Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-035 SE5-040 21-505 SE5-007
Generic Name:	Levetiracetam 250, 500, 750 mg Oral tablets Levetiracetam 100 mg/mL Oral Solution
Trade Name:	Keppra™
Sponsor:	UCB Pharma
Indication:	Adjunctive Therapy in the Treatment of Partial Onset Seizures
OND Clinical Division:	DNDP (HFD-120)
OCPB Division:	DPE1 (HFD-860)
Submission Type:	Priority- Response to Pediatric Written Request
Submission Date:	12/20/04, 4/15/05, 5/26/05
Pharmacometric Reviewer:	Leslie Kenna, Ph.D.
Pharmacometric Team Leader:	Joga Gobburu, Ph.D.
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1. Recommendation

Based on the data submitted to the Human Pharmacokinetics and Bioavailability section of NDA 21-035 SE5-040 and 21-505 SE5-007, the information provided to support the approval of Keppra Oral tablets and Oral Solution for use in children (4 – 12 years) is acceptable.

1.2. Phase 4 commitments

The reviewer is not recommending any phase IV commitments

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Keppra oral tablets and solution have been approved as adjunctive therapy in the treatment of partial onset seizures in adults. A pediatric written request was issued which included a request for pharmacokinetic data of levetiracetam in children.

The pharmacokinetic studies performed include study N1052 where levetiracetam was administered as a 10% oral solution to children 4 years of age and younger. The pivotal pharmacokinetic study was N01010, in which children 4 to 12 years old with partial onset seizure were administered 20, 40 and 60 mg/kg/day of levetiracetam. In addition, plasma concentrations were monitored in the pivotal safety and efficacy studies (N159 and N157) consistent with sparse sampling population pharmacokinetic approach. Data from all studies were subjected to population pharmacokinetic meta-analysis. In addition to the meta analysis, exposure response analysis was conducted by the pharmacometric reviewer.

Levetiracetam is rapidly absorbed in epileptic children. The mean Tmax is achieved in about 1 hour post-administration The primary metabolite (ucb L057) was present in children. The ucb L057/levetiracetam AUC ratio is about 3% in children across the range of ages studied, about half that reported in adults. The pharmacokinetics of levetiracetam was linear in children receiving doses from 20 to 60 mg/kg.

Population Pharmacokinetic analyses indicated that the only significant effect was weight on clearance (CL/F) and apparent volume (V/F) and antiepileptic drug (AED) category on CL/F.

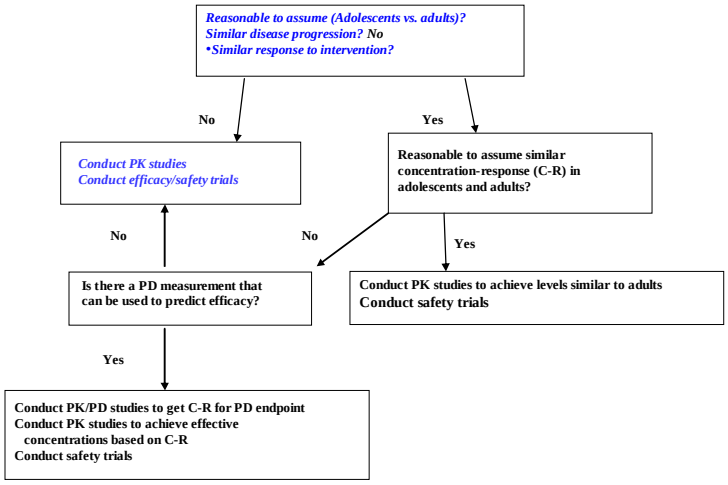
Based on the reanalysis of the Sponsor's data, there was a significant ($p<0.05$) reduction in the number of partial seizures in pediatric patients receiving Keppra compared to pediatric patients receiving placebo. The concentration-response profile of Keppra was similar in the two populations, although the placebo response in pediatric patients was significantly ($p<0.05$) different than in adult patients. The sponsor's plan to dose by matching the concentration in pediatric patients to the concentration in adult patients is reasonable. Based on the modeling and simulation, for children weighing less than 50 kg a dosage regimen of 20 mg/kg/day predicts steady state Cmin and Cmax values within the ranges observed in adults receiving 1000 mg/day. Therefore, a dosing regimen of 20 mg/kg/day for children weighing less than 50 kg and 1000 mg/day for children above 50 kg is reasonable.

Levetiracetam does not affect the concentrations of carbamazepine, valproic acid, lamotrigine and topiramate when they are co-administered together.

Even though enzyme inducing AEDs as a class (e.g. carbamazepine) were found to increase the clearance of levetiracetam by about 22%, dose adjustment is not recommended considering the reported broad efficacy and safety margin of levetiracetam and the therapeutic approach of individual up-titration.

(b) (4)

Pediatric Decision Tree



Kofi A. Kumi, Ph.D._____

Leslie Kenna, Ph.D. (PM Reviewer)_____

Joga Gobburu, Ph.D. (PM Team Leader)_____

RD/FT Initialed by Raman Baweja, Ph.D._____

CPB Briefing: 5/31/05. Attendees: HFD-120 (Howard Chazin), HFD-850 (Chandra Sahajwalla, Joga Gobburu, Kenna Leslie, Christine Garnett), HFD-860 (Mehul Mehta, Roshni Ramchandani, Raman Baweja, Kofi Kumi), HFD-870 (John Hunt), HFD-880 (John Lazor)

CC: NDA 21-035, NDA 21-505, HFD-120, HFD-860 (Mehta, Rahman, Baweja, Gobburu, Kenna, KumiK), CDR (Biopharm)

2. Question Based Review (QBR)

2.1. What are the general attributes

Keppra™ oral 250, 500 and 750 mg oral tablets and 100 mg/mL oral solution are approved as adjunctive treatment of partial onset seizures in adults with epilepsy. A Written Request for pediatric studies was originally issued on 21st August, 2001. The current supplement is a partial response to extend the age range for the indication down to children aged 4 years and above. A deferral has been requested for children less than 4 years old. In discussions with the agency, the sponsor indicated a lower strength than the approved tablets might be used in clinical studies. The sponsor was advised to provide in vitro comparable dissolution testing data for the approved and the pediatric formulations. The sponsor used 166 mg and 166.5 mg pediatric tablets in the pivotal safety and efficacy studies. But the sponsor is not proposing to market these strengths and formulations. The agency recommended to the sponsor that they state apriori the acceptance for declaring dose proportionality (or non-proportionality) when the "Power" model was used. The agency also requested that the sponsor provide the results of the model-independent pharmacokinetic parameter calculations and the results of model-dependent calculations if they were computed.

2.1.1. What are the highlights of the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics

Five different investigational tablet formulations and one oral solution were used in the pediatric development program. Three tablet formulations and the oral solution are approved. A 166 and 166.5 mg levetiracetam tablets were developed for blinding purposes. A comparative dissolution profile of the tablets indicates that greater than (b) (4)% is dissolved in (b) (4) mins for all the strengths used in the clinical studies. The immediate release tablet formulations all have acceptable in vitro dissolution.

2.1.2 What is the mechanism of action and therapeutic indication?

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown.

2.1.3. What are the proposed dosages and route of administration?

Keppra is to be administered orally. It is proposed that treatment should be initiated with a daily dose of 20 mg/kg given in 2 divided doses. The daily dose may be increased (b) (4) by increments of 20 mg/kg to (b) (4) recommended daily dose of 60 mg/kg.

2.1 General clinical pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Formal studies have been performed to assess pharmacokinetics and metabolism of levetiracetam as add-on therapy in the pediatric population. In addition, plasma levels were monitored in Studies N159 and N157. The pivotal pharmacokinetic study (N01010) was an open

label, multi-center, repeated dose study in children 4-12 years old with partial onset seizures. The study consisted of a 2-week titration period, a 4-week withdrawal period and final visits two weeks after the last intake of levetiracetam, for a total of up to 14 weeks of study participation. Subjects were required to be on monotherapy with CBZ or VPA for at least 2 weeks before visit 2 and to have plasma level within the reference of 4 – 10 μg/mL for CBZ and 50 –100 μg/mL for VPA. During the titration period, the dose of levetiracetam was gradually increased by administering 20 mg/kg/day of levetiracetam for the first 2 weeks, followed by 40 mg/kg/day of levetiracetam for 2 weeks, and then followed by 60 mg/kg/day of levetiracetam for the last 2 weeks. A meta analysis of the data collected in five studies was conducted. Nonlinear mixed effects modeling (NONMEM) was used and any child who received levetiracetam, who provided at least one drug concentration, and who had a dosing record on any visit was included. The pharmacokinetics of levetiracetam in pediatric patients was characterized. Inter- and intra-patient variability, optimum dosing regimen and covariates, such as body weight, concomitant medications, were evaluated.

The pivotal efficacy study (N159), was an adequate and well controlled trial in children with partial onset seizures. The study was a randomized, double-blind, placebo-controlled, multi-center trial in pediatric epilepsy patients (4 to 16 years old, inclusive) with refractory partial seizures. Following an 8-week prospective baseline period, patients were randomized to receive placebo or levetiracetam in a double-blind fashion. The levetiracetam dose was titrated up every 2 weeks from 20 to 40 to 60 mg/kg/day (or a maximum of 3000 mg/day). Dosing was on a mg/kg basis and could be adjusted as needed for tolerability. Patients remained at the 60 mg/kg/day dose for a total of 10 weeks.

2.2.2. What is the primary measurement of efficacy?

The primary efficacy parameter was partial onset seizure frequency per week. The endpoint was a direct measure of clinical benefit. Secondary endpoints include response rates, total seizure frequency and proportions of patients who were seizure free.

2.2.3. Are the active moieties in the plasma appropriately identified and measured?

Yes, the active moieties and the metabolites are measured and identified. All analytical methods used to analyze plasma, urine, and saliva was validated and linear over appropriate concentrations ranges. The assays were specific, sensitive, accurate and precise.

Levetiracetam was measured in plasma samples by a validated gas chromatography (GC) with nitrogen-phosphorus detection whereas the metabolite (ucb L057) was measured in plasma samples using a validated LC/ESI/MS assay. Levetiracetam was measured in urine samples by a validated GC assay with NP detection. Levetiracetam was measured in saliva samples by a validated gas chromatographic assay with NP detection.

2.2.4. Exposure-Response Relationship

2.2.4.1. Is the placebo effect similar in pediatric and adult patients?

This question addresses the issue of similarity in disease state for pediatric and adult patients. Formal hypothesis testing showed that placebo response in adults and pediatrics is not the same with 95% confidence. See the “Reviewers Analysis” section entitled **Response to Placebo: Adult vs. Pediatric Patients** in this review for technical details.

Note that patients on the "placebo" arm received the standard of care while patients on the Keppra arm continued to receive the standard of care in addition to Keppra therapy. Thus, in this context, evaluation of "placebo" effect refers to evaluation of effect in subjects that did not receive Keppra. There were several differences in the standard of care among adult and pediatric patients. The list of drugs taken by adult patients is shorter than the list of drugs taken by pediatric patients.

Drugs taken by adult patients in the study:

Carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone,valproic acid and vigabatrin.

Drugs taken by pediatric patients in the study:

Carbamazepine, Clobazam, Clozapine, Clonazepam, Diazepam, Esmolol, Felbamate, Gabapentin, Lamotrigine, Lorazepam, Methsuximide, Oxcarbazepine, Phenobarbital, Phenytoin, Primidone, Tiagabine, Topiramate, Valproic acid and Zonisamide.

2.2.4.2. Is the effect of Keppra similar in pediatric and adult patients?

The concentration-response relationship for Keppra is similar in adults and pediatric patients. See the "Reviewers Analysis" section entitled **Response to Keppra: Adult vs. Pediatric Patients** in this review for technical details.

2.2.4.3. Is the drug efficacious in pediatric patients?

Formal hypothesis testing showed that seizures were significantly decreased ($p<0.05$) in pediatric patients receiving Keppra compared to pediatric patients receiving the standard of care. See the "Reviewers Analysis" section entitled **Effectiveness in Pediatric Patients**
in this review for technical details.

2.2.4.4. Is the dosing strategy for pediatric patients reasonable?

Given that the concentration-response relationship is similar in adult and pediatric patients, the Sponsor's plan to dose by matching the concentration in pediatric patients to the concentration in adult patients is reasonable. See the "Reviewers Analysis" section entitled **Response to Keppra: Adult vs. Pediatric Patients** in this review for technical details.

REVIEWER'S ANALYSIS

Response to Placebo: Adult vs. Pediatric Patients

Figure 1 shows a plot of the cumulative density of the mean percent change from baseline in number of partial seizures in each patient during the Evaluation Period. The green lines (i.e. the two lines furthest to the left on the plot) represent the data in pediatric patients. The red lines represent the data in adult patients (i.e. the two lines furthest to the right on the plot). The solid lines show placebo response and the dotted lines show response to Keppra. Figure 1 shows a clear separation between the placebo responses for Pediatric and Adult patients (i.e. the solid green and solid red lines do not overlap). The green line has a steeper slope than the purple line—indicating that there is a greater response to placebo in pediatric patients than adult patients.

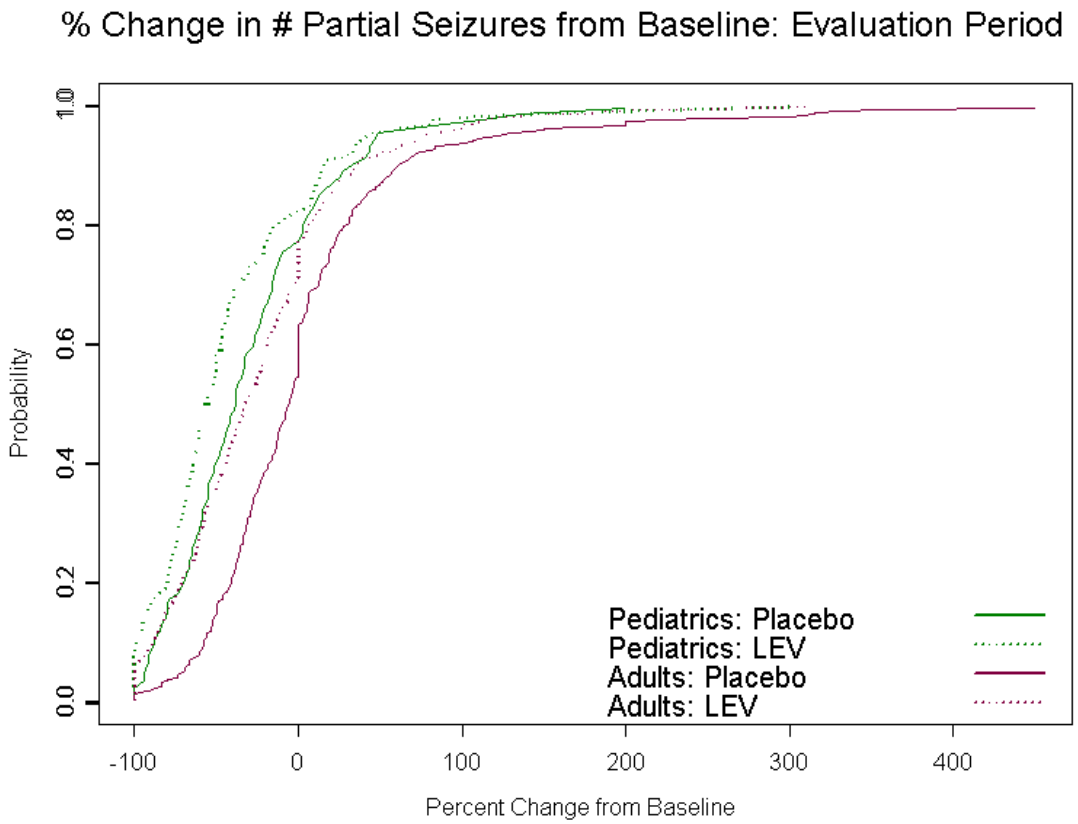


Figure 1. Cumulative Density of Percent Change from Baseline in Partial Seizure Frequency for Adults and Pediatric Patients.

A formal hypothesis test suggests that the difference observed graphically in Figure 1 is statistically significant. A Two-Sample Kolmogorov-Smirnov Test of similarity between Adults and Pediatrics (testing the null hypothesis: Pediatric Placebo effect = Adult Placebo Effect), yielded a Ks test statistic of 0.305 and rejected the null hypothesis with $p<0.05$. Thus, the placebo response in adults and pediatrics is not the same with 95% confidence. Thus, according to this metric, the "placebo" effect did not appear to be the same in adult and pediatric patients.

Response to Keppra: Adult vs. Pediatric Patients

Figure 1 shows a plot of the cumulative density of the mean percent change from baseline in number of partial seizures in each patient during the Evaluation Period. The dotted lines represent the seizure reduction in the Keppra arms. The following results show, the response to Keppra is similar for adults and pediatric patients when evaluated using the concentration-response metric.

A linear mixed effects model with concentration as a covariate for response was fit to the data from pediatric patients. Figure 2 shows the results of the fit. The majority of subjects have a decrease in seizures with increasing concentrations.

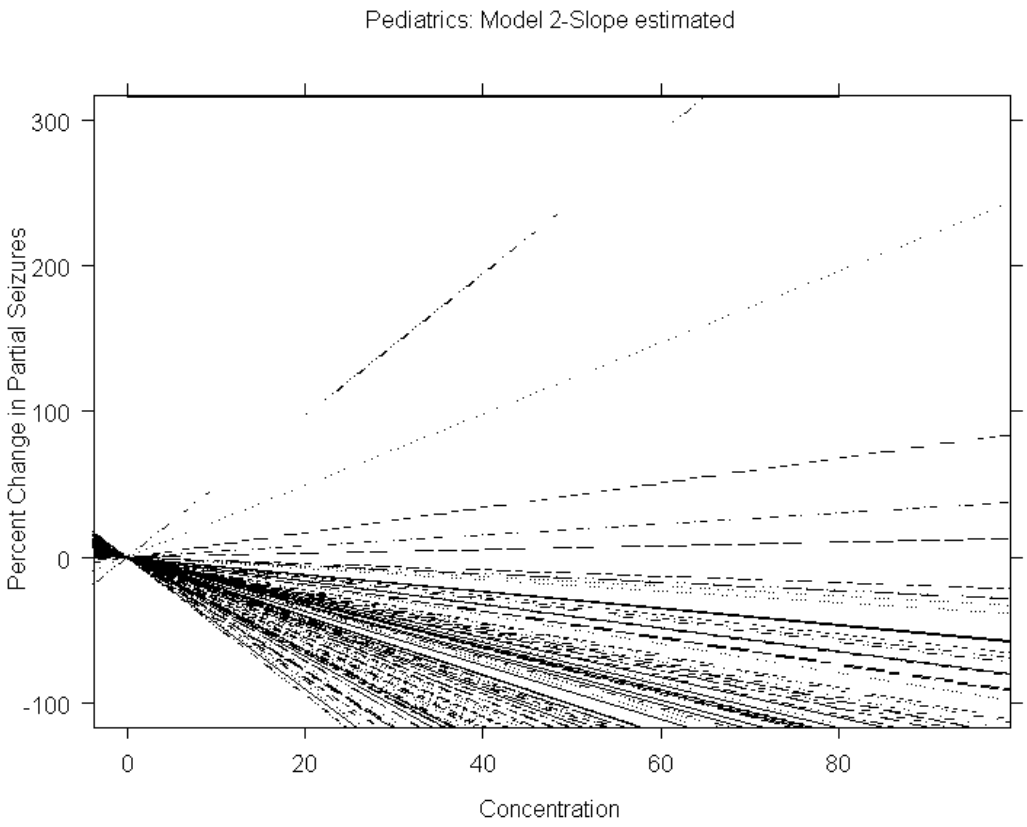


Figure 2. Individual Concentration-Response Curves for Keppra: Pediatric Data. Data fit using a mixed effects model.

Figure 3 highlights the data from several pediatric patients. It shows the population predicted value and individual predicted value of response as a function of concentration. Figure 4 and Figure 5 illustrate the goodness of fit of the model.

Similar to Figure 2, Figure 6 shows the fit of the same model to data in adult patients. Note that the slope of the effect of Keppra as a function of concentration is similar in pediatric and adult patients (slope = -2.0 in pediatric patients and slope = -1.7 in adult patients).

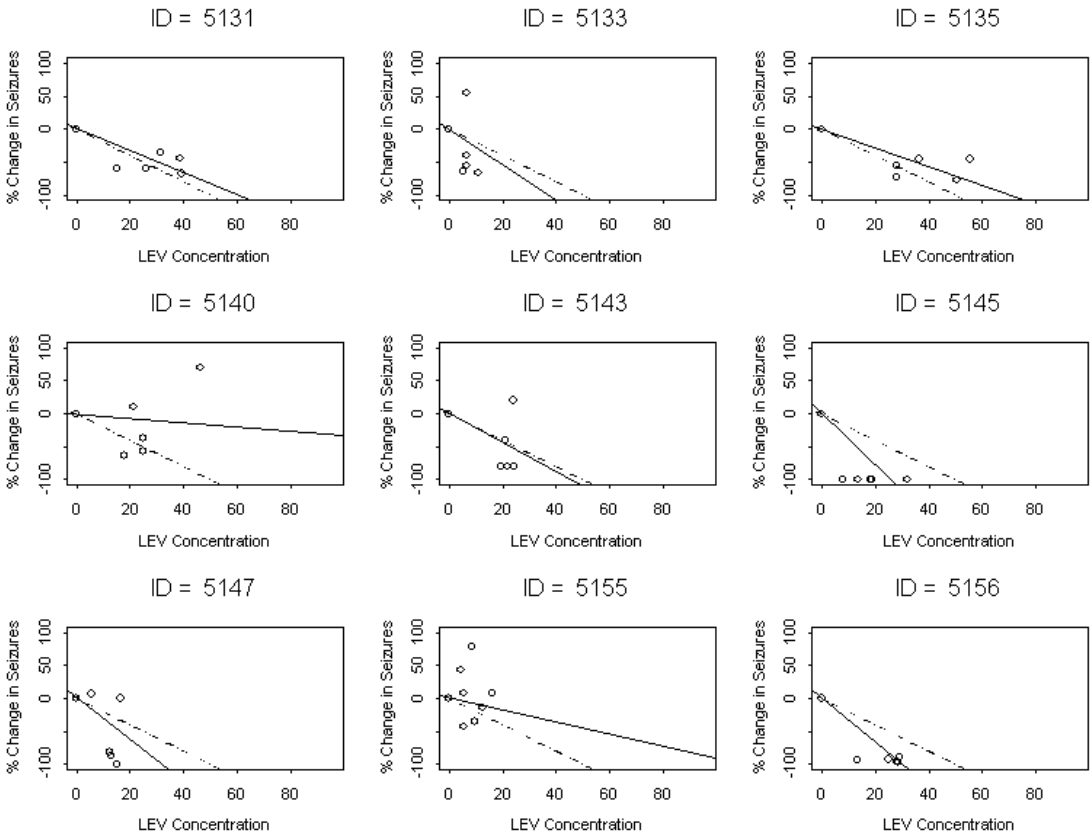


Figure 3. Plots of Individual and Population Predictions of Response Data Using Mixed Effects Model: Pediatric Data.

