reported as serious adverse events that resulted in discontinuation and 1 patient had an outcome of death.

- Patient 163, a 67 y/o female with a 7 year history of hemochromatosis with hepatic cirrhosis, had elevated AST (48 IU/L) and ALT (53 IU/L) after receiving levetiracetam for 254 days in Study N035. The patient was subsequently diagnosed with a hepatoma and died. She is included with the listing of deaths.

- Patient **2321** a 52 y/o male is discussed as a discontinuation in all adult epilepsy studies.This patient's lever enzymes returned towards normal following discontinuation of both levetiracetam and sodium valproate.

- Patient **1582** a 44 y/o male is discussed as a discontinuation in all adult epilepsy studies.

I reviewed listing 6.b.2 and examined the liver functions abnormalities of the remaining 6 patients. None of the transaminase abnormalities were associated with an elevated total bilirubin. The sponsor reports that 2295 was diagnosed with hepatitis A 1 month prior to the elevated liver enzymes. Patient **2617** had elevated ALT, AST and GGT prior to drug treatment and had an adverse event of alcohol abuse. Patient 2910 still had a mildly elevated GGT (49 IU/L) after 815 days of treatment along with an elevated alkaline phosphatase (233 IU/L) and normal AST, ALT and total bilirubin.

8.7.2 Tests Reflective of Kidney Function

8.7.2.1 Controlled Trials: Mean Change From Baseline Analysis

The following table summarizes the results from the mean change from baseline analysis for kidney function in controlled epilepsy studies (both crossover periods of Study N051). The mean changes from baseline are small and comparable between the levetiracetam and placebo-treated groups.

Table 64: Summary of Mean Change from Baseline to Final Visit by Treatment Group: Kidney Function Tests in Adequate and Well Controlled Studies (both crossover periods of Study N051)

Parameter (units)	Levetiracetam Mean change from baseline (n)	Placebo Mean change from baseline (n)
Creatinine (mg/dL)	0.01 (762)	0.00 (435)
Urea (mg/dL)	-0.04 (761)	0.25 (433)
Creatinine clearance (mL/min)	-2.92 (266)	-1.39 (173)

based on sponsor's Table 79A, SU, Vol. 2, p 195

8.7.2.2 Controlled Trials: Patients with Possibly Clinically Significant Abnormalities

There were no PCS creatinine values in either treatment group. With respect to PCS urea values 5 (0.7%) levetiracetam-treated and 4 (0.9%) placebo-treated patients were identified and summarized in the table below (sponsor's Table 81A SU, Vol. 2, p 198).

Table 65: Patients with Possibly Clinically Significant Kidney Function Tests

Summary of Epilepsy Patients with Possibly Clinically Significant Kidney Function Test Abnormalities by Treatment Group (First Occurrence) in Adequate and Well-controlled Studies in Epilepsy

Patient No.	Parameter	Baseline Value	Time on Drug (days)	On-treatment Value	Final Value	Time Post-observation (days)
FIRST PERIOD ONLY						
Levetiracetam Treatment Group						
[illegible]59	Urea	59 mg/dL	88	63 mg/dl	--	--
[illegible]919	Urea	33 mg/dL	77	74 mg/dL	27 mg dL	4 [illegible]
[illegible]595	Urea	68 mg/dl	15	65 mg/dL	59 mg dl	77
Placebo Treatment Group						
1743*	Urea	57 mg/dL	85	64 mg/dl	--	--
2337	Urea	38 mg/dL	99	72 mg dl	--	--
2763	Urea	40 mg/dL	75	61 mg/dL*	--	--
SECOND PERIOD OF STUDY N051						
Levetiracetam Treatment Group						
1744	Urea	57 mg/dL	1	63 mg/dl	84 mg dl	133
1959	Urea	48 mg dL	232	60 mg dL	--	--
Placebo Treatment Group						
2022	Urea	63 mg/dL	59	70 mg/dl	53 mg dl	56

* Judged by the Investigator to be clinically significant

Please refer to Listing 6.a.2 for all occurrences and to Listing 6.a.3 for all laboratory results for the patients on the above table

8.7.2.3 Controlled Trials: Patients with Treatment-Emergent Adverse Events Reflective of Kidney Function

Reduction in creatinine clearance was reported as an adverse event for Patient **1844**, a 52 y/o female. While a participant in Study N051 on levetiracetam 1000 mg/day for 223 days a reduction in creatinine clearance was noted that resolved following a dose reduction.

