SAFETY REVIEW: sNDA FOR LEVETIRACETAM USE IN PEDIATRIC PATIENTS WITH REFACTORY PARTIAL ONSET SEIZURES

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Established Name	Levetiracetam
(Proposed) Trade Name	Keppra®
Therapeutic Class	Anti-Epileptic Drug (AED)
Applicant	UCB, Inc.
Formulation	250 mg, 500 mg, 750 mg, 1000mg Oral solution (100 mg/mL)
Dosing Regimen	Variable
Indication	Partial Onset Seizures
Intended Population	Patients with Refractory Partial Onset Seizures

TABLE OF CONTENTS

1. INTRODUCTION 4

1.1 DOCUMENTS USED IN THIS REVIEW 4
1.1.1 Sponsor Documents 4
1.1.2 FDA Documents 4
1.2 REVIEW CONTENT 5
1.3 BACKGROUND 6
1.3.1 Regulatory History 6
1.3.2 Pharmacology/Pharmacokinetics 7
1.4 SUMMARY OF STUDIES WITHIN THE PEDIATRIC DEVELOPMENT PROGRAM 7

2. STUDIES IN PEDIATRIC PATIENTS: METHODS 10

2.1 PLACEBO-CONTROLLED STUDIES 10
2.1.1 Study N019009 10
2.1.2 Study N01103 11
2.2 OPEN-LABEL STUDIES 11
2.2.1 Study N01148 11
2.2.2 Study N0157 12
2.3 DOSING 12
2.4 PATIENT COHORTS 13
2.5 NEUROPSYCHOLOGICAL TESTING 13

3. VERIFICATION OF FDA RECOMMENDATIONS DURING STUDY DEVELOPMENT 14

4. RESULTS: DEMOGRAPHIC AND EXPOSURE DATA 15

4.1 BASELINE DEMOGRAPHIC CHARACTERISTICS 15
4.1.1 Month to < 4 Year 15
4.1.2 4 Years to 16 Years 16
4.2 EXPOSURE 17
4.2.1 Exposure by Patient 17
4.2.2 Exposure by Time 17
4.2.3 Exposure by Dose 19
4.2.4 Titration and Maintenance 21

5. RESULTS: SAFETY DATA 21

5.1 DEATHS 21
5.1.1 Methods for Capture and Analysis of Deaths 21
5.1.2 Narrative Summaries 22
5.1.3 Reviewer Analysis and Discussion 24
5.2 SERIOUS ADVERSE EVENTS 28
5.2.1 SAEs: 1 Month to 4 Years 29
5.2.2 SAEs: 4 Years to 16 Years 31
5.3 DISCONTINUATIONS 32
5.3.1 Discontinuations: 1 Month to <4 Years 32
5.3.2 Discontinuations: 4 Years to 16 Years 34
5.3.3 Discontinuations: Data from Placebo-Controlled Studies 36
5.4 COMMON ADVERSE EVENTS 37
5.4.1 Issues in the Capture and Calculation of Adverse Events 37
5.4.2 Common Adverse Events: 1 Month to < 4 Years 38
5.4.3 Common Adverse Events: 4 Years to 16 Years 40
5.5 PSYCHIATRIC ADVERSE EVENTS 43
5.5.1 Overview 43
5.5.2 Literature Reports 43

5.5.3 Psychiatric Adverse Events: 1 Month to < 4 Years *44*
5.5.4 Psychiatric Adverse Events: 4 Years to 16 Years *46*
5.5.5 Psychiatric Adverse Events: Placebo-Controlled Trials *46*
5.5.6 Psychiatric Adverse Events: Open-Label Data *47*
5.5.7 Cognitive and Neuropsychological Assessments *47*
5.5.8 Psychiatric Adverse Events: Reviewer Conclusions *49*
5.6 LABORATORY DATA 50
5.6.1 Laboratory Data Collection *50*
5.6.2 Laboratory Data Results *50*
5.7 VITAL SIGN DATA 51
5.7.1 1 Month to <4 Years *51*
5.7.2 4 Years to 16 Years *53*
5.8 ECGS 54

6. CONCLUSIONS AND RECOMMENDATIONS 56

7. ATTACHMENTS 59

7.1 ALL CLINICAL STUDIES IN PEDIATRIC PATIENTS TREATED WITH LEVETIRACETAM 59
7.2 LIVER FUNCTION TEST RESULTS WITHIN THE LEVETIRACETAM PEDIATRIC DEVELOPMENT PROGRAM FOR PATIENTS WITH FATAL OUTCOME ..... **ERROR! BOOKMARK NOT DEFINED.**

1. INTRODUCTION

1.1 Documents Used in this Review

1.1.1 Sponsor Documents

1. NDA 021-035 (Levetiracetam). Cover letter: Submission of Pediatric Study Reports – Pediatric Exclusivity Determination Requested. Prepared by UCB. Dated March 18, 2008.
2. NDA 021-035 (Levetiracetam). Summary of Clinical Safety. Prepared by UCB. Dated March 18, 2008.
3. NDA 021-035 (Levetiracetam). Clinical Overview. Prepared by UCB. Dated March 18, 2008.
4. NDA 021-035 (Levetiracetam). Integrated Summary of Safety (ISS). Dated March 18, 2008.
5. NDA 021-035 (Levetiracetam). Final Study Report: N01009. Prepared by UCB. Dated March 18, 2008.
6. NDA 021-035 (Levetiracetam). Final Study Report: N01103. Prepared by UCB. Dated March 18, 2008.
7. NDA 021-035 (Levetiracetam). Final Study Report: N01148. Prepared by UCB. Dated March 18, 2008.
8. NDA 021-035 (Levetiracetam). Final Study Report: N157. Prepared by UCB. Dated March 18, 2008.

1.1.2 FDA Documents

1. NDA 021-035 (Levetiracetam). End of Phase 2 Meeting. Dated July 20, 1999.
2. NDA 021-035 (Levetiracetam). Follow-up to End of Phase 2 Meeting. Dated May 25, 2000.
3. NDA 021-035 (Levetiracetam). UCB's Proposed Changes in Written Request for Pediatric Exclusivity. Dated October 24, 2001.
4. NDA 021-035 (Levetiracetam). Teleconference to Discuss Pediatric Exclusivity. Dated February 4, 2002.
5. NDA 021-035 (Levetiracetam). Teleconference to Discuss Studies N01009, N01103 and N01148. Dated January 15, 2004.
6. NDA 021-035 (Levetiracetam). UCB's Written Request Amendment. Dated March 19, 2004.
7. NDA 021-035 (Levetiracetam). FDA's Response to Written Request Amendment. Dated July 2, 2004.
8. NDA 021-035 (Levetiracetam). Teleconference to Discuss N01103 Design. Dated December 2, 2005.
9. NDA 021-035 (Levetiracetam). Pre-sNDA Meeting for pediatric (1 month<4 years) sNDA. Dated September 17, 2007.

10. NDA 021-035 (Levetiracetam). Waiver granted to submit the sNDA following the instructions contained in the withdrawn Memorandum 6. Dated November 19, 2007.

1.1.3 Publications from the Medical Literature

1. Kossoff EH, Bergey GK, Freeman JM and Vining E. Levetiracetam psychosis in children with epilepsy. Epilepsia 2002; 42(12):1611-1613.
2. Petra MC. Callenbach,Westendorp RG, Geerts AT et al. Mortality Risk in Children with Epilepsy: The Dutch Study of Epilepsy in Childhood. Pediatrics 2001;107;1259-1263.
3. White JR, Walczak TS, Lepik IE et al. Discontinuation of levetiracetam because of behavioral side-effects: a case-control study. Neurology 2003;61:1218–1221.
4. Youroukos S, Lazopoulou D, Michelakou D, Karagianni J. Acute psychosis associated with levetiracetam. Epileptic Disord. 2003 Jun;5(2):117-9.

1.2 Review Content

This safety review examines the supplemental New Drug Application (sNDA) submitted by sponsor UCB on the use of Keppra ® (levetiracetam) as an adjunctive treatment for partial onset refractory seizures in pediatric patients. UCB conducted studies in pediatric patients from 1 month to 16 years of age as part of a written request for pediatric exclusivity.

Significant findings from the safety review of the levetiracetam pediatric development program include the following:

- ***Deaths***: There were four deaths among a total of 168 levetiracetam-treated patients, all occurring in patients aged 1 Month to 4 Years. Two of the deaths involved fatal brain edema preceded by non-serious viral infections. A third death also fit this pattern (death following an apparently minor respiratory illness), but this patient had discontinued levetiracetam two months prior to death. The elevation of the death rate in the levetiracetam development program (24 per 1000 person-years) as compared with the background population of pediatric epilepsy patients (3.1 to 6.2 per 1000 person-years), as well as the similarity to Reye's syndrome in several deaths, are a source of concern.
- ***SAEs*:** In both age groups, the most commonly reported SAEs related to seizure activity. Depending on the exact comparison, the rate in levetiracetam-treated patients was sometimes equivalent and sometimes lower than in placebo-treated patients. Other SAEs occurring in levetiracetam-treated patients were neutropenia and abdominal pain, each occurring in one subject.
- ***Discontinuation due to AEs:*** Twelve subjects (7.1%) in the 1 Month to <4 Years cohort and 11 subjects (9.4%) in the 4 Years to 16 Years cohort permanently discontinued study medication due to adverse events. The AEs leading to discontinuation differed somewhat between the two age cohorts, with convulsion (5 subjects, 3%) and aggression (2 subjects, 1.2) as the most common AEs in the 1

Month to <4 Years cohort and abnormal behavior, somnolence, and rash (2 subjects, 1.7% each) as the most common in the 4 Years to 16 Years cohort.

- ***Common AEs*:** In the placebo-controlled Study N01009 (patient ages 1 month to <4 years), common AEs with the largest predominance in the levetiracetam-treated subjects were somnolence (1.8% placebo versus 13.3% levetiracetam) and irritability (0% placebo versus 12% levetiracetam). In the placebo-controlled Study NO1003 (patients ages 4 years to 16 years), common AEs with the largest predominance in levetiracetam-treated patients were nasal congestion (0% placebo vs. 9.4% levetiracetam), abnormal behavior (0% placebo vs. 7.8% levetiracetam), decreased appetite (2.9% placebo vs. 7.8% levetiracetam), anxiety and mood altered (each 0% vs. 6.3%), insomnia (2.9% placebo vs. 6.3% levetiracetam), and depression/irritability (each 0% vs. 4.7%).
- ***Psychiatric adverse events:*** The primary non-serious AE with levetiracetam treatment of pediatric patients was psychiatric adverse events. Behavioral and psychiatric adverse events were consistently more frequent in levetiracetam-treated patients than placebo patients within and across the placebo-controlled the trials. Literature studies have suggested that the risk of psychiatric adverse events is greater in patients with pre-existing behavioral symptoms, as well as when shorter titration periods are used. In younger patients (those aged 1 Month to < 4 Years), psychiatric adverse events were generally manifested as irritability and agitation, whereas hallucinations and delusions were recognizable in older and more articulate patients. One patient within the pediatric development program attempted suicide.
- ***QT Prolongation:*** In the 4 years to 16 years patients within placebo-controlled study NO1103, 6.8% of patients treated with levetiracetam had a PCS increase in the QT interval by the Fridercia correction method compared to 3.8% in the placebo group.

The principle limitations of the safety data within the levetiracetam pediatric development program were the brief placebo-controlled period for patients aged 1 Month to 4 Years (only six days) and not correcting for time exposures (using risk instead of rate) in the presentation of the data.

1.3 Background

1.3.1 Regulatory History

Levetiracetam (Keppra®) tablets were approved in 1999 (NDA 21- 035), and the oral solution was approved in 2003 (NDA 21-505). UCB reported that the original NDA contained 87 clinical studies composed of approximately 3439 subjects[1], only 29 of whom were children under age 16. In 2005, levetiracetam was approved for use as an adjunctive therapy in the treatment of partial onset seizure in adults and children over age four. The supplemental NDA (sNDA) which supported the use in children and adolescents aged 4 to 16 years included 239 subjects (124 males/115 females) in the pooled safety database (Clinical Overview, pg. 3).

[1] These figures are based on Safety Update to NDA 21-035.

1.3.2 Pharmacology/Pharmacokinetics

The mechanism by which levetiracetam exerts its antiepileptic effect is not fully understood. *In vitro* and *in vivo* recordings of the hippocampus have shown that levetiracetam inhibits burst firing, suggesting that levetiracetam may selectively prevent propagation of seizure activity[2].

UCB explained that the Tmax for levetiracetam occurs between 0.25 and 4 hours after administration. The sponsor asserted that this range was consistent across studies, dose-independent and was not changed following repeated administration (Clinical Overview, pg. 8).

Reviewer comment: *This is a fairly broad range for Tmax, suggesting that the Tmax in individual patients may be difficult to predict.*

The sponsor stated that there has been no specific study of protein binding with levetiracetam in the pediatric population. This was due to the fact that it was presumed to be low based on "negligible" rates in adult volunteers (Clinical Overview, pg. 8). When adjusted to body surface area, the clearance in infants and in children was similar to that reported in adults (Clinical Overview, pg. 8).

The sponsor reported that the plasma elimination half-life in children is 5 to 6 hours in the age ranges studied (<12 years). UCB predicted the plasma elimination half-life in children over aged 10 to be around seven hours (Clinical Overview, pg. 8).

1.4 Summary of Studies within the Pediatric Development Program

The current sNDA is based on the results from the following pediatric clinical studies (Sponsor sNDA cover letter, pg. 3):

1. **Study N01009[3] (N=116; 56 Levetiracetam and 60 placebo):** This 6-day, randomized, double-blind, placebo-controlled, multi-center study collected data on levetiracetam as an adjunctive treatment of partial seizures in children aged one month to less than four years. The study collected data on an inpatient population in 14 countries.
2. **Study N01103[4] (N=98; 65 Levetiracetam and 33 placebo):** This 12-week, randomized, double-blind, multi-center, placebo-controlled safety study evaluated the

[2] Keppra ® Prescribing Information/Package Insert

[3] Study N01009 is entitled titled "A Double-Blind, Randomized, Multicenter, Placebo-Controlled, In-Patient, Maximum 34 Day Study of Levetiracetam Oral Solution (20-50 mg/kg/day) as Adjunctive Treatment of Partial Onset Seizures in Pediatric Epileptic Subjects Ranging in Age from 1 month to less than 4 Years of Age."

[4] Study N01103 was entitled "A 19-Week, Randomized, Double-Blind, Multicenter, Placebo-Controlled Safety Study to Evaluate the Cognitive and Neuropsychological Effects of Levetiracetam 20-60 mg/kg/day, Divided in Twice Daily Dosing, as Adjunctive Treatment in Children 4 – 16 Years Old, Inclusive, with Refractory Partial Onset Seizures."

cognitive and neuropsychological effects of levetiracetam as an adjunctive treatment of partial seizures in children four to sixteen years old. It was conducted in the United States, Canada and South Africa in an outpatient population.

3. **Study N01148[5] (N=255):** This open-label study enrolled pediatric patients (aged 1 month to 16 years) following completion of studies NO1009 and NO1103. It was conducted in 85 sites from 16 countries.
4. **Study N157[6] (N=223):** Study 157 had been previously submitted to the FDA in the Pediatric Supplement in 2004. It was an open-label study conducted in the United States (38 sites), Canada (9 sites) and Mexico (3 sites). This trial consisted of four phases: a Screening Phase (Visit 1), a blinded Titration Phase lasting up to 6 weeks (for subjects in prior study N159), a Maintenance Phase lasting until market approval or completion of development of levetiracetam for the pediatric indication, and a Withdrawal Phase lasting up to 6 weeks.

Reviewer comments: *As also noted later in the review, for the patients aged one month to four years (Study N01009), the double-blind period consisted of a 6-day, inpatient observation period. Because there were only 56 patients randomized to levetiracetam, the amount of placebo-controlled data for the 1 Month to 4 Year patient cohort is small, and the number of patients limits the analysis that can be formed in age subgroups within the overall cohort.*

These studies are summarized in the following table.

FDA Table 1: Total Studies Providing Data to the Pediatric sNDA (Adapted from Tabular Listing of Studies within the Levetiracetam sNDA)

Study	Design	Subject Age Range	N (M/F)	Duration of Treatment	Dose
Placebo-Controlled Studies					
N01009 **(Safety and Efficacy)**	Randomized DB, parallel, Placebo-controlled	1 Month to <4 years	116 (57/59)	6 days (20 days if not continuing to N01148)	20 mg/kg/day to 50 mg/kg/day Oral solution
N01103 **(Safety, focus on psychiatric AEs)**	Randomized DB, parallel, Placebo-controlled	4 years to 16 years	98 (56/42)	12 Weeks	20 to 60 mg/kg/day Tablets or Oral solution
N159	Randomized,	4 years to	216	28 Weeks	20 to 40 to 60

[5] Study N01148 was titled "A Multi-Center, Open-Label, Long-Term, Follow-Up Study of the Safety and Efficacy of Levetiracetam in Children with Partial Onset Seizures."
[6] Study 157 was titled "A Multi-Center, Open-Label, Long-Term, Follow-Up Study of the Safety and Efficacy of Levetiracetam (ucb L059) in Children."

(Safety and Efficacy)	Double-Blind, Placebo-Controlled	16 years	(110/116)		mg/kg/day Tablets
Open-Label Studies					
N01148 **(Long-term Safety)**	Open label	1 Month to 16 Years	255 (139/116)	48 Weeks	20 to 80(c) mg/kg/day Tablets or Oral solution
N157 **(Long-Term Safety)**	Open-Label	1 month to 16 years	223 (118/105)	Up to 7.5 years	20 to 99 mg/kg/day Tablets or Oral solution

Reviewer comment: *The sponsor stated that in order to qualify for pediatric exclusivity, and in response to the FDA's written request, they conducted the following pediatric studies: NO1009, NO1103, N157, NO1148, N159, as well as pharmacokinetic studies NO1052, NO1010, and N151 (Clinical Overview, pg. 3). There were a total of approximately 53 subjects in the pharmacokinetic studies, and this review does not address these studies except to examine them for adverse event data.*

In the current sponsor submissions and review, the sponsor primarily relies on data from the two placebo-controlled studies NO1009 (patients ages 1 month to 4 Years) and NO1103 (4 Years to 16 Years) as well as two long-term, open-label studies NO1148(1 month to 16 Years) and N157 (1 month to 16 Years). However, the sponsor at times also includes data from Study 159, a study which was performed as part of the 2005 sNDA. In this review, I concentrate on the four primary studies, and include data from Study 159 as a secondary source.

