OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDAs	21035
Submission Dates	03/18/2008
Brand Name	KEPPRA® (250mg, 500, 750, 1000 mg tablet, and 100 mg/ml liquid)
Generic Name	Levetiracetam
Reviewer	Hao Zhu, Ph.D.
	Ju-Ping Lai, Ph.D.
Pharmacometrics Team Leader	Jogarao Gobburu, Ph.D.
Clinical Pharmacology Team Leader	Ramana Uppoor, Ph.D.
OCP Division	DCP (HFD-860)
OND Division	DNP (HFD-120)
Sponsor	UCB, Inc.
Relevant IND	45151
Submission Type	SE5 (Pediatric Supplement in response to Pediatric Written Request)

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1 EXECUTIVE SUMMARY

The sponsor seeks approval of levetiracetam as adjunctive therapy in treating partial onset seizure in pediatric patients 1 month to less than 4 years of age under the Section 505 (b) of the Federal Food, Drug, and Cosmetic Act. The submission is made to fulfill the Written Request issued on 21 August 2001 and amended on 22 March 2002, 03 July 2002, 10 May 2004, 23 July 2004, and 31 January 2006. Following the Written Request, the sponsor conducted one traditional PK study (N01052), one primary efficacy and safety study (N01009), one 12-week safety study (N01103), and two long-term safety studies (N157 and N01148) in this age group. Pharmacokinetic samples were also collected in 3 studies (N01148, N01103, and N01009) and pharmacokinetic properties in pediatric patients 1 month and less than 4 years of age are evaluated.

Our findings, based on the exposure-response analyses, are:

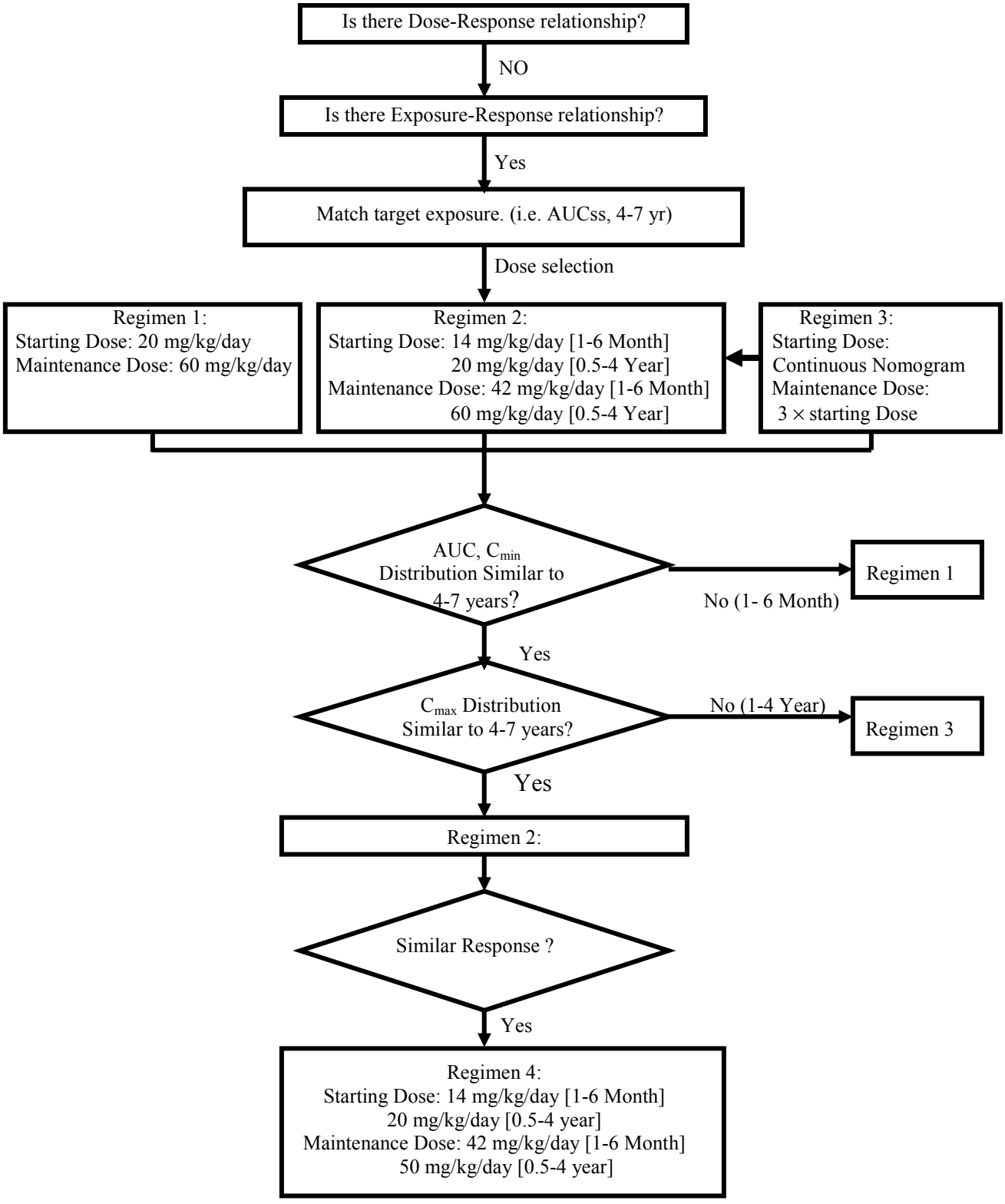
- There is evidence to suggest that levetiracetam is efficacious in the treatment of pediatric patients down to 1 month – 6 month old.
    - In Study N01009, the levetiracetam group exhibited consistently greater percent seizure reduction from baseline compared to placebo group across different age groups – including 1 to 6 month olds.

- A two-step dosing, which is illustrated in Table 1 is recommended.
    - Our recommended dose is similar to the sponsor's proposal, except we recommend that the maintenance dose for pediatric patients 6 month to 4 years of age is 50 mg/kg/day, (b) (4) .
    - Our recommended dose is derived based on the decision tree illustrated in Figure 1.

Table 1 Difference between the Clinical Evaluated Doses, the Sponsor Proposed Doses and the Reviewer Recommended Doses

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

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



1.1 Recommendations

The sponsor demonstrated that levetiracetam is efficacious in treating partial onset seizure for pediatric patients down to 1 – 6 month old. We recommend a different two-step dose regimen based on the modeling and simulation evaluation (Table 1, reviewer's recommended dose). The pharmacokinetic characteristics of levetiracetam, including the relevant covariate effects, in pediatric patients aged 1month – 4 years have been adequately evaluated. We recommend the sponsor fully evaluate the race effect on levetiracetam pharmacokinetics by pooling PK observations from different trials.

The Office of Clinical Pharmacology has found this sNDA to be acceptable provided that satisfactory agreement is reached between the sponsor and the division regarding the language in the package insert (PI) and patient prescription information (PPI). Recommendations for consideration for the final labeling are included in the Labeling Section (Section 3) of the review.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

In addition to the findings summarized previously in the executive summary, we also found:

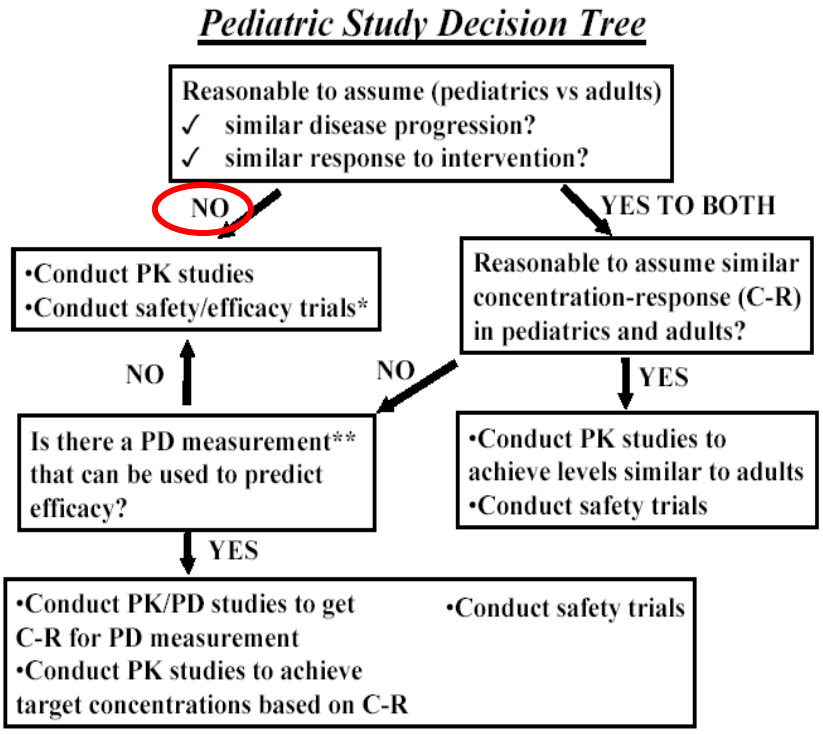
- An adequate link has been established between the commercial formulations and the clinical trial formulations in clinical development for pediatric studies. Totally five different investigational tablet formulations and one oral solution were used in the pediatric development program. Different tablet formulation strengths (250 mg, 500 mg, 750 mg, and 1000 mg) and the oral solution (100 mg/mL) are approved products. The oral solution has been previously shown to be bioequivalent to the marketed tablets. Additional 250 mg, 166 mg and 166.5 mg levetiracetam tablets were developed for blinding purposes in the studies. Because levetiracetam is a BCS Class I drug, the dissolution test is adequate to compare the different formulations. A comparative dissolution profile of the tablets indicates that almost 100% is dissolved in 15 minutes for all the strengths used in the clinical studies.

- The pharmacokinetics of levetiracetam has been adequately characterized in pediatric patients aged 1 month – 4 years. Based on population pharmacokinetic results, both clearance and volume of distribution increase as the patient body weight and age increase. Besides body weight effect, age mainly affects clearance in patients less than 3 years old. No clinically meaningful drug-drug interaction has been identified.