8.7.2.4 All Adult Epilepsy Patients: Mean Change from Baseline Analysis

Among levetiracetam-treated patients (1362 with creatinine and 1357 with urea values), there was a slight increase in mean creatinine (0.90 mg/dL to 0.93 mg/dL) and almost no change in mean urea from baseline to the final visit. The range of final creatinine and urea values was

Creatinine clearance was calculated for 464 patients. The mean baseline was 117.9 with a final visit mean of 114.6 mL/min.

The sponsor examined the subset of patients (968) who remained on treatment for at least 6 months (sponsor's Table 83A, SU, Vol. 2 p 199) and there is no clinically significant trend in mean values of creatinine and urea.

All Adult Epilepsy Patients: Possibly Clinically Significant Abnormalities

The sponsor identified 1 additional patient (not already identified in the controlled trials) who met the criteria of a PCS creatinine level and 17 patients with a PCS urea level. Patient **2576** had an isolated creatinine value of 3.9 mg/dl. A follow-up creatinine 5 days later was 0.6 mg/dl. Among the 17 patients with PCS elevated urea values ($\geq$ 60 mg/dl) 4 still had an elevation at the time of the last treatment value. Patient **179**, a 78 y/o male had a baseline urea of 33 mg/dl and a PCS value of 65 mg/dl after 74 days of levetiracetam treatment. On completion of treatmet the urea was 74 mg/dl with a creatinine of 1.2 mg/dl. Patients **2022** and **2449** had elevated ureas at baseline (58 mg/dl and 63 mg/dl) and final treatment values in the same range after over 1000 days of treatment (60 mg/dl and 66 mg/dl). Patient **2749**, a 60 y/o male had a baseline urea of 46 mg/dl and final treatmentvalue of 86 mg/dl with a creatinine of 1.8 mg/dl. A post-treatment value 9 days later showed a urea of 66 mg/dl with a creatinine of 1.6 mg/dl. This patient had a gradual and steady rise in urea and creatinine during the course of treatment.

8.7.3 Electrolytes

8.7.3.1 Controlled Trials: Mean Change From Baseline Analysis

The following table summarizes the results from the mean change from baseline analysis for electrolytes in controlled epilepsy studies (both crossover periods of Study N051). The mean changes from baseline are small and comparable between the levetiracetam and placebo-treated groups.

Table 66: Summary of Mean Change from Baseline to Final Visit by Treatment Group: Electrolytes in Adequate and Well Controlled Studies (both crossover periods of Study N051)

Parameter (units)	Levetiracetam Mean change from baseline (n)	Placebo Mean change from baseline (n)
Sodium (mEq/L)	-0.18 (762)	-0.27 (435)
Potasium (mEq/L)	-0.03 (735)	0.02 (422)

based on sponsor's Table 84A, SU, Vol. 2, p 201

8.7.3.2 Controlled Trials: Patients with Possibly Clinically Significant Abnormalities

There were no PCS sodium values in either treatment group. One (0.2%) levetiracetam-treated patient had a PCS low potassium value. Fifty-five (7.2%) levetiracetam-treated and 35 (8.2%) placebo-treated patients had a PCS elevated potassium value.

8.7.3.3 All Adult Epilepsy Patients: Mean Change from Baseline Analysis

Among levetiracetam-treated patients (1361with sodium values), there was a slight decrease in mean sodium (139.57 mEq/L to 139.31 mEq/L).

8.7.3.4 All Adult Epilepsy Patients: Possibly Clinically Significant Abnormalities

The sponsor identified 7 additional patients (not already identified in the controlled trials) who met the criteria of a PCS decreased potassium level and 148 patients with a PCS elevate potassium level.

