JOINT CLINICAL AND STATISTICAL REVIEW

Application Type	SNDA
Submission Number	21-035
Submission Code	S 073
Letter Date	March 18, 2008
Stamp Date	March 18, 2008
PDUFA Goal Date	September 19, 2008
Reviewer Name	Gerald D. Podskalny (Clinical) Fanhui Kong (Statistical)
Review Completion Date	September 18, 2008
Established Name	Levetiracetam
(Proposed) Trade Name	Keppra
Therapeutic Class	Antiepileptic
Applicant	UCB, Inc.
Priority Designation	P
Formulation	Tablets and Oral Solution
Dosing Regimen	Twice daily
Indication	Adjunctive Therapy for Partial Onset Seizures
Intended Population	Children with Epilepsy Ages 1 Month to 4 years

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1 Executive Summary

1.1 Recommendations/Risk Benefit Assessment

1.2 Recommendation on Regulatory Action

This clinical reviewer recommends approval of the oral solution and tablet forms of Levetiracetam (LEV) as adjunctive therapy for the treatment of partial seizures in children 6 month to <4 years old with partial onset epilepsy. The recommendation for approved dose of Keppra is 14 mg to 42 mg/kg/day in children < 6 months old and 20-50 mg/kg/day in children < 4 years old. The recommended dose is different from the (b) (4) mg/kg/day dose in children 6 month to < 4 years old sought by the sponsor. The recommendation to approve the lower dose range is based on 2 insufficiencies contained in the available clinical trials data. The first insufficiency is that the size of the < 6 month old cohort is too small to be able to demonstrate a statistically significant result. The problem of insufficient power in the < 6 month old cohort is balanced a robust treatment effect in the 4 children age < 6 months who were treated with LEV in the pivotal double blind trial (N01009). The second area of insufficiency is sponsor's justification the recommended maintenance dose of LEV in children 1 month to <4 years of (b) (4) mg/kg/day, which is based on a PK (Study N01128) and exposure-response model (study N01308) rather than data from well controlled clinical trials using this dose of LEV. The predicted exposure-response data in children was designed to replicate a level of exposure in children at a dose of (b) (4) mg/kg/day that is similar to the exposure associated with a (b) (4) dose of LEV in adults. The pivotal efficacy trial N01009 studied LEV in doses up to 50 mg/kg/day in children ages 6 months to < 4 years, which according to the sponsor, is similar to the exposure associated with a 2000 mg/day of LEV in adults. The sponsor's own exposure-response model does not predict a significant reduction in seizure frequency (2% or less) by administering the higher target dose of (b) (4) mg/kg/day compared to 50 mg/kg/day (see table 1.1).

Table 1.1-Exposure-Response Predicted By The Sponsor's Model Comparing Adult to Children Ages-1 Month to 4 Years

Table 10:4 Predicted reduction in seizure frequency from baseline for children receiving a 12-week treatment with 20, 40 and (b) mg/kg/day versus a 12-week treatment of 1000, 2000 (b) (4) mg/day in adults.

Treatment	Predicted reduction in seizure frequency from baseline	
	Median (5-95% quantiles)	
	Children	Adults
Children: 20 mg/kg/day Adults: 1000 mg/day	39% (-77% to 95%)	30% (-87% to 92%)
Children: 40 mg/kg/day Adults: 2000 mg/day	43% (-77% to 96%)	36% (-87% to 94%)
Children: (b) mg/kg/day Adults: (b) (4) mg/day	45% (-77% to 96%)	39% (-87% to 95%)

The review team recommends approval of the actual dose studied in the pivotal clinical trial (N01009) of 50 mg/kg/day since there appears to be little additional reduction in seizure frequency associated with the model predicted optimum dose of (b) (4) mg/kg/day.

2 Introduction and Regulatory Background

2.1 Product Information

Levetiracetam formerly UCB L059

Chemically Name: (S)-(-ethyl-2-oxo-1-pyrrolidone acetamide

Molecular weight: 170.21

Molecular formula: $C_8H_{14}N_2O_2$.

The Agency approved Keppra in tablet form (250 mg, 500 mg and 1000 mg), oral solution (100 mg/ml) and as an intravenous injection (500 mg/5 ml). The approval history for each of the different dose forms of Keppra are listed in Table 2.1. The sponsor is not seeking approval of a new dose form or strength of Keppra in this application. Two currently unapproved tablet strength of Keppra were tested in 3 of the clinical trials used to support this application. A 166 mg or a 166.5 mg tablet was administered to subjects in the N157, N01148 and N01103.

Table 2.1 Product Approval History for Keppra

Drug/Dose	Indication	Approved Population	Date Approved
Keppra 250 mg, 500 mg, 750 mg and 1000 mg tablets	Adjunctive therapy in the treatment of partial onset seizures	adults with epilepsy (NDA 21-035)	250 mg and 500 mg tabs Nov. 30 1999 1000 mg tab Jan 6, 2006
Keppra (levetiracetam) oral solution (100 mg/mL)	Adjunctive therapy in the treatment of partial onset seizures	adults with epilepsy (NDA 21-505)	July 15, 2003
Keppra tablets and oral solution	Treatment of partial onset seizures	children 4 years of age and older with epilepsy	June 21, 2005
Keppra tablets and oral solution	Adjunctive therapy in the treatment of myoclonic seizures	patients 12 years and older	Aug. 15, 2006
Keppra tablets and oral solution	Treatment of primary generalized tonic-clonic seizures	patients 6 years and older with idiopathic generalized epilepsy	March 19, 2007
Keppra injection 500 mg/5 mL (100 mg/mL)	Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy	Adults (NDA 21-872)	July 31, 2006
Keppra injection 500 mg/5 mL (100 mg/mL)	Myoclonic seizures	Adults with juvenile myoclonic epilepsy	Sept. 12, 2007
Keppra XR, extended release tablets, 500 mg once daily	Adjunctive therapy in the treatment of partial onset seizures	(b) years of age and older (NDA 22-285)	Filed Nov. 13, 2007

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2.2- Currently Used Pediatric AEDs.

Drug
Acetazolamide
Carbamazepine
Clobazam
Clonazepam
Diazepam
Ethosuximide
Felbamate
Fosphenytoin
Gabapentin
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital
Phenytoin
Primidone
Tiagabine
Topiramate
Valproate
Vigabatrin
Zonisamide

Modified from:Ravat SH, Gupta R. Antiepileptic drugs in pediatric epilepsy. J Pediatr Neurosci 2008;3:7-15

2.3 Summary of Presubmission Regulatory Activity Related to Submission

The agency issued the Pediatric Written Request to the sponsor on August 21, 2001. The original PWR was modified several times before a final version was negotiated with the sponsor. The PWR was reissued on July 3, 2002 under BPCA. The sponsor negotiated a two tiered approach to meeting the requirements of the PWR. The first tier addressed the PWR in children from ages 4 years to 16 years, the second tier addressed children from age 1 month to < 4 years. LEV given orally was approved for use in children from age 4 to 16 years for the adjunctive treatment of partial onset seizures on June 21, 2005. The second tier of sponsor's plan to meet the requirements of the PWR is addressed in this submission.

Table 2.3-Regulatory History Relating to the Pediatric Written Request (UCB)

Table 1:2 Summary of General Correspondence

Date	Type of Correspondence/Subject
20 July 1999	IND 45,151, 07 January 2000, Serial No. 303: UCB End of Phase 2 Meeting Minutes
25 May 2000	IND 45,151, 12 July 2000 (received 23 August 2000) FDA Follow-up End of Phase 2 Meeting Minutes
25 May 2000	IND 45,151, 14 July 2000, Serial No. 377: UCB Follow-up End of Phase 2 Meeting Minutes
21 February 2001	IND 45,151, 21 February 2001, Serial No. 446, UCB submitted a Proposed Pediatric Study Request
28 February 2001	IND 45,151, 27 March 2001, Serial No. 457: UCB Minutes of meeting to discuss sample size of Study N159
21 August 2001	NDA 21-035, FDA issues Written Request
24 October 2001	NDA 21-035, UCB submitted Proposed Changes in Written Request for Pediatric Studies
04 February 2002	NDA 21-035, 25 February 2002, UCB Pediatric Exclusivity Teleconference Meeting Minutes
22 March 2002	NDA 21-035, FDA amended the Written Request to delete "(at least 50 patients)" from the population pharmacokinetic approach
03 July 2002	NDA 21-035, FDA reissue Written Request under Best Pharmaceuticals for Children Act
25 November 2002	NDA 21-035, UCB Response to 29 October 2002 FDA Request Regarding Pediatric Exclusivity.
18 March 2003	IND 45,151, 18 March 2003, Serial No. 737: Protocol Synopsis for Study N01103 submitted for comment
09 May 2003	IND 45,151, 09 May 2003, Serial No. 762: Protocol synopsis for Study N01009 submitted for comment.
01 July 2003	IND 45,151, 01 July 2003, Amended synopsis for Study N01103 submitted by e-mail

The agency granted a waver to release UCB from studying LEV in children 12 and under for the treatment of juvenile myoclonic epilepsy (JME). The waiver was granted because JME is only rarely diagnosed in children below 12 years-old. UCB was notified of the waiver on

August 28, 2006. The waiver is applicable for the oral tablet form and oral suspension NDA 21-035/S050 and NDA 21-505/S-009.

Other Relevant Background Information

NDA 22-285 for Keppra XR, extended release tablets, 500 mg, for once daily dosing as adjunctive therapy in the treatment of partial onset seizures in patients (b) (4) years of age and older with epilepsy was filed on 13 November 2007. This application is being reviewed by The Division of Neurology Products

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Study N01009:

"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."

Site monitoring in the US and Canada for study N01009 was conducted by (b) (4) designated by UCB. On-site monitoring, medical monitoring and serious adverse event (SAE) reporting for sites in Europe (Western and Eastern) was contracted to (b) (4) was responsible for on-site monitoring, medical monitoring and SAE reporting for sites in Mexico and Brazil. The sponsor conducted 4 site personnel train meetings, 2 for the E.U. sites and 2 for North and South American sites. Site audits were conducted for 3 enrollment sites in the U.S, 3 in the E.U. and 2 sites in Brazil. All of the study vendors were audited, including the blinded central EEG reading site ((b) (4)). Data entry was by double entry technique with 100% comparison and reconciliation of differences. The sponsor's QC audit of data entry found no errors in their 10% sample. The clinical reviewer reviewed sample CRFs from 5 sites and found no serious omissions or documentation concerns. DSI inspections were not requested for clinical site in study N01009 since even the largest enrolling sites randomized a maximum of 4 subjects to the LEV group (7 subjects overall).

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3.2 Compliance with Good Clinical Practices

Table 3.1-Subjects with Reported Major Protocol Violations (UCB)

Table 10:1 Number and Percentage of Subjects with Major Protocol Violations (ITT Population)

Major Protocol Violations[a]	PBO (N=56) n (%)	LEV (N=60) n (%)	Overall (N=116) n (%)
Subject was taking more than 2 AEDs 2 weeks prior to Day -8 and during the study.	1 (1.8%)	1 (1.7%)	2 (1.7%)
The evaluation period 48 Hour Video EEG was done but the data was lost. Therefore, the Central Reader evaluation was not done.	1 (1.8%)	0	1 (0.9%)
The response to Inclusion Criteria question 6 (stable regimen of 1 or maximum of 2 AEDs) is NO (no waiver granted).	1 (1.8%)	0	1 (0.9%)
The response to Inclusion Criteria question 6 (stable regimen of 1 or maximum of 2 AEDs) is NO (waiver granted).	1 (1.8%)	0	1 (0.9%)
The selection period 48 Hour Video EEG was done. The subject had qualifying seizures but the EEG data was inadvertently deleted at the site. Therefore, the Central Reader evaluation was not completed.	1 (1.8%)	0	1 (0.9%)
The subject had an addition or deletion of an AED less than 2 weeks prior to Randomization.	2 (3.6%)	4 (6.7%)	6 (5.2%)
The total number of evaluable hours for the Evaluation (post-baseline) Visit 48 hour Video EEG Central Reader Evaluation was less than 24 hours.	1 (1.8%)	0	1 (0.9%)
The total number of evaluable hours for the selection (baseline) period 48 hour Video EEG Central Reader evaluation was less than 24 hours.	1 (1.8%)	1 (1.7%)	2 (1.7%)
The total number of partial seizures was '000' for the selection period 48 Hour Video EEG Central Reader evaluation.	1 (1.8%)	4 (6.7%)	5 (4.3%)
Total Number of Subjects with at Least One MPV	9 (16.1%)	8 (13.3%)	17 (14.7%)

[a] Subjects may have more than one major protocol violation, and lines are not mutually exclusive.
Source: Table 14.1.1:3

UCB attested that all of the referenced clinical trials were conducted in accordance with the International Conference on Harmonization (ICH) E6 notes for Guidance on Good Clinical Practice (ICH / CPMP/135/95) , EMEA ICH E11 in Europe, and the principles contained in the Declaration of Helsinki.

The number of subjects with major protocol violations was slightly greater in the placebo group, 9 verses 8 in the LEV arm. The majority of major protocol violations involved loss of 24-hour video EEG data or inappropriate alteration of concomitant anticonvulsant medications within the two weeks prior to the Baseline visit. A total of 7 subjects (5 placebo and 2 LEV) were excluded from the ITT analysis, all cases were excluded because of incomplete EEG data. Neither the major protocol violations nor the subjects excluded from the ITT analysis are expected to influence the trial outcome data.

All 15 subjects from site 419 in long-term study N157 were excluded from the study summaries and analyses. The site was closed and the data was excluded based on information gathered by the sponsor and study monitor regarding poor compliance with record completion requirements (CRFs and source documents) despite multiple attempts enforce compliance. The sponsor decided to close the study site and remove data from this site from pooled safety data affecting study N157 and PK studies.

3.3 Financial Disclosures

The sponsor did not provide a list of investigators who failed to submit a financial disclosure for the pivotal studies (N01009 or N01103) or a list of investigators who reported a disclosable financial arrangement defined in the Agency's guidance and 21CFR part 54.4. The sponsor supplied a list of investigators who participated in the trial and a list of investigators who provided a financial disclosure in Module 1 of this submission. An email was forwarded to the sponsor to obtain a list of the delinquent investigators and a list of investigators who reported disclosable financial agreements on August 4, 2008. UCB responded on August 12, 2008 listing only one sub-investigator at study site 503 in the Czech Republic who did not file a form 1572. There were three investigators who reported a disclosable financial relationship with UCB. None of the investigators who were require to disclose a financial relationship with the sponsor enrolled enough patients into the clinical trial to influence the trial outcome.

Table-3.2 Study Site Investigators Reporting a Disclosable Financial Relationship with UCB For Studies N01009 and N01103

Study	Site	Investigator	Disclosable Relationship with UCB	# Subjects Enrolled at Site
N01009	#(b) (6)	(b) (6)	Disclosed a grant or significant other payment from UCB amount not specified	5
N01009	#(b) (6)	(b) (6)	Honoraria totaling an amount greater than $25,000	1
N01009	#(b) (6)	(b) (6)	The Investigator (b) (6) (b) (6) and has received research grant from UCB totaling 50,000 Euro/year from 1999-2004	1

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Clinical Pharmacology Reviewer's Summary

Brief Summary:

- Summary of Findings:
  1. There is evidence to suggest that levetiracetam is efficacious in the treatment of pediatric patients down to 1 month of age.

- In Study N01009, the levetiracetam group exhibited consistently greater percent seizure reduction from baseline compared to placebo group across different age groups – including 1 to 6 month olds.

2. A two-step dosing, as illustrated in Table 1, is recommended.
   - Our recommended dose is similar to the sponsor's proposal, except we recommend that the maintenance dose for pediatric patients 6 month to 4 years of age is 50 mg/kg/day, rather than the sponsor proposed (b) (4) mg/kg/day - due to no additional benefit.
   - Our recommended dose is derived based on the decision tree illustrated in Figure 1.

Table 3.3 Difference between the Clinical Evaluated Doses, the Sponsor Proposed Doses and the Reviewer Recommended Doses

	Trial Evaluated Doses		Sponsor Proposed Doses		Reviewer Recommended Doses	
Age	**Starting Dose**	**Maintenance Dose**	**Starting Dose**	**Maintenance Dose**	**Starting Dose**	**Maintenance Dose**
1Month - 6 Month	20 mg/kg/day	40 mg/kg/day	14 mg/kg/day	42 mg/kg/day	14 mg/kg/day	42 mg/kg/day
6 Month - 4 Years	25 mg/kg/day	50 mg/kg/day	20 mg/kg/day	(b) (4) mg/kg/day	20 mg/kg/day	50 mg/kg/day

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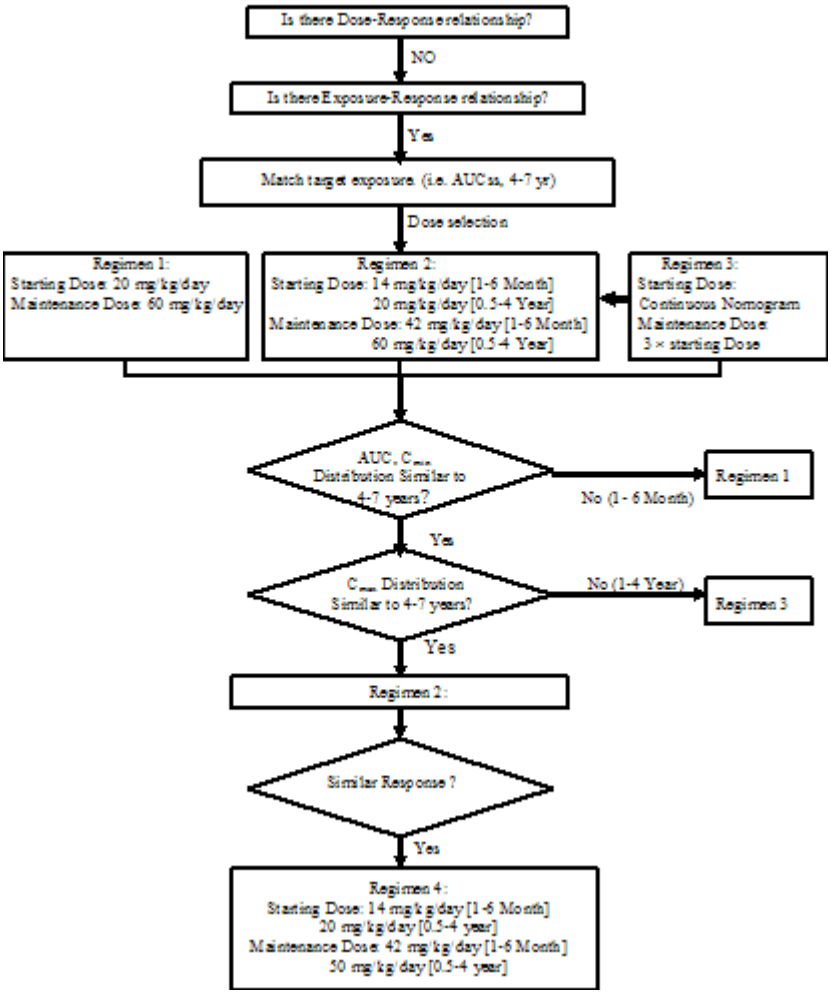
Figure 1 Selection of the Proper Dose Regimens in the Pediatric Patients 1 Month – 4 Years



Clinical Pharmacology Reviewer Recommendation:

The sponsor demonstrated that levetiracetam is efficacious in treating partial onset seizure for pediatric patients down to 1 month of age. We recommend a two-step dose regimen based on the modeling and simulation evaluation (see Table 1 above, reviewer's recommended dose). The pharmacokinetic characteristics of levetiracetam, including the relevant covariate effects, in pediatric patients aged 1month – 4 years have been adequately evaluated.

Major Issues for discussion:

1. Is there evidence of consistent effectiveness across different age groups?
2. What are the recommended doses for pediatric patients aged 1 month - 4 years?

4.1 Mechanism of Action (UCB Description)

Recent studies have shown that the antiepileptic effect of levetiracetam is linked to a novel mechanism of action, based on the binding of the drug to the synaptic vesicle protein SV2A. The extent to which this binding contributes to levetiracetam's mode action remains to unknown.

4.2 Pharmacodynamics

Levetiracetam at concentrations of up to 10 μM did not demonstrate binding affinity for a variety of known receptors, such as those associated with benzodiazepines, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites, and second messenger systems. Furthermore, *in vitro* studies have failed to find an effect of levetiracetam on neuronal voltage-gated sodium or T-type calcium currents and levetiracetam does not appear to directly facilitate GABAergic neurotransmission. However, *in vitro* studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA- and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells.

4.3 Exposure Response Relationships

The sponsor has demonstrated a dose-response relationship for a clinical efficacy endpoint (reduction in partial onset seizure frequency) in adults receiving LEV up to 3000 mg/day in two double blind studies N=180 and N=101. However, a similar dose response relationship in children age 1 month-4 years was developed using actual clinic trials data from a relatively small number of children. The number of children < 1 year old and less than 6 months old (N=3 double-blind study N01009) were the smallest cohorts included in UCB's exposure-response database. The exposure-response (and dose-response) model in adults was extended to children ages 1 month to <4years in study N01308 (see quote below) the model data was used to develop final dosing recommendations for children in this age group. The actual clinical response in children < 4 years old at (b) (4) mg/kg/day (equal to (b) (4) /day in adults) was not studied in double blind trial. The pivotal trial double blind N01009 used 50 mg/kg/day as the target dose in children ages 6 months to <4 years.