- A consistent exposure-response relationship has been identified across pediatric patients in different age groups and adults. Exposure is defined as steady state AUC. The response is defined as percentage seizure reduction from baseline. The same dose in pediatric patients with different body weights will result in different exposures. Therefore, the simulation the sponsor conducted to derive dosing recommendations in pediatric patients 1 month to 6 month of age based on the dose-response (and not exposure-response) model developed in pediatric patients aged 4 – 16 years is not acceptable. The reviewer

conducted exposure-response analysis, which forms the basis for the dosing recommendations.

1.4 Pediatric Decision Tree



Indication: Levetiracetam is indicated in the treatment of adults with partial onset seizure, myoclonic seizure, and primary generalized tonic-clonic seizure. The sponsor has gained approval in treating partial onset seizure in pediatric patients aged 4-16 years. In the current submission, the sponsor is seeking approval in the treatment of partial onset seizure in pediatric patients 1 month to 4 years of age.

1. Is it reasonable to assume that pediatric patients are similar to adults with regard to disease progression?

- No. There is no adequate reason to assume that pediatric patients with partial onset seizure are similar to adults on disease progression. In addition, seizure measurements are performed using vEEG in pediatric patients and in adults the seizure episodes are recorded.

2. Is it reasonable to assume that pediatric patients are similar to adults with regard to response to intervention?

- No. Pediatric patients can be more refractory than adults with regard to response to drug intervention. Drugs shown to be effective in older pediatric patients (> 2yrs) were not found to be efficacious in younger pediatric patients.

Because two "No" to the two questions in Box 1, the Pediatric Study Decision Tree suggests:

- Conducting PK studies
- Conducting safety and efficacy trials

These studies were performed by the Sponsor.

1.5 **Written Request (WR) Fulfillment-Clinical Pharmacology Related**

The following table (Table 2) summarized CP-related WR requests and information submitted:

Table 2 Summary of the Clinical pharmacology Written Requests and Relevant Information Submitted

<table>
<tr><th>WR Items</th><th>Information Submitted</th></tr>
<tr><td>Pharmacokinetic study
(1 month to 16 years)</td><td>(1) Sponsor performed 3 traditional PK studies in age groups of 1 month to 12 years. The studies are listed below:
• Study N01052 –1 month to < 4 years
• Study N01010 –4 to 12 years
• Study N151 –5 to 12 years

(2) Sponsor performed 2 population pharmacokinetic analyses which covered age of 1 month to 16 years.
• N01139 was submitted previously
• N01288 was submitted in this sNDA</td></tr>
<tr><td>To determine the steady-state pharmacokinetics and to support dose selection in pediatric patients with partial onset seizures ages 1 month to 16 years.</td><td>Steady-state pharmacokinetics was determined by a traditional multiple dose PK (N01010), and population PK analysis (N01288) of sparse samples after multiple dosing in several studies (N01052, N151, N01009, N01103 and N01148). 2 population pharmacokinetic analyses (N01139 and N01288), and a dose-response report (N01308) supported dose selection in pediatric patients with partial onset seizures ages 1 month to 16 years.</td></tr>
<tr><td>Age group and population in which study will be performed:

1 month to 16 years</td><td>(1) Traditional PK: At least 6 patients were included in each of the age groups.
<table>
<tr><th>Age Range</th><th>Number of Patients</th><th>Total</th></tr>
<tr><td>1 month < 2 years</td><td></td><td>9</td></tr>
<tr><td>N01052</td><td>9</td><td></td></tr>
<tr><td>2 years < 6 years</td><td></td><td>8</td></tr>
<tr><td>N01052</td><td>4</td><td></td></tr>
<tr><td>N01010</td><td>1</td><td></td></tr>
<tr><td>N151</td><td>3</td><td></td></tr>
<tr><td>6 years < 12 years</td><td></td><td>32</td></tr>
<tr><td>N01010</td><td>15 (14 for PPK)</td><td></td></tr>
<tr><td>N151</td><td>17</td><td></td></tr>
<tr><td>12 years to 16 years</td><td></td><td>9</td></tr>
<tr><td>N01010</td><td>5 (4 for PPK)</td><td></td></tr>
<tr><td>N151</td><td>4</td><td></td></tr>
</table>
</td></tr>
</table>

(2) Population PK (N01288): Total of 197 patients were included in the population PK analysis.

Age Range	Number of Patients	Total
1 month < 1 years		8
N01052	4	
N01009	2	
N01148	2	
1 years < 2 years		19
N01052	5	
N01009	6	
N01148	8	
2 years < 6 years		50
N0151	3	
N01010	1	
N1052	4	
N01009	11	
N01103	7	
N01148	24	
6 years < 12 years		77
N0151	17	
N01010	14	
N01103	18	
N01148	28	
12 years to 16 years		43
N0151	4	
N01010	4	
N01103	17	
N01148	18	

For all age groups of pediatric patients (ages 1 month to 16 years), the pharmacokinetic study design could be either a traditional pharmacokinetic design (frequent sampling) or a population pharmacokinetic design using sparse sampling approach. If a sparse sampling approach is followed, approximately 3 – 4 blood samples per patient in 3 – 4 time brackets should be collected instead of blood samples at 3 - 4 fixed time points after levetiracetam dose.

Pharmacokinetic measurements as appropriate and assessment of blood levels of concomitant anti-epileptic medications and

Studies N151, N01052, and N01010, which used a traditional pharmacokinetic analysis design with frequent sampling, covered the age ranges of 1 month to 12 years old. In addition, two population pharmacokinetic analyses (N01139 and N01288) were performed covering the whole requested ranges of 1 month to 16 years old.

- Sponsor did not have a specific study in pediatric patients 13 to 16 years of age. In this age group, sponsor proposed to use the sparse sampling approach, with 3 to 4 blood samples in 3 to 4 time brackets to complete the pharmacokinetic information. This proposal was approved at the February 4, 2002 teleconference. In response to this, sponsor performed two population pharmacokinetic analyses N01139 (submitted in the 2004 sNDA) and N01288 (included in the current sNDA).

PK measurements and assessment of blood levels of concomitant anti-epileptic medication and levetiracetam to determine potential drug interaction were performed (e.g. N01010, N151, and N01139).

levetiracetam to determine potential drug interactions where feasible. Pharmacokinetic parameters such as AUC, Cmax, oral clearance, terminal half-life, etc. should be reported.	Pharmacokinetic parameters, including the following were reported: • Study N151 – Cmax, Cmaxnorm, tmax, AUC(0-24), AUC, AUCnorm, λz, t1/2, CL/f, Fe(0-24), CLR, CLNR • Study N01010 – Cmax, tmax, AUC(0-t), λz, t1/2, CL/f, CL/f normalized for body weight and body surface area, CLR, CLNR, Ae, and Fe. • Study N01052 – Cmax, tmax, AUC, AUC(0-t), λz,, t1/2, CL/f, CL/f normalized for body weight and body surface area, Vd/f, and Vd/f normalized for body weight.
Dosage Form: Oral tablet or other formulations as appropriate for younger patients. If a formulation other than the approved tablet is to be studied, its relative bioavailability needs to be assessed. The full study reports of the relative bioavailability study(ies) should be submitted to the Agency. If age-appropriate formulation(s) can not be developed, you will need to provide completed documentation of your attempts along with justification as to why this was not possible as part of your letter requesting an amendment to this Written Request.	**Dosage Form:** • Tablet strengths of 166 mg, 250 mg, and 500 mg were approved in November 1999 (NDA 21-035) for use in adults and have been and are being used to treat children. • The immediate release tablet formulations all have acceptable *in vitro* dissolution profiles. A comparative dissolution report for the investigational formulations is provided. • An oral solution (100 mg/ml) was approved in July 2003 for use in adults and showed bioequivalence to tablet formulations. • Both dosage forms were approved for the use in children down to the age of 4 years in June 2005.
Assessment of the effect of age on pharmacokinetic parameters and comparison to historic data in adults (who received the same concomitant medications). In addition, effects of other covariates such as body weight, body surface area, gender and concomitant medications on levetiracetam pharmacokinetic parameters should be assessed. Evaluation of effect of levetiracetam on other antiepileptics should be done where feasible.	• The effect of age on pharmacokinetic parameters was evaluated in the population PK study (N01288). Comparison to historic adult data was performed in the dose response study (N01308). • Effects of covariates, such as body weight, body surface area, age, gender, and concomitant medications on levetiracetam PK parameters were assessed in Study N151, N01010, and N01052 and the population pharmacokinetic analyses (N01139 and N01288). • Evaluation of effects of levetiracetam on other antiepileptics was performed (N01010 and N01139).

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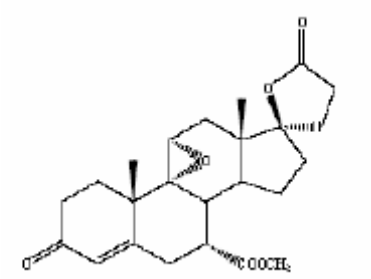
2 QUESTION BASED REVIEW

2.1 General Attributes:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and the formulation of the drug product?

The chemical name of levetiracetam, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C8H14N2O2 and its molecular weight is 170.21. 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.)



Levetiracetam is an antiepileptic drug available as 250 mg (blue), 500 mg (yellow), 750 mg (orange), and 1000 mg (white) tablets and as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration.

2.1.2 What is the proposed mechanism of drug action? What are therapeutic indications of Levetiracetam?

The precise mechanism(s) by which levetiracetam exerts its antiepileptic effect is unknown. *In vitro* and *in vivo* recordings of epileptiform activity from the hippocampus have shown that levetiracetam inhibits burst firing without affecting normal neuronal excitability, suggesting that levetiracetam may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.

Levetiracetam is an antiepileptic drug and has been approved as adjunct therapy for: 1.) Partial onset seizures in patients ≥ 4 years with epilepsy, 2.) Myoclonic Seizures in patients ≥ 12 years with juvenile myoclonic epilepsy, and 3.) Primary Generalized Tonic-Clonic Seizures in patients ≥ 6 years with idiopathic generalized epilepsy.

2.1.3 What are the approved doses and route of administration in adults and pediatric patients aged 4-16 years in treating partial onset seizure?

Levetiracetam is administered orally. The approved doses in treating partial onset seizure are summarized in Table 3.

