CLINICAL REVIEW

Application Type	NDA
Submission Number	21-035 (S-040) and 21-505(S-007)
Submission Code	Supplement
Letter Date	December 20, 2004
Stamp Date	December 20, 2004
PDUFA Goal Date	June 21, 2005
Reviewer Name	Howard D. Chazin, MD, MBA
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Established Name	levetiracetam
Trade Name	Keppra ®
Therapeutic Class	antiepileptic
Applicant	UCB Pharma
Priority Designation	P
Formulation	oral tablets and solution
Dosing Regimen	BID
Indication	adjunctive epilepsy
Intended Population	pediatric ages (ages 4-16)

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The pediatric supplemental NDA for Keppra® (levetiracetam) should be approved based on efficacy results. There was substantial evidence from a single adequate and well controlled trial that provided clinically relevant, statistically significant (p=0.0002) reductions over placebo in partial onset seizure frequency per week among children ages 4-16 during the treatment period. [26.8% (95% CI; 14.0%- 37.6%)]

The pediatric supplemental NDA for Keppra ® (levetiracetam) was essentially safe in this pediatric subpopulation, exhibiting adverse events similar to those seen in adults. The majority of adverse events were neuropsychiatric in origin.

1.2 Recommendation on Postmarketing Actions

It is unclear from this submission if Keppra ® initiates or potentiates underlying neuropsychiatric/mood/behavioral disorders. For those patients at higher risk of underlying neuropsychiatric/mood/behavioral disorders, the potential for worsening of the underlying condition has not been fully explored given the small numbers of patients studied. The risk of suicidal ideation in this pediatric patients taking Keppra ® has not been fully explored. The validity of the exploratory endpoints such as various neuropsychiatric and cognitive scales has not been fully explored as of the date of this submission. The sponsor has not performed a formal analysis on the effects on growth. The sponsor may wish to address these issues in future postmarketing activities.

1.2.1 Risk Management Activity

Continued evaluation of neuropsychiatric side effects has been discussed in the past with the sponsor (see next section). A request from another medical officer (Norm Hershkowitz, MD) to the Office of Drug Safety was initiated to evaluate the potential for thrombocytopenia in adults, however there was no signal for thrombocytopenia in children based on the data provided in this submission.

1.2.2 Required Phase 4 Commitments

The Sponsor and the Division have discussed continued studies in children to validate several cognitive scales including the CHQ (Child Health Questionnaire). The sponsor has only partially responded to the pediatric written request and still needs to submit a separate submission to include evaluation of efficacy and safety of levetiracetam in children ages 1 month to 4 years.

An additional required Phase 4 commitment requested by the Division was a formal QT analysis to be performed in adult patients. This was requested to address concerns related to prolonged QTc intervals seen in several patients in the safety database.

1.2.3 Other Phase 4 Requests

The sponsor should consider an educational program to physicians in order to alert them to the possibility of levetiracetam worsening preexisting neuropsychiatric conditions and to consider alternatives or dose adjustments when necessary.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Keppra ® (levetiracetam) is an oral antiepileptic drug. It is an approved drug for adjunctive treatment for partial seizures in adult epilepsy patients. The sponsor presented the results of a single efficacy study to support a claim of adjunctive treatment for partial onset seizures in pediatric epilepsy patients ages 4 to 16. That study (referred throughout this review as Study N159 or N159) was a double-blind, placebo-controlled, multi-center clinical trail conducted in children with refractory partial seizures. Following an 8-week prospective baseline period, 198 patients were randomized to receive placebo (N=97) or levetiracetam (N=101) in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day (or a maximum of 3000 mg/day).

Patients remained at the 60 mg/kg/day dose for a total of 10 weeks. Dosing was adjusted on a mg/kg basis as needed for tolerability. Patients could be treated with a maximum of two other antiepileptic drugs (AEDs) while participating in the trial. To enter the trial, patients were required to have at least four partial onset seizures per week during two 4-week periods of the 8-week baseline phase. Treatment groups were comparable for demographics, baseline seizure history and concomitant AED usage representing a wide selection of refractory pediatric epilepsy patients.

For safety, the sponsor included information from Study N159 along with several other single and multiple dose pharmacokinetic studies. The total safety database included 239 patients, the majority of whom continued treatment from Study N159 into a large open label trial (Study N157). The sponsor also provided information from over 300 postmarketing safety reports for review. These included reports on children taking levetiracetam for a variety of seizures and other off label conditions.

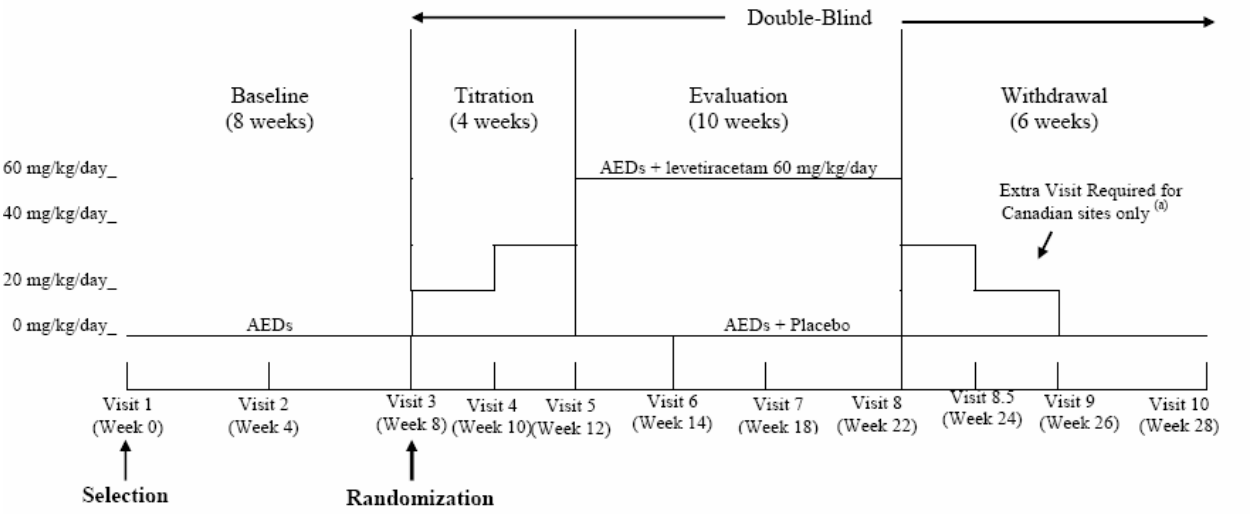
This pediatric supplement was a partial response to a pediatric written request. The sponsor has ongoing studies evaluating patients between the ages of 1 month and 4 years. Also the sponsor has ongoing studies designed to validate the Child Health Questionnaire (CHQ).

1.3.2 Efficacy

A single adequate and well-controlled study (N159) was performed in order to demonstrate efficacy. The objective was to determine the efficacy of levetiracetam as add-on treatment in pediatric patients (age 4 to 16 years) with refractory partial onset seizures. Patients being treated with a maximum of two other AEDs were included in the trial. Patients had to be 4-16 years old and recently diagnosed with uncontrolled partial onset seizures whether or not secondarily generalized. All were to have experienced at least 4 seizures in the 4 weeks prior to screening and 4 partial onset seizures in each of the (2) 4 week periods during the 8 week baseline period. The diagnosis of epilepsy had to be made at least 6 months prior to selection. EEG, MRI and/or CT were required to confirm absence of a progressive brain lesion since being diagnosed with epilepsy. Patients were excluded if they required more than 2 concomitant AEDs, or had seizures that were too close to count accurately. Also patients with epilepsy secondary to progressive cerebral disease or history of status epilepticus with hospitalization within 3 months prior to screening were also excluded.

A schema of the study design for N159 is copied from the submission below.

Figure 4:1 N159 Study Design



Patients who completed the study and enrolled in the open-label follow-up study (N157) did so at Visit 8 (Week 22). Patients wishing to terminate participation entered a withdrawal/down-titration period.
Patients terminating the study early entered the withdrawal period for down-titration of study medication.
Patients **not** enrolling in the open-label follow-up study (N157) had a final visit two weeks after the last dose of study medication.
(a) This visit was **required** only for Canadian sites and was optional for the sites in the US.

Following an 8-week prospective baseline period, patients were randomized to receive placebo or levetiracetam in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks to a maximum of 3000 mg/day).

Patients remained at the 60 mg/kg/day dose for a total of 10 weeks. After the evaluation period, patients could either continue on the drug in the open label Study N157 or be titrated off the drug.

No substantial differences were noted between treatment for demographic characteristics, history and etiology of epilepsy or concomitant antiepileptic drug use. A diverse group of patients were enrolled.

Doses achieved were close to the goal dose of 60mg/kg/day with the mean dose of 52 mg/kg/day noted in the levetiracetam group (versus 51mg/kg/day in the placebo group). The average duration of study treatment was 100 days (14 weeks) with a range of 91-147 days. More patients discontinued in the placebo group than in the treatment group due to adverse events. The most frequent reasons for premature discontinuation, in decreasing order of frequency, were adverse events (14 patients), loss to follow- up (3 patients), lack of efficacy (2 patients), and other (2 patients). Lack of adequate response was a more common reason for discontinuation among patients randomized to placebo (5 patients or 5.0%) than to levetiracetam (1 patient or 1.0%).

All statistical analyses were performed on the ITT (intent to treat) population defined as any patient who took at least one dose of study medication (N=101) or placebo (N=97).

Primary efficacy variable – partial seizures frequency per week during the treatment (titration and evaluation) period. The treatment period represents the entire time on study drug (14 weeks including 4 week titration and 10 week evaluation).

Result - There was a statistically significant reduction in weekly partial seizure frequency in the patients randomized to levetiracetam as compared to those randomized to placebo (p = 0.0002). The percent reduction over placebo was 26.8% [two- sided 95% confidence interval (CI) 14.0% - 37.6%]. The interaction between treatment and $\log_e(\times + 1)$ transformed baseline seizure frequency was not significant (p= 0.7724). No significant violations of assumptions for normal distribution and equal variances for the two treatment groups were detected.

Regarding secondary efficacy parameter, response rate, (defined as the percentage of patients experiencing at least a 50% reduction from baseline in seizure frequency per week) this was significantly larger for levetiracetam than for placebo for partial onset seizures and total seizures.

1.3.3 Safety

The Sponsor included 5 studies in the pooled safety database. These included the single, randomized, double-blind, placebo-controlled phase 3 study (N159), one open- label phase 2 study (N151), two open label pharmacokinetic studies (N01052 and N01010) and one open-label long-term follow-up study, N157. The pharmacokinetic study N01052 was the only single dose study and the others were all repeated dose studies, with the patients titrated to the maximum protocol- specified dose. These studies are summarized in Sponsor Table 3:1.

Table 3:1 Overview of Exposure to Levetiracetam in Pediatric Studies Included in Application

Study No.	Dates of Conduct [Country(ies)]	Children Exposed (Males / Females)	Mean Age (Range)	Overview of Design
Studies in Pooled Safety Database (Add-on Therapy in Partial Onset Seizures): Data Cut-off Date 30 April 2004				
N159	9/99 – 3/03 (U.S. and Canada)	101 (54 / 47)	10.2 yrs (4.1 – 17 yrs)	Double-blind, placebo controlled, randomized, 28-week (8-week baseline, 4-week titration, 10-week evaluation, 6-week withdrawal) study of escalating doses of 20, 40, 60 mg/kg/day
N151	9/97 – 9/98 (U.S.)	24 (15 / 9)	9.5 yrs (5.6 – 12.7 yrs)	Open-label, single and multiple dose PK, safety and efficacy study of escalating doses of 10, 20, 40 mg/kg/day
N01010	1/02 - 7/03 (U.S., Mexico)	21 (12 / 9)	9.8 yrs (4.5 – 12.8 yrs)	Open label, multiple dose, 6-week, PK and AED interaction study of escalating (every 2 weeks) doses of 20, 40, 60 mg/kg/day
N01052	9/02 – 5/03 (U.S.)	13 (7 / 6)	20.2 mo. (2.4 – 46.8 mo.)	Open-label, single dose PK study (20 mg/kg) in patients with epilepsy
N157	2/98 – ongoing (International)	80 *de novo* (44 / 36)	9.7 yrs (0.2-17)	Open-label, long-term follow-up study (20 – 99 mg/kg/day)
Subtotal	–	**239**	**2.3 mo – 17 yrs**	–
Non-Pooled Studies: Data Cut-off Date 31 August 2004				

There were 239 treated patients in the pooled database, compared to 101 treated patients in Study N159. Adverse events were listed using the COSTART (rather than MedDRA) preferred term. In addition, the Sponsor used its own UCB AE grouping terms that offered an alternative, focused approach to grouping similar events.

In addition, the Sponsor provided information on 300 postmarketing spontaneous AE reports, the majority of which were neuropsychiatric related.

Regarding the double blind study N159, 89 of the 101 patients in the treatment group experienced a total of 462 treatment emergent adverse events with 10 patients experiencing a treatment emergent adverse event (TEAE) classified as severe in intensity. Major adverse events occurring more likely than not related to drug treatment included somnolence, accidental injury, hostility, nervousness, asthenia, anorexia, depression, emotional lability, rhinitis, and agitation.

In terms of overall patient exposures, 234 of the 239 patients exposed to levetiracetam experienced at least one TEAE; a total of 2713 adverse events were reported. The most common adverse events affected the nervous system, with somnolence, hostility, nervousness, and asthenia the most common in children. Somnolence and nervousness tended to occur within the first few weeks of treatment and improved. Fewer than 10% of the children discontinued treatment due to an adverse event and when they did, it was primarily due to a nervous system event.

Overall in the total database, 21 patients (8.9%) discontinued levetiracetam due to an adverse event. The identified single primary event that led to discontinuation most often pertained to the

nervous system. The most common reason was hostility and nervousness, leading to the discontinuation of 3 patients each. Other nervous system events leading to discontinuation were convulsion or status epilepticus, hyperkinesia, depression, psychotic depression and ataxia. In addition to these, other more rare events leading to discontinuation were asthenia, headache, vomiting, cardiovascular disorder (described as left ventricular hypertrophy), and rash.

When any adverse events that resulted in dose change and/ or discontinuation were taken into consideration, 72 patients (30.1%) were affected. The most common events were somnolence, hostility, headache, nervousness, and personality disorder, thinking abnormal and asthenia. Of these, only hostility and asthenia more commonly resulted in discontinuation or dose adjustment among patients randomized to levetiracetam in the placebo-controlled trial. Failure of efficacy leading to convulsions was more common among patients randomized to placebo who discontinued. Hostility tended to result in discontinuation or dose adjustment within the first few weeks of treatment.

Post- treatment adverse events were not common, regardless of whether patients down- titrated as planned or discontinued abruptly.

Other common adverse effects (AEs) that were reported over time on drug included many childhood conditions, however the AEs that may have a potential to be drug related to this reviewer included the terms convulsion, hostility, nervousness, personality disorder, somnolence and rash. These also were reported at higher incidences over long term treatment (>48 weeks). Somnolence was noted initially and tended to improve with time. Somnolence may limit use in some refractory epilepsy patients. The incidence of rash may be confounded by rashes related to concomitant medications throughout treatment.

Major safety concern – Neuropsychiatric side effects.

As requested by FDA, the sponsor performed additional analyses for psychiatric and behavioral events due to a modestly elevated risk for psychiatric and behavioral events in children with refractory partial onset seizure disorder who were treated with levetiracetam. The majority of these adverse events were in the category of non- psychotic/ mood/ anxiety/ behavioral symptoms. In controlled trial, non psychotic mood/ anxiety/ behavior events were reported in 37.6% versus 18.6% of pediatric patients in the levetiracetam and placebo groups, respectively. Overall, there was a two fold or greater relative risk of levetiracetam treated patients as compared to placebo for incidences of agitation, nervousness and depression. The Sponsor felt that this was similar to the incidences seen in adults; however, children may be more likely to have agitation.

The Sponsor provided alternative explanations for the high incidence of psychiatric and behavior adverse effects. These included: association of behavioral disorders with refractory partial seizures, limbic processes in seizure patients, concomitant risks such as preexisting psychiatric history, history of febrile seizures or status epilepticus, and other concomitant drug effects. The Sponsors related that 99 patients in study N159 had a past neuropsychiatric history. This was similar in that 160 of the 239 patients in the pooled database also had some neuropsychiatric history. Even so, this does not explain the much higher incidences and risk ratios (relative risk)

of these events in the treated population versus placebo. It only explains the high overall incidence in both groups. These incidences also speak to a possible limitation of the use of levetiracetam in patients with partial seizures and neuropsychiatric history. On the other hand, patients with refractory seizures (and their caretakers) might be more willing or able to tolerate such side effects.

There is a potential for worsening of mood disorders and suicidal ideation with levetiracetam. One 13 year old patient with mood disorder and history of complex partial seizures and generalized tonic clonic seizures began to have suicidal ideation after one month on levetiracetam. The drug was withdrawn and the seizure disorder was poorly controlled, however the mood disorder improved. There were 6 additional cases of suicidal ideation reported in the sponsor's postmarketing database. Most of these patients suicidal symptoms resolved when the Keppra ® dose was decreased or the drug was discontinued. One has to be cautious in evaluating the postmarketing data as this is primarily related to off label use of the drug and not under controlled circumstances. Still, this risk, albeit small, should be further explored by the sponsor in postmarketing risk management activities.

Safety concern – Low WBC and Neutrophil counts.

A small, but statistically significant, decrease in WBC and neutrophil counts was seen in patients randomized to levetiracetam as compared to placebo. The mean decreases from baseline in the levetiracetam group were – 0.4 × 103/ μ L and – 0.3 × 103/ μ L, respectively, compared to small increases in the patients randomized to placebo. Mean lymphocyte count increased by 1.7 × 103/ μ L in patients randomized to levetiracetam (statistically significantly for relative count), most likely consistent with common childhood illnesses. There were no other statistically significant differences between treatment groups in any of the hematology parameters.

Safety Concern – Prolonged QTc intervals

Regarding potential cardiac effects, levetiracetam had a small effect on increasing QTc intervals in children with the mean difference between the placebo group and treatment group of approximately 8 milliseconds (msec). Most of this difference related to a 6 msec decrease seen in the placebo group. Three patients in the open label database had QTc measurements of greater than 500msec. Each of these patients was reviewed in more detail and after different correction factors were applied, only a single patient remained with a QTc measurement greater than 500msec. The significance of this finding in children remains unclear. The evaluation is limited by lack of ECG timing to dose and some data being machine generated versus calculated individually by hand. The Division requested the sponsor evaluate this further by performing a QT study in adults as a required Phase 4 commitment.

Safety Concern – Body Weight –

Levetiracetam had a mixed effect on body weight in that about 21 patients with a normal body weight at baseline experienced at least one body measurement above the 97% bound of the normal growth curve. 56 patients were identified to have a normal body weight at baseline with at least one body measurement below the 3% lower bound of the normal growth curve. In terms

of adverse events related to weight, the Sponsor recognized 45 children with weight loss or anorexia reported as adverse events and 18 patients with obesity, weight gain or increased appetite. These adverse events were mostly mild and did not result in changes in drug dosing for the majority. However, there were a number of confounding factors that make interpretation difficult, including the related body weight effects of other AEDs used by the patients.

1.3.4 Dosing Regimen and Administration

The sponsor treated patients by beginning each patient at 20mg/kg/day in BID divided doses for 2 weeks, followed by 40mg/kg/day for 2 weeks with a goal dose of 60mg/kg/day. Doses were always divided BID. For larger patients, the sponsor (b) (4) proposes the following dosing regimen. Since this mirrors the drug dosing regimen in the clinical trial (N159) this reviewer agrees with the proposal. (b) (4)

> *Treatment should be initiated with a daily dose of 20 mg/kg given in 2 divided doses (10 mg/kg BID). The daily dose may be increased* (b) (4) *by increments of 20 mg/kg to* (b) (4) *recommended daily dose of 60 mg/kg (30 mg/kg BID). The maintenance dosage should be based on the patient's clinical response and tolerance. Patients with body weight ≤ 20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution.*

1.3.5 Drug-Drug Interactions

There were no notable drug-drug interactions associated with levetiracetam.

1.3.6 Special Populations

This application is specific to the pediatric population.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Keppra® is an antiepileptic medication. The drug substance, levetiracetam, is a pyrrolidone derivative that is not related to any existing antiepileptic medications. Keppra® tablets (250mg, 500mg and 750mg) were approved in November 1999 (NDA 21-035) and Keppra ® liquid formulation (oral solution 100mg/mL) was approved in July 2003 (NDA 21-505).

Keppra® is currently indicated as adjunctive treatment for partial seizures in adults with epilepsy.

The method of action of Keppra® is unknown but may work by reduction of high voltage activated Ca+2 current in CAI pyramidal neurons (as seen in rat hippocampus slices). In addition, Keppra® may bind to synaptic vesicle protein SV2A, which has been correlated with anticonvulsant activity.

2.2 Currently Available Treatment for Indications

Approved treatments for epilepsy are summarized in the following table.

Per FDA COMIS, the following antiepileptic medications are approved for the treatment of epilepsy. Specifics regarding each drug are summarized in the following table.

Drug Name	Sponsor	Indication
DILANTIN (PHENYTOIN)	PFIZER	Partial seizures, Primary generalized tonic clonic seizures.
PHENOBARBITOL	PARKE DAVIS	Primary generalized tonic clonic seizures.
TEGRETOL, TEGRETOLXR (CARBAMAZEPINE)	NOVARTIS	Partial seizures, Primary generalized tonic clonic seizures.
CARBATROL(CARBAMAZEPINE)	SHIRE PHARM	Partial seizures, Primary generalized tonic clonic seizures.
DEPAKOTE(DIVALPROEX SODIUM) ER 500MG TAB	ABBOTT	Epilepsy, monotherapy and adjunctive therapy for partial seizures in isolation or in combination with other seizures.
CEREBYX (FOSPHENYTOIN)	PARKE DAVIS	Treatment of epilepsy
FELBATOL (FELBAMATE) CHEWABLE TABS 600MG	MEDPOINTE PHARM HLC	Monotherapy and adjunctive therapy for partial seizures with and without secondary generalization and for monotherapy for Lennox Gastaut Syndrome.
NEURONTIN (GABAPENTIN) CAPSULES	PARKE DAVIS/ PFIZER	Adjunctive therapy in the treatment of partial seizures.
LAMICTAL (LAMOTRIGINE)		Adjunctive treatment of partial seizures, primary generalized tonic clonic seizures, typical and atypical absence, atonic and myoclonic seizures, Lennox Gastaut Syndrome. Also approved for titration to monotherapy.
GABATRIL (TIAGABINE)		Adjunctive therapy for partial seizures.
TOPAMAX (TOPIRAMATE)		Adjunctive treatment of partial seizures, primary generalized tonic clonic seizures, atonic, tonic, tonic-clonic seizures, Lennox Gastaut Syndrome.
ZONEGRAN (ZONISAMIDE) 100 MG CAPSULES	DAINIPPON	Adjunctive therapy for partial seizures.
TRILEPTAL (OXCARBAZEPINE) 150/300/600MG	NOVARTIS	Monotherapy or adjunctive therapy for partial seizures in adults and children.
KEPPRA(LEVETIRACETAM)	UCB	Adjunctive therapy for partial seizures with and without secondary generalization in adults.

This application is a **partial response** to a pediatric written request (WR). The sponsor studied patient from age 4 to 16 in this trial and deferred evaluation of patients ages 1 month to 4 years at the time of this submission.

2.3 Availability of Proposed Active Ingredient in the United States

Keppra is already approved and marketed for the adjunctive treatment of partial onset seizures in adult patients.

2.4 Important Issues With Pharmacologically Related Products

There are no pharmacologically related products.

2.5 Presubmission Regulatory Activity

The Division and UCB met for an end of phase II (EOP2) meeting on July 20, 1999. The Pediatric Written Request (WR) was finalized on August 21, 2001 and amended on March 22, 2002, July 3, 2002, May 10, 2004 and July 23, 2004.) The sponsor had two meetings with the Division regarding the pediatric development plan and the pediatric supplemental NDA (January 15, 2004 and July 27, 2004). Overall, the sponsor agreed to perform 3 studies – a pharmacokinetic study, a pediatric efficacy and safety study (short term) and a long term safety study. Although the original WR stated that the sponsor should study children ages 1 month to 16 years for all three studies, the sponsor submitted this pediatric sNDA as a partial response to the written request encompassing patient ages 4-16 years. For the clinical portion, we requested the double blind study evaluate a single standard measurement of seizure frequency as the primary outcome measure and standard measures of safety including monitoring of cognitive/neuropsychiatric side effects. For the long term safety study, we requested, "appropriately frequent standard measures of safety" including long term monitoring of cognitive/neuropsychiatric side effects.

Regarding the clinical portions of the WR, we asked that the statistical analysis include an "assessment of the between group difference on a standard measure of partial seizure frequency by a statistical methodology appropriate to the data generated and descriptive analysis of safety data. A sufficient number of pediatric patients to be able to detect a statistically significant difference between treatment and control should be included." For the long term safety data we requested a descriptive analysis.

2.6 Other Relevant Background Information

In addition to the studies included in the safety database, the sponsors included additional small studies of levetiracetam use in other groups of children. One open label study evaluated 5 children ages 5-12 with Lennox Gastaut syndrome. These patients were titrated for 8 weeks and received an 8 week maintenance period. Results of the study were inconclusive as 2 patients improved, 2 worsened and one patient did not change. Another open label study was done in

children with partial onset seizures. Patients with refractory partial seizures received between 10-40mg/kg/day in two divided doses for up to 98 days. The sponsor collected single dose PK data in 24 children aged 5-12 years that revealed that the drug is cleared 30-40% faster in children than adults. The drug half life was determined to be 6 hours and the median percent reduction in seizure frequency from baseline was 53%. Adverse events were similar to adult patients. The sponsors felt that to reach an adult equivalent dose of 3000mg daily, they estimated that the goal dose for children would be about 60mg/kg/day.

Note regarding Pediatric Exclusivity - During the January 15, 2004 meeting between the sponsor and the Division, the parties negotiated agreements regarding a clinical study enrolling 100 patients to validate the CHQ (Child Health Questionnaire) in relation to cognitive neuropsychiatric safety evaluations. That study, N01103, (not included in this supplement NDA application) was required for pediatric exclusivity, but may apply to this sNDA evaluation of neuropsychiatric side effects in the current database. Because Study N01103 was not completed, and validation of the CHQ has not been agreed upon, this reviewer did not assess the validity of this test and other exploratory outcome measures as part of the efficacy evaluation of this supplemental NDA.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to CMC review.

3.2 Animal Pharmacology/Toxicology

Please refer to Pharm/Tox review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

For efficacy, the main efficacy results were limited to the primary and other major secondary outcome results from Study N159.

For the safety evaluation, the database included pooled results from 5 major studies (see table below) and where significant, compared to the results from the single double blind efficacy study N159. The extension study N157 was still ongoing and the sponsors used a cutoff date of April 30, 2004 for the pooled safety database. Additional safety information, primarily serious adverse events and ongoing adverse events resulting in discontinuation were included from six UCB sponsored completed or ongoing studies that included children with other seizure types. In

addition the sponsor provided information from their database regarding spontaneously reported (postmarketing) events through August 31, 2004 (the safety data cut off date) and to February 15, 2005 via a 120 day safety update. A total of **239** children were included in the total safety database among all the studies included in the submission.

4.2 Tables of Clinical Studies

As noted above, five pediatric studies were performed for the sNDA. They are summarized in the sponsor provided table below.

Table 2:1 Overview Of Pediatric Studies Included In Application
(Data Cut-Off Date 30 April 2004)

Study No.	Dates of Conduct (Country(ies))	Children Exposed to LEV (Boys / Girls)	Mean Age (Range)	Overview of Design
Studies in Pooled Database (ITT Population)				
N159	9/99 – 3/03 (U.S. and Canada)	101 (54 / 47)	10.2 yrs (4.1 – 17 yrs)	Randomized, double-blind, placebo controlled, 28-week (8-week baseline, 4-week titration, 10-week evaluation, 6-week withdrawal) efficacy and safety study of flexible escalating doses of 20, 40, 60 mg/kg/day
N157	2/98 – ongoing (International)	80 *de novo* (44 / 36)	9.8 yrs (0.9 – 16 yrs)	Open-label, long-term follow-up study (20 – 99 mg/kg/day)
N151	9/97 – 9/98 (U.S.)	24 (15 / 9)	9.5 yrs (5.6 – 12.7 yrs)	Open-label, single and multiple dose PK, safety and efficacy study of escalating doses of 10, 20, 40 mg/kg/day)
N01010	1/02 - 7/03 (U.S., Mexico)	21 (12 / 9)	9.8 yrs (4.5 – 12.8 yrs)	Open label, multiple dose, 6-week, PK study of escalating (every 2 weeks) doses of 20, 40, 60 mg/kg/day as well as bi-directional AED interactions
N01052	9/02 – 5/03 (U.S.)	13 (7 / 6)	20.2 mo. (2.4 – 46.8 mo.)	Open-label, single dose PK study (20 mg/kg) in patients with epilepsy

4.3 Review Strategy

I read the study report for the main efficacy study, N159, along with the ISS and ISE. I also read appropriate CRFs, CRTs, narratives, data listings and the proposed label for this indication.