The sponsor described the data collection in the pediatric development program as "two-tiered."

1. In the first tier, efficacy and safety data was collected in pediatric patients with a minimum age of four years (Study 159).

2. In the second tier, the pediatric development program was expanded to include:
   - Children down to the age of one month (Study N01009)
   - A safety study examining cognition / neuropsychiatric behavior in children 4 to 16 years of age (Study N01103)
   - A long-term safety study (Study N01148)

Reviewer comment: *The sponsor generally presents the safety data divided into the two age cohorts: 1 month to <4 years and 4 Years to 16 Years. The sponsor does not explain or provide any support for this age division other than the history of the development*

program as described immediately above. However, it seems appropriate that the wide age range should be subdivided in some manner, and I believe four years is a suitable cut-off point.

2. STUDIES IN PEDIATRIC PATIENTS: METHODS

2.1 Placebo-Controlled Studies

2.1.1 Study N019009

UCB described Study N01009 as a Phase III, double-blind, randomized, parallel-group, multicenter, placebo-controlled, add-on study. Pediatric subjects (aged 1 month to <4 years) diagnosed with refractory partial onset seizures, whether or not secondarily generalized, were included in the study. Inclusion and exclusion criteria include (Clinical Overview, pg. 13):

- Subjects were required to be on a stable regimen of at least one, but no more than two other AEDs for two weeks prior to entering the study.
- Subjects had to have experienced at least two partial onset seizures (i.e., seizures of focal onset) with or without secondary generalization during each 7-day period during the two weeks prior to entering the study.
- Subjects aged 1 month to <6 months had to have at least 2 partial onset seizures (i.e., seizures with focal paroxysmal discharges of 10 or more seconds), whether or not secondarily generalized, during the 48-hour video-EEG performed prior to randomization. These seizures did not need to be accompanied by a corresponding clinical event.
- Subjects aged 6 months to <4 years had to have at least 2 partial onset seizures (i.e., seizures with focal paroxysmal discharges of 10 or more seconds), whether or not secondarily generalized, during the 48-hour video-EEG performed prior to randomization. These seizures had to be accompanied by a corresponding clinical event as noted on video or as reported by a qualified observer (Clinical Overview, pg. 13).

A total of 116 subjects were randomized in a 1:1 levetiracetam/placebo ratio. Study medication was administered as an oral solution. Subjects aged 1 month to <6 months randomized to levetiracetam titrated from 20 mg/kg/day to a maintenance dose of 40 mg/kg/day and subjects aged 6 months to <4 years randomized to levetiracetam titrated from 25 mg/kg/day to a maintenance dose of 50 mg/kg/day (Clinical Overview, pg. 13).

The study consisted of up to a 9-day Selection Period, a 5-day in-patient Evaluation Period (1 day of up-titration followed by 4 days of full dose), a 14-day Down-Titration Period, and a 4 ± 1-day Post-Treatment Period. Subjects had the option to enroll in N01148, an open-label extension study, after completing the Evaluation Period where subjects were converted to levetiracetam open-label treatment "in a manner that maintained the blind of the previous double-blind study." Subjects who failed the screening for this study or prematurely discontinued the study during the Evaluation Period could also enroll in N01148. These patients were referred to by the sponsor as

"Screen Failure/Direct Enrolment"[SF/DE] patient). Only subjects not enrolling in N01148 were to complete the Down-Titration and Post-Treatment Periods (Clinical Overview, pg. 13).

A total of 175 subjects were screened, 116 subjects were randomized, and 111 subjects completed the study and entered the long-term follow-up study. Of the randomized subjects, 56 received placebo and 60 received levetiracetam. Most subjects completed the 5-day double-blind treatment. Three subjects in the placebo group and two subjects in the levetiracetam group discontinued the study (Clinical Overview, pg. 14).

2.1.2 Study N01103

UCB described Study N01103 as a "Phase II", 19-week, randomized, double-blind, multicenter, placebo-controlled safety study. The primary objective was to characterize potential cognitive and neuropsychological effects of levetiracetam (20 to 60 mg/kg/day) as adjunctive treatment in children aged 4 to 16 years with partial onset seizures. The study consisted of a Baseline Period (up to 7 days), a 12-week Evaluation Period, and a 6-week Withdrawal Period for subjects not enrolling in an open-label extension. The sponsor noted that the Evaluation Period included 4 weeks of up-titration followed by 8 weeks of maintenance treatment (Clinical Overview, pg. 16).

The randomization ratio was 2:1 levetiracetam/placebo, and the final randomized sample contained 65 levetiracetam subjects and 34 placebo subjects. The sponsor stated that 78% of levetiracetam-treated subjects and 85% of placebo-treated subjects completed the study (Clinical Overview, pg. 16).

2.2 Open-Label Studies

2.2.1 Study N01148

UCB described Study N01148 as a Phase III, multicenter, open-label, long-term follow-up study of the safety and efficacy of levetiracetam in children with partial onset seizures. The primary objective of this study is to obtain long-term descriptive safety and efficacy data in pediatric epileptic subjects with partial onset seizures receiving long-term treatment with LEV at individualized doses of up to 80 mg/kg/day. Subjects may enroll in this study after receiving treatment in N01009 or N01103 (termed SF/DE[7] patients). Additionally subjects may enter N01148 after having screen-failed either N01009 or N01103. Subjects 1 month to 16 years may also directly enroll into N01148. This study consists of a Titration Period of up to 8 weeks followed by maintenance treatment for up to a total of 48 weeks of levetiracetam exposure (Clinical Overview, pg. 18).

The sponsor stated that 255 subjects were enrolled in Study NO1148 and treated: 152 subjects in the 1 month to <4 years group and 103 subjects in the 4 year to 16 year group. Of the 255 subjects enrolled and treated, 191 (74.9%) continued from a prior

[7] SF/DE = Screen Failure Direct Enrollment

levetiracetam study (N01009 or N01103). Thirty-four subjects (13.3%) enrolled in this study after failing to qualify for N01009 or N01103 (screen failures), and 30 subjects (11.8%) were directly enrolled into this study without being screened for N01009 or N01103. Of the 191 subjects who continued from N01009 or N01103, 83 previously received placebo (PBO/LEV) and 108 previously received levetiracetam (LEV/LEV). As of the clinical cut-off of September 18, 2007, all subjects had either completed Visit 5 (Week 24) or discontinued early from the study. At the clinical cut-off, 213 subjects (83.5%) had completed Visit 5 (Week 24)(Clinical Overview, pg. 18).

The sponsor noted that the study is currently ongoing and data are available as of the submission cut-off date, September 18, 2007 (Clinical Overview, pg. 18).

2.2.2 Study N0157

UCB described Study N157 as a Phase III, open-label, multicenter, non-comparative, non-randomized, long-term follow-up study in children with epilepsy who had completed a previous pediatric levetiracetam study (N151, N01010, N159, or N01052). This study consisted of 4 phases: a Screening Visit, a blinded Titration Phase lasting up to 6 weeks (for subjects from N159), a Maintenance Phase lasting until market approval or completion of development of levetiracetam for the pediatric indication, and a Withdrawal Phase lasting up to 6 weeks. A total of 238 subjects were enrolled and treated. (Clinical Overview, pg. 19).

UCB noted that all 15 subjects from one site were excluded from the subsequent summaries and analyses due to data irregularities. This exclusion resulted in a total of 223 subjects in the analysis. The mean ± SD duration of exposure was 781.9 ± 582.3 days (approximately two years) (Q1, 286; Q3, 1059) days. The median exposure was 735.0 days with a range of 1 to 2694 days (approximately 7.5 years)(Clinical Overview, pg. 18).

2.3 Dosing

The sponsor summarized the levetiracetam dosing in the various studies in the table below.

FDA Table 2: Overview of "Planned" Levetiracetam Dosing (mg/kg/day) by Study (Adapted from Sponsor Table 2.7.4.4, Summary of Clinical Safety, pg. 10)

	N01009 (N=60)	N01103 (N=64)	N01148 (N=255)	N157 (N=233)
Age range	1 month to <4 years	4 to 16 years	1 month to 16 years	1 month to 16 years
Dose range	Up to 40 or 50	Up to 60	Up to 80[(a)]	Up to 99[(a)]
Up-Titration	20 or 25 x 1 d	20 × 2 wks 40 × 2 wks	Varied	Varied
Stable Dose	Up to 40 or 50 x 4 d	Up to 60 × 8 wks	NA	NA
Down-titration	20 or 25 x 2 wks	40 × 2 wks 20 × 2 wks	10 to 20 decrements every 2 wks	10 to 20 decrements every 2 wks

d=days; LEV=levetiracetam; NA=not applicable; wks=weeks
[(a)] Doses >80 mg/kg/day to be discussed with Sponsor before implementation.

2.4 Patient Cohorts

The sponsor typically presented pooled safety data divided into two age cohorts: one for patients aged 1 Month to 4 Years and one for patient 4 years to 16 years. The studies which composed these two safety cohorts are summarized below (Clinical Overview, pg. 20):

1. **1 Month to <4 Years Safety Cohort (N=168)**
   The 1 month to <4 year safety pool consisted of the combined data for subjects aged 1 month to <4 years from Studies N01009, N01148, N01052, and N157.

   Reviewer comment: *The sponsor notes a number of times in their submissions that the patients in the 1 Month to 4 Year cohort had more severe baseline medical conditions, for both epilepsy and other concomitant conditions, than those in the 4 to 16 years cohort.*

2. **4 Years to 16 Years Safety Cohort (N=117)**
   The 4 years to 16 years safety pool consisted of the combined data for subjects aged 4 years to 16 years from Studies N01103 and N01148. Subjects between the ages of 4 and 16 years exposed to levetiracetam in one or both of these studies were included in this cohort.

Reviewer comment *The cohorts above were apparently based on the age cut-offs of studies during the development program, in which pediatric data was initially collected only down to age four, with data for ages 1 month to age 4 collected later (Clinical Overview, pg 3). As noted previously, the use of age 4 as the divider between age groups seems appropriate.*

2.5 Neuropsychological Testing

To better evaluate neuropsychiatric adverse events identified early in the levetiracetam pediatric development program, the sponsor incorporated neuropsychological testing into later trials. The sponsor stated the subjects from studies with testing were assembled into three safety pools based on cognitive and neuropsychological safety endpoints. These three data testing pools are described in the following (Clinical Overview, pg. 21):

1. ***BSID-II***[8] (1 Month to <4 Years) Safety Pool: All subjects who provided BSID-II data in either N01009 or N01148 were included in this safety pool. This pool contains 53 subjects treated with levetiracetam.

2. ***Leiter-R***[9] ***and CBCL***[10] (4 Years to 16 Years) Safety Pool: This pool was composed of all subjects who provided Leiter-R or CBCL data in either N01103 or N01148. Not all subjects had data for both the Leiter-R and CBCL assessments (e.g., CBCL assessments were not done for a majority of the 4- and 5-year-old subjects). This pool contains 121 subjects treated with levetiracetam.

3. ***CHQ-PF50***[11] (4 Years to 16 Years) Double-Blind, Placebo-Controlled Safety Pool: All subjects who provided CHQ-PF50 data in either N01103 or N159 were included in this pooled sample. This pool contains 118 subjects treated with placebo and 149 subjects treated with levetiracetam.

   Reviewer comment: *I briefly researched the number of neuropsychological tests available to determine whether the tests above considered well validated. These tests appear to be frequently used in the assessment of neuro-cognitive dysfunction.*

3. VERIFICATION OF FDA RECOMMENDATIONS DURING STUDY DEVELOPMENT

I reviewed the FDA's correspondence (listed in Section 1.1.2 of this review) with UCB during the development of the pediatric studies to ensure that the FDA's requests were addressed. Aside from requests for resubmissions of modified protocols[12], the primary FDA request was to require submitted reports to include more specific information on racial and ethnic minorities. The sponsor collected the requested data, although it remained unavailable for some patients in studies early in the development program (Summary of Clinical Safety, pg. 31).

[8] BSID= Bayley Scale of Infant Development II
[9] Leiter-R= Leiter International Performance Scale-Revised
[10] CBCL=Achenbach Child Behavior Checklist
[11] CHQPF-50 = Child Health Questionnaire – Parent Form 50 Item
[12] I do not include FDA requests regarding pharmacokinetic studies.

4. RESULTS: DEMOGRAPHIC AND EXPOSURE DATA

4.1 Baseline Demographic Characteristics

4.1.1 Month to < 4 Year

The sponsor summarized the baseline characteristics of the patients in the 1 Month to < 4 Year cohort in the following table.

FDA Table 3: Summary of Demographic and Other Baseline Characteristics in the 1 Month to <4 Year Cohort (Adapted from Sponsor Table 2.7.4.13, Summary of Clinical Safety, pg. 25)

Parameter	Original Treatment Assignment N01009 + N01148			N01052 + N157 (N=14)	Overall (N=168)
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
Age (months)					
N	53	60	41	14	168
Mean (SD)	23.15 (11.90)	23.40 (13.43)	23.02 (12.27)	19.22 (13.81)	22.88 (12.65)
Median	22.00	21.00	21.00	16.74	21.00
Min-Max	2.0-46.0	1.0-47.0	2.0-47.0	2.3-46.2	1.0-47.0
1 month to <6 months, n (%)	4 (7.5)	4 (6.7)	2 (4.9)	3 (21.4)	13 (7.7)
6 months to <12 months, n (%)	6 (11.3)	8 (13.3)	6 (14.6)	2 (14.3)	22 (13.1)
12 months to <24 months, n (%)	18 (34.0)	20 (33.3)	15 (36.6)	5 (35.7)	58 (34.5)
24 months to <48 months, n (%)	25 (47.2)	28 (46.7)	18 (43.9)	4 (28.6)	75 (44.6)
Gender, n (%)					
Male	26 (49.1)	30 (50.0)	22 (53.7)	7 (50.0)	85 (50.6)
Female	27 (50.9)	30 (50.0)	19 (46.3)	7 (50.0)	83 (49.4)
Race, n (%)					
Caucasian	37 (69.8)	54 (90.0)	28 (68.3)	10 (71.4)	129 (76.8)
American Indian/Alaskan Native	2 (3.8)	4 (6.7)	0	0	6 (3.6)
Other/Mixed Race	8 (15.1)	2 (3.3)	3 (7.3)	0	13 (7.7)
Black	5 (9.4)	0	10 (24.4)	4 (28.6)	19 (11.3)
Asian	1 (1.9)	0	0	0	1 (0.6)
Ethnicity, n (%)					
Hispanic or Latino	16 (30.2)	22 (36.7)	6 (14.6)	NA[a]	44 (26.2)
Not Hispanic or Latino	37 (69.8)	38 (63.3)	35 (85.4)	NA[a]	110 (65.5)

UCB noted that the different treatment groups were similar with regard to age, gender, race and BMI. The subjects were predominantly Caucasian (76.8%). The majority of subjects were taking two concomitant AEDs at baseline, with all subjects entering open-label study NO1148 treated with at least one concomitant AED at entry (Summary of Clinical Safety, pg. 25).

With the exception of a difference in the number of concomitant anti-epileptic drugs (AEDs) used by the SF/DE subjects (51.2% used 1 AED) compared with the placebo and

levetiracetam subjects (18.9% and 25.0% used 1 AED), the sponsor maintained that there were no notable differences in demographic or other baseline characteristics between groups (Summary of Clinical Safety, pg. 25).

The sponsor described the seizure history and baseline frequency of each groups extensively. For the 1 month to <4 Year group, UCB reported that the mean age of onset of first seizure was 5.88 months and the mean duration of epilepsy at time of entry into their first levetiracetam study was 17.32 months. The sponsor noted that the vast majority of subjects (97.0%) were diagnosed with partial (Type I) seizures, although 16.7% and 6.0% of subjects had experienced generalized (Type II) or unclassified (Type III), respectively, in the past (Summary of Clinical Safety, pg. 25).

4.1.2 4 Years to 16 Years

The sponsor summarized the baseline characteristics of the patients in the 4 Year to 16 Year cohort in the following table.

FDA Table 4: Summary of Baseline other Other Demographic Characteristics in the 4 Year to 16 Year Cohort (Adapted from Sponsor Table 2.7.4.14, Summary of Clinical Safety, pg. 26)

Parameter	Original Treatment Assignment N01103 + N01148			Overall (N=117)
	PBO (N=30)	LEV (N=64)	SF/DE (N=23)	
Age (years)				
N	30	64	23	117
Mean (SD)	10.28 (3.82)	10.58 (3.49)	9.13 (3.58)	10.22 (3.61)
Median	9.82	10.49	9.25	10.04
Min-Max	4.1-16.4	4.8-16.7	4.4-16.4	4.1-16.7
4 years to <8 years, n (%)	9 (30.0)	18 (28.1)	10 (43.5)	37 (31.6)
8 years to <12 years, n (%)	9 (30.0)	21 (32.8)	7 (30.4)	37 (31.6)
12 years to 16 years, n (%)	12 (40.0)	25 (39.1)	6 (26.1)	43 (36.8)
Gender, n (%)				
Male	17 (56.7)	39 (60.9)	14 (60.9)	70 (59.8)
Female	13 (43.3)	25 (39.1)	9 (39.1)	47 (40.2)
Childbearing potential	3 (23.1)	7 (28.0)	2 (22.2)	12 (25.5)
Race, n (%)				
Caucasian	15 (50.0)	40 (62.5)	3 (13.0)	58 (49.6)
Other/Mixed Race	5 (16.7)	6 (9.4)	0	11 (9.4)
Black	7 (23.3)	15 (23.4)	0	22 (18.8)
Asian	3 (10.0)	3 (4.7)	20 (87.0)	26 (22.2)
Ethnicity, n (%)				
Hispanic or Latino	3 (10.0)	6 (9.4)	1 (4.3)	10 (8.5)
Not Hispanic or Latino	27 (90.0)	58 (90.6)	22 (95.7)	107 (91.5)

UCB noted that the majority of patients were Caucasian (49.6%). The sponsor commented that age, gender, and race distribution were generally similar across groups by original treatment assignment, with the exception of race in SF/DE subjects. UCB noted that the majority of SF/DE subjects were from India. UCB further commented

demographics and other baseline characteristics were generally similar across groups by original treatment assignment; however, SF/DE subjects were mostly Asian, slightly younger, weighed less, had a lower BMI, and had a lower IQ compared with the other two groups (Summary of Clinical Safety, pg. 27).