8.7.4 Hematologic Studies

There were statistically significant differences between levetiracetam-treated patients and placebo-treated patients for several hematologic parameters. Therefore, the sponsor has undertaken a more detailed review of patients with PCS values and those with adverse events related to hematologic abnormalities (SU, Vol. 2, p 345-354). For this review the sponsor has chosen cut points which are more clinically severe. At my request the sponsor has provided a listing of the ISS/ISE numbers of patients included in these reviews for purposes of verification. Discussion of the sponsor's more detailed review of these events will be incorporated with the results from the routine analyses of the hematologic parameters.

8.7.4.1 Controlled Trials: Mean Change From Baseline Analysis

The following table summarizes the results of from the mean change from baseline analysis for hematologic parameters in controlled epilepsy studies. There were statistically significant changes from baseline for RBC, hemoglobin, WBC and neutrophils in the levetiracetam group. In addition, the differences between levetiracetam and placebo were significant for RBC, hemoglobin and hematocrit. There was a statistically significant change from baseline for platelets in the placebo group.

Table 67: Summary of Mean Change from Baseline to Final Visit by Treatment Group: Hematologic Parameters in Adequate and Well-Controlled Studies (both periods of Study N051)

Parameter (unit)	Levetiracetam mean change from baseline (n)	Placebo mean change from baseline (n)	Between Treatment p-value
RBC (x 10^9/L)	-0.04[a] (761)	-0.01 (435)	0.010
Hemoglobin (g/dL)	-0.10[a] (761)	-0.01 (435)	0.009
Hematocrit (%)	-0.33[a] (760)	0.05 (435)	0.004
WBC (x 10^9/L)	-0.10[a] (761)	-0.01 (435)	0.160
Neutrophils (x 10^9/L)	-0.06[a] (757)	0.00 (432)	0.087
Lymphocytes (x 10^9/L)	-0.03 (757)	0.39 (432)	0.108
Monocytes (x 10^9/L)	-0.01 (743)	0.00 (425)	0.271
Basophils (x 10^9/L)	0.00 (743)	0.00 (425)	0.332
Eosinophils (x 10^9/L)	0.00 (757)	0.00 (432)	0.995
Platelets (x 10^9/L)	-2.81 (761)	-3.97[a] (435)	0.597

based on sponsor's Tables 98A, 102A and, 108A, SU, Vol. 2

[a] Statistically significant with-in group change from baseline by Wilcoxon signed rank test $p<0.001$

The clinical significance of the mean changes from baseline for these hematologic parameters is difficult to interpret based on the mean change from baseline analyisis alone. The sponsor has identified patients with possibly clinically significant hematologic laboratory values that are reviewed below.

8.7.4.2 Controlled Trials: Patients with Possibly Clinically Significant Abnormalities

The sponsor identified patients with on-treatment values that met the criteria for a possibly clinically significant abnormality (Table 68). There were 37 (4.9%) of levetiracetam-treated and 15 (3.4%) of placebo-treated patients with a PCS low hematocrit. A PCS low WBC was observed for 23 (3.0%) levetiracetam-treated and 8 (1.8%) placebo-treated patients. A PCS low neutrophil count was observed for 16 (2.1%) levetiracetam-treated and 6 (1.4%) placebo-treated patients. A review by individual parameter follows.

Table 68: Possibly Clinically Significant Low Hematologic Paramaters by Treatment Group in Adequate and Well-Controlled Studies in Epilepsy

Parameter (unit)	Levetiracetam % on-treatment	Placebo % on-treatment
Hemoglobin	0.4% (3/761)	0.2% (1/435)
Hematocrit	4.9% (37/760)	3.4% (15/435)
WBC	3.0% (23/761)	1.8% (8/435)
Neutrophils	2.1% (16/757)	1.4% (6/432)
Lymphocytes	0.04% (3//757)	(0/432)
Platelets	0.01% (1/761)	0.5% (2/435)