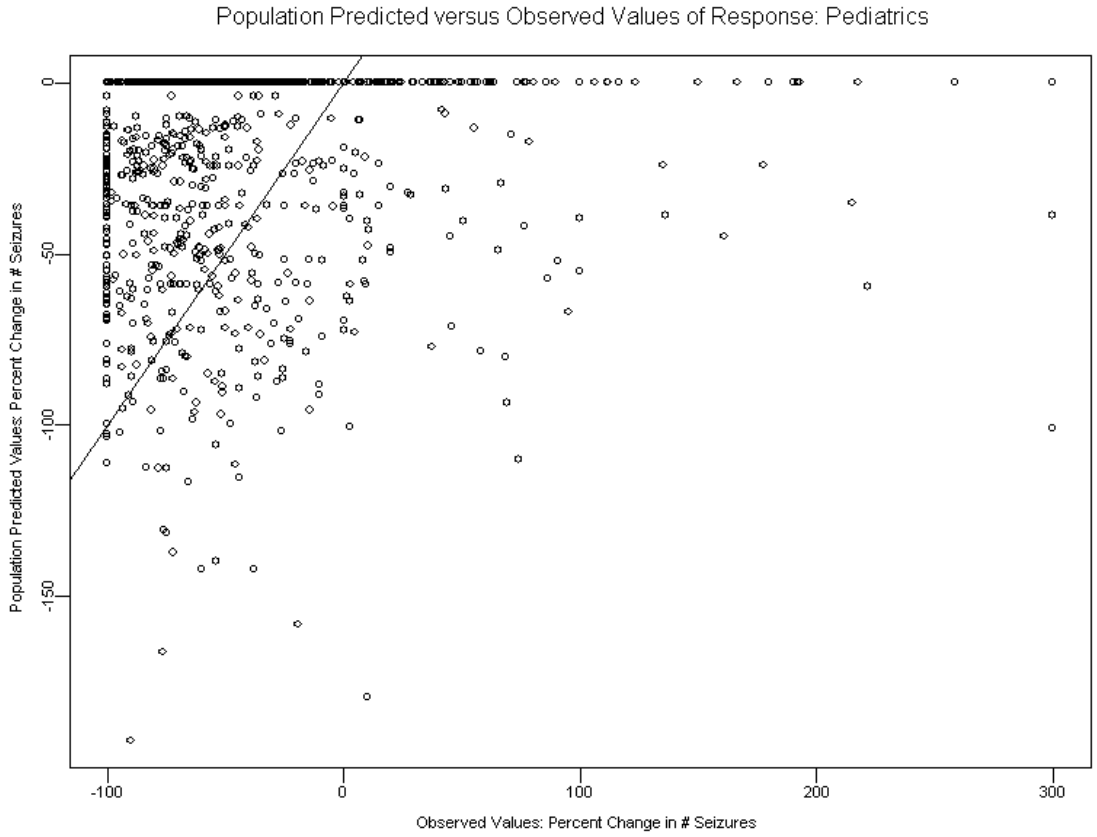


Figure 4. Goodness of Fit: Population Predicted versus Observed Percent Change in Number of Seizures.

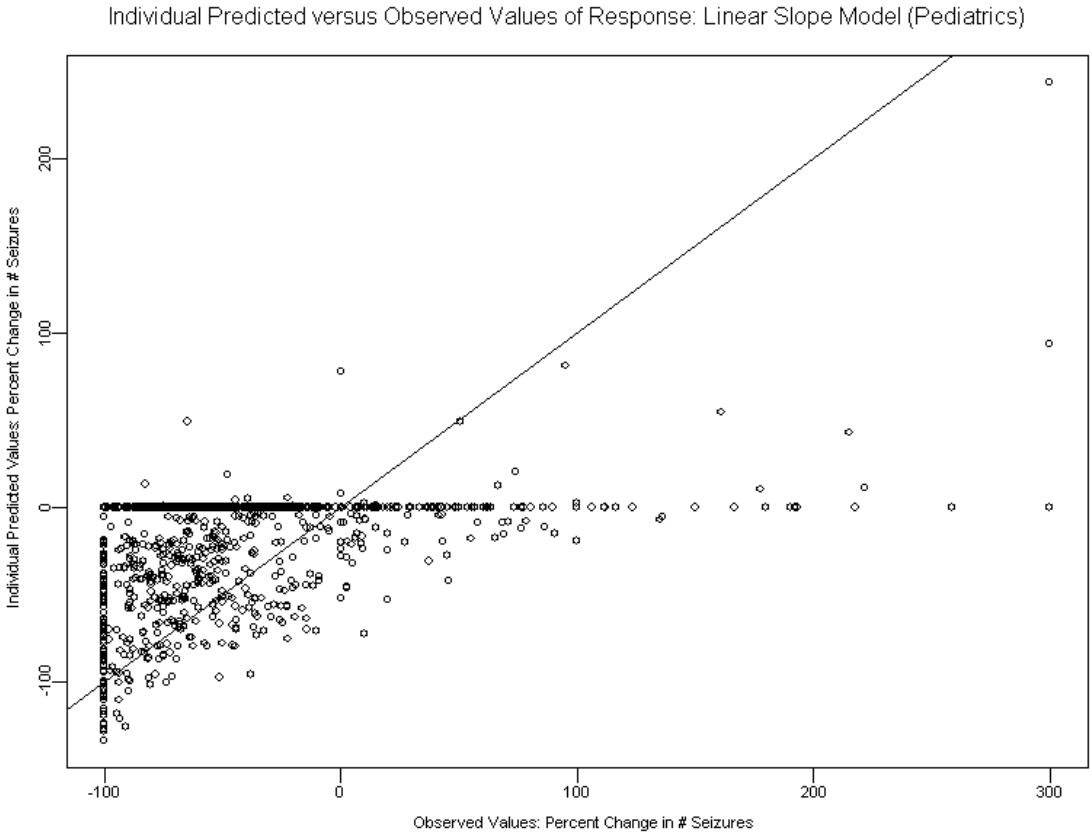


Figure 5. Goodness of Fit: Individual Predicted versus Observed Percent Change in Number of Seizures.

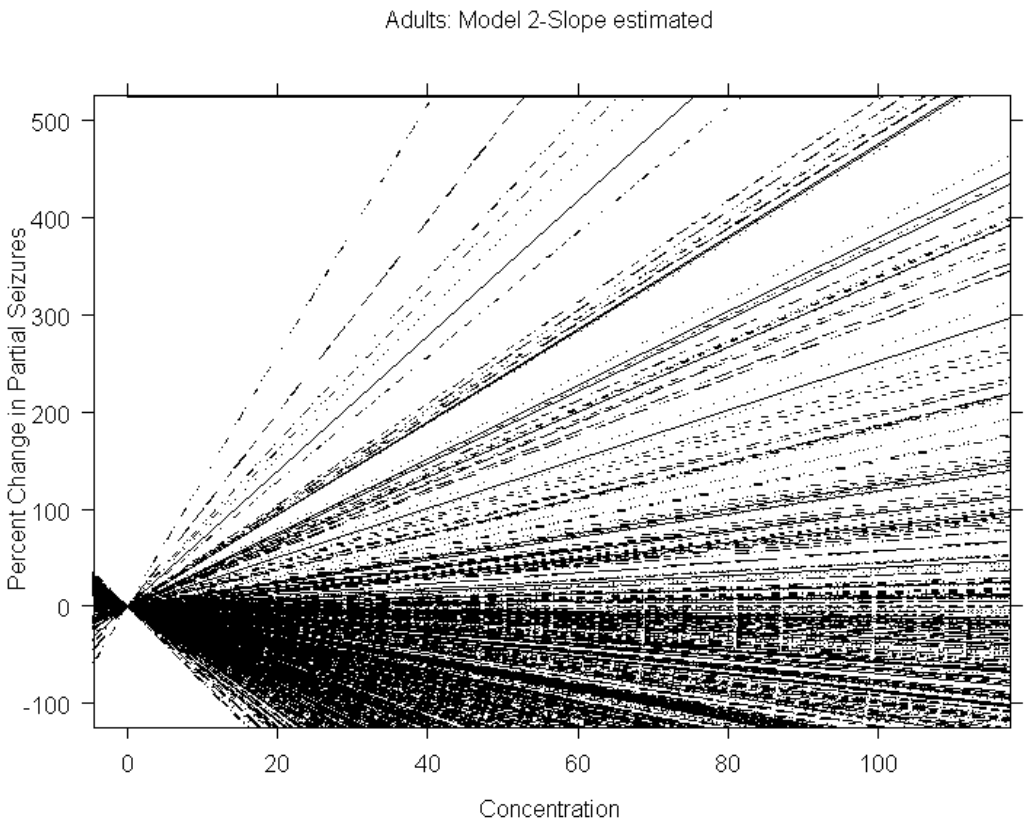


Figure 6. Individual Concentration-Response Curves for Keppra: Adult Data. Data fit using a mixed effects model.

Effectiveness in Pediatric Patients

Figure 1 shows a plot of the cumulative density of the mean percent change from baseline in number of partial seizures in each patient during the Evaluation Period. The green lines represent the data in pediatric patients. The solid lines show placebo response and the dotted lines show response to Keppra. Figure 1 shows a clear separation between the Keppra response and Placebo response in Pediatric patients (i.e. the dotted green and solid green lines do not overlap).

A formal hypothesis test suggests that the difference observed graphically in Figure 1 is statistically significant. A Two-Sample Kolmogorov-Smirnov Test of similarity between the pediatric Keppra and Placebo arms (testing the null hypothesis: Pediatric Keppra effect = Pediatric Placebo Effect), yielded a Ks test statistic of 0.2089 and rejected the null hypothesis with $p<0.05$. Thus, Keppra and placebo responses are not the same in pediatric patients with 95% confidence.

Figure 7 shows the median response to Keppra in pediatric patients during the four study periods. A beneficial effect of Keppra relative to placebo was observed during the titration and maintenance periods. The number of seizures in the two study groups was equivalent after the drug washed out.

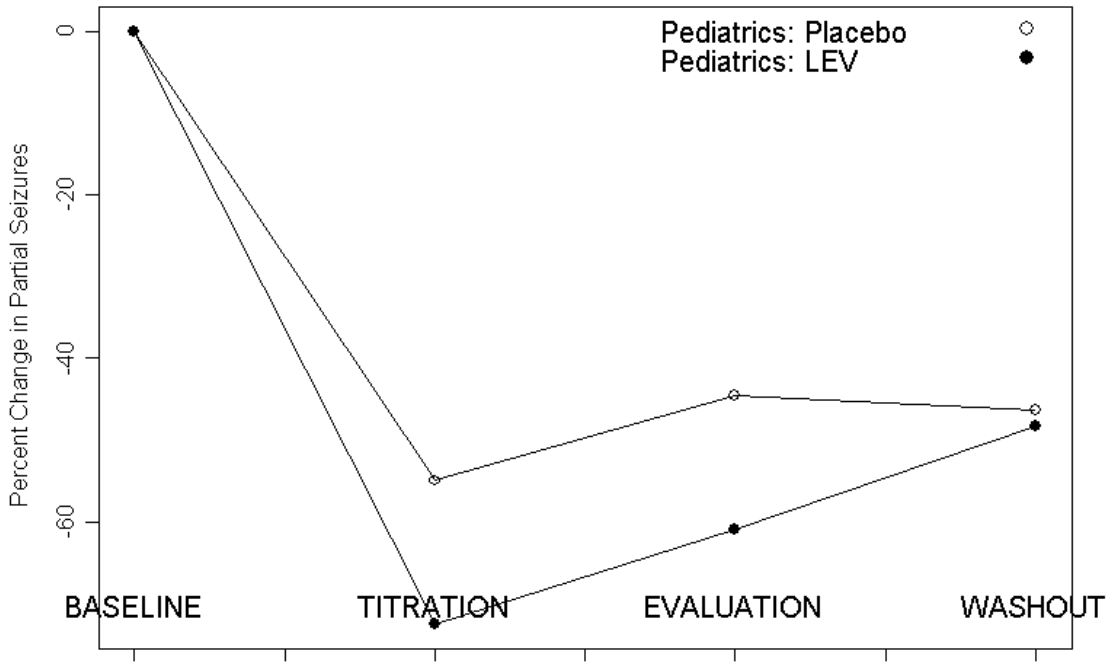


Figure 7. Median Change in Baseline Corrected Percent Change in Partial Seizures for Keppra and Placebo Arms as a Function of Treatment Period: Pediatric Patients.

Note that a model for response as a function of dose was also tested for adult and pediatric data. Table 1 shows that the fit of the models using concentration as a covariate was better than the fit using treatment as a covariate.

Data	Covariate of Response	Akaike Information Criterion
Adult	Treatment	83042.4
Adult	Concentration	82251.78
Pediatric	Treatment	16907.9
Pediatric	Concentration	16776.7

Table 1. Comparison of Model Goodness of Fit: Akaike Information Criterion.

STUDY DESIGNS

Pediatric patients

Study N159 was a Phase III dose escalation study of Keppra in pediatric patients. Patients initiated treatment with 20 mg/kg/day and escalated in 20 mg/kg/day increments every two weeks up to a maximum of 60 mg/kg/day. Trough PK samples were collected at biweekly visits during the titration and evaluation periods. Figure 8 is a schematic of the design of Study N159.

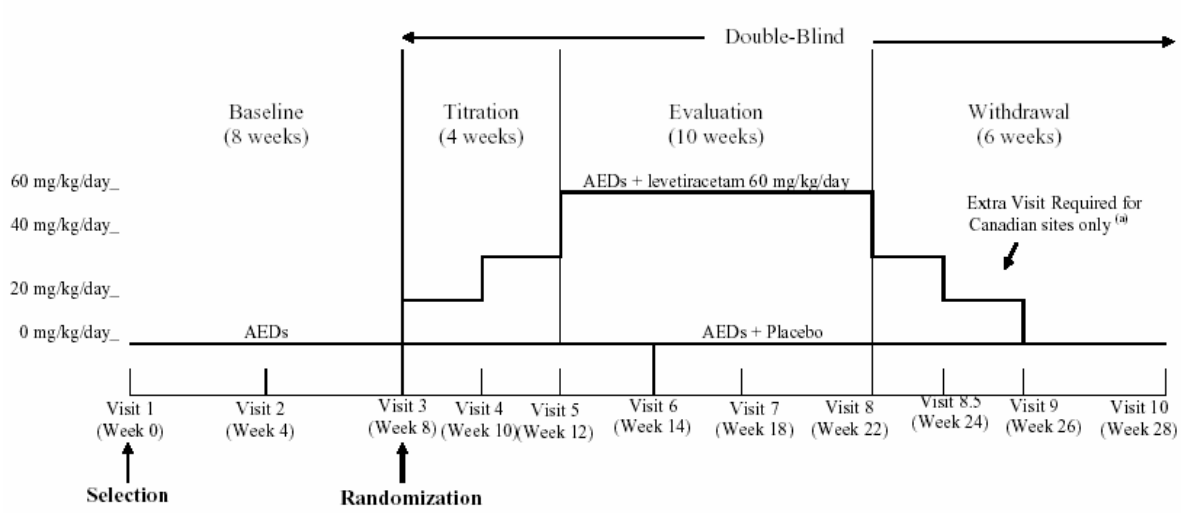


Figure 8. Schematic of Pediatric Study N159.

Adult patients
The following Phase III studies were performed in adult epilepsy patients:
• Study N132 was a Phase III, placebo-controlled, parallel study of 500 mg and 1500 mg b.i.d. doses of Keppra as an add-on therapy in a total of 294 subjects ranging in age from 16 to 70 years of age. Refractory epileptic patients with partial onset seizures receiving up to two approved anti-epileptic drugs were included in the study. The study was conducted for 38 weeks.

• Study N051 was a Phase III placebo-controlled, crossover study of 500 mg and 1000 mg b.i.d. doses of Keppra as an add on therapy in a total of 324 subjects ranging from 16 to 70 years of age. Refractory epileptic patients with partial onset seizures receiving up to two approved anti-epileptic drugs were included in the study. The study was conducted for 32 weeks.

• Study N138 was a Phase III placebo-controlled, parallel study of 1500 mg b.i.d. doses of Keppra as an add on treatment and a monotherapy in a total of 286 subjects ranging in age from 16 to 70 years of age. Patients with complex partial onset seizures receiving a single approved anti-epileptic drug were included in the study. The study was conducted for 16 weeks.

• Study N052 was a Phase III placebo-controlled, parallel study of 1000 mg and 2000 mg b.i.d. doses of Keppra as an add-on therapy in a total of 119 subjects ranging in age from 16 to 72 years of age. Patients with epileptic seizures receiving up to 3 approved anti-epileptic drugs were included in the study. The study was conducted for 24 weeks.

Figure 9 is a schematic of the study design for each of the studies in adult patients.

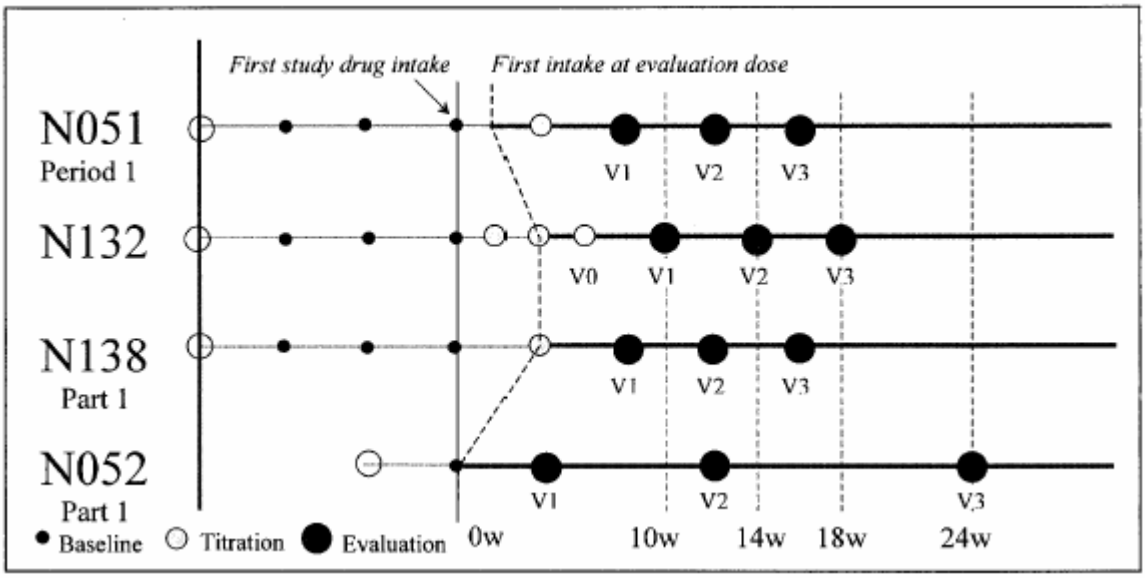


Figure 9. Schematic of Adult Study Designs.

DATA

• Pediatric patients

Seizure count data and anti-epileptic drug concentration data were available in a total of 198 pediatric patients; 101 subjects received Keppra and 97 received placebo. A trough concentration and the record of seizures for the previous dosing period were collected in each subject at every study visit.

The data set analyzed was submitted by the Sponsor on April 15, 2005. The location of the dataset is:

Cdsesub1\\n21035\\S_040\\2005-04-15\\Analysis Datasets\\
Meta PK Analysis\\fda02q.xpt

• Adult patients

Seizure count data and anti-epileptic drug concentration data were available in a total of 1022 adult patients from studies N051, N132, N138 and N052; 671 subjects received Keppra and 351 received placebo. A trough concentration and the record of seizures for the previous dosing period were collected in each subject at every study visit.

The data set analyzed was submitted by the Sponsor on April 15, 2005. The location of the dataset is:

Cdsesub1\\n21035\\S_040\\2005-04-15\\Analysis Datasets\\
Meta PK Analysis\\fda04q.xpt

METRICS

• Percent Change from Baseline

The percent change from baseline in the number of partial seizures was computed at each time point during the study for each subject (subject i) as follows:

$$\%\ \text{Change from Baseline}_{TIME = t, i} = 100\% * \frac{S_{TIME = t, i} - \bar{S}_{TIME = BASE, i}}{\bar{S}_{TIME = BASE, i}}$$

Where

$S_{TIME = t, i}$ = Number of seizures at time = t for subject i

$\bar{S}_{TIME = BASE, i}$ = Mean number of seizures at baseline for subject i

The number of seizures at baseline was computed as the mean over all measures in a given subject during the predose period.

For the analysis of mean response during the Evaluation period (e.g. presented in Figure 1), the percent change from Baseline was computed as follows:

$$\%\ \text{Change from Baseline}_{TIME = EVALUATION\ PERIOD, i} = 100\% * \frac{\bar{S}_{TIME = EVAL, i} - \bar{S}_{TIME = BASE, i}}{\bar{S}_{TIME = BASE, i}}$$

Where

$\bar{S}_{TIME = EVALt, i}$ = Mean # of seizures during the Evaluation period: subject i

$\bar{S}_{TIME = BASE, i}$ = Mean number of seizures during Baseline for subject i

MODELS

Percent change from baseline was modeled via a linear mixed effects formulation using: (1) dose, or (2) concentration as the fixed effect. In both cases, models with: (1) parameters for both slope and intercept, and (2) a parameter for slope were estimated.

MODEL SELECTION

The model including parameters for both slope and intercept did not yield a significantly better fit to the data than a more parsimonious model estimating a term for slope only. Thus, the model with just a slope parameter was selected as best fitting model.

Models incorporating concentration as a fixed effect predicted seizure response better than models incorporating dose as a fixed effect. Goodness of fit was assessed with regards to the objective function and Akaike Information Criterion and visual inspection of goodness of fit plots.

STATISTICS

The Kolmogorov-Smirnoff test statistic was used to compare the distributions of response to Keppra and placebo for adult and pediatric patients during the Evaluation period. The KS test statistic assesses the similarity between the underlying distributions of two samples by comparing their cumulative distribution functions. It is approximately chi-squared distributed.

Stated formally, the cumulative distribution functions S_1 and S_2 are formed by

$S_k(X)$ = (number of scores in sample $k \leq X$) / (size of sample k)

for k=1,2; and a suitable set of points X. The procedure uses the set of values taken by one or other of the samples, i.e. {X: X is in DATA}. The maximum absolute difference

$$MD = \max(\text{abs} \{ S_1(X) - S_2(X) \})$$

is used as the basis for significance tests. The chi-square approximation (2 degrees of freedom) to this statistic is CH:

$$CH = 4 \times MD \times MD \times (n_1 \times n_2 / (n_1 + n_2))$$

where n_1, n_2 are the sizes of the samples.