4.4 Data Quality and Integrity

All studies were GLP studies. The reports were concise, clear and easy to navigate.

4.5 Compliance with Good Clinical Practices

The sponsor appears to have complied with good clinical practices. The sponsor identified a single study center did not meet their criteria for GCP and did not include the 16 enrolled patients from that study in their analyses. The FDA Division of Scientific Investigations identified another site that enrolled 9 patients with missing data.

4.6 Financial Disclosures

The sponsor submitted information from 73 investigator sites. There were no financial interests reported. The stock of the company is not publicly traded in the United States or Canada. In addition, no single clinical site enrolled enough patients to affect overall efficacy.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics of levetiracetam have been studied in healthy adult subjects, adults and pediatric patients with epilepsy, elderly subjects and subjects with renal and hepatic impairment. Levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetics are linear and time-invariant. Bioavailability of levetiracetam is not affected by food. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. Plasma half-life of levetiracetam across studies is approximately 6-8 hours. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.

The current pediatric supplement provides nonlinear mixed effects modeling characterizing the PK of levetiracetam in pediatric patients. The following is proposed labeling for the pediatric indication summarizing pediatric PK. The reader is also referred to the Biopharm review.

> *Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after single dose (20 mg/kg). The body weight adjusted apparent clearance of levetiracetam was approximately 40% higher than in adults.*
>
> *A repeat dose pharmacokinetic study was conducted in pediatric patients (age 4-12 years) at doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. The evaluation of the pharmacokinetic profile of levetiracetam and its metabolite (ucb L057) in 14 pediatric patients demonstrated rapid absorption of levetiracetam at all doses with a C_{max} of about 1 hour and a $t_{1/2}$ of 4.9 hours across the three dosing levels. The C_{max} and AUC increased proportionally based on dose. The potential interaction of levetiracetam with carbamazepine and valproate was also evaluated in these patients.*

Consistent with formal pharmacokinetic studies in adults, there has been no evidence of clinically significant drug interactions in pediatric patients 4-12 years old receiving 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day. However, there was a suggestion for about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme inducing AEDs. This finding was not considered to be clinically significant and dose adjustment is not required. Levetiracetam had no apparent effect on plasma concentrations of carbamazepine or valproate.

5.2 Pharmacodynamics

The mechanism of action of levetiracetam is unknown. There are no major pharmacodynamic effects of levetiracetam.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The efficacy of levetiracetam as add-on therapy in patients with partial seizures was studied in children ages 4-16. The sponsor's base efficacy claims on one well controlled study (Study N159) that recruited 198 patients.

6.1.1 Methods

I read the study report from Study N159, and the Integrated Review of Efficacy. I also read the review and discussed the results with the assigned statistician, Ohiddul Siddiqui, Ph.D. I looked at the original statistical plan and compared it to the actual analyses performed. I looked at the number of patients dropouts to see if this had an effect on the overall results.

The study duration was up to 26 weeks with an 8 week baseline period, a 6 week up titration of drug (or matching placebo) from 20-40-60mg/kg/day and 8 weeks at a stable dose of 60mg/kg/day. (This was "reinterpreted" by the sponsor into a 4 week up titration of drug with two weeks each at the 20 and 40mg/kg/day doses followed by 10 weeks on the stable dose of 60mg/kg/day. Nonetheless, the treatment period including titration and evaluation was 14 weeks.) Per the sponsor, the dose was increased regardless of response but could be down titrated if needed.

Seizure data were evaluated over the 14 week treatment period and data were collected via daily record cards with date, type of seizure and duration recorded. Seizures were categorized by the investigators as type I (partial or focal), type II (generalized) or type III (unclassified). Clusters of seizures were counted as single seizures of the appropriate type.

6.1.2 General Discussion of Endpoints

The primary efficacy parameter for Study N159 was the **partial onset seizure frequency per week** during the 14 week treatment period (including the entire up-titration and evaluation period.) While on treatment, patients were seen every 2 weeks for the first 6 weeks and then once every 4 weeks. Patients who discontinued or who decided not to enter the long-term extension study (N157) were to be down-titrated in 20-mg/kg/day decrements every 2 weeks. They were seen every 2 weeks for a total of 4 weeks following discontinuation.

6.1.2.1 Methods (per sponsor)

Efficacy analyses were conducted by treatment group using descriptive methods for all variables. Two basic methods of presenting the data descriptively were employed. For dichotomous and categorical variables (whether ordered or not), a frequency distribution containing the numbers of observations and the corresponding percentages was presented. For continuous variables, the number of available observations, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum were calculated.

The primary efficacy variable was analyzed using analysis of covariance (ANCOVA). The partial onset [Type I (A-simple partial, B-complex partial); Type IC-partial with secondarily generalization included)] seizure frequency per week during the Treatment Period (Titration and Evaluation Periods) was computed as follows:

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

6.1.2.2 Primary efficacy analysis:

The seizure frequency per week data were not normally distributed; therefore, the ANCOVA model was applied on the $\log_e(x+1)$ transformed data (seizure frequency per week), including treatment as a factor and the $\log_e(x+1)$ transformed baseline seizure frequency per week as a covariate. The difference in treatment LSMEANS with a 2- sided, 95% confidence interval was computed and expressed as a percentage reduction over placebo. This analytical model also was used to assess the primary efficacy variable in the per protocol population (N=168) and the total seizure frequency per week over the Treatment Period.

For absolute change and percent change of partial onset seizure frequency per week, the Kruskal-Wallis test was used for between treatment comparisons.

A logistic regression model was used to compare treatment groups with respect to response rate over the treatment period. The fitted model only included a term for treatment group. An odds ratio with a 95% confidence interval also was computed.

Secondary endpoints included response rates, total seizure frequency, and proportions of patients who were seizure free.

- Absolute change from baseline in partial onset seizure frequency per week during the Treatment Period, during the Titration Period, and during the Evaluation
- Percent change from baseline in partial onset seizure frequency per week during the Treatment Period, during the Titration Period, and during the Evaluation Period
- Partial onset seizure frequency per week during the Titration Period and during the Evaluation Period
- Total seizure frequency per week (Types I + II + III) during the Treatment Period, during the Titration Period, and during the Evaluation Period
- Response rate, defined as the percent of patients experiencing at least a 50% reduction from baseline in the seizure frequency per week during the Treatment Period, was determined for partial onset seizure frequency per week and total seizure frequency per week
- Response to treatment during the Treatment Period based on the percent reduction from baseline in seizure frequency per week grouped in six categories as follows: <- 25%, -25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100%
- Change from baseline in the average duration of seizure free intervals and the number of seizure free days during the Treatment Period
- Cumulative percentage of patients who were seizure- free since the beginning of the Evaluation Period

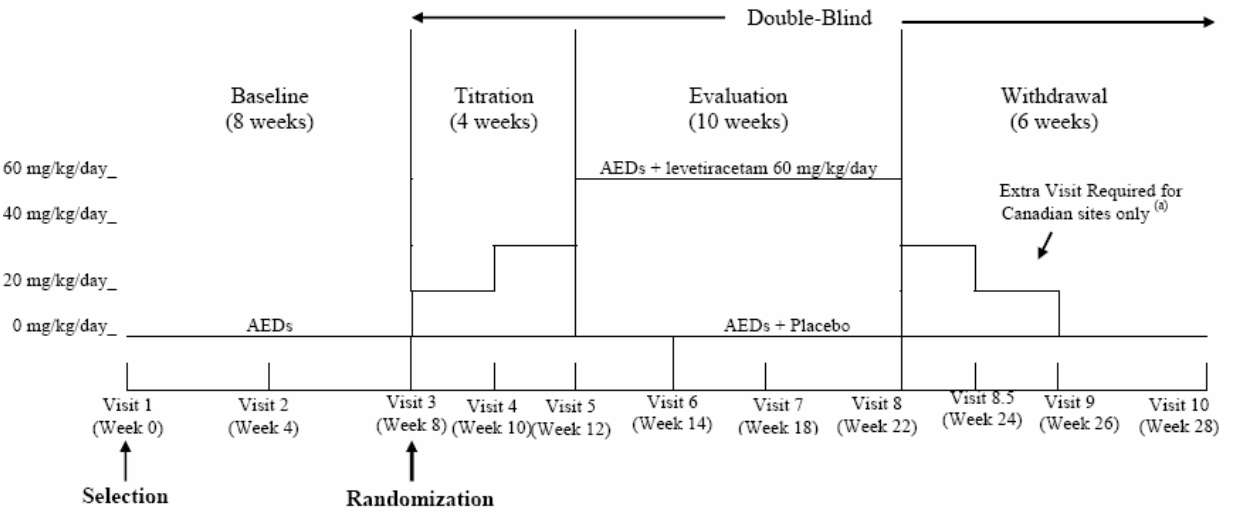
6.1.3 Study Design (Study N159)

One adequate and well-controlled study (N159) was performed in order to demonstrate efficacy. The objective was to determine the efficacy and tolerability of levetiracetam as add-on treatment in pediatric patients (age 4 to 16 years) with refractory partial onset seizures. Following an 8-week prospective baseline period, patients were randomized to receive placebo or levetiracetam in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day (or a maximum of 3000 mg/day).

Patients remained at the 60 mg/kg/day dose for a total of 10 weeks. Dosing was initiated on a mg/kg basis and could be adjusted as needed for tolerability. Patients being treated with a maximum of two other AEDs were included in the trial. To enter the trial the patients were required to have at least four partial onset seizures per each 4-week period during the 8-week baseline.

A schema of the study design for N159 is copied from the submission.

Figure 4:1 N159 Study Design



Patients who completed the study and enrolled in the open-label follow-up study (N157) did so at Visit 8 (Week 22). Patients wishing to terminate participation entered a withdrawal/down-titration period.
Patients terminating the study early entered the withdrawal period for down-titration of study medication.
Patients **not** enrolling in the open-label follow-up study (N157) had a final visit two weeks after the last dose of study medication.
(a) This visit was **required** only for Canadian sites and was optional for the sites in the US.

Amendments

The study design was amended twice. One amendment was an increase in the sample size from 120 patients to 194 patients due to greater than expected overall (non-aggregated to treatment group) variability. This was based on blinded review of variability when 64 patients were analyzed (via a planned interim analysis). The second amendment added an additional study visit at 24 weeks (visit 8.5) to all Canadian sites.

The study was performed at 49 centers in the US and 10 centers in Canada. With the exception of one site (**55)** the trial was conducted in accordance with the ICH E6 note for Guidance on Good Clinical Practice. Data from the one site in the study that did not meet the standard was excluded due to lack of verifiable source documents and other protocol and GCP violations. The site was closed prior to the end of the study. All patients in that site (N=16) discontinued the study.

Extension study N157

Following the conclusion of study N159, patients who entered N157, were titrated using a combination of open label and double-blind tablets such that they were either maintained at their prior dose level (if on levetiracetam) or were titrated from 20 to 40 to 60 mg/kg/day every 2 weeks. The previous treatment assignment remained blinded. Patients who participated in an open-label trial directly entered maintenance treatment. Dosing was flexible, depending on tolerability and response. Doses greater than 80 mg/kg/day were only to be used by prior Sponsor approval. Changes in concomitant AEDs were also allowed. During up and down-

titration phases, patients were seen every 2 weeks, otherwise, the visits were scheduled every 2 months. As of April 30, 2004, the data cut-off date for the pooled database, 100 patients remained on study. At the August 31, 2004 safety data cut-off, 90 patients remained on therapy in N157. As of the February 15, 2005 safety data cutoff, 85 patients remained on therapy.

6.1.4 Efficacy Findings/Results of Double Blind Study N159

6.1.4.1 Number of patients

The protocol had originally planned for randomizing 194 patients to the study. 282 patients were screened for the study and 216 were randomized. 16 patients at study site 55 were excluded due to "unreliability of the data reported". Two additional patients were excluded from the ITT population because they discontinued before taking any study medication. Therefore, the ITT population consisted of 198 patients, 101 patients randomized to levetiracetam and 97 randomized to placebo.

6.1.4.2 Diagnosis and main criteria for inclusion/exclusion

To be enrolled in Study N159, patients had to be 4-16 years old and recently diagnosed with uncontrolled partial onset seizures whether or not secondarily generalized. All were to have experienced at least 4 seizures in the 4 weeks prior to screening and 4 partial onset seizures in each of the (2) 4 week periods during the 8 week baseline. The diagnosis of epilepsy had to be made at least 6 months prior to selection. EEG, MRI and/or CT were required to confirm absence of a progressive brain lesion since being diagnosed with epilepsy.

Patients were excluded if they required more than 2 concomitant AEDs, or had seizures that were too close to count accurately. Also patients with epilepsy secondary to progressive cerebral disease or history of status epilepticus with hospitalization within 3 months prior to screening were also excluded.

6.1.4.3 Treatment and Demographics

The intent-to-treat (ITT) population consisted of 198 patients, 97 randomized to placebo and 101 randomized to levetiracetam. There were 100 (50.5%) male patients and 98 (49.5%) female patients ranging from 3 to 17 years of age; the mean age overall was 10 years. All patients fell within this range with the exception of 2 patients randomized to placebo who were just under 4 years of age and 3 patients randomized to placebo who were > 17-years old. Most of the patients (about two-thirds) were Caucasian. No substantial differences between treatment groups were observed for demographic characteristics. Demographics of Study N159 are summarized in Sponsor Table 5:1 below.

Table 5:1 Summary Of Demographic Characteristics (ITT Population In N159)

Characteristic		Levetiracetam (N=101)	Placebo (N=97)
Age (Years)	Mean (SD)	10.2 (3.2)	9.8 (3.4)
	Median	10.4	9.7
	Min-Max	4.1 - 17.0	3.3 - 17.2
Age Class (Years)			
<4	n (%)[a]	0 (0.0%)	2 (2.1%)
≥4 to <8	n (%))	25 (24.8%)	30 (30.9%)
≥8 to <12	n (%)	46 (45.5%)	42 (43.3%)
≥12 to <17	n (%)	30 (29.7%)	20 (20.6%)
≥17	n (%)	0 (0.0%)	3 (3.1%)
Gender			
Female	n (%)	47 (46.5%)	51 (52.6%)
Male	n (%)	54 (53.5%)	46 (47.4%)
Race			
White/Caucasian	n (%)	74 (73.3%)	65 (67.0%)
Black/African-American	n (%)	13(12.9%)	12 (12.4%)
Hispanic	n (%)	9 (8.9%)	11 (11.3%)
Asian/Pacific Islander	n (%)	2 (2.0%)	1 (1.0%)
American Indian / Alaska Native	n (%)	0 (0.0%)	2 (2.1%)
Indiana/Pakistani	n (%)	1 (1.0%)	0 (0.0%)
Other/Mixed Race	n (%)	2 (2.0%)	6 (6.2%)
Weight (kg)	Mean (SD)	36.6 (16.9)	37.1 (17.2)
	Median	34.0	32.8
	Min-Max	12.5 - 86.9	11.8 - 83.0

[a] Each percent is the number of randomized patients in the treatment group
Ref: Table 14.1.1:1 in N159 study report (Module 5, Section 5.3.5.1.1.1)

6.1.4.4 History and Etiology of Epilepsy

In order to be enrolled, patients were to have a diagnosis of epilepsy for at least 6 months prior to the initial visit. They also had to be experiencing uncontrolled partial onset seizures despite treatment with up to 2 concomitant AEDs (further defined as 4 partial seizures during the 4 weeks prior to visit 1 and at least 4 partial seizures per each of the two 4 week periods during the baseline phase.)

Few patients required the protocol suggested MRI, CT or EEG as most patients' results were available from medical history.

Epilepsy history and etiology for Study N159 is summarized in Sponsor Table 5:2 below.

Table 5:2 Summary Of Epilepsy History And Epilepsy Etiology (ITT Population In N159)

Characteristic	Levetiracetam (N=101)	Placebo (N=97)
Median weekly Seizure frequency in Baseline Period		
Partial onset seizures (Type I)	4.7	5.3
Total seizures (Types I+II+III)	5.1	5.5
Age at Diagnosis (Years)		
Mean (SD)	2.9 (2.9)	3.1 (3.1)[a]
Median	1.8	2.0
Range	0.0 - 12.5	0.0 - 12.8
Epilepsy Duration (years)		
Mean (SD)	7.4 (3.7)	6.8 (3.5)
Median	6.7	6.7
Range	1.1 - 15.1	0.7 - 16.0
Seizure Type n (%)[b]		
Partial Onset Seizures	101 (100%)	97 (100%)
Simple Partial Onset Seizures	26 (25.7%)	27 (27.8%)
Complex Partial Onset Seizures	88 (87.1%)	86 (88.7%)
Partial Onset Seizures Secondarily Generalized	56 (55.4%)	50 (51.5%)
Primary Generalized Seizures	25 (24.8%)	26 (26.8%)
Unclassified Epileptic Seizures	1 (1.0%)	4 (4.1%)
Clusters (Flurries)	11 (10.9%)	11 (11.3%)
Etiology n (%)[b]		
Genetic Origin (Familial Epilepsy)	12 (11.9%)	6 (6.2%)
Congenital Malformation	12 (11.9%)	13 (13.4%)
Perinatal Events	4 (4.0%)	12 (12.4%)
Cranial Trauma	3 (3.0%)	1 (1.0%)
Cerebral Neoplasm	2 (2.0%)	1 (1.0%)
Brain Surgery	1 (1.0%)	0 (0.0%)
Cerebrovascular Accident	5 (5.0%)	4 (4.1%)
Cerebral Infection	7 (7.0%)	5 (5.1%)
Other	16 (15.8%)	10 (10.3%)
Unknown	49 (48.5%)	50 (51.5%)

[a] N = 96
[b] Patients may have reported more than one seizure type or etiology. Rows are not mutually exclusive.
Ref: Table 14.1.1:6; Table 14.1.1:7; and Listing 16.2.4:7 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

For definition purposes, Type I seizures are partial seizures (including A- simple, B-complex partial and C-partial secondarily generalized). Type II seizures are generalized seizures and Type III are unclassified seizures. As one can see from this table, although all patients had a history of partial seizures, there is considerable overlap in additional types of seizures with a large majority with complex partial seizures and even approximately 25% of patients with primary generalized seizures in each group. Both groups compare well to seizure types, age at diagnosis and epilepsy duration as well. The majority of patients in both groups had unknown etiologies, common in the pediatric epilepsy population.

6.1.4.5 Concomitant AED use

Patients were allowed up to 2 AEDs during the study, provided a stable dose was established. The use of benzodiazepines for more than 7 consecutive days was considered a concomitant AED and could be used in addition to two AEDs on an as-needed basis. All patients in each treatment group took at least one concomitant AED during the baseline phase, 2/3 took two

concomitant AEDs. A few patients in each treatment group took benzodiazepines with their 2 AEDs on an as-needed basis. These patients were counted as taking more than 2 AEDs. Concomitant AED use is summarized in Sponsor Table 5:3 below.

Table 5:3 Summary Of Concomitant AEDs Used During The Baseline Period By Treatment Group In N159

		Levetiracetam N=(101)	Placebo (N=97)
Concomitant AED n (%)	None	0 (0%)	0 (0%)
	1	31 (30.7%)	36 (37.1%)
	2	61 (60.4%)	54 (55.7%)
	> 2	9 (8.9%)	7 (7.2%)

Ref: Table 14.3.7:8 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

The most common administered AEDs during the baseline period are noted in Sponsor Table 5:4 below. In addition, the sponsor related that the most common non benzo combinations of two AED drugs used were lamotrigine+topiramate (8 patients), carbamazepine+valproate (7 patients), carbamazepine+topiramate (6 patients), and carbamazepine+lamotrigine (5 patients).

Table 5:4 Most Commonly Administered Concomitant AEDs During The Baseline Period (ITT Population In N159)

	Levetiracetam (N=101)	Placebo (N=97)
Carbamazepine	35 (34.7%)	37 (38.1%)
Topiramate	29 (28.7%)	31 (32.0%)
Valproic acid	26 (25.7%)	28 (28.9%)
Lamotrigine	23 (22.8%)	20 (20.6%)
Oxcarbazepine	12 (12.9%)	10 (10.3%)

Ref: Table 14.3.7:6 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

6.1.4.6 Dosing and duration / Doses achieved

During the evaluation period, the total daily dose was expected to be 60mg/kg/day or the maximum tolerated dose (not to exceed 3000mg daily). Due to limitations with the available tablet strengths, some patients at the lower end of the weight range received a dose that was higher than the target dose and patients at the upper end of the weight range received a dose that was lower than the target dose. A summary of the doses achieved during the titration period is summarized in Sponsor Table 5:5

Table 5:5 Summary Of Study Drug Dose In Each 2-Week Up-Titration Interval (ITT Population In N159)

	Actual Mean Dose (mg/kg/day)	
Weeks (Target Dose Level)	Levetiracetam N=101	Placebo N=97
	Mean (SD)	Mean (SD)
First 2 Weeks (20 mg/kg/day)	18.6 (3.1)	18.4 (3.0)
Second 2 Weeks (40 mg/kg/day)	38.6 (6.5)	37.3 (9.5)
Third 2 Weeks (60 mg/kg/day)	53.3 (10.2)	52.7 (9.1)

Ref: Table 14.3.7:B in N159 CSR (Module 5, Section 5.3.5.1.1.1)

Table 5:6 summarizes the mean daily dose of study drug during the 10 week evaluation period, including the first two weeks on the goal dose of 60mg/kg/day. The mean and median doses, as expected were lower than the target doses.

Table 5:6 Summary Of Actual Levetiracetam Dosing (mg/kg/day) During The Evaluation Period[(a)] (ITT Population In N159)

Group		Levetiracetam (N = 101)	Placebo (N = 97)
All Patients	n (%)	97 (96.0%)	91 (93.8%)
	Mean (SD)	51.6 (10.8)	51.4 (9.0)
	Median	52.9	52.4
	Minimum-Maximum	16.5 - 79.2	29.6 - 71.2
Completed Patients	n (%)	94 (93.1%)	83 (85.6%)
	Mean (SD)	51.6 (10.9)	51.9 (8.6)
	Median	52.9	52.4
	Minimum-Maximum	16.5 - 79.2	29.6 - 71.2

(a) Includes the 10-week period at the target dose, *i.e.*, the final 2 weeks of up-titration are included
Ref: Table 14.3.7:1B, Table 14.3.7:2, and Listing 16.2.5:1 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

6.1.4.7 Duration of Treatment

The average number of days on study drug was 100 days (14 weeks) with a range of 91-147 days. Duration of treatment is summarized by the Sponsor in Table 5:7 below.

Table 5:7 Number Of Days On Study Drug During The Treatment Period[a] (ITT Population In N159)

		Levetiracetam (N = 101)	Placebo (N = 97)
All Patients	n (%)	101 (100%)	97 (100%)
	Mean (SD)	99.8 (20.1)	95.0 (22.6)
	Median	101.0	100.0
	Minimum – Maximum	13.0 - 147.0	20.0 - 131.0
Completed Patients	n (%)	94 (93.1%)	83 (85.6%)
	Mean (SD)	104.4 (9.0)	102.6 (8.3)
	Median	102.0	102.0
	Minimum – Maximum	91.0 - 147.0	75.0 - 131.0
Discontinued Patients	n (%)	7 (6.9%)	14 (14.4%)
	Mean (SD)	38.1 (26.6)	49.9 (27.6)
	Median	31.0	40.5
	Minimum - Maximum	13.0 - 94.5	20.0 - 105.5

[a] Includes Titration and Evaluation Periods
Ref: Table 14.3.7:5A and Listing 16.2.5:2 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

6.1.4.8 Discontinuations (Study N159)

More patients discontinued in the placebo group than in the treatment group due to adverse events. The most frequent reasons for premature discontinuation, in decreasing order of frequency, were adverse events (14 patients), loss to follow- up (3 patients), lack of efficacy (2 patients), and other (2 patients). Lack of adequate response was a more common reason for discontinuation amongst patients randomized to placebo (5 patients or 5.0%) than to levetiracetam (1 patient or 1.0%).

Table 5:8 Summary Of Number (%) Of Patients By Premature Termination Category During The Treatment Period (ITT Population in N159)

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

Ref: Table 14.3.6:4 and Listing 16.2.1:2 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

6.1.4.9 Primary Efficacy Variable- Partial Onset Seizure Frequency

All statistical analyses were performed on the ITT population defined as any patient who took at least one dose of study medication (N=101) or placebo (N=97) except for all 16 patients excluded at site 55 who were excluded by the Sponsor due to unreliability of the data.

The per protocol (PP) population was defined as 168 patients in the ITT population who did not have a major protocol violation affecting the primary efficacy variable. The PP population consisted of 85 patients randomized to levetiracetam and 83 patients randomized to placebo. Approximately 15% of each group of patients was excluded. Per the Sponsor the results for the excluded subgroup were no different than the total population.

Primary efficacy variable – partial seizures frequency per week during the treatment (titration and evaluation) period. The treatment period represents the entire time on study drug (14 weeks including 4 week titration and 10 week evaluation).

There was a statistically significant reduction in weekly partial seizure frequency in the patients randomized to levetiracetam as compared to those randomized to placebo (p = 0.0002). The percent reduction over placebo was 26.8% [two- sided 95% confidence interval (CI) 14.0% - 37.6%]. The interaction between treatment and $\log_e(\times + 1)$ transformed baseline seizure frequency was not significant (p= 0.7724). No significant violations of assumptions for normal distribution and equal variances for the two treatment groups were detected. Results are summarized in Sponsor Table 2:1 below.

Table 2:1 Percent Reduction Over Placebo in Partial Onset Seizure Frequency per Week and Response Rate Over the Treatment Period (ITT Population)

	Levetiracetam (N = 101)	Placebo (N = 97)
Partial Onset Seizure Frequency[a]		
Least Square Means[b]	1.57	
Difference between LS Means	0.31	1.88
95% Confidence Interval (2-sided)	0.15, 0.47	
Percent Reduction Over Placebo[c]	26.8%	
95% Confidence Interval (2-sided)	14.0% - 37.6%	
p-value	0.0002	
Response Rate[d]		
Response rate [n (%)]	45 (44.6%)	19 (19.6%)
Odds Ratio[e]	3.3	
95% Confidence Interval (2-sided)	1.75 - 6.24	
p-value[e]	0.0002	

[a] Seizure frequency = 7 x [Total number of partial onset seizures during the Treatment Period / Number of days with seizure count ≥0 in the Treatment Period].
[b] From ANCOVA model using $\log_e$ (partial seizure frequency per week + 1) as the response variable and the $\log_e$ (baseline seizure frequency per week + 1) as a covariate.
[c] Percent reduction over placebo = 100 x [1- Exp (LSM Treatment – LSM Placebo)].
[d] Percentage of patients with ≥50% reduction from baseline in partial onset seizure frequency/week.
[e] From logistic regression analysis.

Results were similar when the two study periods, the Titration Period and the Evaluation Period, were analyzed separately. This is summarized in Sponsor Table 11:8 below.

Table 11:8 Partial Onset Seizure Frequency per Week and Percent Reduction Over Placebo (Log-Transformed Data, ITT Population)

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

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

When the study periods were analyzed separately, levetiracetam significantly reduced the partial onset seizure frequency over placebo by 31.2% and 22.4% in the Titration and Evaluation Periods, respectively. Reviewer note: Although I was initially concerned that that drug might be losing effectiveness over time, the reason for the difference could just be the amount of time a patient is followed. For refractive seizure disorders, the longer a patient remains on drug, the more likely they may have an event for multiple reasons – the disease process, poor compliance, or other complications. The sponsors checked their results using last observation carried forward (LOCF) and on the PP population and still had statistically similar results. In addition, the sponsor provided a sensitivity analysis of partial seizure frequency for the ITT population with the addition of the 16 patients who were originally excluded. This demonstrated a percent reduction over placebo of levetiracetam (25.2%) comparable to that of the ITT population (26.8%).

6.1.4.10 Onset of effectiveness

The Sponsor's evaluated the first 6 weeks (titration period) separately in order to evaluate the onset of effectiveness. Per the Sponsor, efficacy was noted early during the treatment period as the dose increased from 20 to 40 to 60 mg/kg/day and remained stable throughout the rest of the treatment period for partial onset seizure frequency, response rate, percent change from baseline in partial onset seizure frequency per week and number of seizure free days. This reviewer remains cautious when comparing outcomes early in the trial as these doses were not maintained at the lower levels, so continued efficacy at a lower dose for any of these outcome measures was not properly evaluated at the lower doses. The Sponsors summarize the efficacy during titration in Sponsor Tables 5:10 and 5:11 below.

Table 5:10 Partial Onset Seizure Frequency Per Week[a] In Each 2-Week Up Titration Interval And Percent Reduction Over Placebo ITT Population In N159)

Analysis Interval	Least Square Means[b]				
	Levetiracetam (N=101)	Placebo (N=97)	Difference (95% CI)	*p*-value[b]	Percent Reduction[c] (95% CI)
First 2 Weeks (20/mg/kg/day)	1.49	1.92	0.50 (0.24, 0.63)	< 0.0001	35.4% (21.6 – 46.8%)
Second 2 Weeks (40 mg/kg/day)	1.51	1.83	0.32 (0.12, 0.53)	0.0021	27.6% (11.2 – 40.9%)
Third 2 Weeks (60/mg/kg/day)	1.55	1.80	0.25 (0.04, 0.46)	0.0201	21.9% (3.9 – 36.6%)

[a] Seizure frequency per week = 7 × (total number of seizures during the time period / number of days with seizure count ≥ 0 during the time period)

[b] From ANCOVA model using $\log_e$ (partial seizure frequency per week + 1) as the response variable and the $\log_e$ (baseline seizure frequency per week + 1) as a covariate.