> "An existing model for the effect of LEV on seizure frequency in refractory epilepsy patients developed for adults was extended to data obtained from 2 separate pediatric studies."

4.3 Pharmacokinetics

Peak plasma concentrations were observed approximately 1 hour after dosing. For these pediatric subjects, the $t_{1/2}$ was shorter (5.3 h) than it was for adults (7.2 h), and apparent clearance was faster 1.5 mL/min/kg pediatrics verses 0.96 mL/min/kg adults. The results were consistent with observations in pediatric subjects aged 5 to 12 years. Levetiracetam appeared to

well tolerated, and safety assessments were consistent with the established safety profile of levetiracetam.

Table 3.4-PK parameters of LEV by Age 1 Month to < 6 Months and 6-24 Months (UCB) 24 < 48 Months Applicable to The Application.

Table 2.7.2.3 Mean Levetiracetam Noncompartmental Pharmacokinetic Parameter Values Following Single Doses in Pediatric Patients (N01052 and N151), Young Adults (N069) and Elderly Patients (N083)

	Pediatric (1-<6mo.)	Pediatric (6-<24mo.)	Pediatric (24-<48mo.)	Pediatric (5 - 12 yrs)	Young Adults (22 - 28 yrs)	Elderly (61 - 88 yrs)	
	Single Dose						10 days
Parameter (unit)	20 mg/kg				1000 mg.[a]	500 mg.[b]	500 mg b.i.d.
N	3	6	3	24	12	16	16
C_{max} (µg/mL)	37.1	28.8	30.6	25.8	23.0	19.1	31.2
Median t_{max} (hours)	1.0	1.0	1.0	2.3	0.97	0.97	1.2
AUC (µg·hr/mL)	283	237	234	241	222.[c]	251.[c]	248.[d]
V/F (L/kg)	0.57	0.65	0.63	0.7	0.7	0.5	0.5
$t_{1/2}$ (hours)	5.4	5.3	5.2	6.0	7.8	10.3	10.4
CL/F (mL/min/kg)	1.23	1.57	1.46	1.43	1.08	0.60	0.60
Urinary excretion$_{24-48}$ $_{hr}$ (% dose)	NR	NR	NR	51.9	51.5	45.5	75.[e]

NR=not required
[a] corresponds to a dose of 17 mg/kg
[b] corresponds to a dose of 7 mg/kg
[c] AUC(0-∞)
[d] AUC(0-12) hours
[e] Cumulative urinary excretion over 12 hours at steady state

Study N01052 was an open-label, multicenter, single dose PK study in children aged ≥1 month to <4 years with a diagnosis of epilepsy. Study N01052 evaluated the PK profile of LEV and its metabolite (UCB L057) following a single 20 mg/kg oral dose of LEV. 13 pediatric subjects (aged 1 month to <4 years) were included in the study only 12 subjects are reported in table 3.4, three subjects were between 1 month and <6 months, 6 subjects were between 6 months and <24 months, and 4 subjects were between 24 months and 48 months a total of 4 subjects were < 1 year old at the time they entered the trial. The PK database appears particularly small for children < 12 months old.

4.3 ADME

4.3.1Absorption

Levetiracetam was rapidly absorbed following a single 20 mg/kg dose of 10% oral solution resulting in a median Tmax at approximately 1 hour in all groups of children <4 years old and in adults. The exception was the group of children 5-12 years old occurring at 2.3 hours after a 20 mg oral dose. The half-life was shorter in children at 5.3-5.4 hours compared to adults at 7.2 hours. The extent of bioavailability of LEV is not affected by food.

4.3.2 Distribution

Levetiracetam and its major metabolite are < 10% bound to plasma proteins; therefore, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. Levetiracetam's volume of distribution is close to the volume of intracellular and extracellular water.

4.3.3 Metabolism

The primary metabolite of LEV is L057, which is inactive in adults and children. The sponsor reported in the results of their PK study N01052, L057 accounted for 3% of the parent compound in children 1 month – 4 years.

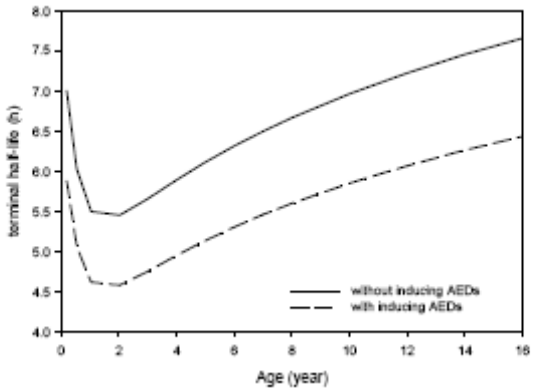
4.3.4 Elimination

When adjusted to body surface area, the clearance in children aged 6 months to 2 years is 57.0 mL/min/1.73 m^2 and in children greater than 2 years old to less than 4 years old it is 58.5 mL/min/1.73 m^2 close to the clearance reported in adults. In children below 6 months, clearance was 30% lower, because glomerular filtration rate (GFR) at birth is only 30-40% of the GFR in older children and healthy young adults. The exposure to UCB L057 the primary inactive metabolite of LEV, is lower in children then adults with a mean half-life varied from 6 to 8 hours in the 3 age groups. Dose reduction is recommended in adults and children with moderate to advanced renal failure and in patients with hepatic impairment.

4.3.5 Drug Interactions With AEDs

There is no clear evidence of clinically significant drug-drug interactions in children. Data from pooled retrospective data analysis in children receiving at least 1 enzyme-inducing AED from studies N01139 and N01288, showed that children taking enzyme inducing AEDs have approximately 20% (22% and 19%, respectively) higher body clearance of LEV, compared with the group receiving non-inducing AEDs. The sponsor did not consider this clinically significant and they did not recommend a dose adjustment in children takind enzyme inducing AEDs. PK data from placebo-controlled clinical studies indicate that LEV does not influence the plasma concentration of existing AEDs and that these AEDs do not influence the pharmacokinetics of LEV. In children taking concomitant inducing AED, alone or with other AEDs, the shape of the $t_{1/2}$ curve was the same but had to be shifted downward by approximately 20%.

Table 4.1-Change in Half-Life of LEV by Age Associated With Co-administration of an Inducing AED Predicted By PK Model Analysis in N01288. (UCB)



Data from previous drug interaction studies performed in adults finds that LEV has no effect on the pharmacokinetics of oral contraceptives, warfarin, or digoxin. The renal tubular secretion-blocking agent, probenecid had no effect on the excretion of LEV, but it reduced the renal clearance of metabolite, UCB L057.

5 Data Sources, Review Strategy and Data Integrity

5.1 Sources of Clinical Data

The current SNDA clinical review considered the results of the following pediatric clinical studies:

Study N01009: "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."

Study N01103: "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."

Study N01148: "A Multi-Center, Open-Label, Long-Term, Follow-Up Study of the Safety and Efficacy of Levetiracetam in Children with Partial Onset Seizures.

Study N157. “"A Multi-Center, Open-Label, Long-Term, Follow-Up Study of the Safety and Efficacy of Levetiracetam (UCB L059) in Children With Epilepsy".

*Study N157 was previously submitted as an interim report in the 2004 Pediatric Supplement. Data from 13 subjects were included in the long-term safety database and in the long-term efficacy summaries.

5.1 Tables of Clinical Studies (UCB)

Table 2.7.6:1 Tabular Listing of All Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of Study	Study Design and Type of Control	Test Product(s): Regimen, Route of Administration per protocol	Number of Subjects (M/F) [Age Range]	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status: Type of Report
Safety	N157	Module 5	Long-term safety follow-up of LEV as adjunctive therapy	Open Label	Levetiracetam 20 to 99 mg/kg/day Tablets (166, 166.5, 250, and 500 mg) and Oral Solution (10%)	223 (118/105) 1mo to 16 yrs	Children age 1mo-16yrs with Partial Onset Seizures	Up to 7.5 years	Complete Full
Efficacy and Safety	N01009	Module 5	Efficacy and safety of LEV as adjunctive therapy	Randomized DB, parallel, placebo controlled	Levetiracetam 20, 25, 40 and 50 mg/kg/day Oral Solution (10%)	116 (57/59) 1mo to <4 yrs	Children age 1m to <4yrs with Partial Onset Seizures	6 days (20 days if not continuing to N01148)	Complete Full
Safety	N01103	Module 5	Safety study including cognitive and neuropsychiatric effects of LEV as adjunctive therapy	Randomized DB, parallel, placebo controlled	Levetiracetam 20, 40, 60 mg/kg/day Tablets (166, 166.5, 250, and 500 mg) and Oral Solution (10%)	98 (56/42) 4 to 16 yrs	Children age 4 to 16 years with Partial Onset Seizures	12 Weeks	Complete Full
Safety	N01148	Module 5	Long-term safety follow-up of LEV as adjunctive therapy	Open label	Levetiracetam 20, 25, 40, 50, 60 mg/kg/day Tablets (166, 166.5, 250, and 500mg) and Oral Solution (10%)	255 (139/116) 1mo to 16 yrs	Children age 1mo-16yrs with Partial Onset Seizures	48 Weeks	Ongoing Interim

5.3 Review Strategy

The primary clinical review of the supplemental, pediatric NDA application was divided into separate efficacy and safety reviews. The efficacy review was performed by Gerald Podskalny, D.O. in The Division of Neurology Products (DNP). The safety review was performed by Lisa, Jones, M.D. Safety Reviewer in the DNP.

The efficacy review centered on Study N01009 as the pivotal study. Study N01103 was designed with safety primary endpoints and efficacy endpoints were considered exploratory. Subjects enrolled into study N01103 were also older (age 4-16 years) than the age of the children addressed in this supplemental NDA application (1 month to < 4 years). Studies N01128 was a retrospective PK meta-analysis that used clinical trials data from children and adults to develop a LEV dosing nomogram for children divided in to 2 age groups < 6 months and > 6 months of age. Study N01308 was an exposure-response analysis that created a model to predict the

exposure response relationship in children and develop an optimal dose for children < 4 years old. Both of these studies were reviewed from the perspective of the quality and sufficient quantity of the clinical data from children in the age groups of interest and the soundness of sponsor's rational to support the recommended dose of LEV.

Long-term studies N0157 and N01148 were both open label, studies but the efficacy review for these was focused on the long-term maintenance of the treatment effect.

Joint statistical-clinical reviewers meetings to discuss the evaluation of efficacy and safety endpoints were held with Fanhui Kong, Ph.D. (statistical reviewer).

6 Review of Efficacy

6.1 Indication

Proposed New Indication

Partial Onset Seizures

KEPPRA is indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy.

6.2 Methods

UCB conducted a single efficacy study to complete the second phase of their plan to fulfill the requirement of the pediatric written request. The primary efficacy study N01009 sought to enroll subjects ages 1 month up to 4 years with refractory epilepsy who were being treated with no more than 2 AEDs. Subjects had 48 hour video EEGs performed to collect data for analysis of the primary endpoint. Clinical trial N01103 was designed with safety as the primary objective, efficacy data was considered an exploratory endpoint. Study N01103 recruited children age 4-16 years old with partial onset seizures. This was intended to meet the safety requirements of the PWR regarding potential cognitive and behavioral adverse effects associated with LEV. Efficacy data was not collected using 48 hour EEG recordings, instead seizure diaries and global impression scales were collected to determine the exploratory efficacy endpoints. Data from the long-term open-label, flexible dose trials N01148 and N157 is not typically considered an appropriate data source for information to support efficacy claims. Information from the long-term trials was used to evaluate the persistence or tolerance of the treatment effect of LEV for this review. The sponsor used PK data from samples taken from subjects who participated in these clinical trials to develop the recommended dosing regimen, discussed later in this review.

6.2.1 Discussion of Individual Studies

6.2.2 Double-Blind Efficacy

6.2.2.1 Study N01009

The N01009 was designed as a phase III, double blind, placebo controlled, short-term efficacy trial in children ages 1 month up to <4 years old with refractory partial-onset epilepsy. This study is considered the primary source of data to support the efficacy claim for children in this age group. The N01009 study also addressed part 2 of the sponsor's plan to meet the requirement of the agency's pediatric written request (PWR) to establish the safety and efficacy of LEV for adjunctive treatment of partial onset seizures in children. A total of 116 subjects were randomized in a 1:1 ratio LEV/PBO. Study medication was administered as an oral solution. 60 subjects were assigned to the LEV group and 56 to placebo. Subjects aged 1 month to < 6 months who received LEV were titrated to a maintenance dose of 40 mg/kg/day and subjects aged 6 months to <48 months randomized to LEV were titrated to a maintenance dose of 50 mg/kg/day. After the Selection Phase subjects received placebo or 20 or 25 mg/kg/day dose of LEV for a single day followed by 6 days of maintenance dose LEV appropriate to their age (evaluation phase) category. The Evaluation Phase24 hour EEG data was collected while subjects received maintenance dose LEV. After the Evaluation phase the dose of LEV was reduced and discontinued over the 2 week down titration phase with follow up extending 24 hours or after LEV was discontinued.

Pharmacokinetic data from study N01052 suggest the plasma clearance of LEV (CL/f) normalized by body weight in children 6 months to < 4 years of age is approximately 50% higher than in adults. In children 1 month to < 6 months of age the CL/f normalized by body weight is similar to that of adults. Based on this information, the dose of levetiracetam the dose of LEV oral solution administered to children in study N01009 was determined by age. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for children 1 month to < 6 months old and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for children 6-month to < 4-years old, was used in this study.

Partial onset seizure frequency was recorded on 48-hour video EEG recordings performed at baseline (Selection period), which was compared to the 48-hour video EEG performed in the Evaluation period on day 4-6 on LEV (steady state). A central blinded EEG reader was responsible for determining if the EEG met criteria for an adequate study (at least 24 hours of interpretable data) and for determining the seizure frequency captured during the EEG recordings. All EEG tracings with < 24 hours of interpretable data were counted as treatment failures for the mITT analysis.

The primary efficacy variable of N01009 was the responder rate of subjects who experienced a reduction in average daily seizure frequency (ADF). The responder rate was defined as the number of mITT subjects with a ≥ 50% reduction from Baseline in their ADF for

partial onset seizures (Type I) divided by the total number of mITT subjects. The absolute and percent changes in average daily seizure frequency (ADF) were chosen as secondary endpoints for this study. The primary analysis of the primary endpoint did not adjust for baseline characteristics. There was an imbalance between the 2 study groups in baseline average daily seizure frequency. The LEV treated group had almost 3 times the number of seizures at baseline compared to the placebo group. The race distribution was not balanced between the two treatment groups either. Ninety percent of Caucasians were assigned to the LEV group and only 70% of Caucasians were assigned to the placebo group. None of the black study participants were assigned to the LEV group. To investigate the effects of the difference in baseline ADF, the sponsor conducted a post hoc analysis to incorporate baseline seizure frequency and treatment into a statistical model. The reviewer also conducted such post hoc analyses to adjust for the race factor. Both the planned and unplanned analyses of the primary endpoint demonstrated a statistically significant increase in % responder rate in the LEV group. The difference in the absolute and percent reduction in ADF of partial onset seizures was also statistically significant in favor of the LEV treated patients.

6.2.3 Double-Blind Safety

6.2.3.1 Study N01103

Study N01103 is supporting double blind, placebo controlled, short-term study, designed with safety as the primary objective. The study was a Phase II, 19-week, randomized, double-blind, multicenter, placebo-controlled safety study in children (4 to 16 years old) with partial onset seizures. The study targeted cognitive and behavioral changes associated with LEV required by the Agency in the PWR. The reduction in partial onset seizure frequency and global improvement were also examined as exploratory endpoints. The randomization ratio was 2:1 (LEV/ PBO) and the final group totals were 65 subjects in the LEV group and 34 PBO subjects. Efficacy data supports efficacy in children 4 year and older but the sponsor was already granted approval to use LEV for partial onset seizures in the 4 – 16 year age group. The study does not include new efficacy data for children in the 1 month to < 4 year age group but the results of this trial will be considered by the safety reviewer.

6.2.4 Open-Label Long-Term Safety

Open label, long-term safety and efficacy studies N01148 (duration up to 48 weeks) and N157 (duration up to 7.5 years) enrolled subjects who had participated in earlier double blind studies and subjects who did not participate in previous clinical trials of LEV. The efficacy data will be reviewed from the perspective of looking for evidence that supports a persistent treatment effect in subjects taking LEV for periods of longer than the 34 day duration of trial N01009.

6.2.4.1 Study N01148

N01148 is a Phase III, multicenter, open-label, flexible dose long-term follow-up study of the safety and efficacy of LEV in children 1 month to 16 years old with refractory partial onset

seizures. The maximum dose of LEV subjects could receive was up to 100 mg/kg/day. The study duration was up to 48 weeks. A total of 255 subjects were enrolled and treated, 152 in the 1 month to <4 years group and 103 in the 4 to 16 years group. The study was still ongoing at the submission cut-off date of September 18, 2007.

6.2.4.2 Study N157

The present study enrolled subjects who had participated in a previous levetiracetam study, either N159, N01010, N151, or N01052. Only study N01052 enrolled subjects ages >1 month to < 4 years old the remaining studied sought subjects who were 4-16 years old. The total number of subjects enrolled in the N01052 study in the 1 month to < 4 years age range was 15. The study duration was up to 7.5 years but approximately 2/3 of the subjects discontinued participation before the trial ended. The large number of subjects who discontinued trial participation before the trial end was not unusual given its long duration.

6.3 General Discussion of Endpoints Study Pivotal Trial N01009

The primary efficacy analysis was based on the mITT population. The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time as determined by a blinded central reader. The sponsor hired (b) (4) as the Central EEG Reader. Selection video-EEG data interpreted by the central reader was used for analysis. Subjects included in the mITT analysis had at least 24 hours of usable Evaluation video-EEG time. Subjects who had < 24 hours usable Evaluation video-EEG and withdrew due to lack or loss of efficacy were considered as non-responders (for the primary endpoint).

The selection of the difference in the percent responder rate between the two treatment groups was not selected as the primary efficacy endpoint for previous pivotal trials of Keppra. The usual primary endpoint has been the difference in the percent or absolute seizure frequency from baseline to the steady state treatment period is reported, instead it was chosen as a secondary endpoint in trial N01009. In the past clinical trials the sponsor has chosen the difference in the percent responder rate as a secondary outcome measure. In the case of study N01009 results for the percent responder rate and the change in seizure frequency were statistically significant (p=0.013 and <0.001, respectively for these two outcome variables) in favor of the LEV treated group.

6.3.1 Efficacy Analysis Study N01009

6.3.2 Data Collection For Primary Efficacy Variable Study N01009 (Video-EEG Analysis)

The primary efficacy variable is the Responder Rate for total partial onset seizures (Type I) for subjects in all age groups. The sponsor defined the Responder Rate as follows:

Responder Rate = # of mITT subjects with a ≥ 50% reduction from baseline in ADF
Total number of mITT subjects.

ADF was computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline) as follows:

ADF = # of seizures recorded during video-EEG time × 24
# hours of usable video-EEG time

*Usable selection video-EEG time was defined as total video-EEG time minus total uninterpretable time.

6.3.3 Seizure Counts

- For children 1 month to < 6 months old, partial onset seizure counts were based on electro-clinical seizures (Seizures recorded on EEG accompanied by a clinical manifestation of the electrographic event, i.e. convulsion) plus electrographic (recorded on EEG only without clinical manifestation) seizures.
-

For children in the remaining age groups, 6 months to < 4 years old, partial onset seizures were based on electro-clinical (seizure recorded on EEG with a clinical manifestation of seizure, i.e. convulsion) seizures only.

-

6.3.4 Primary Efficacy Data Analysis Study N01009

The primary efficacy analysis was based on the mITT population (repeated on the PP population as a supportive analysis). The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time as determined by the blinded central reader. Selection video-EEG data interpreted by the central reader was used for analysis. Subjects included in the mITT analysis had at least 24 hours of usable Evaluation video-EEG time. Subjects who had < 24 hours usable Evaluation video-EEG and withdrew due to lack or loss of efficacy were considered as non-responders (for the primary endpoint).

6.3.5 Secondary Endpoints Study N01009

6.3.5.1 Secondary Efficacy Variables

1. Subgroup Analyses by Age Group - mITT Population (required in the Pediatric Written Request)

    - 1 month to < 12 month age group

- 12 month to < 24 month age group
- 24 month to < 48 month age group.