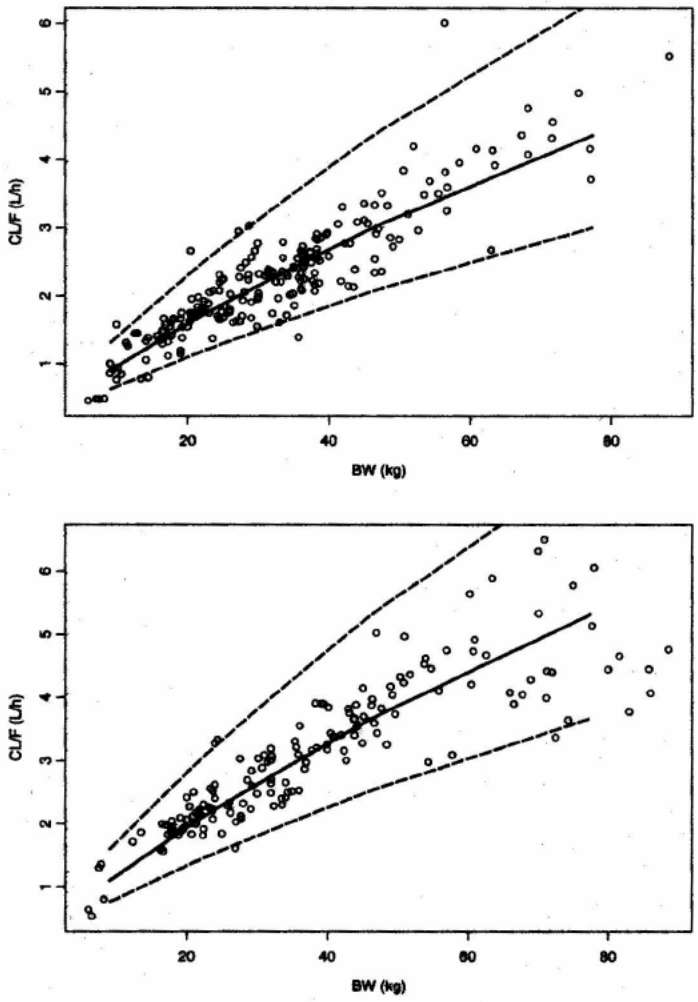
SOFTWARE
All data manipulation and data analyses were performed using S-PLUS 6.2 for Windows.

2.2.4.5. Does the proposed dosing regimen in pediatrics ensure similar exposure in pediatrics and adults?

Yes the proposed dosing regimen schemes produce similar exposure in adults and children.

In the final model, the body weight had the most significant effect on both CL/F and V/F. Based on the modeling and simulation, for children weighing less than 50 kg the dosage regimen of 20 mg/kg/day predicts steady state Cmin and Cmax values within the ranges observed in adults receiving 1000 mg/day. A dosing recommendation of 20 mg/kg/day for children weighing less than 50 kg, and 1000 mg/day, similar to adults, for children above 50 kg is recommended. In adult subjects receiving 500 mg b.i.d, mean Cmin and Cmax values of 5.95 µg/mL and 15.1 µg/mL, respectively have been reported. The pivotal clinical study studied doses starting at 20 mg/kg/day escalating every 2 weeks up to 60 mg/kg/day. The sponsor is recommending a dosing regimen starting at 20 mg/kg/day given in 2 divided doses and it could escalate every 2 weeks up to a maximum of 60 mg/kg/day in two divided doses.

Figure 7:13 Population Prediction and Post-Hoc Estimate at First Visit for CL/F versus BW. Upper Panel: without Inducers. Lower Panel: with Inducers



Typical Value - Continuous Line - and 95% CI –Dashed Lines

For both groups, with or without inducers, the vast majority of the individual posterior estimates for CL/F were within the 95% CI.

Fig. 10

2.2.5. What are the pharmacokinetic characteristics of the drug and its major metabolite?

2.2.5.1. What are the pharmacokinetics of levetiracetam in pediatric population ?

Levetiracetam was rapidly absorbed following a single dose of 10% oral solution administered to pediatric subjects aged ≥ 1 to 48 months. Peak concentrations were observed approximately 1 hour after dosing. The half life of levetiracetam in this population was comparable to the half-life in children 5 to 12 years old (t ½ = 6 hours) and shorter than the half-life observed in adults (7.2 hours

Levetiracetam was rapidly absorbed following oral administration of tablet to pediatric subjects age 4 to 12 years. Peak plasma concentrations were observed 0.5 to 1 hour after dosing. T ½ was shorter for these pediatric subjects (approximately 5 hours) than it was for adults (7.2 h). Dose proportional increases were observed for AUC and Cmax following administration of levetiracetam in doses of 20, 40, 60 mg/kg/day. No clinically significant differences were observed for levetiracetam between subgroups based on concomitant AED. And levetiracetam did not affect trough plasma concentrations of either CBZ and VPA.

An open label, multi-center trial that was conducted to assess the pharmacokinetics of levetiracetam in pediatric patients age 4 to 12 years old. The study consisted of a 2-week titration period, a 4-week withdrawal period and final visits two weeks after the last intake of levetiracetam, for a total of up to 14 weeks of study participation. Subjects were required to be on monotherapy with CBZ or VPA for at least 2 weeks before visit 2 and to have plasma level within the reference of 4 – 10 µg/mL for CBZ and 50 –100 µg/mL for VPA. Twenty-one subjects participated and received study medication. Thirteen subjects were on carbamazepine (CBZ) and 8 subjects were on valproic acid (VPA). During the titration period, the dose of levetiracetam was gradually increased by administering 20 mg/kg/day of levetiracetam for the first 2 weeks, followed by 40 mg/kg/day of levetiracetam for 2 weeks, and then followed by 60 mg/kg/day of levetiracetam for the last 2 weeks. Subjects completed a 12-hour PK assessment at the end of dosing with levetiracetam 20 mg/kg/day (Day 14), 40 mg/kg/day (Day 28), and 60 mg/kg/day (Day 42).

Another open-label, multi-center, single dose PK study in children with a diagnosis of epilepsy was conducted. Thirteen subjects ranging in age from 2.3 to 46.2 months were enrolled. Each subject received a single oral dose of levetiracetam 20 mg/kg body weight administered as a 10% oral solution on Day 1.

Levetiracetam mean pharmacokinetic parameters are summarized by dose and concomitant AED in the following tables. The mean pharmacokinetic parameters were similar for the two treatment group. Cmax increased with each increasing doses. Apparent clearance was faster for subjects treated with CBZ than for subjects treated with VPA. There was a shorter t ½ and smaller AUC in the CBZ group than in the VPA group for each of the three levetiracetam doses. The amount of unchanged levetiracetam excreted in urine (Ae) increases as the administered dose increased. The mean fraction excreted unchanged (fe) was smaller for subjects in the CBZ group than for subjects in the VPA group.

Table 1: Mean Pharmacokinetic Parameters for Levetiracetam Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
CBZ Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	6	6	6
	Cmax (µg/mL)	24.5 ± 6.5	51.9 ± 9.6	72.2 ± 14.1
	Tmax (h)	0.5 (0.2 – 1.0)[a]	0.8 (0.5 – 3.0)[a]	0.5 (0.5 – 3.0)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	123.3 ± 32.6	291.3 ± 22.2[b]	392.3 ± 40.9
	T ½ (h)	4.4 ± 0.5	4.7 ± 0.5[b]	4.4 ± 0.8
	CL/F (mL/min/kg)	1.2 ± 0.1	1.2 ± 0.2[b]	1.2 ± 0.2
Urine				
	Ae (mg)	220.4 ± 108.6	491.8 ± 185.3	775.2 ± 224.5
	Fe (% dose)	60.7 ± 18.6	55.9 ± 9.5	68.7 ± 9.8

[a]Median
b n=5

Table 2: Mean Pharmacokinetic Parameters for Levetiracetam Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
VPA Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	8	8	8
	Cmax (µg/mL)	25.0 ± 9.8	61.0 ± 17.5	73.9 ± 23.3
	Tmax (h)	0.8 (0.5 – 3.0)[a]	0.5 (0.4 – 1.0)[a]	0.8 (0.5 – 3.2)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	161.5 ± 46.5	341.4 ± 84.7	464.3 ± 112.9
	T ½ (h)	5.2 ± 0.5	5.0 ± 0.4[b]	5.3 ± 0.5
	CL/F (mL/min/kg)	1.1 ± 0.2	1.0 ± 0.2	1.1 ± 0.2
Urine				
	Ae (mg)	226.4 ± 110.2	528.1 ± 289.1	750.2 ± 275.4
	Fe (% dose)	73.3 ± 19.3	79.3 ± 21.9	88.2 ± 29.6

2.2.5.2. Are the pharmacokinetics of levetiracetam linear after administration of Keppra?

The pharmacokinetics of levetiracetam in children receiving doses of 20 to 60 mg/kg was linear as determined by a power model.

In study 1010, the sponsor used the power model to evaluate dose proportionality. For Cmax, the linearity parameter β (90% CI) was 1.003 (0.810 – 1.197) and 1.066 (0.895 – 1.236) for the CBZ group and the VPA group, respectively. For AUC (0-t), β (90% CI) was 1.145 (1.038 – 1.252) and 0.995 (0.901 – 1.089) for the CBZ group and the VPA group, respectively.

Figure 11:4 Dose Proportionality Study: $AUC_{(0-t)}$ Mean and 90% CIs (PP Population)

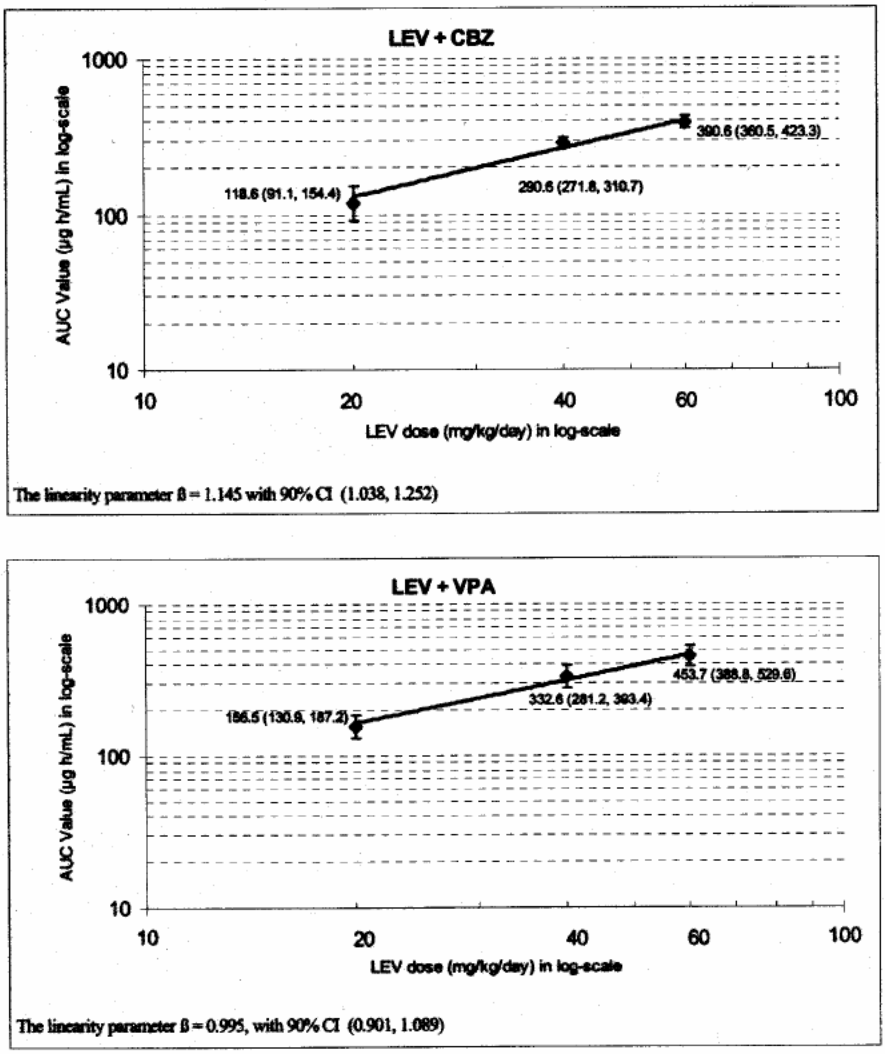
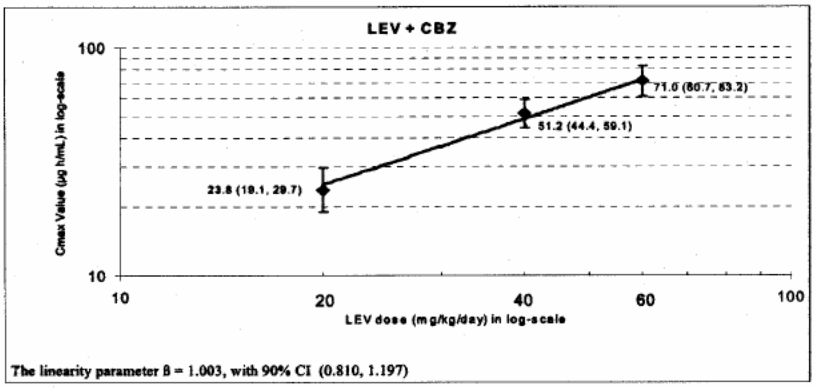
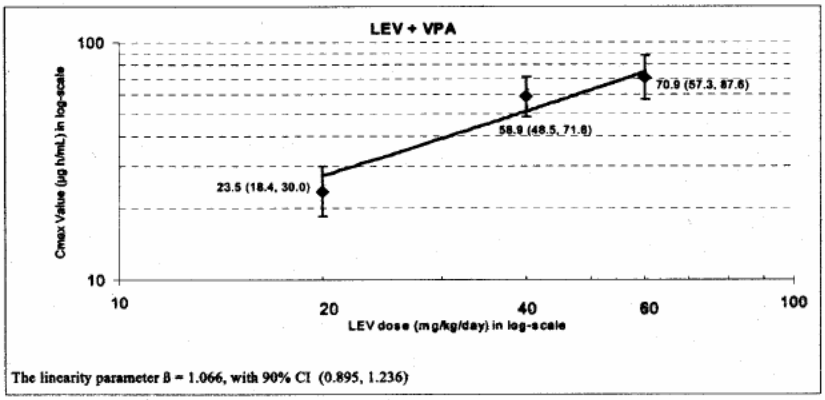


Fig. 11

Figure 11:5 Dose Proportionality Study: C_{max} Mean and 90% CIs (PP Population)

Study N01010





The values presented are the geometric mean and log-transformed confidence interval.

Fig. 12

2.3. Intrinsic Factors

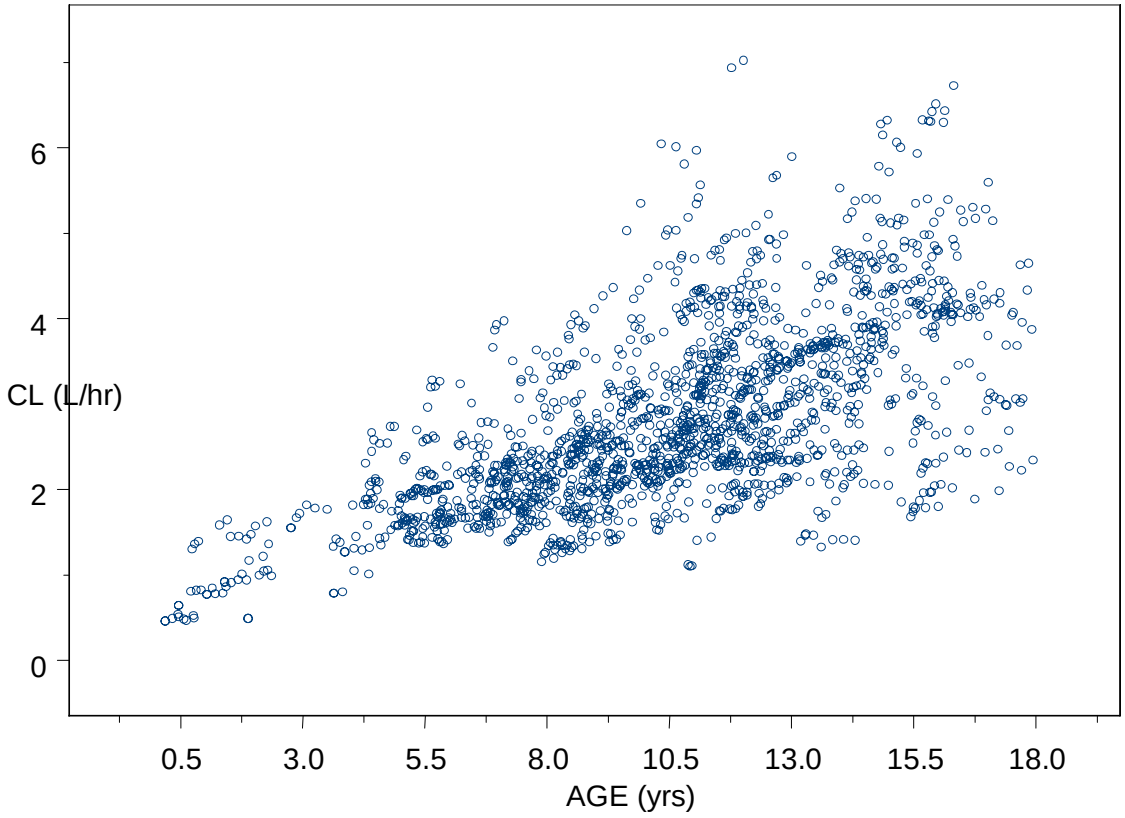
2.3.1. How does the pharmacokinetics compare across the age ranges?

The clearance of levetiracetam increases as body weight increased which in turn increases with increase in age. Plasma elimination half-life in children is 5 to 6 hours across the age ranges studied. Children less than 6 months of age appear to have lower levetiracetam clearance and a smaller volume of distribution, resulting in greater exposure to levetiracetam and its primary metabolite, ucb L057, for the same dose than do the children in the older age categories. The mean pharmacokinetic parameters across studies are provided in the following table

Table 3: Mean Levetiracetam Pharmacokinetic Parameter Values Following Single Doses in Pediatric Patients (N0152 and N151), Young Adults (N069) and Elderly Patients (N083) (Across Studies Comparison)

	Pediatric (1 - < 6 months)	Pediatric (6 -<24 months)	Pediatric (24 – <48 months)	Pediatric (5 – 12 yrs)	Young Adults (22-28 yrs)	Elderly (61 – 88 yrs)	
	Single Dose						
Parameter (unit)	20 mg/kg				1000 mg	500 mg	
N	3	6	3	24	12	16	
Cmax (µg/mL)	37.1	28.8	30.6	25.8	23.0	19.1	
Median Tmax (h)	1.0	1.0	1.0	2.3	0.97	0.97	
AUC (µg*h/mL)	283	237	234	241	222	251	
Vd (L/kg)	0.57	0.65	0.63	0.7	0.7	0.5	
T ½ (h)	5.4	5.3	5.2	6.0	7.8	10.3	
Cl/F (mL/min/kg)	1.23	1.57	1.46	1.43	1.08	0.60	

Fig. 13: Relationship Between Individual Estimates of CL and Age



2.3.2. What are the effects of covariates on the pharmacokinetics of Levetiracetam in pediatric population?

The association between the pharmacokinetic parameters KA, CL/F and V/F and the covariates age, gender, race, body weight, BMI, BSA, Dose, CL_{CR} and categories of concomitant anti-epileptic drug categories, (AEDs) were examined in the analysis. In the final model, the only significant effect was body weight on both CL/F and V/F and of the AED categories on CL/F.

A retrospective analysis based on data from 5 studies, each including both genders. In all the studies, the doses were divided as 2 equal doses given b.i.d., apart from N01052 which was a single dose. All the studies except N159 were open studies. N01052 and N01010 were single and multiple dose PK studies, conducted in 13 (1 month to 4 years old) and 21 (4 to 12 years old) children with epilepsy respectively, receiving solution (20 mg/kg/day) or tablet (20 to 60 mg/kg/day. The mean age and weight of the patients 9.56 ± 3.67 years and 35.2 ± 17.3 kg. The mean BSA was 1.12 ± 0.36 m^2. Levetiracetam plasma concentrations were used for non-linear mixed effects modeling by extended least squares regression using NONMEM. The analysis strategy was first to select a basic model, then to perform both a univariate and a multivariate forward selection analyses to get a full model including covariates, followed then by a backward elimination analysis. The association between the pharmacokinetic parameters and the covariates age, gender, race, body weight (BW), BMI, BSA, Dose, Clcr and categories of concomitant AEDs were examined in the univariate and forward selection analyses. The following figures depict the correlation between CL and weight, CL and dose, CL and CL_{CR} and CL and AED

Figure 7:15 Relation Between Individual Posterior Estimates of CL/F from Final Model and BW, Dose, CL_{CR} and AEDC – All Data

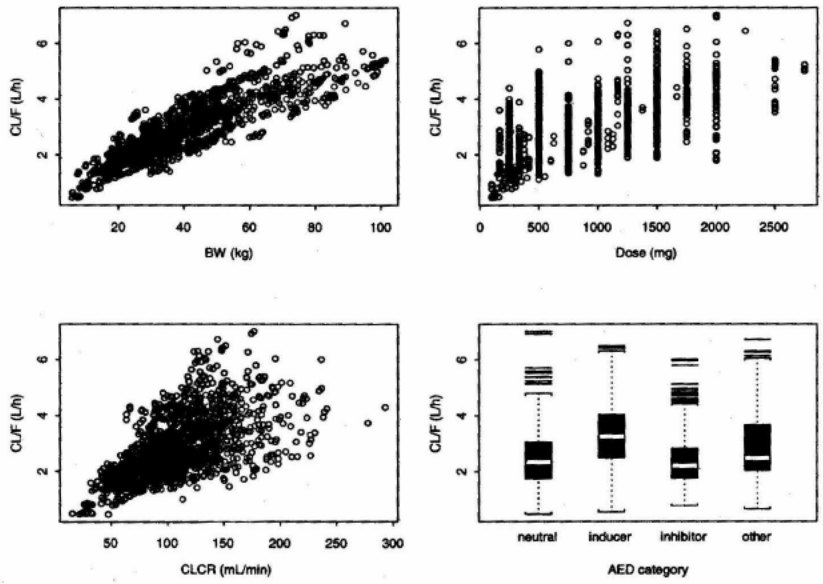


Figure 7:15 shows that levetiracetam CL/F increased with body weight, dose and CL_{CR} as predicted from the final model. However, the relative contribution of each factor appears bigger than it actually is due to the correlation between the 3 factors (see Figure 7:3 and

2.3.3. Is there a linear correlation between plasma and saliva levetiracetam concentrations?

Salivation concentrations were higher than plasma concentrations, especially for the oral solution at the early time points of analysis. There was a correlation between plasma concentrations and saliva concentration. The correlation coefficient was less than 0.9 for both oral solution and the tablet. (b) (4)

A phase I, open-label, single dose, parallel group study in 8 healthy male volunteers. During the study treatment, four subjects received under fasting conditions the following: 7.5-mL (100 mg/mL) levetiracetam 10% oral solution. During the same study period, the other four subjects (group 2) received under fasting conditions three 250 mg levetiracetam oral tablets.