Table 3 the Approved Dose in Adults and Pediatric Patients aged 4 – 16 Years

Age Group	Starting dose	Increments	Maintenance Dose	Regimen
Adults	1000 mg / day	1000 mg/day every 2 weeks	3000 mg/day	BID
4 – 16 Years	20 mg/kg/day	20 mg/kg/day every 2 weeks	60 mg/kg/day	BID

2.1.4 What are the proposed doses for pediatric patients aged 1 month- 4 years for partial onset seizure?

The sponsor proposed two different doses for pediatric patients aged 1 month – 4 years. They are summarized in Table 4.

Table 4 the Sponsor Proposed Dose for Pediatric Patients aged 1 Month – 4 Yearsin the Label

Age Group	Starting dose	Increments	Maintenance Dose	Regimen
1 month - 6 month	14 mg/kg/day	14 mg/kg/day every 2 weeks	42 mg/kg/day	BID
6 month - 4 year	20 mg/kg/day	20 mg/kg/day every 2 weeks	(b) (4) mg/kg/day	BID

2.2 General Clinical Pharmacology

2.2.1 What were the major PK characteristics for pediatric patients of various age groups

Different pharmacokinetic parameters are identified in pediatric patients in different age groups. The major pharmacokinetic parameters are estimated based on population pharmacokinetic analysis and summarized by age group in Table 5. The analysis results indicated that older pediatric patients have larger clearance, volume of distribution. For example, the clearance and volume of distribution in patients aged 2-4 years is about 2 fold higher than those in patients aged 1 month – 1 year.

Table 5 Summary of PK Parameters in Different Age Groups

		Median (5th - 95th Percentile)	
Age	N	CL (L/hr)	V (L)
1M - 1 Yr	8	0.54 (0.33-0.92)	4.10 (3.04-5.53)
1 - 2 Yr	19	0.82 (0.68-1.29)	6.78 (5.72-7.73)
2 - 4 Yr	29	1.32 (0.75-1.87)	10.02 (8.12-11.91)
4 - 7 Yr	27	1.71 (1.27-3.28)	15.37 (12.20-21.00)
7 - 16 Yr	101	2.74	24.58

		(1.67-4.13)	(17.30-44.32)

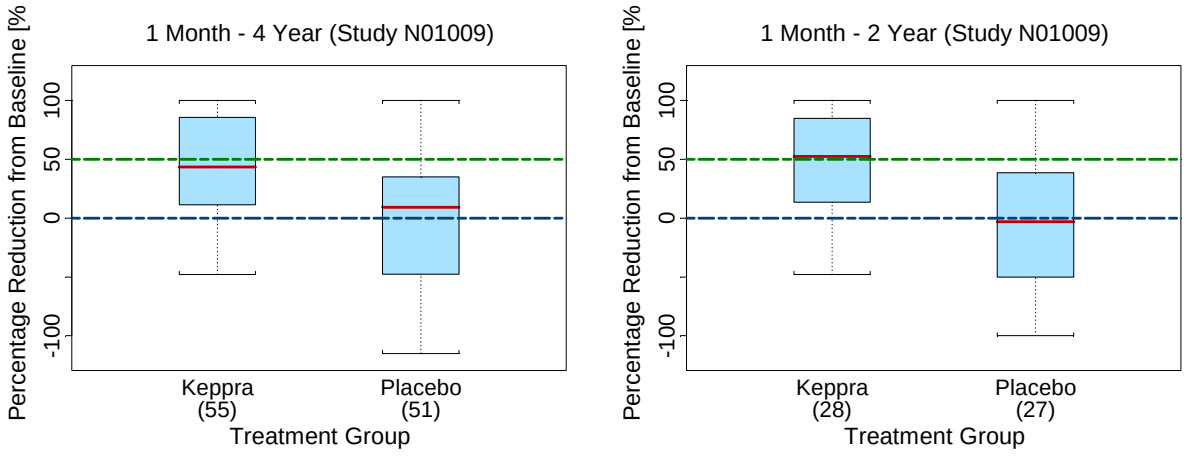
2.2.2 What were the doses tested in the pediatric efficacy and safety clinical trials?

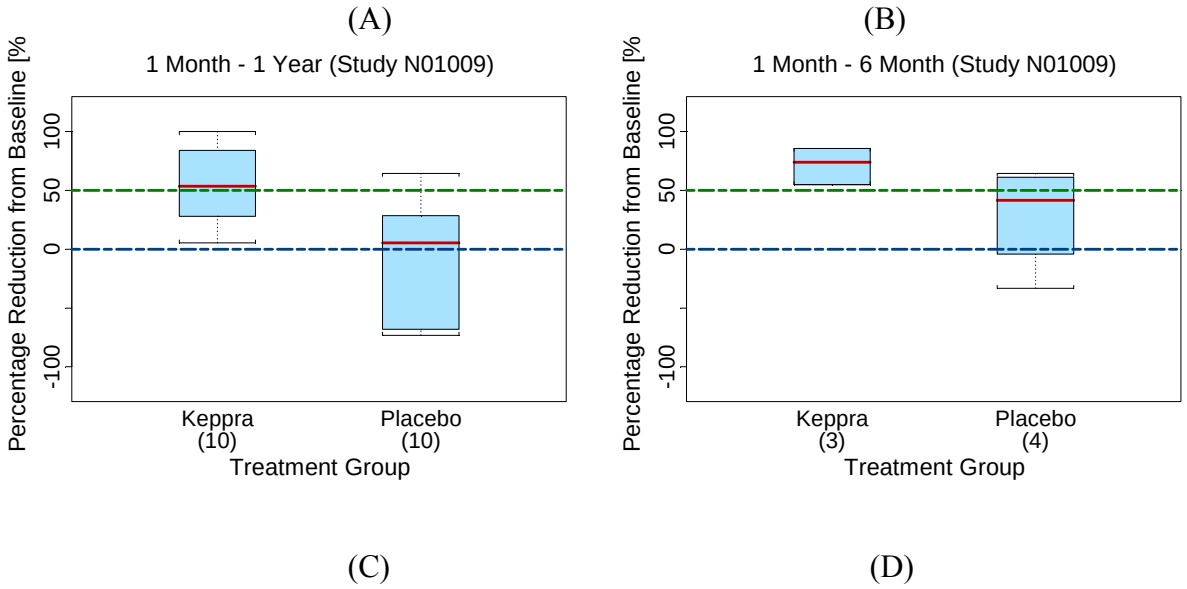
The sponsor conducted one pivotal efficacy safety trial (Study N01009). In this trial, pediatric patients aged 1 month – 6 month received 20 mg/kg/day on Day 1. Then the dose is increased and maintained to 40 mg/kg/day from Day 2 to Day 5. Pediatric patients aged 6 month – 4 years, on the other hand, were given 25 mg/kg/day on Day 1. The dose was escalated and maintained as 50 mg/kg/day from Day 2 to Day 5.

2.2.3 Is there evidence of consistent effectiveness across different age groups?

Yes. There is evidence of consistent effectiveness across different age groups and evidence to support that levetiracetam is efficacious for pediatric patients down to 1 – 6 month old. Our analyses were based on the percent reduction of daily partial onset seizure from baseline, which is used as a standard primary efficacy variable in evaluating antiepileptic drugs in most clinical trials. Because the pivotal study (Study N01009) was not powered to determine whether there was a significant difference in levetiracetam treatment as compared to placebo in various age subgroups, our analysis was to demonstrate whether there was a numerical difference between the two groups. The results are presented in Figure 2. For all patients aged 1 month – 4 years in Study N01009 (N=106) and receiving placebo - the median percentage change from baseline across the study was approximately zero (i.e., very small to no placebo effect). However, the median percentage change from baseline in levetiracetam group was about 50%, which was much higher than the placebo group (A). Similar pattern can be found in pediatric patients less than 2 years old (B) and less than 1 year old (C). Even though there were only 7 pediatric patients aged 1 month – 6 month included in the study, levetiracetam treatment group still demonstrated larger percent seizure change from baseline as compared to placebo. In summary, the levetiracetam treatment effect is consistent across all age groups, including patients aged 1 month – 6 month.

Figure 2 Consistent Levetiracetam Treatment Effect across Different Age Groups

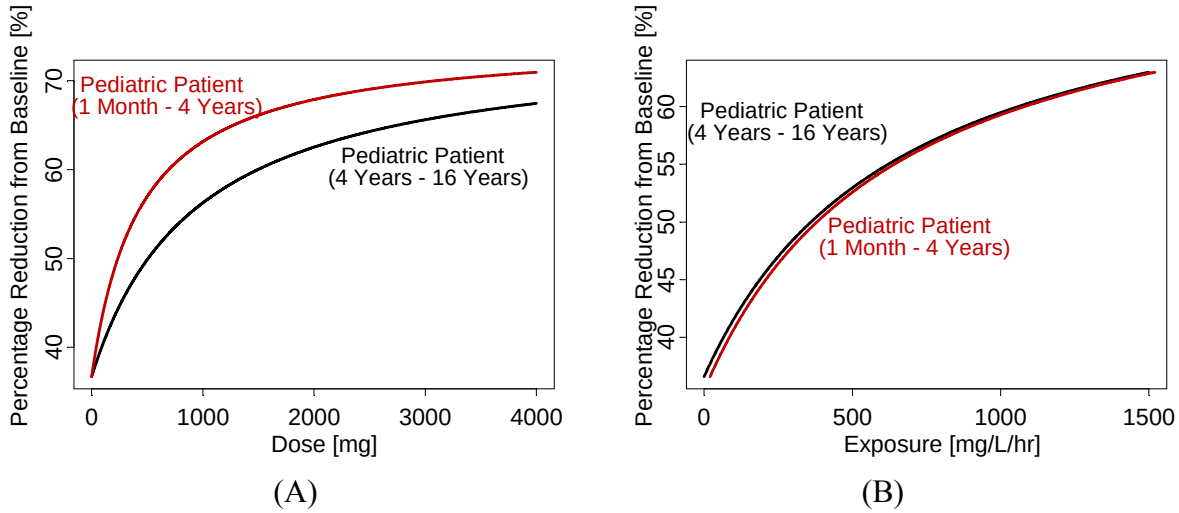




2.2.4 Is there consistent exposure-response relationship in pediatric patients at various age groups?

Yes. Consistent exposure-response relationship was identified in pediatric patients less than 4 years of age and pediatric patients 4 to 16 years of age. This finding served as a basis for matching exposure in pediatric patients less than 4 years of age and greater than 4 years of age. Dose-response evaluation when exposure varies heterogeneously across the population is inappropriate. For the same dose, a 10 kg patient and a 20 kg patient will have considerably different exposures or concentrations. Therefore, the simulation results based on dose-response relationship in one body size group should not be extended to another body size group (Figure 3).