[c] % Reduction over placebo = 100 × [1-exp (LSM levetiracetam-LSM placebo)]

Ref: Table 14.2.1:48 and Table 14.3.7:5B and Listing 16.2.6:1 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

Table 5:11 Summary Of The Percent Change In Partial Onset Seizure Frequency Per Week In Each 2-Week Up Titration (Visits 3, 4 And 5) (ITT Population In N159)

Analysis Interval	Levetiracetam (N = 101)			Placebo (N = 97)			
	% Change from Baseline[a]			% Change from Baseline			
	n	Median (Q1, Q3)	Mean (SD)	n	Median (Q1, Q3)	Mean (SD)	*p*-value[b]
First 2 weeks (Visit 3)	100	-44.2 (-82.6, -9.1)	-37.2 (59.0)	96	-6.4 (-34.6, 30.1)	5.5 (77.2)	< 0.0001
Second 2 weeks (Visit 4)	97	-45.6 (-82.6, -4.3)	-36.8 (55.1)	95	-12.9 (-51.2, 34.5)	-1.6 (77.9)	0.0004
Third 2 weeks (Visit 5)	96	-48.4 (-76.4, -14.7)	-35.2 (61.7)	90	-18.4 (-60.0, 30.9)	- 4.1(57.3)	0.0022

[a] 100 × (Seizure frequency per week during the period – Baseline seizure frequency per week) + Baseline seizure frequency per week

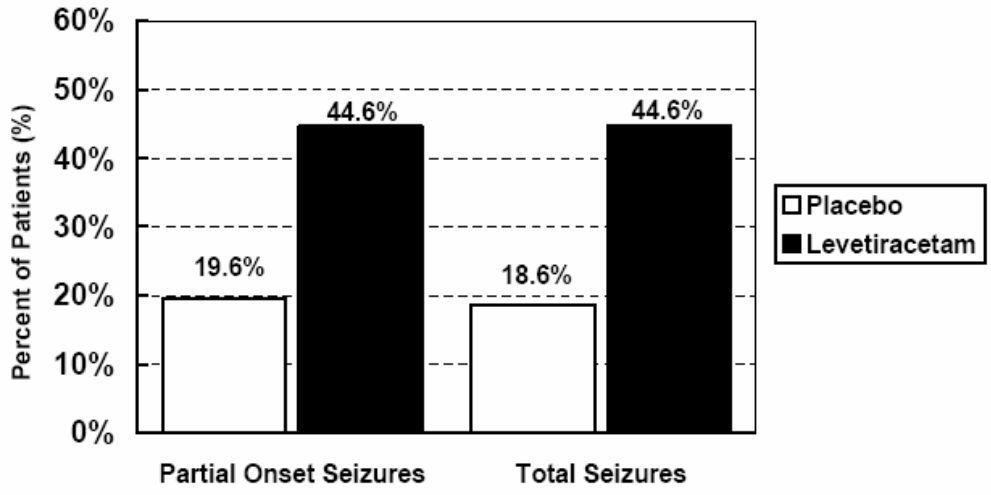
[b] From Kruskal-Wallis test for the between-treatment comparison of medians

Ref: Table 14.2.1:51 in N159 study report. (Module 5, Section 5.3.5.1.1.1)

6.1.4.11 Secondary outcome measure - Response rate

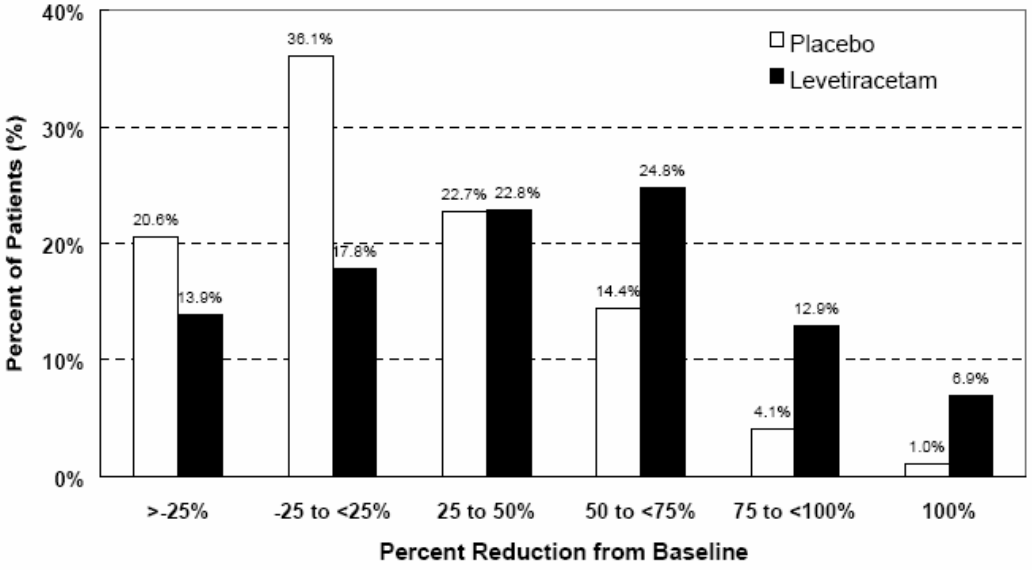
Secondary outcome measure response rate, (summarized in Sponsor Figure 5:3 below) defined as *the percent of patients experiencing at least a 50% reduction in partial onset seizure frequency over the entire treatment period* was significantly larger for levetiracetam (44.6%) than for placebo (19.6%) (p=0.0002). For total seizures, the response rate was again larger for levetiracetam (44.6%) vs placebo (18.6%) (p=0.0001). Categorical response was seen via set categories corresponding to partial onset seizure frequency per week and was summarized in Sponsor Figure 5:3 below. A negative reduction from baseline indicated that there was an increase in partial onset seizure frequency per week. This reviewer noted a strong placebo response essentially matching treatment in the categorical response of 25-50% reduction in percent change from baseline in partial onset seizure frequency per week.

Figure 5:2 Number (%) Of Patients With At Least 50% Reduction Of Seizure Frequency Per Week During The Treatment Period (ITT Population In N159)



Ref: Table 14.2.1:16 in N159 CSR (Module 5, Section 5.3.5.1.1.1)

Figure 5:3 Categorical Response To Treatment During The Treatment Period: Percent Change From Baseline In Partial Onset Seizure Frequency Per Week (ITT Population In N159) [a]



[a] A negative reduction from baseline indicates an increase in partial onset seizure frequency per week.

6.1.4.12 Secondary Outcome Measures - Seizure frequency per week by Study Period and Visit, absolute change and median percent change in seizure frequency.

The Sponsors noted that for partial onset and total seizure frequency by week, the median values were comparable between treatments during the baseline period, but began to separate during titration and evaluation. These are summarized in the following Sponsor Table 11:10.

Table 11:10 Seizure Frequency per Week by Study Period and Visit (ITT Population)

Period/ Visit/(Weeks)		Partial Onset Seizures		Total Seizures	
		Levetiracetam (N = 101)	Placebo (N = 97)	Levetiracetam (N = 101)	Placebo (N = 97)
Baseline	N	101	97	101	97
	Mean (SD)	19.6 (71.6)	18.5 (50.9)	19.8 (71.7)	18.8 (51.0)
	Median (Q1-Q3)	4.7 (2.6-17.2)	5.3 (2.5-14.1)	5.1 (2.8-12.2)	5.5 (2.5-14.1)
1 (0-4)	N	101	97	101	97
	Mean (SD)	20.5 (75.0)	15.9 (29.5)	20.8 (75.2)	16.3 (29.7)
	Median (Q1-Q3)	5.3 (2.3-14.2)	5.1 (2.2-15.7)	5.4 (2.5-14.2)	5.5 (2.5-15.7)
2 (4-8)	N	101	96	101	96
	Mean (SD)	18.6 (69.1)	21.1 (76.7)	18.8 (69.1)	21.4 (76.7)
	Median (Q1-Q3)	4.4 (2.5-10.9)	4.6 (2.3-15.0)	4.9 (2.6-10.9)	5.4 (2.3-17.2)
Titration	N	101	97	101	97
	Mean (SD)	9.4 (20.5)	14.4 (30.2)	9.6 (20.5)	14.9 (30.8)
	Median (Q1-Q3)	3.1 (0.8-7.3)	5.3 (1.9-13.2)	3.6 (1.0-7.4)	5.4 (2.0-14.9)
3 (8-10)[a]	N	101	97	101	97
	Mean (SD)	9.4 (21.3)	15.3 (33.8)	9.6 (21.3)	15.8 (34.3)
	Median (Q1-Q3)	2.9 (0.5-7.4)	5.2 (1.5-13.5)	3.5 (0.5-7.8)	5.6 (1.5-13.5)
4 (10-12)	N	98	96	98	96
	Mean (SD)	9.4 (20.8)	13.2 (27.1)	9.5 (20.8)	13.8 (27.8)
	Median (Q1-Q3)	3.1 (1.0-7.7)	4.9 (1.3-13.5)	3.4 (1.0-7.7)	5.4 (1.5-14.0)
Evaluation	N	97	92	97	92
	Mean (SD)	12.8 (49.7)	12.0 (17.3)	13.0 (49.7)	12.4 (18.0)
	Median (Q1-Q3)	2.6 (0.8-7.7)	4.9 (1.6-14.4)	3.0 (0.8-8.8)	5.0 (1.8-15.6)
5 (12-14)	N	97	91	97	91
	Mean (SD)	10.7 (31.8)	12.4 (17.7)	11.0 (31.8)	13.1 (18.8)
	Median (Q1-Q3)	2.8 (0.8-8.2)	5.8 (1.5-16.0)	3.0 (0.9-8.4)	5.9 (1.7-16.5)
6 (14-18)	N	95	87	95	87
	Mean (SD)	11.2 (40.8)	11.8 (18.5)	11.5 (40.8)	12.2 (19.1)
	Median (Q1-Q3)	2.9 (0.7-7.7)	3.6 (1.2-14.2)	3.1 (0.8-8.7)	3.6 (1.4-15.8)
7 (18-22)	N	95	85	95	85
	Mean (SD)	15.6 (69.4)	10.5 (17.6)	15.9 (69.4)	11.0 (18.3)
	Median (Q1-Q3)	2.4 (0.6-7.8)	3.1 (0.9-11.8)	2.8 (0.6-9.0)	3.3 (1.2-12.1)
Treatment	N	101	97	101	97
	Mean (SD)	12.1 (40.2)	12.5 (20.4)	12.4 (40.2)	13.0 (21.1)
	Median (Q1-Q3)	2.9 (1.0-9.1)	4.5 (1.8-13.9)	3.2 (1.1-10.3)	4.5 (2.2-14.5)

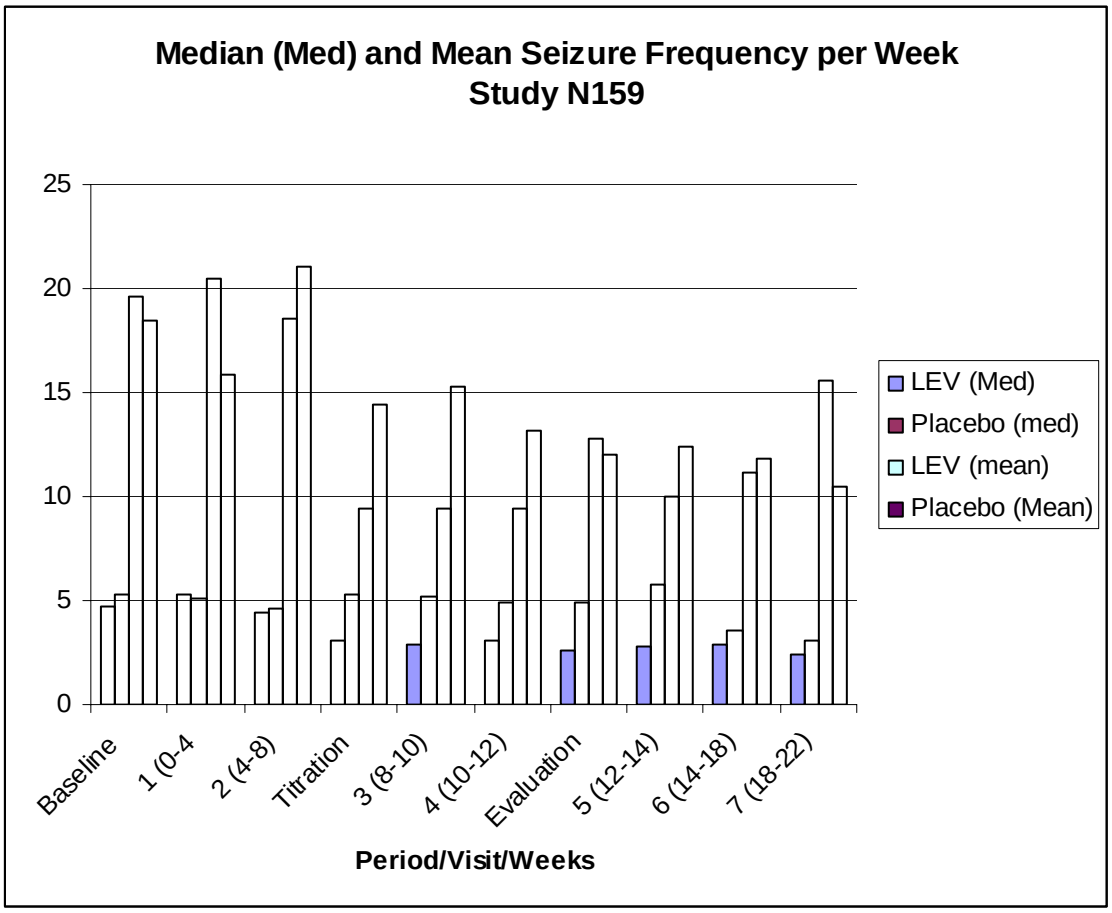
[a] Randomization visit

Ref: Table 14:2.1:6 and Listing 16.2.6:2

Of note to this reviewer is that the median seizure frequency rate in the placebo partial onset seizure group falls from a baseline period median of 5.3 seizures to a median of 3.1 by Visit 7. This compares to a baseline median of 4.7 seizures in the levetiracetam group at baseline to a median of 2.4 at Visit 7. Similar findings were noted in the total seizure groups. The Sponsors believe that this finding was artifactual due to the number of dropouts in the placebo group (6 patients) during that time. However, even the mean seizure rates were lower for the placebo groups at Visit 7 and almost identical at Visit 6 across all groups. I have no explanation for the significant improvement in mean seizures seen in the placebo group by the end of the trial other

than a robust placebo effect overall. I graphed the means and median reduction in partial seizure rates to illustrate the improvement in the placebo group.

Figure 1 – Illustration of median and mean partial seizure frequency per week from Study N159.



The placebo group mean and median partial seizure frequency per week improve during the treatment period, illustrating a somewhat robust placebo effect. Perhaps this is because the patients are already on two antiepileptic drugs and we are treating "residual seizures". Additionally, the enrollees of the trial were taking a diverse group of antiepileptics and had a diverse group of seizure types making it difficult to assess the potential placebo effect.

The sponsor compared and analyzed the absolute changes in seizure rates versus the median percent change in seizure rates in Table 11:11 below.

Table 11:11 Summary of the Absolute Change and Percent Change from Baseline in Partial Onset Seizure Frequency per Week by Study Period (ITT Population)

	Levetiracetam (N = 101) Change from Baseline			Placebo (N = 97) Change from Baseline			
	n	Median (Q1, Q3)	Mean (SD)	n	Median (Q1, Q3)	Mean (SD)	*p*-Value[a]
Absolute Change[b]							
Titration Period	101	-1.6 (-5.8, -0.4)	-10.2 (57.2)	97	-0.4 (-1.7, 1.2)	- 4.1 (25.6)	< 0.0001
Evaluation Period	97	-1.5 (-5.3, -0.4)	- 6.2 (27.7)	92	-1.0 (-4.7, 0.6)	- 7.3 (42.5)	0.1147
Treatment Period	101	-1.6 (-4.5, -0.5)	- 7.5 (35.1)	97	-0.7 (-2.7, 0.7)	- 5.9 (36.6)	0.0030
Percent Change[c]							
Titration Period	100	-36.7 (-77.0, -14.1)	-36.4 (47.5)	96	-7.4 (-31.5, 32.0)	1.4 (59.7)	< 0.0001
Evaluation Period	96	-43.8 (-71.8, -10.0)	-34.1 (56.4)	91	-23.3 (-58.4, 19.0)	-14.5 (59.2)	0.0076
Treatment Period	100	-43.3 (-67.7, -14.6)	-35.0 (49.4)	96	-16.3 (-42.0, 17.6)	- 7.0 (57.3)	< 0.0001

[a] From Kruskal-Wallis test for the between-treatment comparison of medians
[b] Seizure frequency per week in the period - Baseline seizure frequency per week.
[c] 100 x (Seizure frequency per week during the period - Baseline seizure frequency per week) / Baseline seizure frequency per week
Ref: Table 14.2.1:22, Table 14.2.1:24, and Listing 16.2.6:3.

At first glance, one can see that there is no difference in mean or median absolute change from baseline in partial onset seizure frequency between the groups during the evaluation period. This is an artifact of the raw data as the absolute change does not take into account the severity of the seizure disorder. However the median percent change in seizure rates were strong for the treatment period (-43.3 vs -16.3 for treatment and placebo groups respectively). The evaluation of median percent change takes into account disease severity and is a stronger indicator of efficacy, despite the robust placebo effect.

6.1.4.13 Secondary Outcome Measure - Percent Seizure free/Seizure Free intervals

For each patient, the average length of seizure free intervals was calculated and used as the patient's observation for analysis. The mean average seizure- free interval during the Baseline Period was similar for levetiracetam (4.2 days) and placebo (5.5 days). During the Treatment Period, the mean average seizure- free interval was 18.4 days for levetiracetam and 10.6 days for placebo, increases of 14.2 days and 5.0 days from the respective baseline values.

The mean number of seizure- free days during the Baseline Period was similar for levetiracetam (13.9 days) and placebo (14.7 days). During the Treatment Period, the mean number of seizure-free days was 18.2 days for levetiracetam and 16.1 days for placebo, increases of 4.3 days and 1.4 days from the respective baseline values.

The percent of patients who were continuously seizure free during the Evaluation Period was 10.2% (7 patients) for levetiracetam as compared to 3.2% (1 patient) for placebo.

6.1.4.14 Subgroup analyses

The sponsor evaluated subgroups for gender and age. However since stratification on age at randomization was not performed the groups were not equally balanced. The results are more variable for the younger age categories (<8 years old). No major trends were noted for gender or age differences related to the primary outcome measure.

6.1.4.15 Exploratory analyses

Global evaluation scales, Quality of Life in Epilepsy Inventory for adolescents (QOLIE-AD-48), the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) and the Hague Seizure Severity Scale (HASS) were performed. Since these are exploratory analyses and not validated, the results are difficult to assess and are not discussed here.

6.1.6 Efficacy Conclusions

The results of Study N159 demonstrated that levetiracetam was effective in treating pediatric patients with refractory partial onset seizures based on the following observations. Additional reviewer comments are in noted in italics. Additional reviewer comments are amended to the bulleted list.

- Levetiracetam provided clinically relevant, statistically significant (p= 0.0002) reductions over placebo in partial onset seizure frequency per week during the treatment period. [26.8% (95% CI; 14.0%- 37.6%)]
- Levetiracetam also provided clinically relevant, statistically significant reductions over placebo in total seizure frequency per week over the treatment period. [26.2 %(p= 0.0003; 95% CI 13.2%- 37.2%)]
- The percentage of patients with a > 50% reduction from baseline in seizure frequency per week over the Treatment Period was significantly larger for levetiracetam (44.6%) than for placebo (19.6%) for partial onset seizures (p= 0.0002) and total seizures (p< 0.0001).
- The change from baseline in partial onset seizure frequency per week over the Treatment Period was significantly larger for levetiracetam than for placebo for both the absolute change (p = 0.003) and median percent change (p < 0.0001) from baseline. *(The absolute change in seizure rate does not account for the severity of the seizure disorder and can be misleading. Results were not statistically significant during the evaluation period alone. (p=0.1172). However, the median percent change was significantly larger for levetiracetam than for placebo during the treatment period (-43.3 vs -16.3, p<0.0001) reflecting strong efficacy of levetiracetam in the study.*
- The percent of patients who were continuously seizure free during the Evaluation Period was 10.2% (7 patients) for levetiracetam as compared to 3.2% (1 patient) for placebo.
- Reductions from baseline in median seizure frequency per week were observed across subgroups based on age, gender and study drug dose.
- Significant efficacy was seen at each dose level, during up- titration beginning with dose levels of 20 mg/ kg/ day. (*However, these earlier titration doses were only maintained for*

two weeks so these results only suggest short term efficacy at these doses. The sponsor may consider further evaluation via a longer duration multiple fixed dose study.)

- Scores for the HASS, QOLIE- 48- AD and CHQ-PF50 were stable or slightly improved between baseline and evaluation in both treatment groups. *(These exploratory tests have not been validated, making it difficult in evaluate these results. The sponsor should consider validation of these exploratory endpoints before drawing conclusions.)*

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This reviewer read the ISS, the summaries of clinical safety, appropriate narratives, CRFs and CRTs related to serious adverse events, and literature reviews.

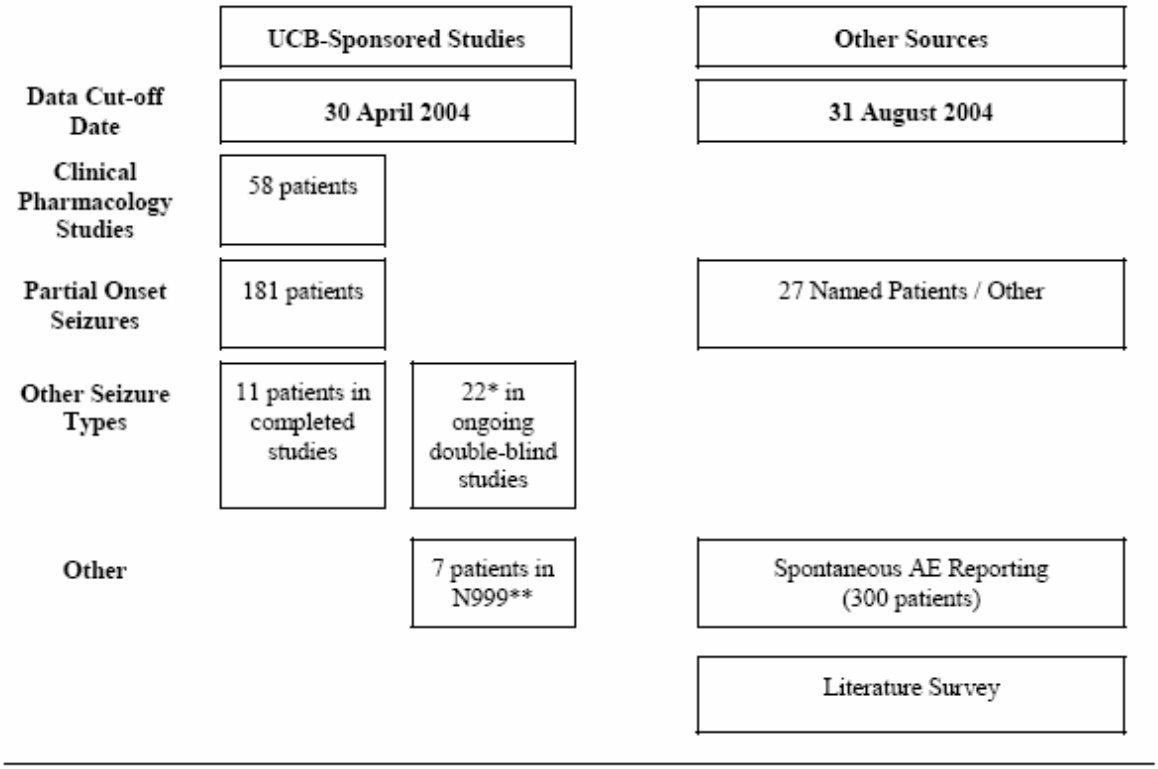
The Sponsor included 5 studies in the pooled safety database. These included the single, randomized, double-blind, placebo-controlled phase 3 study (N159), one open-label phase 2 study (N151), two open label pharmacokinetic studies (N01052 and N01010) and one open-label long-term follow-up study, N157. The pharmacokinetic study N01052 was the only single dose study and the others were all repeated dose studies, with the patients titrated to the maximum protocol- specified dose. These studies were noted earlier in the review, but are reproduced again here for reference as part of Sponsor Table 3:1.

Table 3:1 Overview of Exposure to Levetiracetam in Pediatric Studies Included in Application

Study No.	Dates of Conduct [Country(ies)]	Children Exposed (Males / Females)	Mean Age (Range)	Overview of Design
Studies in Pooled Safety Database (Add-on Therapy in Partial Onset Seizures): Data Cut-off Date 30 April 2004				
N159	9/99 – 3/03 (U.S. and Canada)	101 (54 / 47)	10.2 yrs (4.1 – 17 yrs)	Double-blind, placebo controlled, randomized, 28-week (8-week baseline, 4-week titration, 10-week evaluation, 6-week withdrawal) study of escalating doses of 20, 40, 60 mg/kg/day
N151	9/97 – 9/98 (U.S.)	24 (15 / 9)	9.5 yrs (5.6 – 12.7 yrs)	Open-label, single and multiple dose PK, safety and efficacy study of escalating doses of 10, 20, 40 mg/kg/day
N01010	1/02 - 7/03 (U.S., Mexico)	21 (12 / 9)	9.8 yrs (4.5 – 12.8 yrs)	Open label, multiple dose, 6-week, PK and AED interaction study of escalating (every 2 weeks) doses of 20, 40, 60 mg/kg/day
N01052	9/02 – 5/03 (U.S.)	13 (7 / 6)	20.2 mo. (2.4 – 46.8 mo.)	Open-label, single dose PK study (20 mg/kg) in patients with epilepsy
N157	2/98 – ongoing (International)	80 *de novo* (44 / 36)	9.7 yrs (0.2-17)	Open-label, long-term follow-up study (20 – 99 mg/kg/day)
Subtotal	–	**239**	**2.3 mo – 17 yrs**	–
Non-Pooled Studies: Data Cut-off Date 31 August 2004				

The total database sources are summarized by the Sponsor in Figure 3:1

Figure 3:1 Overview of Sources of Pediatric Subjects Exposed to Levetiracetam Included in Integrated Summary of Safety



* As of 31 August 2004, 13 have entered open-label extension
** patients less than 16 years of age enrolled by protocol exception

Per the Sponsor, adverse events are listed using the COSTART (rather than MedDRA) preferred term. In addition, the Sponsor used its own UCB AE grouping terms that offer an alternative, focused approach to grouping similar events.

Additional information on AEs was pooled from completed studies in 11 children with other seizure types and 22 children who have entered ongoing double blind studies. Additional information regarding SAEs and AEs resulting in discontinuation were available and are discussed under the appropriate headings.

In addition, the Sponsor provided information on 300 postmarketing spontaneous AE reports. These are discussed more fully in Section 7.1.17 of this review.)

In the information related to the double blind study N159, 89 of the 101 patients in the treatment group experienced a total of 462 treatment emergent adverse events with 10 patients experiencing a TEAE classified as severe in intensity. Major adverse events occurring more likely related to drug treatment included somnolence, accidental injury, hostility, nervousness, asthenia, anorexia, depression, emotional lability, rhinitis, and agitation.

In the total database, in terms of the overall patient exposures, 234 of the 239 patients exposed to levetiracetam experienced at least one treatment-emergent adverse event; a total of 2713 adverse events were reported. The most common adverse events affected the nervous system, with somnolence, hostility, nervousness, and asthenia the most common in children. Somnolence and nervousness tended to occur within the first few weeks of treatment and improved. There were no clear temporal or dose related trends nor were there adverse events uniquely associated with long- term treatment. Fewer than 10% of the children discontinued treatment due to an adverse event and when they did, it was primarily due to a nervous system event. The major safety issues requiring more than casual discussion include: neuropsychiatric side effects, low WBC and neutrophil counts, and effects on body weight.

7.1.1 Deaths

There were no deaths during double blind study N159.

In the open label extension study N157, there was one death.

> ISS No. 5267 was a 15- year old Caucasian girl, who had received levetiracetam for a total of approximately 1 year, first in N159 and then in N157. In the 2 months before her death, she was noted to have serious worsening behavioral problems. She was admitted to the hospital for status epilepticus, thought to be fever- induced. She had had symptoms of respiratory infection and was being treated. En route to the hospital, she experienced a respiratory arrest and subsequently went into cardiopulmonary arrest. Ultimately, she experienced multi- organ failure due to massive ischemic insult. The death was judged by the Investigator to be unrelated to study drug.

Postmarketing deaths – Per the Sponsor, sudden death in epilepsy (SUDEP) for patients receiving levetiracetam on the basis of patient treatment years is 0.08% (14/ 182,495). Although SUDEP are related to risk factors in the epilepsy population, in general including male sex, poor compliance with medication and polypharmacy, there may be different risk factors in the pediatric population. 10 cases of SUDEP among pediatric patients were identified in the UCB global database. Overall, there seems to be a low risk of death associated with levetiracetam use among pediatric patients.