Reviewer comment: *It is unclear why there should be a predominance of Asian/Indian subjects in the "Screen Failure/Direct Enrollment" (SF/DE) group.*

4.2 Exposure

4.2.1 Exposure by Patient

The sponsor reported that in the total pooled safety database there were a total of 285 unique new pediatric patients who were treated with levetiracetam (Summary of Clinical Safety, pg. 16).

FDA Table 5. Overview of Enrollment in the Clinical Studies composing the Pooled Safety Data (Adapted from Sponsor Table 2.7.4.2, Summary of Clinical Safety, pg. 9)

Study	Total	PBO	LEV	Unique exposures to LEV
	Number of Subjects			
1 Month to <4 Years Pool[a]	168	NA	168	168
4 Years to 16 Years Pool[b]	117	NA	117	117
N01009	116	56	60	60
N01103	99[c]	34	64	64
N01148	255	NA	255	147
N157 (N01052)	223	NA	223	14[d]

LEV= levetiracitam; NA=not applicable; PBO=placebo
Note: There were 285 unique subject exposures. Exposure in the individual studies is a subset of exposure in the pooled databases. A total of 255 subjects received at least 1 dose of LEV in N01148; of these, 117 subjects had not taken LEV in a prior study. A total of 223 subjects received at least 1 dose of LEV in N157; of these, 79 subjects had not taken LEV in a prior study.
[a] Includes subjects aged 1 month to <4 years from N01009, N01148, N01052, and N157 who were exposed to LEV at least once in 1 or more of these studies.
[b] Includes subjects aged 4 years to 16 years from N01103 and N01148 who were exposed to LEV at least once in either of these studies.
[c] One subject in the LEV group discontinued the study before receiving study medication and was lost to follow-up.
[d] Only 14 subjects coming from N01052 and their follow-up data in N157were included in the pooled safety database in the 1 Month to <4 Years Pool. There were a total of 79 unique new exposures to LEV in N157.
Source: ISS Table 16.1.1:1, Table 16.1.1:2, Table 16.1.1:3, and Table 16.1.1:4; N011048 Table 14.1.1:1; N157 Table 14.1.1:1

4.2.2 Exposure by Time

4.2.1.1 Time: One Month to Four Year Cohort

In the 1 Month to <4 Years cohort, UCB reported that the overall subject-years of exposure was 125.2 years, with a mean duration of exposure of 272.2 days (Summary of Clinical Safety, pg. 16). Subjects in Studies N01052 and N157 had a longer duration of exposure (534.4 days) than subjects whose original treatment assignment was in N01009 + N01148. The sponsor asserted that the duration of exposure was generally similar among demographic subgroup regardless of original treatment assignment (Summary of Clinical Safety, pg. 12).

UCB stated that the majority of subjects (69.0%) had a duration of exposure of 24 to <60 weeks; overall, the highest percentage of subjects (36.3%) had a duration of exposure of 48 to <60 weeks. The sponsor explained that this was not an unexpected finding because Study N01148 was a 48-week study (Summary of Clinical Safety, pg. 13).

FDA Table 6: Summary of Cumulative Levetiracetam Exposure by Time (Adapted from Sponsor Table 2.7.4.5, Summary of Clinical Safety, pg. 11)

Duration of Exposure	Original Treatment Assignment			N01052 + N157 (N=14)	Overall (N=168)
	N01009 + N01148				
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
	n (%)				
Any exposure	53	60	41	14	168
≥2 weeks	53 (100.0)	58 (96.7)	40 (97.6)	13 (92.9)	164 (97.6)
≥4 weeks	53 (100.0)	57 (95.0)	39 (95.1)	12 (85.7)	161 (95.8)
≥6 weeks	53 (100.0)	55 (91.7)	38 (92.7)	12 (85.7)	158 (94.0)
≥8 weeks	50 (94.3)	51 (85.0)	37 (90.2)	12 (85.7)	150 (89.3)
≥12 weeks	47 (88.7)	50 (83.3)	37 (90.2)	12 (85.7)	146 (86.9)
≥16 weeks	43 (81.1)	48 (80.0)	34 (82.9)	11 (78.6)	136 (81.0)
≥20 weeks	41 (77.4)	46 (76.7)	33 (80.5)	10 (71.4)	130 (77.4)
≥24 weeks	40 (75.5)	45 (75.0)	30 (73.2)	10 (71.4)	125 (74.4)
≥36 weeks	32 (60.4)	41 (68.3)	20 (48.8)	9 (64.3)	102 (60.7)
≥48 weeks	17 (32.1)	30 (50.0)	14 (34.1)	9 (64.3)	70 (41.7)
≥60 weeks	0	1 (1.7)	0	8 (57.1)	9 (5.4)
≥72 weeks	0	0	0	8 (57.1)	8 (4.8)
≥96 weeks	0	0	0	5 (35.7)	5 (3.0)
≥120 weeks	0	0	0	4 (28.6)	4 (2.4)
≥144 weeks	0	0	0	4 (28.6)	4 (2.4)

LEV=levetiracetam; PBO=placebo; SF/DE=screen failure/directly enrolled
Source: ISS Table 16.3.1:3

3.2.1.2 Time: Four Year to Sixteen Year Cohort

The sponsor reported that the mean duration of exposure was 285 days for levetiracetam subjects, 282 days for placebo subjects and 146 days for SF/DE subjects. UCB added that the mean duration of exposure was similar between genders, but differed somewhat by age subgroup (237 days for patients 4 to 8 years versus 263 days for patients 8 to 16 years) and race (181 days for Asian subjects versus up to 290 days for others subjects of other races)(Summary of Clinical Safety, pg. 14).

The sponsor stated that the majority of subjects (73.5%) had an exposure of 24 weeks or more. UCB explained that the differences at ≥60 weeks between cumulative levetiracetam exposure for subjects originally treated with placebo (0%) and levetiracetam (26.6%) in N01103 is due to the fact that subjects in the levetiracetam group received an additional 3 months of levetiracetam exposure in N01103 (Summary of Clinical Safety, pg. 16).

The table below shows the cumulative exposure to levetiracetam by time for the 4 to 16 year old age cohort.

FDA Table 7: Summary of Cumulative LEV Exposure by Time in the 4 to 16 Year Cohort (Adapted from Sponsor Table 2.7.4.7, Summary of Clinical Safety, pg. 13)

Duration of Exposure	Original Treatment Assignment			Overall (N=117)
	N01103 + N01148			
	PBO (N=30)	LEV (N=64)	SF/DE (N=23)	
	n (%)			
Any exposure	29	64	23	116
≥2 weeks	29 (96.7)	62 (96.9)	22 (95.7)	113 (96.6)
≥4 weeks	29 (96.7)	60 (93.8)	22 (95.7)	111 (94.9)
≥6 weeks	28 (93.3)	57 (89.1)	21 (91.3)	106 (90.6)
≥8 weeks	28 (93.3)	55 (85.9)	20 (87.0)	103 (88.0)
≥12 weeks	28 (93.3)	53 (82.8)	19 (82.6)	100 (85.5)
≥16 weeks	28 (93.3)	50 (78.1)	18 (78.3)	96 (82.1)
≥20 weeks	26 (86.7)	47 (73.4)	18 (78.3)	91 (77.8)
≥24 weeks	24 (80.0)	47 (73.4)	15 (65.2)	86 (73.5)
≥36 weeks	21 (70.0)	44 (68.8)	0	65 (55.6)
≥48 weeks	15 (50.0)	37 (57.8)	0	52 (44.4)
≥60 weeks	0	17 (26.6)	0	17 (14.5)

LEV=levetiracetam; PBO=placebo; SF/DE=screen failure/directly enrolled
Source: ISS Table 16.3.1.4

4.2.3 Exposure by Dose

4.2.3.1 Dose: One Month to Four Year Cohort

For the 1 Month to <4 Years Pool, the sponsor stated that the mean levetiracetam daily dose by body weight was 49.75 mg/kg/day. UCB asserted that the mean levetiracetam daily dose by body weight was similar between the two age cohorts, despite the fact that subjects 1 month to <6 months were assigned to a lower dose (up to 40 mg/kg/day) in N01009. In addition, the sponsor noted that mean levetiracetam daily dose by body weight was generally similar among demographic subgroups regardless of original treatment assignment (Summary of Clinical Safety, pg. 16).

UCB stated that the highest percentage of subjects (48.2%) had a levetiracetam mean daily dose of 50 to <80 mg/kg/day, followed by 29 to <50 mg/kg/day (38.1%). The

sponsor stated that the majority of subjects were escalated to target doses of up to 50 mg/kg/day and "appeared to remain on those doses" (Summary of Clinical Safety, pg. 13).

Reviewer comment: *It is somewhat disconcerting for the sponsor to state that patients "appeared to" remain on reported doses. UCB may have made this statement out of consideration that doses in the studies were not fixed (although the sponsor should have been carefully tracking dose changes) or that there may have been incomplete compliance with drug administration (although the placebo-controlled trials in the 1 Month to <4 Year cohort were performed in hospitalized patients.)*

FDA Table 8: Duration of Exposure by Subject stratified by Mean Daily Dose in the 1 Month to 4 years Cohort (Adapted from Sponsor Table 2.7.4.6, Clinical Summary of Safety, pg. 12)

Duration of Exposure (weeks)	LEV Mean Daily Dose (mg/kg/day) (N=168) n (%)				
	0 to <29	29 to <50	50 to <80	≥80	Total
>0 to <2	3 (1.8)	1 (0.6)	0	0	4 (2.4)
2 to <4	3 (1.8)	0	0	0	3 (1.8)
4 to <6	0	3 (1.8)	0	0	3 (1.8)
6 to <8	1 (0.6)	5 (3.0)	2 (1.2)	0	8 (4.8)
8 to <10	0	1 (0.6)	1 (0.6)	0	2 (1.2)
10 to <12	0	1 (0.6)	1 (0.6)	0	2 (1.2)
12 to <16	0	5 (3.0)	5 (3.0)	0	10 (6.0)
16 to <20	2 (1.2)	2 (1.2)	2 (1.2)	0	6 (3.6)
20 to <24	1 (0.6)	1 (0.6)	3 (1.8)	0	5 (3.0)
24 to <36	2 (1.2)	9 (5.4)	12 (7.1)	0	23 (13.7)
36 to <48	2 (1.2)	8 (4.8)	19 (11.3)	3 (1.8)	32 (19.0)
48 to <60	5 (3.0)	23 (13.7)	32 (19.0)	1 (0.6)	61 (36.3)
60 to <72	0	0	1 (0.6)	0	1 (0.6)
72 to <96	0	3 (1.8)	0	0	3 (1.8)
96 to <120	0	1 (0.6)	0	0	1 (0.6)
≥144	0	1 (0.6)	3 (1.8)	0	4 (2.4)

LEV=levetiracetam
Source: ISS Table 16.3.1:9

4.2.3.2 Dose: Four Year to Sixteen Year Cohort

UCB reported that overall the mean levetiracetam daily dose by body weight for the 4 to 16 year cohort was 45.00 mg/kg/day. The sponsor asserted that the mean levetiracetam daily dose by body weight was generally similar among demographic subgroups regardless of original treatment assignment (Summary of Clinical Safety, pg. 14).

The sponsor stated that "The majority of subjects were escalated to doses of up to 60 mg/kg/day and appeared to remain on those doses."

UCB summarized the exposure by mean daily dose and duration of exposure for the 4 Years to 16 Years Pool is shown in the table below.

FDA Table 9: Duration of Exposure by Subject stratified by Mean Daily Dose in the 4 Years to 16 years Cohort (Adapted from Sponsor Table 2.7.4.8, Clinical Summary of Safety, pg. 14)

Duration of Exposure (weeks)	LEV Mean Daily Dose (mg/kg/day) (N=117) n (%)				
	0 to <29	29 to <50	50 to <80	≥80	Total
>0 to <2	3 (2.6)	0	0	0	3 (2.6)
2 to <4	2 (1.7)	0	0	0	2 (1.7)
4 to <6	0	4 (3.4)	1 (0.9)	0	5 (4.3)
6 to <8	1 (0.9)	2 (1.7)	0	0	3 (2.6)
8 to <10	0	1 (0.9)	0	0	1 (0.9)
10 to <12	0	2 (1.7)	0	0	2 (1.7)
12 to <16	1 (0.9)	1 (0.9)	2 (1.7)	0	4 (3.4)
16 to <20	0	4 (3.4)	1 (0.9)	0	5 (4.3)
20 to <24	1 (0.9)	3 (2.6)	1 (0.9)	0	5 (4.3)
24 to <36	5 (4.3)	7 (6.0)	9 (7.7)	0	21 (17.9)
36 to <48	0	4 (3.4)	8 (6.8)	1 (0.9)	13 (11.1)
48 to <60	4 (3.4)	13 (11.1)	18 (15.4)	0	35 (29.9)
≥60	1 (0.9)	6 (5.1)	10 (8.5)	0	17 (14.5)

LEV=levetiracetam
Source: ISS Table 16.3.1:10

4.2.4 Titration and Maintenance

The sponsor stated that the mean duration of the Up-Titration/Conversion Phase was 39.72 days for the 1 month to <4 years group and 48.71 days for the 4 years to 16 years group. The mean duration of the Maintenance Phase was 220.50 days for the 1 month to <4 years group and 199.29 days for the 4 years to 16 years group. The mean duration of the Down-titration/Withdrawal Phase was 28.22 days for the 1 month to <4 years group and 20.92 days for the 4 years to 16 years group. UCB stated that the duration of the Maintenance Phase ranged from 1 to 337 days (N01148 Table 14.3.7:1)(Summary of Clinical Safety, pg. 15).

5. RESULTS: SAFETY DATA

5.1 Deaths

5.1.1 Methods for Capture and Analysis of Deaths

Reviewer comment: *Because the manner in which deaths are monitored in clinical trials can affect the subsequent data, I examined the methods for identifying deaths in each of the trials. For placebo-controlled Study NO1109, placebo-controlled Study NO1103 and open-label study NO1148 a search of the final study report using the key word "death" did not yield any details on how fatality-related data was collected.*

The primary reason I wanted to assess the method in which deaths were captured was to evaluate whether an appropriate follow-up after study completion or discontinuation was used. (For example, would a death occurring after a month-long hospitalization be captured and included in the drug-treatment arm if the subject discontinued levetiracetam at the time of their admission to the hospital.) Although the sponsor did not specify the window of time in which deaths were registered if they occurred after participation in the study, one of the four deaths noted by the sponsor occurred two months after the patient's last dose of levetiracetam. From this death one may assume that the follow-up period of deaths extended to two months after levetiracetam-treatment, which is more than adequate given the short half-life (5 to 7 hours).

5.1.2 Narrative Summaries

The sponsor reported that a total of four[13] deaths had occurred in the levetiracetam pediatric studies at the time of the writing of the sNDA application. One case (ISS No. 5267) had previously been reported to the FDA in 2004[14], and the other three occurred in the open label Study N01148. All three deaths that had not been previously reported occurred in patients within the 1 Month to 4 Years cohort. The four deaths are summarized below:

1. ***ISS No. 5817 (Patient 503/1007):*** This 17-month-old boy, who had previously been treated with levetiracetam in Study N01009, died on Study Day (b) (6) of the open-label study N01148 after developing severe brain edema following bronchitis. On (b) (6) (Day (b) of study N01148), two days prior to the death, the patient developed a cough and "mild bronchitis." At 4 AM of the day of his death, "he was left alone in his bed in the prone position" and his mother found him dead later in the morning. According to the autopsy, the cause of death was brain edema, with severe degenerative changes to the brain in addition to "massive permeation of the pia mater." The autopsy also confirmed that the presence of "non-serious" bronchitis. The sponsor asserted that "the status of seizures was not worsened before death."(Summary of Clinical Safety, pg. 60).

   Reviewer comment: *Review of the CRF/full narrative showed that the patient had a history of bacterial meningitis and microcephaly. He was being treated concomitantly with vigabatrin and topiramate.*

2. ***ISS No. 5841 (Patient 518/1001)*****:** This 27-month-old boy died on (b) (6) of severe brain edema. His death occurred on Day (b) (6) (after initiation of levetiracetam) of Study N01148. He had previously completed Study N01009.

[13] The sponsor excluded a fifth death due to

[14] Information on this death was reported to the FDA in the 2004 sNDA, S-040, Module 5, Volume 151, Section 5.3.5.3.1

The patient had a history of drug-resistant focal epilepsy symptomatic of malformation of cortical development. On (b) (6) the patient underwent an intracerebral EEG recording with stereo-EEG as a diagnostic procedure for an epilepsy surgery program. Levetiracetam 82.9 kg/mg/day was discontinued the same morning. The day before his death, he was admitted to the hospital with malignant brain edema. An MRI performed some hours before death confirmed diffuse brain edema. In addition to the study drug, the subject received concomitant topiramate 100 mg daily since May 2005 (Summary of Clinical Safety, pg. 60).