Figure 3 Levetiracetam Dose-Response (A) and Exposure-Response (B) in two Different Age Groups



2.2.5 What are the recommended doses for pediatric patients aged 1 month – 4 years?

We propose a slightly different two-step dose for pediatric patients aged 1 month – 4 years (Table 1). Similar to the sponsor's proposal, pediatric patients aged 1-6 month receive 14 mg/kg/day twice daily as the starting dose. The dose is escalated to 42 mg/kg/day as maintenance dose. The starting dose for pediatric patients 6 month to 4 years of age is 20 mg/kg/day. Unlike the sponsor proposed maintenance dose of **(b) (4)** mg/kg, our recommended maintenance dose is 50 mg/kg/day. Our rationale for the recommended dosing is described below. Briefly, we explored several alternative dosing regimens, in their ability to match the target exposure, before arriving at the final one. All simulations were performed for the maintenance dosing. The starting dose is 1/3rd of the maintenance dose for all dosing regimens explored. Hence recommendations valid for maintenance dose are valid for starting dose as well.

Target Maintenance Exposure

The steady state AUC and C min in patients 4-7 years of age (most proximal to 1mo – 4 year patients) and the AUC in the pivotal efficacy and safety trial (Study N01009) were used as the target with respect to effectiveness. The Cmax distribution in the patients 4-7 years of age was used as the safety target (i.e., upper limit). The goal of the simulations was to find a suitable dosing algorithm that provides high probability of achieving target AUC while staying below the target Cmax.

Alternative Maintenance Dosing Regimens

We explored the following dosing regimens:

a. 30 mg/kg dosing: All patients irrespective of age receive 30 mg/kg according to this regimen.
b. **(b) (4)** two-step dosing

	(b) (4)	
Age	Starting Dose	Maintenance Dose
1Month - 6 Month	14 mg/kg/day	42 mg/kg/day
6 Month - 4 Years	20 mg/kg/day	60 mg/kg/day

c. Continuous nomogram

According to this regimen, dose is determined using the equation for CL (Figure 6). Each combination of body weight and age will have a unique dose. This can be considered as the perfect dosing and serves as a reference to evaluate other dosing regimens.

d. FDA's Two-step dosing (similar Sponsor's, **except for 6 mo – 4 year maintenance dose**)

	FDA Recommended	
Age	Starting Dose	Maintenance Dose
1Month - 6 Month	14 mg/kg/day	42 mg/kg/day
6 Month - 4 Years	20 mg/kg/day	**50 mg/kg/day**

Deriving Rational Dosing Regimen

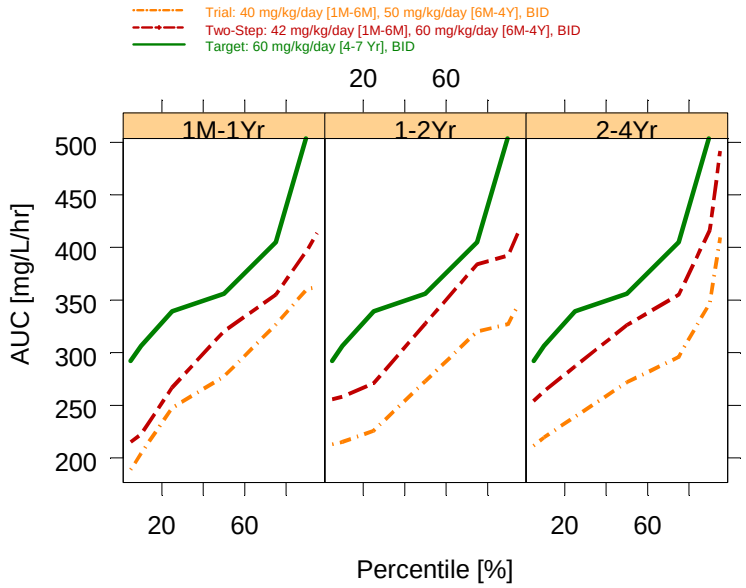
AUCs and Cmaxs were simulated under each of the above dosing regimens for 1 mo – 4 year and 4 year – 7 year patients. The latter group served as the target or reference. Another reference exposure range available was that directly observed in the clinical trial. This trial met its primary effectiveness objective.

Maintenance Dose

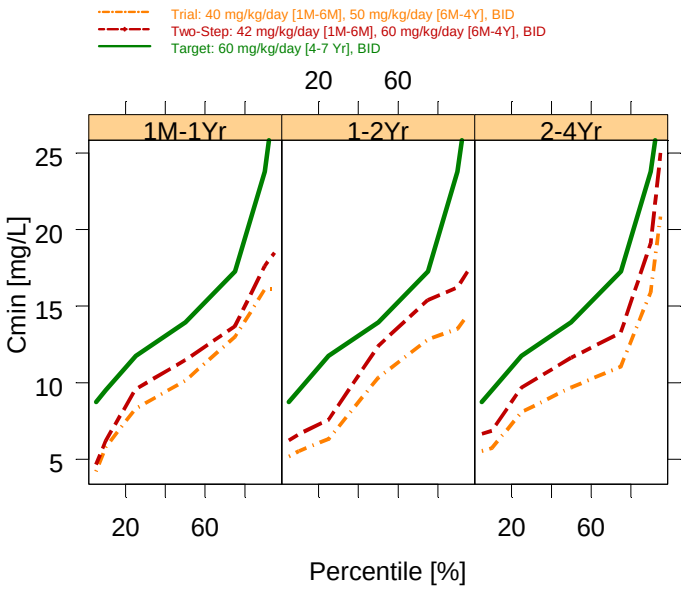
We found that a fixed 30 mg/kg dose led to increased exposure in 1 month- 6 months patients. Even though, the continuous nomogram dose provided sufficient match on steady state AUC, the maximum concentration distribution was consistently higher than target maximum concentration (i.e. in patients 4-7 years of age). The sponsor proposed two-step doses look appealing because this dosing regimen resulted in lower than the target C_{max} distribution, thus limiting exposures to those at approved doses. Even though the C_{min} and AUC are slightly lower than the target exposure, they are indeed higher than the exposure in patients 1 to 4 years of age in the pivotal efficacy and safety study (Study N01009) in which levetiracetam demonstrated significant treatment effect as compared to placebo (Figure 4).

We further investigated the maintenance dose for patients aged 6 month – 4 year. Our recommended dose is 50 mg/kg/day, compared to the (b) (4) mg/kg/day by the sponsor. Importantly, 50 mg/kg was directly studied in the pivotal trial. Our exposure-response analysis indicated that there are similar response rates for the two maintenance-doses across the entire age group, because only 2% difference in the response rate was expected (Figure 5). Therefore, it does not seem to be necessary to over-expose the pediatric patients by (b) (4) in order to gain 2% additional benefit on the response.

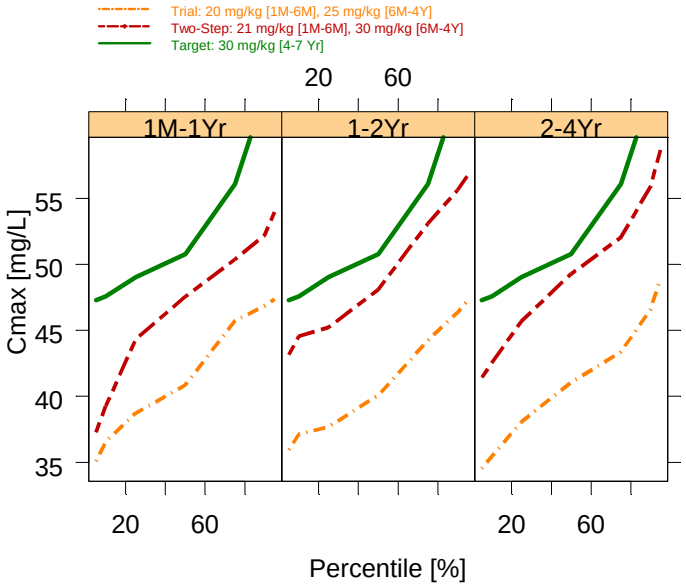
Figure 4 Comparison of Exposures under Different Maintenance Doses by Different Age Group



(A)



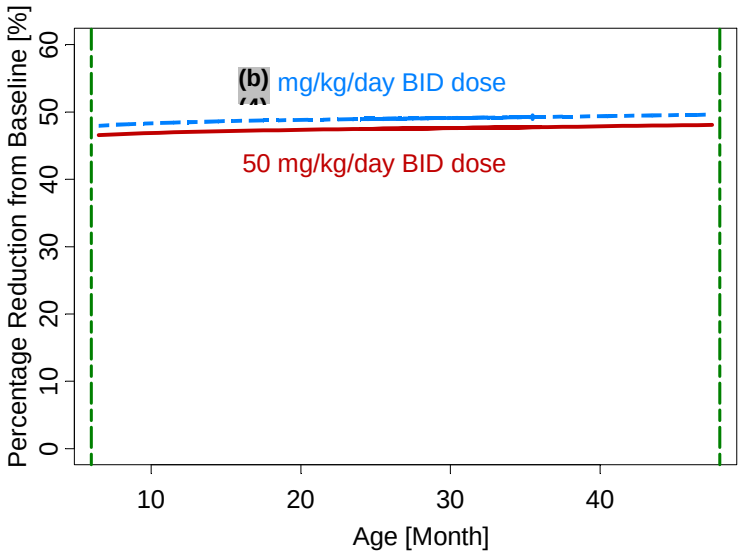
(B)



(C)

Note: A= Comparison of AUC Distribution
B= Comparison of C_{min} Distribution
C= Comparison of C_{max} Distribution

Figure 5 Response-Age Relationship Following 50 mg/kg or (b) (4) mg/kg Dose (6 Month – 48 Month)



Starting Dose

Starting dose is the (b) (4) of the maintenance dose.