based on sponsor's Tables

8.7.4.2.1 Hemoglobin and Hematocrit

With respect to hematocrit 37 (4.8%) levetiracetam and 15 (3.4%) placebo-treated patients met the criteria of a PCS low hematocrit value in the controlled trials of epilepsy. I requested that the sponsor provide follow-up hematocrits (for patients who continued in extension studies) on the 37 levetiracetam-treated patients identified in sponsor's Table 99A with a PCS low hematocrit during a controlled epilepsy study (Table 69). 8/37 (22%) levetiracetam-treated had a PCS low hematocrit at baseline. The lowest on-treatment hematocrit was 29% in patient **1974** (baseline hematocrit of 29%) who continued in an extension study (final value 26%). Fourteen patients still had a PCS low hematocrit on completion of the controlled trial and nine are still participating in an extension study. Among the 9 patients continuing 2 patients still have a PCS low hematocrit at the time it was last checked (patient **2449** hematocrit 30.8%, and patient 2888 hematocrit 29.1%). Among the 5 patients who have completed levetiracetam treatment only patient 2749 still had a PCS low hematocrit of 32.5% 19 days after discontinuation.

Table 69: Levetiracetam-Treated Epilepsy Patients with a Possibly Clinically Significant Low Hematocrit in a Controlled Epilepsy Study

	Controlled Trial			Extension Study		Post -Treatment	
ISS Number (Gender)	Baseline Value (%)	PCS Value (%)	Final Value (%)	Final Value (%)	Total Exposure Days[a]	Final Value (%)	Post Treatment Days[b]
1800 (F)	53.0	32	35				
1829 (F)	31.6	30.5	**30.6**	34.1	1302	Ongoing	
1840 (F)	38.3	31.4	33.2			31.4	8
1872 (M)	41.4	36.9	43.1			41.1	43
1884 (F)	35.5	31.8	**31.8**	35.2	905	35.2	8
1886 (M)	35.6	34.7	**35.6**	39.6	1430	Ongoing	
1891 (M)	37.9	36.7	39.2			37.7	113
1918 (M)	36.6	36.2	**33.3**	39.6	1381	Ongoing	
1935 (M)	41.0	36.9	41.4	39.0	1149		
1945 (M)	38.4	35.7	39.1			41.3	13
1974 (F)	29.0	29	32.0	26.0	419		
1983 (M)	42.8	36	38.9	42.0	558	42.0	9
2007 (M)	38.0	36.4	41.1	35.5	666	35.5	25
2240 (M)	40.0	35	41.0	37.3	1500	Ongoing	
2284 (M)	37.0	36.4	37.1	35.1	1246	Ongoing	
2344 (M)	36.1	36.5	**36.4**	37.1	338	37.1	15
2391 (M)	40.0	37	**36.7**	37.9	1085	37.9	19
2396 (M)	39.7	35.1	38.2	39.8	1199	Ongoing	
2408 (M)	41.9	36.7	43.4	42.3	1159	Ongoing	
2436 (M)	40.8	36.4	42.0	39.8	270	39.8	15
2449 (F)	31.5	29.6	**30.9**	30.8	1179	Ongoing	
2493M)	37.4	35.1	37.1			36.3	18
2568 (M)	39.3	36.4	37.4	41.8	1185	Ongoing	
2569 (M)	38.3	36.9	39.1			36.9	21
2603 (F)	37.9	30.6	**31.8**	33.1	1304	Ongoing	
2632 (M)	38.4	36.8	38.3	36.7	1177	Ongoing	
2646 (F)	34.0	31.4	**28.2**	32.5	344	32.5	19
2700 (M)	36.5	35.6	38.3	41.5	682		
2749 (M)	42.1	36.2	**36.2**	33.2	860	33.2	9
2829 (F)	33.1	31	**31.0**	32.7	1090	Ongoing	
2836 (M)	39.8	34.5	41.7	40.9	996	Ongoing	
2888 (F)	30.0	30.1	**29.8**	29.1	758	Ongoing	
2892 (M)	37.9	36.2	**36.4**	39.1	623	Ongoing	
3004 (M)	42.0	35.5	43.2	45.1	590	Ongoing	
3057 (M)	39.5	36.9	**36.8**	39.3	620	Ongoing	
3075 (M)	39.4	35.9	39.4	38.2	604	Ongoing	
3113 (F)	34.2	31.9	39.6	36.5	554	Ongoing	

[a] Cumulative exposure to levetiracetam at the time the last hematocrit was obtained.
[b] Number of days between the discontinuation of levetiracetam and drawing of the post-treatment

When all adult epilepsy studies were examined, 20 additional patients had on-treatment hemoglobin values that met PCS criteria (overall incidence 1.8%) and 73 additional patients with a hematocrit value that met PCS criteria (overall incidence 8.1%).