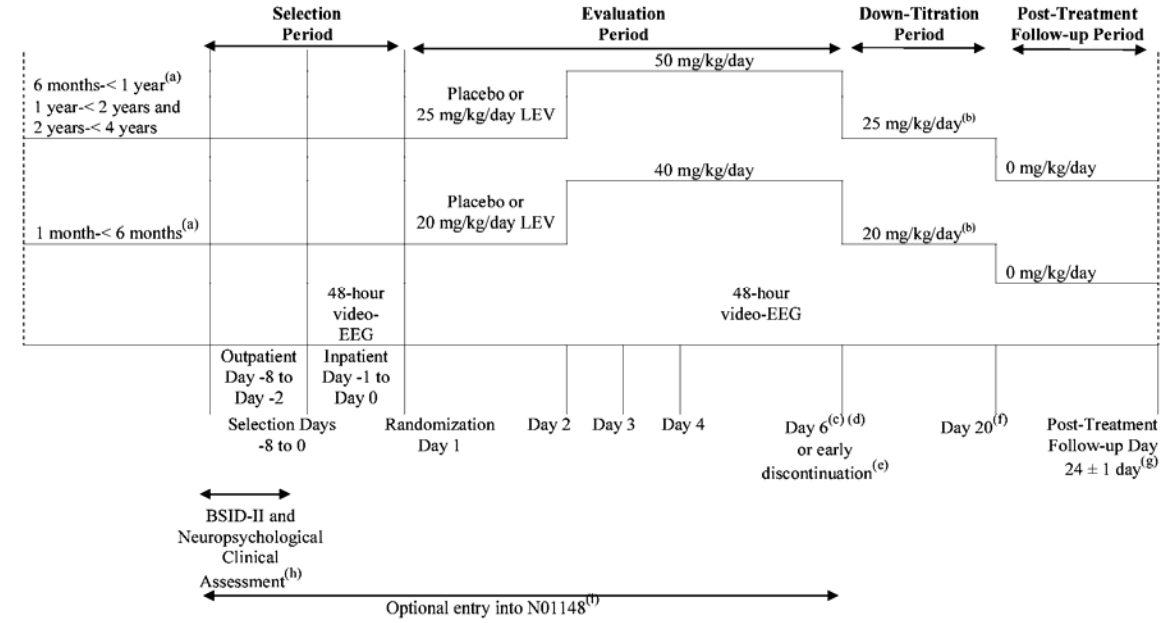
2. 50% Responder ADF seizure analyses for total seizures (Type I + II + III).
    - Types: I=Partial onset, II=generalized at onset, III=Unclassified
3. Absolute and Percent Reduction in ADF Seizure Analyses.
    - The percent reduction from baseline in ADF of partial onset seizures (Type I).
    - The percent reduction from baseline in ADF of total seizures (Type I + II + III).
    - The absolute reduction from baseline in ADF of partial onset seizures (Type I).
    - The absolute reduction from baseline in ADF of total seizures (Type I + II + III).
    - The percent reduction from baseline in ADF of electro-clinical partial onset seizure (analyses exclusive of subjects 1 month to less than 6 months of age).
4. Seizure Count Data Collected from the Case Report Form during Evaluation
5. Seizures recorded on the CRF from Day 1 to Day 6 observed by the hospital staff and/or family members were summarized by day, type, and treatment group.

6.4 Study design

The N01009 was designed as a phase III, double blind, placebo controlled, short-term efficacy trial in children ages 1 month up to <4 years old with refractory partial-onset epilepsy. This study is considered the primary source of data to support the efficacy claim for children in this age group. The N01009 study was designed to address part 2 of the sponsor's plan to meet the Agency's requirement to establish the safety and efficacy of LEV for adjunctive treatment of partial onset seizures in children 1 month to < 4 years old stated in the PWR. A total of 116 subjects were randomized in a 1:1 ratio of LEV/PBO. Study medication was administered as an oral solution. 60 subjects were assigned to the LEV group and 56 to placebo. Subjects aged 1 month to <6 months who received LEV were titrated to a maintenance dose of 40 mg/kg/day or matching placebo and subjects aged 6 months to <48 months randomized to LEV were titrated to a maintenance dose of 50 mg/kg/day or matching placebo. After the Selection Phase subjects received placebo or 20 or 25 mg/kg/day dose of LEV for a single day followed by 5 days of maintenance dose LEV appropriate to their age (evaluation phase) category. The Evaluation Phase 24 hour EEG data was collected while subjects were receiving their maintenance dose of LEV typically days 4-6. After the Evaluation phase the dose of LEV was reduced and discontinued over the 2 week down titration phase with follow up extending 24 hours after LEV was discontinued.

Fig.6.1-Trial Design Schematic

Figure 9:1 Schematic Diagram of the Study



6.5 Efficacy Findings Study N01009

6.5.1 Primary Outcome Variable

Table 6.2- Primary Efficacy Variable (UCB Table)

Table 14.2.1:1 Responder Rate in Average Daily Frequency (ADF) for Partial Onset Seizures – mITT Population

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	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio LEV/PBO	95% Confidence Interval	P-value(b)
Responder (a)	10 (19.6%)	25 (43.1%)	3.11	1.22 - 8.26	0.013
Non-Responder	41 (80.4%)	33 (56.9%)			

Each % is based on the number of mITT subjects in the treatment group. Seizure counts include clusters.
(a) Subjects with =>50% reduction in ADF from Selection video-EEG to Evaluation video-EEG and had =>24 hours usable video-EEG at both time points.
(b) Fisher's exact test.

The pre-specified primary outcome variable, the difference in the percent responder rate for the two treatment groups, demonstrated a statistically significant at (p=0.013) between group difference favoring the group treated with LEV.

6.5.2 Key Secondary Outcome Variables Study N01009

Responder Rate By Age Group

Table 6.3 The Responder Rate For Subject By Age (UCB Table)

Table 11:10 Responder Rate in ADF for Partial Onset Seizures Adjusted for Age and Subgroup Analyses by Age Group - mITT Population

Age Group	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio		P-value[b]
			LEV/ PBO	95% CI	
All Ages[a]	10/51 (19.6%)	25/58 (43.1%)	3.13	1.31 – 7.48	0.009
1M to < 12M	2/10 (20.0%)	6/11 (54.5%)	4.80	0.51 – 62.31	0.183
12M to < 24M	4/16 (25.0%)	9/19 (47.4%)	2.70	0.53 – 15.43	0.293
24M to < 48M	4/25 (16.0%)	10/28 (35.7%)	2.92	0.68 – 14.71	0.129

[a] Odds ratio is derived from the stratified (by age group) model.
[b] p-value for the all ages analysis is from the Cochran-Mantel-Haenszel (CMH) test (stratified by age group); p-values for the individual age groups are from Fisher's exact test.
Source: Table 14.2.2:1

The overall p-value (p=0.009) was calculated using the Cochran-Mantel-Haenszel (CMH) Test in order to adjust for the age groups as opposed to the Fishers Exact test which combines all the age groups together and gives a p-value (0.013) in the analysis of the primary outcome variable. The corrected (Yates) CMH yields a p-value =0.0157. The statistical reviewer's logistic regression analysis gives a p-value of 0.010 after the adjustment of age group.

Due to the small size of the sub-groups, none of the individual sub-group analyses gave statistically significant results. However, the treatment effect remained consistent across the age groups. The odds ratio of favorable response in mITT population for the levetiracetam group as compared to placebo was 4.80 for the 1 month to < 12 month age group, 2.70 for the 12 month to < 24 month age group, and 2.92 for the 24 month to < 48 month age group. The overall age adjusted odds ratio stratified by age group was 3.13 (95% CI 1.31 – 7.48) and was nearly identical to the unadjusted estimate.

6.2.2 Absolute Change in Seizure frequency

Table 6.4-Absolute Change in Number and Percent of Partial Onset Seizures From Selection (Per-treatment) to Evaluation Period (On-treatment) (UCB Table)

Table 11:11 Absolute and Percent Reduction from Baseline in ADF for Partial Onset Seizures - mITT Population

				LEV – PBO		
Assessment	**Statistics**	**PBO (N=51)**	**LEV (N=58)**	**Median Difference[a]**	**95% CI**	**P-value[b]**
Selection	Mean (SD)	15.37 (22.92)	31.13 (46.09)			
	Median	6.82	15.20			
	Q1 - Q3	2.00 – 16.22	4.48 – 38.95			
	Min - Max	0 - 98.03	0 - 211.8			
Evaluation	Mean (SD)	16.23 (24.16)	22.60 (37.32)			
	Median	6.48	8.34			
	Q1 - Q3	1.51 – 16.99	0.51 – 24.97			
	Min - Max	0 – 106.4	0 – 184.3			
Absolute Change	Mean (SD)	-0.86 (13.81)	8.54 (25.67)			
	Median	0.13	4.77	4.99	2.24 – 7.99	<0.001
	Q1 - Q3	-2.15 – 2.49	0 – 10.48			
	Min - Max	-56.89 – 41.27	-51.48 – 156.35			
% Reduction[c]	Mean (SD)	-20.93 (111.47)	24.98 (91.49)			
	Median	7.12	43.61	39.21	17.52 – 62.23	<0.001
	Q1 - Q3	-42.29 – 35.14	11.72 – 85.71			
	Min - Max	-450.58 – 100	0 – 148.3			

[a] Hodges-Lehman method used to estimate median difference
[b] P-values are from the Mann-Whitney test.
[c] Four subjects (1 on PBO and 3 on LEV) are excluded from this analysis due to having 0 seizures at baseline.
Source: Table 14.2.2:4 and Table 14.2.2:6

The median reduction in the absolute number (4.99) and percent (39.21%) from baseline of the ADF of partial onset seizures was also statistically significant in favor of the group treated with LEV (p=<0.001). The median reduction in seizure frequency is typically chosen as the primary efficacy variable in studies reviewed by the division for pivotal trials involving approval of AEDs for adjunctive therapy in patients with uncontrolled epilepsy.

Table 6.5-Responder Rate in ADF For All Seizure Types-I, II, III (UCB Table)

Table 14.2.2:2 Responder Rate in Average Daily Frequency (ADF) for All Seizures – mITT Population

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	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio LEV/PBO	95% Confidence Interval	P-value(b)
Responder (a)	10 (19.6%)	25 (43.1%)	3.11	1.22 - 8.26	0.013
Non-Responder	41 (80.4%)	33 (56.9%)			

The responder rate for all seizure types was identical to the responder rate for partial onset seizures (type I) only because subjects recruited into the trial had predominately partial onset seizure disorder.

7 Additional Clinical Issues

7.1 Dosing Regimen and Administration

7.1.2 Analysis of Clinical Information Relevant to Dosing Recommendations

The range of doses of LEV administered to subjects in the primary efficacy study for children 1 month to < 4 years (N01009) was 20-50 mg/kg/day of LEV divided bid. The maintenance dose in children 1 month to < 6 months was 40 mg/kg/day (oral solution) and in children > 6 months to < 4 years, the maintenance dose was 50 mg/kg/day. The sponsor is seeking approval for a dose of 20-(b) (4) mg/kg/day in children age 1 month to < 4 years: including a daily recommended dose of 42 mg/kg/day in children 1 month to < 6 months of age and (b) (4) mg/kg/day for children 6 months to 16 years Children age 1 month to < 4 years age received doses of LEV up to 100 mg/kg/day in two long-term, open-label, flexible-dose, design studies, N157 (3 subjects in the 1 month to < 4 year range) and N01148 (152 children 1 month to < 4 years). The recommended dose of (b) (4) mg/kg/day is (b) (4) higher than the maximum dose of 50 mg/kg/day administered to children 6 months to < 4 years in UCB's only placebo controlled efficacy trial (N01009). The recommended daily dose for children ages 1 month to < 6 months differs a little form the dose that was studied in the pivotal clinical trial (42 mg/kg/day [recommended] vs 40 mg/kg/day [studied]). Data from a population PK meta-analysis (N01288), exposure-response model analysis (N01308) created using retrospective clinical trials data from children and adult exposure-response data was presented by the sponsor to justify approval of a higher dose of LEV (b) (4) mg/kg/day).

7.1.2.1 Data Sources

Study N01288 was retrospective population pharmacokinetic analysis of pediatric patients with epilepsy aged 1 month to 16 years. The model generation and analysis was performed using data from 6 clinical studies of levetiracetam in pediatric patients N151, N01010, N01052, N01103, N01009, and N01148. Data from a previous PK model generated by the sponsor in 2004 for children ages 4 to 16 was also included in this model. The current model also included data from previously conducted adult clinic trials. Upon review, it appears the model contains very little data from children 1 month to < 1 year. Eight children between the ages of ages 1 month to <1 year, provided PK samples included in study N01128 (see Table 7.1). The dose of LEV given to subjects in N01009 ranged from 20 to 50 mg/kg/day. Subjects in the 1 month to < 4 years age group who completed the N01009 study were given the opportunity to enter the long-term, open-label study N01148. Children who entered study N01148 after completing N01009 continued on their previous dose of LEV 20 to 50 mg/kg/day and patients who received placebo also received a maintenance dose of 50 mg/kg/day. Subjects who were directly enrolled into N01148 could receive a LEV maintenance dose as high as 60 mg/kg/day, however only 2 children who were less than 1 year-old at the time they entered the study. In study N01052 levetiracetam oral solution was administered as a single dose of 20 mg/kg with full PK profiles taken up to 24 hours. The remaining studies collected PK data in children 4 to

16 years old leaving 8 as the total number of unique subjects, ages 1 month to < 1 years who provided samples for the PK analysis and for the development of the dosing nomogram described in the PK meta-analysis, UCB study N01288.

Table-7.1-Age Distribution of Subjects Providing Samples For Study N01128

Age	Number (%)
< 1 year*	8
1 to 2 years	19
2 to 6 years	50
6 to 12 years	77
> 12 years	43

*< 1 year from studies N01052, N01009 and N01148.

The nomogram was developed to guide dosing of LEV in patients in 2 categories divided by age; ages 1 to < 6 months and > 6 months of age. The sponsor's recommended dose titration schedule and the nomogram are provided below in Table 7.2. The dose of LEV listed in table 7.2 is only for 1 of the 2 required daily doses of LEV. LEV is given bid therefore the total daily dose is 2 times the dose listed below the nomogram (i.e. 7 mg/kg/dose X 2 = 14 mg/kg/day).

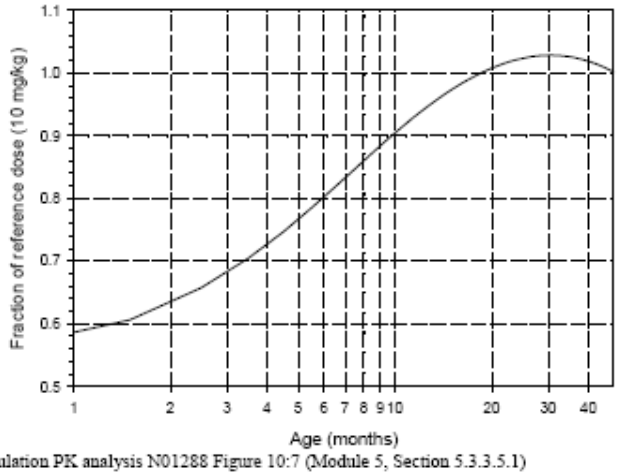
Reviewer Comment

The nomogram and dosing schedule was developed using relatively little data from children in the 1 month to < 1 year age group. It appears that the majority of PK data from children < 1 year old was contributed by 8 children who received a maximum dose of 50 mg/kg/day of LEV or less.

Table 7.2-The Sponsor's Proposed Dosing Nomogram for Children 1 Month-< 4 Years Receiving LEV (UCB)

The nomogram is presented in Figure 2.7.2.3.

Figure 2.7.2.3 Dose adjustment factor in pedicatric age 4 years or younger



Source: Population PK analysis N01288 Figure 10:7 (Module 5, Section 5.3.3.5.1)

As an example, to get a similar exposure to that observed in a 4 year old receiving the recommended 10 mg/kg per intake starting dose, (b) (4) mg/kg per intake, the following doses would be recommended:

Age range (months)	1-6	Above 6
Recommended starting dose (mg/kg bid)	7	10
(b) (4)		
Recommended level 3 dose (mg/kg bid)	21	(b)

7.1.2.2 The Sponsor's Rational for The Proposed Dosing Recommendations

The nomogram recommends reducing the starting dose of LEV in children < 6 months old to 14 mg/day, then advancing the dose to 28 mg/kg/day and then to the recommended dose of 42 mg/kg/day. The reduced dose of LEV given to in children < 6 months old is because children < 1 year old have reduced renal clearance of LEV. The reduced clearance of LEV in children < 1 year is reported by the sponsor to be due to immaturity of the kidney (reduced GFR). In children older than 6 months the nomogram recommends a daily dose of (b) (4) mg/kg/day because GFR and renal clearance of LEV increases to near that of a 4 year old by 6 months. This is the same dose as is presently recommended in children ≥ 4 years old in the presently approved label.

The doses recommended by the sponsor are different from those actually studied in the pivotal clinical trial N01009. For children 1 month to < 6 months the recommended starting dose is lower 14 mg/kg/day compared to 20 mg/kg/day studied in clinic trial. The recommended maintenance dose (42 mg/kg/day) is 2mg/kg higher than the dose administered during the clinical trial of 40 mg/kg/day. The difference of 2 mg/kg/day is not likely to be clinically meaningful or lead to a significant increase in adverse events. In children ≥ 6 months old the starting dose recommended by the sponsor based on the PK model is (b) (4) day, which is lower than the 25 mg/kg/day than the starting dose in study N01009. The maximum

recommended maintenance dose of LEV in children > 6 months old is (b) (4) mg/kg/day, which is (b) (4) higher than the 50 mg/kg/day dose administered in the pivotal clinical trial (N01009).

The sponsor reported children enrolled in long-term, open-label studies received doses of LEV as high as 100 mg/kg/day. However, it is unlikely many children ages 1 month to < 4 years were exposed to doses above 50 mg/kg/day since there were only 5 children in the 1 month to < 1 year range in study N157. In the open-label, long-term study N01148, this reviewer found 15 subjects in the 1 month to < 1 year age range received an average daily maintenance doses of LEV (b) (4) mg/kg/day or greater for at least 7 days. Of these 15 subjects only 5 were < 6 months old and took an average dose of LEV ≥ (b) (4) mg/kg/day for at least 7 days.

Table 7.3-Subjects in Long-Term Pediatric Studies of LEV

Age Range	Number of Patients	Total
ITT Population		
1 month < 6 months		**12**
N157	3	
N01148	9	
6 months < 12 months		**21**
N157	2	
N01148	19	
12 months < 24 months		58
N157	5	
N01148	53	
24 month < 4 years		76
N157	5	
N01148	71	
4 years < 8 years		90
N157	56	
N01148	34	
8 years < 12 years		134
N157	92	
N01148[a]	42	
12 years – 16 years		85
N157	58	
N01148[b]	27	
> 17 years		2
N157	2	

(a)Includes 12 years old; (b) Does not include 12 years old

UCB study N01308 was a retrospective population based exposure- response analysis using data from children and adults. The data for children ages 1 month to 16 years was taken from previously conducted double-blinded placebo controlled clinical trials N159, N01009 and N01103. The sponsor created a model using data clinical trials data from these studies and ran 2000 trial simulations to predict seizure response. 1month-6 months and 6 months to < 4 years.

The effect on seizure frequency predicted by the model is presented in the table 7.4 below. The same exposure-response was used to simulate the effects on seizure frequency of administering a higher dose of LEV up to 25/50/75 mg/kg/day. The sponsor's model predicted that a higher dose of LEV would not result in a significant reduction in seizure frequency compared to the 20/40/(b) (4) mg/kg/day dose regimen. The model data in children was compared to the exposure-response data from adult epilepsy patients. UCB concluded a similar exposure-response relationship exists in children 1 month to 16 years old receiving LEV at 20 tc(b) (4) /kg/day and in adults taking 1000(b) (4) mg/day.

Table 7.4-Exposure-Response Predicted By The Sponsor's Model Comparing Adult to Children Ages-1 Month to 4 Years

Table 10:4 Predicted reduction in seizure frequency from baseline for children receiving a 12-week treatment with 20, 40 and (b mg/kg/day versus a 12-week treatment of 1000, 2000 (b) (4) mg/day in adults.

Treatment	Predicted reduction in seizure frequency from baseline	
	Median (5-95% quantiles)	
	Children	Adults
Children: 20 mg/kg/day Adults: 1000 mg/day	39% (-77% to 95%)	30% (-87% to 92%)
Children: 40 mg/kg/day Adults: 2000 mg/day	43% (-77% to 96%)	36% (-87% to 94%)
Children: (b mg/kg/day Adults: (b) mg/day	45% (-77% to 96%)	39% (-87% to 95%)

Table 7.5 Study N01009 Absolute and Percent Reduction In Seizure Frequency From Baseline (dose 40 mg/kg/day in ages 1month to <6 month and 50 mg/kg/day in Ages 6 months to < 4 years)

Table 11:11 Absolute and Percent Reduction from Baseline in ADF for Partial Onset Seizures - mITT Population

				LEV – PBO		
Assessment	**Statistics**	**PBO (N=51)**	**LEV (N=58)**	**Median Difference**[a]	**95% CI**	**P-value**[b]
Selection	Mean (SD)	15.37 (22.92)	31.13 (46.09)			
	Median	6.82	15.20			
	Q1 - Q3	2.00 – 16.22	4.48 – 38.95			
	Min - Max	0 - 98.03	0 - 211.8			
Evaluation	Mean (SD)	16.23 (24.16)	22.60 (37.32)			
	Median	6.48	8.34			
	Q1 - Q3	1.51 – 16.99	0.51 – 24.97			
	Min - Max	0 – 106.4	0 – 184.3			
Absolute Change	Mean (SD)	-0.86 (13.81)	8.54 (25.67)			
	Median	0.13	4.77	4.99	2.24 – 7.99	<0.001
	Q1 - Q3	-2.15 – 2.49	0 – 10.48			
	Min - Max	-56.89 – 41.27	-51.48 – 156.35			
% Reduction[c]	Mean (SD)	-20.93 (111.47)	24.98 (91.49)			
	Median	7.12	43.61	39.21	17.52 – 62.23	<0.001
	Q1 - Q3	-42.29 – 35.14	11.72 – 85.71			
	Min - Max	-450.58 – 100	0 – 148.3			

[a] Hodges-Lehman method used to estimate median difference
[b] P-values are from the Mann-Whitney test.
[c] Four subjects (1 on PBO and 3 on LEV) are excluded from this analysis due to having 0 seizures at baseline.
Source: Table 14.2.2:4 and Table 14.2.2:6

7.1.2.3 Comparison of The Model Prediction to Actual Clinical Trial Results (N01009)

The exposure-response model in study N01308 predicts the would be a 45% reduction in median seizure frequency at an LEV dose of (b) (4) mg/kg/day in children from 1 month to < 4 years (Table 7.4). The clinical trials data from trial N01009 reports a 43.61% (Table 7.5) reduction in median seizure frequency for children in the 1 month to < 4 years age group receiving a target dose of up to 50 mg/kg/day. The additional (b) (4) increase in dose to (b) (4) mg/kg/day is predicted to result in an additional 1.39% reduction in seizure frequency. The benefit of an additional reduction in seizure frequency of 1.39% does not justify a (b) (4) increase in dose.