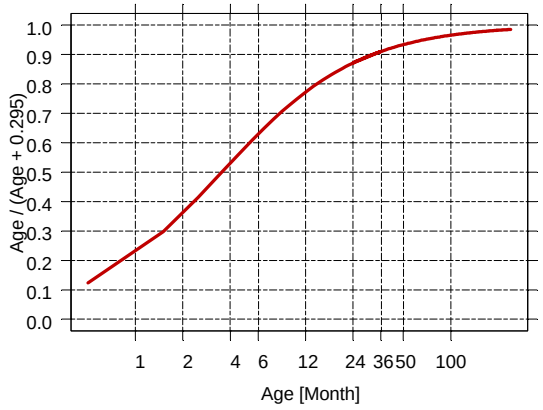
2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence PK of levetiracetam?

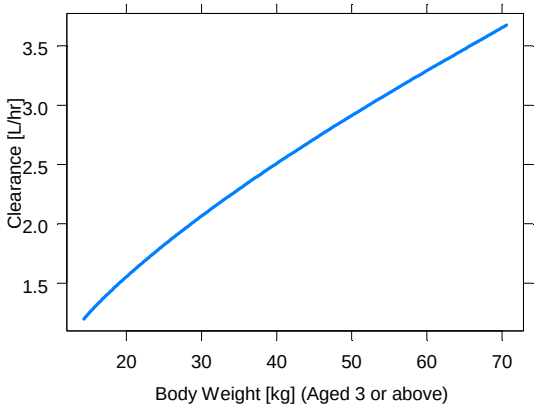
Population PK analysis indicated that clearance and central volume of distribution are both affected by body weight and age.

The relationship between clearance and both body weight and age can be found in Figure 6. For pediatric patients aged 1 month to 17 years, the clearance is mainly affected by body weight. Additional age effect can be identified for patients aged 1 month – 2 years. This age effect diminishes for patients aged 3 and above.

Figure 6 Body Weight and Age Effect on Clearance



(A)



(B)

Note: A.) = Age Effect on Clearance
B.) = Clearance vs. Body Weight [Age ≥ 3 Yr]

2.3.2 What is the race effect on the PK of levetiracetam?

Based on current population pharmacokinetics data, race does not appear to affect the pharmacokinetics of levetiracetam. However, a separate on-going clinical pharmacology review for Keppra XR formulation indicates about 40% difference in levetiracetam exposures between Hispanic versus non-Hispanic subjects. Therefore, to determine the race effect on levetiracetam by pooling historic data appears to be necessary.

Current population PK analysis includes the PK observations in 184 subjects aged 2 month – 17 years from 5 different races. The number of subjects by different races is summarized in Table 6. No statistical significant race effect is identified. Furthermore, a detailed comparison of levetiracetam pharmacokinetics between Caucasian vs. Non-Caucasian, Black vs. Non-Black, Hispanics vs. Non-Hispanics, and American Indian vs. Non-American Indian is shown in Table 7. The results do not indicate any clinical meaningful race effect on levetiracetam pharmacokinetics.

Table 6 Summary of Number of Subjects by Race in the Population PK Analysis Dataset

Race	Number of Subjects
Caucasian	111
Black	28
Hispanic	12
Asian	8
American Indian	6
Unknown	0
Others / Mixed	19
Total	184

Table 7 Summary of Race Effect

Comparison	Objective Function	Point Estimate	Standard Error	Lower Bound of 95% CI	Upper Bound of 95% CI
Caucasian vs. Non-Caucasian	5374.087	0.96	0.037	0.89	1.03
Black vs. Non-Black	5374.829	0.98	0.051	0.88	1.07
Hispanic vs. Non-Hispanic	5374.831	1.03	0.067	0.90	1.16
Asian vs. Non-Asian	5373.924	0.93	0.077	0.78	1.09
American Indian vs. Non-American Indian	5375.045	1.03	0.077	0.88	1.18

2.4 Extrinsic Factors

2.4.1 Is there drug-drug interaction in pediatric patients aged 1 month – 4 years?

No clinical meaningful drug-drug interaction has been identified in pediatric patients aged 1 month – 4 years.

Levetiracetam is given to pediatric patients as adjunctive therapy for the treatment of partial onset seizure. It is common for pediatric patients aged 1 month – 4 years to receive additional one or two antiepileptic agents. Therefore, potential drug-drug interaction needs to be evaluated.

Based on population PK analysis, the sponsor demonstrated that clearance in pediatric patient in various age groups is decreased by about 20% when levetiracetam is co-administered with another enzyme inducer or neutral drug. It is to note that the sponsor did not specify the name of drugs which are defined as inducer or neutral drugs. The results appear difficult to interpret because the same subject can receive multiple comedication. More importantly, 20% change in exposure usually does not lead to dose adjustment.

Furthermore, extensive drug-drug interaction is not expected for levetiracetam. In adults, 66% of the administered drug is eliminated in urine as parent compound. The major mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. Levetiracetam is not extensively metabolized in human. The major metabolic pathway is enzymatic hydrolysis of acetamide group, and it is not dependant on P450 isoenzyme.

2.5 General Biopharmaceutics

2.5.1 Is an adequate link established between the clinical and commercial formulations?

Yes. The sponsor has demonstrated adequate link between the clinical and commercial formulations. Five different investigational tablet formulations and one oral solution were used in the pediatric development program. Different tablet formulation strengths (250 mg, 500 mg,

750 mg, and 1000 mg) and the oral solution (100 mg/mL) are approved products. The oral solution has been previously shown to be bioequivalent to the marketed tablets. Additional 250 mg, 166 mg and 166.5 mg levetiracetam tablets were developed for blinding purposes in the studies. Because levetiracetam is a BCS Class I drug, the dissolution test is adequate to compare the different formulations. A comparative dissolution profile of the tablets indicates that almost 100% is dissolved in 15 minutes for all the strengths used in the clinical studies. A sufficient link among the commercial tablet and clinical trial tablets is thus established.

2.5.2 What is the effect of food on the bioavailability of the drug from the dosage forms?

The food effect has not been studied in pediatric patients.

2.5.3 Are the active moieties in the plasma appropriately identified and measured?

The bioanalysis of the active moiety is generally acceptable. The active moiety was measured and identified by two analytical methods, GC/NPD and HPLC/UV. The first method, GC/NPD, was previously developed in UCB and was validated and performed in three laboratories, including UCB, (b) (4). The second method, HPLC/UV, was developed, validated and performed in (b) (4). The matrix used in this method for calibration curves and QCs are different from the matrix of analyzed samples. By comparing the QCs samples with levetiracetam spiked in human plasma and bovine serum, the responses obtained from both matrices fall within 10 % coefficient variation and ± 8 % deviations.

The samples from N151, N01010 and N01052, were analyzed by GC/NPD in UCB and previously reviewed. For study N01103, plasma levetiracetam concentration was determined by (b) (4), using GC/NPD method. The samples from N01009 and N01148 were analyzed partly by GC/NPD and partly by a newly developed HPLC/UV method in another research laboratory, (b) (4), depending on the time of sample processing.

The GC/NPD method was performed by three different laboratories. Validation reports from the respective laboratories were provided. The assay validation for HPLC/UV method was also provided by (b) (4). However, no cross-validation between these two different bioanalytical methods was reported. The potential influence of bioanalytical method change was tested in NONMEM by incorporating a covariate as "analytical method" in the model in the population PK analysis. Based on the sponsor, the inclusion of the covariate did not result in an improvement in the model, implying that the 3 methods (GC/NPD in-house, GC/NPD done by CROs, HPLC-UV done by (b) (4)) were not statistically different and that the use of one or another method had no significant influence on the concentrations.

Table 8: Validation Results for Levetiracetam Assay in Bovine serum

PARAMETERS	LABORATORY DATA
Reference Range	N/A
Therapeutic Range	See attached
Specimen of Choice	Serum or plasma
Standard Verification	As supplied by UCB Pharma
LOD	24.5 %.CV @ 0.50 mcg/mL
LOQ	8.8 % CV @ 1.0 mcg/mL
Reportable Range (Upper & Lower)	Linear from 1.0 to 80 mcg/mL
Within Run Precision	4.0% CV @ 6.1 mcg/mL, 1.5% CV @ 27.3 mcg/mL
Between Run Precision	4.0% CV @ 6.2 mcg/mL, 3.1% CV @ 27.9 mcg/mL
Interfering Subs (specificity)	Commonly used substances do not interfere. See attached list of compounds.
% Recovery	39.5 to 46.3% over the range of calibration
Stability	Stable at room temperature for up to 23 days. Stable when refrigerated for up to 9 days. Stable for at least 120 days when frozen below -10°C

Table 9 Bioanalytical method performance for Levetiracetam Assay in Bovine Serum

Bioanalytical Method Performance Summary			
Lower Limit of Quantitation	1.0 mcg/mL		
Upper Limit of Quantitation	80.0 mcg/mL		
Inter-Assay Performance	**Target = 5 mcg/mL**	**Target = 25 mcg/mL**	**Target = 65 mcg/mL**
Precision (RSD)	6.5 %	9.4 %	4.9 %
Accuracy (% of target)	97 %	99 %	101 %
Stability			
Room Temperature	Stable for a minimum of 9 days.		
Refrigerated (2°C)	Stable for a minimum of 23 days.		
Frozen (-20°C)	Stable for up to 4 months.		
Analyte Specificity	A wide variety of drugs encountered in human serum, plasma and blood, including other anticonvulsant drugs, commonly used non-narcotic analgesics, antihistamines and stimulant drugs have been excluded as interferences with this analysis.		
Matrix Specificity	No significant interferences have been observed in human serum, plasma, and blood specimens.		

3 REVIEWER'S ANALYSIS

The focus for FDA reviewer's analysis was to: 1.) identify the evidence of effectiveness for pediatric patients at different age groups, 2.) evaluate the dose and dosing regimen for pediatric patients aged 1 month to 4 years, and 3.) evaluate the maintenance dose in pediatric patients 6 month to 4 years of age.