The sponsor identified and reviewed 14 patients in all studies (11 in adult epilepsy studies) that had a **decrease of hemoglobin of greater than 2g/dL**. In all epilepsy patients the hemoglobin improved while continuing treatment. I reviewed the hemoglobin values and concur with the sponsor's review.

8.7.4.2.2 White Blood Cell Indices

Overall 34 (4.5%) patients levetiracetam-treated patients and 14(3.2%) placebo-treated patients had a PCS low WBC, neutrophil and or lymphocyte count. Three levetiracetam-treated patients had a PCS increase in WBCs. With respect to eosinophils, 13 (2.0%) levetiracetam-treated patients compared to 13 (3.8%) placebo-treated patients had a PCS elevated value.

The sponsor identified 16 (2.1%) levetiracetam-treated patients and 6 (1.4%) placebo-treated patients with PCS low neutrophil counts in the controlled epilepsy studies. I reviewed and plotted (Table 70) pertinent laboratory data (from listing 6.b., and sponsor's Table 130A, SU Vol. 2, p 225) for the 16 levetiracetam-treated patients with PCS low neutrophils. The neutrophil count was less than or equal to 1.5 x 10^9/L (normal 3000 to 5800 x 10^9/L) for 5 (31%) of the 16 levetiracetam-treated patients with PCS low neutrophils. Twelve patients no longer had a PCS low neutrophil count upon completion of the clinical trial in which they were participating. Four patients (**2112**, **2571**, **2646**, and **2648**) still had a PCS low neutrophil count upon completion of their participation in a controlled trial and continued study treatment in an extension study. Cumulative levetiracetam exposure for these four patients ranged from 253 to 542 days and none of the four patients had a PCS low neutrophil count upon completion of an extension study. However, patient **2646** had a PCS low neutrophil count of 0.45 x 10^9/L 19 days following the cessation of levetiracetam treatment. Patient **1959** had normal neutrophil counts on completion of the clinical trial and extension study but a borderline PCS low neutrophil count of 0.96 x 10^9/L at post-treatment. Two patients (2269 and **2840**) are continuing treatment in an extension study. For most of these patients low neutrophil counts resolved with continued treatment and none of the PCS low neutrophil counts resulted in death, discontinuation or a serious adverse event.

Table 70: **Levetiracetam-Treated Epilepsy Patients with a Possibly Clinically Significant Low Neutrophil Count in a Controlled Epilepsy Study**

	Controlled Trial			Extension Study		Post-Treatment	
ISS Number	Baseline Value (x 10^9/L)	PCS Value (x 10^9/L)	Final Value (x 10^9/L)	Final Value (x 10^9/L)	Total Exposure Days[a]	Final Value (x 10^9/L)	Post Treatment Days[b]
1884	1.5	0.9	1.1	1.7	905	2.1	8
1959	2.7	0.9	1.6	1.5	562	0.96	76
2032	2.1	0.85	1.95	3.0	1138	2.0	21
2112	1.2	0.97	**0.97**	1.6	542		
2260	1.1	1.0	1.1	1.2	818	2.9	82
2269	2.0	0.8	2.0			3.3	29
2339	1.3	0.71	1.6	2.1	1193	ongoing	
2344	1.7	0.78	1.8	2.9	254	3.4	15
2436	1.7	0.87	2.2	1.2	270	1.4	15
2518	1.6	0.64	1.2			1.2	23
2571	2.2	0.56	**0.56**	1.3	253	1.5	16
2617	1.6	0.77	1.4	2.3	694	3.4	21
2646	0.96	0.75	**0.53**	1.0	344	0.45	19
2648	1.4	0.98	**0.14**	4.8	505		
2840	3.6	0.61	1.5	2.0	850	ongoing	
3059	4.2	0.82	1.3	2.4	264		

[a] Cumulative exposure to levetiracetam at the time the last neutrophil count was obtained.
[b] Number of days between the discontinuation of levetiracetam and drawing of the post-treatment neutrophil count. This time period was provided by the sponsor.