Reviewer comment: *It is unclear if the patient's underlying cortical malformation could be associated with cerebral edema.*

3. ***ISS No. 5772 (Patient 321/2003)***: This 22-month-old boy "who was a screen failure from N01009" died (b) (6) days after initiation of levetiracetam and two months after the last dose of levetiracetam. On (b) (6) days after first study drug intake in N01148, the patient was found without respiration and pulse. At 7:00 AM Emergency Medical Services arrived at the patient's home and found him lying in his crib unresponsive. His tympanic temperature was 85.5°F and asystole was confirmed on the monitor. The hospital record indicated that the cause of death was an unknown/chronic medical condition. The sponsor attributed the death to "excessive bronchial secretions and chronic pulmonary congestion." UCB stated that the onset of obstructive airways disorder occurred about two months after the final study drug administration on (b) (6) (Summary of Clinical Safety, pg. 60).

   Reviewer comment: *Clearly, the fact that this patient discontinued levetiracetam two months prior to death, and that the half-life in children is about 5 to 7 hours in children (Section 1.3),lessens the chance that this patient's death was related to his treatment with levetiracetam. In addition, review of the CRF showed that this subject had a number of underlying medical conditions, including premature birth and cerebral palsy.*

4. ***ISS No. 5267:*** The death of this 15-year old girl in open-label Study 157 was previously reported to the FDA[15]. She had received levetiracetam for a total of approximately one year, first in N159 and then in N157. In the two months before her death, she was noted to have "serious worsening behavioral problems." Before her death, she was admitted to the hospital for status epilepticus, which was thought to be fever-induced because she was being treated for a respiratory infection. En route to the hospital, she experienced respiratory arrest and subsequently went into cardiopulmonary arrest. Ultimately, she experienced multi-organ failure due to massive ischemic insult.

Reviewer comment: *In the report for Study NO1009 (pg. 109), the sponsor noted that "no deaths occurred in the study," followed by:*

[15] Information on this death was provided in the 2004 sNDA, S-040, Module 5, Volume 151, Section 5.3.5.3.1

Subject 519/0001 in the LEV group expired (b) (6) days after the single day of study treatment and discontinuation from the study due to moderate intermittent convulsions. A Necropsy was not performed, and therefore the cause of death was not confirmed. The Investigator considered the death not related to the study drug. The event occurred more than 30 days after discontinuation from the study, therefore, the event did not meet the criteria for a SAE for this study, but the event was reported to the UCB Global Safety Database.

It is unclear why the sponsor did not include the death immediately above (which occurred one month after discontinuing levetiracetam in the total death count), but did include a death which occurred two months after discontinuing levetiracetam. However, this subject did only receive one dose of levetiracetam one month prior to death, greatly reducing the possibility that his death was related to the drug.

5.1.3 Reviewer Analysis and Discussion

5.1.3.1 Death Rate

The sponsor did not provide any analysis of the deaths within the levetiracetam pediatric patients other than to note that investigators considered the deaths as unrelated to drug treatment.

There were a total of five deaths among a total of 168 pediatric patients aged 1 month to 4 years treated with levetiracetam (See Section 4.2.1 of this review). Excluding one death which occurred a month after a single levetiracetam dose and another which occurred two months after discontinuing levetiracetam as unlikely to be levetiracetam-related, there were a total of three deaths. All of the deaths occurred in open-label studies, so no placebo comparator group was available. The risk of death in patients 1 month to 4 years is therefore 1.8% (3 deaths per 168 patients age 1 to 4). As I was unable to find a large-scale estimate of deaths in pediatric epilepsy patients by risk (except for SUDEP), I also calculated the frequency of death in the levetiracetam pediatric development program as a rate. For the deaths in the levetiracetam development program, the three deaths occurred among a total of 125 patient-years exposure in the 1 Month to 4 Year age group (See Section 4.2.2 of this review) for a rate of 24 per 1000 person-years. Rates of deaths in children with epilepsy has been estimated from 3.1 to 6.2 per 1000 person-years[16], making the rate in the levetiracetam pediatric development program approximately ten fold higher. Some of this elevation in rate is likely due to the fact that these were younger pediatric patients (I was unable to find rates in children under 4 alone) with more severe epilepsy, and the estimates of mortality with epilepsy in general were based on all patients with epilepsy. However, it is unclear if these factors would account for the total elevation in rate.

[16] Petra MC. Callenbach,Westendorp RG, Geerts AT et al. Mortality Risk in Children with Epilepsy: The Dutch Study of Epilepsy in Childhood. Pediatrics 2001;107;1259-1263.

5.1.3.3 Deaths Associated with Respiratory Infections

The most notable finding regarding the deaths was the fact that two patients suffered brain edema and respiratory infections in conjunction with their deaths. A third fatality (ISS No. 5772) also had respiratory involvement in the form of "excessive bronchial secretions and chronic pulmonary congestion." This patient, however, had discontinued levetiracetam approximately two months prior to his death, which considerably lessens the probability that the death was related to the levetiracetam treatment. I summarize the presence or absence of brain edema and infection in the table below.

FDA Table 10: Summary of Selected Characteristics of Deaths in the Levetiracetam Pediatric Development Program

Pt. ID	Age/Sex	Levetiracetam Treatment	Brain Edema?	Respiratory Infection?
Patients on Active Levetiracetam Treatment				
ISS No. 5817 (Pt. 503/1007)	17 month/male	Until Study Day [redacted] of open-label study NO1148 (following NO1009), Dose: 50 mg/kg/day	Yes	Yes (Bronchitis, "non-serious")
ISS No. 5841 (Pt. 518/1001)	27 month/male	Until Study Day [redacted] of open-label study NO1148, Dose: 83 kg/mg/day	Yes (seen on MRI prior to death)	None reported
ISS No. 5267	15 year/female	Approximately one year of treatment (Study 159, then Study 157) Dose: 53.5 mg/kg/day	None reported	Yes (stated to have died of "fever-induced" status epilepticus from respiratory infection)
Patients who had Discontinued Levetiracetam Treatment				
ISS No. 5772 (Pt. 321/2003)	22 month/male	Died 2 months after last dose of levetiracetam Dose: 19.6 mg/kg/day	No	Yes (excessive bronchial secretions and pulmonary congestion)

To explore this issue further, I examined related data within the serious adverse events (SAEs) related to these seen in these fatal cases. A search of the ISS revealed no other cases of brain edema, although this finding is not likely to be observed outside of a fatal or very serious event. As expected in a pediatric population, a large number of respiratory infections were reported, especially in the 1 month to 4 years age cohort. In the 1 Month to 4 Year, for the combined placebo-controlled and open-label data, 28% of levetiracetam-treated patient (N=17) and 20% of placebo-treated patients (N=11) experienced treatment emergent infections. Looking only at the placebo-controlled

portion of Study NO1009 (1 Month to 4 Years), 18% of placebo patients (N=10) and 13% of levetiracetam patients (N=8) reported TEAEs coded to the MedDRA SOC term infections. There was a slight predominance of viral and lower respiratory tract infections in the levetiracetam-treated patients compared to placebo, but there was only one case and no cases in each group respectively. The placebo-controlled data for older patients (those aged 4 Years to 16 Years in Study N01103) also did not display a predominance of infections in the levetiracetam-treated patients, with 44% of placebo patients and 47% of levetiracetam patients reporting infections. The only infection sub-category to show a levetiracetam predominance was nasopharyngitis (16% levetiracetam, 12% placebo).

The manner of the death (brain edema and death when the patients during or after a non-serious infection) in at least one levetiracetam-treated patient resembles that seen in Reye's syndrome.[17] As seen in the preceding table, only one of the deaths in patients actively treated with levetiracetam was documented to have both cerebral edema and an infection, but the other two deaths each had one of the two factors. Given the general lack of detail in the narratives provided by the sponsor, the other factors may have been present but unobserved or unreported.

Reye's syndrome is characterized by fat accumulation in the liver and other organs accompanied by an increase in cerebral pressure. Multiple literature and text book sources note that cerebral edema is seen in cases of Reye's syndrome, although this may be a non-specific finding. In addition, Reye's syndrome has been associated with medication use, especially salicylates. A "Reye's-like" syndrome has also been described with the anti-epileptic drug valproic acid (Depakote ®), characterized by hyperammonemia.[18] In fact, valproic acid has been used to induce Reye's syndrome in animals for preclinical research.[19] In addition, Reye's syndrome occurs almost exclusively in children, which could explain why similar deaths were not prevalent in the adult levetiracetam development program.

Some of the pediatric patients who died during the levetiracetam development program were taking concomitant medications at the time of their death. These included are summarized below:

1. Patient 503/1007 (17 months old): Topiratmate, vigabatrin, desmopressin
2. Patient 518/1001 (27 months old): Valproic acid, topiramate
3. Patient 375/003 (15 years old): Valproic acid, acetazolamide, Marvelon, Norgestimate, beclometasone, primidone
4. Patient 321/2003 (22 months old): Concomitant medications on Narrative described as "None"

[17] The connection of the deaths to Reye's syndrome was made by Dr. Norman Hershkowitz of the FDA's Department of Neurology Products.
[18] Crocker JF, Bagnell PC. Reye's syndrome: a clinical overview. Canadian Medical Association 1981;124:374- .
[19] Changed in GFAP immunoreactivity of astrocytes in rats with Reye's syndrome induced by valproic acid and the effects of carnitine supplementation. J Korean Pediatr Soc. 1999 Jul;42(7):966-979.

5. Patient 519/0001 (5 months old): Valproic acid, lactulose, penicilline, diazepam, phenobarbital, topiramate

Reviewer comment: *The concomitant use of valproic acid in three of the patients who died complicates the evaluation of possible Reye's syndrome with levetiracetam use, because, as discussed above, valproic acid has also been associated with a Reye's-like syndrome.*

Early symptoms of Reye's syndrome include listlessness, neurologic changes and persistent vomiting, followed by behavioral changes (disorientation, aggression, etc), delirium, convulsions and death. (It is notable that levetiracetam has been associated with behavioral adverse events such as agitation and aggression [see Section 5.5 of this review].) Most children with Reye's syndrome do not have any readily recognizable signs of their hepatic dysfunction (such as jaundice), and this is observed only on laboratory testing and biopsy.

5.1.3.4 Reviewer Conclusions

The sponsor did not provide any comment on the deaths in the levetiracetam pediatric development program other than to note that investigators did not consider them drug-related. Given some of concerning aspects discussed above (an apparent elevation in the rate of death and similarities to Reye's syndrome in some cases), this is an inadequate evaluation on the part of the sponsor. The sponsor should be asked to provide additional analysis and documentation regarding whether they believe the cases to be drug-related.

To better evaluate the similarities between the deaths in the levetiracetam development program and Reye's syndrome, I would recommend the sponsor do the following:

1. None of the summaries provided by the sponsor mentioned liver involvement as part of the deaths of the levetiracetam-treated patients. The Division therefore requested that the sponsor provide information on hepatic function tests for the patients who were hospitalized immediately prior to their deaths. The sponsor responded as per the below.

   > "Two patients (375/003 and 518/1001) were hospitalized immediately prior to their deaths. One patient (321/2003) had an emergency room visit within one day of being found dead at home. Two patients (503/1007 & 519/0001) were not hospitalized immediately prior to their deaths.
   >
   > Of the three patients who were hospitalized or visited the emergency room immediately prior to their deaths, only one patient (375/003 - Study N157) had any information on the liver function tests that is available from the hospitalization. The only information we have is rising blood urea nitrogen, creatinine, and liver function tests. No specific values were provided, based on the hospital records that were provided to us (E-mail sent September 15, 2008)."

The Division also requested that the sponsor summarize the hepatic function tests values in the study for the patients with fatal outcome. The sponsor submitted the following table with this information.

FDA Table 11: Hepatic Function Test Results for Levetiracetam-Treated Patients with Fatal Outcome within the Levetiracetam Pediatric Development Program (Sponsor table sent via e-mail after FDA request, received September 15, 2008)

Listing 1 All Liver Function Results for Pediatric Subjects with SAE Outcome of Death

Page 1 of 1 DRAFT - N01311 11SEP2008 at 21:50

Patient ID	Subject Number	Study	Visit (a)	Sample Date	LEV Dose (mg/kg/day)	Days on LEV (b)	AST (U/L)	ALT (U/L)	GGT (U/L) (c)	ALKP (U/L)
5267	009/004	N159	2	(b) (6)	N/A	N/A	14	10	29	150
	009/004	N159	BL		N/A	N/A	13	13	33	125
	009/004	N159	4		23.0	13	13	14	34	141
	009/004	N159	5		41.1	27	13	12	32	115
	009/004	N159	6		40.5	48	14	14	42	118
	009/004	N159	7		40.3	76	12	12	40	126
	009/004	N159	8		45.6	104	18	15	46	117
	375/003	N157	2		54.3	181	12	10	ND	120
	375/003	N157	3		54.1	240	20	15	ND	121
	375/003	N157	4		66.8	311	13	7	ND	93
5772	321/2003	N01148	5		19.6	172	31	32	153	352
5817	503/0007	N01009	BL		N/A	N/A	12	4	13	139
	503/0007	N01009	Day 6		50.0	6	8	5	14	147
5841	519/0001	N01009	BL		N/A	N/A	32	19	18	274
	519/0001	N01009	Day 6		51.1	6	28	18	22	283
	519/1001	N01148	5		91.4	175	30	13	12	273

Note: N01009 subject 519/0001 has no lab data, therefore is not included in the listing.
Note: N01009 subject 503/0007 (N01148 503/1007) discontinued after N01148 V1 and has no N01148 labs.
Note: N01148 subject 321/2003 screen failed N01009 and so has no baseline labs.
(a) Visit is the visit/day within each study where lab testing was required per protocol.
(b) Days on LEV from the very first LEV intake.
(c) GGT not performed during study N157.

Study: N01311 - Data Base Version: no code given
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Reviewer comment: *The table above shows the hepatic function tests throughout the pediatric development program for patients who died. Based upon generally used ranges for normal values[20], the only patient with elevated values was 321/2003, a 22-month-old who died two months after discontinuing levetiracetam.*

2. Reye's is a non-specific syndrome, and may include only some of the symptoms listed above as well as additional symptoms. It would be helpful to consult with a practitioner with some experience in Reye's syndrome to ascertain whether there are aspects of the cases which are consistent with or rule out a diagnosis of Reye's syndrome.

5.2 Serious Adverse Events

[20] The normal values used were: AST 5 to 43 U/L, ALT 4 to 60 U/L, ALKP 30 to 117 U/L, and GGT 5 to 80 IU/L

Reviewer comment: *The organization of the sponsor's summaries of SAEs made it difficult to ascertain the total number of SAEs in the pediatric studies, mainly due to the stratification of the data into multiple subgroups. In addition, the sponsor frequently presented aggregate data as the number of SAEs in the combined placebo and levetiracetam treatment groups. Although I believe I reviewed the narratives for all the SAEs in levetiracetam-treated patients, I had difficulty reconciling the total number of SAEs in the levetiracetam treatment group among the various tables and text.*

5.2.1 SAEs: 1 Month to 4 Years

The sponsor stated that serious adverse events (SAEs) were reported for 49 (29.2%) patients in the 1 Month to <4 Years cohort, with nervous system disorders (15.5%) as the most frequent SOC and convulsion (10.1%) as the most frequent SAE (Clinical Overview, pg. 25).

In the Integrated Summary of Safety table 19.2.1, the 49 SAEs in patients aged 1 Month to <4 Years were divided as 7 in open-label Study 157 and 42 in open-label Study NO1148 (The patient with an SAE in placebo-controlled Study NO1009 progressed to open-label treatment and so was classified by the sponsor as an open-label patient.)

In placebo-controlled Study N01009, only one levetiracetam-treated patient experienced an SAE. Subject 204/0005 in the levetiracetam group experienced pyrexia due to hyaline coryza which was reported as serious due to in-patient hospitalization. The event resolved within five days after the subject had entered the long-term study N01148 (Study NO1009 Study Report, pg. 111).

The sponsor summarized the SAEs in the 1 Month to <4 Years cohort in the table below.

FDA Table 12: SAEs Reported for ≥ Two Patients in the 1 Month to 4 Years Cohort (Adapted from Sponsor Table 2.7.4.26, Summary of Clinical Safety, pg. 61)

Appears This Way On Original

UCB SOC/MedDRA PT	Original Treatment Assignment			N01052 + N157 (N=14)	Overall (N=168)
	N01009 + N01148				
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
Number of subjects with at least 1 SAE	14 (26.4)	15 (25.0)	13 (31.7)	7 (50.0)	49 (29.2)
Gastrointestinal disorders	3 (5.7)	0	0	2 (14.3)	5 (3.0)
Constipation	1 (1.9)	0	0	1 (7.1)	2 (1.2)
Gastroesophageal reflux disease	1 (1.9)	0	0	1 (7.1)	2 (1.2)
General disorders and administration site conditions	0	2 (3.3)	4 (9.8)	1 (7.1)	7 (4.2)
Pyrexia	0	2 (3.3)	3 (7.3)	0	5 (3.0)
Infections and infestations	5 (9.4)	6 (10.0)	5 (12.2)	1 (7.1)	17 (10.1)
Pneumonia	2 (3.8)	1 (1.7)	3 (7.3)	1 (7.1)	7 (4.2)
Viral infection	3 (5.7)	1 (1.7)	1 (2.4)	0	5 (3.0)
Injury, poisoning, and procedural complications	2 (3.8)	1 (1.7)	2 (4.9)	0	5 (3.0)
Head injury	1 (1.9)	0	1 (2.4)	0	2 (1.2)
Nervous system disorders	4 (7.5)	9 (15.0)	8 (19.5)	5 (35.7)	26 (15.5)
Convulsion	2 (3.8)	5 (8.3)	6 (14.6)	4 (28.6)	17 (10.1)
Status epilepticus	2 (3.8)	1 (1.7)	3 (7.3)	1 (7.1)	7 (4.2)
Brain oedema	0	2 (3.3)	0	0	2 (1.2)
Epilepsy	0	1 (1.7)	1 (2.4)	0	2 (1.2)
Respiratory, thoracic, and mediastinal disorders	5 (9.4)	0	4 (9.8)	2 (14.3)	11 (6.5)
Aspiration	1 (1.9)	0	1 (2.4)	0	2 (1.2)
Obstructive airways disorder	1 (1.9)	0	1 (2.4)	0	2 (1.2)
Pneumonia aspiration	0	0	2 (4.9)	1 (7.1)	3 (1.8)
Respiratory disorder	2 (3.8)	0	0	0	2 (1.2)
Respiratory failure	1 (1.9)	0	1 (2.4)	0	2 (1.2)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term
SAE=serious adverse event; SF/DE=screen failure/directly enrolled; SOC=System Organ Class
Note: First study is N01009 for PBO and LEV, N01148 for SF/DE subjects, and N01052 for N157 subjects.
Sorted by descending frequency overall by PT within SOC; corresponding SOCs are included for completeness.
Source: ISS Table 16.4.1:9

Reviewer comment: *The SAE with the largest difference between the levetiracetam and placebo group was convulsions (8.3% levetiracetam, 3.8% placebo). Clearly, the SAE of convulsions is not unexpected in a patient population with treatment resistant epilepsy. However, one would expect that following randomization the risk in the levetiracetam and placebo groups would be similar, whereas the risk is approximately twice as high in the levetiracetam group (8.3% levetiracetam versus 3.8% placebo). This may be attributable to the fact that the safety data is presented as a risk instead of a rate, and there was a longer exposure time in the levetiracetam group due to the inclusion of open-label study NO1148 with placebo-controlled Study NO1109.*

Of note, the sponsor table above provides data on patients with two or more SAEs. I do not believe this to be an appropriate "cut-off"criteria, as it is important to be aware of any rare or particularly severe SAEs occurring in a singe patient. However, I reviewed the CRFs for the SAEs, and so believe that all SAEs were reviewed.