3.1 Background

The current NDA submission includes one efficacy and safety study (Study N01009) in pediatric patients aged 1 month to 4 years. Responder rate, defined as number of mITT subjects with a ≥ 50% reduction in average daily frequency of partial onset seizures from baseline divided by the total number of mITT subjects, was included as the primary efficacy variable. The subjects were randomized into placebo group and levetiracetam group at 1:1 ratio. In levetiracetam treated group, subjects aged 1 month to 6 month received 20 mg/kg/day as the starting dose on Day 1. From Day 2 to Day 5, the dose was titrated to 40 mg/kg/day. For subjects aged 6 month to 4 years, a dose of 25 mg/kg/day was started on Day 1, and then the dose was titrated to 50 mg/kg/day from Day 2 to Day 5. After 5 days of levetiracetam treatment, a 48-hr EEG evaluation started on Day 5. Among the modified Intend-to-treat patients (mITT), the levetiracetam group response rate was 43.1% as compared to 19.6% for placebo (P=0.013).

3.2 Evidence of Effectiveness in Different Age Groups

The first goal for our pharmcometrics analysis was to identify additional supportive evidence that levetiractem is efficacious in young pediatric patients (e.g. Patients aged 1month – 6 month). To determine the consistency of levetiracetam treatment effect among different age groups is important for the agency to extend the indication for treating partial onset seizure into young patients (e.g. patients younger than 6 month). Even though the significant levetiracetam treatment effect has been demonstrated for all pediatrics patients aged 1 month to 4 years, because of the small sample size, it is not feasible to demonstrate statistically significant treatment effect within each age sub-groups. Therefore, we explored additional evidence by comparing the distribution of percentage change from baseline in levetiracetam treated group with the placebo group.

3.2.1 Data for Analysis

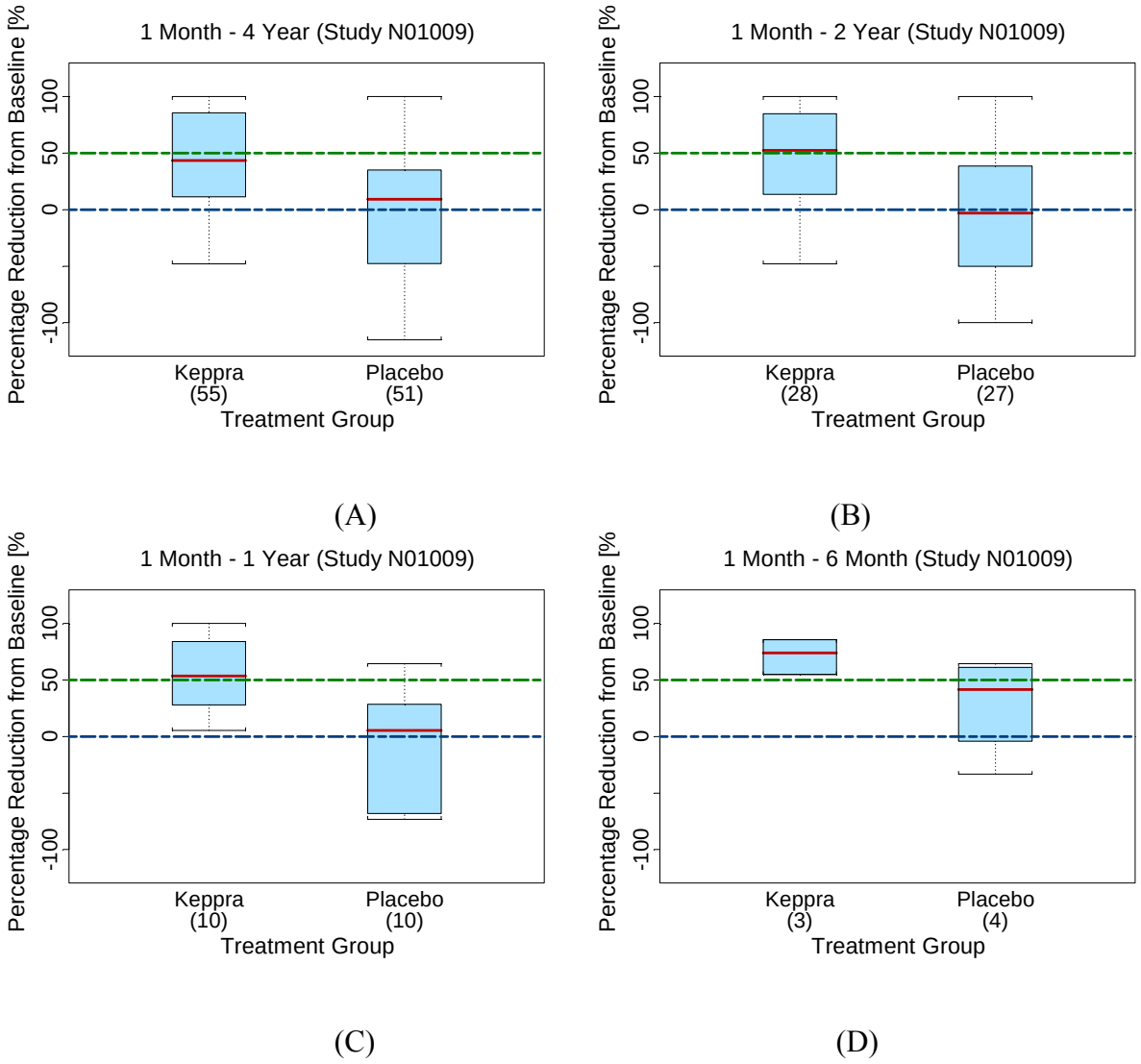
The analysis dataset is ccp02.xpt, which was submitted by the sponsor. Totally 106 patients in the dataset were from the pivotal efficacy and safety study. Among them, 55 patients were less than 2 years old, with 20 of them less than 1 year old. Only 7 subjects were less than 6 months old.

3.2.2 Analysis Results

Our analysis was performed to understand whether there was a consistent effectiveness following levetiracetam treatment among pediatric patients within different age sub-groups. If the significant treatment effect was only derived by patients aged 2 or above, similar response was

expected between levetiracetam and placebo after older patients (i.e. aged 2 or above) were removed from analysis dataset.

Figure 7 Demonstration of Consistent Levetiracetam Treatment Effect in Different Age Groups



Our analysis indicated consistent effectiveness in pediatric patients even 1-6 month of age. Our analyses results were presented in Figure 7. For all patients aged 1 month – 4 years tested in Study N01009 (N=106), the placebo did not seem to provide additional benefit, because the median percentage change from baseline was approximately zero. However, the median percentage change from baseline was about 50% from levetiracetam group, which was much higher than the observation from the placebo group (A). Similar pattern can be found in pediatric patients less than 2 years old (B) and less than 1 year old (C). Even though there were only 7 pediatric patients aged 1 month – 6 month in the study, levetiracetam treatment group still demonstrated larger percentage change from baseline as compared to placebo. In summary, the

levetiracetam treatment effect appeared to be consistent across all age groups, even for patients aged 1 month – 6 month.

3.3 Evaluation of Dose and Dosing Regimen

Our pharmcometrics analysis was conducted to evaluate the dose and dosing regimen for pediatric patients aged 1 month – 4 years. We found that the sponsor proposed two-step dose is acceptable. It was to note that the sponsor proposed different dose and dosing regimen in the label as compared to the doses studied in the primary efficacy and safety study (Study N01009). The difference was summarized in Table 10.

Table 10 Difference between the Labeled Dose and Clinical Studied Dose

	Studied Dose (Study N01009)		Proposed Dose	
Age	Starting Dose	Maintenance Dose	Starting Dose	Maintenance Dose
1Month - 6 Month	20 mg/kg/day	40 mg/kg/day	14 mg/kg/day	42 mg/kg/day
6 Month - 4 Years	25 mg/kg/day	50 mg/kg/day	20 mg/kg/day	(b) (4) mg/kg/day

3.3.1 The Sponsor's Justification for Dose and Dosing Regimen

According to the sponsor, the labeled dose was derived based on the population PK analysis (Study Report N01288) and exposure-response analysis (Study Report N01308). The summary of each study report can be found in Section 5.1. The sponsor's justification for dose is summarized as following. (Source*: P-83 to P-85, Summary of Clinical Efficacy*)

The sponsor stated that the results of dose-response analysis (N01308) showed that only a minor incremental reduction in seizure frequency was predicted in pediatric subjects with partial onset seizures for daily levetiracetam dose above 20 mg/kg/day. The sponsor performed simulation to evaluate different doses. All simulations were based on the model parameters indentified from Study N159, in which only pediatric patients 4 to 16 years of age were studied. The reduction in seizure frequency in children with a levetiracetam dose range of 20 – (b) (4) mg/kg/day was predicted to be slightly higher as compared to the recommended dose range of 1000 – (b) (4) mg /day in adults, therefore a daily levetiracetam dose range of 20 – (b) (4) mg/kg was suggested to be optimal as add-on treatment in refractory pediatric patients with partial onset seizure. Therefore, the results did not indicate a different dose-response and dosing scheme in children less than 4 years as compared to the recommended dosing scheme of levetiracetam in children older than 4 years.

The sponsor also stated that the most recent population PK analysis (N01288) conducted in children ranging from 1 month to 16 years of age, there was a statistically significant association between age and both clearance and volume of distribution. The effect of age on both parameters decreased as age increased, and becomes negligible around the age of 4 years. Simulations of exposure in children 1 month to 4 years of age were performed to evaluate the necessity of a dose adjustment. The simulations showed that the dose should be reduced by a factor that depends on age to obtain an exposure equivalent to that observed in a 4 year old. Children 1 to 6 months of age would require about (b) (4) and children aged from 6 months onward 100% of the dose of children aged 4 years to reach the same exposure. As an example, to get a similar exposure to that observed in a 4 year old child receiving the recommended 10 mg/kg per intake

starting dose, (b) (4) mg/kg per intake, the following doses would be recommended (Table 11).