7.1.2.4 Additional Discussion With Clinical Pharmacology Reviewer

This clinical reviewer met with the Clinical-Pharmacology (CP) reviewer on two occasions to discuss the reliability of the sponsor's retrospective PK and exposure-response analysis and determine if the justification for the 20-(b) (4) mg/kg/day regimen and recommended dosing nomogram was acceptable. The Clinical-Pharmacology reviewer indicated the sponsor's method used to construct the PK and Exposure-Response models appear to be appropriate. The Clinical Pharmacology Reviewer performed independent analysis using NIH data on renal clearance by weight in normal children in the same age groups and data from a model medication with a similar metabolic profile as LEV.

7.1.2.5 Clinical Reviewer's Recommendation on Dosing

The total number of subjects age < 6 month old is relatively small age studied in clinical trials in the group is relatively small. It raises questions concerning how well the data represents the larger intended population. It also raises concern about the exposure in subjects who are close to or just over 6 months old. The sponsor provided data from population PK and exposure-response studies in older children and adults to draw parallels between the exposure-response relationships to justify the recommendation for using a maintenance dose of LEV in children 1 month to <4 years of 20-(b) (4) mg/kg/day. The pivotal efficacy trial N01009 only studied LEV in doses of 20-50 mg/kg/day in children ages 1 month to < 4 years. Furthermore, the benefit associated with a higher LEV dose to (b) (4) kg/day is predicted by the sponsor own exposure-response model to result in little if any additional reduction in seizure frequency. The proposed maximum dose of (b) (4) mg/kg/day was only administered in open-label studies and it was not tested in well controlled, double-blind clinical trials in children in the 1 month to < 4 year group. The dose of 60 mg/kg/day is approved for children ages 4 to 16 years old however the pivotal study (N01009) did not include this dose. (b) (4)

This clinical reviewer recommends LEV be approved for the doses actually studied in clinical trial (20-50 mg/kg/day) in children 1 month to < 4 years as opposed to the higher dose range sought by UCB based on model predictions from pediatric 4-16 year old study data and adult exposure-response comparisons. The dosing recommendation based upon the sponsor's

nomogram is acceptable making the actual dose ranges 14 to 42 mg/kg/day for children < 6 months and 10 to 50 mg/kg/day in children 6 months to < 4 years.

7.3 Discussion of Persistence of Efficacy and/or Tolerance Effects

7.3.1 Study N157

A total of 223 subjects aged 0.2 to 17.5 years at the time of enrollment were exposed to the study drug (maximum exposure was approximately 7.5 years and mean and median exposures were approximately 2 years). The median dose was 52.6 mg/kg with a minimum of 7.3 mg/kg and a maximum of 117.1 mg/kg.

Table 7.6 -Median Percent Reduction in Percent Change in Partial Seizure Frequency From Baseline By Duration of Exposure Cohort and Analysis Visit. (UCB)

Table 11:9 Partial Onset (Type I) Seizure Frequency per Week Median Percent Change from Baseline, Overall by Duration of Exposure Cohort and Analysis Visit, Week 1 to Week 396 (Prior Studies N159, N01010, N151) – ITT Population

	Duration of Exposure							
	≥ 1 Day (Overall)		< 1 Year		≥1 - <2 Years		≥2 -<3 Years	
Analysis Visit	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Weeks >24 - ≤36	170	-70.6 (-92.7, -35.7)	30	-50.4 (-78.7, -13.7)	37	-69.1 (-86.7, -31.7)	52	-75.6 (-99.2, -50.0)
Weeks >36 - ≤48	158	-70.7 (-95.6, -42.4)	18	-68.6 (-100, -7.5)	37	-70.5 (-83.3, -20.4)	52	-69.1 (-99.2, -48.2)
Weeks >48 - ≤60	141	-71.0 (-94.8, -32.2)	3	-77.3 (-100, 54.7)	36	-57.1 (-84.3, -31.2)	51	-82.2 (-97.5, -32.2)
Weeks >60 - ≤ 72	131	-73.4 (-98.9, -33.7)	1	-100 (-100, -100)	28	-52.1 (-88.9, 7.5)	51	-82.2 (-100, -36.7)
Weeks >72 - ≤84	118	-79.6 (-100, -39.5)	1	-100 (-100, -100)	14	-47.8 (-93.7, 27.2)	52	-86.3 (-100, -46.1)
Weeks >84 - ≤96	112	-74.0 (-99.6, -39.7)	-	-	9	-74.1 (-94.2, -9.5)	51	-78.8 (-100, -34.3)
Weeks >96 - ≤108	103	-80.0 (-99.3, -40.3)	-	-	3	-75.6 (-100, -18.6)	50	-77.3 (-100, -46.1)
Weeks >108 - ≤120	99	-82.6 (-100, -42.9)	-	-	-	-	48	-76.1 (-100, -43.0)
Weeks >120 - ≤132	94	-86.9 (-100, -38.8)	-	-	-	-	43	-94.3 (-100, -38.8)
Weeks >132 - ≤144	81	-82.2 (-100, -42.3)	-	-	-	-	30	-91.0 (-100, -15.3)
Weeks >144 - ≤156	65	-84.6 (-100, -52.4)	-	-	-	-	14	-97.3 (-100, -68.7)
Weeks >156 - ≤168	51	-88.4 (-100, -45.3)	-	-	-	-	1	-95.9 (-95.9, -95.9)

	Duration of Exposure									
	≥ 1 Day (Overall)		≥3 - <4 Years		≥4 - <5 Years		≥5 - <6 Years		≥6 Years	
Analysis Visit	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Weeks >24 - ≤36	170	-70.6 (-92.7, -35.7)	18	-80.3 (-99.3, -42.3)	21	-77.9 (-91.1, -44.4)	8	-71.9 (-87.6, -40.4)	4	-82.5 (-93.4, -59.8)
Weeks >36 - ≤48	158	-70.7 (-95.6, -42.4)	18	-78.7 (-100, -33.2)	21	-70.3 (-94.0, -48.9)	8	-65.5 (-84.9, -50.2)	4	-97.3 (-99.2, -83.6)
Weeks >48 - ≤60	141	-71.0 (-94.8, -32.2)	18	-63.8 (-100, -33.3)	21	-75.6 (-96.1, -62.2)	8	-33.3 (-73.7, -9.2)	4	-92.8 (-98.8, -77.1)
Weeks >60 - ≤ 72	131	-73.4 (-98.9, -33.7)	18	-77.8 (-97.8, -24.1)	21	-76.2 (-94.0, -28.9)	8	-67.4 (-94.5, 3.9)	4	-98.0 (-100, -84.8)
Weeks >72 - ≤84	118	-79.6 (-100, -39.5)	18	-68.0 (-100, -30.2)	21	-82.6 (-100, -52.8)	8	-67.8 (-87.0, -42.5)	4	-94.9 (-99.6, -65.3)
Weeks >84 - ≤96	112	-74.0 (-99.6, -39.7)	18	-65.7 (-100, -33.3)	21	-73.9 (-96.8, -53.3)	8	-59.3 (-86.6, -5.9)	4	-79.8 (-98.8, -51.4)
Weeks >96 - ≤108	103	-80.0 (-99.3, -40.3)	18	-71.9 (-100, -11.2)	20	-87.3 (-98.0, -55.1)	8	-76.7 (-86.9, -8.6)	4	-89.9 (-96.5, -80.7)
Weeks >108 - ≤120	99	-82.6 (-100, -42.9)	18	-68.8 (-100, 22.8)	21	-90.6 (-100, -60.2)	8	-75.6 (-95.5, -37.5)	4	-100 (-100, -88.3)
Weeks >120 - ≤132	94	-86.9 (-100, -38.8)	18	-53.3 (-100, 4.8)	21	-79.6 (-97.7, -55.0)	8	-68.5 (-87.0, -23.8)	4	-95.3 (-100, -85.9)
Weeks >132 - ≤144	81	-82.2 (-100, -42.3)	18	-54.2 (-100, 4.8)	21	-83.0 (-99.2, -51.2)	8	-65.5 (-89.5, -36.8)	4	-90.4 (-99.8, -76.3)
Analysis Visit	Duration of Exposure									

Table 11:9 Partial Onset (Type I) Seizure Frequency per Week Median Percent Change from Baseline, Overall by Duration of Exposure Cohort and Analysis Visit, Week 1 to Week 396 (Prior Studies N159, N01010, N151) – ITT Population

	≥1 Day (Overall)		≥3 - <4 Years		≥4 - <5 Years		≥5 - <6 Years		≥6 Years	
	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Weeks >144 - ≤156	65	-84.6 (-100, -52.4)	18	-84.4 (-100, -52.4)	21	-85.5 (-97.1, -56.1)	8	-62.0 (-90.8, -9.0)	4	-88.6 (-100, -75.2)
Weeks >156 - ≤168	51	-88.4 (-100, -45.3)	17	-91.0 (-100, -42.5)	21	-88.4 (-98.9, -57.8)	8	-66.0 (-91.2, 41.7)	4	-94.3 (-100, -80.1)
Weeks >168 - ≤180	44	-75.4 (-97.3, -34.3)	11	-42.5 (-100, 69.4)	21	-79.7 (-95.7, -53.8)	8	-70.9 (-92.0, -31.6)	4	-73.5 (-86.7, -71.9)
Weeks >180 - ≤192	38	-82.8 (-98.9, -55.7)	5	-67.0 (-80.2, 3.2)	21	-83.0 (-97.1, -55.7)	8	-78.3 (-100, -54.8)	4	-92.4 (-100, -78.4)
Weeks >192 - ≤204	37	-80.6 (-97.1, -63.3)	4	-74.0 (-89.3, -57.2)	21	-85.5 (-97.1, -65.8)	8	-76.5 (-90.0, 13.5)	4	-94.6 (-98.4, -75.8)
Weeks >204 - ≤216	36	-82.7 (-98.3, -63.9)	3	-86.4 (-100, -80.2)	21	-82.5 (-93.5, -61.6)	8	-80.6 (-97.6, -33.0)	4	-98.3 (100, -67.4)
Weeks >216 - ≤228	31	-76.8 (-99.2, -50.2)	-	-	19	-76.8 (-100, -64.9)	8	-61.6 (-96.7, -22.4)	4	-88.2 (-99.6, -71.6)
Weeks >228 - ≤240	28	-88.4 (-100, -68.1)	-	-	16	-86.9 (-100, -65.7)	8	-81.0 (-100, -45.8)	4	-95.8 (-99.6, -80.7)
Weeks >240 - ≤252	24	-88.9 (-100, -66.7)	-	-	12	-86.6 (-100, -66.7)	8	-81.8 (-93.1, -53.3)	4	-96.2 (-100, -78.2)
Weeks >252 - ≤264	17	-92.7 (-100, -68.5)	-	-	5	-98.1 (-98.9, -92.7)	8	-72.0 (-100, -46.3)	4	-92.4 (-100, -72.4)
Weeks >264 - ≤276	12	-91.1 (-98.7, -68.3)	-	-	-	-	7	-73.4 (-94.3, -60.5)	4	-97.0 (-1000, -91.1)
Weeks >276 - ≤288	6	-87.6 (-100, -67.3)	-	-	-	-	2	-73.1 (-79.0, -67.3)	4	-98.1 (-100, -75.9)
Weeks >288 - ≤300	5	-96.2 (-99.1, -66.5)	-	-	-	-	1	-66.5 (-66.5, -66.5)	4	-97.6 (-99.5, -80.3)
Weeks >300 - ≤312	4	-100 (-100, -82.4)	-	-	-	-	-	-	4	-100 (-100, -82.4)
Weeks >312 - ≤324	4	-100 (-100, -80.4)	-	-	-	-	-	-	4	-100 (-100, -80.4)
Weeks >324 - ≤336	4	-100 (-100, -82.6)	-	-	-	-	-	-	4	-100 (-100, -82.6)
Weeks >336 - ≤348	4	-100 (-100, -99.8)	-	-	-	-	-	-	4	-100 (-100, -99.8)
Weeks >348 - ≤360	4	-100 (-100, -85.5)	-	-	-	-	-	-	4	-100 (-100, -85.5)
Weeks >360 - ≤372	3	-100 (-100, -76.2)	-	-	-	-	-	-	3	-100 (-100, -76.2)
Weeks >372 - ≤384	1	-100 (-100, -100)	-	-	-	-	-	-	1	-100 (-100, -100)
Weeks >384 - ≤396	1	-100 (-100, -100)	-	-	-	-	-	-	1	-100 (-100, -100)

Note: Prior study N01052 did not capture a baseline and therefore does not contribute to these statistics. Section 9.7.1.3 explains handling of missing subjects/data.
Source: Table 14.2.1.16

The analysis presented by the sponsor demonstrates that a treatment effect that increases with the duration of exposure, however the number of subjects decreases with time, as expected. The reasons listed by the sponsor given by subjects who discontinued participation in the trial is contained in table 7.7 (below). The total percentage of subjects who were listed "Loss or Lack of Efficacy" plus "Adverse Event" totaled 30%. Two thirds discontinued participation before the trial was closed which is not unexpected given the long duration of the trial. The combination of the dropout of subjects over the trial duration, especially those who did not respond or experienced a loss of response likely inflated the weekly percent reduction from baseline in seizure frequency.

Table 7.7-Subject Disposition Long-term Study N157

Table 10:1 Subject Disposition

Final Status	Overall N (%)
Screened Subjects	223
ITT Population	223
Ongoing at Study Close-out	74 (33.2%)
Discontinued from the Study	149 (66.8%)
Adverse Event	15 (6.7%)
Lack of Efficacy	26 (11.7%)
Loss of Efficacy	26 (11.7%)
Withdrawal of Subject's Consent	22 (9.9%)
Lost to Follow-up	5 (2.2%)
Decision of UCB	1 (0.4%)
Other	35 (15.7%)
Protocol Violation	19 (8.5%)
Non-compliance with visit schedule	8 (3.6%)
Non-compliance with study drug intake	7 (3.1%)
Intake of prohibited concomitant medication	2 (0.9%)
Other	6 (2.7%)

Source: Table 14.1.1:1 and Listing 16.2.1:1

Table 7.8-Partial Seizure Frequency By Age Group Of Subjects in Trial N157 Change from baseline and Over The Duration of The Trial (UCB)

Table 11:21 Partial Seizure (Type I) Frequency per Week over the Entire Treatment Period by Subject Age at N157 Screening Visit (Pooled Studies) – ITT Population

Descriptive Statistics	Age Group			
	< 4 years	4-7 Years	8-12 Years	13-17 Years
n	14	55	114	36
Mean (SD)	20.21 (42.62)	21.05 (79.86)	6.69 (19.30)	4.84 (6.83)
Median	1.3	2.8	1.5	1.9
Q1, Q3	0.2, 22.4	0.6, 6.9	0.4, 5.1	1.0, 4.4
Min, Max	0.0, 150.7	0.0, 429.3	0.0, 188.0	0.1, 30.9

Note: Treatment period includes titration (where applicable) and maintenance phases.
Note: n is the number of subjects with valid seizure counts and seizure dates.
Source: Table 14.2.1.19

Table 11:22 Partial Seizure (Type I) Frequency per Week over the Entire Treatment Period - Percent Change from Baseline - by Subject Age at N157 Screening Visit (Pooled Studies) – ITT Population

Descriptive Statistics	Age Group			
	< 4 years[a]	4-7 Years	8-12 Years	13-17 Years
n	1	53	110	36
Baseline Mean (SD)	10.95 (.)	28.55 (95.36)	15.68 (47.96)	10.03 (11.43)
Treatment Period Mean (SD)	1.12 (.)	21.05 (79.86)	6.69 (19.30)	4.84 (6.83)
Percent Change from Baseline[b]				
Mean (SD)	-89.79 (.)	-36.44 (71.83)	-43.21 (74.51)	-40.03 (58.19)
Median	-89.8	-57.4	-65.5	-48.9
Q1, Q3	-89.8, -89.8	-94.2, -3.6	-86.7, -25.8	-74.7, -27.5
Min, Max	-89.8, -89.8	-100.0, 304.7	-100.0, 489.3	-97.9, 199.9

Note: Treatment period includes titration (where applicable) and maintenance phases.
Note: n is the number of subjects with data at both baseline and the Treatment Period.
[a] All but 1 subject (380/003, N159) came from study N01052, which did not collect baseline.
[b] 100 x (seizure frequency per week at the visit - seizure frequency per week at baseline)/seizure frequency per week at baseline.
Source: Table 14.2.1.20

The median percent reduction in weekly seizure frequency over the duration of the N157 trial is most pronounced in the < 4 year age group; however there was only 1 evaluable subject in this group that remained during the entire treatment period of 7.5 years.

7.3.3 Study N01148

This study is an ongoing open-label, long-term safety study that enrolled the first subject on October 23, 2004. The sponsor submitted an interim report with a cut-off date of September 18, 2007 for this submission.

Table 7.9- Age Distribution of Subjects in Study N01148 ITT Population (UCB)

Table 11:1 Number and Percent of Subjects by Study Population

Study Population Period Phase	1m - <4y N (%)	4y - 16y N (%)	Overall N (%)
Screened Subjects	152	104	256
ITT Population	152 (100.0%)	103 (100.0%)	255 (100.0%)
Treatment-emergent period	152 (100.0%)	103 (100.0%)	255 (100.0%)
Up-titration/Conversion Phase	152 (100.0%)	103 (100.0%)	255 (100.0%)
Maintenance Phase	138 (90.8%)	95 (92.2%)	233 (91.4%)
Down-titration/Withdrawal Phase	26 (17.1%)	14 (13.6%)	40 (15.7%)
Post-treatment Phase	34 (22.4%)	15 (14.6%)	49 (19.2%)

Source: Table 14.1.1:1 and Table 14.1.1:3

The sponsor reports 152 subjects overall were enrolled in study N01148, 28 were age < 1 year at the time of trial entry, and only 9 were age < 6 months at the time of trial entry.