Plasma and saliva samples for pharmacokinetic analysis were evaluated. To collect saliva, the subject spit the saliva into a small plastic cup. Then, the saliva was transferred into the storage tube using a pipette. The minimum volume requirement was 0.5 mL. Salivation was eventually augmented by chewing on a small piece of Parafilm™ or equivalent. Drinking or eating was prohibited one hour before each sampling.

Table 4: Simple linear regression between the saliva/plasma ratio and plasma concentrations from 0.25h post-dose after single administration of the 7.5 mL Levetiracetam oral solution or 3 x 250 mg levetiracetam oral tablets

Treatment	Parameter	Parameter Estimate	Standard Error	95% CI
Oral Solution	Intercept Slope	15.22 -0.865	5.01 0.443	5.04; 25.40 -1.765; 0.036
Oral Tablets	Intercept Slope	1.31 -0.013	0.11 0.009	1.08;1.54 -0.031; 0.005

2.4. Extrinsic Factors

Are there significant drug-drug interaction between levetiracetam and concomitant medications taken during the study?

The association between the pharmacokinetic parameters KA, CL/F and V/F and categories of concomitant AEDs were examined in a population pharmacokinetic analysis. The significant covariates included AED categories (AEDC) on CL/F.

2.4.1.Effect of AEDs on Levetiracetam

AEDC had an effect on CL/F of Levetiracetam. The CL/F of the children receiving inhibiting drugs, without inducing drug, was not different from the one who received only “neutral” antiepileptics. However, the children who took concomitant inducing AEDs whether alone or not, had a higher CL/F than the children who did not. A mean increase of about 22% was estimated by the model. Even though enzyme inducing AEDs as a class (e.g. carbamazepine) were found to increase the clearance of levetiracetam, dose adjustment is not recommended considering the reported broad efficacy and safety margin of levetiracetam and the therapeutic approach of individual up- titration. AEDs were categorized as neutral agents with no effect on drug

metabolizing capacity (e.g. gabapentin, lamotrigine and topiramate), enzyme inducers (such as carbamazepine and phenytoin) and enzyme inhibitors (such as valproate).

2.4.2. Effect of Levetiracetam on AEDs

Levetiracetam does not significantly affect the pharmacokinetics of Carbamazepine, Valproic acid, Topiramate and Lamotrigine

In a 6-week escalating dose study, levetiracetam was added to a stable monotherapy regimen of either carbamazepine (CBZ) or valproic acid (VPA) in children between the ages of 4 to 12 years. There was no statistically significant difference between the two groups, but apparent clearance was faster for patients treated with carbamazepine than for patients treated with valproate.

Table 5: Mean (95% CI) Trough Carbamazepine (And Its Epoxide) And Valproate Concentrations In Children 4 to 12 years of Age Before and After the Addition of Levetiracetam

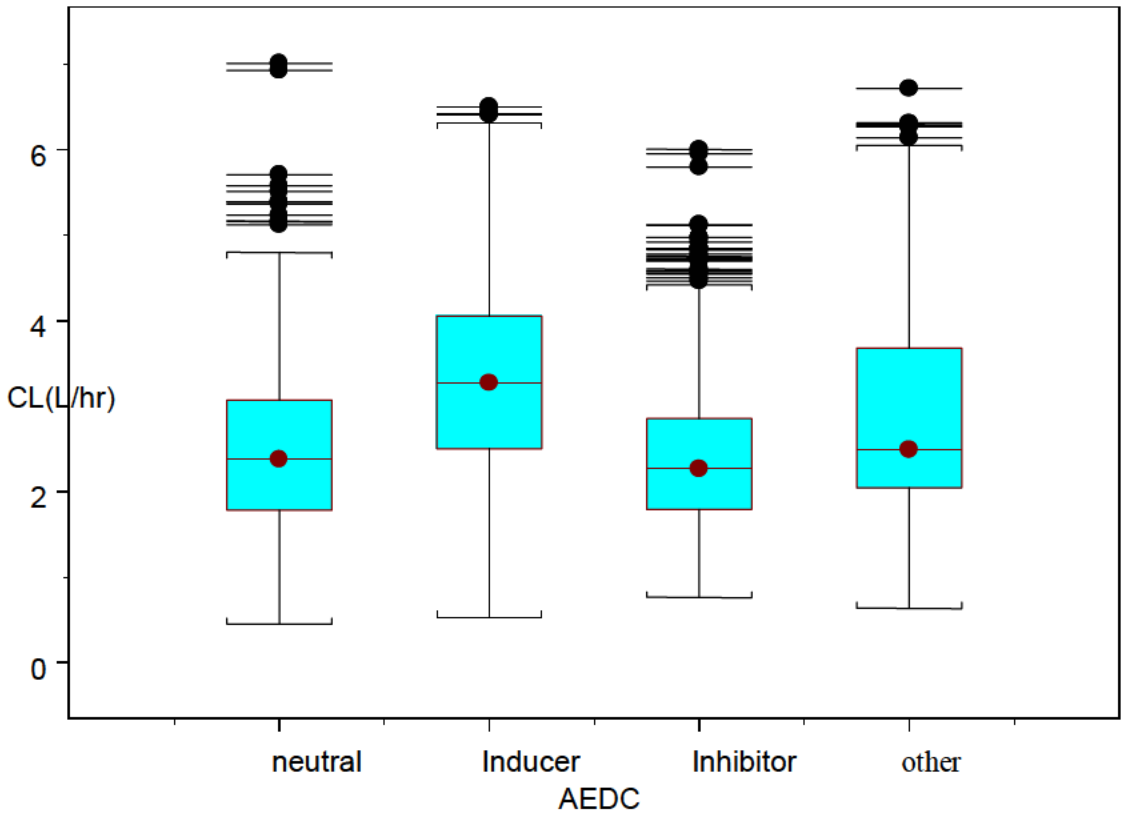
		Levetiracetam Dose		
Parameter (unit)	Pre-LEV	20 mg/kg	40 mg/kg/day	60 mg/kg/day
	Carbamazepine			
N	12	6	6	6
Carbamazepine (µg/mL)	6.8 (5.4 – 8.3)	7.0 (5.0 – 9.0)	6.9 (4.4 – 9.5)	6.9 (4.8 – 8.9)
CBZ-Epoxide (µg/mL)	1.5 (1.1 – 1.9)	1.8 (1.1 – 2.5)	1.9 (1.0 – 2.7)	1.9 (1.3 – 2.0)
	Valproate			
N	15	8	8	8
Valproate (µg/mL)	101.2 (86.2 – 116.2)	106.7 (91.5 – 122.0)	88.3 (67.2 – 109.5)	94.8 (80.1 – 109.5)

Table 6: Summary of AED (CBZ, VPA, TPM and LTG) Plasma Concentrations (µg/mL) before and with Levetiracetam/Placebo Co-Administration – N159

AED[a]	Treatment (N of patients)	Period	Mean (SD)	Ratio of Geometric mean	90% CI
CBZ	Placebo (N=36)	Baseline Treatment	8.97 (2.24) 8.93 (2.46)	0.978	0.933 – 1.025
	Levetiracetam (N=35)	Baseline Treatment	8.71 (2.17) 8.51 (2.58)	0.953	0.909 – 0.999
VPA	Placebo (N=26)	Baseline Treatment	89.7 (34.0) 90.5 (34.0)	0.984	0.940 – 1.029
	Levetiracetam (N=23)	Baseline Treatment	90.7 (33.1) 90.1 (33.9)	0.961	0.917 – 1.007
TPM	Placebo (N=30)	Baseline Treatment	10.66 (6.44) 11.22 (7.14)	0.999	0.930 – 1.037
	Levetiracetam (N=28)	Baseline Treatment	10.18 (8.08) 10.17 (8.31)	0.968	0.900 – 1.041
LTG	Placebo (N=20)	Baseline Treatment	6.34 (4.25) 6.44 (4.14)	0.958	0.853 – 1.075
	Levetiracetam N=22	Baseline Treatment	9.72 (5.19) 9.61 (5.91)	0.971	0.872 – 1.081

CBZ = carbamazepine, VPA = Valproic acid, TPM = Topiramate, LTG = Lamotrigine

Fig. 14: Relationship between Clearance and Antiepileptic Drug Categories



2.5 General Biopharmaceutics

The proposed dosage formulation and strengths to be used for this patient population are approved and commercially available. Keppra tablets are approved in dosage form of 250 mg, 500 mg and 750 mg. A grape flavored oral solution (100 mg/mL) is also approved and commercially available and is intended to provide a convenient dosage form for children and patients who have difficulty swallowing the existing tablets.

For blinding purposes, the sponsor developed a 166 and 165 mg tablets for the pivotal trials. The composition of these investigational formulations is the same as that of the commercial tablets and differ only in size and absence of color. Comparison of dissolution profiles shows that Keppra (b) (4) tablets for clinical use do not vary from the Keppra (b) (4) tablet for commercial use.

3.1 Commercial Keppra (b) (4) tablet

3.1.1 Keppra (b) (4) 500 mg yellow tablet (04E21)

Batch		04E21			
	Time (min)	0	15	30	45
% dissolve	1	0	102	104	106
	2	0	100	102	103
	3	0	102	104	105
	4	0	97	104	105
	5	0	104	107	106
	6	0	100	105	105
	7	0	105	105	107
	8	0	104	106	107
	9	0	104	106	107
	10	0	104	103	105
	11	0	103	105	103
	12	0	106	108	106
Mean		0	103	105	105
Stdev		0	2.54	1.68	1.38
RSD			2.48	1.60	1.31

3.1.2 Keppra (b) (4) 250 mg blue tablet (03I21E)

Batch		03I21E			
	Time (min)	0	15	30	45
% dissolve	1	0	104	104	105
	2	0	102	104	104
	3	0	103	103	104
	4	0	105	105	105
	5	0	103	106	107
	6	0	104	105	102
	7	0	102	104	107
	8	0	103	104	105
	9	0	107	106	106
	10	0	103	104	103
	11	0	104	106	105
	12	0	104	106	105
Mean		0	104	105	105
Stdev		0	1.37	1.06	1.47
RSD			1.32	1.01	1.40

Table 7

3.2 Clincial Keppra (b) (4) tablet

3.2.1 Keppra (b) (4) 166.5 mg white tablet (12905)

Batch	12905				
	Time (min)	0	15	30	45
% dissolved	1	0	102	108	110
	2	0	100	108	111
	3	0	102	107	110
	4	0	97	107	110
	5	0	104	110	111
	6	0	100	108	109
	7	0	108	114	113
	8	0	108	115	112
	9	0	101	113	111
	10	0	99	115	114
	11	0	88	113	113
	12	0	103	114	115
Mean		0	101	111	112
Stdev		0	5.26	3.28	1.83
RSD			5.20	2.95	1.64

3.2.2 Keppra (b) (4) 250 mg white tablet (12496)

Batch	12496				
	Time (min)	0	15	30	45
% dissolved	1	0	105	104	104
	2	0	105	105	106
	3	0	107	106	107
	4	0	104	104	104
	5	0	104	104	105
	6	0	103	103	104
	7	0	103	104	104
	8	0	103	105	103
	9	0	101	102	102
	10	0	101	103	103
	11	0	104	106	106
	12	0	105	104	104
Mean		0	104	104	104
Stdev		0	1.71	1.19	1.44
RSD			1.65	1.15	1.38

Table 8

Table 9

3.2.3 Keppra (b) (4) 166 mg white tablet (12942)

Batch		12942			
	Time (min)	0	15	30	45
% dissolved	1	0	113	112	112
	2	0	106	110	113
	3	0	105	113	110
	4	0	108	111	111
	5	0	103	112	111
	6	0	113	108	108
	7	0	99	106	106
	8	0	105	109	111
	9	0	102	108	109
	10	0	109	112	114
	11	0	109	110	113
	12	0	101	106	110
Mean		0	106	110	111
Stdev		0	4.48	2.38	2.27
RSD			4.22	2.17	2.05

4. CONCLUSIONS

Comparison of dissolution profiles shows that Keppra (b) (4) tablets for clinical use do not vary from the Keppra (b) (4) tablet for commercial use.

2.6. Analytical Method

2.6.1. What bioanalytical method is used to assess levetiracetam and its major metabolite (ucb L057)?

Levetiracetam was measured in plasma samples by a validated gas chromatographic (GC) assay with nitrogen-phosphorus (NP) detection, whereas the metabolite ucb L057 was measured in plasma samples using a validated LC/ESI/MS assay. Levetiracetam was measured in saliva by a validated gas chromatograph.

Levetiracetam assay was linear in the measured concentration range of 0.5 to 40.0 µg/mL of plasma. The lower and upper limits of quantitation were respectively set to the lowest and highest concentration of the calibration range (0.5 to 40.0 µg/mL). The limit of detection was approximately 0.3 µg/mL for levetiracetam in plasma.

Table 10: Validation Results for Levetiracetam Assay in Plasma

Validation Parameter	Results
Linearity	$R \geq 0.9936$
Calibration curve range	0.5 – 40.0 µg/mL
Lower Limit of detection	0.3 µg/mL
Lower Limit of quantitation	0.5 µg/mL
Within-run Precision (RSD%)	$\leq 2.6\%$
Between-run Precision (RSD%)	$\leq 2.4\%$
Total Precision (RSD%)	≤ 3.1
Total Accuracy	$\leq \lvert 3.1 \rvert$
Recovery of analyte	QC mean, low, medium, and high 95.0, 96.4, 95.5

Table 11 Validation Results for Levetiracetam Assay in Urine

Validation Parameter	Results
Linearity	
Calibration curve range	5.00 - 300 µg/mL
Lower Limit of detection	2.88µg/mL
Lower Limit of quantitation	5.00 µg/mL
Within-run Precision (RSD%)	≤ 4.7%
Between-run Precision (RSD%)	≤ 3.9%
Total Precision (RSD%)	≤ 6.1
Total Accuracy	≤ 1.5

Table 12: Validation Results for Levetiracetam in Saliva

Validation Parameter	Results
Linearity	R ≥ 0.995
Calibration curve range	0.5 – 40.0 µg/mL
Lower Limit of detection	0.2 µg/mL
Lower Limit of quantitation	0.5 µg/mL
Within-run Precision (RSD%)	≤ 9.4%
Between-run Precision (RSD%)	≤ 4.2%
Total Precision (RSD%)	≤ 4.6
Total Accuracy	≤ 9.95

3. Detailed Labeling Recommendation

See Label under section 4.1
Reviewer additions are double underlined and deletions are strikeout

4. Appendix

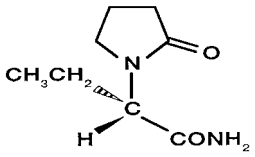
4.1 Package Insert

KEPPRA® (levetiracetam) **Rx only**
250 mg, 500 mg and 750 mg tablets
100 mg/mL oral solution

DESCRIPTION

Keppra® (levetiracetam) is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow) and 750 mg (orange) tablets and as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration.

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is $C_8H_{14}N_2O_2$ and its molecular weight is 170.21. Levetiracetam is chemically unrelated to existing antiepileptic drugs (AEDs). It has the following structural formula:
Levetiracetam is a white to off-white crystalline powder with a faint odor and a bitter taste. It is



very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane. (Solubility limits are expressed as g/100 mL solvent.)

Keppra® tablets contain the labeled amount of levetiracetam. Inactive ingredients: colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:
250 mg tablets: FD&C Blue No. 2,
500 mg tablets: yellow iron oxide,
750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

Keppra® oral solution contains 100 mg of levetiracetam per mL. Inactive ingredients: ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methylparaben, potassium acesulfame, propylparaben, purified water, sodium citrate dihydrate and natural and artificial flavor.

KEPPRA® does not contain lactose or gluten. It does contain carbohydrates. The liquid is dye-free.

Rx Only

This patient leaflet has been approved by the US Food and Drug Administration.

Distributed by
UCB Pharma, Inc.
Smyrna, GA 30080

4.2 Individual Study Reports

Title (Protocol RPCE03H1906, Study N01010): An Open-Label, Multi-Center, Repeated Dose Pharmacokinetic Study of 20, 40 and 60 mg/kg/day of Levetiracetam in Children (4 – 12 Years of Age Inclusive) With Partial Onset Seizures (Volume 10)

Objectives: The primary objectives were to determine the pharmacokinetics of 20 mg/kg/day, 40 mg/kg/day and 60 mg/kg/day of both levetiracetam and its metabolite ucb L057 in children (ages 4 –12 years inclusive) with partial onset seizures; 2) to evaluate the potential interaction of carbamazepine (CBZ) and valproate (VPA) on the pharmacokinetics of levetiracetam; 3) to evaluate the potential interaction of levetiracetam on the plasma levels of AEDs (CBZ and VPA). The exploratory objective was to document the relationship between levetiracetam levels and saliva.

Study Design: The study was an open label, multi-center trial that consisted of a 2-week titration period, a 4-week withdrawal period and final visits two weeks after the last intake of levetiracetam, for a total of up to 14 weeks of study participation. Subjects who were 4 – 12 years old were eligible for inclusion in the study. The diagnosis of epilepsy had to be made at least 6 months prior to the selection visit. Subjects were required to be on monotherapy with CBZ or VPA for at least 2 weeks before visit 2 and to have plasma level within the reference of 4 – 10 μg/mL for CBZ and 50 –100 μg/mL for VPA. Twenty-one subjects participated and received study medication. Thirteen subjects were on carbamazepine (CBZ) and 8 subjects were on valproic acid (VPA). During the titration period, the dose of levetiracetam was gradually increased by administering 20 mg/kg/day of levetiracetam for the first 2 weeks, followed by 40 mg/kg/day of levetiracetam for 2 weeks, and then followed by 60 mg/kg/day of levetiracetam for the last 2 weeks. Plasma, urine and saliva samples were obtained on Days 14, 28 and 42 for pharmacokinetic (PK) assessments. Subjects completed a 12-hour PK assessment at the end of dosing with levetiracetam 20 mg/kg/day (Day 14), 40 mg/kg/day (Day 28), and 60 mg/kg/day (Day 42). After completing the PK assessment on Day 42, the levetiracetam dose was gradually reduced. Levetiracetam 500 mg tablets (Batch No. 1455 and 11566), 250 mg (Batch No. 10601 and 12053) and 166 mg (Batch No. 10600 and 11788) were provided by the sponsor, UCB Pharma.

During each Pharmacokinetic (PK) assessment, blood and saliva samples were obtained pre-dose and 0.25, 0.5, 1, 3, 6 and 12 hours after the morning dose of levetiracetam. Urine samples were collected prior to dosing and 0—3, 3 – 6, and 6 – 12 hours after the morning dose of levetiracetam.

Analytical Method: Concentrations of levetiracetam in plasma, saliva and urine were measured by a gas chromatography technique with NPD detection. The method has a limit of sensitivity of less than 0.5 µg/mL for plasma and 2 µg/mL for urine samples and 0.2 µg/mL for saliva samples. At 0.5 µg/mL for plasma, 10 µg/mL for urine and 0.5 µg/mL for saliva, the precision of the assay is 4%, 11% and 10% RSD, respectively. Concentrations of the metabolite (L057) in plasma were measured by a technique coupling high performance liquid chromatography to electrospray mass spectrometry (LC/ESI/MS). The method has a limit of detection of 12 ng/mL in plasma samples. Assay calibration is linear over the range 20 – 2000 ng/mL in plasma samples. At the lower limit of quantitation, the precision of the assay is < 10% RSD. Concentrations of L057 in urine were measured by LC/ESI/MS. The method has a limit of detection of 2 µg/mL in urine samples. Assay calibration is linear over the range of 10 – 1000 µg/mL in urine samples. At the lower limit of quantitation, the precision of the assay is 8% RSD. Concentrations of carbamazepine (CBZ) and CBZ-E were measured by a high performance liquid chromatography with UV detection. The lower limit of quantitation is 0.7 µg/mL for CBZ and 0.2 µg/mL for CBZ-E. Concentrations of valproic acid (VPA) were measured by fluorescence polarization immunoassay technology. The lower limit of quantitation in plasma is 0.7 µg/mL, and the assay calibration is linear over the range of 12.5 to 150 µg/mL. The precision of the assay was <8%.

Data Analysis: Pharmacokinetic parameters were calculated using model independent approach. Levetiracetam concentrations in plasma were used to determine pharmacokinetic parameters. Levetiracetam concentrations in the urine were used to determine excretion pharmacokinetic variables. The relationship between the concentration of levetiracetam in plasma and in saliva at each time point also was evaluated for each PK assessment. The mean trough concentrations for CBZ and VPA were used to assess the potential interaction between levetiracetam and either Antiepileptic drug (AED). Point estimates and the confidence intervals of the mean AUC(0-t) and Cmax were plotted against the different doses to assess dose proportionality. Dose proportionality was investigated using a power model that assumes, after logarithmic transformation, that there is a linear relationship between AUC(0-t) (or Cmax) and the levetiracetam dose. The effect of the AEDs on levetiracetam pharmacokinetics was reported using descriptive statistics of PK parameters. If there was no interaction of levetiracetam on plasma AEDs, the AED levels should remain the same before and after levetiracetam administered at different doses.

Results: The mean plasma concentration-time profiles for levetiracetam and the metabolite (ucb L057) are provided in the attachments. The mean plasma concentration-time profiles for levetiracetam and ucb L057 for the CBZ and VPA groups are provided in the attachment. Levetiracetam mean pharmacokinetic parameters are summarized by dose and concomitant AED in the following tables. The mean pharmacokinetic parameters were similar for the two treatment group. Cmax increased with each increasing doses. Apparent clearance was faster for subjects treated with CBZ (approximately 50 mL/min) than for subjects treated with VPA (approximately 30 mL/min). There was a shorter t ½ and smaller AUC in the CBZ group than in the VPA group for each of the three levetiracetam doses. The amount of unchanged levetiracetam excreted in urine (Ae) increases as the administered dose increased. The mean fraction excreted unchanged (fe) was smaller for subjects in the CBZ group than for subjects in the VPA group. The contribution of renal clearance to total clearance was smaller for CBZ than for VPA group.

Mean Pharmacokinetic Parameters for Levetiracetam Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
CBZ Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	6	6	6
	Cmax (µg/mL)	24.5 ± 6.5	51.9 ± 9.6	72.2 ± 14.1
	Tmax (h)	0.5 (0.2 – 1.0)[a]	0.8 (0.5 – 3.0)[a]	0.5 (0.5 – 3.0)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	123.3 ± 32.6	291.3 ± 22.2[b]	392.3 ± 40.9
	T ½ (h)	4.4 ± 0.5	4.7 ± 0.5[b]	4.4 ± 0.8
	CL/F (mL/min/kg)	1.2 ± 0.1	1.2 ± 0.2[b]	1.2 ± 0.2
Urine				
	Ae (mg)	220.4 ± 108.6	491.8 ± 185.3	775.2 ± 224.5
	Fe (% dose)	60.7 ± 18.6	55.9 ± 9.5	68.7 ± 9.8

[a]Median
b n=5

Mean Pharmacokinetic Parameters for Levetiracetam Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
VPA Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	8	8	8
	Cmax (µg/mL)	25.0 ± 9.8	61.0 ± 17.5	73.9 ± 23.3
	Tmax (h)	0.8 (0.5 – 3.0)[a]	0.5 (0.4 – 1.0)[a]	0.8 (0.5 – 3.2)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	161.5 ± 46.5	341.4 ± 84.7	464.3 ± 112.9
	T ½ (h)	5.2 ± 0.5	5.0 ± 0.4[b]	5.3 ± 0.5
	CL/F (mL/min/kg)	1.1 ± 0.2	1.0 ± 0.2	1.1 ± 0.2
Urine				
	Ae (mg)	226.4 ± 110.2	528.1 ± 289.1	750.2 ± 275.4
	Fe (% dose)	73.3 ± 19.3	79.3 ± 21.9	88.2 ± 29.6

The pharmacokinetic parameters for the metabolite (L057) are summarized in the following tables. The mean plasma concentration of L057 increased as the dose of levetiracetam increased.