Table 11 the Sponsor Proposed Dose for Different Age Group

Age Range (Month)	1-6	Above 6
Recommended Starting Dose (mg/kg bid)	7	10
(b) (4)		
Recommended Level 3 Dose (mg/kg bid)	21	(b) (4)

3.3.2 FDA's Reviewer's Assessment of Sponsor's Justification for Dose

Our analysis indicated that dose-response relationships were different in pediatric patients aged 4 years and above as compared to pediatric patients less than 4 years of age. Therefore, it is not appropriate to extend the simulation results based on modeling results in patients aged 4 – 16 years to patients less than 4 years of age.

3.3.2.1 Analysis Dataset

In our analysis, the response variable was defined as percentage reduction of average daily frequency (ADF) of onset partial seizure from the baseline. This variable was chosen because it was typically used as a primary efficacy variable in partial onset seizure studies; even though the primary efficacy variable in this pivotal efficacy safety study (Study N01009) was responder rate, which was defined as the number of mITT subjects with a $\geq$ 50% reduction from baseline in their ADF divided by the total number of mITT subjects. Different exposure variables, including dose and steady state AUC, were applied in our analysis in order to select the most appropriate one. Because no PK samples were taken from most subjects in the pivotal efficacy safety study, the AUCs were imputed based the population PK model reported in N01288 using each subject's covariate information.

The dose-response / exposure-response analysis was based on the dataset of cpp02.xpt, which was submitted by the sponsor. This dataset contains total number of partial onset seizures per period (DV) and number of days (DAYS) within each period for each subject. Then the ADF for each period can be calculated by taking the number of partial onset seizures divided by the number of days for each period. The baseline ADF was also provided by the sponsor. This dataset contains information from 1251 subjects with 3941 records of seizure frequency through 6 clinical trials. The detailed information was summarized in Table 12.

Table 12 Summary of the Exposure-Response Dataset

Age Group	1 Month - 4 Years	4- 16 Years	Adults			
Study	N01009	N159	51	52	132	138
Number of Observations	106	575	875	250	1110	1025
Number of Subjects	106	195	302	91	91	272

Our analysis was focused on the responder patients, which were defined as patients experience less onset of type I partial seizure as compared to the baseline observation. Therefore, patients

whose percentage change from baseline values were less than zero (i.e. higher than baseline ADF) were removed from current analysis dataset.

3.3.2.2 Dose-Response / Exposure-Response Analysis

The exposure-response / dose-response relationship was described by using Emax model (Equation 1). For the ith subject, E_i represents drug response. Exposure can be dose or $AUC_{0-\tau}^{ss}$ (i.e. steady state AUC). E_{0i} represented the placebo effect. E_{maxi} was the maximal effect the drug can produce and E_{50i} was the drug exposure (dose or $AUC_{0-\tau}^{ss}$) at 50% of the maximal effect. ε was the residual variability, which was assumed to follow normal distribution with the mean of zero and variance of σ^2. All PD parameters were assumed to be log-normally distributed (Equation 2). Par_i is the PD parameters for ith subject. TVPar was the typical value for the PD parameters. The PD parameter can be E_0, E_{max}, and E_{50}. NONMEM (version 6.1.0) was used to obtain the parameter estimates.

$$E_i = E_{0i} + \frac{E_{\max i} \cdot Exposure_i}{E_{50i} + Exposure_i} + \varepsilon \text{, where } \varepsilon \sim N(0, \sigma^2) \qquad \text{(Equation 1)}$$

$$Par_i = TVPar \cdot \exp(\eta_{par}),\ \eta_{par} \sim N(0, \omega^2) \qquad \text{(Equation 2)}$$

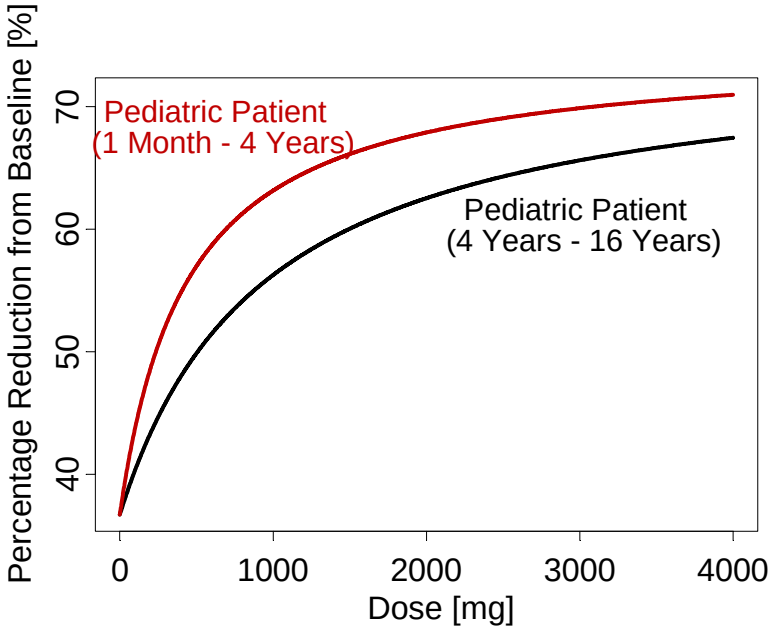
3.3.2.3 Dose-Response Analysis

Our analysis was firstly conducted to understand whether there was a difference in dose-response relationship in pediatric patients among different age groups. We especially tried to understand whether there was a difference in dose-response relationship for pediatric subjects less than 4 years old as compared to pediatric patients aged 4 years and above. It was because that all simulations for pediatric patients conducted by the sponsor in Study Report N01308, including those were used to justify dose and dosing regimen selection, were based on the dose-response relationship derived from Study N159. Study N159 included only pediatric patients aged 4 – 16 years. Unless we could demonstrate that pediatric patients aged 4 – 16 years share the same dose-response relationship with the pediatric patients aged 1 month – 4 years, the simulation results should not been extended from older children (aged 4 – 16 years) to the younger children (aged 1 month – 4 years).

Our analysis indicated that there were different dose-response relationships between pediatric patients aged 1 month – 4 years and 4 – 16 years. A scrutiny of the original dataset demonstrated that dose-response relationships appear to be different among patients at different age groups. We then specifically explored the dose-response relationships for patients aged 1month to 4 years and 4-16 years, and adult patients (aged 16 years and above). Different models were evaluated based on the standard criteria, including reduction of objective functions, attainment of minimization success, etc. The summary of the selected models were found in Table 13. Model with interindividual variability on E_0 and E_{max} was chosen as the final model that adequately described the dose-response relationship. The model parameter estimates were listed in Table 14. The results clearly demonstrated that different ED_{50} values were associated with patients at

different age groups. Completely different dose-response relationship was demonstrated in pediatric patients aged 1month – 4 years and 4 -16 years, with 50% difference in ED_{50} values (Figure 8). Therefore, the simulation results obtained based on dose-response relationship in pediatric patients aged 4 – 16 years should not be extended to pediatric patients aged 1 month – 4 years.

Figure 8 Dose-Response Relationship among Pediatric Patients at Different Age Groups



3.3.3 FDA's Reviewer's Assessment for Dose and Dosing Regimen

FDA's reviewer performed exposure-response analysis and population PK analysis. We found that the two-step dosing proposed by the sponsor is acceptable.

3.3.3.1 Exposure-Response Analysis

Our exposure-response analysis was performed to identify whether there was a consistent exposure-response relationship across different age groups in pediatric patients.

3.3.3.1.1 Dataset and Analysis Method

The exposure-response analysis dataset and method were detailed in 3.3.2.1and 3.3.2.2.

3.3.3.1.2 Exposure-Response Results

Our analysis further demonstrated that there was a consistent exposure-response relationship across patients with different age groups (1month – 4 years and 4 – 16 years). A preview of the dataset indicated that exposure-response relationships appeared to be similar in patients among different age groups. We used steady state AUC as exposure variable and explored the exposure-response relationships for patients aged 1month to 4 years and 4-16 years, and adult patients (aged 16 years and above). Models were evaluated based on the standard criteria, including reduction of objective functions, attainment of minimization success, etc. The summary of the

selected models were found in Table 13. Model with interindividual variability on E_0 and E_{max} was chosen as the final model that adequately described the exposure-response relationship. The model parameter estimates were listed in Table 14. The results demonstrated almost identical exposure-response relationship in pediatric patients aged 1 month – 4 years and 4 – 16 years and in adults, based on current data (Figure 9). Therefore, exposure, rather than dose, was more appropriate to link the effectiveness across different age groups.

Table 13 Summary of Model Selections

Exposure Variable	Run No.	Model	Minimization	Covariance	Objective Function
Dose	22	No IIV	Y	Y	10159.566
	221	IIV on E_0, E_{max}, and E_{50}	Y	A	9990.328
	222	IIV on E_0	Y	Y	10079.093
	223	IIV on E_{max}	Y	Y	10142.103
	224	IIV on E_{50}	Y	Y	10067.78
	225	IIV on E_0 and E_{max}	Y	Y	10060.907
	226	IIV on E_0 and E_{50}	Y	Y	9990.325
	227	IIV on E_{max} and E_{50}	Y	Y	10067.782
AUC	23	No IIV	Y	Y	10158.667
	231	IIV on E_0, E_{max}, and E_{50}	Y	A	9990.395
	232	IIV on E_0	Y	Y	10079.653
	233	IIV on E_{max}	Y	Y	10141.663
	234	IIV on E_{50}	Y	Y	10068.169
	235	IIV on E_0 and E_{max}	Y	Y	10060.403
	236	IIV on E_0 and E_{50}	Y	Y	9990.392
	237	IIV on E_{max} and E_{50}	Y	Y	10068.172