UCB noted that the percentage of subjects with at least 1 SAE in the 1 Month to <4 Years cohort (49 SAEs) was higher than in the 4 Years to 16 Years cohort (2 SAEs). The

sponsor attributed the differences in SAEs between the two age cohorts to the severity of disease and the general medical condition in the younger subjects (Summary of Clinical Safety, pg. 63).

5.2.2 SAEs: 4 Years to 16 Years

Reviewer comment: *The sponsor stated that:*

> *"Overall, 2 subjects (1.7%) in the 4 Years to 16 Years Pool had at least 1 treatment-emergent SAE each. Both subjects were in the LEV group by original treatment assignment. One subject had an SAE of neutropenia; the other had an SAE of abdominal pain." (Integrated Summary of Safety, pg. 156 and 160).*

UCB further stated that both occurred in Study 159. However, in the following pages of the sponsor report and in the table below, the sponsor notes that there were eight levetiracetam-treated subjects with SAEs in Study 159 (patients aged 4 years to 16 years).

FDA Table 13: SAEs Occurring in More than Two Subjects Aged 4 to 16 Years in either Treatment Group for Studies N159 and NO1003 (Adapted from Sponsor Table 7:28, Integrated Summary of Safety, pg. 158)

MedDRA PT	N159		N01103	
	PBO (N=97)	LEV (N=101)	PBO (N=34)	LEV (N=64)
	n (%)			
Subjects with at least 1 SAE	9 (9.3)	8 (7.9)	1 (2.9)	0
Dehydration	0	2 (2.0)	0	0
Pneumonia	2 (2.1)	0	0	0
Status epilepticus	2 (2.1)	1 (1.0)	0	0

ITT=intent-to-treat; LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SAE=serious adverse event; SOC=System Organ Class
Source: N01103 Table 14.3.1:11; ISS Table 16.4.1:82

UCB commented that the percentage of subjects with at least one SAE was lower in N01103 (1 placebo subject and no levetiracetam subjects) than in N159 (nine placebo subjects [9.3%] and eight levetiracetam subjects [7.9%])(Clinical Overview, pg. 25).

Reviewer comment: *The sponsor did not provide an explanation for why the risk of SAEs in the two studies for the same age group of patient (4 Years to 16 Years) varied so considerably. However, this may be partially explained by the longer duration of study 159 (28 weeks) compares to NO1103 (12 weeks).*

It is noteworthy that in study N159 two levetiracetam-treated subjects and no placebo-treated patients experienced dehydration. Another table summarizing common (not

serious) adverse events in studies N159 and NO1103 (Table 7:15, ISS, pg. 129) noted that in N159 two levetiracetam subjects and one placebo subject reported dehydration.

5.3 Discontinuations

Reviewer comment: *The sponsor appears to use the terms "discontinuations," "withdrawals" and "premature terminations" interchangeably. Sponsors sometimes make distinctions between these terms, but as I did not find this stated explicitly in the sponsor documents, I considered all the terms to be equivalent.*

5.3.1 Discontinuations: 1 Month to <4 Years

UCB reported that a total of 168 subjects received levetiracetam treatment in the 1 Month to <4 Years cohort. Of these, 64 subjects (38.1%) discontinued from the trials (i.e., N01009, N01148, and N157) prematurely. The most common reasons for premature discontinuations were AE (18 subjects; 10.7%) followed by lack or loss of efficacy (22 subjects; 13.1%). There were 3.6% of subjects who discontinued due to withdrawal of consent (Clinical Summary of Safety, pg. 18)

Overall subject disposition is summarized in the table below.

FDA Table 14: Summary of Subject Disposition in the 1 Year to <4 Year Cohort (Adapted from Sponsor Table 2.7.4.9, Summary of Clinical Safety, pg. 19)

Parameter	Original Treatment Assignment			N01052 + N157	Overall
	N01009 + N01148				
	PBO	LEV	SF/DE		
	n (%)				
Subjects treated[a]	53	60	41	14	168
Subjects completed[b]	24 (45.3)	29 (48.3)	16 (39.0)	6 (42.9)	75 (44.6)
Subjects ongoing in OL	9 (17.0)	8 (13.3)	12 (29.3)	0	29 (17.3)
Discontinued[c]	20 (37.7)	23 (38.3)	13 (31.7)	8 (57.1)	64 (38.1)
Adverse event	4 (7.5)	7 (11.7)	4 (9.8)	3 (21.4)	18 (10.7)
Lack of efficacy	7 (13.2)	7 (11.7)	2 (4.9)	0	16 (9.5)
Loss of efficacy	2 (3.8)	3 (5.0)	1 (2.4)	0	6 (3.6)
Lost to follow-up	0	2 (3.3)	0	0	2 (1.2)
Protocol violation	1 (1.9)	0	1 (2.4)	1 (7.1)	3 (1.8)
Withdrawal of consent	2 (3.8)	0	4 (9.8)	0	6 (3.6)
Other reason	4 (7.5)	4 (6.7)	1 (2.4)	3 (21.4)	12 (7.1)
Decision of UCB	0	0	0	1 (7.1)	1 (0.6)

LEV=levetiracetam; OL=open-label; PBO=placebo; SF/DE=screen failure/directly enrolled
[a] At least 1 dose of LEV intake.
[b] Subjects who completed enrolled studies. Includes only studies in which the subject was assigned to LEV.
[c] Subjects who discontinued LEV treatment at any time during double-blind or OL treatment. If the subject discontinued 2 studies while on LEV, it was counted only once if the reason was the same; if reasons differ, than each reason was counted.
Source: ISS Table 16.1.1:1

Reviewer comment: *I reviewed the CRFs and other details of the subjects whose discontinuations were classified as "withdrawal of consent,""loss to follow-up," "withdrawal of consent" or "Other" to verify that they did not contain withdrawals due to AEs that had been misclassified.*

The table above demonstrates a fairly high discontinuation rate overall, but it is similar between the various treatment arms (48 of levetiracetam-treated subjects completing the study, compared to 45% of placebo patients).

UCB stated that for the 1 month to <4 year cohort the percentages of subjects who discontinued and the reasons for discontinuations were generally similar regardless of original treatment assignment within the placebo-controlled N01009 and open-label N01148 groups. However, patients in N01052 and N157 had a higher percentage of discontinuations, which the sponsor hypothesized was most likely due to a longer duration of levetiracetam exposure compared to the N01009 and N01148 groups (Summary of Clinical Safety, pg. 18).

FDA Table 15: Adverse Events Leading to Permanent Discontinuation of Study Drug in the 1 Month to <4 Year Cohort (Adapted from Sponsor Table 2.7.4.27, Summary of Clinical Safety, pg. 64)

UCB SOC/MedDRA PT	Original Treatment Assignment N01009 + N01148			N01052 + N157 (N=14)	Overall (N=168)
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
Subjects with at 1 event	4 (7.5)	5 (8.3)	3 (7.3)	0	12 (7.1)
Nervous system disorders	3 (5.7)	2 (3.3)	2 (4.9)	0	7 (4.2)
Convulsion	1 (1.9)	2 (3.3)	2 (4.9)	0	5 (3.0)
Epilepsy	1 (1.9)	0	0	0	1 (0.6)
Infantile spasms	1 (1.9)	0	0	0	1 (0.6)
Psychiatric disorders	1 (1.9)	2 (3.3)	1 (2.4)	0	4 (2.4)
Aggression	1 (1.9)	1 (1.7)	0	0	2 (1.2)
Food aversion	0	1 (1.7)	0	0	1 (0.6)
Irritability	0	0	1 (2.4)	0	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	0	1 (1.7)	0	0	1 (0.6)
Pulmonary congestion	0	1 (1.7)	0	0	1 (0.6)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities: PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: First study is N01009 for PBO and LEV, N01148 for SF/DE subjects, and N01052 for N157 subjects.
Sorted by descending frequency overall by PT within SOC; corresponding SOCs are included for completeness.
Source: ISS Table 16.4.1.11

From the table above of pooled placebo-controlled and open-label data, 8.3% of levetiracetam-treated patients (N=5) and 7.5% of placebo-treated patients (N=4) in the 1 Month to <4 Years Pool had at least 1 TEAE leading to permanent discontinuation of study medication. The most common UCB SOCs were nervous system disorders (4.2%) and psychiatric disorders (2.4%). The most frequent TEAE leading to permanent discontinuation of study medication was convulsion (5 subjects; 3.0%) followed by aggression (2 subjects; 1.2%). UCB asserted that the percentage of AEs leading to permanent discontinuation of study medication was similar across groups by original treatment assignment (Summary of Clinical Safety, pg. 73).

5.3.2 Discontinuations: 4 Years to 16 Years

The sponsor stated that of the total of 117 subjects treated with levetiracetam in the 4 Years to 16 Years cohort, 32 subjects (27.4%) discontinued prematurely. The most common reason for premature discontinuations was AE (11 subjects; 9.4%). Six subjects (5.1%) discontinued due to withdrawal of consent and another six subjects (5.1%) withdrew due to lack or loss of efficacy (Summary of Clinical Safety, pg. 19).

A summary of overall subject disposition in the 4 Year to 16 Year cohort is presented in the table below.

FDA Table 16: Summary of Subject Disposition in the 4 Year to 16 Year Cohort (Adapted from Sponsor Table 2.7.4.10, Summary of Clinical Safety, pg. 19)

Parameter	Original Treatment Assignment			Overall
	N01103 + N01148			
	PBO	LEV	SF/DE	
	n (%)			
Subjects treated[a]	30	64	23	117
Subjects completed[b]	19 (63.3)	24 (37.5)	0	43 (36.8)
Subjects ongoing in OL	6 (20.0)	18 (28.1)	18 (78.3)	42 (35.9)
Discontinued[c]	5 (16.7)	22 (34.4)	5 (21.7)	32 (27.4)
Adverse event	2 (6.7)	9 (14.1)	0	11 (9.4)
Lack of efficacy	2 (6.7)	2 (3.1)	1 (4.3)	5 (4.3)
Loss of efficacy	0	0	1 (4.3)	1 (0.9)
Lost to follow-up	1 (3.3)	2 (3.1)	1 (4.3)	4 (3.4)
Protocol violation	0	0	1 (4.3)	1 (0.9)
Withdrawal of consent	0	5 (7.8)	1 (4.3)	6 (5.1)
Other reasons	0	4 (6.3)	0	4 (3.4)

LEV=levetiracetam; OL=open-label; PBO=placebo; SF/DE=screen failure/directly enrolled
[a] At least 1 dose of LEV intake.
[b] Subjects who completed enrolled studies. Includes only studies in which the subject was assigned to LEV.
[c] Subjects who discontinued LEV treatment at any time during double-blind or OL treatment. If the subject discontinued 2 studies while on LEV, it was counted only once if the reason was the same; if reasons differ, than each reason was counted.
Source: ISS Table 16.1.1:3

In the pooled trial data for the 4 Years to 16 Years cohort, UCB noted that a higher percentage of levetiracetam subjects[21] discontinued (34.4%; n=22), compared with placebo subjects (16.7%; n=5) and 21.7% of SF/DE subjects (21.7%; n=5). For discontinuations due to AEs, 14.1% of levetiracetam-treated[22] subjects discontinued due to AE, compared with 6.7% of placebo subjects. The sponsor asserted that the higher discontinuation rate in the levetiracetam group was attributable to "the longer treatment duration on levetiracetam."(Summary of Clinical Safety, pg. 19).

[21] Levetiracetam subjects as categorized by original treatment assignment.
[22] Levetiracetam subjects as categorized by original treatment assignment.

Reviewer comment: *Although the sponsor attributed the higher risk of discontinuation in levetiracetam-treated subjects to "the longer duration on levetiracetam" they did not provide any rate calculation to support this statement.*

UCB stated that "11 subjects (9.4%) in the 4 Years to 16 Years Pool had at least 1 TEAE leading to permanent discontinuation of the study medication."

Reviewer comment: *In the safety-related documents for the levetiracetam pediatric studies, the sponsor repeatedly provided information for the combined treatment and placebo group data. This method of data presentation (with treatment and placebo patients combined) is unhelpful. In addition, it was frequently unclear whether sponsor statements referred to pooled treatment and placebo data or data from patients in the levetiracetam treatment group. Based on the table below, the 11 subjects with at least one TEAE noted above is composed of 9 levetiracetam-treated patients (14%) and two placebo-treated patients (7%). The risk of discontinuation due to adverse event was therefore approximately two-fold higher in the levetiracetam than in the treatment group, a fact the sponsor did not highlight.*

In the combined placebo-controlled and open-label data for the 4 Years to 16 Years cohort, UCB stated that nervous system and psychiatric disorders (3.4% each) were the leading causes of discontinuation due to adverse event. The sponsor reported that the most frequent individual TEAEs leading to permanent discontinuation were somnolence, abnormal behavior, and rash (1.7% each). UCB noted that all other TEAEs leading to permanent discontinuation of study medication were reported for one subject each. The sponsor asserted that the percentage of TEAEs leading to permanent discontinuation of study medication was similar across groups by original treatment assignment, as shown in the table below (Summary of Clinical Safety, pg. 67).

Reviewer comment: *See Section 5.5 for narratives of the events coded as abnormal behavior.*

FDA Table 17: Adverse Events Leading to a Permanent Discontinuation of Study Medication in the 4 Years to 16 Years Cohort (Adapted from Sponsor Table 2.7.4.30, Summary of Clinical Safety, pg. 67)

UCB SOC/MedDRA PT	Original Treatment Assignment N01103 + N01148			Overall (N=117)
	PBO (N=30)	LEV (N=64)	SF/DE (N=23)	
	n (%)			
Subjects with at least 1 event	2 (6.7)	9 (14.1)	0	11 (9.4)
Blood and lymphatic system disorders	0	1 (1.6)	0	1 (0.9)
Neutropenia	0	1 (1.6)	0	1 (0.9)
General disorders and administration site conditions	1 (3.3)	1 (1.6)	0	2 (1.7)
Chest pain	1 (3.3)	0	0	1 (0.9)
Fatigue	0	1 (1.6)	0	1 (0.9)
Injury, poisoning, and procedural complications	1 (3.3)	0	0	1 (0.9)
Excoriation	1 (3.3)	0	0	1 (0.9)
Musculoskeletal and connective tissue disorders	0	1 (1.6)	0	1 (0.9)
Arthralgia	0	1 (1.6)	0	1 (0.9)
Nervous system disorders	1 (3.3)	3 (4.7)	0	4 (3.4)
Somnolence	0	2 (3.1)	0	2 (1.7)
Dysaesthesia	0	1 (1.6)	0	1 (0.9)
Reflexes abnormal	1 (3.3)	0	0	1 (0.9)
Psychiatric disorders	1 (3.3)	3 (4.7)	0	4 (3.4)
Abnormal behavior	0	2 (3.1)	0	2 (1.7)
Agitation	0	1 (1.6)	0	1 (0.9)
Anger	1 (3.3)	0	0	1 (0.9)
Compulsions	1 (3.3)	0	0	1 (0.9)
Depression	0	1 (1.6)	0	1 (0.9)
Irritability	0	1 (1.6)	0	1 (0.9)
Renal and urinary disorders	0	1 (1.6)	0	1 (0.9)
Enuresis	0	1 (1.6)	0	1 (0.9)
Skin and subcutaneous tissue disorders	1 (3.3)	1 (1.6)	0	2 (1.7)
Rash	1 (3.3)	1 (1.6)	0	2 (1.7)
Pruritus	0	1 (1.6)	0	1 (0.9)
Skin depigmentation	1 (3.3)	0	0	1 (0.9)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Sorted by descending frequency overall by PT within SOC; corresponding SOCs are included for completeness.
Source: ISS Table 16.4.1:12

5.3.3 Discontinuations: Data from Placebo-Controlled Studies

5.3.3.1 N01009

In Study N01009 (ages 1 Month to <4 Years), UCB reported that a total of 116 subjects were randomized and 111 subjects completed the study. Two subjects in the levetiracetam groups and three subjects in the placebo group discontinued from the study. The sponsor stated that both discontinuations in the levetiracetam group were due to AEs (Summary of Clinical Safety, pg 21).