The median Tmax was about 3 hours across doses and concomitant AEDs. The mean Tmax was shorter for the CBZ group than for the VPA group.

Mean Pharmacokinetic Parameters for ucbL057 Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
CBZ Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	6	6	6
	Cmax (µg/mL)	0.5 ± 0.1	1.1 ± 0.3	1.4 ± 0.4
	Tmax (h)	3.0[a]	3.1 (3.0 – 6.0)[a]	3.0 (3.0 – 3.1)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	4.4 ± 1.5	10.8 ± 3.0	13.2 ± 3.2
	T ½ (h)	6.8 ± 0.7	8.2 ± 1.8	9.0 ± 2.9
Urine				
	Ae (mg)	42.1 ± 18.5	93.0 ± 38.0	144.2 ± 52.9
	Fe (% dose)	13.1 ± 3.7	10.6 ± 2.0	12.8 ± 3.2

[a]Median

Mean Pharmacokinetic Parameters for ucb L057 Summarized by Levetiracetam Dose and Concomitant AED

		Mean ± SD		
		Levetiracetam Total Daily Dose		
VPA Subjects	PK Parameter	20 mg/kg	40 mg/kg	60 mg/kg
Plasma	N	8	8	8
	Cmax (µg/mL)	0.6 ± 0.2	1.0 ± 0.3	1.3 ± 0.3
	Tmax (h)	3.0 (3.0 – 6.0)[a]	3.0 (3.0 – 6.0)[a]	3.0 (1.0 – 3.2)[a]
	$AUC_{(0-T)}$ (µg*h/mL)	5.4 ± 1.4	9.6 ± 2.5	12.5 ± 2.8
	T ½ (h)	9.1 ± 2.2	8.8 ± 1.0	11.7 ± 2.9
Urine				
	Ae (mg)	42.1 ± 18.5	86.4 ± 49.0	117.4 ± 49.4
	Fe (% dose)	13.1 ± 3.7	13.0 ± 3.5	13.6 ± 4.7

Dose proportionality analysis is depicted in figures in the attachments. For Cmax, the linearity parameter β (90% CI) was 1.003 (0.810 – 1.197) and 1.066 (0.895 – 1.236) for the CBZ group and the VPA group, respectively. For AUC (0-t), β (90%) was 1.145 (1.038 – 1.252) and 0.995 (0.901 – 1.089) for the CBZ group and the VPA group, respectively. The prospectively defined criterion for declaring dose proportionality was that the entire 90% CI was within the sponsor defined critical region (0.797 – 1.203). Based on this criterion, the PK profile was determined to be linear and dose proportional for the CBZ group based on Cmax and for the VPA group based on AUC(0-t).

Concomitant administration of levetiracetam did not have a significant effect on the mean trough concentrations of CBZ, CBZ-epoxide (CBZ-E, the active metabolite of CBZ) and VPA.

Mean Trough Plasma Concentrations for CBZ and VPA

			Concomitant AED Concentration (µg/mL)	
Treatment	LEV Dose (mg/kg)	N[a]	Mean ± SE	95%
LEV + CBZ				
CBZ	0	12	6.8 ± 2.3	5.4 – 8.3
	20	6	7.0 ± 1.9	5.0 – 9.0
	40	6	6.9 ± 2.4	4.4 – 9.5
	60	6	6.9 ± 1.9	4.8 – 8.9
CBZ-E	0	12	1.5 ± 0.6	1.1 – 1.9
	20	6	1.8 ± 0.7	1.1 – 2.5
	40	6	1.9 ± 0.8	1.0 – 2.7
	60	6	1.6 ± 0.3	1.3 – 2.0
LEV + VPA	0	15	101.2 ± 27.0	86.2 – 116.2
	20	8	106.7 ± 18.2	91.5 – 122.0
	40	8	88.3 ± 25.3	67.2 – 109.5
	60	8	94.8 ± 17.6	80.1 – 109.5

[a]N is the number of observation used in calculations.

A scatter plot showing the relationship between plasma and saliva concentrations of levetiracetam is provided in the ATTACHMENTS. Saliva concentrations were observed prior to dosing for each pharmacokinetic assessment, and the peak mean concentration was observed 0.5 to 1.0 h. Increases in the mean saliva concentration were observed with increasing doses. At most sampling times, the mean levetiracetam concentration was larger in saliva than in plasma, which the sponsor attributes to perhaps because the drug was administered orally. Mean pharmacokinetic parameters are provided in the following table

Mean Pharmacokinetic Parameters in Saliva for Levetiracetam Summarized by Levetiracetam Dose and Concomitant AED

	Levetiracetam Total Daily Dose		
Subject Group	Mean ± SD (n =6)	Mean ± SD (n = 6)	Mean ± SD (n = 6)
CBZ Subjects	20 mg/kg	40 mg/kg	60 mg/kg
Cmax	33.2 ± 13.6	60.6 ± 15.4	92.1 ± 25.4
$AUC_{(0-t)}$	160.3 ± 59.1	337.4 ± 62.3	495.9 ± 83.1
Tmax[a]	0.6 (0.3 – 1.0)	1.0 (0.0 – 3.0)	1.0 (0.5 – 1.1)
VPA Subjects	Mean ± SD (n = 5)	Mean ± SD (n =7)	Mean ± SD (n = 6)
Cmax	34.5 ± 17.4	70. 9 ± 16.1	101.8 ± 52.0
$AUC_{(0-t)}$	196.6 ± 63.6	464.5 ± 162.2	639.2 ± 278
Tmax[a]	1.1 (1.0 – 3.0)	0.7 (0.5 – 3.0)	0.8 (0.0 – 3.0)

The summary of the correlation analysis is provided in the ATTACHMENTS. The correlation coefficients for the plasma and saliva levetiracetam concentrations ranged from 0.783 to 0.924.

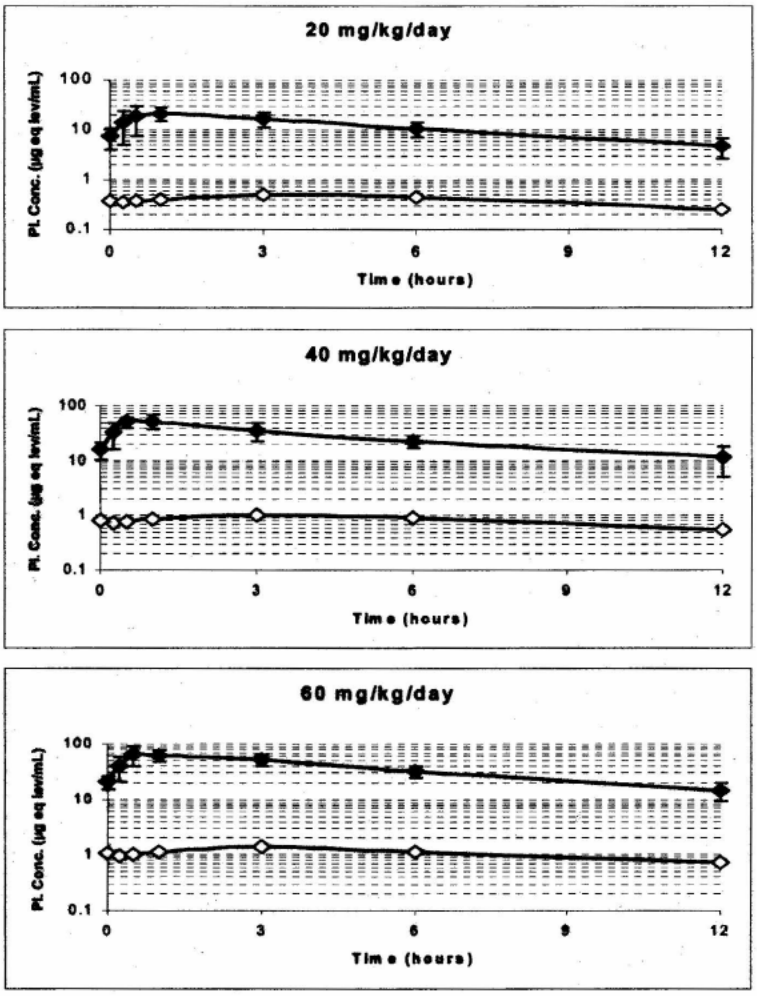
Although the ratio of the saliva to plasma concentration changed over the sampling interval, these changes were not affected by AED type and levetiracetam dose concentrations.

Summary of Pharmacokinetics: Levetiracetam was rapidly absorbed following oral administration of tablet to pediatric subjects age 4 to 12 years. Peak plasma concentrations were observed 0.5 to 1 hour after dosing. T ½ was shorter for these pediatric subjects (approximately 5 hours) than it was for adults (7.2 h). Dose proportional increases were observed for AUC and Cmax following administration of levetiracetam in doses of 20, 40, 60 mg/kg/day. No substantial differences were observed between subgroups based on concomitant AED and levetiracetam did not affect trough plasma concentrations of either CBZ and VPA. Levetiracetam concentrations in plasma and saliva were correlated.

Safety Summary: The sponsor reported no deaths in the study. One subject experienced serious adverse event that was deemed not related to the study drug by the investigator. All of the treatment emergent adverse events (TEAE) were described as being of mild or moderate intensity. The sponsor reports that the safety assessments in this study were consistent with the established safety profile of levetiracetam.

Reviewer's comments: *The mean concentration did not always increase proportionally to dose. The increase was less than proportional to dose. However, the confidence intervals were within the sponsor's apriority definition of dose proportionality and linearity. Levetiracetam did not affect the concentrations of carbamaezepine (CBZ) or valproic acid (VPA). But the effect of CBZ and VPA was not evaluated in this study. Concentrations of levetiracetam in Saliva correlated with that in plasma, but the correlation was not linear.*

Figure 11:1 Mean (±SD) Plasma Concentration-Time Profile (in log-lin Scale) of LEV (Closed Symbol) and ucb L057 (Open Symbol) by Target Dose (PP Population)



Ref: Figure 14.2.7:2

Figure 11:2 Mean (±SD) Plasma Concentration-Time Profile (in log-lin Scale) of LEV (Closed Symbol) and ucb L057 (Open Symbol) for Treatment group of LEV + CBZ by Target Dose (PP Population)

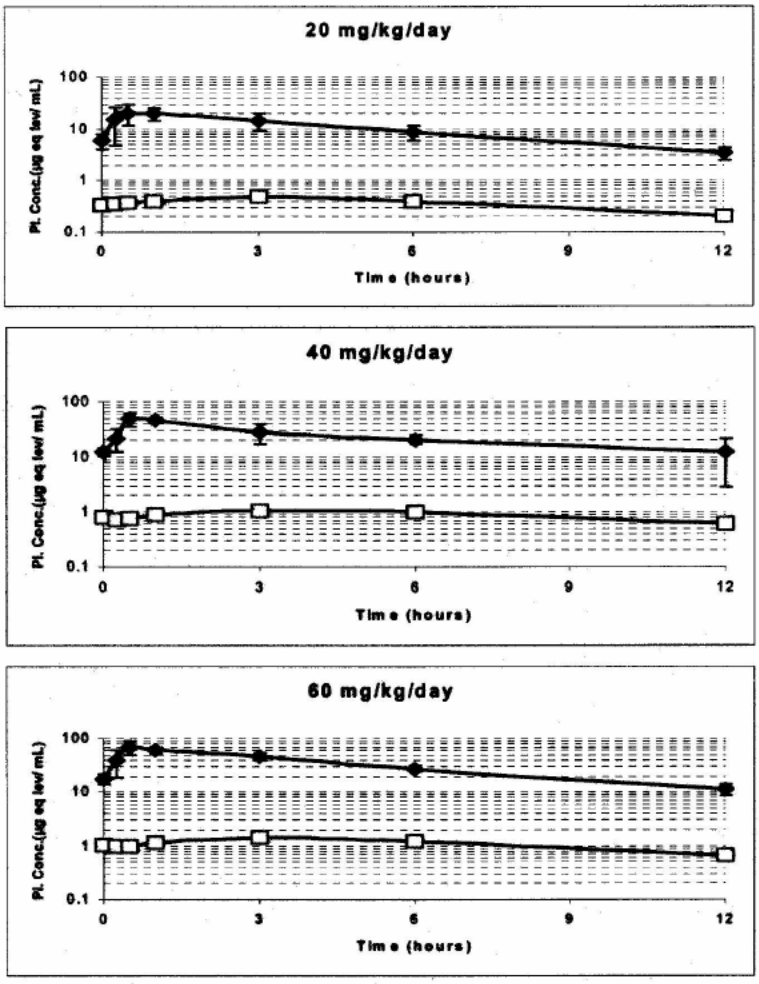


Figure 11:3 Mean (±SD) Plasma Concentration-Time Profile (in log-lin Scale) of LEV (Closed Symbol) and ucb L057 (Open Symbol) for Treatment group of LEV + VPA by Target Dose (PP Population)

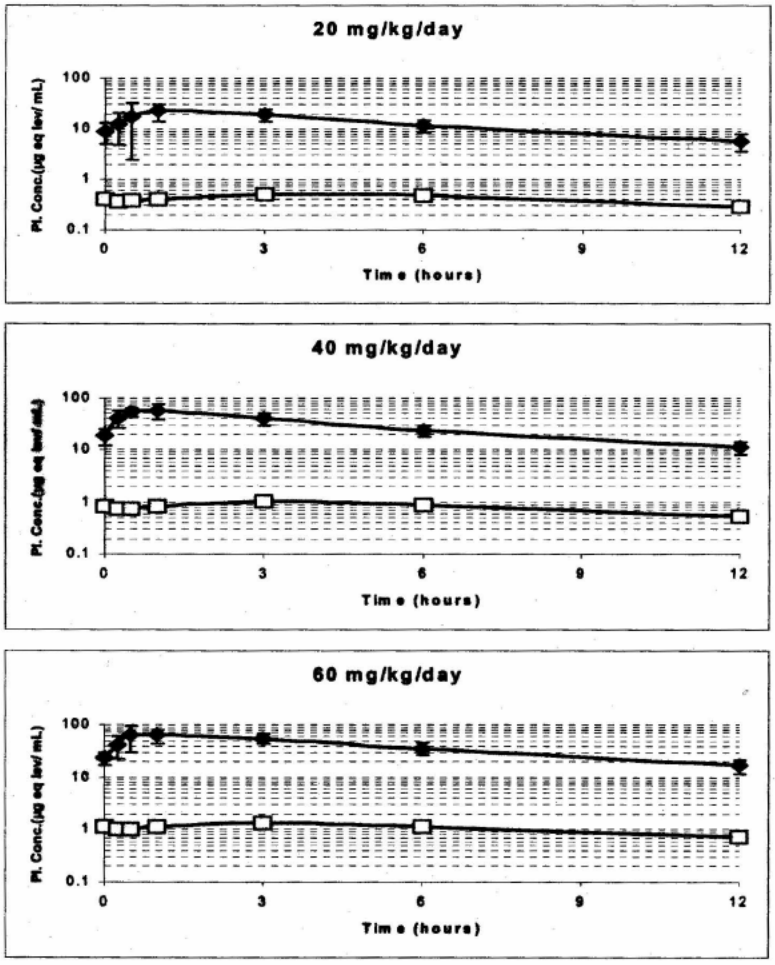
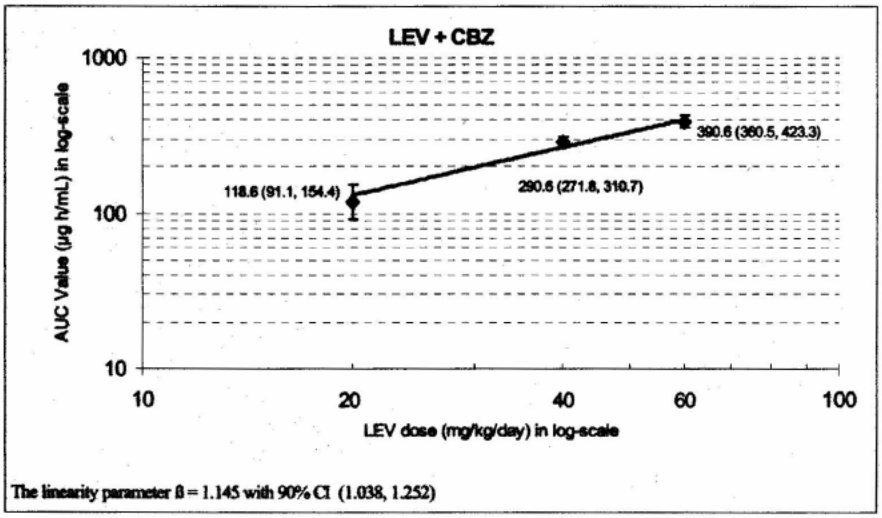


Figure 11:4 Dose Proportionality Study: $AUC_{(0-t)}$ Mean and 90% CIs (PP Population)



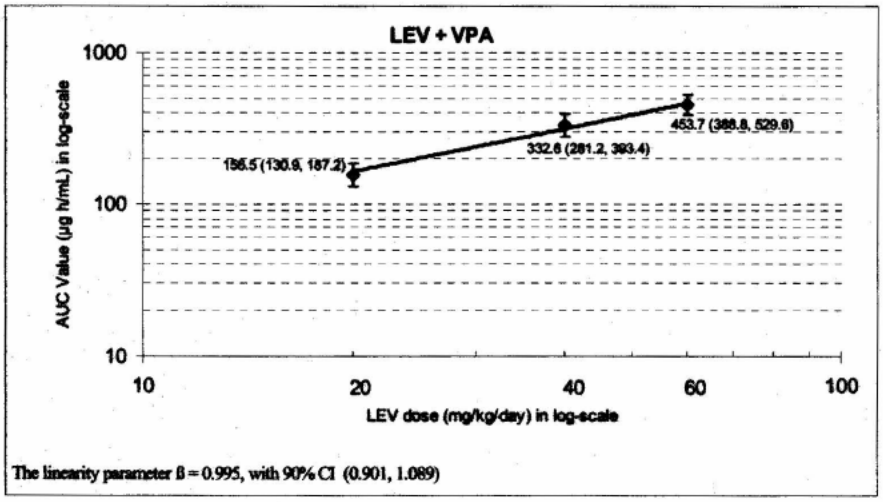
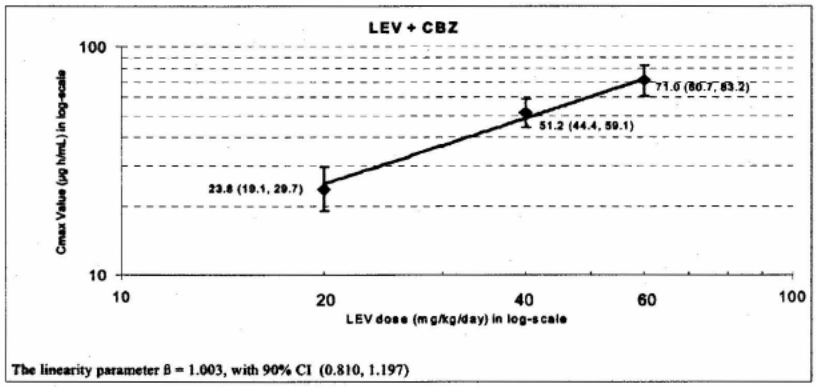
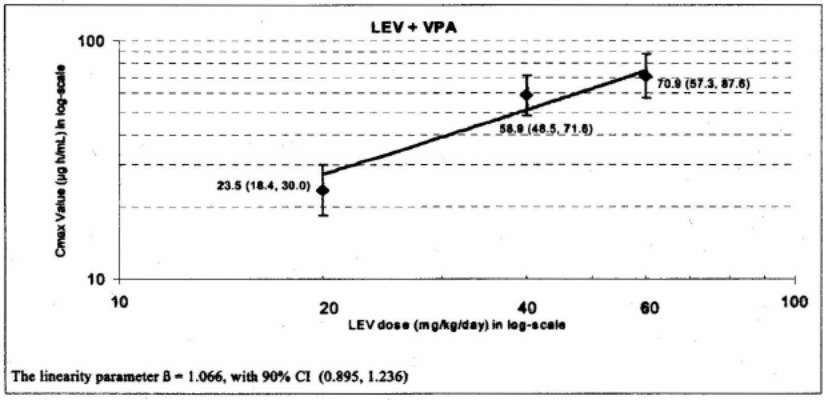


Figure 11:5 Dose Proportionality Study: C_{max} Mean and 90% CIs (PP Population)

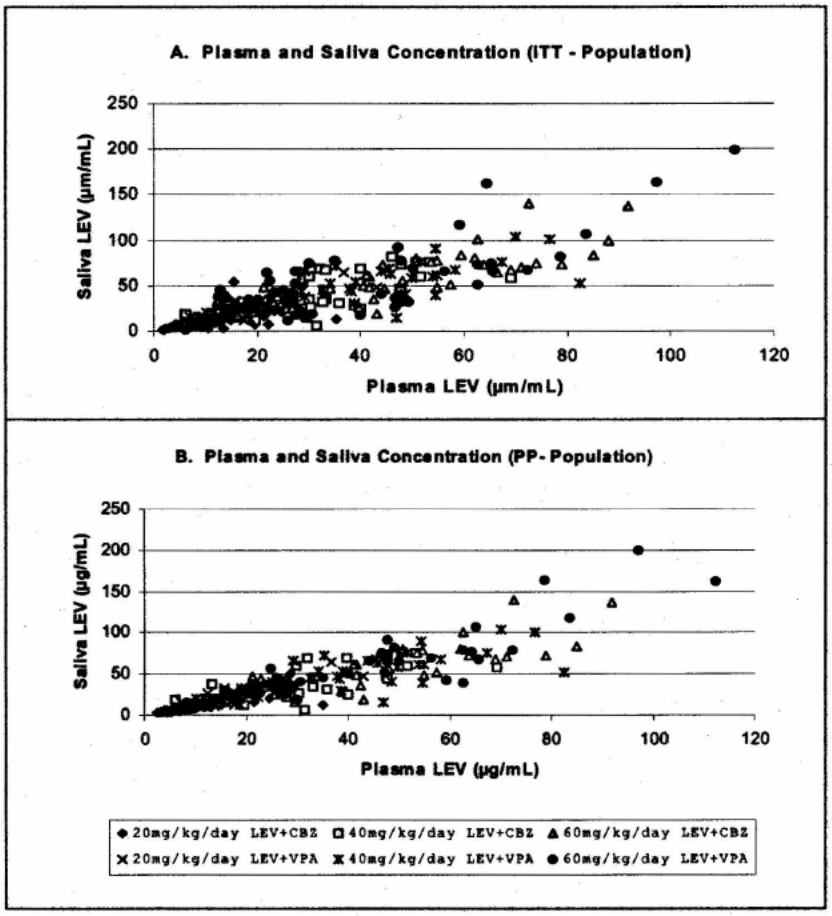
Study N01010





The values presented are the geometric mean and log-transformed confidence interval.