The sponsor identified and reviewed 23 patients in all studies (19 in adult epilepsy studies) with a **neutrophil count less than 0.75 x 10^9/L**. Among the 19 patients in adult epilepsy studies, 5 are listed above in Table 70 (**2339, 2518, 2571, 2646,** and **2480**). Of the remaining 14 patients in adult epilepsy studies with a neutrophil count $\leq$ 0.75 x 10^9/L 13 had a final treatment value that was no longer possibly clinically significant. Patient **163**, a 67 y//o female who had splenomegaly and subsequently died of a hepatoma had a neutrophil count of 0.88 x 10^9/L at baseline and persistently low neutrophil counts during 450 days of levetiracetam treatment (post-treatment value 0.32 x 10^9/L). Among the four patients in studies of other indications two patients (**4114** and **4192**) had baseline neutrophil counts $\geq$ 4.0 x 10^9/L and both had a PCS low neutrophil count of 0.6 x 10^9/L. In both patients the final treatment neutrophil count after 28 days was also 0.6 x 10^9/L. No further values are provided. Patient **1613** had a baseline neutrophil count of 2.35 x 10^9/L and on-treatment value of 0.17 x 10^9/L. A final treatment neutrophil value after 84 days was 3.01 x 10^9/L. A post-treatment neutrophil count obtained 15 days after the final treatment neutrophil count was 0.17 x 10^9/L. No further values are reported for this patient. Patient **1622** had a baseline neutrophil count of 2.93 x 10^9/L and an on treatment count of 0.34 x 10^9/L. Only a 15 day post-treatment neutrophil count is reported of 2.47 x 10^9/L.

8.7.4.2.3 Platelets

With respect to platelet count 1 (0.2%) levetiracetam and 2 (0.5%) placebo-treated patients met the criteria of a PCS low platelet count.

The sponsor identified and reviewed 14 patients in all studies (8 in adult epilepsy studies) with a **platelet count less than 75 x 10^9/L**. Among the 8 patients in adult epilepsy studies, 3 were in controlled studies (1 levetiracetam, 2 placebo). A summary of the levetiracetam-treated patient follows:

Patient **2792**, a 39 y/o female, had a baseline platelet count of 171 x 10^9/L. An isolated platelet count of 21 x10^9/L was noted after 57 days of levetiracetam-treatment. The patient was still participating as of November 30, 1988 with a final platelet count recorded of 182 x 10^9/L after 1177 days of treatment. treatment.

I reviewed the laboratory listings for the other epilepsy patients with PCS low platelet counts and all counts improved while continuing treatment. Two patients in trials of other indications still had a PCS low platelet count as a final treatment value. Patient **75** had a baseline and final treatment platelet value of 54 x 10^9/L (values obtained 28 days apart). Patient **4571** had a baseline platelet count of 305 x 10^9/L. A platelet count obtained 15 days later while the patient was receiving levetiracetam 500 mg/day was 34 x 10^9/L. No further values are provided.

8.7.5 Urinalyses

The sponsor discusses methods used to evaluate urinalysis data on page 45 of the Safety Update. Qualitative urine parameters (protein, glucose, red blood cells, and white blood cells) were reported using a descriptive score that varied between laboratories. A value was considered possibly clinically significant abnormal if it was in the 2+ or 3+ categories regardless of baseline.

8.7.5.1 Controlled Trials: Mean Change from Baseline

The mean baseline values for urinary pH in the levetiracetam and placebo groups were 6.2 and 6.4, respectively. At analysis visit window 3 months to < 6 months mean urinary pH values were 6.2 and 6.2, respectively.

8.7.5.2 Controlled Trials: Patients with Possibly Clinically Significant Abnormalities

Possibly clinically significant WBCs in the urine were noted for 69 (14.3%) of levetiracetam-treated patients and 40 (14.3%) of placebo-treated patients. Possibly clinically significant RBCs in the urine were noted for 59 (9.4%) of levetiracetam-treated patients and 35 (10%) of placebo-treated patients.