Table 7.10-Study N01148 Randomized Subjects Age < 12 Months

CENNBR	SBJNBR	AGE	AGEUNIF	TREAT
202	202/1004	0.83	Year	Levetiracetam 10% oral solution - 2 bottles
204	204/1005	0.69	Year	Levetiracetam 10% oral solution - 2 bottles
204	204/1006	0.96	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
307	307/1001	0.97	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
317	317/1001	0.3	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
317	317/1005	0.82	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
321	321/0001	0.74	Year	Levetiracetam open label
321	321/1002	0.19	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
323	323/1001	0.15	Year	Levetiracetam 10% oral solution - 2 bottles
323	323/1002	0.21	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
323	323/2002	0.54	Year	Levetiracetam open label
327	327/1004	0.25	Year	Levetiracetam 10% oral solution - 2 bottles
335	335/1002	0.91	Year	Levetiracetam 10% oral solution - 2 bottles
502	502/2002	0.82	Year	Levetiracetam open label
502	502/2003	0.38	Year	Levetiracetam open label
503	503/1003	0.93	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
503	503/1005	0.9	Year	Levetiracetam 10% oral solution - 2 bottles
503	503/1006	0.44	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
510	510/1001	0.39	Year	Levetiracetam 10% oral solution - 2 bottles

511	511/1002	0.71	Year	Levetiracetam 10% oral solution - 2 bottles
522	522/1001	0.52	Year	Levetiracetam 10% oral solution - 2 bottles
523	523/1002	0.69	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
530	530/1002	0.73	Year	Levetiracetam 10% oral solution - 2 bottles
602	602/0002	0.98	Year	Levetiracetam open label
634	634/1002	0.97	Year	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
634	634/2001	0.25	Year	Levetiracetam open label
702	702/2002	0.84	Year	Levetiracetam open label
705	705/2001	0.72	Year	Levetiracetam open label

Table 7.12-Study N01148 Subjects Randomized Age < 6 months

CENNBR	SBJNBR	GDRF	AGE	TREAT
317	317/1001	Male	0.3	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
321	321/1002	Female	0.19	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
323	323/1001	Female	0.15	Levetiracetam 10% oral solution - 2 bottles
323	323/1002	Female	0.21	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
327	327/1004	Female	0.25	Levetiracetam 10% oral solution - 2 bottles
502	502/2003	Male	0.38	Levetiracetam open label
503	503/1006	Female	0.44	Levetiracetam 10% oral solution - 1 btl LVTM + 1 btl PLACEBO
510	510/1001	Female	0.39	Levetiracetam 10% oral solution - 2 bottles
634	634/2001	Male	0.25	Levetiracetam open label

Table 7.13-Study N01148 Percent reduction in Partial Onset Seizures (UCB)

Table 11:10 Summary of Partial Onset Seizure Percent Reduction from Baseline by Visit during the Maintenance Phase - ITT Population

Visit		1m - <4y (N = 152)	4y - 16y (N = 103)	Overall (N = 255)
Visit 4 (Week 14, 15, or 16)	n	131	93	224
	Median	53.40	88.64	69.88
	Q1 - Q3	-16.94 – 95.29	37.50 – 100.00	1.14 – 100.00
Visit 5 (Week 24)	n	117	89	206
	Median	67.97	91.67	79.99
	Q1 - Q3	-19.49 – 99.47	48.44 – 100.00	4.07 – 100.00
Visit 6 (Weeks 24-36)	n	97	58	155
	Median	75.29	100.00	81.58
	Q1 - Q3	15.15 – 98.55	52.71 – 100.00	26.67 – 100.00
Visit 7 (Weeks 36-48)	n	76	43	119
	Median	76.83	100.00	87.50
	Q1 - Q3	21.36 – 98.73	82.22 – 100.00	41.38 – 100.00

Source: Table 14.2.1:2

The change from baseline to last visit (36-48 weeks) before the cut-off date also demonstrated at least > 50 % reduction in weekly seizure frequency over time associated with open label use of LEV. The percent reduction in median weekly seizure frequency continued to improve as the trial progressed, however the number of dropouts also increased as the trial increased during the follow up period (Table 7.14). In the 1 month to < 4 year age group approximately 24% dropped-out of the study by the cut-off date 8.6% gave "adverse event" as the reason for discontinuing and 14.5% left the trial because of loss or lack of efficacy. A greater number of the subjects remaining in the trial were likely the individuals who continued to experience and a reduction in seizure frequency elevating the positive response figures.

Table 7.14- Disposition of Subjects in Study N01148

Table 10:1 Subject Disposition by Age Group and Overall

	1m - <4y N (%)	4y - 16y N (%)	Overall N (%)
Screened Subjects[(a)]	152	104	256
ITT Population	152	103	255
Enrolled from Prior Study	111 (73.0%)	80 (77.7%)	191 (74.9%)
Screen Failed from Prior Study	33 (21.7%)	1 (1.0%)	34 (13.3%)
Directly Enrolled in N01148	8 (5.3%)	22 (21.4%)	30 (11.8%)
Completed Study	69 (45.4%)	42 (40.8%)	111 (43.5%)
Ongoing at Clinical Cutoff	29 (19.1%)	42 (40.8%)	71 (27.8%)
Ongoing (Awaiting N01183)	6 (3.9%)	0	6 (2.4%)
Discontinued from the Study	54 (35.5%)	19 (18.4%)	73 (28.6%)
Adverse Event	13 (8.6%)	4 (3.9%)	17 (6.7%)
Lack/Loss of Efficacy	22 (14.5%)	6 (5.8%)	28 (11.0%)
Lost to Follow-up	2 (1.3%)	3 (2.9%)	5 (2.0%)
Withdrawal of Consent	6 (3.9%)	2 (1.9%)	8 (3.1%)
Other	9 (5.9%)	3 (2.9%)	12 (4.7%)
Protocol Violation	2 (1.3%)	1 (1.0%)	3 (1.2%)
Intake of prohibited concomitant medication	1 (0.7%)	0	1 (0.4%)
Other	1 (0.7%)	1 (1.0%)	2 (0.8%)

Source: Table 14.1.1:1, Listing 16.2.1:2, and Listing 16.2.2:1
[(a)] Direct enrolled Subject 803/9001 screen failed for reason "ineligibility."

Appendices

Appendix 1

1 Efficacy Review Study N01009

1.1 Title of Study

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 Refractory Partial Onset Seizures in Pediatric Epileptic Subjects Ranging in Age from 1 Month to Less Than 4 Years of Age.

Protocol No. / Study No.: RPCE03B1013 / N01009

Development Phase: Therapeutic Confirmatory/Phase III

Date of Inclusion of First Subject: 15-Oct-2004

Date of Completion of Last Subject: 26-Jan-2007

Sponsor: UCB, Inc
1950 Lake Park Drive
Smyrna, GA 30080
USA

Study Center(s):

81 sites in 14 countries participated in the study, of which 62 sites in 13 countries screened and randomized subjects in the study.

1.2 Objectives

The sponsor's stated objective for study N01009 was:

"To evaluate the efficacy and safety of levetiracetam (LEV) used as adjunctive treatment in pediatric subjects age 1 month to less than 4 years with refractory partial onset seizures."

Study N01009 also addressed part 2 of the sponsor's plan to meet the requirements of the pediatric written request.

1.2.1 Rationale and Aims

Levetiracetam has been approved as adjunctive therapy in the treatment of partial onset seizures with and without secondary generalization in adults and children from 4 years of age with epilepsy, and as follows:

- As adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy by both FDA and EMEA.

- As monotherapy in the treatment of partial onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy by EMEA.

- As adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy by FDA.

- As adjunctive therapy in the treatment of primary generalized tonic-clinic seizures in adults and adolescents from 12 years of age by the EMEA.

UCB agreed to assess the safety and efficacy of LEV in children 1 month to 16 years old in partial response to the Written Request issued by the FDA on 21-Aug-2001. The written request was subsequently amended on 22-Mar-2002, 03-Jul-2002, 23-Jul-2004, and 31-Jan-2006). To comply with the request UCB, Inc performed the following studies:

- N159 an efficacy study of Levetiracetam in 4 to 16 year old subjects

- N01009 the efficacy study of Levetiracetam Oral Solution in 1-month to less than 4-year-old subjects

- N01103 the safety study of Levetiracetam to evaluate cognitive and neuropsychological function in 4 to 16-year-old subjects

- N01148 the long-term safety study

Study N01009 was designed and powered as part 1 of their plan to meet the requirement of the PWR and to acquire additional efficacy and safety information regarding the use of LEV in children 1 month to < 4 years of age.

Pharmacokinetic data from study N01052 suggest the plasma clearance of Levetiracetam (CL/f) normalized by body weight in children 6-months to less than 4-years of age is approximately 50% higher than in adults. Children 1-month to less than 6-months of age the CL/f normalized by body weight is similar to that of adults. Based on this information, the dose of Levetiracetam Oral Solution administered to children in study N01009 was determined by age. A dose of 20 mg/kg/day titrating to 40 mg/kg/day for children one month to less than six months old and a dose of 25 mg/kg/day titrating to 50 mg/kg/day for children 6-month to less than 4-years old, was used in this study. This dosing regimen was designed to provide plasma concentrations similar to a dose of 1000 mg/day titrating to 2000 mg/day in adults.

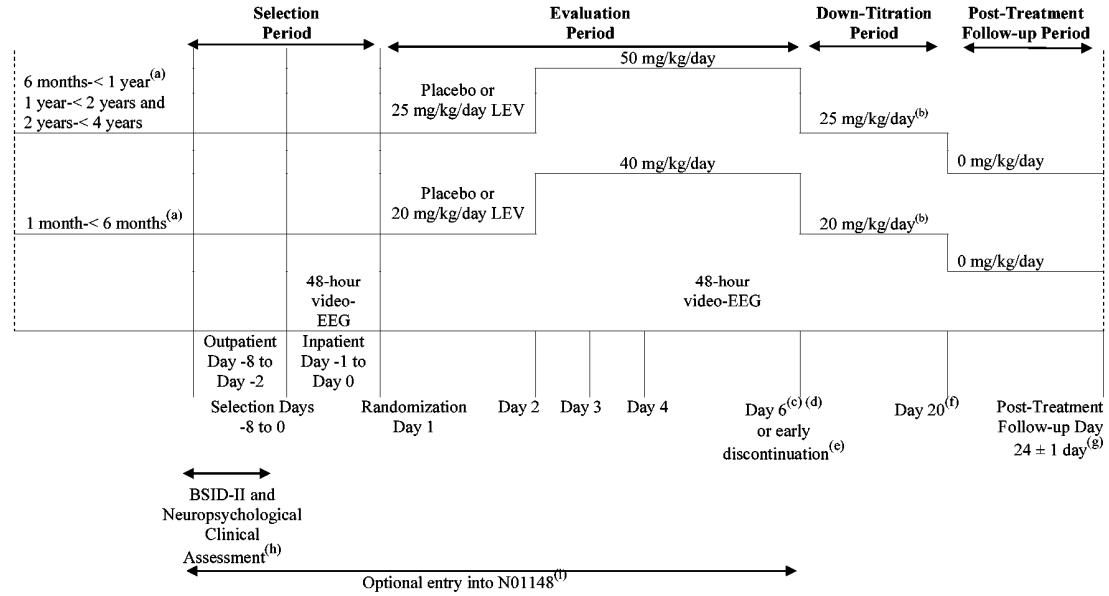
Partial seizures in young children are difficult to diagnose, classify, and count using only clinical observation. To compensate for these difficulties the Division recommended the use of video-EEG to study infants and neonates with partial onset seizures. The N01009 protocol incorporated 48-hour video-EEG monitoring to collect at least 24 hours of video-EEG recording for each subject during the screening phase and for efficacy evaluation. The sponsor concluded it was not practical or ethical to keep subjects on placebo treatment for more than 1 week. Previous pharmacokinetic studies of LEV demonstrated the $t_{1/2}$ is about 6-7 hours and the steady state is typically achieved within 48 hours indicating a shorter evaluation period of 5-day would be adequate to demonstrate efficacy. All subjects were studied as in-patient for a 5-day evaluation period but the maximum duration of study participation was 34 days including a maximum treatment period of 20 days. The study consisted of 4 periods:

- Selection (duration up to 9 days)
- Evaluation (duration 5 days)
- Down-titration (duration 14 days)
- Post-treatment follow-up (duration 4 days+1 day subjects not entering the long-term safety study N01148

2 Trial Design

Fig.2.1-Trial Design Schematic

Figure 9:1 Schematic Diagram of the Study



2.1 Randomization

Randomization was stratified by age range as follows:

- 1-month to less than 6-months of age*
- 6-months to less than 1-year of age*
- 1-year to less than 2-years of age
- 2-years to less than 4-years of age
-

* combined into a < 1 year age group

At least 20 subjects were expected to be randomized in the combined 1 month to < 1 year of age group, a minimum of 36 subjects was expected in the 1 year to < 2 years old group, and a minimum of 36 subjects was expected in the 2 years to < 4 years old group.

2.2 Blinding

This trial was double-blind, subjects were randomly allocated to levetiracetam (10% oral solution) or matching placebo in a 1:1 ratio. Randomization was age stratified using a block size

of 4, and was conducted using an IVRS. In the case of a medical emergency the blind could be broken, if it was necessary to determine the treatment assignment to aid in the subject's medical care.

The study treatment blind was maintained for all subjects except one. Subject 513/0002 in the LEV group reported severe food aversion considered highly probably related to study drug by the Investigator and was discontinued from the study. The subject's treatment was unblinded after the subject was discontinued from the study.

3 Selection Criteria

3.1 Inclusion Criteria

1. The subject's parent(s) or legally authorized representative(s) gave consent and signed and dated the IEC/IRB approved written informed consent form.

2. Subjects must have a diagnosis of epilepsy with refractory partial onset seizures (i.e., seizures of focal onset), whether or not secondarily generalized.

3. Subjects must be male or female from 1 month to less than 4 years of age. Pre-term infants < 1 year old were stratified into an appropriate age category using the best estimate of their corrected gestational age, as determined by UCB. Pre-term infants ≥ 1 year old were stratified into an appropriate age category based on their actual birth date.

4. The Investigator must believe that past or current treatment of the subject with anti-epileptic drug (AED) was unsatisfactory in terms of efficacy and/or safety.

5. Alternative treatment with levetiracetam was thought to be of benefit to the subject.

6. Subjects must be on a stable regimen of one or a maximum of two other AEDs for the Selection and Evaluation periods of the study.

7. Subjects must weighed at least 4.0 kg.

8. Minor adjustments to the dose of current AEDs took place only prior to Day -8.

9. Subjects had no additions of new AEDs or deletions of current AEDs for at least 2 weeks prior to Day -8.

10. Subjects could have Vagus Nerve Stimulation (VNS) which had been implanted for at least 6-months prior to Day -8; the settings had to be stable for at least 2-months prior to Day -8. Activated VNS was counted as one of the two AEDs.

11. Subjects must 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 2 weeks prior to Day -8.

12. Subjects 1 month to less than 6 months of age experienced at least two, partial onset seizures (i.e., seizures of focal onset), whether or not secondarily generalized, during the 48-hour video-EEG performed prior to randomization on Day 1. These seizures did not need to be accompanied by a corresponding clinical event.

3.2 Exclusion Criteria

1. Subjects taking any medication (other than their concomitant AEDs) that influence the central nervous system (CNS) for which they had not been on a stable regimen for at least 1 month prior to Day -8.

2. Subjects taking any medication that may interfere with the absorption, distribution, metabolism, or excretion of the concomitant AEDs or levetiracetam during the course of the study.

3. Subjects who received any investigational medication or device within thirty (30) days prior to Day -8.

4. Subjects who had taken levetiracetam prior to the study.

5. Subjects using felbamate who have presented with clinically significant abnormalities with WBC's, RBC's, platelets, and/or hepatic function during felbamate treatment, and subjects who were taking felbamate less than one year from the date of Day -8.

6. Subjects with a treatable seizure etiology, (i.e., febrile seizures).

7. Subjects with a history of status epilepticus requiring hospitalization during the 1 month prior to Day -8, except for status epilepticus occurring during the first 10 days of life.

8. Subjects who had a current diagnosis of Lennox-Gastaut syndrome.

9. Subjects on a ketogenic diet (concomitantly or within 30 days prior to Day -8).

10. Subjects who have epilepsy secondary to a progressing cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen and Landau-Kleffner diseases.

11. Subjects having clinically significant deviations from reference range values for renal function or any of the other laboratory parameters required for this study, as determined by the Investigator.

12. Subjects having any clinically significant acute or chronic illness (as determined during the physical examination or from other information available to the Investigator).

13. Subjects who have a known an allergy to pyrrolidine derivatives or a history of multiple drug allergies.

14. Subjects who are known to have a terminal illness.

15. Subjects who have a disorder or condition that may interfere with the absorption, distribution, metabolism, or excretion of medications.

16. Subjects who have a history of or presence of pseudo-seizures.

17. Subjects having any medical condition that might interfere with the subject's study participation (i.e., serious infection, scheduled elective surgery, severe scalp eczema, etc).

3.3 Patient Withdrawals

Subjects who withdrew during the Selection Period (Day -8 to Day 1, prior to dosing) could be discharged from the study on the day of the visit as screen failures.

The following events may be considered sufficient reason to discontinue subject participation in the study at the discretion of the Investigator:

- A prolongation or worsening of seizure duration (serial seizures or status epilepticus of any seizure subtype) or increased seizure frequency requiring intervention

- A situation where continued participation in the study would not be in the best interest of the subject

- An inability to tolerate the dose of study medication as scheduled;

- Non-compliance with the dosing schedule of study medication

- Non-compliance with the dosing schedule of concomitant AED(s);

- Poor compliance with the protocol procedures, by either the subject, parent(s)/legally authorized representative(s), or the Investigator;

- Lost to follow-up or inability to remain under medical observation during the entire duration of the study

- Deviation or violation of the protocol which jeopardizes the performance of the study, as agreed by the Investigator or the Sponsor (This deviation must be documented.);

- Withdrawal of the consent by the parent(s) or legally authorized representative(s).

Subjects who withdrew from the study and stopped study treatment were required to return for a follow-up visit on Day 24 ± 1.

3.4 Study Medication

Study medication was provided by the Sponsor as a 10% levetiracetam oral solution or matching placebo. Levetiracetam oral solution is a clear, colorless solution with a grape flavor. The 10% levetiracetam oral solution is equivalent in dose to 100 mg per 1 mL. The placebo oral solution was also a clear, colorless solution with a grape flavor, and was indistinguishable from the levetiracetam oral solution.

Dosing was determined by age and weight as follows:

- Children one month to less than six months old received a dose of 20 mg/kg/day titrating to 40 mg/kg/day

- Children 6 month to less than 4 years old received a dose of 25 mg/kg/day titrating to 50 mg/kg/day.

3.4.1 Permitted Concomitant Therapy

Subjects had to remain on a stable regimen of one or a maximum of two other AEDs for the Selection and Evaluation Periods. No additions of new AEDs or deletions of current AEDs for at least 2 weeks prior to Day -8 were allowed. Minor adjustments to the dose of current AEDs were allowed prior to Day -8 only. Subjects could have VNS for at least 6 months prior to Day -8, as long as the settings had been stable for at least 2 months prior to Day -8. Activated VNS was counted as one of the two AEDs. The use of intermittent benzodiazepines was allowed as long as the frequency was not greater than one single administration per week for at least 2 weeks prior to Day -8 and throughout study participation. If benzodiazepines were used more than once a week, they were considered as one of the AEDs.

3.4.2 Not Permitted Concomitant Therapy

Investigators were instructed to avoid treatment with medications that may influence the central nervous system, such as, neuroleptics, anti-depressants, psycho-stimulants, anticholinergics, tranquilizers, hypnotics, and narcotic analgesics. If the use of CNS influencing medication could not be avoided, a stable regimen of the medication for at least one month prior to Day -8 was required

3.4.3 Compliance

The subject's compliance between 80-120% was required during the entire evaluation period. All subjects maintained at least an 80% medication compliance rate through out the study.

Table 3.1-Number and Percentage of Subjects by Treatment Compliance during the Full Dose Period - ITT Population

Full Dose Period	PBO (N=55) n (%)	LEV (N=60) n (%)	Overall (N=115) n (%)
n	55 (100.0)	60 (100.0)	115 (100.0)
< 80%	0	0	0
80 - 120%	54 (98.2)	58 (96.7)	112 (97.4)
> 120%	1 (1.8)	2 (3.3)	3 (2.6)

4. Efficacy Analysis

4.1 Data Collection For Primary Efficacy Variable (Video-EEG Analysis)

The primary efficacy variable is the Responder Rate for total partial onset seizures (Type I) for subjects in all age groups. The sponsor defined the Responder Rate as follows:

$$\textbf{Responder Rate} = \frac{\text{\# of subjects with a} \geq 50\% \text{ reduction from baseline in ADF}}{\text{Total number of subjects.}}$$

ADF was computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline) as follows:

$$\text{ADF} = \frac{\text{\# of seizures recorded during video-EEG time} \times 24}{\text{\# hours of usable video-EEG time}}$$

*Usable selection video-EEG time was defined as total video-EEG time minus total uninterpretable time.

4.1 Seizure Counts

- For children 1 month to less than 6 months old, partial onset seizure counts were based on electro-clinical seizures plus electrographic seizures.

- For children in the remaining age groups, 6 months to less than 4 years old, partial onset seizures were based on electroclinical seizures only.

4.2 Primary Efficacy Data Analysis

The primary efficacy analysis was based on the mITT population (repeated on the PP population as a supportive analysis). The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable Selection video-EEG time as determined by a blinded central reader. The sponsor hired (b) (4) as the Blinded Central EEG Reader.

Selection video-EEG data interpreted by the central reader was used for analysis. Subjects included in the mITT analysis had at least 24 hours of usable Evaluation video-EEG time. Subjects who had < 24 hours usable Evaluation video-EEG and withdrew due to lack or loss of efficacy were considered as non-responders (for the primary endpoint).

4.2.1 Unplanned Analysis of The Effect of Baseline Characteristics On The Primary Outcome Variable

Baseline seizure ADF was included as a covariate in a post-hoc logistic regression analysis of the primary endpoint. In addition, post-hoc logistic regression was used to simultaneously examine the effects of the following variables: treatment group, baseline seizure ADF, age group, and race. Both the raw and log transformation (natural log +1) of the baseline seizure ADF were examined. The logistic regression analysis did not result in change regarding efficacy. Post-hoc exploratory logistic regression analyses confirmed that the baseline imbalance in seizure ADF did not affect the results of the primary endpoint. When baseline seizure ADF was included as a covariate in the logistic regression model, LEV remained statistically superior to placebo (p=0.006 with untransformed baseline seizure ADF, and p=0.005 with log transformed baseline seizure ADF). In addition, no baseline seizure ADF by treatment group interaction was observed.

4.2.2 Secondary Efficacy Variables

1. Subgroup Analyses by Age Group - mITT Population

    - 1 month to < 12 month age group
    - 12 month to < 24 month age group
    - 24 month to < 48 month age group.

2. 50% Responder ADF seizure analyses for total seizures (Type I + II + III).
    - Types: I=Partial onset, II=generalized at onset, III=Unclassified

3. Absolute and Percent Reduction in ADF Seizure Analyses.

    - The percent reduction from baseline in ADF of partial onset seizures (Type I).