Table 10:74 Fatal Cases in UCB Global Drug Safety Database

	Case	Patient age and gender	Described cause of death
1	2000144	17 mo M	Heart failure during seizure (congenital dilated cardiomyopathy)
2	1004307	22 mo F	Presumed pneumonia
3	1006156	7 F	Status epilepticus, DIC
4	8006415	13 M	Suicide
5	1006290	15 M	Aspiration pneumonia, hepatic failure
6	8006993	14mo M	Found dead in bed
7	8003885	9 M	Found dead in bed
8	1004086	9 M	Found dead in bed (no autopsy)
9	8006961	14 M	Found dead in bed
10	2000396	14 F	Found dead in bed (autopsy performed; result of seizure disorder)

7.1.2 Other Serious Adverse Events

Double blind N159 – Approximately 10% of patients receiving either drug or placebo (8 patients randomized to drug and 9 patients randomized to placebo) experienced a serious adverse evetn (SAE). SAEs for the levetiracetam group included dehydration (2 patients), and intestinal obstruction, kidney calculus, status epilepticus NOS, accidental injury (foreign body ingestion), confusion, meningitis, accidental overdose (of levetiracetam), and depression (reported for 1 patient each). SAEs for the placebo group included: pneumonia (3 patients), status epilepticus NOS (2 patients) and respiratory disorder, pharyngitis, gastroenteritis, viral infection, convulsion, hallucinations, CNS neoplasia, cerebral hemorrhage, procedure therapeutic epilepsy, and procedure diagnostic epilepsy (reported for 1 patient each).

Pooled database – 66 patients (58 in addition to the 8 listed above) exposed to levetiracetam had one or more SAEs. 1 patient in study 151 had an overdose (ISS No 4884). The most common AEs were related to the nervous system or were therapeutic procedures related to epilepsy. All SAEs are summarized in the following Sponsor Table 7:18

Table 7:18 Number (%) of Patients Reporting at Least One Treatment-emergent Serious Adverse Event by COSTART Body System and Preferred Term (Events Reported by 1% or More of Patients Overall) – Adequate and Well-controlled Study and Overall

COSTART Body System / Preferred Term	N159		Overall LEV (N = 239)
	Placebo (N = 97)	LEV (N = 101)	
No. with Non-procedure Related SAE	8 (8.2%)	8 (7.9%)	50 (20.9%)[a]
Body as a Whole	1 (1.0%)	2 (2.0%)	10 (4.2%)
Accidental injury	0	1 (1.0%)	2 (0.8%)
Accidental overdose	0	1 (1.0%)	2 (0.8%)
Fever	0	0	2 (0.8%)
Infection	0	0	2 (0.8%)
Digestive System	1 (1.0%)	1 (1.0%)	8 (3.3%)
Gastroenteritis	1 (1.0%)	0	3 (1.3%)
Metabolic and Nutritional Disorders	0	2 (2.0%)	4 (1.7%)
Dehydration	0	2 (2.0%)	3 (1.3%)
Musculoskeletal System	0	0	2 (0.8%)
Musculoskeletal congenital anomaly	0	0	2 (0.8%)
Nervous System	5 (5.2%)	4 (4.0%)	32 (13.4%)
Convulsion	1 (1.0%)	0	14 (5.9%)
Depression	0	1 (0.1%)	2 (0.8%)
Status epilepticus NOS	2 (2.1%)	1 (1.0%)	4 (1.7%)
Personality disorder	0	0	4 (1.7%)
Psychosis	0	0	2 (0.8%)
Procedure	2 (2.1%)	0	23 (9.6%)
Procedure diagnostic epilepsy	1 (1.0%)	0	12 (5.0%)
Procedure diagnostic NOS	0	0	2 (0.8%)
Procedure therapeutic epilepsy	1 (1.0%)	0	11 (4.6%)
Urogenital System	0	1 (1.0%)	5 (2.1%)
Kidney calculus	0	1 (1.0%)	3 (1.3%)

[a] 16 Patients had only procedures reported as SAEs: 4883, 4894, 5140, 5142, 5174, 5183, 5189, 5196, 5224, 5234, 5284, 5286, 5814, 5366, 5368, 5391.
Source: Table 16.4.2:8; SAEs by interval of onset in Table 16.4.2:10

The Sponsor reevaluated these SAEs by UCB AE grouping terms in Table 7:19 below.

Table 7:19 Number (%) of Patients Reporting at Least One Treatment-emergent Serious Adverse Event by UCB AE Grouping Term – Adequate and Well-controlled Study (ITT in N159) and Overall

UCB AE Grouping Term	N159		Overall LEV (N = 239)
	Placebo (N = 97)	LEV (N = 101)	
Auto-aggressive Behavior	0	0	1 (0.4%)
Cardiac Rhythm	0	0	1 (0.4%)
Coagulation and Bleeding Disorders	0	0	1 (0.4%)
Cognitive Symptoms	0	0	1 (0.4%)
Congenital Disorders	0	0	2 (0.8%)
Convulsions	3 (3.1%)	1 (1.0%)	19 (7.9%)
Endocrine Disorders	0	0	1 (0.4%)
General Symptoms and Complaints	0	0	1 (0.4%)
Genital / Reproductive Symptoms	0	0	1 (0.4%)
Hematopoietic Disorders	0	0	1 (0.4%)
Infections	6 (6.2%)	1 (1.0%)	11 (4.6%)
Injuries	0	1 (0.4%)	2 (0.8%)
Lower GI Symptoms	0	1 (1.0%)	3 (1.3%)
Medical Procedures	2 (2.1%)	0	23 (9.6%)
Metabolic and Nutritional Disorders	0	2 (2.0%)	3 (1.3%)
Nonpsychotic Behavioral Symptoms	0	1 (1.0%)	6 (2.5%)
Oral Cavity Disorders	0	0	1 (0.4%)
Other Neurologic Symptoms	0	0	1 (0.4%)
Overdose	0	1 (1.0%)	2 (0.8%)
Psychotic Symptoms	1 (1.0%)	0	3 (1.3%)
Reaction Unevaluable	0	0	1 (0.4%)
Renal / Urinary Symptoms	0	1 (1.0%)	3 (1.3%)
Sedation	0	0	1 (0.4%)
Skin Reactions	0	0	1 (0.4%)
Upper GI Symptoms	0	0	2 (0.8%)

Source: Table 16.4.2:9

As noted earlier, the most common SAEs in both the double blind study and in the database overall pertained to the nervous system, especially seizure-related events. There were 14 patients (5.9%) who had convulsions while on levetiracetam and 4 patients (1.7%) who had status epileptics NOS (outcome was fatal in one case-see below); 23 patients (9.6%) had procedures related to epilepsy. Of the psychiatric events, events were coded to "personality disorder" (4 patients), depression (2 patients total, 1 previously described), and psychosis (2 patients, ISS Nos. 5210 and 5489).

The Sponsor was well aware of neuropsychiatric side effects of levetiracetam as reported in adults. These are discussed at length in a special safety assessment section and are included later in the review under Section 7.1.12.

7.1.3 Dropouts and Other Significant Adverse Events

Reasons for discontinuation comparing N159 to the total database are summarized in Sponsor table 7:11 below

Table 7:11 Number (%) of Patients by Primary Adverse Event Resulting in Discontinuation (Termination CRF) – Adequate and Well-controlled Study (ITT in N159) and Overall[a]

	N159		
COSTART Body System / Preferred Term	Placebo (N = 97)	LEV (N = 101)	Overall LEV (N = 239)
Total No.	9 (9.3%)	5 (5.0%)	21 (8.9%)[b]
Body as a Whole	0	0	2 (0.8%)
Asthenia	0	0	1 (0.4%)
Headache	0	0	1 (0.4%)
Cardiovascular System	0	0	1 (0.4%)
Cardiovascular disorder	0	0	1 (0.4%)
Digestive System	0	0	1 (0.4%)
Vomiting	0	0	1 (0.4%)
Nervous System	9 (9.3%)	5 (5.0%)	15 (6.3%)
Ataxia	1 (1.0%)	1 (1.0%)	1 (0.4%)
Convulsion	3 (3.1%)	1 (1.0%)	2 (0.8%)
Depression	1 (1.0%)	1 (1.0%)	2 (0.8%)
Emotional lability	1 (1.0%)	0	0
Hallucinations	1 (1.0%)	0	0
Hostility	1 (1.0%)	1 (1.0%)	3 (1.3%)
Hyperkinesia	0	1 (1.0%)	2 (0.8%)
Nervousness	0	0	3 (1.3%)
Psychotic depression	0	0	1 (0.4%)
Speech disorder	1 (1.0%)	0	0
Status epilepticus NOS	0	0	1 (0.4%)
Procedure	0	0	1 (0.4%)
Procedure therapeutic NOS	0	0	1 (0.4%)
Skin and Appendages	0	0	1 (0.4%)
Rash	0	0	1 (0.4%)

[a] See Table 7:12 for additional events in placebo patient ISS No. 5407; uterine hemorrhage for 1 levetiracetam-treated patient (ISS No. 5583) is incorrectly included in Table 16.3.1:3; it preceded levetiracetam in onset and did not result in discontinuation

[b] Includes 3 patients for whom the reason for discontinuation has been re-categorized by the sponsor from "other" to "adverse events", pending confirmation from the site: ISS Nos. 5463 (nervousness), 5368 (hyperkinesias), and 5587 (depression and nervousness)

Source: Table 16.3.1:3

The most common reason for discontinuation related to the nervous system. This was true for both the double blind study and the total safety database. Seizures leading to discontinuation were expected in the placebo group. Incidences of neurologic adverse events were almost equal between treatment and placebo groups. However in the open label phase, depression,

hyperkinesis, and nervousness persisted as reasons for discontinuation. This reviewer adds that reasons for discontinuation would have to be somewhat serious, considering the types of seizures enrolled (refractory partial seizures) and the fact that most patients are already on other antiepileptic drugs.

There were some unusual reasons for discontinuation. ISS No 5407 (placebo in N159) was discontinued on medication in the ER due to lack of information. That patient was eventually diagnosed with glioma and was terminated from the study. ISS No 5204, an 11 year old girl was discontinued due to refractory partial epilepsy and the need to have craniectomy and grid placement. ISS No 5583 was identified in the pooled database as discontinuing N157 due to an adverse event (uterine hemorrhage) but the patient did not discontinue levetiracetam.

Three other patients listed as discontinued for "other reasons" may have had adverse events. ISS 5368, a 5 year old boy discontinued due to irritability, aggressive behavior and ADHD. ISS 5587, a 10 year old girl discontinued levetiracetam after 76 days due to irritability, sadness, and "isolation conduct". ISS 5463 a 1.8 year old boy was noncompliant due to his mother not giving drug for 2 ½ weeks as the mother felt he was irritable (with daily seizures!). Overall, however, reasons for discontinuation mirror the usual and more common side effects.

7.1.3.1 Dose reductions

Per the Sponsor, 72 patients in the pooled database had either a dose reduction and/or discontinued as a result of an adverse event. Patients requiring a dose reduction or who discontinued due to a treatment emergent adverse event are summarized in Sponsor Table 7:14 below.

Table 7:14 Number (%) of Patients with a Dose Reduction or Who Discontinued as a Result of a Treatment-emergent Adverse Event by COSTART Body System and Preferred Term (Events Reported by 1% or More of Patients Overall) – Adequate and Well-controlled Study (ITT in N159) and Overall

	Based on AE CRF (N ≥ 1%)		Termination Form
	N159		
COSTART Body System / Preferred Term	Placebo (N = 97)	LEV (N = 101)	Overall LEV (N = 239)
Body as a whole	3 (3.1%)	4 (4.0%)	15 (6.3%)
Asthenia	0	3 (3.0%)	5 (2.1%)
Headache	1 (1.0%)	1 (1.0%)	6 (2.5%)
Digestive System	3 (3.1%)	0	5 (2.1%)
Vomiting	1 (1.0%)	0	3 (1.3%)
Nervous System	17 (17.5%)	14 (13.9%)	51 (21.3%)
Agitation	0	2 (2.0%)	2 (0.8%)
Ataxia	1 (1.0%)	1 (1.0%)	2 (0.8%)
Convulsion	7 (7.2%)	2 (2.0%)	9 (3.8%)
Depression	1 (1.0%)	1 (1.0%)	2 (0.8%)
Dizziness	0	0	2 (0.8%)
Emotional liability	2 (2.1%)	1 (1.0%)	2 (0.8%)
Hostility	2 (2.1%)	7 (6.9%)	11 (4.6%)
Hyperkinesia	0	2 (2.0%)	3 (1.3%)
Insomnia	1 (1.0%)	1 (1.0%)	2 (0.8%)
Nervousness	0	0	6 (2.5%)
Personality disorder	1 (1.0%)	2 (2.0%)	6 (2.5%)
Somnolence	3 (3.1%)	3 (3.0%)	16 (6.7%)
Status epilepticus NOS	1 (1.0%)	2 (2.0%)	3 (1.3%)
Thinking abnormal	1 (1.0%)	1 (1.0%)	5 (2.1%)
Procedure	0	0	7 (2.9%)
Procedure diagnostic epilepsy	0	0	6 (2.5%)

Source: Table 16.4.2:3

As noted in the table, hostility was the number one reason for discontinuation during the first few weeks of treatment. Other common events that most often resulted in dose reductions were somnolence, diagnostic procedure for epilepsy, hostility, convulsion and personality disorder.

7.1.4 Other Search Strategies

The Sponsor included data from completed studies in children with other epilepsies. Some of these patients with more severe epilepsy syndromes might have a different risk and are presented separately.

Study N130 was a study in children with Lennox Gastaut syndrome. In that study, 5 patients reported 18 SAEs; one was aggravated convulsions requiring hospitalizations, not so unusual in that population. Severe AEs also included drowsiness in 2 patients and hyperkinesias in 1 patient. AEs were more frequent at higher doses of levetiracetam including behavior problems and worsening of seizures. One patient was withdrawn prematurely due to drowsiness, hyperkinesias, and aggravated convulsions.

Study N162/164 enrolled patients with atypical absence in childhood or juvenile absence epilepsy. In N162, 12 SAEs were reported by 4 of the 6 patients including mild somnolence and moderate nervousness; however none led to discontinuation or dose reduction. In the follow on study N164, 4 children reported 39 adverse events of which three were considered related to levetiracetam (1 patient each experienced hyperkinesias, aggressiveness and nervousness.) Again none led to discontinuation or dose reductions.

7.1.5 Common Adverse Events

Double Blind Study 159 - Adverse events that were more common among patients randomized to levetiracetam than to placebo were somnolence, hostility, nervousness, and asthenia. Anorexia also tended to be more common in the levetiracetam treatment group. However, pre- treatment anorexia was also observed more commonly in the levetiracetam treatment group than in the placebo group. Pain, increased cough, and rhinitis were also more common in the levetiracetam treatment group, but their incidence did not appear to be much greater than during the baseline period. On the other hand, abdominal pain, convulsion, insomnia, and rash were more common in the placebo treatment group.

Pooled safety database – Common adverse events affecting 20% or more of the pooled safety sample, included infection (125 patients or 52.3%), somnolence (71 patients or 29.7%), fever (64 patients or 26.8%), accidental injury (61 patients or 25.5%), headache (59 patients or 24.7%), and pharyngitis (56 patients or 23.4%).

Long term treatment (subset N=166) - The incidence in the subset of 166 patients exposed to levetiracetam for more than 48 weeks was discussed in the ISS. When expressed as the incidence rate of first occurrence per 10,000 person- days, the most common were infection (17.53 per 10,000 person-days), somnolence (6.78 per 10,000 person- days), fever (5.46 per 10,000 person-days), accidental injury (5.23 per 10,000 person-days), and headache (5.04 per 10,000 person- days). These were also the most common adverse events overall.

7.1.5.1 Common adverse event tables

Table 12:6 lists the most common AEs by COSTART body system and preferred term for Study 159, reported by > or = to 2% in either treatment group.

Table 12:6 Incidence of TEAEs Summarized by COSTART Body System and Preferred Term for TEAEs Reported by ≥ 2% of Patients in Either Treatment Group (ITT Population)

	Levetiracetam N=101	Placebo N=97
Body System / Preferred Term	n (%)	n (%)
Body as a Whole[a]	**59 (58.4)**	**63 (64.9)**
Infection	29 (28.7)	28 (28.9)
Headache	14 (13.9)	14 (14.4)
Accidental Injury	17 (16.8)	10 (10.3)
Fever	8 (7.9)	10 (10.3)
Abdominal pain	4 (4.0)	13 (13.4)
Asthenia	9 (8.9)	3 (3.1)
Pain	6 (5.9)	3 (3.1)
Allergic reaction	2 (2.0)	3 (3.1)
Flu syndrome	3 (3.0)	2 (2.1)
Digestive[a]	**37 (36.6)**	**37 (38.1)**
Vomiting	15 (14.9)	13 (13.4)
Anorexia	13 (12.9)	8 (8.2)
Diarrhea	8 (7.9)	7 (7.2)
Nausea	3 (3.0)	5 (5.2)
Gastroenteritis	4 (4.0)	2 (2.1)
Constipation	3 (3.0)	1 (1.0)
Increased appetite	1 (1.0)	3 (3.1)
Increased salivation	1 (1.0)	3 (3.1)
GGT increased	0 (0.0)	3 (3.1)
Hemic and Lymphatic[a]	**6 (5.9)**	**2 (2.1)**
Ecchymosis	4 (4.0)	1 (1.0)
Metabolic and Nutritional[a]	**4 (4.0)**	**10 (10.3)**
Weight gain	1 (1.0)	3 (3.1)
SGPT increased	0 (0.0)	3 (3.1)

Table 12:6 Incidence of TEAEs Summarized by COSTART Body System and Preferred Term for TEAEs Reported by ≥ 2% of Patients in Either Treatment Group (ITT Population) (Continued)

	Levetiracetam N=101	Placebo N=97
Body System / Preferred Term	n (%)	n (%)
Nervous[a]	**59 (58.4)**	**46 (47.7)**
Somnolence	23 (22.8)	11 (11.3)
Convulsion	7 (6.9)	16 (16.5)
Hostility	12 (11.9)	6 (6.2)
Nervousness	10 (9.9)	2 (2.1)
Personality Disorder	8 (7.9)	7 (7.2)
Emotional lability	6 (5.9)	4 (4.1)
Dizziness	7 (6.9)	2 (2.1)
Insomnia	4 (4.0)	5 (5.2)
Thinking abnormal	4 (4.0)	5 (5.2)
Tremor	3 (3.0)	5 (5.2)
Agitation	6 (5.9)	1 (1.0)
Hyperkinesia	3 (3.0)	3 (3.1)
Ataxia	2 (2.0)	2 (2.1)
Depression	3 (3.0)	1 (1.0)
Status epilepticus[b]	2 (2.0)	2 (2.1)
Speech disorder	1 (1.0)	3 (3.1)
Amnesia	0 (0.0)	2 (2.1)
Nystagmus	0 (0.0)	2 (2.1)
Respiratory[a]	**31 (30.0)**	**28 (28.9)**
Rhinitis	13 (12.9)	8 (8.2)
Cough increased	11 (10.9)	7 (7.2)
Pharyngitis	10 (9.9)	8 (8.2)
Sinusitis	6 (5.9)	7 (7.2)
Epistaxis	2 (2.0)	3 (3.1)
Pneumonia	0 (0.0)	4 (4.1)
Skin and Appendages[a]	**10 (9.9)**	**13 (13.4)**
Rash	3 (3.0)	6 (6.2)
Herpes zoster	0 (0.0)	2 (2.1)
Maculopapular rash	0 (0.0)	2 (2.1)
Special Senses[a]	**13 (12.9)**	**9 (9.3)**
Otitis media	4 (4.0)	5 (5.2)
Conjunctivitis	3 (3.0)	2 (2.1)

Table 12:6 Incidence of TEAEs Summarized by COSTART Body System and Preferred Term for TEAEs Reported by ≥ 2% of Patients in Either Treatment Group (ITT Population) (Continued)

	Levetiracetam N=101	Placebo N=97
Body System / Preferred Term	n (%)	n (%)
Urogenital System[a]	**10 (9.9)**	**9 (9.3)**
Urinary incontinence	2 (2.0)	5 (5.2)
Albuminuria	4 (4.0)	0 (0.0)
Dysmenorrhea	0 (0.0)	2 (2.1)

[a] Table 14.3.1:3
[b] Listed in tables and listings as Grand Mal Convulsion
Ref: Table 14.3.1:8

The number and percentage of common adverse events are compared between all groups, N159, overall and long term in Sponsor Table 7:2 below.

Table 7:2 Number (%) of Patients Reporting at Least One Treatment-emergent Adverse Event by COSTART Body System and Preferred Term (Events Reported by 10% or More of Patients Overall) – Adequate and Well-controlled Study (ITT in N159) and Overall

	N159		Exposed to LEV	
COSTART Body System / Preferred Term	**Placebo (N = 97)**	**LEV (N = 101)**	**Overall (N = 239)**	**>48 Weeks (N = 166)**
Body as a whole	62 (63.9%)	61 (60.4%)	204 (85.4%)	159 (95.8%)
Abdominal pain	13 (13.4%)	4 (4.0%)	31 (13.0%)	27 (16.3%)
Accidental injury	11 (11.3%)	17 (16.8%)	61 (25.5%)	50 (30.1%)
Asthenia	3 (3.1%)	9 (8.9%)	30 (12.6%)	24 (14.5%)
Fever	10 (10.3%)	8 (7.9%)	64 (26.8%)	59 (35.5%)
Headache	13 (13.4%)	14 (13.9%)	59 (24.7%)	45 (27.1%)
Infection	28 (28.9%)	29 (28.7%)	125 (52.3%)	104 (62.7%)
Pain	3 (3.1%)	7 (6.9%)	31 (13.0%)	25 (15.1%)
Digestive System	36 (37.1%)	37 (36.6%)	128 (53.6%)	102 (61.4%)
Anorexia	8 (8.2%)	13 (12.9%)	37 (15.5%)	30 (18.1%)
Diarrhea	7 (7.2%)	8 (7.9%)	33 (13.8%)	28 (16.9%)
Gastroenteritis	2 (2.1%)	4 (4.0%)	35 (14.6%)	31 (18.7%)
Vomiting	12 (12.4%)	15 (14.9%)	52 (21.8%)	42 (25.3%)
Nervous System	47 (48.5%)	60 (59.4%)	182 (76.2%)	136 (81.9%)
Convulsion	16 (16.5%)	8 (7.9%)	45 (18.8%)	32 (19.3%)
Emotional lability	4 (4.1%)	6 (5.9%)	24 (10.0%)	19 (11.4%)
Hostility	6 (6.2%)	12 (11.9%)	36 (15.1%)	25 (15.1%)
Insomnia	6 (6.2%)	4 (4.0%)	30 (12.6%)	25 (15.1%)
Nervousness	2 (2.1%)	9 (8.9%)	32 (13.4%)	25 (15.1%)
Personality disorder	7 (7.2%)	8 (7.9%)	34 (14.2%)	26 (15.7%)
Somnolence	11 (11.3%)	23 (22.8%)	71 (29.7%)	56 (33.7%)
Respiratory System	29 (29.9%)	31 (30.7%)	132 (55.2%)	107 (64.5%)
Cough increased	7 (7.2%)	11 (10.9%)	39 (16.3%)	35 (21.1%)
Pharyngitis	9 (9.3%)	10 (9.9%)	56 (23.4%)	49 (29.5%)
Rhinitis	8 (8.2%)	13 (12.9%)	44 (18.4%)	35 (21.1%)
Sinusitis	7 (7.2%)	6 (5.9%)	32 (13.4%)	27 (16.3%)
Skin and Appendages	13 (13.4%)	10 (9.9%)	64 (26.8%)	53 (31.9%)
Rash	6 (6.2%)	3 (3.0%)	24 (10.0%)	20 (12.0%)
Special Senses	11 (11.3%)	12 (11.9%)	74 (31.0%)	63 (38.0%)
Otitis media	7 (7.2%)	3 (3.0%)	48 (20.1%)	43 (25.9%)

Source: Table 16.4.1:4; long-term Table 16.4.1:10

This reviewer arrived at several conclusions from the tables above. Nervous system events overall were very high and possibly increase over long term treatment.

Generally, this reviewer is also concerned for the increased incidence of adverse event terms hostility, insomnia, nervousness and personality disorder. Although the placebo group has a low percentage for any of these (2-7%) the percentages in the longer term treatment cohorts increase to 15% or more each.

Somnolence is also noted to be high in the treatment groups, but this is discussed as a transient finding in the Sponsor's analysis. With teenage patients, it would be difficult to tease out the causative effect of somnolence, but the degree reported over the long term is concerning (33.7%). The respiratory issues are not significant to this reviewer considering that these are common pediatric complaints and expected in this population.

Adverse events were also grouped by UCB AE grouping terms to better focus the events of interest. As noted by the Sponsors, non psychotic behavior symptoms occurred in more patients randomized to levetiracetam (39 patients or 37.6%) than to placebo (18 patients or 18.6%) Overall, there were 111 patients (46.4%) treated with levetiracetam who had non-psychotic behavior symptoms. Cognitive symptoms occurred in 30 patients (12.6%) with a similar incidence in placebo and drug treated in the double blind study. Other common AEs are grouped and are best explained by common events in the overall pediatric population (such as general symptoms and respiratory symptoms).

Table 7:3 Number (%) of Patients Reporting at Least One Treatment-emergent Adverse Event by Most Common UCB AE Grouping Terms (10% or More Overall) – Adequate and Well-controlled Study (ITT in N159) and Overall

	N159		Exposed to Levetiracetam	
UCB AE Grouping Term	**Placebo (N = 97)**	**LEV (N = 101)**	**Overall (N = 239)**	**>48 Weeks (N = 166)**
Coagulation and Bleeding Disorders	5 (5.2%)	6 (5.9%)	32 (13.4%)	24 (14.5%)
Cognition / Mental Acuity Symptoms	6 (6.2%)	6 (5.9%)	30 (12.6%)	29 (17.5%)
Convulsions	17 (17.5%)	10 (9.9%)	54 (22.6%)	40 (24.1%)
General Respiratory Symptoms	14 (14.4%)	20 (19.8%)	76 (31.8%)	62 (37.3%)
General Symptoms and Complaints	9 (9.3%)	15 (14.9%)	59 (24.7%)	49 (29.5%)
Infections	52 (53.6%)	47 (46.5%)	182 (76.2%)	146 (88.0%)
Injuries	11 (11.3%)	17 (16.8%)	61 (25.5%)	50 (30.1%)
Lower GI Symptoms	8 (8.2%)	11 (10.9%)	49 (20.5%)	42 (25.3%)
Medical Procedures	2 (2.1%)	0	24 (10.0%)	22 (13.3%)
Metabolic and Nutritional Disorders	14 (14.4%)	17 (16.8%)	65 (27.2%)	53 (31.9%)
Non-psychotic Behavioral Symptoms	18 (18.6%)	38 (37.6%)	111 (46.4%)	82 (49.4%)
Other Abdominal Symptoms and Disorders	13 (13.4%)	4 (4.0%)	33 (13.8%)	29 (17.5%)
Other Neurologic Symptoms	15 (15.5%)	14 (13.9%)	63 (26.4%)	47 (28.3%)
Renal / Urinary Symptoms	5 (5.2%)	7 (6.9%)	26 (10.9%)	22 (13.3%)
Sedation	11 (11.3%)	23 (22.8%)	71 (29.7%)	56 (33.7%)
Sleep Symptoms	6 (6.2%)	4 (4.0%)	30 (12.6%)	25 (15.1%)
Skin Reactions	9 (9.3%)	8 (7.9%)	53 (22.2%)	44 (26.5%)
Upper GI Symptoms	17 (17.5%)	19 (18.8%)	74 (31.0%)	60 (36.1%)

Source: Table 16.4.1:5; long-term grouping terms Table 16. 4.1:11

7.1.5.2 Identifying common and drug-related adverse events

Per the Sponsor, investigators were asked to judge the treatment relationship of all adverse events. The most common ones (those occurring in 10% or more of the patients overall) were somnolence (48 patients or 20.1%), hostility (26 patients or 10.9%), and nervousness (25 patients or 10.5%). As illustrated in the table below, these tended to be more prevalent among patients randomized to levetiracetam in N159. Sponsor Table 7: 4, presents treatment- related events reported for 5% or more of the patients overall. The majority of the events listed (asthenia, headache, anorexia, dizziness, and emotional liability) have a greater incidence among patients randomized to levetiracetam; the exception is emotional lability disorder.