Figure 11:6 Scatter Plot of Plasma and Saliva LEV Concentrations (µg/mL)



Title (Study N01052, RRCE03H2101): An Open Label, Single Dose, Pharmacokinetic Study of 20 mg/kg of LEV Oral Solution In Epileptic Patients Ranging in Age From 1 Month to Less Than 4 Years Old.

Objectives: The primary was to document the pharmacokinetic (PK) parameters of both levetiracetam (LEV) and its metabolite ucb L057 (L057) in epileptic pediatric subjects (1 month to less than 4 years of age) after a single dose of 20 mg/kg of levetiracetam.

Study Design: This was an open-label, multi-center, single dose PK study in children with a diagnosis of epilepsy. Thirteen subjects were enrolled. They ranged in age from 2.3 to 46.2 months. The mean age was 17.9 months, and 3 subjects, 6 subjects and 3 subjects were 1 month to < 6 months of age, 6 months to 24 months of age, and 24 to < 48 months of age. Each subject received a single oral dose of levetiracetam 20 mg/kg body weight administered as a 10% oral solution on Day 1. The batch numbers for the study drug were UKS0102-ST and UKS0201-1. The pharmacokinetic of LEV and L057 required collection of blood samples prior to and 1, 2, 4, 9, 12, 16 and 24 hours after administration of a single dose of LEV.

Analytical Method: Levetiracetam was measured in plasma samples by a validated gas chromatography assay with nitrogen-phosphorus detection. At the nominal concentration of 0.5 µg/mL, the error of measurement was 0.3% and the precision was 10.6%. The analytical method had a limit of quantitation of 0.5µg/mL. The means of relative deviations of levetiracetam in QC samples were 0.1, 0.5 and 0.0% at nominal concentrations of 1.0, 8.0, and 30.0 µg/mL, respectively. L057 was measured in plasma samples using a validated LC/ESI/MS assay. Calibration curves ranging from 20 to 2000 ng eq levetiracetam were used. The means of relative deviations of ucb L057 in QC samples were 0.7, -1.8 and -0.1% at nominal concentrations of 60, 200 and 1000 ng eq levetiracetam/mL, respectively.

Data Analysis: Descriptive statistics were used to summarize plasma concentrations of LEV and L057. PK parameters were determined for both LEV and L057 using non-compartmental model. Results of plasma concentrations of L057 were expressed in µg eq levetiracetam/mL by multiplying the concentrations of L057 in µg/mL by a factor 0.994258, corresponding to the ratio of molecular weights.

Results: The per protocol (PP) population used for the PK analyses consisted of 12 subjects who completed the PK assessments. The PP population consisted of 5 female subjects and 7 male subjects ranging in age from 2.3 to 46.2 months of age. The mean age was 17.9 months and 3 subjects were 1 month to < 6 months of age, 6 subjects were 6 to 24 months old and 3 subjects were 24 to < 48 months old. The mean plasma concentration-time profiles of LEV and L057 are provided in the attachment. The mean pharmacokinetic parameters for LEV and L057 are provided in the following table

Pharmacokinetic Parameter Values for Levetiracetam and ucb L057 Following a Single Oral Dose of Levetiracetam 20 mg/kg

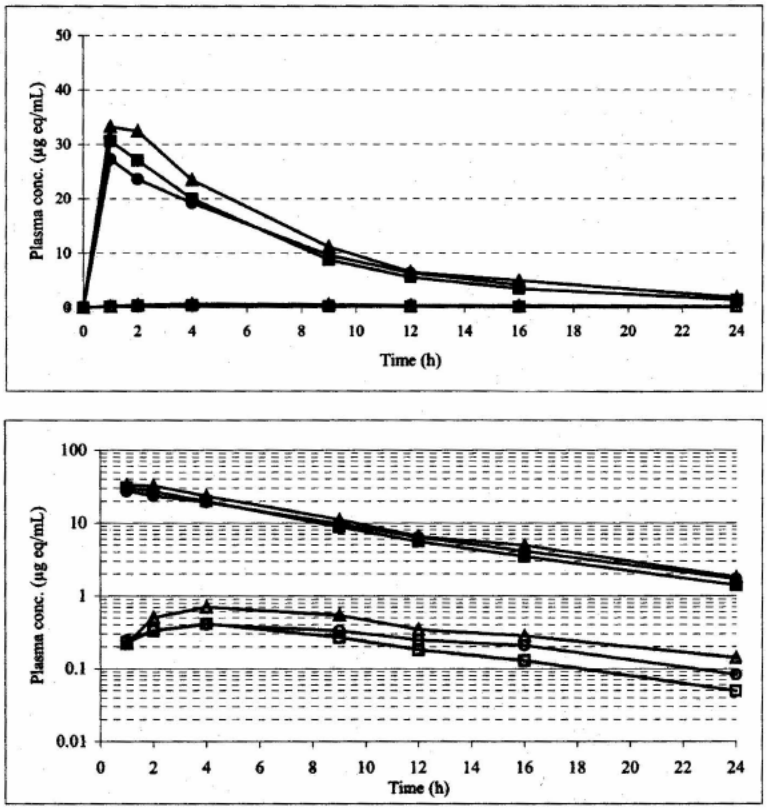
Parameter	Units	All subjects (n=12_	Male Subjects (n=7)	Female Subjects (n=5)
	Mean ± SD			
Levetiracetam				
Cmax	µg/mL	31.3 ± 6.7	30.5 ± 8.0	32.5 ± 4.9
Tmax	h	1.0 (1.0 -4.0)[a]	1.1 (1.0-4.0)[a]	1.0 (1.0-2.1)[a]
AUC	µg*h/mL	248 ± 75	253 ± 92	240 ± 49
T ½	h	5.3 ± 1.3	5.4 ± 1.6	5.0 ± 1.0
Cl/F	mL/min	14.5 ± 6.5	13.8 ± 5.5	15.4 ± 8.3
	mL/min/kg	1.46 ± 0.42	1.47 ± 0.52	1.44 ± 0.30
	mL/min/1.73m^2	53.0 ± 16.29	52.5 ± 18.01	53.7 ± 15.56
Vz/f/Wt	L/Kg	0.63 ± 0.08	0.64 ± 0.10	0.61 ± 0.06
ucb L057				
Cmax	µg eq LEV/mL	0.50 ± 0.19	0.48 ± 0.23	0.53 ± 0.14
Tmax	h	4.0 (1.1 – 9.0)	4.0 (1.1-9.0)[a]	4.0 (2.0-4.0)[a]
AUC	µg eq LEV*h/mL	7.5 ± 4.5	7.2 ± 5.4	7.9 ± 3.3
T ½	h	6.9 ± 1.9	6.6 ± 1.6	7.3 ± 2.3

The mean apparent total body clearance in infants aged less than 6 months, infants aged 6 months to less than 2 years and in children aged 2 years to less than 4 years were about 28, 64 and 52% higher than that reported in adults. When adjusted to body surface area, the clearance in infants aged 6 months to 2 years (57 mL/min/1.73 m^2) and in children greater than 2 years old to less than 4 years old (58.5 mL/min/1.73 m^a) was close to that reported in adults. In the group of infants 6 months, clearance was 30% lower.

Overall Summary: Levetiracetam was rapidly absorbed following a single dose of 10% oral solution administered to pediatric subjects aged ≥ 1 to 48 months. Peak concentrations were observed approximately 1 hour after dosing. The half life of levetiracetam in the population in this study was comparable to the half-life in children 5 to 12 years old (t ½ = 6 hours) and shorter than the half-life observed in adults (7.2 hours). Apparent clearance was approximately 50% faster in subjects ≥ 1 month to < 48 months old (1.5 mL/min/kg) than it was in adults (0.96 mL/min/kg). There was no significant difference in the pharmacokinetics of Levetiracetam between male and females. Levetiracetam was reported to be well tolerated and safety assessments were consistent with the established safety profile.

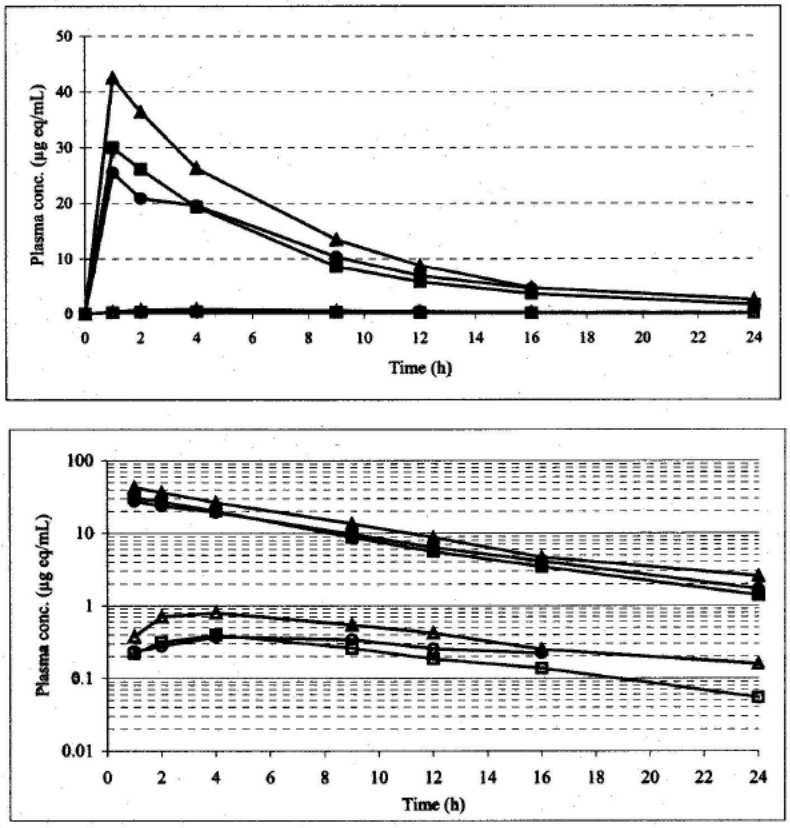
Reviewer Comments: *The reviewer agrees with sponsor's conclusion. The clearance of levetiracetam is slower in the ≥1 month to < 6 months group compared to the ≥6 months to < 24 months and ≥ 24 months to < 48 months age group.*

Figure 11:1 Plasma Concentrations-Time Profile of Levetiracetam (Closed Symbol) and ucb L057 (Open Symbol) in Epileptic Pediatric Subjects Ranging in Age from 1 Month to Less Than 4 Years Old Following a Single Oral Administration of Levetiracetam Given as Oral Solution at a Target Dose of 20 mg/kg [a] (PP Population – By Age Group)



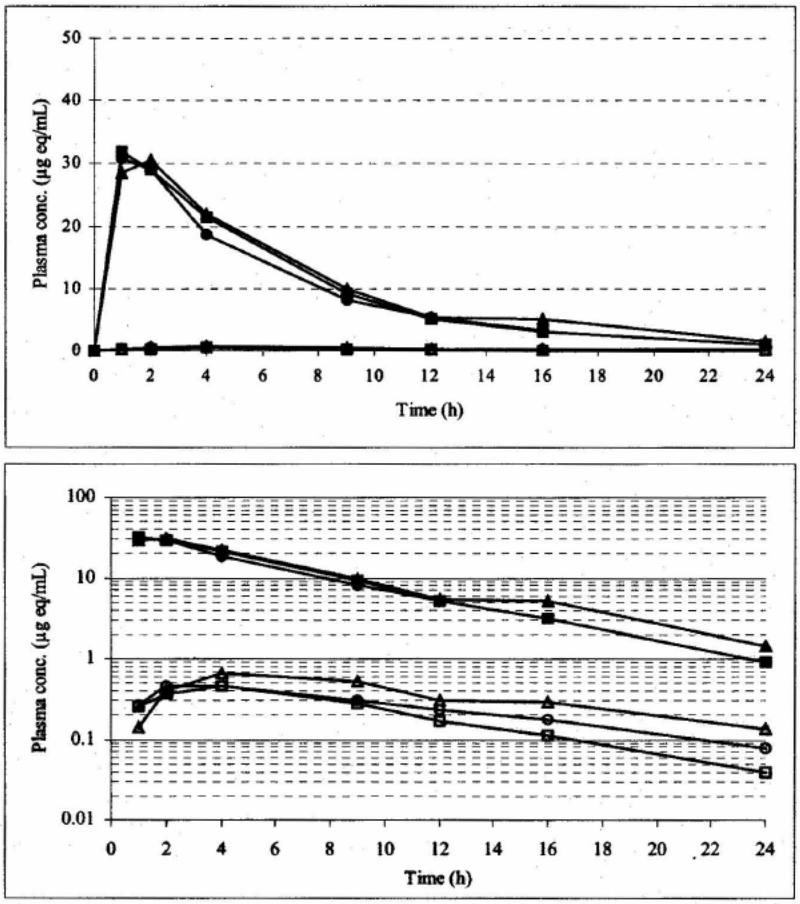
[a] Mean for male and females combined (n=3 for 1-6 months old, triangle; n=6 for 6 months-2 years old, circle; and n=3 for 2-4 years old, square). Data are presented in lin-lin scale (top) and log-lin scale (bottom)

Figure 11:2 Plasma Concentrations-Time Profile of Levetiracetam (Closed Symbol) and ucb L057 (Open Symbol) in Epileptic Pediatric Subjects Ranging in Age from 1 Month to Less Than 4 Years Old Following a Single Oral Administration of Levetiracetam Given as Oral Solution at a Target Dose of 20 mg/kg [a] (PP Population - Male Subjects by Age Group)



[a] n=1 for 1-6 months old, triangle; n=4 for 6 months-2 years old, circle; and n=2 for 2-4 years old, square. Data are presented in lin-lin scale (top) and log-lin scale (bottom)

Figure 11:3 Plasma Concentrations-Time Profile of Levetiracetam (Closed Symbol) and ucb L057 (Open Symbol) in Epileptic Pediatric Subjects Ranging in Age from 1 Month to Less Than 4 Years Old Following a Single Oral Administration of Levetiracetam Given as Oral Solution at a Target Dose of 20 mg/kg [a] (PP Population - Female Subjects by Age Group)



[a] n=2 for 1-6 months old, triangle; n=1 for 6 months-2 years old, circle; and n=2 for 2-4 years old, square. Data are presented in lin-lin scale (top) and log-lin scale (bottom)

Title (RPCE02B1402): Monocentre, open label, parallel group study of the correlation between plasma and saliva concentrations of levetiracetam after a 750-mg single oral dose, given either as 7.5 mL of a 10% oral solution or as tablets in 8 healthy male volunteers.

Objectives: 1) To assess the relationship between saliva and plasma concentrations of levetiracetam, after a 750-mg oral dose given after either as 250-mg tablets or as 7.5 mL of a 10% oral solution, using conditions that mimics the administration in pediatric patients. 2) To assess the potential for cross-contamination of saliva samples after intake of a liquid formulation 3) To gain additional information on the safety of both levetiracetam formulations.

Study Design: This was a Phase I, open-label, single dose, parallel group study in 8 adult healthy male volunteers. The mean ± SD age and weight were 38.48 ± 10.04 years and 78.63 ± 3.38 kg, respectively. The BMI from 19 to 28 kg/m^2. During the study treatment, four subjects received under fasting conditions the following: 7.5-mL (100 mg/mL) levetiracetam 10% oral solution. During the same study period, the other four subjects (group 2) received under fasting conditions three 250 mg levetiracetam oral tablets. The batch numbers for levetiracetam oral solution was 11363 and batch number for the tablets was 1494.

Plasma and saliva samples for pharmacokinetic analysis were obtained at pre-dose (0), 0.25, 0.5, 1, 2, 4, 6, 9, 12 and 24 hours. Blood (5 mL) and saliva (about 1 to 2 mL) samples were obtained at each time point for assay of parent drug. To collect saliva, the subject spit the saliva into a small plastic cup. Then, the saliva was transferred into the storage tube using a pipette. The minimum volume requirement was 0.5 mL. Salivation was eventually augmented by chewing on a small piece of Parafilm™ or equivalent. Drinking or eating was prohibited one hour before each sampling.

Analytical Method: Plasma and saliva levetiracetam concentrations were determined using a validated gas chromatographic methods. The saliva samples were frozen at about -20°C until analyzed. The limits of quantitation (LOQ) of the assay for levetiracetam in saliva and plasma were both 0.5 µg/mL.

Data Analysis: The relationship between plasma and saliva concentrations of levetiracetam was evaluated using a linear regression approach. Linear regression analysis of the saliva/plasma ratio in function of the plasma concentration was established for each formulation from 0.25h onward. Similarly linear regression analysis of the plasma concentration in function of the saliva concentration was established for each formulation from the first time pose-dose and a linear regression analysis of the plasma concentration in function of the saliva concentration was established for each formulation from the first time post-dose. Slope and intercept of these linear regressions together with their 95% confidence intervals were estimated. Residual analysis against concentration was used for validation of the regression model.

Results: Mean plasma and saliva concentration time profile are provided in the attachments. After administration of the oral solution, the levetiracetam plasma level increased up to a maximum ranging from 13.9 to 20.2 µg/mL. The peak was reached in about 0.5 to 1 hour after administration. The maximum levetiracetam saliva concentration was observed in 15 mins after intake of the oral solution and ranged from between 78 to 227 µg/mL. The saliva concentration decreased rapidly and reached a concentration on average approximately 1.5 times higher than the plasma concentration 4 hours after administration. Then, the saliva and plasma concentrations versus time profiles paralleled each other until the end of the collection period. After

administration of the oral tablets, the levetiracetam concentration was higher in the saliva than in the plasma, but the saliva/plasma ratio remained. The average saliva/plasma ratio ranged from 1.06 to 1.37. Simple linear regression allowed an estimation of the plasma from the concentration measured in the saliva for the whole range of 24 hours post-dose after administration of the tablets and for the range from 2 to 24 hour post-dose after administration of the oral solution. Statistical analysis of the saliva/plasma ratio after administration of the oral solution detected highly significant time effect ($p<0.001$). Pairwise comparisons showed that this time effect was due to a significantly higher ratios at the first time point than at following time points. Comparisons between samples taken between 0.5 h and 24 hour did not detect any significant difference. Individual saliva vs plasma concentration relationship was fitted by a linear model over the entire sampling time after administration of the tablets (R^2 ranging from 0.66 to 0.86) and from 4 hours post-dose after the administration of the solution (R^2 ranging from 0.66 to 0.97).

Pharmacokinetic Summary: After administration of the oral solution, the maximum levetiracetam saliva concentration was observed at the first time point (15 min) and was 19 to 74 times higher than the corresponding plasma level. The sponsor states that this high level was due to the contamination of the saliva samples by the oral solution still remaining in the mouth. Statistical analysis detected a significant effect of time on the ratio. The saliva/plasma ratio rapidly decreased and became stable from 4 hour post-dose onwards. After administration of a 750-mg levetiracetam oral dose as the 250-mg tablets, the saliva and plasma profiles were parallel, with saliva levels higher than plasma levels. The average saliva/plasma ratio remained constant during the 24-hour observation period, and ranged from 1.06 to 1.37. No significant time effect was detected.

The results of the present study showed that the levetiracetam concentration was higher in saliva than in the plasma. The saliva/plasma ratio was similar for the two formulations. Based on the regression analysis, the saliva/plasma ratio was 1.75 after the oral solution (data from 4 hour post dose) and 1.31 after the oral tablets. A ratio of 1.58 was obtained when the data from both treatments were analyzed (data from 4 hour post dose).

Safety Summary: The two formulations were reported to be well tolerated. None of the subjects reported adverse events after intake of the study medication.

Reviewer: Salivation concentrations were higher than plasma concentrations, especially for the oral solution at the early time points of analysis. There was a correlation between plasma concentrations and saliva concentration. The correlation coefficient was less than 0.9 for both oral solution and the tablet. (b) (4)

Figure 11:1: Average saliva and plasma concentrations (± SD) vs. time profiles after administration of 7.5-mL (100 mg/mL) levetiracetam 10 % oral solution. (top: log-linear scales; bottom: linear scales; n=4).

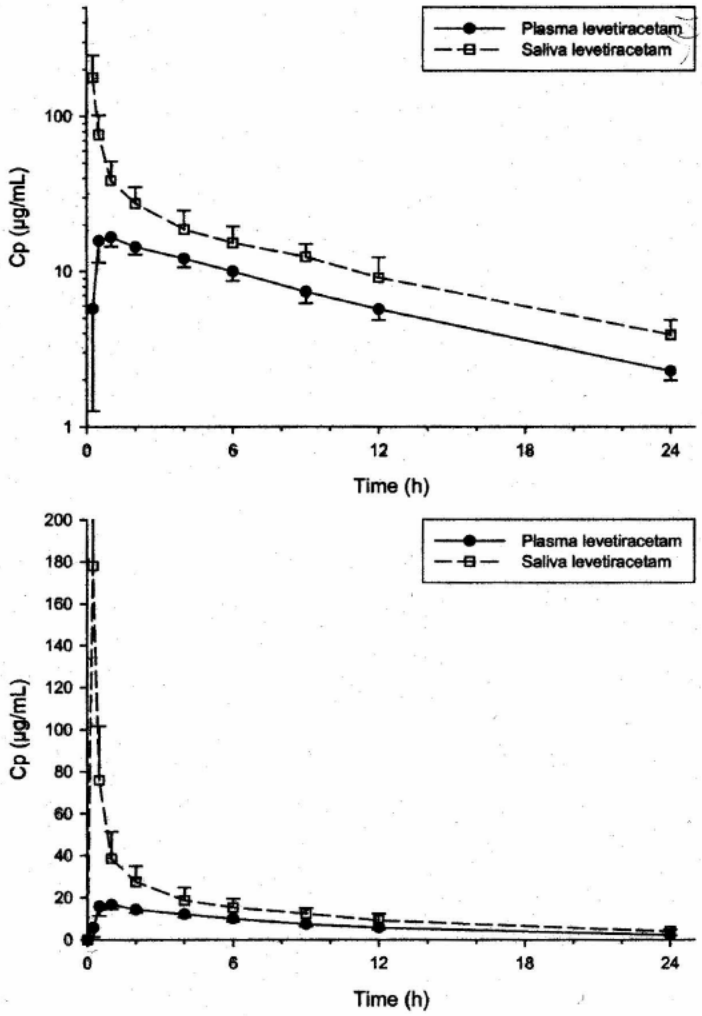


Figure 11:2: Average saliva and plasma concentrations (± SD) vs. time profiles after administration of 3 x 250-mg levetiracetam oral tablets.
(top: log-linear scales; bottom: linear scales; n=4).