- The percent reduction from baseline in ADF of total seizures (Type I + II + III).
- The absolute reduction from baseline in ADF of partial onset seizures (Type I).
- The absolute reduction from baseline in ADF of total seizures (Type I + II + III).
- The percent reduction from baseline in ADF of electro-clinical partial onset seizure (analyses exclusive of subjects 1 month to less than 6 months of age).

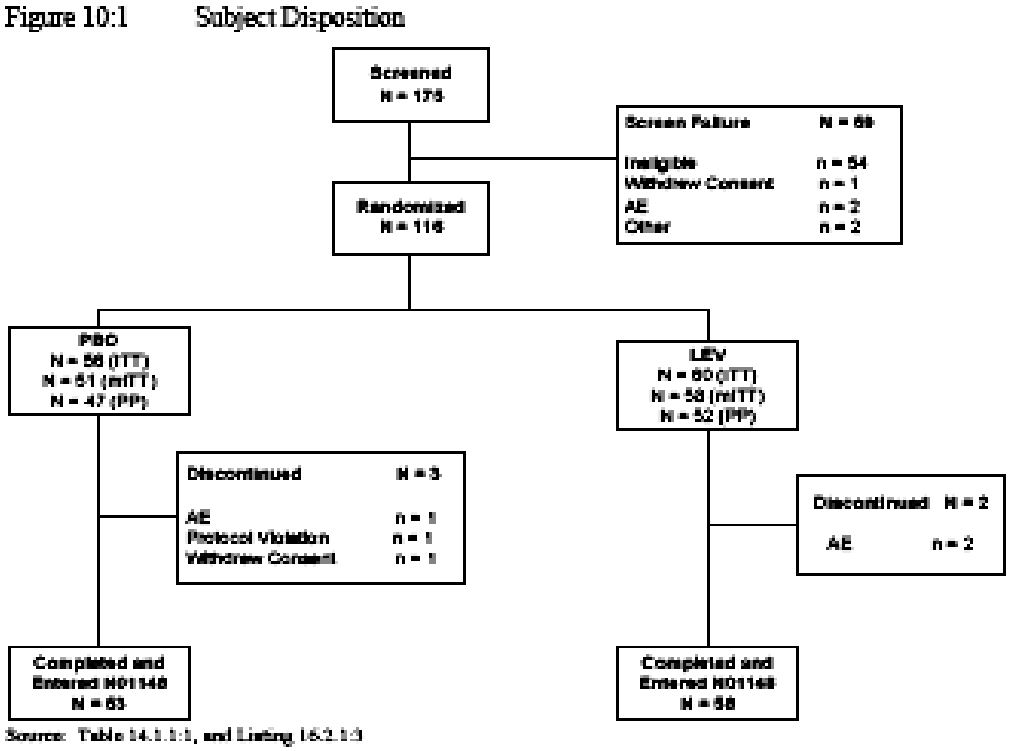
4. Seizure Count Data Collected from the Case Report Form during Evaluation
5. Seizures recorded on the CRF from Day 1 to Day 6 observed by the hospital staff and/or family members were summarized by day, type, and treatment group.

Secondary efficacy variables that were analyzed on the ITT population only:

- The percentage of dropouts for any reasons.
- The percentage of dropouts due to lack or loss of efficacy.
- The percentage of dropouts with < 24 hours of usable Evaluation video-EEG for reasons other than lack or loss of efficacy.
- The Time to Exit (TTE) in the Evaluation period. For early termination subjects in the Evaluation period the TTE is the time to discontinuation from the study for any reason. TTE was defined as the day of study discontinuation – the day of randomization + 1. For completed subjects, the TTE was censored on Day 6.

5 Subject Disposition

Fig.5.1-Schematic of Subject Disposition (UBC)



5.1 Withdrawals Due to Adverse Events

Five patients withdrew from the study, 3 from the placebo group and 2 in the LEV group. One of the withdrawals in the placebo group was due to an adverse event and both subjects in the LEV group withdrew because of an adverse event. The subject in the placebo group withdrew from the trial because of aspiration pneumonia. One subject in the LEV group discontinued because of convulsions and the other because of food aversion. The subject (519/0001) who withdrew from the trial because of convulsion, was described as having "moderate seizures" they received 1 day of study treatment and discontinued from the trial. The subject expired 40 days later with the cause of death listed as undetermined. Because the death occurred more than 30 days after stopping study medication the event was not counted as an SAE. Subject 513/0002 in the LEV group discontinued from the study after 3 days of treatment with LEV because of severe food aversion. The subject's treatment was unblinded after the subject was discontinued from the study. None of the subjects withdrew from either limb of the trial the trial because of lack of efficacy.

5.2 Subjects Excluded From The ITT Analysis (UCB Table)

Table 10:2 Subjects Excluded from the mITT Population

Subject	Group	Reason for Exclusion from mITT
307/0001	PBO	The selection period 48 Hour Video EEG was done. The subject had qualifying seizures but the EEG data was inadvertently deleted at the site. Therefore, the Central Reader evaluation was not done.
317/0003	PBO	The evaluation period 48 Hour Video EEG was done but the data was lost. Therefore, the Central Reader evaluation was not done.
325/0001	PBO	For the selection period 48 Hour Video-EEG, the number of electrographic seizures was not done.
521/0002	PBO	The total number of evaluable hours for the Evaluation Visit 48 hour Video EEG Central Reader Evaluation is less than 24 hours.
525/0003	PBO	The total number of evaluable hours for the selection period 48 hour Video EEG Central Reader evaluation is less than 24 hours.
516/0001	LEV	The total number of evaluable hours for the selection period 48 hour Video EEG Central Reader evaluation is less than 24 hours.
519/0001	LEV	Two selection period video-EEGs were performed: one at the Days -8 to -2 visit and one at the Days -1 to 0 visit.

Source: Listing 16.2.2:1 and Listing 16.2.2:2

Five subjects in the placebo group and 2 subjects in the LEV subjects excluded from the ITT analysis. The reason for all of these subjects involved incomplete EEG data except subject 519/0001 who withdrew from the study after 1 day of treatment with LEV. The sponsor reported this subject had an additional major protocol violation of taking more than 2 AEDs during the trial. The possible effect of the exclusion of these subjects is discussed in Section 7.1.

6. Subject Characteristics

6.1 Baseline Characteristics

Table 6.1-Subject Demographic Characteristics (UCB Table)

Table 11:1 Demographic Characteristics by Treatment Group (ITT Population)

	Descriptive Statistics	PBO (N=56)	LEV (N=60)	Overall (N=116)
Age (a) (months)	Mean (SD)	23.46 (12.06)	23.40 (13.43)	23.43 (12.73)
	Min - Max	2.0 - 46.0	1.0 - 47.0	1.0 - 47.0
Age Class (months)				
< 6	n (%)	4 (7.1%)	4 (6.7%)	8 (6.9%)
6 to < 12	n (%)	7 (12.5%)	8 (13.3%)	15 (12.9%)
12 to < 24	n (%)	18 (32.1%)	20 (33.3%)	38 (32.8%)
24 to < 48	n (%)	27 (48.2%)	28 (46.7%)	55 (47.4%)
Gender				
Male	n (%)	27 (48.2%)	30 (50.0%)	57 (49.1%)
Female	n (%)	29 (51.8%)	30 (50.0%)	59 (50.9%)
Race				
Caucasian	n (%)	39 (69.6%)	54 (90.0%)	93 (80.2%)
American Indian/Alaskan	n (%)	2 (3.6%)	4 (6.7%)	6 (5.2%)
Other/mixed race	n (%)	8 (14.3%)	2 (3.3%)	10 (8.6%)
Black	n (%)	6 (10.7%)	0	6 (5.2%)
Asian	n (%)	1 (1.8%)	0	1 (0.9%)
Ethnicity				
Hispanic or Latino	n (%)	16 (28.6%)	22 (36.7%)	38 (32.8%)
Not Hispanic or not Latino	n (%)	40 (71.4%)	38 (63.3%)	78 (67.2%)
Weight (kg)	Mean (SD)	11.74 (4.05)	11.17 (3.63)	11.45 (3.83)
	Min - Max	4.7 - 24.0	5.0 - 20.0	4.7 - 24.0
Height (cm)	Mean (SD)	82.73 (12.90)	84.02 (13.07)	83.41 (12.95)
	Min - Max	48.0 - 108.0	54.0 - 110.0	48.0 - 110.0
BMI (kg/m²)	N	N=53	N=60	N=113
	Mean (SD)	16.37 (2.63)	15.51 (2.12)	15.91 (2.40)
	Min - Max	12.8 - 25.0	11.6 - 19.8	11.6 - 25.0
BSA (m²)	N	N=54	N=60	N=114
	Mean (SD)	0.093 (0.076)	0.089 (0.075)	0.091 (0.075)
	Min - Max	0.01 - 0.29	0.01 - 0.31	0.01 - 0.31

Source: Table 14.1.2:1

There was a statistically significant difference in race between the placebo and the LEV treated groups. The Fisher exact test gave a p-value of 0.004. More Caucasians were assigned to the LEV group (90%) compared to the placebo group (70%). None of the black study participants were assigned to the LEV group.

Table 6.2-Age of Subjects-ITT Population N01009

	PBO (N=56)	LEV (N=60)	Overall (N=116*)
Age Class (a) (months)			
< 6	4 (7.1%)	4 (6.7%)	8 (6.9%)
6 to <12	7 (12.5%)	8 (13.3%)	15 (12.9%)3
12 to <24	18 (32.1%)	20 (33.3%)	38 (32.8%)
24 to <48	27 (48.2%)	28 (46.7%)	55 (47.4%)

(a) Corrected for pre-term infants less than 12 months of age.
*Data from 1 subject excluded after study withdrawal and unblinding ITT N=115

Table 6.3-Baseline History of Epilepsy (UCB Table)

Table 11:2 History of Epilepsy (ITT Population)

	Statistics	PBO (N=56)	LEV (N=60)	Overall (N=116)
Age of Onset (months)[a]	Mean (SD)	6.78 (8.31)	5.82 (8.40)	6.28 (8.34)
	Median	3.47	2.30	2.83
	Min - Max	0.0 - 34.1	0.0 - 36.9	0.0 - 36.9
Age of Diagnosis (months) [a]	Mean (SD)	8.72 (8.27)	7.76 (10.30)	8.22 (9.35)
	Median	4.90	3.35	4.30
	Min - Max	0.0 - 34.1	0.0 - 42.0	0.0 - 42.0
Duration of Epilepsy (months)	Mean (SD)	16.95 (10.84)	17.86 (12.38)	17.42 (11.62)
	Median	14.90	16.03	15.21
	Min - Max	1.0 - 41.6	1.6 - 44.6	1.0 - 44.6
Seizure History				
Type I	n (%)	56 (100.0%)	58 (96.7%)[b]	114 (98.3%)
Type II	n (%)	5 (8.9%)	16 (26.7%)	21 (18.1%)
Type III	n (%)	8 (14.3%)	3 (5.0%)	11 (9.5%)

[a] Corrected for pre-term infants less than 12 months of age
[b] Subjects 310/0002 and 507/0001 didn't have POS during the 2 weeks prior to selection, but had at least 2 POS during the 48 hour selection video EEG.
Note: Subjects could report more than one seizure type history. Type I = Partial Onset Seizures, Type II = Generalized Onset Seizures, and Type III = Unclassified Epileptic Seizures
Source: Table 14.1.3:1

There were no significant differences in the baseline history of epilepsy characteristics between the placebo and LEV groups with regards to age of onset, age of diagnosis, duration of epilepsy or seizure type. However, the LEV group had nearly twice the average number of daily partial seizures (group mean type I) during the 2 weeks prior to selection compared to the placebo group (5.05 placebo vs 10.17 LEV). The greater historical average number of daily seizures in the LEV group at baseline would appear to favor the placebo group because the LEV group would have to experience a greater reduction in the number seizure per day to be considered a responder, ≥ 50% reduction in average daily seizure frequency (ADF).

Table 6.4-Concomitiant AEDs Taken During The Study (UCB Table)

Table 14.1.5:5 Number (%) of Subjects Taking Concomitant AEDs by Generic Name and Analysis Period - ITT Population

Up-Titration
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Generic Name	PBO (N=56) n (%)	LEV (N=60) n (%)
Subjects Taking AEDs during Period	56 (100.0%)	60 (100.0%)
All Other Therapeutic Products	0	1 (1.7%)
Antiepileptics	0	1 (1.7%)
Carbamazepine	12 (21.4%)	5 (8.3%)
Chloral Hydrate	0	1 (1.7%)
Clobazam	2 (3.6%)	6 (10.0%)
Clonazepam	6 (10.7%)	4 (6.7%)
Diazepam	2 (3.6%)	4 (6.7%)
Ethosuximide	0	2 (3.3%)
Lamotrigine	5 (8.9%)	3 (5.0%)
Lorazepam	1 (1.8%)	0
Nitrazepam	1 (1.8%)	4 (6.7%)
Oxcarbazepine	7 (12.5%)	10 (16.7%)
Phenobarbital	17 (30.4%)	21 (35.0%)
Phenytoin	2 (3.6%)	0
Prednisone	1 (1.8%)	0
Sultiame	1 (1.8%)	1 (1.7%)
Topiramate	15 (26.8%)	19 (31.7%)
Valproic Acid	19 (33.9%)	23 (38.3%)

Each % is based on the number of ITT subjects in the treatment group presence in the period considered.

A significantly greater percentage of subjects in the placebo group were treated with Carbamazepine compared to LEV group. Phenobarbital and carbamazepine were the two most common concomitant AEDs taken by subjects in the trial. Since the study's goal was to recruit young children with partial seizures, the more common use of phenobarbital and carbamazepine is consistent with the intended population.

7 Efficacy Results

7.1 Primary Outcome Variable

The primary efficacy variable was the responder rate in ADF for partial onset seizures (Type I), and was defined as the number of mITT subjects with a ≥ 50% reduction from baseline in their ADF divided by the total number of mITT subjects.

Table 7.1-Primary Efficacy Variable (UCB Table)

Table 14.2.1:1 Responder Rate in Average Daily Frequency (ADF) for Partial Onset Seizures – mITT Population

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	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio LEV/PBO	95% Confidence Interval	P-value(b)
Responder (a)	10 (19.6%)	25 (43.1%)	3.11	1.22 - 8.26	0.013
Non-Responder	41 (80.4%)	33 (56.9%)			

Each % is based on the number of mITT subjects in the treatment group. Seizure counts include clusters.
(a) Subjects with ≥50% reduction in ADF from Selection video-EEG to Evaluation video-EEG and had ≥24 hours usable video-EEG at both time points.
(b) Fisher's exact test.

The pre-specified primary outcome variable demonstrates a statistically significant difference favoring the LEV treated group that is below the pre-specified alpha (< 0.05). Due to the reason that this is not the usual ITT population, which consists of all the randomized subjects who took at least one dose of study medication, we conducted some sensitivity analyses. Seven subjects were excluded from the ITT population, 5 from placebo and 2 from LEV group. Using worst case scenario, consider all the excluded subjects in placebo group are the responders and all the excluded subjects in LEV group are non-responders. This gives 27% (15 out or 56) responders in the placebo group and 42% (25 out 60) responders in LEV group. The Fisher's exact test gives a p-value of 0.12 and the Mantel-Haenszel test gives a p-value of 0.09. Both of them are non-significant. Although this may not likely be the case, it gives the maximum possible effect these excluded subjects may have on the efficacy results. It gives some indication that the evidence may not be as strong as the data in mITT population suggests.

Key Secondary Outcome Variables

Responder Rate By Age Group

Table 7.2 The Responder Rate For Subject By Age (UCB Table)

Table 11:10 Responder Rate in ADF for Partial Onset Seizures Adjusted for Age and Subgroup Analyses by Age Group - mITT Population

Age Group	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio		P-value[b]
			LEV/ PBO	95% CI	
All Ages[a]	10/51 (19.6%)	25/58 (43.1%)	3.13	1.31 – 7.48	0.009
1M to < 12M	2/10 (20.0%)	6/11 (54.5%)	4.80	0.51 – 62.31	0.183
12M to < 24M	4/16 (25.0%)	9/19 (47.4%)	2.70	0.53 – 15.43	0.293
24M to < 48M	4/25 (16.0%)	10/28 (35.7%)	2.92	0.68 – 14.71	0.129

[a] Odds ratio is derived from the stratified (by age group) model.
[b] p-value for the all ages analysis is from the Cochran-Mantel-Haenszel (CMH) test (stratified by age group); p-values for the individual age groups are from Fisher's exact test.
Source: Table 14.2.2:1

The overall p-value (p=0.009) was calculated using the Cochran-Mantel-Haenszel (CMH) Test in order to adjust for the age groups as opposed to the Fishers Exact test which combines all the age groups together and gives a p-value (0.013) in the analysis of the primary outcome variable. The corrected (Yates) CMH yields a p-value =0.0157. The logistic regression analysis gives a p-value of 0.010 after the adjustment of age group.

Due to the small size of the sub-groups, none of the individual sub-group analyses gave statistically significant results. However, the treatment effect remained consistent across the age groups. The odds ratio of favorable response in mITT population for the levetiracetam group as compared to placebo was 4.80 for the 1 month to < 12 month age group, 2.70 for the 12 month to < 24 month age group, and 2.92 for the 24 month to < 48 month age group. The overall age adjusted odds ratio stratified by age group was 3.13 (95% CI 1.31 – 7.48) and was nearly identical to the unadjusted estimate.

7.3 Absolute Change in Seizure frequency

Table 7.3-Absolute Change in Number of Partial Onset Seizures and Percent From Selection (Per-treatment) to Observation Periods (on-treatment). (UCB Table)

Table 11:11 Absolute and Percent Reduction from Baseline in ADF for Partial Onset Seizures - mITT Population

				LEV – PBO		
Assessment	**Statistics**	**PBO (N=51)**	**LEV (N=58)**	**Median Difference[a]**	**95% CI**	**P-value[b]**
Selection	Mean (SD)	15.37 (22.92)	31.13 (46.09)			
	Median	6.82	15.20			
	Q1 - Q3	2.00 – 16.22	4.48 – 38.95			
	Min - Max	0 - 98.03	0 - 211.8			
Evaluation	Mean (SD)	16.23 (24.16)	22.60 (37.32)			
	Median	6.48	8.34			
	Q1 - Q3	1.51 – 16.99	0.51 – 24.97			
	Min - Max	0 – 106.4	0 – 184.3			
Absolute Change	Mean (SD)	-0.86 (13.81)	8.54 (25.67)			
	Median	0.13	4.77	4.99	2.24 – 7.99	<0.001
	Q1 - Q3	-2.15 – 2.49	0 – 10.48			
	Min - Max	-56.89 – 41.27	-51.48 – 156.35			
% Reduction[c]	Mean (SD)	-20.93 (111.47)	24.98 (91.49)			
	Median	7.12	43.61	39.21	17.52 – 62.23	<0.001
	Q1 - Q3	-42.29 – 35.14	11.72 – 85.71			
	Min - Max	-450.58 – 100	0 – 148.3			

[a] Hodges-Lehman method used to estimate median difference
[b] P-values are from the Mann-Whitney test.
[c] Four subjects (1 on PBO and 3 on LEV) are excluded from this analysis due to having 0 seizures at baseline.
Source: Table 14.2.2:4 and Table 14.2.2:6

The median reduction in the absolute number and percent from baseline of the ADF of partial onset seizures was also statistically significant in favor of the group treated with LEV (p=<0.001). The median reduction in seizure frequency is often selected as the primary efficacy variable in studies submitted in support of an NDA application seeking approval for a similar indication. The significance of these two (p<0.001 for both endpoints) endpoints provides positive support to the regulatory claim of the effectiveness of LEV in reducing refractory partial onset seizures as adjunctive treatment in pediatric subjects age 1 month to less than 4 years.

Table 7.4-Responder Rate in ADF For All Seizure Types-I, II, III (UCB Table)

Table 14.2.2:2 Responder Rate in Average Daily Frequency (ADF) for All Seizures – mITT Population

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	PBO (N=51) n (%)	LEV (N=58) n (%)	Odds Ratio LEV/PBO	Odds Ratio 95% Confidence Interval	P-value(b)
Responder (a)	10 (19.6%)	25 (43.1%)	3.11	1.22 - 8.26	0.013
Non-Responder	41 (80.4%)	33 (56.9%)			

The responder rate for all seizure types was identical to the responder rate for partial onset seizures (type I) only because subjects recruited into the trial had predominately partial onset seizure disorder.

7.4 Subpopulations

Age group was the most important secondary variable regarding efficacy and labeling. The study only randomized 8 subjects age 6 months or less of whom only 4 received LEV. In the 6 months to < 1 year group there were only 15 total subjects and only 8 received LEV. Sub group analysis conducted the Clinical Pharmacology Reviewer agreed with the sponsor's analysis that despite the small number of subjects the treatment effect of LEV in reducing seizure frequency was approximately 50% for the 1 month to < 1 year age group and approximately 80% for the 1 month to < 6 month group.