Reviewer comment: *The sponsor did not specify the two AEs leading to discontinuation of levetiracetam-treated patients. Review of the NO1009 study report (Table 14.3.2.1*

showed three levetiracetam-treated subjects listed as discontinuing the study (204/005, 513/002 and 519/001). These patients discontinued due to pyrexia/hyaline coryza, food aversion and an increase in seizure activity, respectively.

5.3.3.2 N01103

In Study N01103 (ages 4 years to 16 years), of the 98 ITT[23] subjects beginning the trial (64 levetiracetam subjects/34 placebo subjects), 76 subjects completed NO1103 and entered the open-label follow-up study N01148.

UCB reported that five subjects in the placebo group and 14 subjects in the levetiracetam group discontinued from the study. The most frequent reason for discontinuation was adverse event, with two subjects (5.9%) in the placebo group and seven subjects (10.9%) in the levetiracetam group discontinuing due to AEs (Summary of Clinical Safety, pg. 21). UCB added that four subjects (6.3%) in the levetiracetam group withdrew consent (Summary of Clinical Safety, pg. 21).

Reviewer comment: *In their summaries of safety, the sponsor stated that one levetiracetam-treated patient discontinued the study due to thrombocytopenia. This patient and other data related to thrombocytopenia are discussed in more detail in Section 5.7 of this review.*

5.4 Common Adverse Events

Reviewer comment: *Psychiatric adverse events are discussed in more detail in Section 5.5 of this review.*

5.4.1 Issues in the Capture and Calculation of Adverse Events

I identified three primary issues regarding the capture and examination of adverse event data within the levetiracetam pediatric studies.

First, at the beginning of their summary of common adverse events, the sponsors noted that:

- "In the 1 Month to <4 Years Pool, subjects in N157 had the potential to be exposed to levetiracetam for a duration of up to 3 years, while subjects in N01148 had the potential to be exposed to LEV for a duration of up to approximately 49 weeks. Therefore, when comparing cumulative percentages, subjects in N01052 + N157 would be expected to have a higher percentage due to a longer surveillance period for collection of TEAE data in N157 (Summary of Clinical Safety, pg. 40)"
- In the 4 Years to 16 Years Pool, the levetiracetam group had a longer duration of exposure (an additional 12 weeks of levetiracetam in N01103) compared with

[23] The sponsor defined the ITT subjects as subjects who were randomized and received at least one dose of study medication.

both the PBO and SF/DE groups by original treatment assignment (Summary of Clinical Safety, pg. 40)."

Reviewer comment: *Based on the unequal time lengths between studies, it is unclear why the sponsor did not present their safety data as rates as opposed to risks. However, as shown below, most of the sponsors' tables are stratified by study, and comparisons can therefore be made between drug and placebo arms within the same study. This reduces the effect of the differential exposures between studies, but this should be kept in mind whenever the development program data is pooled across studies.*

A second issue regards the sponsor's use of the term "treatment emergent adverse events" or "TEAEs" to refer to adverse events within the pediatric trials reviewed here.

Reviewer comment: *The use of the term "treatment-emergent" adverse event raises the concern that the sponsor may have disregarded some adverse events that occurred during treatment under the rationale that if the subject had similar events prior to entering the study, the event was not "treatment emergent." However, in Study NO1009, the sponsor clarified that "treatment emergent" referred to "any event with an onset date on or after the date of first study drug administration."*

Finally, the sponsor defined *common* adverse events as those experienced by at least 2% of subjects. The most common adverse events were defined as those occurring in at least 5% of patients.

Reviewer comment: *Different development programs utilize different cut-off values for common and most common adverse events. I believe that using a 2% prevalence for common adverse events is appropriate and provides for good case capture without inclusion of an excessive amount of "noise" through a cut-off value that is too low.*

5.4.2 Common Adverse Events: 1 Month to < 4 Years

UCB summarized the *most* common adverse events (those occurring ≥5 of patients) within the 1 month to <4 year cohort in the table below.

FDA Table 18: Common TEAEs Occurring in ≥5 of Subjects Overall in the 1 Month to <4 Years Cohort (Adapted from Sponsor Table 2.7.4.20, Summary of Clinical Safety, pg. 41)

MedDRA PT	Original Treatment Assignment			N01052 + N157 (N=14)	Overall (N=168)
	N01009 + N01148				
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
	n (%)				
Pyrexia	13 (24.5)	30 (50.0)	18 (43.9)	7 (50.0)	68 (40.5)
Upper respiratory tract infection	11 (20.8)	17 (28.3)	11 (26.8)	8 (57.1)	47 (28.0)
Vomiting	7 (13.2)	11 (18.3)	8 (19.5)	4 (28.6)	30 (17.9)
Convulsion	7 (13.2)	9 (15.0)	7 (17.1)	6 (42.9)	29 (17.3)
Diarrhoea	5 (9.4)	14 (23.3)	7 (17.1)	2 (14.3)	28 (16.7)
Nasopharyngitis	6 (11.3)	8 (13.3)	10 (24.4)	4 (28.6)	28 (16.7)
Irritability	4 (7.5)	13 (21.7)	6 (14.6)	3 (21.4)	26 (15.5)
Otitis media	3 (5.7)	7 (11.7)	7 (17.1)	6 (42.9)	23 (13.7)
Cough	6 (11.3)	7 (11.7)	7 (17.1)	2 (14.3)	22 (13.1)
Somnolence	2 (3.8)	13 (21.7)	4 (9.8)	3 (21.4)	22 (13.1)
Constipation	6 (11.3)	12 (20.0)	0	3 (21.4)	21 (12.5)
Ear infection	5 (9.4)	6 (10.0)	5 (12.2)	3 (21.4)	19 (11.3)
Rash	2 (3.8)	8 (13.3)	6 (14.6)	2 (14.3)	18 (10.7)
Bronchitis	6 (11.3)	7 (11.7)	2 (4.9)	2 (14.3)	17 (10.1)
Rhinitis	6 (11.3)	6 (10.0)	4 (9.8)	0	16 (9.5)
Pharyngitis	4 (7.5)	5 (8.3)	4 (9.8)	1 (7.1)	14 (8.3)
Head injury	4 (7.5)	3 (5.0)	5 (12.2)	0	12 (7.1)
Influenza	6 (11.3)	4 (6.7)	2 (4.9)	0	12 (7.1)
Viral infection	4 (7.5)	4 (6.7)	3 (7.3)	1 (7.1)	12 (7.1)
Gastroenteritis	1 (1.9)	6 (10.0)	1 (2.4)	3 (21.4)	11 (6.5)
Pneumonia	4 (7.5)	2 (3.3)	4 (9.8)	1 (7.1)	11 (6.5)
Anorexia	2 (3.8)	8 (13.3)	0	0	10 (6.0)
Decreased appetite	1 (1.9)	4 (6.7)	2 (4.9)	3 (21.4)	10 (6.0)
Teething	1 (1.9)	5 (8.3)	2 (4.9)	2 (14.3)	10 (6.0)
Urinary tract infection	2 (3.8)	6 (10.0)	2 (4.9)	0	10 (6.0)
Upper respiratory tract congestion	2 (3.8)	4 (6.7)	2 (4.9)	1 (7.1)	9 (5.4)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; TEAE=treatment-emergent adverse event
Sorted by descending frequency overall.
Source: ISS Table 16.4.1:25

In the 1 Month to <4 Years cohort, based upon the table above UCB stated that the most frequently reported common AEs in levetiracetam-treated patients overall were pyrexia (40.5%), upper respiratory tract infection (28.0%), vomiting (17.9%), and convulsion (17.3%). The sponsor asserted that "the percentage of common adverse events was generally similar across groups by original treatment assignment." Exceptions included pyrexia, which was reported for 24.5% of subjects with placebo as their original treatment assignment, compared with 50.0% levetiracetam and 43.9% for SF/DE.

Reviewer comment: *Reviewing the table above, I observe a number of AEs which show an approximately two-fold difference between the levetiracetam and placebo groups, including diarrhea (23% levetiracetam, 9% placebo), otitis media (11.7% levetiracetam, 5.7% placebo), and constipation (20.0% levetiracetam, 11.3% placebo). In addition, the table above labels the AEs listed as occurring in "N01009 +N01148," and so is apparently a combination of AE data from a placebo-controlled study (N01009) and open-label (N01148) studies. Because of this, and because the data is presented as*

absolute numbers and risk (as opposed to rate, which would have been more appropriate as the sponsor commented several times on the longer exposure time to drug than placebo), the interpretation of the data in this table is not straightforward. Data from within the placebo-controlled portions of single trials is presented in Section 5.4.4 below.

UCB commented on the differential occurrence of somnolence, which was reported by 3.8% of placebo subjects and 9.8% of SF/DE subjects, compared with 21.7% of levetiracetam subjects. In Study N01009, somnolence (1.8% placebo, 13.3% levetiracetam) and irritability (0% placebo, 11.7% levetiracetam) occurred in ≥5% of subjects in the levetiracetam group and were at least two-fold higher in the levetiracetam group compared to placebo. The sponsor described both events as "transient and likely related to the rapid up-titration of levetiracetam in Study NO1009," as most of the events occurred in this short-term study (6 treatment days in the placebo-controlled phase)(Clinical Overview, pg. 22).

Reviewer comment: *In longer-term, open-label studies in the 1 Month to <4 Years cohort, somnolence and irritability remained among the most commonly reported adverse events. The risk of these events may be increased in settings of rapid titration, but they are not limited to them.*

5.4.3 Common Adverse Events: 4 Years to 16 Years

The most common adverse events (those occurring ≥5 of patients) within the 4 Years to 16 Years cohort are shown in the table below.

FDA Table 19: Common Adverse Events Occurring in ≥5% of Subjects in the 4 Years to 16 Years Cohort (Adapted from Sponsor Table 2.7.4.21, Summary of Clinical Safety, pg. 42)

Appears This Way On Original

MedDRA PT	Original Treatment Assignment N01103 + N01148			Overall (N=117)
	PBO (N=30)	LEV (N=64)	SF/DE (N=23)	
	n (%)			
Headache	11 (36.7)	24 (37.5)	2 (8.7)	37 (31.6)
Upper respiratory tract infection	8 (26.7)	18 (28.1)	2 (8.7)	28 (23.9)
Pyrexia	4 (13.3)	15 (23.4)	4 (17.4)	23 (19.7)
Nasopharyngitis	7 (23.3)	12 (18.8)	1 (4.3)	20 (17.1)
Abdominal pain upper	2 (6.7)	17 (26.6)	0	19 (16.2)
Vomiting	3 (10.0)	13 (20.3)	1 (4.3)	17 (14.5)
Fatigue	3 (10.0)	11 (17.2)	0	14 (12.0)
Somnolence	1 (3.3)	11 (17.2)	2 (8.7)	14 (12.0)
Aggression	3 (10.0)	10 (15.6)	0	13 (11.1)
Rash	5 (16.7)	6 (9.4)	1 (4.3)	12 (10.3)
Irritability	2 (6.7)	8 (12.5)	1 (4.3)	11 (9.4)
Nasal congestion	1 (3.3)	10 915.6)	0	11 (9.4)
Abnormal behaviour	1 (3.3)	8 (12.5)	1 (4.3)	10 (8.5)
Diarrhoea	1 (3.3)	7 (10.9)	2 (8.7)	10 (8.5)
Dizziness	3 (10.0)	7 (10.9)	0	10 (8.5)
Cough	0	8 (12.5)	1 (4.3)	9 (7.7)
Pharyngolaryngeal pain	2 (6.7)	7 (10.9)	0	9 (7.7)
Decreased appetite	2 (6.7)	6 (9.4)	0	8 (6.8)
Nausea	2 (6.7)	6 (9.4)	0	8 (6.8)
Epistaxis	0	6 (9.4)	1 (4.3)	7 (6.0)
Gastroenteritis viral	2 (6.7)	5 (7.8)	0	7 (6.0)
Psychomotor hyperactivity	3 (10.0)	4 (6.3)	0	7 (6.0)
Rhinorrhoea	1 (3.3)	5 (7.8)	1 (4.3)	7 (6.0)
Back pain	3 (10.0)	3 (4.7)	0	6 (5.1)
Convulsion	2 (6.7)	4 (6.3)	0	6 (5.1)
Influenza	1 (3.3)	5 (7.8)	0	6 (5.1)
Insomnia	0	5 (7.8)	1 (4.3)	6 (5.1)
Otitis media	2 (6.7)	3 (4.7)	1 (4.3)	6 (5.1)
Pain in extremity	3 (10.0)	3 (4.7)	0	6 (5.1)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; TEAE=treatment-emergent adverse event
Source: ISS Table 16.4.1:26

Regarding the table above, UCB wrote "The percentage of TEAEs was generally higher in the LEV group than the PBO and SF/DE groups and may be due to the longer duration of exposure for the LEV compared with the other groups by original treatment assignment. The percentage of common TEAEs was lowest in the SF/DE group and is probably related to the short duration of exposure to LEV and to regional differences."

Reviewer comment: *As noted previously, if there is a significant difference in exposure times between study arms, the data is best shown as a rate, as opposed to a risk. In addition, as with the table for the 1 Month to <4 Years cohort, this table also combined data from a 12-week, placebo-controlled study (NO1103) and a 48-week open-label data (NO1148). As such, the levetiracetam-treated subjects, with the additional open-label exposure, likely had a longer exposure period than placebo, and therefore more time for AEs to development, whether drug related or not.*

The sponsor did not comment on the most common adverse events with the greatest difference between the drug and placebo arms. From the table above, these adverse events were: somnolence (17% levetiracetam, 3% placebo), upper abdominal pain (27% levetiracetam, 7% placebo), nasal congestion (16% levetiracetam, 3% placebo), abnormal behavior (12% levetiracetam, 3% placebo), vomiting (20% levetiracetam, 10% placebo), pyrexia (23% levetiracetam, 13% placebo) and irritability (12% levetiracetam, 7% placebo).

5.4.4 Common AEs: Data from Placebo-Controlled Studies

5.4.4.1. Study N01009

In Study NO1009 (patient ages 1 month to < 4 years) the sponsor listed the common AEs (those occurring in ≥2% of levetiracetam subjects at a percentage at least two-fold higher than placebo) as: ***Somnolence*** (1 subject [1.8%] in the placebo group and 8 subjects [13.3%] in the levetiracetam group), ***Irritability*** (0 subjects in the placebo group and 7 subjects [11.7%] in the levetiracetam group), as well as ***convulsion***, ***fatigue*** and ***food aversion*** (each with 0 subjects in the PBO group and 2 subjects [3.3%] in the LEV group).

UCB commented that the common AEs in N01009 were generally similar to those in the overall 1 Month to <4 Years cohort, although "common TEAEs generally occurred at a higher percentage in the 1 Month to <4 Years Pool due to the longer duration of exposure to levetiracetam (Summary of Clinical Safety, pg. 43)."

5.4.4.2 Study N01103

In Study N01103 (patient ages 4 years to 16 years), the drug-related TEAEs that were reported by >5% of subjects and reported proportionally more frequent in the levetiracetam group were somnolence (placebo 8.8%; levetiracetam 14.1%), aggression (placebo 8.8%; levetiracetam 10.9%), fatigue (placebo 8.8%; levetiracetam 9.4%), headache (placebo 5.9%; levetiracetam 7.8%), mood altered (placebo 0; levetiracetam 6.3%), abdominal pain upper (placebo 2.9%; levetiracetam 6.3%), and insomnia (placebo 2.9%; levetiracetam 6.3%)(Study N01103 Study Report, pg. 8).

5.4.4.3 Reviewer Conclusions

Certain findings from the controlled trial data are notable. First, it is interesting that somnolence is a common adverse event with a predominance in the levetiracetam group in younger patients (1 Month to <4 Years – Study NO1009), while both somnolence and insomnia were common adverse event with a levetiracetam predominance in older patients (4 years to 16 years).

In addition, nasal congestion was one of the most common AEs in the older pediatric patients (those 4 years to 16 years), but was not commonly reported for the younger patients. As discussed in the analysis of patient deaths (Section 5.1.3.3), although the

combined placebo-controlled and open-label data showed a greater risk of infections for levetiracetam in all ages, the data from the controlled trials alone showed infections to be less or equivalent in the levetiracetam group compared to placebo.

5.5 Psychiatric Adverse Events

5.5.1 Overview

After nervous system adverse events, the second most common SOC for adverse events in levetiracetam-treated patients was psychiatric. To address concerns raised by early reports of psychiatric adverse events with levetiracetam treatment of pediatric patients, the sponsor performed a subsequent study (NO1103) and testing included a more detailed assessment of psychiatric events. These results of these testing are summarized in the sections below.

5.5.2 Literature Reports

As part of the evaluation of the topic, I performed a literature search for case reports of psychiatric adverse events in children treated with levetiracetam. The search revealed a number of case reports, commentary and a case-control study, as summarized below.

FDA Table 20: Summary of Case Reports in the Literature of Psychiatric Adverse Events in Children treated with Levetiracetam

Publication	Summary of Events
Kossoff et al. 2002[24]	A 13-year-old developed auditory hallucination, insomnia and "screaming behavior" three months after initiation of levetiracetam.
	A 16-year-old became agitated, hyperreligious and had persecutory delusions seven days after starting treatment with levetiracetam.
	A 17-year-old girl experienced auditory hallucinations telling her to sing and yell after 30 days of levetiracetam treatment.
	A 5-year-old girl experienced visual hallucination of spiders in her room 14 days after starting levetiracetam.
Youroukos et al. 2003[25]	A 12-year-old-girl with idiopathic partial epilepsy with secondary generalization developed acute psychosis 10 days after starting on levetiracetam. The patient was already receiving sodium valproate, when levetiracetam was added (final dosage of 60 mg/kg). Complete seizure control was achieved but the patient developed hallucinations, agitation and self-harming behavior, as well as poor social contact. The psychotic behavior resolved completely soon after the

[24] Kossoff EH, Bergey GK, Freeman JM and Vining E. Levetiracetam psychosis in children with epilepsy. Epilepsia 2002; 42(12):1611-1613.

	discontinuation of levetiracetam.