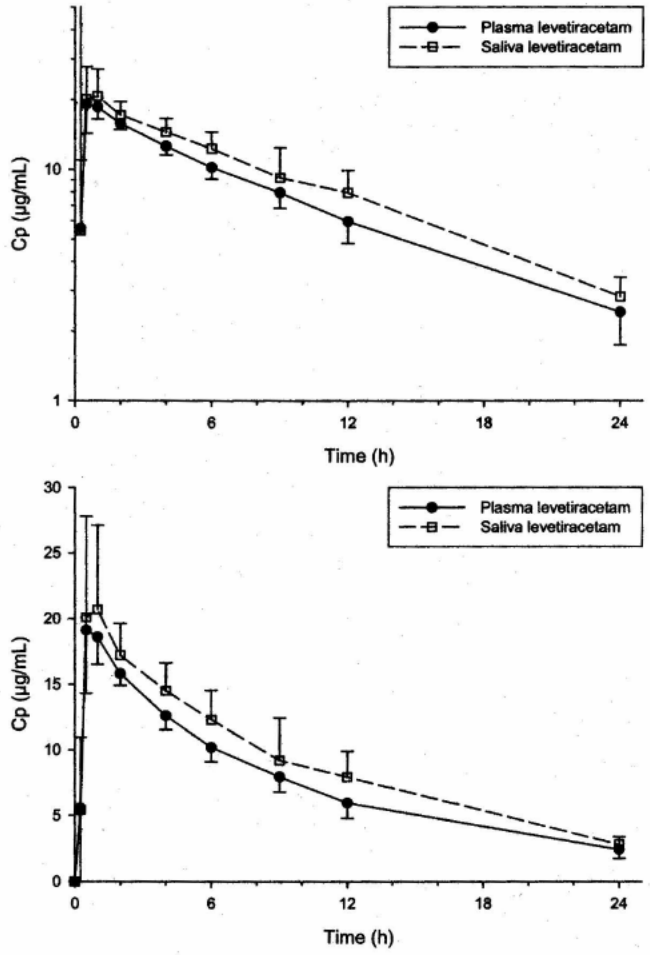


Figure 11:3: Average saliva/plasma concentrations ratio (± SD) vs. time profiles after administration of 7.5-mL (100 mg/mL) levetiracetam 10 % oral solution. (linear scales; n=4).

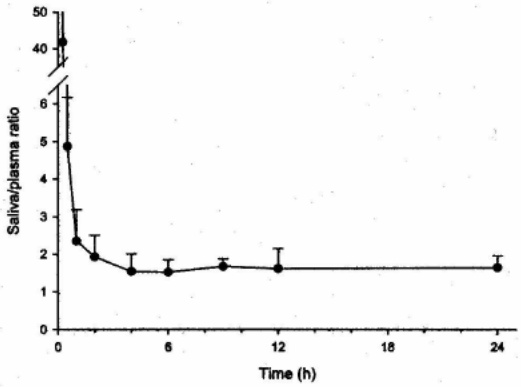
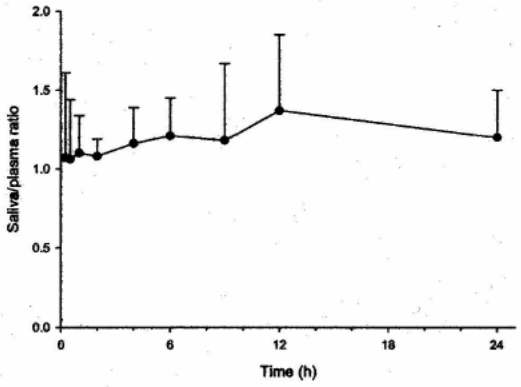


Figure 11:4: Average saliva/plasma concentrations ratio (± SD) vs. time profiles after administration of 3 x 250-mg levetiracetam oral tablets. (linear scales; n=4).



Title (Study N01139): Retrospective population pharmacokinetic analysis of levetiracetam in children with epilepsy (1-month to 16 –year)- including determination of significant covariates- and assessment of potential drug interaction on or by concomitant antiepileptic drugs.

Objectives: 1) To characterize the pharmacokinetics of levetiracetam in pediatric subjects, including estimation of the inter- and intra- individual variability in the main pharmacokinetic parameters, using data pooled from 5 clinical trials. 2) To identify important demographic and/or physiologic determinants of levetiracetam disposition, including if possible a potential influence of concomitant antiepileptic drugs (AEDs), in that population. 3) To assess dose linearity, i.e. independence of the PK parameters (KA, Cl/F) to the dose. 4) To define optimal dosing regimens in function of the relevant covariates. 5) To evaluate the effect of levetiracetam on the plasma concentrations of other AEDs (drug-drug interactions) in a pediatric epileptic population. The AEDs investigated were carbamazepine (CBZ), valproate (VPA), topiramate (TPM) and lamotrigine (LTG) as they are the most frequently co-administered drugs in the studies.

Study Design: This was a retrospective analysis based on data from 5 studies (N151, N159, N01010, N01052 and N157) each including both genders. In all the studies, the doses were divided as 2 equal doses given b.i.d., apart from N01052 which was a single dose. All the studies except N159 were open studies. N01052 and N01010 were single and multiple dose PK studies, conducted in 13 (1 month to 4 years old) and 21 (4 to 12 years old) children with epilepsy respectively, receiving solution (20 mg/kg/day) or tablet (20 to 60 mg/kg/day). N151 was an open-label exploratory study in which 24 children with epilepsy (6 to 12 years old) were administered oral tablets of levetiracetam at doses ranging from 10 to 40 mg/kg/day. N159 study was a therapeutic confirmatory, double blind placebo-controlled study to evaluate efficacy and safety of levetiracetam (up to 60 mg/kg/day as oral tablet). Two hundred and sixteen children with epilepsy (4 to 16 years) were enrolled in the study, half of whom received levetiracetam. Seven pre-dose samples were to be taken per subject. N157 was an open-label, long term follow-up study of the 4 previously mentioned studies. The children received levetiracetam (oral tablet or solution) at individualized doses (maximum 60 mg/kg/day). The mean age and weight of the patients 9.56 ± 3.67 years and 35.2 ± 17.3 kg. The mean BSA was 1.12 ± 0.36 m^2
An evaluable subject was one having a baseline concentration and at least one plasma concentration in evaluation period, who received at least two-week constant dose of investigational study medication (LEV/placebo), who kept a constant AED dose(s) and received the same dose AED for at least 14 days during baseline.

Levetiracetam was administered orally in various formulations (100 mg/mL solution, various strengths of tablets) and dosage regimens in the different studies. Levetiracetam was administered twice a day. The duration of treatment ranged from one day up to several years. The AED studied included CBZ, TPM, LTG, VPA, phenytoin, oxycarbazepine, felbamate, gabapentin, phenobarbital. The primary variable was the difference between the log-transformed concentration of a given AED per visit in the evaluation period and the log-transformed mean concentration of that AED at a baseline. The following table contains a summary of the study designs.

Summary of Study Designs

Study Number	Type	Number (Age in years)	Formulation and Dose (mg/kg/day)	PK Samples for LEV	AEDs (max)	PK Samples for AED
N151	Exploratory	24 (6 to 12)	Tablet 10 to 40	1 full PK to 24 hours + 5 pre-dose + 3 post-dose	1	Trough pre visit
N159	Pivotal Efficacy and Safety	216 (4 to 16) ½ on LEV	Tablets 20 to 60	7 pre-dose	2	Trough per visit
N01010	Multiple dose PK	21 (4 to 12)	Tablets 20 to 60	3 full profiles to 12 hours	1 (CBZ or VPA)	Trough per visit
N01052	Single dose PK	13 (1 month to 4 years)	Solution 20	1 full to 24 hours	2	Trough at baseline
N157	Follow up of 4-previous studies	239 (1 month to 16 years)	Solution or Tablets Up to 60	Trough	2	Trough at baseline

Data Analysis: Levetiracetam plasma concentrations from 228 patients were used for non-linear mixed effects modeling by extended least squares regression using NONMEM. The analysis strategy was first to select a basic model, then to perform both a univariate and a multivariate forward selection analyses to get a full model including covariates, followed then by a backward elimination analysis. The association between the pharmacokinetic parameters and the covariates age, gender, race, body weight (BW), BMI, BSA, Dose, Clcr and categories of concomitant AEDs were examined in the univariate and forward selection analyses. To obtain dosing recommendation for starting treatment with levetiracetam in children, simulations of different dosing regimens were performed to achieve similar concentrations to those reached in adults at the recommended starting dose (500 mg b.i.d). AEDs were grouped into 4 categories: neutral (agents considered having no effect on drug metabolizing capacity), inducer (enzyme inducers alone or in combination with AEDs from the first group), inhibitor (alone or in combination with AEDs from the first group) and others (combination of inducer and inhibitor) to try and assess the potential effect of the different groups on LEV PK.

The population analysis from the model development using log-transformed concentrations showed a one-compartment open model with first-order absorption and elimination, and first order method to best characterize plasma concentration versus time profiles of LEV in children. Initially, a model with CL/F, V/F and KA as the structural parameters, with an exponential error term for inter-individual variability on CL/F and V/F and a proportional error term on residual variability for all concentrations was examined. To minimize the objective function, it was decided to include η and IOV on KA, as the vast majority of the children had blood samples on

more than one occasion. This addition resulted in a decreased OBJF. The error model selected for residual variability was a proportional one. A model with three structural parameters (CL/F, V/F and KA), exponential error terms for inter-individual variability on each parameter and IOV on KA, proportional error model (coded as additive in the log-transformed domain) and using the log transformed concentrations was used as the Base 1 and used in the analyses. The power model describing the effect of body weight on levetiracetam CL/F had the largest decrease in OBJF and was termed BASE 2 model for the subsequent forward selection analysis. The effects of 8 other covariates were included in the model. Similar to univariate selection, all 8 covariates were included one by one in model BASE 2. The process was repeated until no covariate inclusion lead to a significant decrease in OBJ function. The final model evaluated the effect of BW on CL/F and BW on V/F, effect of AEDC on CL/F, and effect of Dose on CL/F, and effect of AGE on KA and effect of CL_{CR} The final population pharmacokinetic was used in simulations of dosing regimen. The dosage schemes considered for simulations were based on available formulations. The various dosing scenarios are provided in the following table.

Possible Dose Adjustment Rules for Levetiracetam in Children Tested in Simulations

Scenario	Adults Reference	Children		
		Step 1	Step 2	Step 3
1	100 – 50 kg 500 mg b.i.d.	70 – 50 kg 500 mg b.i.d.	50 – 25 kg 250 mg b.i.d.	< 25 kg 7.5 mg/kg b.i.d
2	100 – 50 kg 500 mg b.i.d.	70 – 50 kg 500 mg b.i.d.	50 – 25 kg 250 mg b.i.d.	< 25 kg 10 mg/kg b.i.d.
3	100 – 50 kg 500 mg b.i.d.	70 – 40 kg 500 mg b.i.d.	40 – 20 kg 250 mg b.i.d.	< 20 kg 10 mg/kg b.i.d.
4	100 – 50 kg 500 mg b.i.d.	70 – 50 kg 500 mg b.i.d.	< 50 kg 10 mg/kg b.i.d.	--

Pharmacokinetic Results:

Scatter plots of population predicted and individual predicted vs. observed concentrations showed even distribution around the line of unity. Scatter plots of weighted residuals vs. population predicted concentration and vs. time showed the WRES to be evenly distributed. The parameters of the structural model (KA, CL/F, V/F) were estimated with %CV of 15% for KA, < 5% for CL/F and V/F. The relationship between the parameters and the statistically significant covariates are

KA = 1.46*(AGE/10)**0.27

If the subject takes a concomitant inducing AED,

Cl/F = 2.17* (BW/30) **0.640*(DoSE/500)**0.0443*(CLCR/100)**0.111*1.22

V/F = 2.15*(BW/30)**0.901

The inter-individual variability for levetiracetam for CL/F and V/F was 19.0% and 19.1%, respectively. The inter-individual variability for KA was 100%. The interindividual variance parameters were estimated with %CV of 16.8% for CL/F and 60.8% for V/F. The residual variability (CV) in levetiracetam concentration was estimated at 30.5%.

To evaluate the relative influence of the covariates on CL/F, the contributing factors of each covariate in the model have been calculated. For each covariate, the correction factor to estimate CL/F for each group has been calculated based on the median. A final and a reduced models (without Dose and CL_{cr}) were ran and compared. The differences between the two models were minimal except for $\theta_{CL, BW}$ which increased from 0.64 to 0.753 as would be expected. The significant effect of Dose and CL_{CR} is likely due to a confounding effect with body weight: as children get older, their body weight increase and so do the absolute dose and CL_{CR}. The population estimates of CL/F, V/F and t ½

Population Estimates of CL/F, V/F and T ½

Categories		Population Estimates				
Median AGE (y)	Median BW (kg)	CL/F (L/h)		V/F (L)	T ½ (h)	
		No inducer	Inducer		No inducer	Inducer
6.12	19.0	1.55	1.89	14.2	6.36	5.22
8.10	24.5	1.86	2.27	17.9	6.66	5.46
10.2	31.4	2.23	2.73	22.4	6.95	5.70
10.9	37.3	2.55	3.11	26.2	7.11	5.83
11.9	46.5	3.03	3.69	31.9	7.31	5.99
14.2	67.8	3.95	4.82	44.8	7.86	6.44

Since the rate of increase of CL/F with body weight is slower than that of V/F, the half-life increased by about 25% over the weight range presented. The half-life is estimated to be 22% shorter in children receiving an inducing concomitant AED.

The ratio of the metabolite (L057) to LEV was about 0.05 which is similar to the values found in adults. Over the age range studied, the ratio seems constant vs. age.

Summary of POPPK Analysis

Levetiracetam concentration vs. time profiles were available after single and multiple dosage regimens of levetiracetam in 228 children suffering from epilepsy, majority with partial onset seizures, from 1 month to 18 years of age with body weight ranging between 6 and 101 kg. A one compartment model with first order absorption and first-order elimination was found to best characterize the plasma concentration-time profile for levetiracetam, with inter-individual variability on KA, CL/F and V/F, and inter-occasion variability (IOV) on KA. The association between the pharmacokinetic parameters KA, CL/F and V/F and the covariates age, gender, race, body weight, BMI, BSA, Dose, CL_{CR} and categories of concomitant AEDs were examined in the analysis. Weight, BSA, BMI, CL_{CR}, AGE and Dose were correlated, with very high correlation between BW and BSA. Body weight on CL/F was the most significant covariate in the univariate selection. After multiple linear regression analysis with forward selection, the significant covariates were AGE on KA, BW, DOSE, CL_{CR}, and AEDC on CL/F and BSA on V/F. Because dosing in children is generally based on either age or weight and because BSA and BW are highly correlated, BW on V/F was used instead of BSA. In the final model, the only significant effect is body weight on both CL/F and V/F and of the AED categories on CL/F. Both CL/F and V/F were linked to BW by a power function with the exponent equal to 0.901 for V/F and for CL/F 0.640. As CL/F increased with body weight more slowly than V/F, the terminal half-life increased with body weight, the terminal half-life increased with body weight from 6.4 hours for 19 kg to 7.86 for 68 kg. AED categories (AEDC) had an effect on CL/F. The CL/F of the children receiving inhibiting drugs, without inducing drug, was not different from the one who received only "neutral" antiepileptics. However, the children who took concomitant medications inducing

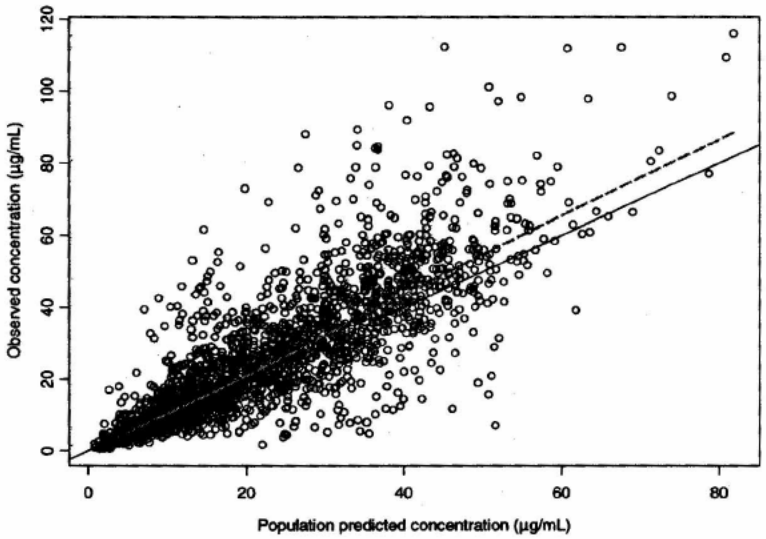
AEDs whether alone or not, had a higher CL/F than the children who did not. A mean increase of about 22% was estimated by the model. The resulting terminal half-life in children receiving inducing AEDs with body weight ranging from 19 to 68 kg was calculated as 5.22 h and 6.44 h, respectively. KA was found to increase with age. This is not a confounding factor of the formulation: the smaller children received the solution, hence, if the effect of the age on KA was a formulation effect, a decrease with age would have been expected. Even though enzyme inducing AEDs as a class (CBZ, PHT, PB or PRM) were found to increase the clearance of levetiracetam, dose adjustment is not recommended considering the reported broad efficacy and safety margin of levetiracetam and the therapeutic approach of individual up- titration.

Based on the modeling and simulation, for children weighing less than 50 kg the dosage regimen of 20 mg/kg/day predicts steady state Cmin and Cmax values within the ranges observed in adults receiving 1000 mg/day. A dosing recommendation of 20 mg/kg/day for children weighing less than 50 kg, and 1000 mg/day, similar to adults, for children above 50 kg is recommended. To take advantage of the formulations of levetiracetam currently marketed, another dosing recommendation would be 20 mg/kg/day as a solution for children weighing less than 20 kg, then 500 mg/day for children weighing between 20 to 40 kg, then 1000 mg/day for children above 40 kg. The clinical pivotal clinical study studied doses starting at 20 mg/kg/day escalating every 2 weeks up to 60 mg/kg/day. The sponsor is recommending a dosing regimen starting at 20 mg/kg/day given in 2 divided doses and could escalate every 2 weeks up to a maximum of 60 mg/kg/day in two divided doses.

Reviewer Comments:

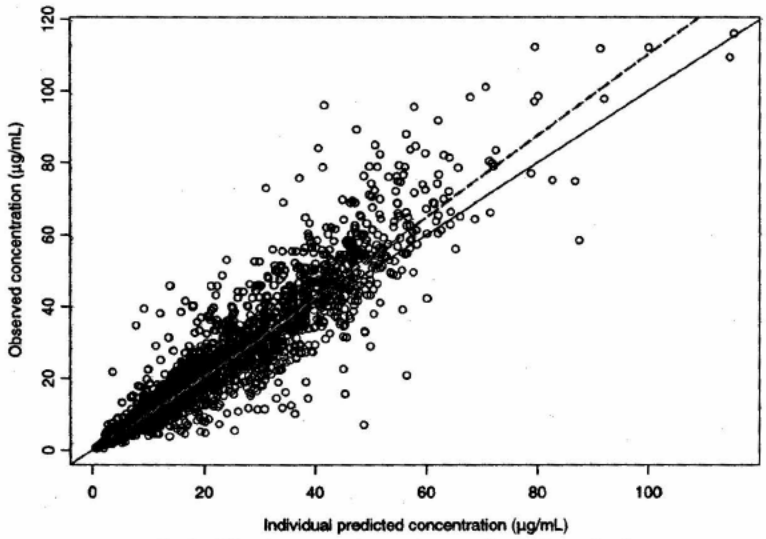
The population pharmacokinetic analysis revealed that body weight was the most important factor in determining the dosage regimen of levetiracetam in children. In addition, simulations revealed that children weighing less than 50 kg could be dosed at 10 mg/kg b.i.d. to obtain concentrations as adults receiving 500 mg b.i.d. Based on the modeling and simulation performed, the proposed dosing regimen renders similar concentrations in pediatrics and adults.