Table 7.5-Subjects Age < 6 months Study N01009

SBJNBR	PT	B'date	Age/yrs	Age/ Months	Treat
323/0001	100046	(b) (6)	0.14	1.68	Levetiracetam 50 mg/kg/day max of a 10% oral solution
327/0004	100014	(b) (6)	0.24	2.88	Levetiracetam 50 mg/kg/day max of a 10% oral solution
510/0001	100201	(b) (6)	0.38	4.56	Levetiracetam 50 mg/kg/day max of a 10% oral solution
519/0001	100285	(b) (6)	0.3	3.6	Levetiracetam 50 mg/kg/day max of a 10% oral solution
317/0001	100031	(b) (6)	0.28	3.36	Placebo oral bid
321/0002	100037	(b) (6)	0.18	2.16	Placebo oral bid
323/0002	100145	(b) (6)	0.2	2.4	Placebo oral bid
503/0006	100298	(b) (6)	0.43	5.16	Placebo oral bid

Table 7.6-Subjects Age 6 to < 12 months Study N01009

SBJNBR	PT	B'date	Age/yrs	Age/Months	Treat
202/0004	100095	(b) (6)	0.81	9.72	Levetiracetam 50 mg/kg/day max of a 10% oral solution
204/0005	100160	(b) (6)	0.67	8.04	Levetiracetam 50 mg/kg/day max of a 10% oral solution
335/0002	100065	(b) (6)	0.9	10.8	Levetiracetam 50 mg/kg/day max of a 10% oral solution
503/0005	100300	(b) (6)	0.87	10.44	Levetiracetam 50 mg/kg/day max of a 10% oral solution
511/0002	100252	(b) (6)	0.72	8.64	Levetiracetam 50 mg/kg/day max of a 10% oral solution
513/0002	100292	(b) (6)	0.58	6.96	Levetiracetam 50 mg/kg/day max of a 10% oral solution
522/0001	100173	(b) (6)	0.51	6.12	Levetiracetam 50 mg/kg/day max of a 10% oral solution
530/0002	100320	(b) (6)	0.72	8.64	Levetiracetam 50 mg/kg/day max of a 10% oral solution
204/0006	100158	(b) (6)	0.94	11.28	Placebo oral bid
307/0001	100011	(b) (6)	0.96	11.52	Placebo oral bid
317/0005	100121	(b) (6)	0.81	9.72	Placebo oral bid
335/0001	100066	(b) (6)	0.88	10.56	Placebo oral bid
346/0002	100196	(b) (6)	0.95	11.4	Placebo oral bid

503/0003	100222	(b) (6)	0.92	11.04	Placebo oral bid
523/0002	100176	(b) (6)	0.67	8.04	Placebo oral bid

8.0 Data Handling and Statistical Analysis

8.1 Missing Data

All subjects with < 24 hours of usable Evaluation video-EEG time were excluded from the mITT population. There was no attempt to impute missing EEG data. However, if a subject had < 24 hours of usable evaluation video-EEG time but withdrew due to lack or loss of efficacy, this subject would have been included in the analysis as a non-responder, however no subjects met these criteria.

8.2 Additional Efficacy Issues/Analyses

There was an imbalance in the median baseline ADF partial onset seizures between treatment groups. The baseline median ADF of Type I seizures (from the Selection Period video EEG assessment) was higher in the LEV group (15.2) compared to the PBO group (6.8). In order to examine the possible effects of the different baseline seizure ADF rates on the primary endpoint, the sponsor conducted exploratory post-hoc analyses on the mITT population. Logistic regression methods were used to examine the effect of baseline seizure ADF as well as baseline seizure ADF by treatment group interaction. Both the raw (untransformed) baseline seizure ADF and the log transformed (ln [baseline ADF + 1]) baseline seizure ADF values were evaluated. When baseline seizure ADF was adjusted, the treatment effect of LEV was still statistically significantly (odds ratio = 3.43 and p = 0.006 for the untransformed baseline seizure ADF model and odds ratio = 3.72 and p = 0.005 for the log transformed baseline seizure ADF model). In addition, baseline seizure ADF by treatment group interaction was not found to be statistically significant (p=0.929 untransformed model and p=0.755 log transformed model).

There was a statistically significant imbalance in race between treatment groups. More Caucasians were assigned to the LEV group (90%) compared to the placebo group (70%). None of the black study participants were assigned to the LEV group. After the adjustment of race, the CMH test gives a p-value of 0.015. After the adjustment of race in the logistic regression model, the significance level becomes 0.016. After the dichotomized race into Caucasian and non-Caucasian, the similar results hold.

These post-hoc exploratory analyses suggest that the imbalance in the baseline seizure ADF and race may account for the significant treatment effect observed in the trial, in favor of LEV. However, due to the post-hoc nature, the reliability of the results from these analyses is still a question.

Table 8.1-Results of The Exploratory Logistic regression Analysis to Correct for a Baseline Imbalance in ADF between the LEV and Placebo Groups. (UCB)

Table 14.2.1:3 Responder Rate in Average Daily Frequency (ADF) for Partial Onset Seizures (Logistic Regression Sensitivity Analyses: Untransformed Baseline Seizure ADF) – mITT Population

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Model	Effect	Odds Ratio LEV/PBO	95% Confidence Interval		P-value(a)
Responder = Trt Group	Trt Group	3.11	1.31 -	7.38	0.010
Responder = Baseline ADF + Trt Group	Baseline ADF	0.99	0.98 -	1.01	0.287
	Trt Group	3.43	1.42 -	8.32	0.006

The p-value for baseline seizure ADF by treatment group interaction is 0.929 and is derived from the full model (Responder = baseline seizure ADF + treatment group + baseline seizure ADF x treatment group). (a) P-values are from the Wald test.

8.2.1 Adjustments

The primary efficacy analysis of the primary endpoint did not include adjustments for covariates. However, a supportive analysis of the primary endpoint did include age group as a covariate. Study center was not included as a covariate because most study centers randomized only 1 or 2 subjects and comparison by center was not feasible.

The sponsor did not adjust for multiple comparisons because they did not make labeling claims for the secondary outcome variables.

8.2.2 Interim Analysis

The sponsor's analysis plan did not call for an interim analysis of the data.

8.2.3 Dose Response/Concentration Response Relationships

The study was not designed to examine drug-dose or drug-concentration versus response relationships.

8.2.4 Drug-Drug and Drug-Disease Interactions

The study was not designed to examine drug-drug or drug-disease interactions.

9. Efficacy Conclusions

Analysis of the primary efficacy endpoint, the responder rate, a ≥ 50% reduction in the ADF of seizures baseline compared to evaluation Video-EEG (48 hours) demonstrated a overall treatment effect that is statistically significant in children ages 1 month to < 4 years old. The

final version of the pediatric written request directed the sponsor to study LEV in 3 subgroups of children 4 years or younger, children < 12 month, 12 to< 24 months and 24 months to 48 months. The size of the age divided subgroups were too small to reveal a statistically significant advantage of LEV compared to the placebo treated subgroups but treatment effects of LEV in these groups seem to be consistent with the overall effect in the sponsor's data.

Table 9.1-Number Randomized into the ITT Population Study N01009

	PBO (N=56)	LEV (N=60)	Overall (N=116*)
Age Class (a) (months)			
< 6	4 (7.1%)	4 (6.7%)	8 (6.9%)
6 to <12	7 (12.5%)	8 (13.3%)	15 (12.9%)3
12 to <24	18 (32.1%)	20 (33.3%)	38 (32.8%)
24 to <48	27 (48.2%)	28 (46.7%)	55 (47.4%)

(a) Corrected for pre-term infants less than 12 months of age.
**Data from 1 subject excluded after study withdrawal and unblinding N=115*

The number of evaluable subjects in the < 6 month age group and to a lesser degree the 6 month to < 12 month age groups is small and the treatment effect is hard to evaluate. This reviewer recommends approval of the application for the use of oral Keppra in children from 1 month to < 4 years old for adjunctive treatment of refractory partial onset seizures. The approved dose should closely mimic the target dose administered in study N01009. For children ages 1 month to < 6 months the approved recommended dose should be 42 mg/kg/day in children 1 month to < 6 months and 50 mg/kg/day in children ages 6 months to 4 years.

Appendix 2

1. Study N01103

A 19-week, Randomized, Double-blind, Multicenter, Placebo controlled Safety Study to Evaluate the Cognitive and Neuropsychological Effects of Levetiracetam 20-60 mg/kg/d, Divided in Twice Daily Dosing, as Adjunctive Treatment in Children 4-16 Years Old, Inclusive, with Partial Onset Seizures

Protocol No. / Study No. RPCE03B1012 / N01103

First Subject Enrolled 27-Sep-2004

Date of Completion of Last Subject 21-Mar-2007

Study Sites

Forty-five centers were initiated in the United States, South Africa, and Canada. Subjects were screened at 29 study centers with 28 enrolling centers.

2. Study Rational and Aims

This trial will specifically study cognitive and neuropsychological effects of adjunctive treatment with LEV in children and adolescents, ages 4-16 years, with inadequately controlled epilepsy, using neuropsychological instruments that are valid and reliable in assessing memory, learning, attention, concentration, behavior, and quality of life.

2.1Objectives:

2.1.1 Primary:

To characterize potential cognitive and neuropsychological effects of levetiracetam (LEV) (20-60 mg/kg/d) as adjunctive treatment in children 4-16 years old, inclusive, with partial onset seizures, as non-inferior when compared to adjunctive treatment with placebo (PBO).

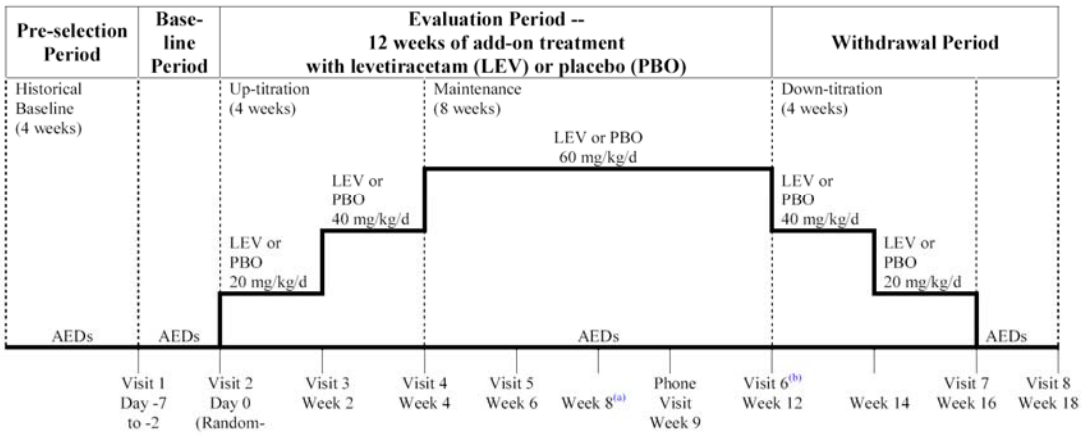
2.1.2 Secondary:

To generate additional double-blind, placebo-controlled safety and efficacy data for LEV (20-60 mg/kg/d), as compared to PBO, as adjunctive treatment in children 4-16 years old, inclusive, with partial onset seizures.

3. Study Design

Table 3.1 Trial Design Schematic

Table 9:1 Study Schematic



The study design consists of 4 periods:

Pre-selection Period: At Visit 1 (Day -7 to -2) Information relating to the trial was discussed with patients and their parents or guardians. After consenting appropriate subjects were screened according to the study Inclusion and Exclusion criteria

Baseline Period: At Visits 1 – 2 the estimated baseline seizure frequency was calculated from:

- The history provided by parents or guardians to establish the 4-week Historical Baseline Period
- Observations of seizure frequency during the 5 to 7-day Baseline Period.

Evaluation Period: The Evaluation Period includes a 4-week Titration Period and an 8-week Maintenance Period. Subjects start at a dose of 20 mg/kg/d for the first 2 weeks, followed by 40 mg/kg/d for the next 2 weeks, ending a maintenance dose of 60 mg/kg/d for the remaining 8 weeks of the study. Subjects received either a tablet or oral solution form of their assigned treatment.

Withdrawal Period: Subjects who did not to continue enroll in the open-label study or if they withdrew from the study, their doses were titrated down at the rate of 20 mg/kg/d every 2 weeks.

3.2 Randomization

Randomization to LEV or matching PBO occurred in a 2:1 ratio (2 LEV to 1 PBO). Randomization occurred in blocks of 3 and was stratified by subject's age (4-7, 8-12, and 13- 16 years old) and number of concomitant AEDs (1 or 2) at entry. To ensure sufficient representation within each age group, no fewer than 25%, and no more than 50% of the subjects were to be enrolled into any one age group. Randomization was implemented by using the (b) (4) .

3.3 Blinding

Study medications were administered in a double-blind manner. The PBO tablets and solution were identical in appearance to the LEV counterparts. The study blind could be broken only in cases of medical emergency. The randomization list was generated and kept by UCB Inc. The subject's treatment assignment was disclosed at the end of the study after the locking of the database.

The study treatment blind was maintained for all but 1 subject, whose assigned treatment was revealed after discontinuation from the study because of medical necessity. Subject 611/0002 in the LEV group withdrew from the study due to an AE of rash that was thought to be possibly related to study medication.

4 Selection Criteria

4.1 Inclusion Criteria

Subjects were eligible to participate in this study if all of the following criteria were met:

1. Subjects had parent or guardian gave consent and, if appropriate, the subject gave assent to participate in the study. A signed and dated IRB-approved, written informed consent form was required, and an assent form, if appropriate.

2. Subjects had a confirmed diagnosis of epilepsy with partial onset seizures, whether or not secondarily generalized, for a minimum of 6 months prior to Visit 1.

3. Subjects must be male or female, between 4 and 16 years of age, inclusive. Females were not pregnant or nursing. Females of childbearing potential were required to have had a negative pregnancy test at Visit 1. In order to participate in the study, females of childbearing potential were to be:

    - Surgically sterile (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy).

- . Or using a medically acceptable method of birth control for the duration of study participation (intrauterine device, barrier method plus spermicide, oral contraceptive at a stable dose for 1 menstrual cycle prior to the start of the study, contraceptive implant inserted at least 1 month prior to the start of the study, or contraceptive injection administered 1 month prior to the start of the study).

- Abstinence is considered an acceptable method of contraception on a case-by-case basis upon approval of UCB Inc. or its representative.

4. The Investigator must believe that the subject's current AED treatment was unsatisfactory in terms of efficacy and/or safety, and for whom alternative treatment with LEV might be of benefit.

5. Subjects must be on a stable regimen of 1 or a maximum of 2 other AEDs. No additions of new AEDs or deletions of previous AEDs were allowed for at least 2 weeks prior to Visit 1. Minor adjustments to the dose of the current AEDs were allowed only prior to Visit 1.

6. Subjects must be on a stable regimen of Attention Deficit Hyperactivity Disorder (ADHD) medication for at least 1 month prior to Visit 1, if the subject was taking medication for ADHD.

7. Subjects may have had vagus nerve stimulation (VNS), implanted for at least 6 months prior to Visit 1, and the settings were stabilized for at least 2 months prior to Visit 1. activated VNS was counted as 1 of the 2 AEDs.

8. Subjects have an intelligence quotient (IQ), as assessed during the Baseline Period, of at least 65.

9. Subjects must weigh ≤ 100 kg at Visit 1.

10. Subjects have a documented failed epilepsy surgery outcome greater than 6 months prior to Visit 1, if epilepsy surgery had been performed.

11. Subjects have at least 1 partial onset seizure during the 4 weeks prior to Visit 1.

12. The subject's epilepsy is classifiable according to the "Proposal for Revised Classification of Epilepsies and Epileptic Syndromes" and his/her seizures were classifiable according to the "Proposal for Revised Clinical and Electroencephalographic Classification of Epileptic Seizures."

13. Concomitant AED and ADHD medication intake remain unchanged during the Baseline, Titration, and Evaluation Periods of the study.

14. Subjects and parents/guardians are fluent in English.

15. Subjects and their parent/guardian or family member are able to cooperate with the Investigator and study personnel involved in carrying out the study.

4.2 Exclusion Criteria

Subjects are not eligible to participate in this study if any of the following criteria were present:

1. Subjects participated (were randomized) or withdrawn from any LEV study.

2. Subjects had previous treatment with LEV unless, in the opinion of the Investigator, the subject's previous treatment was inadequate in dose or duration to provide an accurate assessment of the therapy, or the effect of LEV was confounded by concomitant medication.

3. Subjects took any medication (other than their concomitant AEDs) that influences the central nervous system (CNS) during the course of the study that was not on a stable regimen for at least 1 month prior to Visit 1.

4. Subjects received phenobarbital or primidone prior to Visit 1.

5. Subjects received a benzodiazepine on a routine or chronic basis and was unable to discontinue use 4 weeks prior to Visit 1.

6. Subjects used felbamate for less than 18 months prior to Visit 1, if the subject was using felbamate.

7. Subjects received any investigational drug or device during the 30 days prior to Visit 1.

8. Subjects are on a ketogenic diet (currently or within 30 days prior to Visit 1).

9. Subjects have seizures too close together to accurately count (i.e., the subject's seizures must be countable).

10. Subjects have a treatable seizure etiology other than epilepsy (e.g., febrile seizures).

11. Subjects have a history of status epilepticus, which required hospitalization during the 3 months prior to Visit 1.

12. Subjects have a current diagnosis of Lennox-Gastaut Syndrome.

13. Subjects have epilepsy secondary to a progressive cerebral disease or any other progressively neurodegenerative disease, such as Rasmussen and Landau-Kleffner diseases.

14. Subjects have clinically significant deviations from reference range values for laboratory parameters, as determined by the Investigator.

15. Subjects have any clinically significant acute or chronic illness (as determined during the physical examination or from other information available to the Investigator) such as, but not limited to, cardiac disease, liver disease, renal disease, or endocrinological disease.

16. Subjects have a current, serious, unstable psychiatric diagnosis that may have confounded the Investigator's ability to conduct the trial or that may have prevented the subject from completing the protocol-specified tests. Examples that excluded a subject were significant suicide risk within the past 6 months, current psychotic disorder, or acute mania.

17. Subjects have a history of, or the presence of, pseudoseizures.

18. Subject has a terminal illness.

19. Subjects have any medical condition that might interfere with the subject's study participation (e.g., serious infection, scheduled elective surgery, etc.).

20. Subjects have a known history of an allergy to pyrrolidone derivatives or a history of multiple drug allergies.

21. Subjects have any disorder or condition that may have interfered with the absorption, distribution, metabolism, or excretion of drugs.

5. Study Related Treatments

Subjects were randomly assigned to receive either LEV or PBO. The target dose of LEV was determined by the sponsor to be 60 mg/kg/d. Study medication was administered as oral tablets or oral solution (determined by subject weight and investigator discretion). Study medication (LEV or PBO) was taken b.i.d in 2 equal doses separated by approximately 12 hours. The starting dose was 20 mg/kg/d LEV or PBO, which was titrated upwards by 20 mg/kg/d every 2 weeks for a 4-week period to the maximum tolerated dose or a maximum of 60 mg/kg/d of LEV or PBO at the start of the 8 weeks evaluation period. The dose of study medication could be adjusted during the evaluation period to 20 mg/kg/d or 40 mg/kg/d, based on safety and efficacy considerations.

At the end of the evaluation period (week 12/Visit 6), subjects either down-titrated their dose before discontinuing study medication before the final study visit. Subjects reduced their study medication by 20 mg/kg/d decrements each week for 2 weeks before stopping, or they continued on their current dose in the open-label, follow-up study N01148.

The PBO tablets and oral solution were identical in appearance to the LEV tablets and oral solution, Investigators and subjects, and parents/guardians were blinded to the assigned treatment.

Table 5.1- Study Medication Dosing Regimen For Tablets

Table 9:4 Oral Tablet Dosing Scheme: Titration and Evaluation Periods

Subject's Weight[a]	Total Daily Dose					
	Days 1 - 13		Days 14 - 27		Day 28 to end of Evaluation Period	
	20 mg/kg/d[b]		40 mg/kg/d[c]		60 mg/kg/d[d]	
	AM	PM	AM	PM	AM	PM
13.5-20 kg	1 LEV 166 mg or 1 PBO	1 LEV 166 mg or 1 PBO	2 LEV 166 mg or 2 PBO	2 LEV 166 mg or 2 PBO	2 LEV 250 mg or 2 PBO	2 LEV 250 mg or 2 PBO
20.1-30 kg	1 LEV 250 mg or 1 PBO	1 LEV 250 mg or 1 PBO	2 LEV 250 mg or 2 PBO	2 LEV 250 mg or 2 PBO	3 LEV 250 mg or 3 PBO	3 LEV 250 mg or 3 PBO
30.1-40 kg	2 LEV 166 mg or 2 PBO	2 LEV 166 mg or 2 PBO	3 LEV 250 mg or 3 PBO	3 LEV 250 mg or 3 PBO	4 LEV 250 mg or 4 PBO	4 LEV 250 mg or 4 PBO
40.1-50 kg	1 LEV 500 mg or 1 PBO	1 LEV 500 mg or 1 PBO	2 LEV 500 mg or 2 PBO	2 LEV 500 mg or 2 PBO	2 LEV 500 mg 1 LEV 250 mg or 3 PBO	2 LEV 500 mg 1 LEV 250 mg or 3 PBO
50.1-100 kg	1 LEV 500 mg or 1 PBO	1 LEV 500 mg or 1 PBO	2 LEV 500 mg 1 LEV 166.5 mg or 3 PBO	2 LEV 500 mg 1 LEV 166.5 mg or 3 PBO	3 LEV 500 mg or 3 PBO	3 LEV 500 mg or 3 PBO

[a] Tablet strengths of 166.5 mg, 250 mg, and 500 mg were used from the high total tablet weight formulation for subjects > 40 kg, and tablet strengths of 166 mg and 250 mg were used from the low total tablet weight formulation for subjects ≤ 40 kg.
[b] 10 mg/kg administered twice per day; once in the morning and again approximately 12 hours later in the evening.
[c] 20 mg/kg administered twice per day; once in the morning and again approximately 12 hours later in the evening.
[d] 30 mg/kg administered twice per day; once in the morning and again approximately 12 hours later in the evening.