Table 7:4 Number (%) of Patients Reporting at Least One Treatment-Related Treatment-emergent Adverse Event by COSTART Body System and Preferred Term (Events Reported by 5% or More of Patients Overall) – Adequate and Well-controlled Study (ITT in N159) and Overall

	N159		
COSTART Body System / Preferred Term	**Placebo (N = 97)**	**LEV (N = 101)**	**Overall LEV (N = 239)**
Body as a Whole	9 (9.3%)	17 (16.8%)	54 (22.6%)
Asthenia	1 (1.0%)	7 (6.9%)	22 (9.2%)
Headache	1 (1.0%)	5 (5.0%)	19 (7.9%)
Digestive System	15 (15.5%)	15 (14.9%)	39 (16.3%)
Anorexia	5 (5.2%)	10 (9.9%)	20 (8.4%)
Nervous System	26 (26.8%)	40 (39.6%)	126 (52.7%)
Dizziness	0	4 (4.0%)	12 (5.0%)
Emotional lability	4 (4.1%)	5 (5.0%)	16 (6.7%)
Hostility	6 (6.2%)	10 (9.9%)	26 (10.9%)
Nervousness	1 (1.0%)	7 (6.9%)	25 (10.5%)
Personality disorder	6 (6.2%)	6 (5.9%)	19 (7.9%)
Somnolence	7 (7.2%)	17 (16.8%)	48 (20.1%)

Source: Table 16.4.2:2

7.1.5.3 Additional analyses and explorations

Adverse events by Dose and Time of Onset

Per the Sponsor, no dose comparison studies were performed in children.

Given the different designs of the pooled studies, an analysis of dose would be confounded by time on drug since the titration in N159 was fixed at 2 weeks per dose.

Per the Sponsor, few adverse events were time or dose related. Somnolence and nervousness occurred during the first weeks of treatment. Whereas somnolence improved over time, nervousness, hostility and personality disorder persisted. Other nonspecific events that occurred

late in treatment were events that were considered common in children such as AEs confined to the respiratory system, fever, and accidental injury. Common AEs related to time on drug are summarized in Sponsor Table 7:7 below. Common AEs related to dose at onset in the database are summarized in Sponsor Table 7:8 below.

Table 7:7 Number (%) of Patients Reporting at Least One Treatment-emergent Adverse Event by COSTART Body System and Preferred Term (Events Reported by 10% or More of Patients Overall) Categorized by Time on Levetiracetam at Time of First Onset – Overall

COSTART	Weeks on Levetiracetam at time of First Onset					
Body System / Preferred Term	<=1 (N=239)	>1 – 6 (N=237)	>6 – 14 (N=229)	>14 – 24 (N=219)	>24 – 48 (N=202)	>48 (N = 166)
Body as a Whole	35 (14.6%)	85 (35.9%)	83 (36.2%)	88 (40.2%)	92 (45.5%)	106 (63.9%)
Abdominal pain	3 (1.3%)	8 (3.4%)	8 (3.5%)	7 (3.2%)	7 (3.5%)	10 (6.0%)
Accidental injury	4 (1.7%)	11 (4.6%)	15 (6.6%)	13 (5.9%)	11 (5.4%)	25 (15.1%)
Asthenia	6 (2.5%)	10 (4.2%)	2 (0.9%)	7 (3.2%)	2 (1.0%)	7 (4.2%)
Fever	4 (1.7%)	9 (3.8%)	12 (5.2%)	13 (5.9%)	18 (8.9%)	30 (18.1%)
Headache	10 (4.2%)	14 (5.9%)	24 (10.5%)	15 (6.8%)	12 (5.9%)	25 (15.1%)
Infection	8 (3.3%)	34 (14.3%)	34 (14.8%)	35 (16.0%)	42 (20.8%)	62 (37.3%)
Pain	2 (0.8%)	7 (3.0%)	2 (0.9%)	3 (1.4%)	9 (4.5%)	14 (8.4%)
Digestive System	23 (9.6%)	40 (16.9%)	28 (12.2%)	37 (16.9%)	44 (21.8%)	44 (26.5%)
Anorexia	10 (4.2%)	14 (5.9%)	4 (1.7%)	5 (2.3%)	5 (2.5%)	9 (5.4%)
Diarrhea	6 (2.5%)	5 (2.1%)	4 (1.7%)	5 (2.3%)	12 (5.9%)	8 (4.8%)
Gastroenteritis	0	7 (3.0%)	7 (3.1%)	5 (2.3%)	5 (2.5%)	16 (9.6%)
Vomiting	6 (2.5%)	10 (4.2%)	8 (3.5%)	15 (6.8%)	15 (7.4%)	14 (8.4%)
Nervous System	47 (19.7%)	69 (29.1%)	53 (23.1%)	49 (22.4%)	67 (33.2%)	77 (46.4%)
Convulsion	2 (0.8%)	6 (2.5%)	10 (4.4%)	10 (4.6%)	12 (5.9%)	17 (10.2%)
Emotional lability	5 (2.1%)	7 (3.0%)	4 (1.7%)	1 (0.5%)	8 (4.0%)	2 (1.2%)
Hostility	3 (1.3%)	12 (5.1%)	6 (2.6%)	2 (0.9%)	11 (5.4%)	9 (5.4%)
Insomnia	3 (1.3%)	8 (3.4%)	3 (1.3%)	4 (1.8%)	5 (2.5%)	10 (6.0%)
Nervousness	6 (2.5%)	10 (4.2%)	6 (2.6%)	5 (2.3%)	5 (2.5%)	8 (4.8%)
Personality disorder	5 (2.1%)	8 (3.4%)	4 (1.7%)	3 (1.4%)	9 (4.5%)	11 (6.6%)
Somnolence	24 (10.0%)	16 (6.8%)	11 (4.8%)	13 (5.9%)	10 (5.0%)	22 (13.3%)
Respiratory System	7 (2.9%)	44 (18.6%)	36 (15.7%)	40 (18.3%)	56 (27.7%)	53 (21.9%)
Cough increased	2 (0.8%)	10 (4.2%)	7 (3.1%)	11 (5.0%)	10 (5.0%)	10 (6.0%)
Pharyngitis	1 (0.4%)	12 (5.1%)	12 (5.2%)	13 (5.9%)	16 (7.9%)	20 (12.0%)
Rhinitis	3 (1.3%)	17 (7.2%)	10 (4.4%)	10 (4.6%)	12 (5.9%)	12 (7.2%)
Sinusitis	1 (0.4%)	6 (2.5%)	6 (2.6%)	4 (1.8%)	11 (5.4%)	13 (7.8%)
Skin and Appendages	4 (1.7%)	12 (5.1%)	8 (3.5%)	10 (4.6%)	25 (12.4%)	25 (15.1%)
Rash	0	2 (0.8%)	4 (1.7%)	5 (2.3%)	7 (3.5%)	8 (4.8%)
Special Senses	7 (2.9%)	12 (5.1%)	14 (6.1%)	15 (6.8%)	24 (11.9%)	39 (23.5%)
Otitis media	4 (1.7%)	4 (1.7%)	7 (3.1%)	8 (3.7%)	20 (9.9%)	26 (15.7%)

Source: Table 16.4.2:4; a similar display by UCB AE Grouping Term table in Table 16.10.2:2

As one can see, the most common AEs that could tend to persist over time include common childhood conditions. The most concerning issues with the potential to be drug-related (to this reviewer) were convulsion, hostility, nervousness, personality disorder, somnolence and rash. Convulsions would be expected over time. The other issues, hostility, nervousness, and

personality disorder seem to be stable throughout treatment, but remain at low rates throughout. Somnolence is a larger problem that could improve initially and then could worsen again over longer term treatment. Somnolence alone may limit use in some refractory seizure patients. Rash also seems to be increasing with increasing use. It may be difficult to determine if this is due to levetiracetam alone or related to other concomitant AEDs.

Table 7:8 Number (%) of Patients Reporting at Least One Treatment-emergent Adverse Event by COSTART Body System and Preferred Term (Events Reported by 10% or More of Patients Overall and More Common on Levetiracetam Than on Placebo) Categorized by Dose (mg/kg/day) at Time of Onset – Overall

COSTART Body System / Preferred Term	Levetiracetam Dose at Onset (mg/kg/day)				
	0 (N = 38)	> 0 - < 29 (N = 235)	29 - < 50 (N = 228)	50 - < 80 (N = 213)	≥ 80 (N = 53)
Body as a Whole	5 (13.2%)	74 (31.5%)	101 (44.3%)	146 (68.5%)	20 (37.7%)
Abdominal pain	1 (2.6%)	9 (3.8%)	12 (5.3%)	16 (7.5%)	0
Accidental injury	0	14 (6.0%)	23 (10.1%)	33 (15.5%)	2 (3.8%)
Asthenia	0	11 (4.7%)	9 (3.9%)	10 (4.7%)	1 (1.9%)
Headache	1 (2.6%)	17 (7.2%)	29 (12.7%)	32 (15.0%)	2 (3.8%)
Infection	0	25 (10.6%)	43 (18.9%)	85 (39.9%)	13 (24.5%)
Pain	1 (2.6%)	10 (4.3%)	5 (2.2%)	15 (7.0%)	2 (3.8%)
Digestive System	5 (13.2%)	40 (17.0%)	56 (24.6%)	73 (34.3%)	12 (22.6%)
Anorexia	2 (5.3%)	11 (4.7%)	18 (7.9%)	16 (7.5%)	2 (3.8%)
Diarrhea	2 (5.3%)	10 (4.3%)	8 (3.5%)	16 (7.5%)	4 (7.5%)
Gastroenteritis	1 (2.6%)	4 (1.7%)	15 (6.6%)	14 (6.6%)	5 (9.4%)
Vomiting	1 (2.6%)	8 (3.4%)	19 (8.3%)	26 (12.2%)	5 (9.4%)
Nervous System	3 (7.9%)	76 (32.3%)	84 (36.8%)	113 (53.1%)	24 (45.3%)
Convulsion	1 (2.6%)	8 (3.4%)	15 (6.6%)	22 (10.3%)	5 (9.4%)
Emotional lability	0	10 (4.3%)	6 (2.6%)	10 (4.7%)	0
Hostility	0	6 (2.6%)	13 (5.7%)	21 (9.9%)	1 (1.9%)
Insomnia	0	9 (3.8%)	8 (3.5%)	13 (6.1%)	3 (5.7%)
Nervousness	1 (2.6%)	11 (4.7%)	7 (3.1%)	11 (5.2%)	5 (9.4%)
Personality disorder	0	9 (3.8%)	11 (4.8%)	16 (7.5%)	4 (7.5%)
Somnolence	1 (2.6%)	29 (12.3%)	24 (10.5%)	32 (15.0%)	4 (7.5%)
Respiratory System	1 (2.6%)	31 (13.2%)	52 (22.8%)	87 (40.8%)	14 (26.4%)
Cough increased	0	8 (3.4%)	8 (3.5%)	27 (12.7%)	2 (3.8%)
Pharyngitis	0	10 (4.3%)	25 (11.0%)	28 (13.1%)	6 (11.3%)
Rhinitis	0	9 (3.8%)	15 (6.6%)	25 (11.7%)	3 (5.7%)
Sinusitis	1 (2.6%)	5 (2.1%)	9 (3.9%)	18 (8.5%)	3 (5.7%)
Skin and Appendages	0	13 (5.5%)	25 (11.0%)	27 (12.7%)	8 (15.1%)
Rash	0	4 (1.7%)	10 (4.4%)	8 (3.8%)	2 (3.8%)
Special Senses	0	17 (7.2%)	25 (11.0%)	46 (21.6%)	8 (15.1%)
Otitis media	0	9 (3.8%)	17 (7.5%)	27 (12.7%)	8 (15.1%)

Source: Table 16.10.1:1; UCB AE Grouping Term table in Table 16.10.2:1

Referring to the table above, the most common AEs by dose at onset are common childhood conditions such as infection, gastroenteritis, pharyngitis, rhinitis, sinusitis and otitis media. The incidence of the adverse events of hostility, insomnia, nervousness and personality disorder

appear to be trending up with increasing dose. Somnolence also persistent regardless of dose at onset. Overall, the trend is one of increased AEs with increasing dose.

7.1.5.4 Adverse events occurring in Severe Intensity

In N159, there were 11 patients on placebo with severe events (11.3%) and 10 patients on levetiracetam with severe events (9.9%). Convulsions were more common among patients randomized to placebo.

In the open label database (N=239) 64 patients (26.8%) had one or more adverse events that occurred in severe intensity. The most common severe events overall pertained to the nervous system and were **convulsion** (9 patients or 3.8%), **personality disorder** (7 patients or 2.9%), **hostility** (6 patients or 2.5%), **status epilepticus NOS** (6 patients or 2.5%), **emotional lability** (5 patients or 2.1%), and **somnolence** (5 patients or 2.1%). The remaining severe events occurred in 4 or fewer patients.

7.1.6 Less Common Adverse Events

Rash and skin findings were rare with only one case considered to be an SAE.

> ISS No. 4876 a 10 year old female, experienced a rash on her arms and chest after 224 days of levetiracetam that was thought to be an allergic reaction to levetiracetam. The dose at onset was 2250 mg/ day, which had been increased from 2000 mg/ day about 16 days prior. The rash was moderate in intensity. The Investigator discontinued study drug and hospitalized the patient for observation due to the abrupt withdrawal of study medication. The rash ultimately resolved.

Other rashes, eosinophilia cases and edema cases were reported, however were either mild or considered not related to study drug. The Sponsor did report 4 other cases of rash, 2 of which were moderate to severe (and interestingly were associated in combination with valproate) in off label use of levetiracetam in children. One of the two cases was Stevens Johnson syndrome. However, the patient was taking concomitant lamotrigine, clobazam and valproate. This patient improved with steroids, antihistamines and withdrawal of levetiracetam. Another 10 year old boy had a rash consisting of skin peeling off his heels. He was taking valproate in addition to levetiracetam. After discontinuing levetiracetam, the rash resolved.

Although rare occurrences, the Sponsor may want to evaluate skin reactions potentially related to a combination of levetiracetam and valproate.

7.1.7 Laboratory Findings

The sponsors presented data in the ISS for the N159 double blind ITT population and on the safety database for the primary discussion on laboratory findings.

7.1.7.1 Overview of laboratory testing in the development program

The sponsor provided information on routine laboratory testing done in Study N159 and in the pooled database. No other lab testing was reviewed for this sNDA.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Lab results (mean and median) along with summaries of major adverse events related to lab data are summarized in subsection (7.1.7.3.1) below.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Hematology

Hematologic changes in Study N159 are summarized by the sponsor in Sponsor Table 12:12 below.

Table 12:12 Summary of Change in Hematology Parameters from Baseline to Last On-Treatment Visit (ITT Population)

Parameter	Change from Baseline Levetiracetam (N = 101)		Change from Baseline Placebo (N = 97)	
	Mean (SD)	Median	Mean (SD)	Median
Basophils (relative %)	-0.1 (0.5)	0.0	-0.1 (0.5)	-0.1
Eosinophils (relative %)	0.3 (2.2)	0.2	-0.3 (2.2)	-0.3
Hematocrit (%)	0.0 (2.0)	0.0	0.0 (2.2)	-0.1
Hemoglobin (g/dL)	0.0 (0.7)	0.1	0.0 (0.7)	0.0
Lymphocytes (relative %)	1.7 (10.2)	2.7	-4.0 (11.8)	-4.1
Lymphocytes (10^3/µL)	-0.4 (0.6)	0.0	-0.2 (0.7)	-0.1
Mean corpuscular hemoglobin (pg)	0.0 (1.0)	0.0	0.1 (0.9)	0.0
Mean corpuscular hemoglobin concentration (g/dL)	0.1 (1.0)	0.0	0.1 (0.8)	0.0
Mean corpuscular volume (fl)	-0.1 (2.0)	0.0	-0.1 (1.7)	0.0
Monocytes (relative %)	-0.3 (2.5)	-0.3	0.1 (2.6)	0.0
Platelets (10^3/L)	-6.9 (60.7)	-6.5	3.0 (48.4)	4.0
Red Blood Cells/Erythrocytes (10^6/L)	0.0 (0.2)	0.0	0.0 (0.2)	0.0
Segmented neutrophils (relative %)	-1.8 (10.6)	-1.8	4.2 (12.7)	3.0
Segmented neutrophils (10^3/µL)	-0.3 (1.6)	-0.1	0.4 (1.8)	0.2
White Blood Cells/Leukocytes (10^3/L)	-0.4 (1.9)	-0.3	0.2 (1.9)	0.1

Ref: Table 14.3.4:5 and Listing 16.2.8:2

Overall there were small mean decreases in total white cell, neutrophil counts and platelet counts. No effects on RBCs were noted. Statistically significant changes related to white cells were noted in Sponsor Table 8:1 below, mostly affecting WBC and neutrophil cell lines. These findings were similar to those in adults where the drug results in small but significant decreases in WBC and neutrophil counts. In the pediatric studies, 16.3% of patients (N=39) had low WBC and /or neutrophil counts. None had concomitant clinical manifestations nor resulted in dose change or discontinuation.

Table 8:1 Summary of Change in Absolute White Blood Cell Indices ($10^3/\mu L$) from Baseline to Last On-Treatment Visit (ITT Population in N159)

Parameter	Levetiracetam (N = 101)		Placebo (N = 97)		p-value (Kruskal-Wallis test)
	Mean ± SD	Median	Mean ± SD	Median	
WBCs	-0.4 ± 1.9	-0.3	0.3 ± 1.9	0.1	0.0366
Neutrophils	-0.3 ± 1.7	-0.1	0.4 ± 1.9	0.2	0.0037
Lymphocytes	0.0 ± 0.6	0.0	-0.2 ± 0.7	-0.1	0.1458[a]
Monocytes	-0.1 ± 0.2	0.0	0.0 ± 0.2	0.0	0.1533
Basophils	0.0 ± 0.0	0.0	0.0 ± 0.0	0.0	0.3617
Eosinophils	0.0 ± 0.2	0.0	0.0 ± 0.2	0.0	0.3993

[a] p-value = 0.0003 when relative % lymphocytes compared
Ref: Table 14.3.4:5 and Listing 16.2.8:2 in N159 Study Report Module 5, Volume 26, Section 5.3.5.1.1

Regarding reduced platelet counts (N.B. This was a recent safety concern in adults raised by another reviewer Norm Hershkowitz, MD who initiated an ODS consult) there were small mean and median decreases in platelet counts in both treatment and placebo group, but greater changes in the levetiracetam treated group. The changes to platelets were summarized in Sponsor Tables 8:9 for N159 and broken out into age subgroups from the overall database in Table 8:10 below.

Table 8:9 Summary of Change in Platelets (Hematology) from Baseline to Last On-Treatment Visit (ITT Population in N159)

	Levetiracetam (N = 101)			Placebo (N = 97)			p-value (Kruskal-Wallis Test
Parameter	n	Mean ± SD	Median	n	Mean ± SD	Median	
Platelets (10^3/L)	100	-7.0 (60.7)	-6.5	95	3.0 (48.4)	4.0	0.1708

Ref: Table 14.3.4:5 and Listing 16.2.8:2 in N159 Study Report Module 5, Volume 26 , Section 5.3.5.1.1

Table 8:10 Mean (S.D.) Baseline and Final On-treatment Platelet Count ($10^3/\mu L$) by Age Group and Change from Baseline (Overall) (a)

		Age Category (years)			
		< 4	4 - <8	8 - <12	12 - <18
		(N = 15)	(N = 62)	(N = 102)	(N = 54)
Baseline	Mean ± S.D.	386.8 ± 129.99	311.3 ± 70.77	266.9 ± 72.01	248.0 ± 61.37
Final	Mean ± S.D.	322.1 ± 108.11	272.0 ± 66.12	246.3 ± 57.69[b]	223.6 ± 50.46
	Mean Change	-56.7 ± 155.03	-36.1 ± 55.71	-20.7 ± 50.36	-24.4 ± 43.38
	Median Change	-73.0	-25.0	-16.5	-19.0
	(95% CI)[c]	(-139.5 – 21.50)	(-49.50 – -24.50)	(-28.50 – -11.0)	(-34.00 – -14.50)

[a] Normal range for the children <4 years of age who participated in N01052 is 229-435 × $10^3/\mu L$ for girls and 228-433 × $10^3/\mu L$ for boys; for the rest of the children, it is 140-450 × $10^3/\mu L$, regardless of age

Blood Chemistry

Changes in blood chemistry from baseline in Study N159 are summarized below in Sponsor Table 12:11.

Table 12:11 Summary of Change in Blood Chemistry Parameters from Baseline to Last On-Treatment Visit (ITT Population)

	Change from Baseline Levetiracetam (N = 101)		Change from Baseline Placebo (N = 97)	
Parameter	Mean (SD)	Median	Mean (SD)	Median
Albumin (g/dL)	0.0 (0.3)	-0.1	-0.1 (0.3)	0.0
Alkaline Phosphatase (IU/L)	2.9 (58.8)	-1.0	-20.4 (174.7)	-1.0
ALT (IU/L)	-0.9 (6.2)	-0.5	0.2 (9.0)	0.0
AST (IU/L)	-0.3 (6.0)	0.0	0.9 (7.5)	0.0
BUN (mg/dL)	-0.5 (3.5)	-1.0	0.0 (4.0)	0.0
Calcium (mg/dL)	0.0 (0.4)	-0.1	-0.1 (0.4)	-0.1
Creatinine (mg/dL)	0.0 (0.1)	0.0	0.0 (0.1)	0.0
Creatinine Clearance (mL/min)[a]	2.7 (44.5)	1.5	4.9 (40.6)	2.0
GGT (IU/L)	-1.7 (15.4)	2.0	0.1 (13.2)	0.0
Globulin (g/dL)	0.1 (0.3)	0.1	0.1 (0.3)	0.1
Glucose (non-fasting) (mg/dL)	0.3 (15.6)	1.0	1.1 (19.6)	3.5
Phosphorous (mg/dL)	0.2 (0.6)	0.1	0.0 (0.7)	0.1
Potassium (mEq/L)	0.0 (0.4)	0.0	-0.1 (0.3)	-0.1
Serum Iron (µg/dL)	2.2 (45.4)	-3.5	2.4 (51.1)	-3.0
Sodium (mEq/L)	0.3 (3.3)	0.0	-0.6 (3.3)	-1.0
Total Bilirubin (mg/dL)	0.0 (0.1)	0.0	0.0 (0.2)	0.0
Total Protein (g/dL)	0.1 (0.4)	0.1	0.0 (0.4)	0.0
Uric Acid (mg/dL)	-0.1 (0.7)	-0.1	0.1 (0.8)	0.1

[a] Calculated

Liver Function Tests

For the double blind study, liver function tests mean and median changes were small and comparable for both treatment groups. For the overall database, changes were noted but there were no major trends. For comparison, normal labs ranges for LFTs were summarized in Sponsor Table 8:13.

Table 8:13 Representative Laboratory Normal Ranges for Liver Function Tests

Parameter		N01052[a]	N151, N157, N159, N01010[b]		
(unit)	Sex	< 4 years	4 - <6	6 - <12	12 - <18
Alk. Phos.	Male	104 - 345	104 - 390	50- 400[c]	58 – 420[c]
(IU/L)	Female	108 - 317			44 - 295[c]
ALT	Male	5 - 30	10 – 25	6 - 48	10 - 45
(IU/L)	Female				
AST	Male	10 – 55	15 – 50	10 – 45	15 - 45
(IU/L)	Female	10 - 68			
T. Bilirubin	Male	0.0 – 1.1	0.2 – 1.2	0.2 – 1.2	0.2 – 1.2
(g/dL)	Female				

[a] ICON labs was used in N01052 and continued to be used in N157 for those children
[b] Quintiles Laboratories was used as the central laboratory for all of the other studies; the normal range changed in 1999; the values presented in this table are from this recent version
[c] For this parameter, the ranges given are for 6 - <13 year olds and 13 - <16 years; for children who are 16 years of age, the normal range for males is 42-250 IU/L and for girls is 38-180 IU/L and for 17-year olds of both sexes it is 38-180 IU/L

Changes in LFTs from baseline split out by age category were summarized in Sponsor Table 8:14 below. Changes in LFTs were not an issue in the adult studies and were not discussed in the current label. Regarding treatment in children in the controlled trial, there were no meaningful differences in LFTs between those treated with placebo or drug.

Table 8:14 Mean (S.D.) Baseline and Final On-treatment Blood Chemistry (Liver Function Test) Results by Age Group and Change from Baseline (Overall)

		Age Category (years)			
		< 4	4 - <8	8 - <12	12 - <18
		(N = 16)	(N = 62)	(N = 103)	(N = 54)
Alkaline Phosphatase (U/L)					
Baseline	Mean ± S.D.	289.5 ± 101.80	334.7 ± 246.07	306.3 ± 97.41	265.0 ± 127.35
Final	Mean ± S.D.	523.4 ± 802.68	329.2 ± 90.48	356.0 ± 128.79	239.5 ± 127.57
	Mean Change	233.9 ± 804.41	-7.1 ± 227.95	49.0 ± 100.60	-25.50 ± 114.18
	Median Change	6.0	13.0	37.0	-32.0
	(95% CI)[a]	(-44.0 – 255.0)	(2.0 – 40.0)	(28.5 – 62.5)	(-52.5 – -11.0)
ALT (U/L)					
Baseline	Mean ± S.D.	23.4 ± 13.62	20.4 ± 9.10	20.2 ± 9.99	19.2 ± 8.70
Final	Mean ± S.D.	29.8 ± 21.38	23.5 ± 12.01	26.6 ± 17.98	26.2 ± 23.40
	Mean Change	6.4 ± 17.72	3.0 ± 10.38	6.0 ± 13.98	7.0 ± 22.11
	Median Change	4.0	2.0	3.0	3.5
	(95% CI) [a]	(-2.50 – 12.00)	(0.50 – 4.50)	(2.50 – 6.00)	(2.00 – 6.50)
AST (U/L)					
Baseline	Mean ± S.D.	37.5 ± 21.85	30.3 ± 8.20	26.5 ± 7.85	23.1 ± 6.79
Final	Mean ± S.D.	44.9 ± 22.29	32.3 ± 8.46	29.6 ± 9.05	27.6 ± 11.23
	Mean Change	7.4 ± 10.21	2.0 ± 7.63	2.8 ± 7.78	4.5 ± 11.16
	Median Change	5.0	2.0	2.0	2.0
	(95% CI) [a]	(1.50 – 12.50)	(0.50 – 3.50)	(1.50 – 4.50)	(1.50 – 6.00)
GGT (U/L)					
Baseline	Mean ± S.D.	26.0[b]	32.6 ± 24.87[c]	32.5 ± 29.09[d]	40.7 ± 54.41[e]
Final	Mean ± S.D.	21.0[b]	31.3 ± 19.50[c]	32.7 ± 28.27[d]	39.7 ± 41.75[e]
	Mean Change	-5.0[b]	-1.4 ± 11.16[c]	0.0 ± 8.58[d]	-1.2 ± 18.38[e]
	Median Change	-5.0[b]	1.0[c]	0[d]	1.0[e]
	(95% CI) [a]	–	(-0.50 – 2.50)	(-0.50 – 2.50)	(-2.00 – 4.00)
Total Bilirubin (mg/dL)					
Baseline	Mean ± S.D.	0.2 ± 0.17	0.3 ± 0.15	0.3 ± 0.13	0.3 ± 0.18
Final	Mean ± S.D.	0.2 ± 0.10	0.3 ± 0.14	0.4 ± 0.16	0.5 ± 0.23
	Mean Change	0.0 ± 0.14	0.1 ± 0.17	0.1 ± 0.18	0.1 ± 0.23
	Median Change	0	0.1	0.1	0.1
	(95% CI) [a]	(-inf – -0.50)	(0.05 – 0.15)	(0.10 – 0.20)	(0.10 – 0.25)

[a] 95% CI of median change
[b] N=1
[c] N=45
[d] N=72
[e] N=43
Source: Table 16.5.1:2

Kidney/Renal Function/Urinalysis

Although mean changes in BUN and creatinine were minimal in N159, in the pooled safety sample, BUN and creatinine levels were higher than baseline values but still within normal ranges. These results were promising considering that levetiracetam metabolism and excretion is primarily done via the kidneys. The Sponsor also reported no significant changes in serum total protein, albumin or serum iron.

The Sponsor presented data for serum glucose, blood chemistry (including potassium, calcium, phosphorus and uric acid.) One significant difference was the difference between treatment groups for sodium with a trend for a slightly increased sodium level in all groups. This median result is slight in the overall group (median increases of 1.0-2.0 mEq/L.) However, even the upper ranges including means +/- standard deviations are all less than 150mEq/L.

Regarding urinalysis, there were small non-clinically significant increases in specific gravity. No major changes were seen in urine pH.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor did not provide a formal evaluation or outlier analyses (or extreme outlier analyses for the next section). The sponsor did evaluate possibly clinically significant laboratory test values (hereafter referred to as PCST criteria) and discussed selected narratives in the ISS. This reviewer went back to the actual listings and compared them to the PCST criteria focusing on outliers and extreme outliers for this section.

Hematology-

The sponsor summarized outliers related to hematologic parameters in Table 10:26 below.