For the cases reported by Kossoff et al., the onset of symptoms ranged from 2 days to 3 months after initiation of levetiracetam. In all four patients the symptoms resolved following dose reduction (in one patient) or discontinuation (in three patients). The authors recommended slower titration, beginning at 10 mg/kg/day and increasing to 20 mg/kg/day over four weeks, to reduce the risk of psychiatric adverse events.

In a case-control study conducted by White et al.[26] the investigators assembled a study population of 553 patients treated with levetiracetam, with patients who discontinued levetiracetam due to behavioral reasons used as index cases. The controls consisted of patients starting levetiracetam "immediately after the index cases." The investigators considered the following as potential risk factors: age, gender, cognitive function, history of psychiatric diagnosis, epilepsy syndrome, number of AEDs, titration rate, maximal dose of levetiracetam, and levetiracetam level at maximal dose.

The investigators found that 38 (6.9%) of patients discontinued levetiracetam due to behavioral abnormalities. The variables associated with discontinuation included faster titration rate to maximal dose, a history of a psychiatric disorder, and diagnosis of symptomatic generalized epilepsy.

Reviewer comment: *Of note, the White et al. investigators found that patients discontinuing levetiracetam due to behavioral reasons had a significantly lower maximal dose than controls. This suggests that behavioral adverse events may not fit a dose-response pattern, but instead may occur at lower doses in susceptible individuals, such as those with a history of prior neuropsychiatric symptoms. Although both the White investigators and the sponsor have associated titration with increased risk, one case of psychosis in the levetiracetam development program (ISS No. 5466) was reported during the Down-Titration/Withdrawal Phase, suggesting that changes in doses, and not only increases, may elevate risk.*

5.5.3 Psychiatric Adverse Events: 1 Month to < 4 Years

In combined placebo-controlled and open-label data for the 1 Month to <4 Years cohort, 42% of levetiracetam-treated patients and 20% of placebo-treated patients had at least

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[25] Youroukos S, Lazopoulou D, Michelakou D, Karagianni J. Acute psychosis associated with levetiracetam. Epileptic Disord. 2003 Jun;5(2):117-9.

[26] White JR, Walczak TS, Lepik IE et al. Discontinuation of levetiracetam because of behavioral side-effects: a case-control study. Neurology 2003;61:1218–1221.

one psychiatric adverse event. UCB noted that irritability (26 subjects, 15.5%) was the only event reported for ≥5% of subjects. The sponsor asserted that the events "occurred early in treatment (0 to <4 weeks)"(Clinical Overview, pg. 24).

Reviewer comment: *In the literature sources and the case reports in the levetiracetam-treated patients within the pediatric development program, the psychiatric adverse events in the 1 month to 4 Year patients are manifested primarily as irritability, agitation and aggression, as opposed to more overtly psychotic symptoms in older children. However, the etiology of the psychiatric events may be the same for both age groups, with the youngest patients unable to express themselves sufficiently for psychosis to be recognized. The fact that the psychiatric adverse events in younger children are primarily irritability is therefore less reassuring.*

UCB summarized the psychiatric adverse events in patients aged 1 month to <4 Years in the table below.

FDA Table 21: Psychiatric AEs Occurring in ≥2% in the 1 Month to <4 Year Cohort (Adapted from Sponsor Table 2.7.4.33, Summary of Clinical Safety, pg. 73)

UCB HLGT/MedDRA PT	Original Treatment Assignment N01009 + N01148			N01052 + N157 (N=14)	Overall (N=168)
	PBO (N=53)	LEV (N=60)	SF/DE (N=41)		
	n (%)				
Number of subjects with at least 1 event	11 (20.8)	25 (41.7)	12 (29.3)	4 (28.6)	52 (31.0)
Anxiety disorders	1 (1.9)	5 (8.3)	1 (2.4)	0	7 (4.2)
Restlessness	1 (1.9)	3 (5.0)	1 (2.4)	0	5 (3.0)
Non-psychotic behavior	0	4 (6.7)	0	0	4 (2.4)
Irritability[a]	0	4 (6.7)	0	0	4 (2.4)
Non-psychotic behavioural disorders	8 (15.1)	15 (25.0)	10 (24.4)	3 (21.4)	36 (21.4)
Aggression	1 (1.9)	2 (3.3)	3 (7.3)	0	6 (3.6)
Agitation	2 (3.8)	2 (3.3)	1 (2.4)	0	5 (3.0)
Irritability[a]	4 (7.5)	9 (15.0)	6 (14.6)	3 (21.4)	22 (13.1)
Sleep disorders	4 (7.5)	10 (16.7)	1 (2.4)	0	15 (8.9)
Insomnia	0	6 (10.0)	1 (2.4)	0	7 (4.2)

HLGT=high level group term; LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; TEAE=treatment-emergent adverse event

[a] Irritability was coded to the UCB HLGTs non-psychotic behavior (4 subjects) and non-psychotic behavioral disorders (22 subjects), for a total of 26 subjects (15.5%).

Source: ISS Table 16.4.1:23

Reviewer comment: *To better characterize exactly what was entailed by the adverse events coded as irritability, aggression and agitation in the table above, I reviewed the relevant sponsor narratives. However, the "narratives" for the patients in the 1 Month to <4 Years cohort contained no description of the events, but merely stated that "abnormal behavior,""irritability" etc. was reported on a particular study day, along with an assessment of severity and a determination on its relation to drug treatment. A typical example of a narrative stated "On 04-Sep-2006, 19 days after starting treatment,*

continuous aggression described as aggressive behavior was reported." I consulted the case report forms for three patients for further detail, but also was unable to find a verbatim description of the events. A request will be made to the sponsor to provide descriptions of the behaviors coded to the psychiatric adverse events in the 1 Month to <4 Years cohort.

The narratives for older patients (4 Years to 1 Years) are only slightly better than those for the younger children, which is disconcerting because the primary purpose of placebo-controlled Study N01103 was to better characterize psychiatric adverse events in this age group. Summaries of the behaviors for the older patients are provided in the following section of this review.

5.5.4 Psychiatric Adverse Events: 4 Years to 16 Years

The sponsor stated that, overall in the 4 Years to 16 Years cohort, a psychiatric TEAE was reported for 48 subjects (41.0%). The most frequently reported high level group term (HLGT) was non-psychotic behavioral disorders, reported for 35 subjects (29.9%). The most frequent PTs were aggression, reported for 13 subjects (11.1%), and irritability, reported for 11 subjects (9.4%). Abnormal behavior, aggression, insomnia, and irritability were reported for ≥5% of subjects, and most of these events occurred early in treatment (0 to <4 weeks)(Clinical Overview, pg. 24).

Reviewer comment: *As noted above, the narratives provided by the sponsor lacked a detailed description of the actual behaviors coded as psychiatric adverse events. I was able, however, to summarize some information on the behaviors involved from the narratives of patients in Study NO1103. The following table shows the verbatim descriptions and preferred terms for selected patients.*

FDA Table 22: Verbatim Descriptions and Preferred Terms for Selected Patients with Psychiatric Adverse Events in Study NO1103

Pt. ID	***Coded Term***	***Description of Behavior***
606/0012	*Dematillomania*	*Skin picking on fingers*
606/0012	*Negativism*	*"Worsened oppositional behavior"*
606/0013	*Excessive masturbation*	*Increase in masturbation activity*
623/0001	*Anxiety attack*	*Anxiety*

5.5.5 Psychiatric Adverse Events: Placebo-Controlled Trials

In the double-blind, placebo-controlled studies for both age cohorts, UCB acknowledged that patients in the levetiracetam group experienced more psychiatric adverse events than those in the placebo group. In N01009 (ages 1 month to <4 years), psychiatric AEs were reported for 16.7% of levetiracetam subjects compared to 5.4% of placebo subjects. In both N159 and N01103 (ages 4 Years to 16 Years), psychiatric AEs were reported for a higher percentage of subjects in the levetiracetam group (38.6% and 40.6%, respectively), than in placebo group (27.8% and 20.6%, respectively). The most frequent

PTs in the levetiracetam group of N159 were irritability (8.9%) and aggression (7.9%); aggression was the most frequent PT in N01103 (12.5%)(Clinical Overview, pg. 24).

UCB maintained that, in general, the percentage of psychiatric AEs occurring in ≥2% of levetiracetam subjects in the HLGT[27] non-psychotic behavioral disorders, non-psychotic mood disorders, and "sleep disorders" on LEV are generally very similar between the placebo-controlled studies for the two age cohorts (Clinical Overview, pg. 24).

Reviewer comment: *As noted above, the finding of a predominance in psychiatric adverse events in levetiracetam compared to placebo patients is consistent across studies and age cohorts, supporting a causal association.*

5.5.6 Psychiatric Adverse Events: Open-Label Data

At <48 weeks of exposure, UCB stated that 84 subjects (40.2%) in Study N157 had a psychiatric AE, compared with 30 subjects (29.1%) in Study N01148. At any exposure, 108 subjects (51.7%) in N157 had a psychiatric AE. The most frequent AEs in both studies were non-psychotic behavioral disorders, with a higher percentage in N157. In N157, "abnormal behavior" and aggression were also the most frequent AEs at any exposure (24 subjects [11.5%] and 22 subjects [10.5%], respectively). Aggression and irritability were the most frequent TEAEs in N01148, each reported for 8 subjects (7.8%)(Clinical Overview, pg. 24).

Reviewer comment: *The labeling and the summary of prior clinical studies within the final report for Study NO1103 make reference to a suicide attempt in a levetiracetam-treated patient in an unspecified trial. However, a search of the N01103 study report and all the sponsor's summaries of safety data (ISS, Summary of Clinical Safety and Clinical Overview)for "suicid" did not provide any further information on this subject of the nature of the suicide attempt. Of note, in Study NO1103 patients with a history of suicidal acts or ideation in the past six months were excluded from study participation. The sponsor did actively ask about the suicidal and self-injurious behaviors via the Achenbach Behavioral Checklist, which is preferable to open-ended questioning on adverse events.*

5.5.7 Cognitive and Neuropsychological Assessments

- The Bayley Scales of Infant Development-II (BSID-II) was performed in children 1 month to <4 years in N01009 and N01148.
- The Leiter International Performance Scale-Revised (Leiter-R), Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2), Achenbach Child Behavior Checklist (CBCL), and Child Health Questionnaire–50-item Parent Form (CHQ-PF50) were performed in N01103.
- In N01148, the Leiter-R and CBCL were performed for children aged 4 to 16 years.

[27] HLGT=Higher Level Group Term in the MedDRA coding system

- For N159 and N157[28], the CHQ-PF50 was completed.

Reviewer comment: *I did not see evidence in the written requests that the FDA specifically asked for the above-listed neurocognitive scales to be used. However, these appear to be widely used scales.*

In the BSID-II Pool, the sponsor stated that the raw scores for the BSID-II Mental and Motor Development scales and the Behavior Rating scales for both 24 weeks and 48 weeks suggest there was progressive mental development, while motor development and behavioral functioning were relatively stable over time in subjects aged 1 month to <4 years. The sponsor asserted that the BSID-II results provided no evidence of a pattern of developmental and behavioral deterioration in subjects on long-term LEV treatment (Clinical Overview, pg. 30).

In N01103 (the placebo-controlled study in patients aged 4 to 16 years), the sponsor stated that the primary cognitive and neuropsychological safety measure, (change in Leiter-R AM Memory Screen Composite score from Baseline to Week 12/EDV) was analyzed using a covariance (ANCOVA) model with treatment as the main effect. UCB reported that the change in score was similar in the placebo group (mean=5.17) and the levetiracetam group (mean=5.36). The secondary cognitive and neuropsychological safety variables were the changes in index scores on the WRAML-2 from Baseline to Week 12/EDV. UCB stated that no statistically significant treatment group differences were observed for any of the indexes (General Memory, Visual Memory, Verbal Memory, or Attention/Concentration) (Clinical Overview, pg. 29).

For the testing related to cognitive function in N01103, UCB reported that the descriptive and inferential analyses revealed little difference between the levetiracetam and placebo treatment groups. The treatment groups were not statistically significantly different in the change from Baseline to Week 12/EDV for either the Cognitive/Social Composite Standard Score or the Emotions/Regulations Composite Standard score from the Leiter-R Examiner's Rating Scale. The sponsor also stated that long-term treatment (N01148) in 4 to 16 year olds with levetiracetam did not show a negative effect on cognitive function as measured by Leiter-R AM Memory Screen Composite score. Leiter-R AM Memory Screen LS mean Composite scores showed similar improvement from Baseline, when compared to PBO, during double-blind treatment (N01103), and the small improvement from Baseline was maintained during open-label LEV treatment up to Week 48 (N01148)(Clinical Overview, pg. 29).

The sponsor stated that some neuropsychiatric testing indicated differences between treatment groups that reached statistical significance. Specifically, on the CBCL syndrome scores, the treatment group differences reached statistical significance on the Aggressive Behavior (LS mean=3.07; p=0.0126; 95% CI: 0.68, 5.46),and Total Problems scores (LS mean=11.54; p=0.0203; 95% CI: 1.85, 21.23). The sponsor characterized the

[28] The sponsor stated that in N157 the tests were performed after implementation of N157 Amendment 7 for subjects enrolled from N159 only.

pattern of mean performance for these scores as showing improvement in the placebo group, and worsening in the levetiracetam group (Clinical Overview, pg 29).

Reviewer comment: *The finding of a statistically significant increase in the risk of aggressive behavior in levetiracetam-treated patients compared to placebo is consistent with the adverse event reports of aggressive behavior.*

The sponsor noted that the CBCL scores indicated that subjects who entered and were assessed in long-term study N01148 did not experience a worsening, on average, in their behavioral or emotional functioning (Clinical Overview, pg. 29).

The sponsor noted that for some testing, the results during open-label treatment (N01148) appeared to show somewhat different trends than those seen during the double-blind, placebo-controlled study (N01103). For instance, for the CBCL Aggressive Behavior, Externalizing Syndromes, and Total Problems scores, the levetiracetam-treated patients showed a statistically significant worsening compared to the placebo-treated subjects, during double-blind treatment. UCB noted that this worsening largely resolved during subsequent open-label treatment (Clinical Overview, pg. 30).

The sponsor noted that the slight worsening seen in levetiracetam -treated subjects from N01103 and N159 for Externalizing Behavior scores (captured with the CBCL and with the CHQ-PF50) "is consistent with the safety profile described in the drug label."

5.5.8 Psychiatric Adverse Events: Reviewer Conclusions

A number of factors are supportive of a causal relationship between the psychiatric adverse events and levetiracetam treatment. These are listed below.

1. ***Strength of Association:*** *In the placebo-controlled studies, the rate of psychiatric adverse events among levetiracetam-treated patients was higher than that in patients receiving placebo.*

2. ***Consistency Between Studies:*** *The elevation in adverse events compared to placebo was observed across placebo-controlled studies, and across neuropsychological testing.*

3. ***Consistency Between Age Groups:*** *Psychiatric adverse events were also observed in the adult development program for levetiracetam.*

4. ***Clinical Relevancy of Symptoms****: Behavioral and psychiatric adverse effects with levetiracetam are apparently known within the community of neurologists and other providers familiar with AED treatment, as judged by the number of case reports and other publications on the topic.*

If not done previously, a search of the AERS database may be helpful in further understanding the course and extent of psychiatric events during treatment with levetiracetam. However, I believe there is already sufficient evidence within the

levetiracetam development program to establish a causal link. One question the AERS analysis may be able to address is whether levetiracetam is associated with more psychiatric abnormalities than other anti-epileptic drugs.

The neuropsychiatric testing performed throughout the levetiracetam pediatric development program provided some reassurance that overall development is not harmed by levetiracetam treatment. However, if approved these issues should continued to be monitored in the post-marketing period.

5.6 Laboratory Data

5.6.1 Laboratory Data Collection

In patients aged 4 Years to 16 Years (NO1103), samples for laboratory evaluation were collected at the fist and sixth study visit. Laboratory testing was performed by a central laboratory.

5.6.2 Laboratory Data Results

UCB stated that in the 1 Month to <4 Years cohort, no "clinically relevant differences from Baseline" were noted in hematology laboratory parameters.

Reviewer comment: *The primary concern with laboratory values in the levetiracetam pediatric patients is thrombocytopenia. The Office of Drug Safety is currently reviewing cases of thrombocytopenia with levetiracetam treatment in the AERs database. In the pediatric levetiracetam development program, the data was mixed. The sponsor asserted that no trends of continuing decrease of platelet count, lymphocyte count, or eosinophil count over time by analysis interval were observed "(Clinical Overview, pg. 26). However, two subjects had TEAEs of platelet count decreased and one subject discontinued the study due to an TEAE of thrombocytopenia. During open-label, long-term levetiracetam treatment, the sponsor stated that there was a statistically significant decrease from Baseline in platelet count. However, during double-blind treatment, mean platelet count was essentially unchanged from Baseline in the levetiracetam group, while the placebo group showed a decrease after 5 days of treatment.*

Reviewer comment: *Given the short placebo-controlled phase for patients aged 1 Month to 4 Years (6 days), the longer-term, open-label data are likely more relevant in assessing laboratory values over time.*

In the 4 Years to 16 Years cohort, the sponsor stated that there were "very few" possibly clinically significant (PCS) hematology values or hematology-related TEAEs reported in the 4 Years to 16 Years cohort, and that "Overall, none of the subjects had treatment-emergent PCS platelet count values" (Clinical Overview, pg. 26).

In both placebo-controlled studies (N01009 and N01103), the sponsor reported that there were no relevant differences between levetiracetam and placebo patients in hematological values reported as a TEAE (specifically, platelet count decreased). In N01103, two subjects (6.1%) in the placebo group and five subjects (8.6%) in the levetiracetam group had a high eosinophil count values that met PCS criteria. UCB noted that both levetiracetam subjects and one placebo subject with PCS high eosinophil counts also had TEAEs of rash, and that an allergic reaction could have contributed to the (Clinical Overview, pg. 27).