Table 5.2- Study Medication Dosing Regimen For Oral Solution

Table 9:5 Oral Solution Dosing Scheme

Solution Strength	Dose Calculation
Oral solution LEV or PBO (20 mg/kg)	20 mg/kg x (Subject weight in kg) / 100 mg/mL = Total dose in mLs
Oral solution LEV or PBO (40 mg/kg)	40 mg/kg x (Subject weight in kg) / 100 mg/mL = Total dose in mLs
Oral solution LEV or PBO (60 mg/kg)	60 mg/kg x (Subject weight in kg) / 100 mg/mL = Total dose in mLs

5.1 Enrollment

The protocol planned for 110 subjects to be screened in order to randomize the required 87 subjects. A total of 120 subjects were screened and 99 randomized (34 assigned to PBO and 65 to LEV).

Table 5.3-Number and Percent of Subjects Randomized to Each treatment Arm For ITT and PP Populations (UCB)

Table 11:1 Number and Percent of Subjects by Study Population

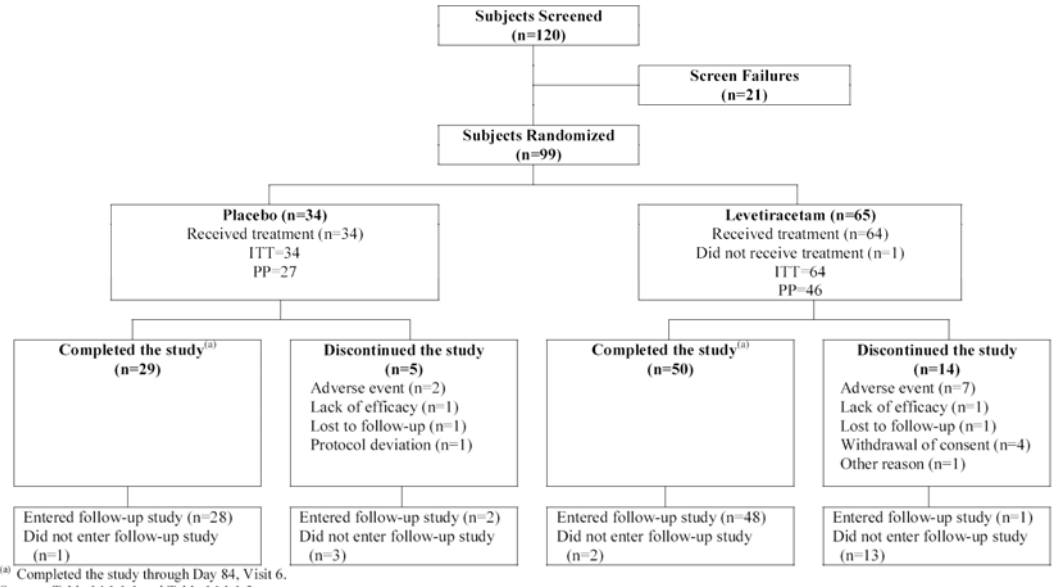
Study Population	PBO n (%)	LEV n (%)	Total n (%)
Intention-to-treat[a]	34 (100%)	64 (100%)	98 (100%)
Per Protocol[b]	27 (79.4%)	46 (71.9%)	73 (74.5%)

[a] All randomized subjects who took at least 1 dose of study medication.
[b] All randomized subjects without a major protocol deviation.
Source: Table 14.1.1:2

6. Subject Disposition

Table 6.1-Subject Disposition (UCB Table)

Table 10:1 Subject Disposition



[a] Completed the study through Day 84, Visit 6.
Source: Table 14.1.1:1 and Table 14.1.1:3

6.2 Withdrawals

A larger percentage of subjects discontinued the study were in the LEV group (21.9%) than in the PBO group (14.7%). The most frequently recorded reason for discontinuation was AEs, and these were more common in the LEV group (PBO 5.9%; LEV 10.9%). The majority of subjects entered the follow-up study at Week 12/Visit 6 (PBO 30 subjects; LEV 49 subjects). Only one subject in each group withdrew for "Lack of Efficacy".

7. Endpoints

7.1 Safety

The primary cognitive and neuropsychological safety variable was change from baseline (Visit 2) to the end of the Evaluation Period (Week 12 or the Early Discontinuation Visit [EDV]) in the Leiter International Performance Scale-Revised (Leiter-R) Attention and Memory (AM) Battery's Memory Screen Composite Score. Secondary cognitive and neuropsychological safety variables were change from baseline to Week 12/EDV in the following:

- Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) General Memory Index
- WRAML-2 Visual Memory Index
- WRAML-2 Verbal Memory Index
- WRAML-2 Attention/Concentration Index.

Exploratory cognitive and neuropsychological safety variables were change from baseline to Week 12 in the following:

- Leiter-R Composite scores for Recognition Memory, Associative Memory, Memory Span, Attention, and Memory Process
- Leiter-R Examiner's Rating: Composite scores for cognitive/social and emotions/regulations
- Achenbach Child Behavior Checklist (CBCL): Raw Competence scale scores (Activities, Social, School) and Total Competence score; Raw Syndrome scale scores (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior and Aggressive Behavior), and summary syndrome scores (Internalizing, Externalizing, and Total Problems score)
- Child Health Questionnaire (CHQ-PF50): Scale scores (Physical Functioning, Role/Social– Emotional/Behavioral, Role/Social–Physical, Bodily Pain/Discomfort, Behavior, Mental Health, Self Esteem, General Health Perceptions, Change in Health, Parental Impact-Emotional, Parental Impact-Time, Family Activities, and Family Cohesion) and summary scores (Physical and Psychosocial).

- Standard clinical safety variables were the following: extent of exposure, adverse events (AEs), laboratory tests, electrocardiograms (ECGs), physical and neurological exams, and vital signs. LEV, concomitant AED, and benzodiazepine concentrations in plasma were also measured.

7.2 Efficacy

There were no primary or secondary efficacy variables all efficacy variables were considered exploratory. The sponsor listed the following exploratory efficacy variables:

- Total Seizure Weekly Frequency
- Partial Onset Seizure Weekly Frequency
- Reduction in Total Seizure Weekly Frequency
- Reduction in Partial Onset Seizure Weekly Frequency
- Responder Rate (≥50% reduction in Partial Onset Seizure Weekly Frequency)
- Total Responder Rate (≥50% reduction in Total Seizure Weekly Frequency)
- Global Evaluation Scales (GES) responses from Investigator, Parent/Guardian, and Subject (aged 8 years or older)

7.1 Calculation of Exploratory Efficacy Endpoints

Table 7.1-Methods Used To Calculate Partial Onset Seizure (type I) Frequency (UCB Table)

Table 9:8 Calculation of Seizure Variables

Partial Onset (Type 1) Seizure Frequency Per Week Calculations	
Period	**Definition**
Historical Baseline Period	7×(Number of Historical Period Type I Seizures/Historical Period Evaluable Days), where: • Number of Historical Period Type I Seizures = Sum of Historical Period Type I Seizure Count and Number of Type I Clusters • Historical Period Evaluable Days = 28 (4 weeks)
Prospective Baseline Period	7×(Number of Prospective Period Type I Seizures/Prospective Period Evaluable Days), where: • Number of Prospective Period Type I Seizures = Sum of Prospective Period Type I Seizure Counts and Number of Type I Clusters • Prospective Period Evaluable Days = Evaluable Days between Visit 1 and Visit 2
Combined Baseline	7×(Number of Complete baseline Type I Seizures/Complete BL Evaluable Days), where: • Number of Complete baseline Type I Seizures = Sum of Historical and Prospective Periods Type I Seizure Counts and Number of Type I Clusters • Complete baseline Evaluable Days = (28 + Evaluable Days between Visit 1 and Visit 2)
Evaluation Period	7×(Number of Evaluation Period Type I Seizures/Evaluable Period Evaluable Days), where: • Number of Evaluation Period Type I Seizures = Sum of Evaluation Period Type I Seizure Counts and Number of Type I Clusters • Evaluation Period Evaluable Days = Evaluable Days between Visit 2 and Visit 6

Note: An Evaluable Day is a seizure day with a non-missing seizure count or number of clusters.
Note: Total Weekly Seizure Frequency is calculated exactly the same but Total includes Types I, II, and III.

7.2 Calculation of Reduction of Seizure Frequency

Parents or guardians recorded seizures counts including all types into a daily seizure diary. Information concerning clusters and individual seizures were collected at each study visit during the Baseline and Evaluation Periods. The final version of the protocol did not describe a plan to instruct parents or guardians on the proper identification of seizures in general or the classification of seizure types recorded in the daily seizure diary. This may impact the accurate recording of seizure counts and therefore many of the exploratory variables.

Reduction in absolute seizure frequency from baseline was also calculated for both partial onset seizures (Type I) and total seizures (types I+II+III)

Percent reduction in seizure frequency from baseline was also calculated for both partial onset seizures and total seizures, as follows:

$$100 \times \frac{(\text{Combined Baseline frequency}) - \text{Evaluation Period frequency})}{\text{Combined Baseline Frequency}}$$

The method used by the sponsor to calculate the efficacy variable of seizure frequency appears appropriate and consistent with the study objectives.

8 Baseline Characteristics

8.1 Subject Baseline Demographic Characteristics (UCB Table)

Table 11:2 Demographic and Baseline Characteristics by Treatment Group and Overall (ITT Population)

Characteristic	Statistic	PBO (N=34)	LEV (N=64)	Overall (N=98)
Age (years)	Mean (SD)	10.27 (3.67)	10.58 (3.49)	10.47 (3.54)
	Min – Max	4.1 – 16.4	4.8 – 16.7	4.1 – 16.7
Age Class (years)				
4 to 7	n (%)	10 (29.4%)	18 (28.1%)	28 (28.6%)
8 to 12	n (%)	15 (44.1%)	28 (43.8%)	43 (43.9%)
13 to 16	n (%)	9 (26.5%)	18 (28.1%)	27 (27.6%)
Gender				
Male	n (%)	17 (50%)	39 (60.9%)	56 (57.1%)
Female	n (%)	17 (50%)	25 (39.1%)	42 (42.9%)
Race				
Caucasian	n (%)	18 (52.9%)	40 (62.5%)	58 (59.2%)
Other/Mixed Race	n (%)	5 (14.7%)	6 (9.4%)	11 (11.2%)
Black	n (%)	8 (23.5%)	15 (23.4%)	23 (23.5%)
Asian	n (%)	3 (8.8%)	3 (4.7%)	6 (6.1%)
Ethnicity				
Hispanic or Latino	n (%)	4 (11.8%)	6 (9.4%)	10 (10.2%)
Not Hispanic or Latino	n (%)	30 (88.2%)	58 (90.6%)	88 (89.8%)
Weight (kg)	Mean (SD)	44.62 (23.70)	40.82 (18.91)	42.14 (20.65)
	Min – Max	16.8 – 100.8	17.1 – 85.0	16.8 – 100.8
Height (cm)	Mean (SD)	140.83 (20.28)	139.99 (19.80)	140.28 (19.86)
	Min – Max	104.4 – 173.5	106.7 – 182.0	104.4 – 182.0
BMI (kg/m^2)	Mean (SD)	20.97 (6.51)	19.80 (5.08)	20.20 (5.61)
	Min – Max	14.4 – 40.1	11.3 – 39.1	11.3 – 40.1
Leiter-R Brief IQ Score	Mean (SD)	89.06 (14.89)	89.81 (18.23)	89.55 (17.07)
	Min – Max	67.0 – 124.0	42.0 – 135.0	42.0 – 135.0
Leiter-R Brief IQ Score Class				
≤ 64	n (%)	0	5 (7.8%)	5 (5.1%)
65 to 89	n (%)	17 (50%)	26 (40.6%)	43 (43.9%)
≥ 90	n (%)	17 (50%)	33 (51.6%)	50 (51.0%)

There was a greater percentage of male subjects enrolled into the LEV arm (60.9%) of the study compared the placebo arm (39.1%). In addition, the subjects in the LEV arm weighed slightly less than the subjects in the placebo group at baseline. Neither of these two imbalances at baseline were likely to have impacted the efficacy outcome of the study.

8.2-Baseline Number of Concomitant AEDs Taken By Subjects In The Trial (UCB Table)

Number of AEDs	PBO (N=34)	LEV (N=64)
1 AED	23 (67.6%)	45 (70.3%)
2 AEDs	11 (32.4%)	18 (28.1%)
3 AEDs[a]	0	1 (1.6%)

[a] Subject 671/0001 used a third AED during the Withdrawal Period only.
Source: Table 14.1.6:5

Although use of up to 2 concomitant AED was permitted during the trial, the majority of subjects were taking only 1 AED in conjunction with study medication. The one subject who took 3 AEDs only used clonazepam only during the withdrawal period. The slight differences between the groups the percentage of subjects 1 or 2 AEDs appears small and not significant.

8.3-Concomitant AED Used During the Trial

	PBO %	LEV%
oxcarbazepine	38.2	39.1
carbamazepine	29.4	15.6
lamotrigine	20.6	23.4
valproic acid	14.7	25.0
topiramate	23.5	7.8

Carbamazepine and Oxcarbamazepine were the 2 most frequently used concomitant medications. The pattern of concomitant AED use was reasonably similar for both the placebo and LEV groups and did not likely influence the efficacy outcome of the trial.

8.1.1-Use Of Rescue Medication (Benzodiazepines)

Benzodiazepines were allowed as rescue medication, but subjects were discontinued from the study if benzodiazepine use exceeded 1 single administration per week. Overall the percentage of subjects who used a rescue benzodiazepine (lorazepam preferred) during the Evaluation Period was greater in the placebo group. There were no protocol violations reported because subjects had taken a benzodiazepine within the 6 days preceding administration of Leiter-R assessment.

Benzodiazepines were used as rescue medication by 6 subjects (17.6%) in the PBO group and 6 subjects (9.4%) in the LEV group. One subject (2.9%) in the PBO group and 1 subject (1.6%) in the LEV group used a benzodiazepine as a non-AED medication. Three subjects (4.7%) in the LEV group used a benzodiazepine as an AED medication.

Table 8.4-The Use of Rescue Medication During Trial N01103 (UCB Table)

Table 14.1.6:6 Number (%) of Subjects Taking Benzodiazepines - ITT Population

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	PBO (N=34) n (%)	LEV (N=64) n (%)
Recorded on the		
Rescue Medication CRF	6 (17.6%)	6 (9.4%)
AED Medication CRF	0	3 (4.7%)
Non-AED Medication CRF	1 (2.9%)	1 (1.6%)
Used During		
Historical Period (a)	2 (5.9%)	3 (4.7%)
Baseline Period Only	0	0
Evaluation Period Only	5 (14.7%)	5 (7.8%)
Baseline and Evaluation Period	2 (5.9%)	2 (3.1%)
Withdrawal Period	0	2 (3.1%)
Used Within 6 Days of a Leiter-R Assessment		
Baseline	0	0
End of Evaluation	0	0
Baseline and Evaluation	0	0

Note: Concomitant drugs are defined in section 16.1.9.
(a) From 30 days prior to Visit 1 up to the day before Visit 2.

Table 8.5- Compliance With Study Medication

Table 11:9 Number and Percent of Subjects at each Level of Treatment Compliance during the Evaluation Period (ITT Population)

Level of Compliance from Visit 2 to Visit 6	PBO (N=34) n (%)	LEV (N=64) n (%)
Less than 80%	1 (2.9%)	2 (3.1%)
80% - 120%	31 (91.2%)	60 (93.8%)
Greater than 120%	2 (5.9%)	2 (3.1%)

Note: Evaluation period compliance was a weighted average of compliance recorded by the site at each visit.
Source: Table 14.1.5:1

Medication compliance among subjects in both limbs of the trial was acceptable.

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8.1.2 Results of Exploratory Efficacy Outcomes

Table 8.6-Change in Weekly Seizure Frequency (UCB)

Table 11:10 Summary of Partial Onset Seizure Weekly Frequency at Baseline and during the Evaluation Period (ITT Population)

	Statistic	PBO (N=34)	LEV (N=64)
Combined Baseline[a]	n	34	64
	Mean (SD)	8.19 (21.37)	7.06 (37.25)
	Median	1.37	0.91
	Q1 – Q3	0.40 – 5.16	0.39 – 1.87
	Min – Max	0.2 – 100.3	0 – 295.1
Evaluation Period[b]	n	34	64
	Mean (SD)	10.72 (31.59)	2.87 (6.88)
	Median	1.25	0.08
	Q1 – Q3	0.33 – 4.17	0 – 1.94
	Min – Max	0.0 – 174.3	0 – 32.0
Evaluation Period Absolute Reduction from Baseline	n	34	64
	Mean (SD)	-2.53 (18.58)	4.19 (33.77)
	Median	0.20	0.40
	Q1 – Q3	-1.04 – 0.84	0.17 – 1.00
	Min – Max	-93.9 – 37.3	-24.2 – 267.3
Evaluation Period Percent Reduction from Baseline	n	34	63[c]
	Mean (SD)	-54.81 (199.61)	-31.09 (457.88)
	Median	26.50	91.54
	Q1 – Q3	-108.51 – 62.69	19.26 – 100.0
	Min – Max	-797.6 – 100.0	-3387.5 – 100.0

[a] Includes the combined Historical and Prospective Period baselines.
[b] Evaluation Period is Visit 2 through Visit 6 (Week 12), which consists of the Titration Period + Maintenance Period.
[c] Because 1 subject (Subject 628/0002) had a baseline frequency of 0, percent reduction could not be calculated for this subject.
Source: Table 14.2.3:1

Table 8.7-Number and Percent of Subjects who responded to Treatment (> 50 % Reduction In Weekly Seizure Frequency

Table 11:11 Number and Percent of Subjects who Responded to Treatment (ITT Population)

Response Value	PBO (N=34) n (%)	LEV (N=64) n (%)
Partial Onset Seizure Weekly Frequency		
Responder[a]	14 (41.2%)	40 (62.5%)
Non-Responder[b]	20 (58.8%)	24 (37.5%)
Total Seizure Weekly Frequency		
Responder[a]	13 (38.2%)	40 (62.5%)
Non-Responder[b]	21 (61.8%)	24 (37.5%)

[a] A responder is a subject with a ≥ 50% reduction in seizure weekly frequency from the Combined Baseline Period to the Evaluation Period.
[b] A subject with no seizure data before or after Visit 2 was classified as a non-responder.
Source: Table 14.2.3:3

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Table 8.8-Clinical Global Impression of Change During Treatment

Table 11:13 Number (%) of Subjects by Global Evaluation Scale Ratings at Week 12 (or Early Discontinuation), as rated by Investigators, Subjects, and Parents/Legal Guardians (ITT Population)

Rater Direction of Change	PBO (N=34) n (%)	LEV (N=64) n (%)
Parent/Legal Guardian (n)[a]	31	58
Improvement	17 (54.8%)	43 (74.1%)
No Change	9 (29.0%)	8 (13.8%)
Worsening	5 (16.1%)	7 (12.1%)
Subject[b] (n)[a]	24	38
Improvement	13 (54.2%)	29 (76.3%)
No Change	8 (33.3%)	4 (10.5%)
Worsening	3 (12.5%)	5 (13.2%)
Investigator (n)[a]	31	57
Improvement	14 (45.2%)	43 (75.4%)
No Change	12 (38.7%)	6 (10.5%)
Worsening	5 (16.1%)	8 (14.0%)

[a] The denominator for percents was the number of subjects with valid GES data at Week 12/EDV.
[b] Only subjects who were 8 years or older were eligible to complete the GES.
Source: Table 14.2.3:4

The analysis of all three key exploratory efficacy outcome measures demonstrated a benefit improvement in LEV treated patients compared o the PBO treated group. The percent and absolute change in weekly seizure frequency was greater in the LEV treated group. The number and percent of subjects considered as treatment responders (> 50 % reduction of partial onset seizures) was also greater in the LEV treated group. The results indicate the treatment effect associated with LEV is at least as in this long-term as the effect observed in short-term, double-blind trial.

The Clinical Global Impression of Change (CGI) rating scale was judged as improved by the majority (approximately 75%) of raters in all 3 groups of eligible raters (patients, parents/guardians and the site investigator) for LEV treated patients compared to 45-54% of the placebo group.

8.2 Efficacy Conclusion

The change in absolute and percent of the average weekly seizure frequency, percentage of responders and the global impression of change are all numerically better in the LEV treated patients the conclusion of the trial. The sponsor did not design the trial to support efficacy in children 4-16 years but the results are consistent with the treatment effects of LEV observed in double blind clinical trials.

Literature Review/References

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2. Chiron C, Dulac O, Pons G. Antiepileptic Drug Development in Children:Considerations for a Revisited Startegy. Drugs 2008:68;1;17-25.

Labeling Recommendations

(b) (4)