Table 10:26 Number of Patients with Possibly Clinically Significant White Blood Cell Abnormalities (Study N159 and Overall Population Exposed to Levetiracetam)

Parameter	N159		Overall LEV
	Placebo	LEV	
WBCs			
N	96	101	237
Total	0	3 (3.0%)	14 (5.9%)
Below	0	3 (3.0%)	12 (5.1%)
Above	0	0	2 (0.8%)
Neutrophils (absolute)			
Total	4 (4.2%)	5 (5.0%)	19 (8.0%)
Below	4 (4.2%)	5 (5.0%)	19 (8.0%)
Neutrophils (relative)			
Total	4 (4.2%)	2 (2.0%)	5 (2.1%)
Below	4 (4.2%)	2 (2.0%)	5 (2.1%)
Lymphocytes (absolute)			
Total	2 (2.1%)	1 (1.0%)	11 (4.6%)
Below	2 (2.1%)	1 (1.0%)	7 (3.0%)
Above	0	0	4 (1.7%)
Lymphocytes (relative)			
Total	1 (1.0%)	0	5 (2.1%)
Below	0	0	3 (1.3%)
Above	1 (1.0%)	0	2 (0.8%)
Monocytes (Absolute)			
Total	1 (1.0%)	0	2 (0.8%)
Above	1 (1.0%)	0	2 (0.8%)

Source: 16.5.1:4, Section 19 ISS SAP

For WBCs, the PCST lab parameter was $\leq 2800/mm^3$ or $> 16000mm^3$. Although the sponsor noted 14 patients with mean reductions in WBCs overall, on closer examination, only 3 patients had levels below $2800/mm^3$ and only 2 patients had WBCs greater than $16000mm^3$. The 3 patients (ISS 4892, 5420, 5524) with reductions had only slight reductions in WBC (to 2600 or $2700mm^3$.) The 2 patients with elevations in WBC (ISS 5455 and 5461) had other reasons such as infection for the high WBC counts ($20\text{-}21000mm^3$).

For Neutrophils (relative or absolute), the PCST lab parameters were $\leq$ 15% or $\leq$ to $1000mm^3$ respectively. Some patients neutrophil counts were already low at baseline. 24 patients met the criteria for either absolute or relative low neutrophil counts. The lowest neutrophil counts in two patients were 420 and $560mm^3$. Almost all of the low neutrophil counts were just below $1000mm^3$ on treatment with many values improving over time. Per the sponsor, no low neutrophil counts were considered SAEs. None of the patients discontinued or had the dose reduced.

For Lymphocytes (relative or absolute) the PCST lab parameters were $\leq$ 10% or $\geq$ 80%; $\leq$ 500mm3 or $\geq 4500mm^3$. Per these criteria, one patient (ISS 5236) had significant reductions in lymphocyte counts ($430\ mm^3$ down from a baseline of $1560mm^3$). Two other patients had mild

decreases in lymphocytes to 7 or 8% of total. Conversely, 6 patients had increases in lymphocytes above these cutoffs with the largest increases ranging from 7560 to 12280 mm^3. One patient (ISS 5465) had persistent elevations in lymphocytes, but had elevated baseline levels.

Hemoglobin and Hematocrit

The PCST lab parameter for Hemoglobin was $\leq$ 11.5g/dL for males and $\leq$ 9.5g/dL for females. In terms of hematocrit, the PCST parameters were $\leq$ 37% for males and $\leq$ 32% for females. On review of the data listings for hematocrit and hemoglobin, all but one hematocrit levels were above 30% either for males or females, the lowest value was 28.7% (baseline 36%) after 965 days on treatment (ISS 5314). This same patient had low hemoglobin of 9.54g/dL. Final values for this patient were normal measured about 1 year later.

Platelets

No patients met the PCST criteria of $\leq$ 75000mm^3 or $\geq$ 700000mm^3

However, 2 patients were *reported* to have treatment- emergent thrombocytopenia. ISS No. 4898 was reported with thrombocytopenia after 1 day of levetiracetam. The dosage at onset was 500 mg/ day. The event was judged moderate in intensity and unrelated to treatment. No action was taken and the event resolved after 42 days. The platelet count at baseline was low, 107 × 103/ μ L, with a nadir on- treatment of 86 × 103/ μ L on Day 27. The final on- treatment measurement on Day 2111 was 371 × 103/ μ L. ISS No. 5208 was found to have thrombocytopenia (platelet count 130 × 103/ μ L) after 1091 days on levetiracetam, from a baseline of 287 × 103/ μ L. The dose at onset was 2000 mg/ day. The event was mild and judged not related to treatment. No action was taken. At the next visit, approximately 3 months later, the count had increased to 149 × 103/ μ L. Subsequent counts fluctuated but did not fall below 120 × 103/ μ L.

Blood Chemistry - Hepatobiliary effects

In N159, no patient met PCST criteria for elevated ALT, AST, alkaline phosphatase or bilirubin. This reviewer examined the listings for LFTs to determine outliers and any cases of concern in the database regarding elevations in AST, ALT, alkaline phosphatase, bilirubin and GGT. Overall, although there were some elevations in liver enzymes noted, none were considered SAEs and none resulted in discontinuation or dose reductions. It would be difficult to isolate if any of these liver enzyme elevations were related to levetiracetam, considering that patients were on at least one or two concomitant AEDs, many primarily metabolized by the liver.

AST, ALT and Alkaline phosphatase

PCST criteria for these three indices were $\geq$ 3X upper limit of normal (ULN). Of three patients with increased values meeting these criteria for elevations in any of these indices, all three patients' elevations occurred either after discontinuation on the drug, or normalized off drug.

GGT

The PCST criteria was either ≥ 3X ULN if < 3X ULN at baseline. Most of the patients that met PCST criteria had elevated levels at baseline that either remained the same or reduced on drug. Only 2 patients had significant on treatment elevations. ISS 5593, an 11 year old boy had nearly a doubling in GGT (baseline 84U/L elevated to 176U/L). This patient discontinued drug and remained with an elevated baseline level. ISS No. 5261, a 14 year old male, had a more than three-fold increase (42U/L to 218U/L). In both patients, baseline values were already above laboratory normal range; the elevations occurred early in treatment (13 to 28 days). Both patients continued on drug without a change in dose but discontinued within roughly 1 to 2 months for reasons not associated with adverse events.

Bilirubin

The PCST criterion for bilirubin was ≥ 2mg/dL. Five subjects had levels of either 2 or 3 mg/dL. All 5 individuals were on treatment for over 300 days. All levels went back to normal in all patients.

Kidney/Renal/Urinalysis.

A single patient met criteria for PCST BUN level (>30mg/dL). That patient (ISS 5376), a 10 year old male, had a level of 32mg/dL after 709 days on treatment that went back into the normal range (22mg/dL).

No patients met criteria for PCST creatinine (≥ 2.0 mg/dL).

Regarding adverse events related to abnormal urinalysis, there were few adverse events in the database of note. However three children were reported with kidney stones, all of whom were receiving topiramate. A fourth child who continued in Study N157 had chronic abdominal pain. A workup revealed polycystic kidneys. This patient was tapered off drug and was further evaluated by a specialist.

There were 4 cases reported as albuminuria. These were also coded as proteinuria and were all mild. All 4 cases were based on urine dipstick evaluations that did not persist.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

Marked outliers and dropouts are included in the section above.

7.1.7.4 Additional analyses and explorations

None

7.1.8 Vital Signs

Per the Sponsor, median changes from baseline in blood pressure and pulse were small. In the pooled database, with continued treatment, there was a trend towards a small (3-5mmHg) reduction in seated blood pressure in children 8 years of age and older. There was also an increase in diastolic blood pressure. Post treatment pulse was decreased as well (4-6 bpm decrease) in pulse in the same age group. There were no reports of hypotension or bradycardia. These changes are summarized in Table 9:1 for the double blind data and Table 9:2 for the database, split out by age categories.

Table 9:1 Change in Seated and Standing Blood Pressures (mmHg) and Pulses (bpm) from Baseline to the Last On-Treatment Visit (N159)

Vital Sign Parameter	Levetiracetam (N = 101)			Placebo (N = 97)			p-value Kruskal -Wallis Test
	n	Mean ± S.D.	Median	n	Mean ± S.D.	Median	
Seated							
Systolic Blood Pressure	99	-0.1 ± 12.7	0.0	97	2.9 ± 11.0	2.0	0.0836
Diastolic Blood Pressure	99	1.3 ± 9.3	0.0	97	-0.7 ± 8.8	0.0	0.0597
Heart Rate	100	-0.1 ± 14.8	-1.0	97	0.4 ± 12.7	-1.0	0.9721
Standing							
Systolic Blood Pressure	90	1.6 ± 11.9	2.0	81	0.1 ± 12.6	0.0	0.3971
Diastolic Blood Pressure	90	0.6 ± 10.7	1.0	81	-0.2 ± 9.7	0.0	0.4477

Ref: Table 14.3.5:1 and Listing 16.2.9:1 in N159 study report Module 5, Volume 26, Section 5.3.5.1.1
a summary by visit of the change from baseline in vital signs is provided in Table 14.3.5:1
Source: Table 16.6.1:7 = statistical comparison table.

As seen in Table 9:1 the changes were small, but more than in the placebo group especially with standing systolic blood pressure. In addition, orthostatic hypotension was reported in 2 treated patients (1 in the placebo group) during Study N159.

Table 9:2 Mean (S.D.) Baseline and Final On-treatment Sitting Blood Pressure and Pulse Measurements by Age Group and Change from Baseline (Overall)

		Age Category (years)			
		< 4	4 - <8	8 - <12	12 - <18
	N	12	61	104	54
Systolic Blood Pressure (mmHg)					
Baseline	Mean ± S.D.	96.7 ± 10.65	102.2 ± 11.95	104.8 ± 11.68	109.9 ± 11.42
Final	Mean ± S.D.	104.6 ± 17.94	108.6 ± 14.49	110.9 ± 16.73	109.1 ± 17.08
Change	Mean	9.6 ± 20.88	6.8 ± 15.23	5.9 ± 16.34	-0.9 ± 14.19
	Median	10.5	9.0	6.0	-2.0
	95% CI[a]	-5.5 – 27.00	2.50 – 11.00	3.50 – 10.00	-6.00 – 3.00
Diastolic Blood Pressure (mmHg)					
Baseline	Mean ± S.D.	58.3 ± 11.47	62.8 ± 8.27	64.2 ± 9.34	68.4 ± 8.82
Final	Mean ± S.D.	48.9 ± 16.97[b]	62.7 ± 13.81[c]	61.3 ± 12.95	63.0 ± 10.94
Change	Mean	-10.5 ± 18.70	0.5 ± 15.45	-3.1 ± 11.93	-5.4 ± 11.03
	Median	-9.5	1.0	-2.5	-5.0
	95% CI[a]	-22.50 – 2.50	-4.50 – 4.00	-6.50 – -0.50	-10.00 – -3.50
Pulse Rate (bpm)					
Baseline	Mean ± S.D.	114.9 ± 22.54[d]	96.4 ± 13.30[e]	90.3 ± 14.14	83.2 ± 11.69
Final	Mean ± S.D.	125.3 ± 17.46[d]	93.6 ± 18.76[c]	83.9 ± 19.33	78.7 ± 20.19
Change	Mean	10.31 ± 18.39[d]	-2.35 ± 16.47[e]	-6.49 ± 16.92	-4.44 ± 16.11
	Median	12.00[d]	-3.00[e]	-8.00	-6.50
	95% CI[a]	-1.00 – 20.50	-7.50 – 1.00	-10.50 – -4.00	-10.00 – -1.50

[a] 95% CI of median change
[b] N=15
[c] N=63
[d] N=16
[e] N=62
Source: Table 16.6.1:2

Despite changes in blood pressure noted, there were very few adverse events related to blood pressure and pulse in the database. There were no SAEs related to vital signs.

7.1.8.1 Body Weight

There was a small to moderate increase in body weight during the 22 week treatment period during Study N159. The findings from the open label data show both weight gain and weight loss on the drug. The results are confounded by expected weight gain in some patients during this time and effects of concomitant medications (such as well known weight gain on valproate and weight loss on topiramate.) The Sponsor evaluated weight gain by age category in Table 9:5 below. For children between 4 and 8 years old, there was an average increase of 2.5kg. For children ages 8-18, there was a 4.3-5.7 kg increase (3.6-7.5kg for the subjects exposed for at least 1 year). This reviewer wonders if the weight gain is continuous or stabilizes, as a 3-8kg increase in body weight per year would be significant. Of note the ranges for weight gain are large with the largest median change seen in the 8-12 year old group who took the medication for longer than 48 weeks. The confidence intervals are also large, making weight gain a potential problem in some children who take the drug long term. Tables 9:5 and 9:6 summarize this below.

Table 9:5 Mean (S.D.) Baseline and Final On-treatment Body Weight (kg) by Age Group and Change from Baseline (Overall)

		Age Category (years)			
		< 4	4 - <8	8 - <12	12 - <18
	N	16	63	104	54
Baseline	Mean ± S.D.	11.1 ± 4.47	23.2 ± 6.68	35.5 ± 11.51	52.4 ± 16.73
Final	Mean ± S.D.	13.6 ± 5.62	26.7 ± 8.52	43.6 ± 16.99	59.3 ± 19.64
Change	Mean Change	0.10 ± 4.29	2.50 ± 8.46	5.70 ± 17.03	4.33 ± 20.60
	Median Change	-1.34	2.15	3.52	4.50
	95% CI[a]	1.45 – 4.70	2.10 – 4.25	5.00 – 8.25	2.95 – 8.09

[a] 95% CI of median change
Source: Table 16.6.1:2

Table 9:6 Mean (S.D.) Baseline and Final On-treatment Body Weight (kg) by Age Group and Change from Baseline (Overall – Subjects Exposed for > 48 Weeks)

		Age Category (years)			
		< 4	4 - <8	8 - <12	12 - <18
	N	9	35	67	39
Baseline	Mean ± S.D.	12.0 ± 3.29	22.8 ± 6.72	35.2 ± 9.53	51.6 ± 16.85
Final	Mean ± S.D.	15.5 ± 4.79	28.0 ± 8.96	46.2 ± 16.46	60.3 ± 20.66
Change	Change	0.64 ± 4.96	2.41 ± 9.31	7.64 ± 17.36	3.59 ± 22.41
	Median Change	-0.67	3.06	7.12	3.54
	95% CI [a]	1.30 – 6.15	3.23 – 6.62	7.41 – 12.11	4.25 – 11.25

[a] 95% CI of median change
Source: Table 16.6.1:2

In order to evaluate weight changes in growing children, the Sponsor used the baseline weight and compared it to a final weight looking for outliers with weight gain described as the upper 97% or lower 3% of the normal growth curve. A total of 21 patients with a normal body weight experienced at least one body measurement above the 97% bound of the normal growth curve. 56 patients were identified to have a normal body weight at baseline with at least one body measurement below the 3% lower bound of the normal growth curve. Either the weight loss or weight gain was first documented within the first 3 months of drug usage and was considered mild in a majority. In study N159, regarding patients taking drug, 17 patients met the criteria for weight loss and 8 patients met the criteria for weight gain. This compares to 9 patients meeting the criteria for weight loss and 18 patients meeting the criteria for weight gain among placebo patients.

In terms of adverse events related to weight, the Sponsor recognized 45 children with weight loss or anorexia reported as adverse events and 18 patients with obesity, weight gain or increased appetite. These adverse events were mostly mild and did not result in changes in drug dosing for the majority. Of course, many of the cases of weight loss or gain would be difficult to evaluate considering the effects of concomitant medications.

7.1.9 Electrocardiograms (ECGs)

ECGs were performed infrequently during the double blind trial and during the extension phase N157. ECGs were also not timed to peak plasma concentration. Regarding the ECG data that was analyzed, there were no differences between treatment group and placebo group in ECG in Study N159. Any abnormalities noted in rhythm, QRS, ST-T, QT and QTc were similar between both groups.

QT and QTc analyzed by identifying patients with prolongations of >450 msec. There were three patients identified in both the treatment and placebo groups in Study N159. In the database, there were 13 patients with a prolongation between 450 and 500msec, and 3 patients with prolongations of greater than 500msec. These three patients are briefly discussed under cardiac adverse events below.

Results from Study N159 related to changes in ECG parameters are summarized in Sponsor Table 9:7. The net change in QTc interval is 8.2 milliseconds, mostly due to a 6 millisecond decrease in the placebo group.

Table 9:7 Change from Baseline in ECG Parameters from Baseline to the Last Visit (N159) (a)

ECG Parameter	Levetiracetam (N = 101)			Placebo (N = 97)			p-value (Kruskal-Wallis Test)
	n	Mean ± S.D.	Median	n	Mean ± S.D.	Median	
Ventricular rate (bpm)	95	−0.6 ± 13.7	-1.0	84	−2.0 ± 14.7	-4.0	0.1902
PR Interval (msec)	95	4.8 ± 23.4	2.0	84	−2.9 ± 23.5	0.0	0.1010
QRS Interval (msec)	95	0.6 ± 12.4	0.0	85	1.6 ± 14.7	0.0	0.6283
QT Interval (msec)	92	3.5 ± 27.1	4.0	84	5.7 ± 30.2	1.5	0.8287
QTc Interval (msec)	94	2.0 ± 17.6	0.5	85	-6.2 ± 44.4	0.0	0.1309

(a) Table 16.7.1:10 = statistical comparisons
Ref: CSR Table 14.3.5:4 and Listing 16.2.9:4 in N159 report Module 5, Volume 26, Section 5.3.5.1.1.1

Data are summarized for the pooled database in Sponsor Table 9:8

Table 9:8 Summary of Change in ECG Parameters from Baseline to Last On-Treatment Visit (Overall): All Durations by Age Groups

		Age Category (years)			
		< 4 (N = 14)	4 - <8 (N = 53[a])	8 - <12 (N = 90[b])	12 - <18 (N = 49[c])
Ventricular Rate (bpm)					
Baseline	Mean ± S.D.	118.57 ± 25.44	96.26 ± 15.79	84.42 ± 14.92	74.37 ± 12.88
Final	Mean ± S.D.	116.29 ± 17.76	91.64 ± 18.57	83.19 ± 18.37	73.23 ± 19.00
Change	Mean ± S.D.	-2.29 ± 22.20	-5.33 ± 17.94	-1.29 ± 14.88	-0.71 ± 16.17
	Median	4.00	-5.00[e]	-2.00	-2.00
	95% CI[d]	-16.00 – 13.50	-9.50 – 0.00	-5.00 – 1.00	-5.50 – 3.00
PR Interval (sec)					
Baseline	Mean ± S.D.	0.11 ± 0.02	0.13 ± 0.02	0.14 ± 0.02	0.14 ± 0.02
Final	Mean ± S.D.	0.12 ± 0.02	0.12 ± 0.02	0.14 ± 0.03	0.14 ± 0.02
Change	Mean ± S.D.	0.00 ± 0.01	-0.01 ± 0.02	0.00 ± 0.02	0.00 ± 0.02
	Median	0	0	0	0
	95% CI[d]	0.00 – 0.01	-0.01 – 0.00	0.00 – 0.01	-0.01 – 0.00
QRS Interval (sec)					
Baseline	Mean ± S.D.	0.06 ± 0.01	0.07 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
Final	Mean ± S.D.	0.07 ± 0.01	0.08 ± 0.01	0.08 ± 0.01	0.09 ± 0.02
Change	Mean ± S.D.	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.01	0.00 ± 0.01
	Median	0	0[e]	0	0[f]
	95% CI[d]	0.00 – 0.01	0.00 – 0.01	0.00 – 0.01	0.00 – 0.01
QTc Interval (sec)					
Baseline	Mean ± S.D.	0.40 ± 0.02	0.41 ± 0.02	0.41 ± 0.03	0.40 ± 0.03
Final	Mean ± S.D.	0.41 ± 0.02	0.41 ± 0.04	0.41 ± 0.02	0.41 ± 0.03
Change	Mean ± S.D.	0.01 ± 0.02	0.01 ± 0.03	0.01 ± 0.03	0.01 ± 0.03
	Median	0	0	0[g]	0.01[h]
	95% CI[d]	0.00 – 0.02	0.00 – 0.01	0.00 – 0.01	0.00 – 0.01

[a] Final on-treatment N = 58
[b] Final on-treatment N = 95
[c] Final on-treatment N = 52
[d] 95% CI of median change
[e] N = 54
[f] N = 48
[g] N = 87
[h] N = 47
Source: Table 16.7.1:2

Per the Sponsor, in controlled clinical trials in adults, there were no effects on PR, QRS or QTc intervals. The current label does not discuss any cardiac related adverse effects. Results in children were similar with no major differences between the treatment and placebo groups in study N159. Regarding QTc interval changes the sponsor further categorized these in Sponsor table 10:53 below.

Table 10:53 Number (%) of Patients Categorized by QT and QTc Interval Prolongation from Baseline

	N159		Overall LEV
	Placebo N (%)	LEV N (%)	N (%)
Number of Patients[(a)]	76	87	210
QT Prolongation from Baseline			
≥ 0.03 - <0.06 (sec)	11 (14.5%)	22 (25.3%)	64 (30.5%)
≥ 0.06 - <0.09 (sec)	1 (1.3%)	1 (1.1%)	14 (6.7%)
≥ 0.09 (sec)	0	1 (1.1%)	5 (2.4%)
QT Actual Value			
≥ 0.45 – 0.5 (sec)	0	1 (1.1%)	3 (1.4%)
≥ 0.5	0	0	0
QTc Prolongation from Baseline			
≥ 0.03 - <0.06 (sec)	8 (10.5%)	12 (13.8%)	37 (17.6%)
≥ 0.06 - <0.09 (sec)	2 (2.6%)	0	9 (4.3%)
≥ 0.09 (sec)	0	0	4 (1.9%)
QTc Actual Value			
≥ 0.45 – 0.5 (sec)	3 (3.9%)	3 (3.4%)	13 (6.2%)
≥ 0.5	0	0	3 (1.4%)

Source: Table 16.7.1:9
[(a)]Number of patients with baseline ECG and at least one post-baseline ECG during that period.

A review of the data listings revealed 26 individuals with any QTc prolongation of greater than 450msec. Many of these patients had elevated readings at baseline. Three patients had individual QTc readings of greater than 500msec. (ISS 5585 – 570msec, ISS 5405-500msec and ISS 5577 – 530msec.) None of these patients had any cardiovascular symptoms or cardiac related adverse events. More information was provided by the sponsor regarding these cases as the Division had concerns for these outliers. UCB used Bazetts formula correction (B) for the QTc but recalculated them using Fridericia Correction (F) and Framingham Linear Correction (L). The evaluation of these patients was limited by lack of ECG timing to dose and some data being machine generated versus calculated individually by hand.

ISS 5585 was a 10 year old Hispanic male with a history of neonatal asphyxia. His baseline QTc was 404msec and his worst on treatment reading was 568 msec (using Bazett's correction). Per the sponsor, this would reduce to 522 using Fridericia and 502msec using Framingham Linear. The sponsor could not provide us with the actual ECG tracings from this patient. He continues in the extension study N157 and has been asymptomatic. Another ECG done while on drug for over a year showed a QT of 320 (no QTc calculated).

ISS 5405 was a 6 year old Caucasian male with infantile spasms and developmental delay. His baseline QTc was 434 msec and his worst on treatment reading was 500msec (495msec (B)). This reduced to 429msec (F) and 410 msec (L). This patient withdrew from the extension phase of the study. Final ECG QTc was the highest reading.

ISS 5577 was a 7 year old Hispanic female with a history of febrile seizures. Her baseline QTc was 347msec and her worst on treatment QTc was 534msec. This reduced to 485msec (F) and 468msec (L). This patient remains in the extension study and has remained asymptomatic.

Only 3 AEs were reported related to cardiovascular events among those treated with study drug: ISS 4874 A 12 year old male with first degree AV heart block, ISS 5202 A 14 year old female with QT prolongation and ISS 5319 an 8.5 year old female with left ventricular hypertrophy. All three of these patients had recorded QTc equal to or greater than 450msec. All three had events that were considered mild by the investigators and none stopped drug.

Due to continued concerns regarding the potential effects of levetiracetam on QT intervals in children, the Division requested the sponsor evaluate this further by performing a thorough QT study in adults as a required phase IV commitment.

7.1.10 Immunogenicity

No discussion of immunogenicity was provided by the sponsors.

7.1.11 Human Carcinogenicity

A total of 7 patients were identified in the database with neoplasms. None were malignant or considered related to the study drug. Two of the 7 patients had tuberous sclerosis, a known entity related to other neoplasms.

7.1.12 Special Safety Studies- Neuropsychiatric Side Effects and Worsening of Seizures

7.1.12.1 Neuropsychiatric Side Effects

The Sponsor identified that nervous system events were the most common treatment emergent events associated with levetiracetam. These adverse events were among the most frequent reasons for discontinuation, dose change and serious adverse events. These were further broken down into psychiatric events, effect on cognition, coordination difficulties, somnolence and events suggestive of worsening of seizures. The sponsor had a separate area of the ISS for this discussion and data presentation. I have divided it into these subsections for further discussion.

7.1.12.1.1 Psychiatric events

In controlled trials of adult patients with epilepsy, 13.3% of levetiracetam treated patients experienced behavior problems (reported as aggression, agitation, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, irritability, etc.) compared to 6.2% of placebo patients. Similarly, in the pediatric database, there was an increase of these type events in pediatric patients (37.6% vs 18.6% in placebo.) Overall, there is a two fold or greater relative

risk of levetiracetam treated patients as compared to placebo for incidences of agitation, nervousness and depression. The Sponsor feels that this is similar to the incidences seen in adults, however, children may be more likely to have agitation (a somewhat higher relative risk in children as compared to adults). Incidences and relative risks are summarized in Sponsor Table 10:1 below. The highest relative risks relating treatment to placebo group are agitation (5.76), depression (2.88) and nervousness (4.32). This reviewer is impressed with the numbers (percentages) of patients who reported these side effects (54.4% overall).

Table 10:1 Number (%) of Patients with at Least One Treatment-Emergent Psychiatric / Behavior Pediatric Adverse Events by UCB Grouping Term: In N159 and in Overall Population Exposed to Levetiracetam

	N159				Overall LEV
UCB AE Grouping Term/COSTART Preferred Term	**Placebo (N = 97)**	**LEV (N = 101)**	**Rel. Risk (LEV/PBO)**	**95% CI**	**(N = 239)**
All Psychiatric / Behavior[a]	27 (27.8%)	39 (38.6%)	1.39	0.93-2.08	130 (54.4%)
Non-Psychotic Mood / Anxiety / Behavior	18 (18.6%)	38 (37.6%)	2.03	1.25-3.30	111 (46.4%)
Agitation	1 (1.0%)	6 (5.9%)	5.76	0.71-46.99	16 (6.7%)
Antisocial reaction	0	0	–	–	1 (0.4%)
Anxiety	1 (1.0%)	0	–	–	8 (3.3%)
Apathy	1 (1.0%)	1 (1.0%)	0.96	0.06-15.14	1 (0.4%)
Depersonalization	1 (1.0%)	0	–	–	2 (0.8%)
Depression	1 (1.0%)	3 (3.0%)	2.88	0.30-27.23	12 (5.0%)
Emotional lability	4 (4.1%)	6 (5.9%)	1.44	0.42-4.95	24 (10.0%)
Euphoria	0	0	–	–	1 (0.4%)
Hostility	6 (6.2%)	12 (11.9%)	1.92	0.75-4.91	36 (15.1%)
Hyperkinesia	3 (3.1%)	3 (3.0%)	0.96	0.20-4.64	14 (5.9%)
Nervousness	2 (2.1%)	9 (8.9%)	4.32	0.96-19.50	32 (13.4%)
Neurosis	1 (1.0%)	0	–	–	0
Personality disorder	7 (7.2%)	8 (7.9%)	1.10	0.41-2.91	34 (14.2%)
Screaming syndrome	0	0	–	–	2 (0.8%)
Psychotic symptoms	1 (1.0%)	1 (1.0%)	0.96	0.06-15.14	7 (2.9%)
Hallucinations	1 (1.0%)	0	–	–	3 (1.3%)
Psychosis	0	1 (1.0%)	–	–	3 (1.3%)
Psychotic depression	0	0	–	–	1 (0.4%)
Self Aggressive Symptoms	1 (1.0%)	0	–	–	3 (1.3%)
Overdose	1 (1.0%)	0	–	–	3 (1.3%)
Sleep symptoms	6 (6.2%)	4 (4.0%)	0.64	0.19-2.20	30 (12.6%)
Insomnia	6 (6.2%)	4 (4.0%)	0.64	0.19-2.20	30 (12.6%)

[a] Includes cognition, which is reviewed in Section 10.1.2
Source: Table 16.4.3:1; relative risk in Table 16.4.3:2

The Sponsor has many explanations for why the incidence of psychiatric and behavior adverse effects would be high. These include: association of behavioral disorders with refractory partial seizures, limbic processes in seizure patients, concomitant risks such as preexisting psychiatric history, history of febrile seizures or status epilepticus, and other concomitant drug effects. The Sponsors related that 99 patients in study N159 had a past neuropsychiatric history. This was

similar in that 160 of 239 patients in the pooled database also had some neuropsychiatric history. Even so, this does not explain the much higher incidences and risk ratios (relative risk) of these events in the treated population versus placebo. It only explains the high overall incidence in both groups. These incidences also speak to a possible limitation of the use of levetiracetam in patients with partial seizures and neuropsychiatric history. On the other hand, patients with refractory seizures (and their caretakers) might be more willing or able to tolerate such side effects.

The Sponsor did not find an increased risk of psychiatric side effects in the subpopulation of seizures with either psychiatric or cognitive impairment. The Sponsors did note that patients in Study N159 taking concomitant medications including carbamazepine, topiramate, and valproate were more likely to have "disproportionate numbers of neuropsychiatric events." This may speak to a potential pharmacodynamic interaction between levetiracetam and these agents or may relate to the incidence of neuropsychiatric side effects of these other AEDs primarily. For the overall open label population, the Sponsors noted increased events of neuropsychiatric side effects reported in patients taking concomitant, diazepam, carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproate, zonisamide, and nasal decongestants.