In both age pools, UCB reported that there were no clinically relevant changes from Baseline for all blood chemistry parameters during levetiracetam treatment. The sponsor noted that in the 1 Month to <4 Years cohort, 0.7% of subjects had PCS AST "too high", 1.3% of subjects had PCS ALT "too high", and 5.1% of subjects had PCS GGT "too high" during the Overall Treatment Phase. Treatment-emergent AEs related to liver function test results included: 1.2% of subjects each with ALT increased and AST increased; and 0.6% of subjects each with GGT /transaminases increased.

In placebo-controlled studies N01009 (aged 1 Month to <4 Years) and N01103 (aged 4 Years to 16 Years), UCB asserted that "no general trend in blood chemistry changes related to levetiracetam exposure could be detected" (Clinical Overview, pg. 27).

Reviewer comment: *I reviewed the laboratory data within placebo-controlled studies NO1009 and NO1103 and found the sponsor's statement above to be overall correct.*

5.7 Vital Sign Data

5.7.1 1 Month to <4 Years

In placebo-control study NO1109 (patients aged 1 Month to <4 Years), vital sign data was collected at baseline and throughout the inpatient placebo-controlled period.

In the 1 Month to <4 Years cohort during open-label treatment, the sponsor stated that the 95% CI around the median change from Baseline to the Last Value in weight percentile did not exclude zero. The sponsor stated, however, that there was a statistically significant decrease from Baseline in height percentile (mean [median] change from Baseline: -4.00 [-1.58], 95% CI: -5.20 to -0.10). UCB commented that this suggests that levetiracetam-treated the children "fell slightly" behind the growth curve in terms of height at the Last Value on Treatment (Clinical Overview, pg. 27).

Reviewer comment: *I was unable to locate other significant sponsor commentary on the apparent decrease in growth in levetiracetam-treated children, as noted above. The sponsor should be asked to assess this in a more thorough manner. Should levetiracetam be approved, consideration should be given to requesting that the sponsor monitor patient height in the post-marketing period. This could be done through a cohort study within a medical records database.*

Pooled placebo-controlled and open-label data: A higher proportion of subjects in the 1 Month to <4 Years cohort had PCS heart rate values too low/decreased (27.5%), compared to PCS heart rate values too high/increased (7.2%). A higher proportion of subjects had PCS systolic blood pressure too high/increased (12.1%) compared to 7.3% of subjects with PCS systolic blood pressure too low/decreased. UCB stated that there was "overall….there was no correlation observed between PCS heart rate too low/decreased, and systolic and diastolic blood pressure too high/increased" (Clinical Overview, pg. 27).

Placebo-controlled data: During N01009, a higher proportion of subjects in the levetiracetam group, compared to the placebo group, had PCS diastolic blood pressure too high/increased (16.7% vs. 1.8% of subjects, respectively) and PCS heart rate too low/decreased (21.7% vs. 12.5% of subjects, respectively).

Reviewer comment: *In Study N01009, Possibly Clinically Significant (PCS) criteria for diastolic blood pressure was defined as:*

- For 1 m to < 12 m: < 40 mmHg and a decrease of > 15 mmHg from baseline or > 60 mmHg and an increase of > 20 mmHg from baseline

- For 12 m to < 6 y: < 45 mmHg and a decrease of > 15 mmHg from baseline or > 80 mmHg and an increase of > 20 mmHg from baseline

The sponsor stated that no correlation was observed between increase in diastolic blood pressure and decrease in heart rate (Clinical Overview, pg. 27). The sponsor also noted that:

> "The subjects were evaluated each day during the hospitalization for the study and the changes were not persistent or uniform each day. Four subjects in the LEV group had more than one post-baseline PCS diastolic blood pressure value too high, however, a majority of these subjects had varied extents of elevated diastolic blood pressure values during screening prior to baseline. None of the PCS diastolic blood pressure values were reported as an AE."

Reviewer comment: *The sponsor did not comment further on the substantial difference in patients with PCS increases in diastolic blood pressure (16.7% in levetiracetam patients, 1.8% in placebo patients) and decreased heart rate (21.7% in levetiracetam patients, 12.5% in placebo).*

For the increase in diastolic blood pressure, in Study N01009 the actual number of patients affected was 10 in the levetiracetam-treatment group (17%) and 1 in the placebo-treatment group (1.8%). Five levetiracetam-treated patients had a diastolic blood pressure increase of greater than 20 mmHg, compared to one placebo-treated patient.

When the average diastolic blood pressure for the levetiracetam- and placebo-treated patients within Study N01009 were compared by hospital day[29], the results were the following (figures taken from Table 14.3.6:1, Study N01009 Report, pg. 583):

Hospital Day	***Levetiracetam-Treated Patients***	***Placebo-Treated Patients***
1	*55.9*	*59.7*
2	*60.6*	*62.1*
3	*58.3*	*59.6*
4	*57.2*	*58.0*
5	*58.0*	*59.9*
6	*58.3*	*59.7*

As such, although there was an imbalance in the number of patients meeting the PCS criteria for diastolic blood pressure increased, there was not an imbalance by treatment group in the average daily diastolic blood pressure.

In the older cohort of patients (aged 4 to 16 years), during the placebo-controlled trial (N01103) 1 levetiracetam-treated patient (1.6% out of a total of 46 levetiracetam patients) and 1 placebo-treated patient (2.9% of a total of 34 placebo patients) were classified as PCS diastolic blood pressure too high/increased.

An increase in diastolic blood pressure is not described in the adult labeling for levetiracetam.

Based on the magnitude of the disparity (17% versus 2%), the increase in the number of patients with PCS diastolic blood pressure increased in the levetiracetam compared to placebo patients in the 1 Month to <4 Year age group is concerning and should be described in labeling. However, a number of the factors just discussed, such as the lack of replication in the other age groups and the equivalent overall diastolic blood pressures in the 1 Month to <4 Years age group, mitigate this concern somewhat.

5.7.2 4 Years to 16 Years

In placebo-controlled study N01103 (patients aged 4 years to 16 years), vital signs were collected from patients at all study visits.

In the 4 Years to 16 Years Pool, the sponsor stated there were no "relevant" changes from Baseline during double-blind treatment for all vital sign parameters. During levetiracetam treatment, the most frequently reported PCS vital sign parameters were weight increase, weight decrease, and diastolic blood pressure too low/decreased. UCB noted that only one vital sign-related TEAE (weight decreased) was reported in the 4 Years to 16 Years pool. The percentage of subjects with abnormal vital sign values or

[29] The placebo-controlled period from this study was 6 days inpatient hospitalization.

TEAEs related to vital signs did not appear to increase with time in the long-term, open-label LEV treatment (Clinical Overview, pg. 28).

The sponsor noted that, "as expected", increases from Baseline to Last Value on Treatment were observed for weight and height. UCB asserted that "no clinically relevant changes in weight percentile and height percentile were noted" (Clinical Overview, pg. 28).

Reviewer comment: *Unlike in the younger children, the older patients (aged 4 to 16 years) did not demonstrate a decrease in growth trends over time.*

5.8 ECGs

In the 1 Month to <4 Years Pool, the sponsor stated that ECGs were not performed during the 6-day double-blind treatment in N01009, but were performed during open-label long-term treatment. These were interpreted locally at each site rather than a central ECG reader (Clinical Overview, pg. 30).

Reviewer comment: *The FDA's guidance on assessing QT intervals recommends use of a central reader.*

In the older patients (those aged 4 Years to 16 Years), the sponsor used the following criteria to classify values as Potentially Clinically Significant (PCS). Separate values were used for the younger patients.

FDA Table 23: Potentially Clinically Significant Criteria for ECG Parameters (Adapted from Sponsor Table 12:37, NO1103 Study Report, pg. 168)

Table 12:37 Potentially Clinically Significant Criteria for ECG Parameters

ECG Parameter	Age	PCS Criteria
Ventricular Rate	3 to <12 years	≤65 bpm and a decrease of ≥20 bpm from baseline or ≥130 bpm and an increase of ≥20 bpm from baseline
	12 to <17 years	≤60 bpm and a decrease of ≥20 bpm from baseline or ≥120 bpm and an increase of ≥20 bpm from baseline
PR Interval	3 to <11 years	≥170 ms or ≥25% increase from baseline
	11 to <17 years	≥175 ms or ≥25% increase from baseline
QRS Interval	1month to <7years	≥78 ms or ≥25% increase from baseline
	7 to <17 years	≥88 ms or ≥25% increase from baseline
QT Interval	≥17 years	≥500 ms or ≥15% increase from baseline
QTc Interval	<17 years	≥440 ms or ≥15% increase from baseline

Source: Appendix 16.1.9

During long-term treatment (open-label studies) with levetiracetam, the sponsor reported that the 95% C.I. around the median change from Baseline to the Last Value included zero for all ECG parameters, except for an increase from Baseline in QTc Fridericia

interval (median increase of 5.87 msec [95% CI: 0.96, 11.51])(Clinical Overview, pg. 30).

Reviewer comment: *In preclinical studies, UCB asserted that levetiracetam did not prolong the cardiac action potential duration in vitro or QT corrected for heart rate in dogs at up to 600 mg/kg po.*

In the 1 Month to <4 Years cohort, UCB stated there were 16 subjects (16.7%) with a post-Baseline PCS value for prolonged QTc, although the sponsor stated that three subjects no longer met PCS criteria based on a post-database lock review. The sponsor further noted that 3 out of 16 subjects had a PCS prolonged QTc interval at Baseline. Overall, 20 subjects had a PCS QTc interval by Bazett or Fridericia at Baseline (Clinical Overview, pg. 30).

Of the 16 subjects with a post-Baseline PCS value by either Bazett or Fridericia, the sponsor reported that seven subjects had a change from Baseline equal or greater to 60 msec, although the sponsor then stated that "two of these subjects did not meet PCS criteria."

Reviewer comment: *According to the E14 Guidance on conducting a thorough QT (TQT) study, a time-matched mean increase of more than 5 msec is considered a positive study. Although the data above was not collected using the detailed methods of a TQT study, an increase in 60 msec compared to baseline values is significant.*

Three subjects had a post-Baseline QTc equal to or greater than 500 ms, although the sponsor again stated that one of these subjects "did not meet PCS criterion." A total of eight subjects had either a change from Baseline ≥60 msec or QTc ≥500 msec (Clinical Overview, pg. 30).

Reviewer comment: *The sponsor has been asked to perform a thorough QT (TQT) study for levetiracetam,* **(b) (4)** .

In the 4 years to 16 years patients within placebo-controlled study NO1103, 6.8% of patients treated with levetiracetam had a PCS increase in the QT interval by the Fridercia correction method compared to 3.8% in the placebo group. When the Bazett's correction was used, however, the risk was similar between groups (8.5% placebo, 9.4% levetiracetam).

One patient in the 4 Year to 16 Year cohort experienced an AE related to QT interval prolongation, for which the sponsor provided the following narrative (NO1103 Study Report, 172):

LEV Subject 672/0001 was an 11.5-year-old Caucasian male with a history of femur fracture and tonsillitis, both of which were surgically treated. Baseline and Week 12 QTc intervals were recorded as 360 ms and 508.6 ms, respectively. No concomitant non-antiepileptic therapy was taken at the time of the ECG at Week 12, although cough medication was stopped 2 days prior to the ECG. The subject was taking carbamazepine (1200 mg/d) and valproic acid (2100 mg/d, then 200 mg/d starting at Visit 4) daily for treatment of epilepsy. The Investigator initially reported the ECG change at Week 12 as a TEAE and requested the opinion of a cardiologist, who considered this evaluation as within normal range. The subject entered the open-label follow-up study, and fourteen days after the reported TEAE of prolonged QTc interval, a follow-up ECG was performed by the consulting cardiologist. At this time, the Investigator considered the TEAE as resolved. In the interest of clarifying this event after database lock, there was follow-up communication with the Investigator. The Investigator, in retrospect, determined this was not an AE and the follow-up ECG data of the patient had been normal.

Aside from the QT changes, the sponsor stated that the only other abnormal ECG showed sinus tachycardia, ST segment elevation, and T wave inversion (Clinical Overview, pg. 30).

6. CONCLUSIONS AND RECOMMENDATIONS

In order to fulfill the requirements for a Pediatric Exclusivity Determination, the sponsor has performed studies on patients aged 1 month to 16 years. The data collected was generally divided into two age groups: patients aged 1 Month to < 4 Years and patients aged 4 years to 16 Years. The pediatric patient data was collected primarily as part of two placebo-controlled studies and two longer-term, open-label studies.

The primary safety issues uncovered during this review are:

1. ***Psychiatric AEs:*** The most frequent AE with levetiracetam treatment of pediatric patients was psychiatric adverse events, which in the clinical trials primarily consisted of irritability, agitation and aggression. Some patients did experience hallucinations, and this has also been published in case reports from the medical literature. The predominance of psychiatric adverse events compared to placebo was consistent across trials and age groups (16.7% in levetiracetam subjects, 5.4% in placebo subjects in the 1 Month to <4 Year cohort [Study N01009], and 41% in levetiracetam subjects, 21% in placebo patients in the 4 to 16 Year cohort [Study N01103]).

   Literature studies have suggested that the risk of psychiatric adverse events is greater in patients with pre-existing behavioral symptoms, as well as when higher doses and shorter titration periods are used. The association of psychiatric adverse events with these factors was generally supported in the clinical trials, although the variable dosing design did not allow for a ready dose-response analysis.

   Particularly in the patients aged 1 Month to <4 Years, the "narratives" provided by the sponsor lacked any details on the actual events that were coded to "abnormal

behavior," "irritability," etc. This is inadequate and the sponsor should be asked to provide narratives which describe the underlying, verbatim events.

2. ***Deaths:*** In the levetiracetam development program, the three deaths in patients actively treated with levetiracetam occurred among a total of 125 patient-years exposure in the 1 Month to 4 Year age group (See Section 4.2.2 of this review) for a rate of 24 per 1000 person-years. Rates of deaths in children with epilepsy has been estimated from 3.1 to 6.2 per 1000 person-years[30], making the rate in the levetiracetam pediatric development program approximately ten-fold higher. Some of this elevation in rate is likely due to the fact that these were younger pediatric patients (I was unable to find rates in children under 4 years alone) with more severe epilepsy, and the estimates of mortality with epilepsy in general were based on all patients with epilepsy. However, it is unclear if these factors would account for the total elevation in rate.

   Some of the death cases showed a clinical scenario similar to that of Reye's syndrome, with death and cerebral edema occurring shortly after a non-serious infection. In addition, other anti-epileptic drugs, specifically valproic acid (Depakote ®) have been associated with a Reye's-like syndrome.

   The sponsor did not provide any commentary on the deaths other than to state the investigators did not consider them drug-related. Given the apparent increase in the rate of death and the similarities of some cases to Reye's syndrome, this is an inadequate on the part of the sponsor. The sponsor should be asked to provide a more thorough discussion and analysis of the deaths throughout the levetiracetam pediatric development program.

3. ***Thrombocytopenia:*** The Office of Drug Safety (ODS) is currently evaluating case reports of thrombocytopenia with levetiracetam use in the AERS database. The information on thrombocytopenia within the levetiracetam pediatric patients is mixed. In the 1 Month to 4 Year group, one subject discontinued due to thrombocytopenia, and two others had AEs of platelets decreased.

4. ***QT Interval:*** The sponsor reported that seven subjects experienced a QTc change from Baseline equal or greater to 60 mec. This is a large value and warrants further investigation. The sponsor has performed a thorough QT study (TQT) in adult patients at the request of the FDA, and results have been submitted. **(b) (4)**

[redacted]

[30] Petra MC. Callenbach,Westendorp RG, Geerts AT et al. Mortality Risk in Children with Epilepsy: The Dutch Study of Epilepsy in Childhood. Pediatrics 2001;107;1259-1263.

5. ***Increased Diastolic Blood Pressure:*** Based on the magnitude of the disparity (17% versus 2%), the increase in the number of patients with PCS diastolic blood pressure increased in the levetiracetam compared to placebo patients in the 1 Month to <4 Year age group is concerning and should be described in labeling. However, a number of factors, such as the lack of replication in the other age groups and the equivalent overall diastolic blood pressures in the 1 Month to <4 Years age group, mitigate this concern somewhat.

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7. ATTACHMENTS

7.1 All Clinical Studies in Pediatric Patients treated with Levetiracetam

(Taken from Sponsor Table 2.7.4.1, Summary of Clinical Safety, pg. 7.)

Table 2.7.4:1 Clinical Studies in Pediatric Population with Levetiracetam

Study Number/ Design	Population	Objective	Dosage and Dosage Form	Duration of Study/ Status
Clinical Pharmacology Studies in Pediatric Epileptic Subjects with Partial Onset Seizures				
N01052 Multicenter, Open-Label, Single-Dose, PK	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=13)	Pharmacokinetic evaluation in infants and children aged <4 years	20 mg/kg Oral solution	3 weeks/ Completed
N01010 Multicenter, Open-Label, PK	Pediatric epileptic subjects with refractory partial onset seizures (4 to 12 years) (N=21)	Pharmacokinetic linearity and bidirectional evaluation of 2 AEDs and LEV	20 to 40 to 60 mg/kg/day Tablets	12 weeks/ Completed
N151 Multicenter, Open-Label, PK	Pediatric epileptic subjects with partial onset seizures (5 to 12 years) (N=24)	Pharmacokinetic, efficacy, and safety	10 to 40 mg/kg/day Tablets	22 weeks/ Completed
Placebo-Controlled Studies in Pediatric Epileptic Subjects with Partial Onset Seizures				
N01009 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=116)	Efficacy and safety	20 mg/kg/day to 50 mg/kg/day Oral solution	34 days/ Completed
N159 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (4 to 16 years) (N=216)[a]	Efficacy and safety	20 to 40 to 60 mg/kg/day Tablets	28 weeks/ Completed
N01103 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects (4 to 16 years) (N=99)	Monitor cognitive and neuropsychiatric effects and safety of LEV	20 to 60 mg/kg/day Tablets or Oral solution	19 weeks/ Completed

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