Figure 11.2:3 Goodness of Fit Plot for Final Model: Observed vs. Population Predicted Levetiracetam Concentrations for Final Model



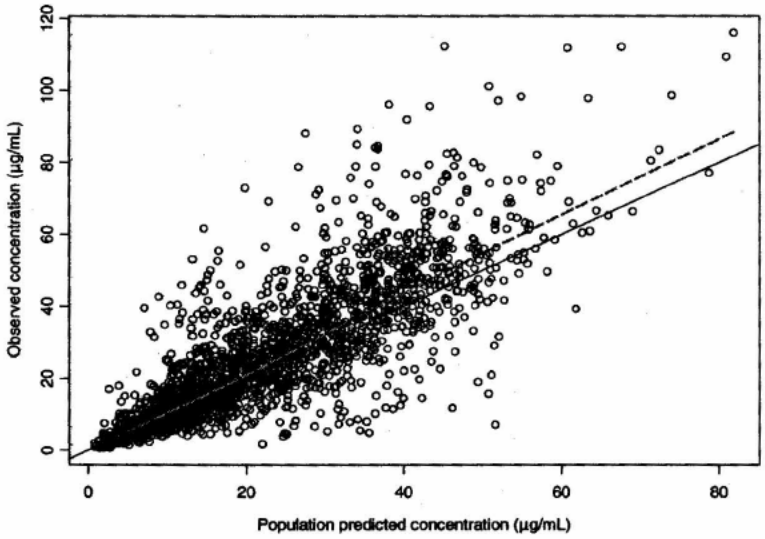
Dashed line is a smooth, continuous line is line of unity

Figure 112:4 Goodness of Fit Plot for Final Model: Observed vs. Individual Predicted Levetiracetam Concentrations



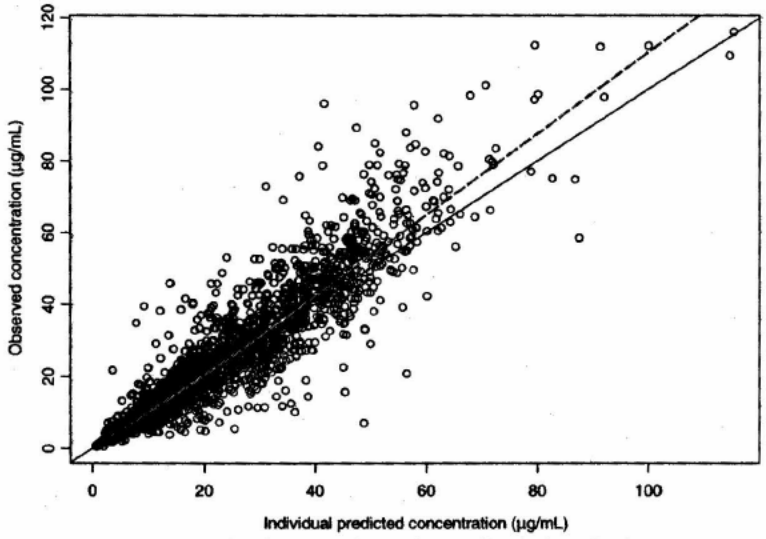
Dashed line is a smooth, continuous line is line of unity

Figure 11.2:3 Goodness of Fit Plot for Final Model: Observed vs. Population Predicted Levetiracetam Concentrations for Final Model



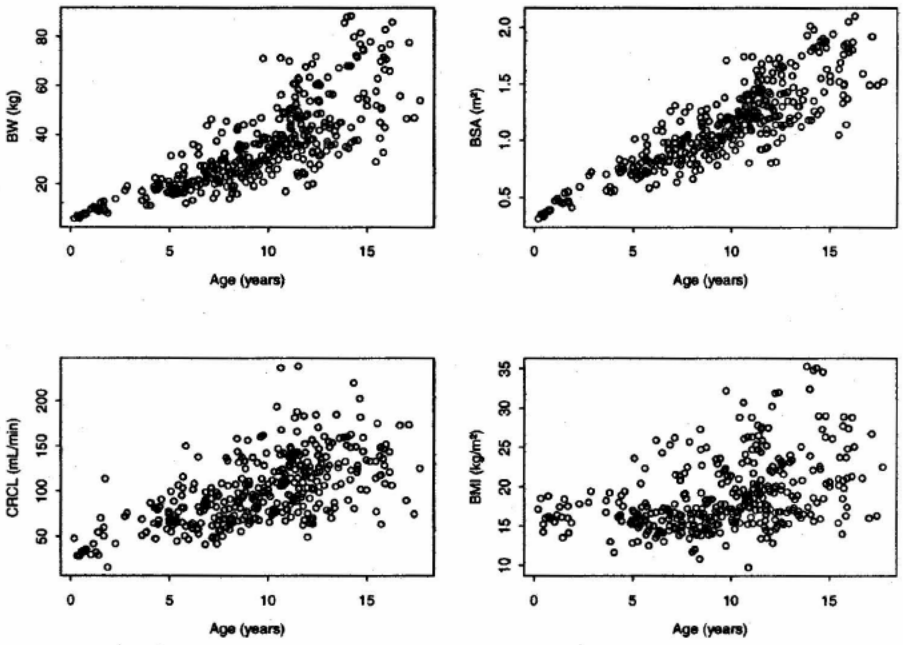
Dashed line is a smooth, continuous line is line of unity

Figure 112:4 Goodness of Fit Plot for Final Model: Observed vs. Individual Predicted Levetiracetam Concentrations



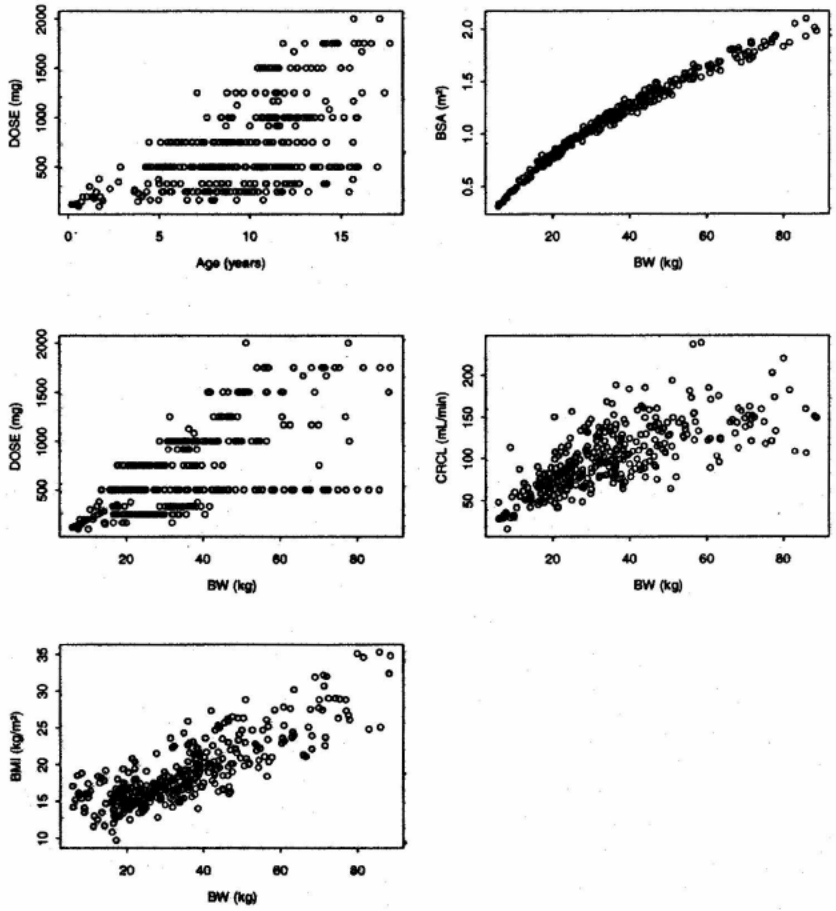
Dashed line is a smooth, continuous line is line of unity

Figure 7:3 Relation between Body Weight (BW), Body Surface Area (BSA), Creatinine Clearance (CL_{CR}) or BMI and Age – All Studies, First Visit



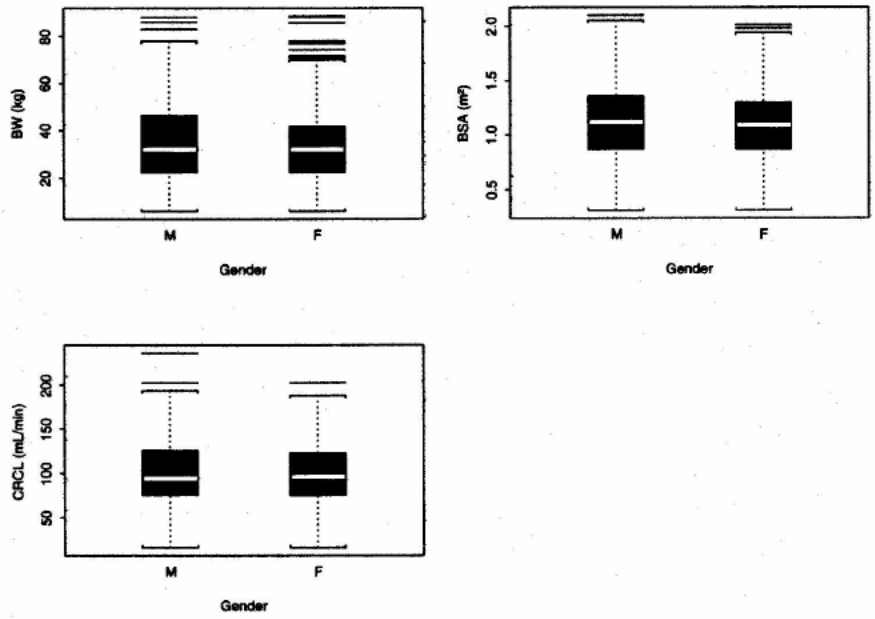
As expected, body weight, BSA and CL_{CR} increased with age and these relationships appeared to be linear (Figure 7:3) but with a wider spread as age increased.

Figure 7:4 Relation between Dose per Intake, BSA, Creatinine Clearance (CL_{CR}) or BMI and Age or Body Weight – All Studies, First Visit



Body weight and BSA were very highly correlated with an asymptotic relation (Figure 7:4).

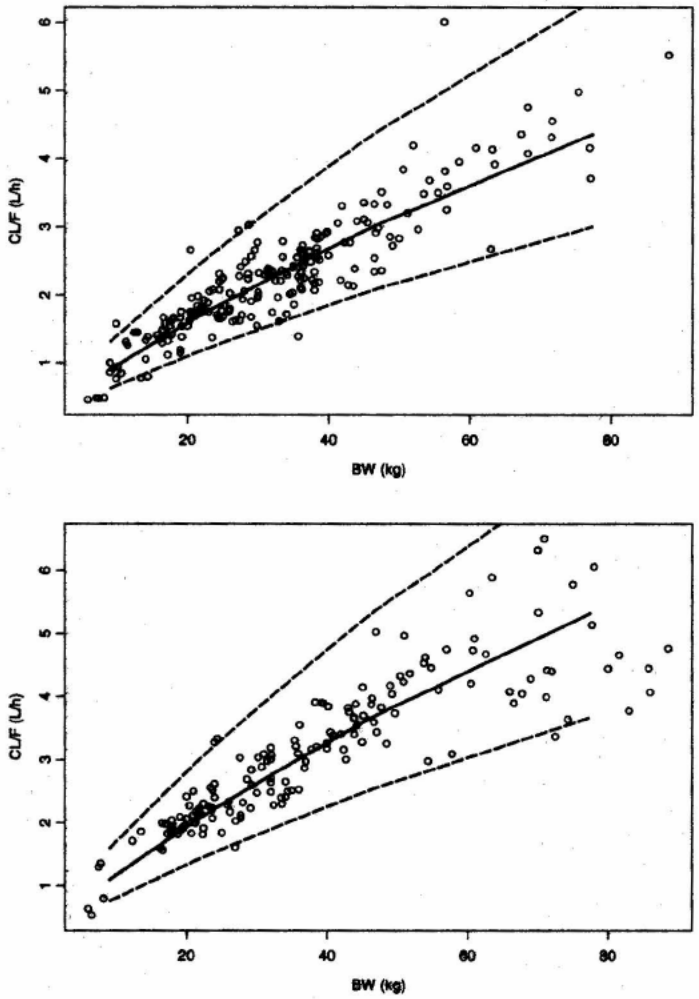
Figure 7:5 Boxplot of BW, BSA and CL_{CR} by Gender – All Studies, First Visit



There were no systematic differences in BW, BSA and CL_{CR} between gender (Figure 7:5).

The frequency distribution of age, body weight and CL_{CR} is depicted in Figure 7:6, Figure 7:7 and Figure 7:8, respectively.

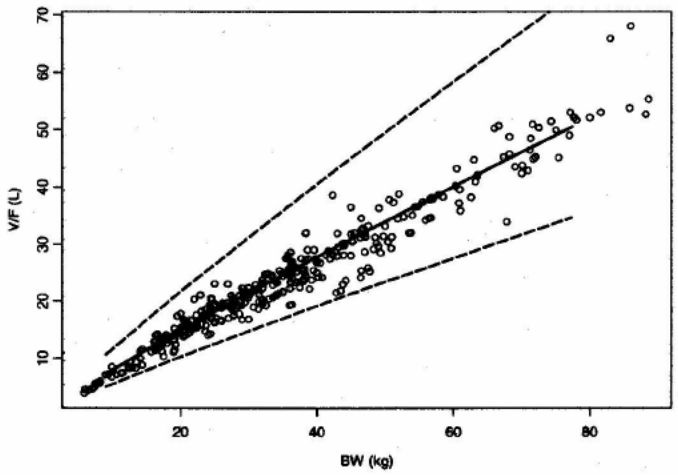
Figure 7:13 Population Prediction and Post-Hoc Estimate at First Visit for CL/F versus BW. Upper Panel: without Inducers. Lower Panel: with Inducers



Typical Value - Continuous Line - and 95% CI –Dashed Lines

For both groups, with or without inducers, the vast majority of the individual posterior estimates for CL/F were within the 95% CI.

Figure 7:14 Population Prediction (Typical Value - Continuous Line - and 95% CI – Dashed Lines) and Post-Hoc Estimate at First Visit for V/F in Function of BW



Typical Value - Continuous Line - and 95% CI –Dashed Lines

All individual posterior estimates for V/F were well within the 95% CI.

Figure 7:15 Relation Between Individual Posterior Estimates of CL/F from Final Model and BW, Dose, CL_{CR} and AEDC – All Data

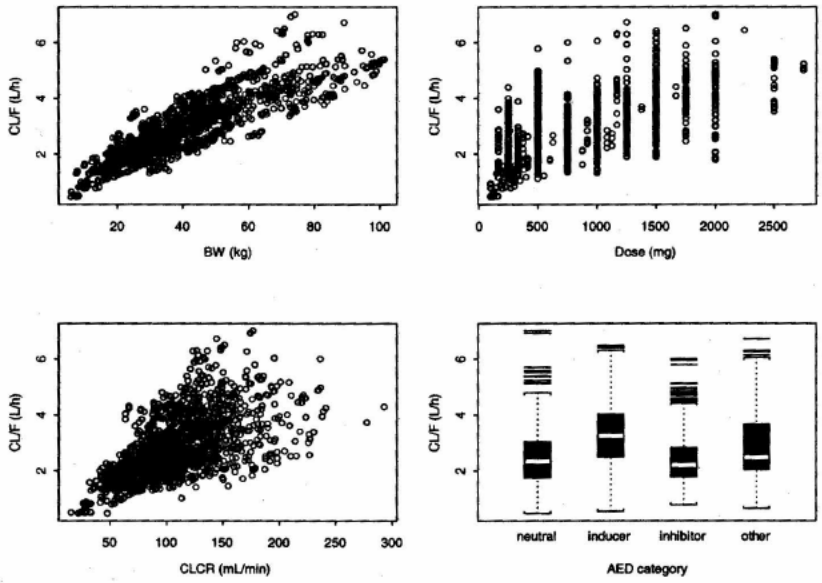


Figure 7:15 shows that levetiracetam CL/F increased with body weight, dose and CL_{CR} as predicted from the final model. However, the relative contribution of each factor appears bigger than it actually is due to the correlation between the 3 factors (see Figure 7:3 and

Table 7:3 Estimates of Population Pharmacokinetic Parameters of Levetiracetam in Children for Base 1 Model

Parameter	Estimate [95% CI]	Precision (%CV)[a]
KA= Θ_{KA} Θ_{KA} (h^{-1})	1.53 [1.13-1.93]	13.3%
CL/F = Θ_{CL} Θ_{CL} (L/h)	2.40 [2.22-2.58]	3.88%
V/F = Θ_{V} Θ_{V} (L)	25.1 [22.3-27.9]	5.62%
Variability	**Estimate in %CV[b]**	**Precision (%CV)[a]**
Inter-individual variability in CL/F	44.9%	16.2%
Inter-individual variability in V/F	64.3%	23.2%
Inter-individual variability in KA	91.2%	69.5%
Inter-occasion variability in KA	134%	27.4%
Residual variability in concentrations	29.8%	7.40%

[a] Precision was calculated as s.e. divided by the parameter estimate x 100.
[b] The %CV for both inter-individual and residual variability is an approximation taken as the square root of the variance x 100.

Table 7:6 Final Estimates of Population Pharmacokinetic Parameters of Levetiracetam in Children

Parameter	Estimate [95% CI]	Precision (%CV)[a]
$KA = \Theta_{KA} * (AGE/10)^{**} \Theta_{KA,AGE}$		
Θ_{KA} (h^{-1})	1.46 [1.04-1.88]	14.5%
$\Theta_{KA,AGE}$	0.270 [0.0583-0.482]	40.0%
$TCL2 = \Theta_{CL} * (BW/30)^{**} \Theta_{CL,BW}$ $CL/F = TCL2 * (DOSE/500)^{**} \Theta_{CL,DOSE} * (CLCR/100)^{**} \Theta_{CL,CLCR}$ If AEDC=2 or 4, $CL/F = TCL2 * \Theta_{CL,AEDC} * (DOSE/500)^{**} \Theta_{CL,DOSE} * (CLCR/100)^{**} \Theta_{CL,CLCR}$		
Θ_{CL} (L/h)	2.17 [2.09-2.25]	2.00%
$\Theta_{CL,BW}$	0.640 [0.542-0.738]	7.78%
$\Theta_{CL,AEDC}$	1.22 [1.16-1.28]	2.34%
$\Theta_{CL,DOSE}$	0.0443 [0.0112-0.0774]	38.1%
$\Theta_{CL,CLCR}$	0.111 [0.0236-0.198]	40.2%
$V/F = \Theta_{V} * (BW/30)^{**} \Theta_{V,BW}$		
Θ_{V} (L)	21.5 [20.1-22.9]	3.43%
$\Theta_{V,BW}$	0.901 [0.774-1.03]	7.19%
Variability	**Estimate in %CV[b]**	**Precision (%CV)[a]**
Inter-individual variability in CL/F	19.0%	16.8%
Inter-individual variability in V/F	19.1%	60.8%
Inter-individual variability in KA	100%	53.5%
Inter-occasion variability in KA	112%	26.8%
Residual variability in concentration	30.5%	8.30%

AEDC = 2 or 4 are the combination of AEDs that contains an inducer, either alone or not.

[a] Precision was calculated as s.e. divided by the parameter estimate x 100.

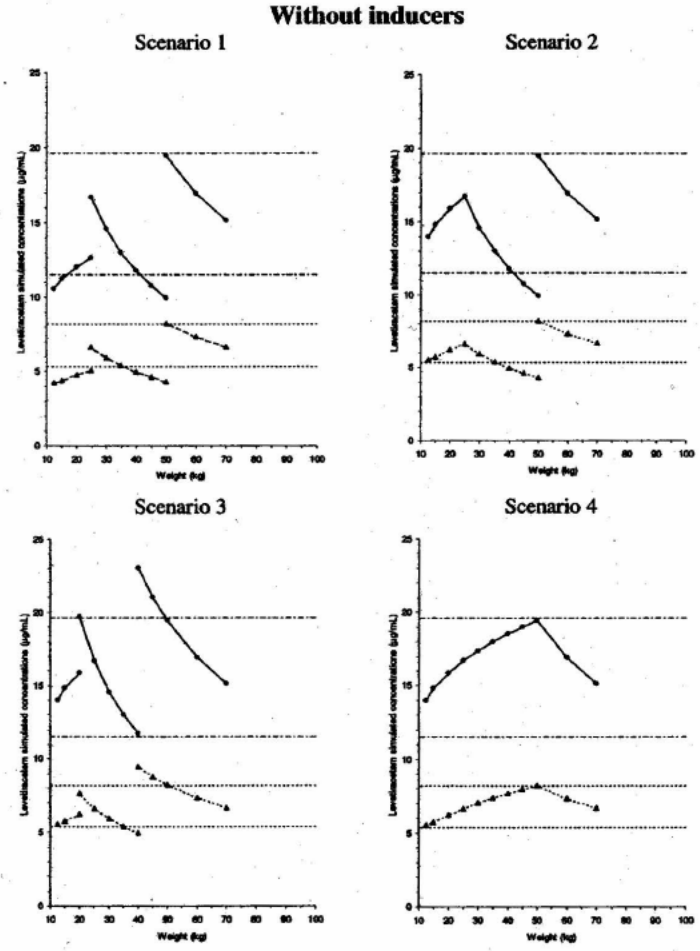
[b] The %CV for both inter-individual and residual variability is an approximation taken as the square root of the variance x 100.

Table 7:12 Simulated Levetiracetam Steady State C_{min}, C_{max} and AUCτ in Adults Receiving 500 b.i.d. and in Children Receiving Possible Body Weight Based Dosage Regimens

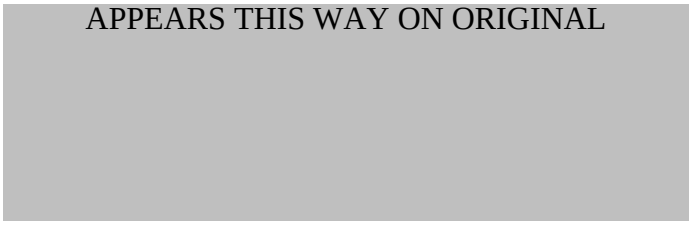
Scenario	Criteria	Dosage Per intake	Weight (kg)	Age (y)	Daily dose (mg/kg)	Without inducers			With inducers		
						C_{min} (µg/mL)	C_{max} (µg/mL)	AUCτ (µg.h/mL)	C_{min} (µg/mL)	C_{max} (µg/mL)	AUCτ (µ.h/mL)
Reference	100 -50 kg	500 mg	100	20	10	5.38	11.5	101.7	3.95	10.0	83.4
			75	20	13.3	6.41	14.4	124.6	4.68	12.6	102.2
			50	20	20	8.21	19.6	166.4	5.93	17.2	136.4
Scenario 1 and 2	70 – 50 kg	500 mg	70	20	14.3	6.68	15.1	130.8	4.87	13.2	107.2
			50	14	20	8.24	19.4	166.2	5.95	17.0	136.2
	50 – 25 kg	250 mg	50	14	10	4.32	9.9	85.7	3.13	8.7	70.2
			25	8	20	6.64	16.7	140.6	4.74	14.7	115.3
Scenario 1	≤ 25 kg	7.5 mg/kg	25	8	15	5.09	12.6	106.8	3.64	11.1	87.6
			12.5	2	15	4.25	10.6	91.1	3.02	9.3	74.7
Scenario 2	≤ 25 kg	10 mg/kg	25	8	20	6.64	16.7	140.6	4.74	14.7	115.3
			12.5	2	20	5.55	14.0	119.9	3.94	12.2	98.3
Scenario 3	70 – 40 kg	500 mg	70	20	14.3	6.68	15.1	130.8	4.87	13.2	107.2
			40	12	25	9.47	23.0	195.0	6.80	20.2	159.9
	40 – 20 kg	250 mg	40	12	12.5	4.97	11.8	100.6	3.59	10.3	82.4
			20	6	25	7.66	19.7	165.2	5.44	17.3	135.4
	≤ 20 kg	10 mg/kg	20	6	20	6.23	15.9	133.5	4.43	13.9	109.4
			12.5	2	20	5.55	14.0	119.9	3.94	12.2	98.3
Scenario 4	70 – 50 kg	500 mg	70	20	14.3	6.68	15.1	130.8	4.87	13.2	107.2
			50	14	20	8.24	19.4	166.2	5.95	17.0	136.2
	≤ 50 kg	10 mg/kg	50	14	20	8.24	19.4	166.2	5.95	17.0	136.2
			12.5	2	20	5.55	14.0	119.9	3.94	12.2	98.3

Simulated steady state levetiracetam C_{min} and C_{max} in adults receiving 500 mg b.i.d. were very similar to values reported in the literature. For example, in subjects receiving 500 mg b.i.d., mean efficacious C_{min} and C_{max} values of 5.95 µg/mL (range 3.06 – 10.03 g/mL) and 17.0 µg/mL (range 10.0 – 25.0 µg/mL), respectively, have been observed[10] . Similarly, for the same dose, Perucca et al[16] have reported a mean steady state $C_{12\,h}$ of 5.9 µg/mL and $C_{1\,h}$ of 15.1 µg/mL. In addition, Perucca and co-authors have reported a mean levetiracetam steady state $C_{12\,h}$ of 5.1 µg/mL and a $C_{1\,h}$ of 13.3 µg/mL in subjects receiving concomitant antiepileptic drug inducers. Therefore, the levetiracetam mean C_{min} and C_{max} concentrations simulated in this report for adults receiving 500 b.i.d., the recommended starting dose in adults, can be qualified as target concentrations to be reached in children for their starting dose.

Figure 7:17 Simulated Levetiracetam Steady State C_{min} (Dotted Line, Triangles) and C_{max} (Continuous Line, Circles) in Children Receiving a Possible Body Weight Based Dosage Regimen. Horizontal Lines Represent the Simulated C_{min} (Dotted) and C_{max} (Dashed) Ranges in Adults. Upper Panel: without Concomitant Enzyme Inducing AEDs, Lower Panel: with Concomitant Enzyme Inducing AEDs



Scenarios are described in Table 7:11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