For specific events more likely than not related to specific concomitant medications that the Sponsor felt were significant (relative risk greater than 2 or greater, 95% confidence interval lower limit of 1 or greater.), these are summarized below.

- Carbamazepine treated patients had an elevated relative risk for hallucinations (RR: 3.56; 95% CI: 0.33- 38.67).
- Lamotrigine treated patients had an elevated relative risk for anxiety (RR: 2.85; 95% CI: 0.74- 11.07), hyperkinesia (RR: 3.81; 95% CI: 1.38- 10.54), screaming syndrome (RR: 2.85; 95% CI: 0.18- 44.96), hallucinations (RR: 5.71; 95% CI: 0.53- 61.88), and overdose (RR: 5.71; 95% CI: 0.53- 61.88).
- Topiramate treated patients had an elevated relative risk for amnesia (RR: 3.48; 95% CI: 0.59- 20.38), anxiety (RR: 6.96; 95% CI: 1.44- 33.66), and screaming syndrome (RR: 2.32; 95% CI: 0.15- 36.57), overdose (RR: 4.64; 95% CI: 0.43- 50.35), and speech disorder (RR: 3.48; 95% CI: 1.01- 11.96).
- Valproic acid treated patients had an elevated relative risk for anxiety (RR: 2.51; 95% CI: 0.65- 9.77) and hostility (RR: 2.25; 95% CI: 1.25- 4.06).

The Sponsor considered that some mild events could become more serious events over time. A total of 22/239 (9.2%) of patients were identified as having a more severe event (for example nervousness, insomnia or emotional lability who later reported personality disorder, agitation or hostility.

7.1.12.1.2 Behavioral effects

Behavioral effects were also discussed by the Sponsor at length. A patient was considered to have a behavioral adverse event if one or more of the following COSTART terms were used:

hostility, agitation, hyperkinesias, and/or nervousness. In addition, certain adverse events ascribed to personality disorder, emotional lability and anxiety were described in terms of behavioral changes and included. The Sponsor also included effects on mood and patients with anxiety disorders.

Overall, in the open label database, 91/239 patients (38.1%) including 55 boys and 36 girls had one or more behavior episodes while receiving levetiracetam. The behavioral effects most commonly reported in this subgroup included nervousness, hostility, agitation and hyperkinesias. In addition, 29 patients had aggressive or other hostile behaviors coded as "personality disorder" as did 16 patients with "emotional lability" and 6 patients with "anxiety". Three patients also had isolated hallucinations, 2 patients with behavioral effects progressed to psychotic episodes, and 2 patients with mixed depressive and psychotic symptoms in addition to behavioral adverse events were noted. Three patients with mood disorders are included here and also described in the subsection on mood disorders. One patient had panic attacks. Insomnia was present in six patients, transient and/or concomitant depressed mood or sadness in 4 patients, and there were single patients with antisocial reaction, screaming syndrome, and apathy.

Due to one or more behavioral events in these 91 patients, 22/91 (24 %) discontinued, reduced their dose or had a dose interruption. For the 8 patients who discontinued for behavioral reasons the events resulting in discontinuation were hostility in 4 patients, nervousness in 2 patients, and personality disorder and hyperkinesia in 1 patient each. These included verbatim descriptions such as irritability, hyperkinesia, decline in behavior, and aggressive behavior. All either resolved or diminished in intensity following discontinuation (with the exception of one case for which the outcome was not known.). Fourteen (of the 22 patients) had changes in dose as a result of hostility, nervousness, personality disorder, agitation, thinking abnormal, hyperkinesia, and emotional lability with aggressive and impulsive behavior. The events resolved or diminished in intensity in 7 of these patients.

A total of 25 events occurred in a severe intensity in 18 patients, including in 7 of the patients with a discontinuation/ dose change. These were emotional lability (5 patients), hostility (5 patients), nervousness (4 patients), personality disorder (4 patients), hyperkinesia (2 patients), agitation (2 patients), and self- abusive behavior (1 patient).

An overview of the 33 patients, 24 boys and 9 girls, with behavioral events that resulted in discontinuation, dose change, or that were severe in intensity were reviewed separately. Many of these patients had underlying psychiatric or neurologic disorders that might explain some of the behavioral problems. The Sponsor was very conservative with most of these cases assessing them as probably or possibly related to the study drug. To be fair, comorbid complicated neurologic or psychiatric history in pediatric epilepsy patients is not uncommon (such as tuberous sclerosis, dysgenesis of the brain, developmental delay, hydrocephalus, cerebral palsy with mental retardation, ADHD, behavioral problems, global developmental delays). This makes it difficult to tease out the drug effect outside of the issues related to the primary or coexisting medical condition. Other patients with these difficulties did not require a dose reduction making it difficult to ascertain just what the threshold is that would require a dose reduction or discontinuation of levetiracetam. This reviewer could understand how parents and

caregivers of a severely impaired child (due to underlying disease) might be more willing to tolerate behavioral effects if the underlying seizure disorder was better controlled.

7.1.12.1.3 Mood Disorders

In the total database, there were 18 cases of mood disorder, 6 were boys and 12 were girls. Twelve of the 18 cases were coded as "depression". This COSTART term encompasses the terms "depression", "sad", major depressive disorder, moderate with atypical features", suicidal ideation", and "sadness". There were 6 cases of "emotional lability" and 1 case of "apathy" were also included in the total. There was a single case of psychotic depression and 5 cases of nonpsychotic mood disorders, one requiring hospitalization (ISS 5222). That case was of a 10 year old male who, after taking the medication for 729 days experienced major depression requiring hospitalization and treatment with chlorpromazine and lorazepam.

I reviewed the case summaries and narratives but did not reproduce them here. The cases are wide ranging with depression, euphoria, hostility, or nervousness as primary symptoms. Of note to this reviewer was a case of a 13 year old girl (ISS No. 5528) with a history of complex partial seizures and generalized tonic clonic seizures who began to have suicidal ideation after one month on the drug. The drug was withdrawn and she continued to have a poorly controlled seizure disorder. However, the mood disorder improved. The patient was on concomitant topiramate and oxcarbazepine at the time of the suicidal ideation.

Since suicidal ideation was a major issue with the antidepressants recently in this Division, this single case may be important if more cases of suicidal ideation or suicidality are reported.

Overall, the cases of mood disorder are concerning for larger effects on mood in this population. Although several of these patients became moody, or had worsening of mood, half did have either a dose reduction or withdrew off the medication. It is difficult, considering the other concomitant medications and conditions to tease out the exact mood effects of levetiracetam. However, it is concerning that addition of the drug to these patients may have exacerbated any underlying mood disorder. This should be addressed in the labeling.

7.1.12.1.4 Anxiety disorders

Eight patients (4 boys and 4 girls) reported anxiety during study N157, but did not report anxiety during the shorter double blind study (either N151 or N159). The COSTART term anxiety encompassed the verbatim terms: anxiety, anxious, scared, and Post Traumatic Stress Disorder. Five of the 8 patients were included with other behavioral events. Three cases were primarily anxiety cases, 2 children with panic attacks and 1 child with post traumatic stress. These patients' doses were either lowered or they were treated with anxiolytic medications.

7.1.12.1.5 Psychotic symptoms

Eight patients (5 boys and 3 girls) exhibited psychotic symptoms, 4 of which were serious adverse events. Due to concomitant underlying conditions, it was difficult to ascertain whether levetiracetam exacerbated or initiated the underlying psychosis. Several patients were diagnosed with either schizoaffective disorder or psychosis. Most patients who stopped the drug did not improve in symptoms and required antipsychotic medication.

Hallucinations alone were reported in three patients (ISS Nos 5277, 5364 and 4883) and attributed to either seizures, bipolar disorder and the third had no alternative explanation. The hallucinations were brief and only lasted a few days. None of those three patients required treatment. ISS No 5210, a 14 year old boy had a 21 day episode of psychosis requiring hospitalization and antipsychotic medication. He remained on levetiracetam throughout. ISS 5271 a 15 year old girl with partial seizures and organic brain damage related to perinatal asphyxia developed auditory hallucinations. She was hospitalized with psychotic depression and stopped the study drug. Her symptoms continued as did her seizures. ISS 5300, an 11 year old boy had multiple psychotic complaints, but stayed on medication. ISS 5489 an 8 year old girl with partial seizures and mental retardation from a head trauma developed extreme agitation with combativeness exhibited by fighting and hitting a teacher and fighting and hitting her grandmother. She was hospitalized, but remained on study drug.

Again with all of these mood and psychiatric symptoms, it is difficult in this population to ascertain whether these are normal other diseases (developing psychosis or childhood psychosis), related to the background seizure disorder, or related to drug interactions. These cases are concerning however, in this population for these type of events and should be discussed in labeling.

7.1.12.1.6 Insomnia

There were 30 patients reporting insomnia, of these, all but 10 were in conjunction with other psychiatric events (non-psychotic). For the 10 cases of primary insomnia, they ranged from within 2 weeks of starting treatment to 2 years after. Many were continuous or intermittent. All were considered mild, with two being moderate. The two moderate cases were considered more likely related to concomitant lorazepam and felbamate.

7.1.12.1.7 Cognitive Disorders

There were a total of 31 patients in the database determined to have at least one treatment emergent cognitive adverse event. Most patients had wide ranging events including decreased concentration, alertness, or attention, poor school performance or increased distractibility. Two thirds of the cases were considered to be possibly related to levetiracetam. Four cases were associated with changes in concomitant AEDs or benzodiazepine use. Six cases were felt to be noteworthy by the Sponsor, 3 of the cases had a reduction in dose with either little or no change in confusion, and 3 improved with dose reduction. Again as with the psychiatric side effects, it

is difficult to decide if most of these cases are directly related to the use of levetiracetam or due to other extenuating factors.

7.1.12.1.8 Coordination difficulties

Fifteen patients were identified in the database to have coordination difficulties (including abnormal gait, ataxia and incoordination). Most events were mild in intensity and transient (1-7 days duration). Three of the events were considered severe intensity resulting in discontinuation in 1 patient. Upon close review, this subset of patients had multiple underlying neurologic problems possibly placing them at higher risk of such problems (such as cerebral palsy, tuberous sclerosis or hypotonia.) The patient who discontinued the drug was a 13 year old girl on 100mg/kg/day who despite multiple reductions in dosage continued to be ataxic and then discontinued the drug due to loss of efficacy.

7.1.12.1.9 Somnolence

In the double blind study, somnolence was reported twice as much in the levetiracetam treated patients than in the placebo group. Per the Sponsor, this finding is similar to that seen in adults (14.8% in levetiracetam patients vs 8.4% in placebo patients). In the database, 71 (29.7%) patients treated with levetiracetam reported somnolence. Most cases were mild or moderate and responded to dose reductions. There was a single SAE among the 71 patients, an overdose (ISS 5393- see section 7.1.16 below) of approximately 10.5 grams of levetiracetam (along with two other AEDs.)

Other general neurological symptoms reported included headache, migraine or nystagmus. Headache was the most common reported neurologic symptom. Incidences were similar in placebo patients in study N159. Overall headache was a common complaint in 63/239 (26.4%) patients in the database.

7.1.12.2 Special assessments – Worsening of seizures

In Study N159, 20 (20.6%) patients randomized to placebo and 17 (13.9%) patients randomized to drug had a 25% or greater **increase** in weekly seizure frequency. Across all studies (N=239) 54 (22.6%) patients treated with drug had seizures reported at least once as an adverse event reported as increase in frequency or intensity.

Thirty one of 54 patients in the database had seizures described as increased in frequency or intensity or worsening. Drug was discontinued permanently in 4 patients and decreased in 2 others. Nine patients (of the 31) had SAEs related to seizure events and were hospitalized. Of the 4 patients who discontinued prematurely, two children were terminated from study drug for status epilepticus, neither of which was judged by the Investigator as related to study drug. The third, ISS No. 4875, experienced a second occurrence of increased seizures after receiving levetiracetam for 51 days (the first being reported on Day 4 with no action taken). The dose at onset was 1000 mg/ day. The dose was decreased to 500 mg/ day for 7 days and discontinued

and the event resolved. The fourth, ISS No. 5428, was reported with aggravation of epilepsy after 11 days on treatment with 500 mg/ day. The dose then increased to 1000 mg/ day for 13 days before being tapered off and discontinued on Day 32.

Six patients experienced a new seizure type but there was no consistency among the reported cases.

To this reviewer, this effect of worsening of seizures is concerning. However the majority of patients treated had improvement of seizures consistent with the primary efficacy analysis. Patients who worsen should be taken off the drug.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

This was not discussed by the sponsor in this supplement.

7.1.14 Human Reproduction and Pregnancy Data

This section is not applicable to this pediatric supplement.

7.1.15 Assessment of Effect on Growth

The sponsor did discuss effects of weight gain or weight loss both in the double blind trial and in the open label studies. These results were somewhat equivocal with some patients gaining weight and some losing weight. No formal assessment of overall effects on growth curves was discussed. The sponsor may wish to consider this as part of postmarketing evaluation.

7.1.16 Overdose Experience

There was a single overdose experience in the double blind study. ISS No. 5393 was a 12 year old Hispanic girl with a history of epilepsy related to cortical dysphasia. On study day 160 she took an overdose of levetiracetam, carbamazepine and topiramate and was hospitalized. Apparently, she took three days worth of medication all at once, ingesting approximately 10.5 grams of levetiracetam, 2.4 grams of carbamazepine and 0.75 grams of Topamax. The patient denied suicidal ideation. She tolerated the overdose well, experiencing somnolence and "severely altered mentation". She was hospitalized for 2 days and discharged. She discontinued levetiracetam 7 months later due to a "protocol violation".

Regarding the pooled database, the Sponsors relate 6 cases of reported or accidental overdose. 1 case was an overdose of another medication (Nauzene®), 2 cases were attributed to concomitant AEDs, 1 was an overdose in N159 on a patient randomized to placebo and the other case, ISS 5393 was described above. The remaining case is ISS 4884, an 8 year old girl who was accidentally given 1500mg/day (71.4 mg/ kg/ day) rather than the intended dose of 1000 mg/ day (48 mg/ kg/ day). This was due to a pharmacy dispensing error. The dose was immediately changed on Day 98 back to the intended dose. The patient did not appear to suffer any ill effects

and seizure frequency decreased on this dose. This event, coded an "accidental overdose" was reported as an SAE due to reporting practices in place at the time.

Regarding post marketing overdose experience, there were 4 cases of accidental overdose or medication error spontaneously reported to UCB. All of the patients recovered with minor adverse effects. The children were young, 12 months, 15 months, 2 years, and 3 years. In 1 case, a 15- month old patient received 100 mg in the morning instead of 50 mg and was more tired than normal that day. In the other 3 cases, the patients ingested much higher doses. The 2- year old accidentally ingested 4 to 4.5 tablets (1000 to 1125 mg) of her mother's Keppra ® and had no deleterious effects. A 12- month old child was accidentally dosed at 200 mg/ kg/ day and experienced dizziness, but recovered. Lastly, a 3- year old was prescribed 7.1 mg/ kg/ day of Keppra ® , but was accidentally administered 71 mg/ kg per day. The patient experienced somnolence, but it resolved 1 or 2 days later. There is one additional case of overdose from literature. A 4 year old boy experienced apnea attacks after overdose of Keppra ® . He was rechallenged at an appropriate dose and there was no return of the apnea episodes.

7.1.17 Postmarketing Experience

7.1.17.1 Neuropsychiatric events

The sponsor provided information from their Postmarketing Drug Safety database consisting of over 300 reports related to the pediatric population. A majority of the reports related to neuropsychiatric events (105 cases). The most frequently reported were: aggression (36), abnormal behavior (19), altered mood/ affect / apathy (16), hallucination (13), depression/ depressed mood or affect (12), anger (10), insomnia/ sleep disorder (10), suicidal / self-injurious behaviors (7), psychotic disorder/ acute psychosis (7), anxiety (7), and crying (7).

7.1.17.1.1 Suicide risk

Of note and potentially a greater concern was that seven patients exhibited suicidal or self-injurious behavior as follows: suicidal ideation (4), completed suicide (1), suicide attempt (1), and self- injurious intention (1). None of the patients were documented to have had a recent history of psychiatric or mental disease; 1 patient was described as having a remote history of psychosis 6 years earlier, and a family history of mental illness was described in 1 patient. Although a majority (71%) of the patients were adolescents (12 to 15 years of age), a suicide attempt was made by a 7- year old girl who stepped out into the street. The patient was not injured, but she was hospitalized in a psychiatric unit for 1 week. In 5 of these 7 patients, neuropsychiatric symptoms (aggression, depression, suicidal ideation, difficulty walking) worsened after the dose of Keppra ® was increased. Per the sponsor, there was a temporal relationship between the start of Keppra ® and the onset of depression or aggressive symptoms, which occurred within a mean of 2.7 weeks (range, 0.25 to 6 weeks; N= 5). The onset of documented suicidal ideation occurred within a mean of 6 weeks (range, 0.25 to 17 weeks; N= 5) after the start of Keppra ® therapy. Among the 7 living patients, the suicidal symptoms resolved

in six when the Keppra ® dose was decreased or the drug were discontinued. The outcome of the seventh patient was unknown.

7.1.17.1.2 Psychotic symptoms/hallucinations

Within the data provided in the postmarketing database, seven patients experienced a psychotic disorder or acute psychosis while taking Keppra ® . Their ages ranged from 5- 13 years (N= 5). Four of these 7 patients were described as having hallucinations. Only one patient was documented as having a previous psychiatric history. The symptoms resolved after Keppra ® was discontinued in 4 patients and when the dose of Keppra ® was decreased in 1 patient. The symptoms did not resolve after Keppra ® was discontinued in one case and the outcome was unknown in the seventh case. In addition to the 3 patients above, another 12 patients were coded as having experienced hallucinations. Their ages ranged from 5 to 15 years (N= 10). Four of the 12 patients were described as having some sort of behavioral or psychiatric history. Hallucinations resolved in 4 patients after Keppra ® was discontinued and in another 4 patients after the dose of Keppra ® was decreased. The outcome was unknown in the remaining 4 cases.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

This is discussed earlier in the ISS Section 7.1.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The Sponsor provided a list of 30 publications that they felt provided pertinent safety information. Most of these studies concluded that levetiracetam was safe and well tolerated with few side effects. Some studies emphasized that side effects tended to be central nervous system and behaviorally related. One study in children concluded that levetiracetam was effective and well tolerated, frequently producing improvements in behavior and cognitive functions. One study in adults and children concluded that in a series of 34 patients, one fifth demonstrated some worsening of seizures. Two studies proposed that the drug should be introduced with caution in young children because of the tendency to increase seizures, whereas another study used a higher maximum dose and a faster titration rate without an increase in significant side effects. Some of the published studies investigated the neuropsychiatric events in epileptic children treated with levetiracetam. Behavioral symptoms including aggression, agitation, altered mood, anxiety/ panic, hallucination, hyperactivity/ inattention, irritability, and aggravation of obsessive- compulsive disorder were reported. A positive effect on alertness and behavior has been observed in children with refractory epilepsy. In another study in children with refractory epilepsy the authors concluded that a history of behavioral and emotional problems appeared to predispose children to an exacerbation of these problems when treated with levetiracetam.

However many parents of children in this group also reported improvements. The children whose behavior worsened were also more likely to have a history of previous treatments causing similar problems. Acute psychosis was also reported in a case report concerning 4 children, including two aged less than 16 years and in a case report concerning 1 child.

Overall, the majority of published data concluded that levetiracetam was safe and well tolerated with few side effects. Some publications specified that the side effects tended to be central nervous system and behaviorally related.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience was adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

This does not apply to this NDA.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing throughout the N159 study were adequate. However ECG was not tested at Tmax of the drug, so that cardiac effects were not adequately assessed and should be considered in a separate clinical safety trial. However, there were very few to no cardiac adverse effects from the study drug, so there is not a strong safety signal to assess.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsors did not discuss these issues in any length throughout the submission.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This section is not applicable to this supplement NDA.

7.2.8 Assessment of Quality and Completeness of Data

UCB Pharma has presented a concise, well written ISS. The safety sections discussion in the N159 study report was very brief, albeit this was only a 12 week study. More discussion on the short term effects versus long term effects would have been helpful.

7.2.9 Additional Submissions, Including Safety Update

The safety update was submitted on April 19, 2005. The original cutoff date for the database was August 31, 2004. The new cutoff date for the safety update was February 15, 2005. The

safety update included 5 additional serious adverse events and a non serious significant event (pregnancy). The majority to the new SAEs related to worsening of seizure events. New postmarketing events were discussed that were in line with the previously reported events, that is, that the majority were neuropsychiatric in origin. 16 additional cases were reported in 7 girls and 9 boys ranging in age from 33months to 15 years. Abnormal behavior was described in 6 patients; aggression was discussed in 5 cases. There were 2 cases of hallucination (one auditory).

- Regarding new hematologic events, there was one additional report of thrombocytopenia (related to cytolytic hepatitis).

- Three new cases of hepatobiliary problems were reported these include two cases with elevated liver enzymes. One of the patients had pancreatitis as well. In this case, levetiracetam was discontinued and the patient recovered.

- Regarding kidney/renal cases, there was one additional case of dysuria (painful urination).

- There were no additional cardiovascular events reported.

- There were two additional reports of overdose. In one case, a 13 month old patient received 5mL instead of 0.5mL, the maximum dose was 20mL (equivalent to 2000mg) with "loose muscle tone". In another case a 2 year old ingested a single 250mg tablet without effects.

- There were no additional deaths.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

These are discussed in the subsections above.

7.4 General Methodology

There was only a single double blind study and 4 additional small pharmacokinetic studies in the pediatric sNDA. Individual study data has already been compared to the safety database in the previous clinical and laboratory sections.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

These have been discussed in the above subsections.

7.4.2 Explorations for Predictive Factors

Due to time constraints, these issues were not fully explored. However subgroup analysis related to gender was discussed briefly in the IND.

Insomnia and nervousness appeared to be more common in boys, however the numbers of patients taking the drug were small. The sponsor summarized treatment emergent adverse effects by gender and body system for study N159 and the overall database in sponsor Table 12:2 below.

Table 12:2 Number (%) of Patients in N159 and Overall Reporting Treatment-Emergent Adverse Events (Reported by More Than 10% of Patients) by COSTART Body System, Preferred Term and Gender

COSTART Body System / Preferred Term	N159				Overall Levetiracetam	
	Placebo		Levetiracetam		Boys (N=124)	Girls (N=115)
	Boys (N=46)	Girls (N=51)	Boys (N=54)	Girls (N=47)		
Body as a whole	29 (63.0%)	33 (64.7%)	34 (63.0%)	27 (57.4%)	106 (85.5%)	98 (85.2%)
Abdominal pain	6 (13.0%)	7 (13.7%)	1 (1.9%)	3 (6.4%)	15 (12.1%)	16 (13.9%)
Accidental injury	4 (8.7%)	7 (13.7%)	9 (16.7%)	8 (17.0%)	37 (29.8%)	24 (20.9%)
Asthenia	1 (2.2%)	2 (3.9%)	6 (11.1%)	3 (6.4%)	16 (12.9%)	14 (12.2%)
Fever	4 (8.7%)	6 (11.8%)	5 (9.3%)	3 (6.4%)	36 (29.0%)	28 (24.3%)
Headache	3 (6.5%)	10 (19.6%)	7 (13.0%)	7 (14.9%)	37 (29.8%)	22 (19.1%)
Infection	18 (39.1%)	10 (19.6%)	18 (33.3%)	11 (23.4%)	68 (54.8%)	57 (49.6%)
Pain	1 (2.2%)	2 (3.9%)	4 (7.4%)	3 (6.4%)	13 (10.5%)	18 (15.7%)
Digestive System	14 (30.4%)	22 (43.1%)	16 (29.6%)	21 (44.7%)	67 (54.0%)	61 (53.0%)
Anorexia	4 (8.7%)	4 (7.8%)	8 (14.8%)	5 (10.6%)	22 (17.7%)	15 (13.0%)
Diarrhea	2 (4.3%)	5 (9.8%)	4 (7.4%)	4 (8.5%)	18 (14.5%)	15 (13.0%)
Gastroenteritis	0 (0.0%)	2 (3.9%)	3 (5.6%)	1 (2.1%)	22 (17.7%)	13 (11.3%)
Vomiting	4 (8.7%)	8 (15.7%)	6 (11.1%)	9 (19.1%)	28 (22.6%)	24 (20.9%)
Nervous System	26 (56.5%)	21 (41.2%)	30 (55.6%)	30 (63.8%)	95 (76.6%)	87 (75.7%)
Convulsion	10 (21.7%)	6 (11.8%)	5 (9.3%)	3 (6.4%)	26 (21.0%)	19 (16.5%)
Emotional lability	1 (2.2%)	3 (5.9%)	2 (3.7%)	4 (8.5%)	14 (11.3%)	10 (8.7%)
Hostility	5 (10.9%)	1 (2.0%)	7 (13.0%)	5 (10.6%)	26 (21.0%)	10 (8.7%)
Insomnia	3 (6.5%)	3 (5.9%)	3 (5.6%)	1 (2.1%)	21 (16.9%)	9 (7.8%)
Nervousness	2 (4.3%)	0 (0.0%)	6 (11.1%)	3 (6.4%)	22 (17.7%)	10 (8.7%)
Personality disorder	4 (8.7%)	3 (5.9%)	5 (9.3%)	3 (6.4%)	15 (12.1%)	19 (16.5%)
Somnolence	7 (15.2%)	4 (7.8%)	11 (20.4%)	12 (25.5%)	40 (32.3%)	31 (27.0%)
Respiratory System	14 (30.4%)	15 (29.4%)	17 (31.5%)	14 (29.8%)	72 (58.1%)	60 (52.2%)
Cough increased	2 (4.3%)	5 (9.8%)	2 (3.7%)	9 (19.1%)	18 (14.5%)	21 (18.3%)
Pharyngitis	2 (4.3%)	7 (13.7%)	5 (9.3%)	5 (10.6%)	30 (24.2%)	26 (22.6%)
Rhinitis	4 (8.7%)	4 (7.8%)	7 (13.0%)	6 (12.8%)	20 (16.1%)	24 (20.9%)
Sinusitis	3 (6.5%)	4 (7.8%)	5 (9.3%)	1 (2.1%)	21 (16.9%)	11 (9.6%)
Skin and Appendages	7 (15.2%)	6 (11.8%)	6 (11.1%)	4 (8.5%)	36 (29.0%)	28 (24.3%)
Rash	3 (6.5%)	3 (5.9%)	2 (3.7%)	1 (2.1%)	11 (8.9%)	13 (11.3%)
Special Senses	5 (10.9%)	6 (11.8%)	7 (13.0%)	5 (10.6%)	40 (32.3%)	34 (29.6%)
Otitis media	3 (6.5%)	4 (7.8%)	1 (1.9%)	2 (4.3%)	26 (21.0%)	22 (19.1%)

With respect to age related effects, the sponsors used standard age categories (1 month to < 4 years (youngest); 4 years to < 8 years, 8 years to < 12 years, and 12 years to < 18 years (oldest). The majority of the children were in the 8-12 range (N=104), followed by 4-8 years (N=63 and 12-18 years (N=56). The database included 16 children in the 1month-4 year range, however this age range was not included in this pediatric supplement. Overall, except for increased infections in the lowest age range, there were no age specific patterns in the occurrence of adverse events.

The study was too small to assess race as the enrollees were predominantly Caucasian. (N=162 or 67%)

7.4.2.4 Explorations for drug-disease interactions

The Sponsor constructed tables comparing adverse events reported in patients with and without a given disease. Due to the high number of neuropsychiatric side effects, several tabular summaries were created to focus on categories pertaining to the nervous system: mental and behavioral disorders, behavioral/ emotional disorders with childhood onset, disorders of psychological development, congenital malformations of the nervous system, mental retardation, and organic mental disorders. Per the Sponsor, there were no predominant trends in adverse events occurring in any one medical condition. Cognitive adverse events tended to be underreported in patients with mental retardation and organic mental disorders.

Table 12:8 Incidence of Nervous System Adverse Events Summarized by UCB Adverse Event Grouping Term for Patients with Selected Diseases at Entry (N159)

UCB Adverse	Mental and Behavioral Disorders[a]				Behavioral/Emotional Disorders with Childhood Onset[a]			
Event Grouping	Placebo		Levetiracetam		Placebo		Levetiracetam	
Term/COSTART Preferred Term	Yes (N = 63)	No (N = 34)	Yes (N = 63)	No (N = 38)	Yes (N = 30)	No (N = 67)	Yes (N = 31)	No (N = 70)
Cog./Mental Acuity	5 (7.9%)	1 (2.9%)	3 (4.8%)	3 (7.9%)	3 (10.0%)	3 (4.5%)	1 (3.2%)	5 (7.1%)
Amnesia	2 (3.2%)	0	0	0	2 (6.7%)	0	0	0
Confusion	0	0	1 (1.6%)	1 (2.6%)	0	0	1 (3.2%)	1 (1.4%)
Thinking abnormal	4 (6.3%)	1 (2.9%)	2 (3.2%)	2 (5.3%)	2 (6.7%)	3 (4.5%)	0	4 (5.7%)
Non-psychotic Sx	14 (22.2%)	4 (11.8%)	23 (36.5%)	15 (39.5%)	10 (33.3%)	8 (11.9%)	12 (38.7%)	26 (37.1%)
Agitation	1 (1.6%)	0	5 (7.9%)	1 (2.6%)	1 (3.3%)	0	2 (6.5%)	4 (5.7%)
Anxiety	1 (1.6%)	0	0	0	0	1 (1.5%)	0	0
Apathy	1 (1.6%)	0	1 (1.6%)	0	1 (3.3%)	0	0	1 (1.4%)
Depersonalization	1 (1.6%)	0	0	0	1 (3.3%)	0	0	0
Depression	1 (1.6%)	0	1 (1.6%)	2 (5.3%)	1 (3.3%)	0	0	3 (4.3%)
Emotional lability	2 (3.2%)	2 (5.9%)	4 (6.3%)	2 (5.3%)	1 (3.3%)	3 (4.5%)	2 (6.5%)	4 (5.7%)
Hostility	4 (6.3%)	2 (5.9%)	7 (11.1%)	5 (13.2%)	4 (13.3%)	2 (3.0%)	4 (12.9%)	8 (11.4%)
Hyperkinesia	2 (3.2%)	1 (2.9%)	2 (3.2%)	1 (2.6%)	1 (3.3%)	2 (3.0%)	1 (3.2%)	2 (2.9%)
Nervousness	2 (3.2%)	0	3 (4.8%)	6 (15.8%)	1 (3.3%)	1 (1.5%)	0	9 (12.9%)
Neurosis	1 (1.6%)	0	0	0	1 (3.3%)	0	0	0
Personality disorder	6 (9.5%)	1 (2.9%)	4 (6.3%)	4 (10.5%)	5 (16.7%)	2 (3.0%)	4 (12.9%)	4 (5.7%)
Psychotic Symptoms	1 (1.6%)	0	1 (1.6%)	0	0	1 (1.5%)	1 (3.2%)	0
Hallucinations	1 (1.6%)	0	0	0	0	1 (1.5%)	0	0
Psychosis	0	0	1 (1.6%)	0	0	0	1 (3.2%)	0
Sedation	6 (9.5%)	5 (14.7%)	14 (22.2%)	9 (23.7%)	4 (13.3%)	7 (10.4%)	6 (19.4%)	17 (24.3%)

[a] Table 16.9.2:2

Table 12:9 Number (%) of Patients with UCB AE Grouping and Preferred Term for Events Reported by ≥ 5% of Patients in the Levetiracetam Group (and More Common than on Placebo) (N159)

UCB Adverse	Disorders of Psychological Development[a]				Congenital Malformations of Nervous System[a]			
Event Grouping	Placebo		Levetiracetam		Placebo		Levetiracetam	
Term/COSTART Preferred Term	Yes (N = 34)	No (N = 63)	Yes (N = 33)	No (N = 68)	Yes (N = 17)	No (N = 80)	Yes (N = 10)	No (N = 91)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cog./Mental Acuity	4 (11.8%)	2 (3.2%)	2 (6.1%)	4 (5.9%)	1 (5.9%)	5 (6.3%)	0	6 (6.6%)
Amnesia	2 (5.9%)	0	0	0	1 (5.9%)	1 (1.3%)	0	0
Confusion	0	0	0	2 (2.9%)	0	0	0	2 (2.2%)
Thinking abnormal	3 (8.8%)	2 (3.2%)	2 (6.1%)	2 (2.9%)	0	5 (6.3%)	0	4 (4.4%)
Non-psychotic Sx	9 (26.5%)	9 (14.3%)	14 (42.4%)	24 (35.3%)	3 (17.6%)	15 (18.8%)	2 (20.0%)	36 (39.6%)
Agitation	1 (2.9%)	0	3 (9.1%)	3 (4.4%)	0	1 (1.3%)	0	6 (6.6%)
Anxiety	0	1 (1.6%)	0	0	0	1 (1.3%)	0	0
Apathy	0	1 (1.6%)	0	1 (1.5%)	0	1 (1.3%)	0	1 (1.1%)
Depersonalization	1 (2.9%)	0	0	0	0	1 (1.3%)	0	0
Depression	1 (2.9%)	0	1 (3.0%)	2 (2.9%)	0	1 (1.3%)	0	3 (3.3%)
Emotional lability	1 (2.9%)	3 (4.8%)	2 (6.1%)	4 (5.9%)	1 (5.9%)	3 (3.8%)	0	6 (6.6%)
Hostility	3 (8.8%)	3 (4.8%)	4 (12.1%)	8 (11.8%)	1 (5.9%)	5 (6.3%)	1 (10.0%)	11 (12.1%)
Hyperkinesia	1 (2.9%)	2 (3.2%)	2 (6.1%)	1 (1.5%)	1 (5.9%)	2 (2.5%)	0	3 (3.3%)
Nervousness	2 (5.9%)	0	3 (9.1%)	6 (8.8%)	0	2 (2.5%)	0	9 (9.9%)
Neurosis	1 (2.9%)	0	0	0	0	1 (1.3%)	0	0
Personality disorder	4 (11.8%)	3 (4.8%)	3 (9.1%)	5 (7.4%)	1 (5.9%)	6 (7.5%)	1 (10.0%)	7 (7.7%)
Psychotic Symptoms	0	1 (1.6%)	0	1 (1.5%)	0	1 (1.3%)	0	1 (1.1%)
Hallucinations	0	1 (1.6%)	0	0	0	1 (1.3%)	0	0
Psychosis	0	0	0	1 (1.6%)	0	0	0	1 (1.1%)
Sedation	3 (8.8%)	8 (12.7%)	9 (27.3%)	14 (20.6%)	2 (11.8%)	9 (11.3%)	4 (40.0%)	19 (20.9%)

[a] Table 16.9.2:2

Table 12:10 UCB Adverse Event Grouping and Preferred Term for Events Reported by ≥ 5% of Patients in the Levetiracetam Group (and More Common than on Placebo) (N159)

UCB Adverse	Mental Retardation[a]				Organic Mental Disorders[a]			
Event Grouping	Placebo		Levetiracetam		Placebo		Levetiracetam	
Term	Yes (N = 23)	No (N = 74)	Yes (N = 28)	No (N = 73)	Yes (N = 12)	No (N = 85)	Yes (N = 12)	No (N = 89)
Cog./Mental Acuity	1 (4.3%)	5 (6.8%)	0	6 (8.2%)	0	6 (7.1%)	1 (8.3%)	5 (5.6%)
Amnesia	0	2 (2.7%)	0	0	0	2 (2.4%)	0	0
Confusion	0	0	0	2 (2.7%)	0	0	0	2 (2.2%)
Thinking abnormal	1 (4.3%)	4 (5.4%)	0	4 (5.5%)	0	5 (5.9%)	1 (8.3%)	3 (3.4%)
Non-psychotic Sx	4 (17.4%)	14 (18.9%)	10 (35.7%)	28 (38.4%)	2 (16.7%)	16 (18.8%)	6 (50.0%)	32 (36.0%)
Agitation	1 (4.3%)	0	3 (10.7%)	3 (4.1%)	0	1 (1.2%)	1 (8.3%)	5 (5.6%)
Anxiety	0	1 (1.4%)	0	0	0	1 (1.2%)	0	0
Apathy	1 (4.3%)	0	1 (3.6%)	0	0	1 (1.2%)	0	1 (1.1%)
Depersonalization	0	1 (1.4%)	0	0	0	1 (1.2%)	0	0
Depression	0	1 (1.4%)	0	3 (4.1%)	0	1 (1.2%)	0	3 (3.4%)
Emotional lability	1 (4.3%)	3 (4.1%)	2 (7.1%)	4 (5.5%)	0	4 (4.7%)	0	6 (6.7%)
Hostility	0	6 (8.1%)	1 (3.6%)	11 (15.1%)	2 (16.7%)	4 (4.7%)	2 (16.7%)	10 (11.2%)
Hyperkinesia	1 (4.3%)	2 (2.7%)	1 (3.6%)	2 (2.7%)	0	3 (3.5%)	1 (8.3%)	8 (9.0%)
Nervousness	1 (4.3%)	1 (1.4%)	1 (3.6%)	8 (11.0%)	0	2 (2.4%)	1 (8.3%)	8 (9.3%)
Neurosis	0	1 (1.4%)	0	0	0	1 (1.2%)	0	0
Personality dis.	1 (4.3%)	6 (8.1%)	3 (10.7%)	5 (6.8%)	1 (8.3%)	6 (7.1%)	1 (8.3%)	7 (7.9%)
Psychotic Symptoms	1 (4.3%)	0	0	1 (1.4%)	0	1 (1.2%)	0	1 (1.1%)
Hallucinations	1 (4.3%)	0	0	0	0	1 (1.2%)	0	0
Psychosis	0	0	0	1 (1.4%)	0	0	0	1 (1.1%)
Sedation	4 (17.4%)	7 (9.5%)	6 (21.4%)	17 (23.3%)	0	11 (12.9%)	4 (33.3%)	19 (21.3%)

[a] Table 16.9.2:2

Explorations for drug-drug interactions

The sponsor assessed potential Drug-Drug interactions between levetiracetam and other antiepileptic drugs by evaluating serum concentrations of each AED. The sponsors did not find any evidence of drug interaction between levetiracetam and other AEDs.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Dosing regimen and administration are reproduced here from the proposed label. This proposed dosing mirrors the dosing used in Study N159. (b) (4)

Treatment should be initiated with a daily dose of 20 mg/kg given in 2 divided doses (10 mg/kg BID). The daily dose may be increased (b) (4) by increments of 20 mg/kg to (b) (4) recommended daily dose of 60 mg/kg (30 mg/kg BID). The maintenance dosage should be based on the patient's clinical response and tolerance. Patients with body weight ≤ 20 kg should be dosed with oral solution. Patients with body weight above 20 kg can be dosed with either tablets or oral solution. Table 9 below provides a guideline for tablet dosing based on weight. Only whole tablets should be administered. Keppra® is given orally with or without food.

Table 9. Keppra® Tablet Weight-Based Dosing Guide For Children

Patient Weight	Daily Dose		
	20 mg/kg/day (BID dosing)	40 mg/kg/day (BID dosing)	60 mg/kg/day (BID dosing)
20.1-40 kg	500 mg/day (1 x 250 mg tablet BID)	1000 mg/day (1 x 500 mg tablet BID)	1500 mg/day (1 x 750 mg tablet BID)
40.1 and above	1000 mg/day (1 x 500 mg tablet BID)	2000 mg/day (2 x 500 mg tablets BID)	3000 mg/day (2 x 750 mg tablets BID)

The following calculation should be used to determine the appropriate daily dose of oral solution for pediatric patients based on a daily dose of 20 mg/kg/day, 40 mg/kg/day or 60 mg/kg/day:

$$\text{Total daily dose (mL/day)} = \frac{\text{Daily dose (mg/kg/day) x patient weight (kg)}}{\text{100 mg/mL}}$$

8.2 Drug-Drug Interactions

There are few if any drug-drug interactions of concern. This is primary due to the fact that Keppra does not interact or influence the pharmacokinetics of other AEDs and vice versa. The Sponsor has performed separate drug interaction studies. These are summarized in Sponsor table 11.1 below.

Table 11:1 Key Conclusions in UCB-Sponsored Formal AED Drug Interaction Studies in Adults

Study No.	Study Design	Conclusions
RRLE91K2401	In vitro / ex vivo protein binding	No effect on phenytoin
	In vitro glucuronidation	No effect on valproate
N017	Single-blind, multiple dose study in patients	Increased plasma levels of phenytoin; no change in carbamazepine, phenobarbital, valproate
N0147	Levetiracetam added to stable phenytoin regimen	In conclusive (trough levels low)
N143	PK interaction (stable isotope) in patients on stable phenytoin monotherapy	No effect on phenytoin
N160	Effect of single levetiracetam dose on steady state valproate levels	No effect

The Sponsor attempted to identify cases in the pediatric database that could be indicative of an adverse drug interaction, or an event that necessitate a change in dose of the concomitant medication. Overall the Sponsor failed to find a signal related to therapeutic failure or drug-drug related interactions in children. In addition the Sponsor ran a formal interaction study in children (Study N01010) in children who were previously on carbamazepine or valproate and found no statistically significant differences in levetiracetam PK parameters. The Sponsor also examined the clearance of levetiracetam when patients were or were not receiving concomitant AEDs that were enzyme inducers and found that levetiracetam clearance is 22% higher in children concomitantly receiving an enzyme inducer. The corresponding T1/2 was also about 22% shorter in patients receiving AEDs that are enzyme inducers. The Sponsor did not feel that this warranted a dose adjustment "considering the lack of a clear dose plasma level relationship with efficacy or safety, the wide safety margin and the therapeutic approach of individual up titration."

8.3 Special Populations

This supplemental pediatric NDA is focused on the pediatric 4-18 age range inclusively.

8.4 Pediatrics

This review pertains to the pediatric population exclusively.

8.5 Advisory Committee Meeting

Not applicable to this submission

8.6 Literature Review

No separate literature review was performed for this review.

8.7 Postmarketing Risk Management Plan

The risk of suicide has not been fully explored and should be considered a high priority issue for postmarketing surveillance. In addition, behavioral and neuropsychiatric side effects being reported in one third of existing cases already, these should continue to be collected and examined for other pertinent related safety signals.

8.8 Other Relevant Materials

Not applicable.

9 OVERALL ASSESSMENT

9.1 Conclusions

Levetiracetam is an effective antiepileptic medication for the proposed indication of adjunctive use in partial seizures in pediatric patients ages 4-16.

Levetiracetam has a low side effect profile, with the majority of adverse effects being neuropsychiatric in origin. Care should be taken when prescribing this drug to patients with underlying neuropsychiatric/mood/behavioral disorders as it is unclear if the drug exacerbates or initiates neuropsychiatric effects. Rare effects such as risk of suicidal ideation or effects on growth have not yet been fully explored.

9.2 Recommendation on Regulatory Action

The pediatric supplemental NDA for Keppra® (levetiracetam) should be approved based on efficacy results There is substantial evidence from a single adequate and well controlled trial

that provided clinically relevant, statistically significant (p=0.0002) reductions over placebo in partial onset seizure frequency per week among children ages 4-16 during the treatment period. [26.8% (95% CI; 14.0%- 37.6%)]

The pediatric supplemental NDA for Keppra ® (levetiracetam) was essentially safe in this pediatric subpopulation, exhibiting adverse events similar to those seen in adults. The majority of adverse events were neuropsychiatric in origin. These effects may limit use in patients with predisposing neuropsychiatric conditions.

9.3 Recommendation on Postmarketing Actions

It is unclear from this submission if Keppra ® initiates or potentiates underlying neuropsychiatric/mood/behavioral disorders. For those patients at higher risk of underlying neuropsychiatric/mood/behavioral disorders, the potential for worsening of the underlying condition has not been fully explored given the small numbers of patients studied. The risk of suicidal ideation in this pediatric patients taking Keppra ® has not been fully explored. The validity of the exploratory endpoints such as various neuropsychiatric and cognitive scales has not been fully explored as of the date of this submission. The sponsor has not performed a formal analysis on the effects on growth. The sponsor may wish to address these issues in future postmarketing activities.

9.3.1 Risk Management Activity

Continued evaluation of neuropsychiatric side effects has been discussed in the past with the sponsor. A request from another medical officer (Norm Hershkowitz, MD) to the Office of Drug Safety was initiated to evaluate the potential for thrombocytopenia in adults; however there was no signal for thrombocytopenia in children in this supplemental NDA

9.3.2 Required Phase 4 Commitments

The Sponsor and the Division have discussed continued studies in children to validate several cognitive scales including the CHQ (Child Health Questionnaire). The sponsor has only partially responded to the pediatric written request and still needs to submit a separate submission to include evaluation of efficacy and safety of levetiracetam in children ages 1 month to 4 years.

An additional required Phase 4 commitment requested by the Division was a formal QT analysis to be performed in adult patients. This was requested to address concerns related to prolonged QTc intervals seen in several patients in the safety database.

9.3.3 Other Phase 4 Requests

The sponsor should consider an educational program to physicians in order to alert them to the possibility of worsening of preexisting neuropsychiatric conditions in patients taking

levetiracetam. Physicians should consider alternative medications or dose adjustments when necessary.

9.4 Labeling Review

See Section 10.2

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Reports – Study N159

10.1.1 Title

Study N159 was a 28 week double blind placebo controlled study to evaluate the efficacy and tolerability of levetiracetam as add on treatment in refractory pediatric patients with partial onset seizures.

10.1.2 Objective/outcome measures

The primary objective was to evaluate the efficacy and safety of levetiracetam doses up to 60mg/kg/day used as adjunctive therapy in the treatment of children (aged 4-16 years) with refractory partial onset seizures. The primary efficacy variable was the partial onset seizure frequency per week during the treatment period (titration and Evaluation) compared to the Baseline period.

Secondary objectives included:

1. Partial onset seizure frequency per week during titration and evaluation periods.
2. Total seizure frequency per week during treatment period (Titration and Evaluation) and during Titration and Evaluation periods.
3. Responder rate (during treatment period): The proportion of patients who have had a greater than or equal to 50% (ε50%) reduction in seizure frequency per week (responder).
4. Response to treatment (during treatment period). The percentage reduction from baseline in seizure frequency per week grouped into six categories as follows: <-25%, -25% to <25%, 25% to 50%, 50% to <75%, 75% to <100%, and 100%.
5. Change from baseline on number of seizure free days.
6. Change from baseline on duration of seizure free intervals.

7. Absolute and percent change from baseline seizure frequency per week during the treatment period and during the titration and evaluation period.

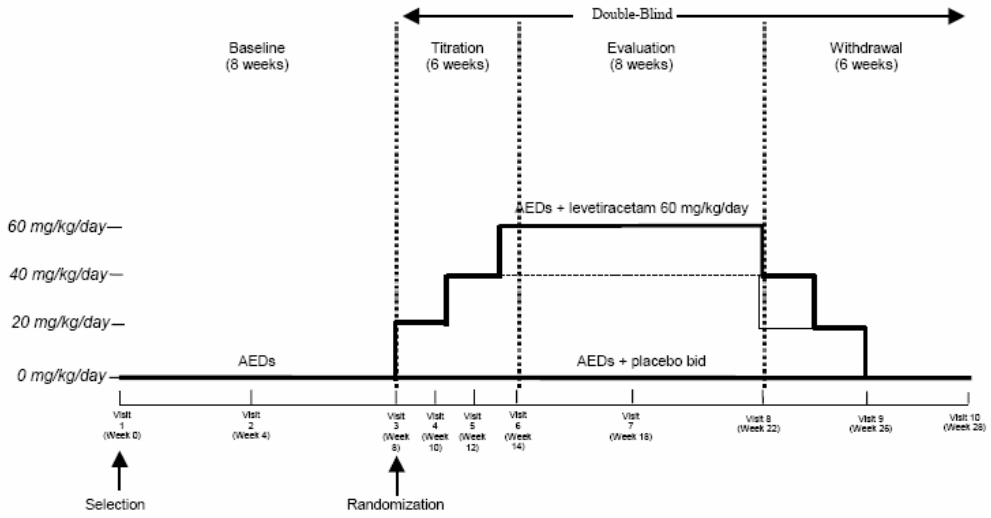
Exploratory variables included:

- Hague Seizure Severity Scale
- Children's Health Questionnaire
- Global Evaluation Scales
- Adolescent Quality of Life Epilepsy Impact Subscale.

10.1.3 Design/Dosage/Duration

The study design is reproduced below.

2.0 SCHEDULE OF STUDY EVENTS



Patients completing the study who wish to enroll in the open-label follow-up study (N157) do so at Visit 8 (Week 22). Patients wishing to terminate participation will enter a four-week withdrawal/down-titration period.

Patients terminating the study early enter the withdrawal period for down-titration of study medication.

Patients not enrolling in the open-label follow-up study (N157) must have a final visit two weeks after the last dose of study medication.

The study included a selection visit, an 8 week baseline period, a 6 week titration period (20mg/kg for 2 weeks followed by 40mg/kg/day for 2 weeks then 60mg/kg/day for the last 2 weeks), an 8 week evaluation period and a 6 week withdrawal period. This was changed to a 4 week titration period and a 10 week evaluation period to include the first two weeks at the goal dose of 60mg/kg/day.

10.1.4 Sample Size

The Sponsors originally planned for randomizing 194 patients into the study (the original protocol stated 120 patients from approximately 24 centers). 282 patients were screened for the study and 218 were randomized. (However 16 patients from one study site (#55) were excluded due to the unreliability of the data collected.) Two other patients discontinued the study before taking study medication. The total number of patients included in the ITT population was 198 (101 levetiracetam and 97 placebo).

10.1.5 Key Inclusion Criteria

- Patients 4-16 years old with a diagnosis of epilepsy with uncontrolled partial seizures (whether or not secondarily generalized)
- Current AED therapy inadequate with at least 4 partial onset seizures in the 4 weeks prior to screening as well as at least 4 partial seizures in each of the 4 week periods during baseline.
- Diagnosis of epilepsy at least 6 months prior to enrollment.
- EEG if none done before
- MRI if no CT or MRI had been performed since diagnosis

10.1.6 Key Exclusion Criteria

- Requiring concomitant administration of more than 2 AEDs
- Seizures too close to count accurately
- Patients with a treatable seizure disorder, epilepsy related to a progressive cerebral or degenerative neurologic disease or history of status epilepticus requiring hospitalization within 3 months prior to screening.
- Patients receiving CNS active drug, ketogenic diet or investigational drug or device within 30 days of enrollment.
- Patients using Felbamate for less than 18 months prior to enrollment.
- Patients with diagnosis of Lennox Gastaut syndrome or pseudo seizures
- Patients with acute or chronic illness that may interfere with study participation
- Allergy to pyrrolidone derivatives or a history of multiple drug allergies.

10.1.7 Concomitant Medications

Patients could take up to two concurrent AEDs. Any changes, additions or deletion were to be reported in the CRFs. Except for AEDs, the Sponsors asked that all other medications be avoided. Benzodiazepines were allowed if on a stable dosage. Benzodiazepines were allowed should seizures worsen to such an extent that medical intervention was required. However, those patients requiring a rescue medication during the Baseline period beyond one administration per week were discontinued.

10.1.8 Schedule

The study timetable is reproduced below.

Study Timetable

Study Period	Selection	Baseline		Titration			Evaluation		Withdrawal	
Week	0	4	8	10	12	14	18	22	26	28
Visit	1	2	3	4	5	6	7	8	9	10
Written Informed Consent	X									
Eligibility criteria check	X	X	X							
Demographics	X									
Medical History	X									
AED Medication History	X									
Seizure Count	X[a]	X	X	X	X	X	X	X	X	X
Physical & Neurological Exam	X	X	X	X		X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X	X	X
Laboratory assessments[c]	X	X[d]	X	X	X	X	X	X	X[d]	X
Hague Seizure Severity Scale	X		X					X		
Child Health Questionnaire			X					X		
Adolescent Quality of Life[e] Epilepsy-Impact Subscale			X					X		
Global Evaluation Scales[e]								X		
Drug Monitoring	X[f]	X[f]	X[f]	X	X	X	X	X	X	X
AE reporting		X	X	X	X	X	X	X	X	X
Concomitant Medication Reporting	X	X	X	X	X	X	X	X	X	X
ECG			X					X		
EEG[g]	X									
MRI[h]	X									
Returned tablet count				X	X	X	X	X	X	
Dispense study medication			X	X	X	X	X	X[i]		
Provide daily record card	X	X	X	X	X	X	X	X[i]	X	

[a] Historical seizure count at selection Baseline seizure quantification begins after selection.
[b] Including body weight, BP, and PR. Height mensured only at visit 1 (Weeks 0 – 4) and visit 8.
[c] Blood chemistry, hematology, urinalysis, and pregnancy test (if applicable).
[d] Laboratory draw only required for pregnancy test if patient is female of childbearing potential.
[e] QOLIE – AD – 48 (Epilepsy Impact Subscale) and Patient Global Evaluation to be completed by patients 8-16 years of age.
[f] Concomitant AEDs only
[g] Required during the Selection Period only if no previous routine electroencephalogram (EEG) has been performed with electroencephalographic features consistent with the diagnosis of partial onset seizures.
[h] Only for patients who (1) have not had a CT Scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or (2) have had changes on physical examination which would suggest a lesion has occurred since the last imaging procedure.
[i] Only for patients terminating the study and not entering the open-label study N157.

10.1.9 Analysis Plan

Per the Sponsor, a sample size of 60 in each group would have 80% power to detect a difference in log transformed seizure frequency per week means of 0.223 assuming the common standard deviation is 0.43 using a two group t-test with a 0.05 two sided significance level. A 0.223 difference in log transformed data corresponds to a reduction from placebo of 20% in seizure frequency per week. This sample size is based on the estimates of the treatment differences seen between L059 and placebo at the lower doses and the variability seen in prior adult patient studies. During a blinded review (the treatment groups will not be identified) UCB will assess the variability in the study. Should the variability observed be larger than what was seen in

previous studies then the sample might be increased to 68/patients per group assuming a common standard deviation of 0.46 in the above sample size calculation.

For the primary efficacy variable

Descriptive statistics and an ANCOVA model will be used to compare the treatment groups with respect to seizure frequency per week over the treatment period. The seizure frequency per week over the baseline period will be included in the model as covariate. This analysis will be applied on the $\log_e (x+1)$ transformed data. This has been selected as the most appropriate transformation (in terms of normalization of the data and stabilization of variances) to use in this and future studies based on investigation of seizure count data in some of the early supportive studies in adults. The model will include terms for treatment and baseline. Difference in treatment LSMEANS with 95% confidence intervals will be computed and expressed as a percentage reduction over placebo. Assumptions underlying these analyses will be checked. An analysis strategy will be specified in the statistical analysis plan should the chosen transformation $\log_e (x+1)$ not fulfill the assumptions underlying the analysis. The consistency of treatment effect across study centers will be investigated including terms for center and treatment by center in the model as well as summary statistics by center. Should the size of the centers not allow to meaningfully investigate the consistency of treatment effect across centers then they will be pooled according to geographical area. The centers to be pooled will be identified at the pre-analysis meeting prior to unblinding of the study.

For secondary efficacy variables

Several standard measures will be derived over the treatment period (titration and evaluation) or byperiod (titration / evaluation) from the seizure count information recorded on the CRF for the following seizure types [partial onset (type I) and total (types I + II + III)]. The following secondary efficacy variables will be computed:

- Partial onset seizure frequency per week (titration and evaluation periods).
- Total seizure frequency per week (Types I +II + III) (titration and evaluation periods).
- Responder rate (only during the treatment period): The proportion of patients who have had a greater than or equal to 50% reduction in seizure frequency per week.
- Response to treatment (over the treatment period): The percentage reduction from baseline in seizure frequency per week grouped into six categories as follows: < -25%, -25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100%, and 100%.
- Change from Baseline on duration of seizure free intervals and on number of seizure free days (over the treatment period).
- Absolute change from baseline in seizure frequency per week (over the treatment period and titration / evaluation periods):
- The seizure frequency per week during each period minus the seizure frequency per week during the baseline period.

- Percentage change from baseline in seizure frequency per week (over the treatment period and titration / evaluation periods).
- The seizure frequency per week during each period minus the seizure frequency per week during the baseline period, divided by the seizure frequency per week during the baseline period and multiplied by 100.

Exploratory variables include:

- Hague Seizure Severity Scale (HASS)
- Child Health Questionnaire (CHQ)
- Global Evaluation Scales (GES)
- Adolescent Quality of Life Epilepsy-Impact Subscale (QOLIE – AD – 48 – Impact Subscale)

Descriptive statistics will be carried out, on all secondary variables, by treatment groups.
The same inferential method as described for the primary efficacy variable will be used for the total seizure frequency per week over the treatment period.

A logistic regression model will be used to compare treatment groups with respect to responder rate over the treatment period. The model fitted will only include a term for treatment group. An odds ratio with a 95% confidence interval will also be computed. Assumptions underlying these analyses will be checked by graphical methods.
A Cochran-Mantel-Haenszel test on the ranks will be used to compare treatment groups on response to treatment over the treatment period.

10.1.10 Safety Monitoring

Safety monitoring included physical examination, neurologic examinations, EEG, MRI or CT (on screening), 12 lead ECG, AED plasma levels, and clinical lab assessments. Plasma drug levels, adverse events were also collected.

10.1.11 Amendments to the protocol.

Amendment 1- April 6, 2001

- The protocol was amended to increase the sample size from 120 randomized patients at 24 sites to 194 randomized patients at up to 45 study sites in US and Canada.

- The Sponsor's limited enrollment of patients ages 12-16 to a total of 58 patients out of the total 194 to be randomized.

- Definition of the per-protocol population was provided as, "a subset of the ITT consisting of those subjects who had no major protocol violations affecting the primary efficacy variable , as confirmed during a pre-analysis meeting prior to unblinding of the data.

Amendment 2- August 24, 2001

This amendment was made in response to Health Canada's Therapeutic Products Directorate requiring an extra visit at Week 24 (Visit 8.5) during the withdrawal period of the study, considered to be optional for the US sites.

10.2 Line-by-Line Labeling Review

Issues pertinent to the labeling sections for this sNDA are discussed below. The proposed labeling sections are reproduced from the label with discussion related to those sections. My edits are added via track changes.

(b) (4)

6 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Howard Chazin
6/21/05 02:37:11 PM
MEDICAL OFFICER

John Feeney
6/21/05 04:27:01 PM
MEDICAL OFFICER
See my cover memo.