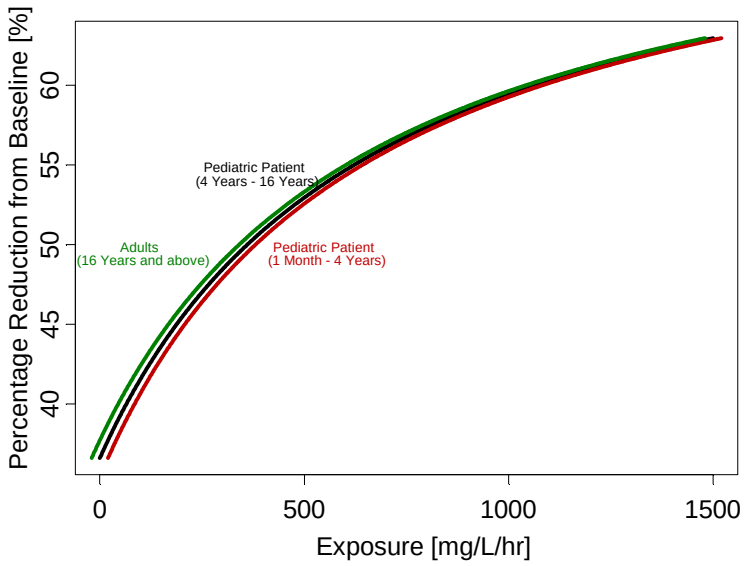
Note: Y = minimization successful or covariance step run successful
A = Aborted
IIV = interindividual variability

Table 14 Parameter Estimates for Dose-Response and Exposure-Response Relationships

Model	Fixed Effect	Parameter Estimates	Random Effect	Parameter Estimates
Dose-Response (Model No. 226)	E_0: (%)	36.7	IIV on E_0	41.80%
	E_{max}: (%)	38	IIV on E_{max}	0% (Fixed)
	E_{50} (4-16 Yr): (mg)	943	IIV on E_{50}	443.80%
	E_{50} (1M - 4 Yr): (mg)	437		-
	E_{50} (Adults): (mg)	2953		-
Exposure-Response (Model No. 236)	E_0: (%)	36.6	IIV on E_0	42.10%
	E_{max}:(%)	38	IIV on E_{max}	0% (Fixed)
	E_{50} (4-16 Yr): (mg/L/hr)	662	IIV on E_{50}	438.20%
	E_{50} (1M - 4 Yr): (mg/L/hr)	662		-
	E_{50} (Adults): (mg/L/hr)	662		-

Note: IIV = Interindividual variability

Figure 9 Exposure-Response Relationship in Pediatric Patients aged 1 Month – 4 Years and 4 – 16 Years, and in Adult Patients (aged 16 years and above)



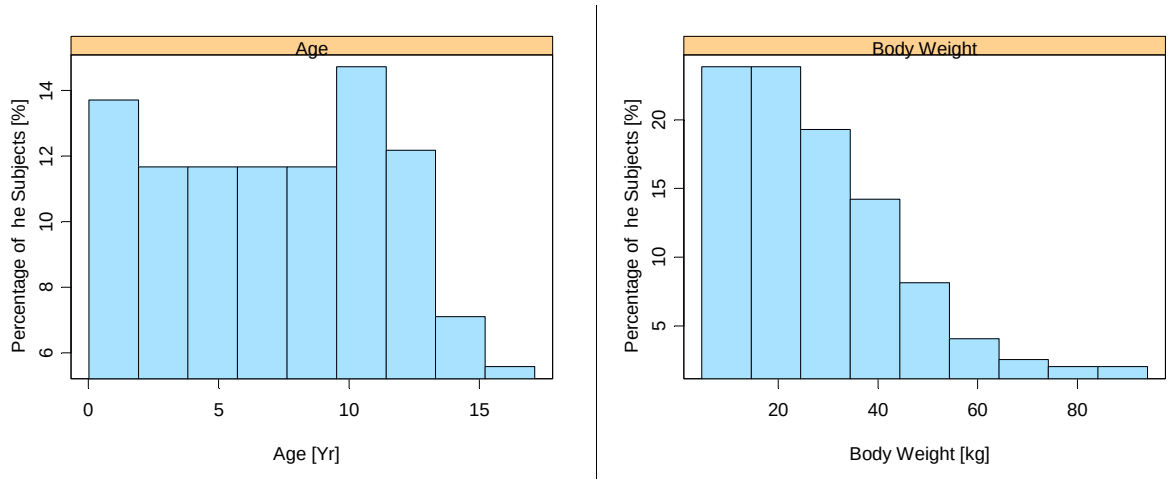
3.3.3.2 Population PK analysis

We subsequently performed population PK analysis to identify the appropriate dose for pediatric patients aged 1month to 4 years. Because we identified identical exposure-response relationships for pediatric patients aged 4-16 years and 1month – 4 years, we then matched the exposure for pediatric patients aged 1 month – 4 years with the exposure of approved dose in pediatric patients aged 4 – 7 years. After evaluation of different proposed doses, we found that the sponsor proposed two-step dose was acceptable.

3.3.3.2.1 Data for Analysis

Our population PK analysis was based on dataset nonmem.xpt, which was submitted by the sponsor. Totally 1182 PK samples taken from 197 subjects in 6 studies (Study N151, N01009, N1148, N1010, N1052, and N1103) were included in the dataset. This dataset contained information for pediatric patients aged from 2 month to 17 years. Detailed age distribution and body weight distribution in the dataset were illustrated in Figure 10.

Figure 10 Age Distribution and Body Weight Distribution



3.3.3.2.2 Population PK Analysis and Results

Our population PK analysis was performed based on the sponsor's analysis results (Study report N01288). We found that the sponsor's population PK analysis was acceptable. The detailed description can be found in Section 5.2.1.

We firstly evaluated the covariate effect on clearance. Levetiracetam is mainly eliminated through kidney. The clearance can be described by both age and body weight. We investigated different models to describe the relationship between the clearance and both age and body weight. The results were listed in Table 15. The sponsor proposed covariate model (model 2) did not seem to explain additional variability on clearance than the model we applied (model 3). Thus, model 3 was chosen to describe the body weight and age effect on clearance (Equation 3). In normal children, the body weight and age relationship can be obtained from National Center for Health Statistics (NCHS). It is to note that the female and male children follows similar growth rate until 12 to 14 years old. Specifically, male and female children younger than 4 years old follow almost identical growth rate. Because no additional gender effect was identified, no body weight growth rate difference was expected for female and male children aged 1 month – 4 years, clearance should be similar for both female and male pediatric patients at the same age. According to the established relationship, the CL/F was mainly driven by body weight for pediatric patients aged 4 and above, because the additional age effect (kidney maturation component) diminished mainly after 3-4 years (Figure 11). Furthermore, we investigated the potential drug-drug interaction effect on clearance. It appeared that co-administration of an inducer or a neutral drug leads to statistical significant effect and resulted in about 20% increase in clearance.

Table 15 Summary of Covariate Selection on Clearance

Model	Covariate Effect	Objective Function
3	$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times (\frac{AGE}{\theta_3 + AGE})$	5398.332
2	$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times \theta_4 (AEDC) \times (\frac{AGE}{\theta_3 + AGE})$	5374.726

1	$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times \theta_4 (AEDC) \times (\frac{AGE \times 12 + 9}{\theta_3 + AGE \times 12})^{2.5}$	5373.791

$$CL/F = 1.89 \times (BW/25)^{0.75 \times 0.873} \times 1.21(AEDC) \times \frac{AGE}{0.295 + AGE} \qquad \text{(Equation 3)}$$

Where BW is the body weight, AGE is age, AEDC is the indicator for co-administered drug, if it is an inducer or a neutral drug, the equation is multiplied by 1.21; Otherwise the equation is multiplied by 1.

We then evaluated the covariate effect on volume of distribution of central compartment (Vc). Vc can be described by both body weight and age. We investigated different covariate relationship on Vc. The results were summarized in Table 16. The results indicated that interindividual variability on Vc can be adequately described by both body weight and age. The relationship was described by equation 4. The final covariate model parameters were listed in Table 14.

Table 16 Summary of Covariate Effect Selection on Volume of Distribution in Central Compartment

Model	Covariate Effect	Objective Function
3	$V/F = \theta_5 \times (\frac{BW}{25})^{\theta_6}$	5385.025
2	$V/F = \theta_5 \times (\frac{AGE}{8})^{\theta_7}$	5417.710
1	$V/F = \theta_5 \times (\frac{BW}{25})^{\theta_6} \times (\frac{AGE}{8})^{\theta_7}$	5374.726

$$V/F = 17.8 \times (\frac{BW}{25})^{0.678} \times (\frac{AGE}{8})^{0.199} \qquad \text{(Equation 4)}$$

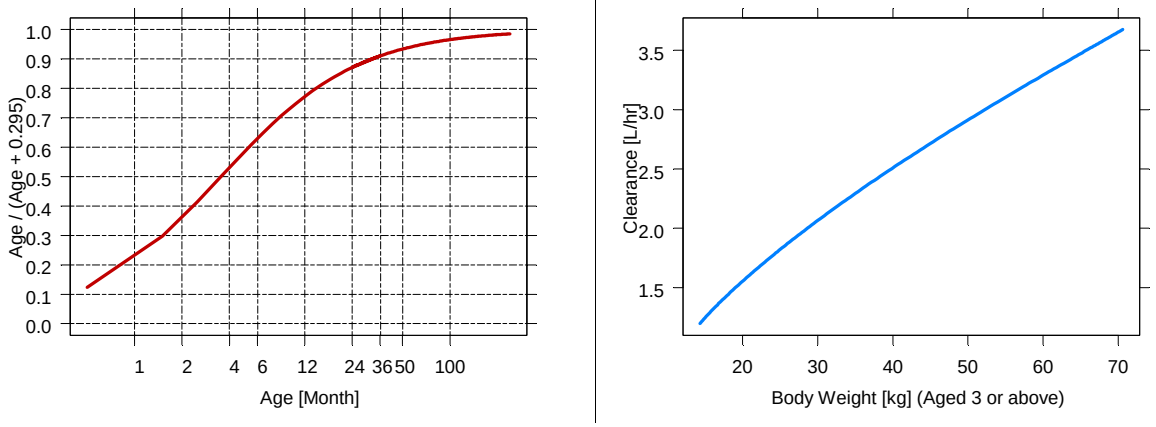
Where BW is the body weight and AGE is the age.

Table 17 Parameter Estimates for Dose-Response and Exposure-Response Relationships

Model	Fixed Effect	Parameter Estimates	Random Effect	Parameter Estimates
Final 3	Ka	4.67	IIV on Ka	37.0%
	$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times \theta_4 (AEDC) \times (\frac{AGE}{\theta_3 + AGE})$	-	IIV on CL	23.3%
	θ1	1.89	-	
	θ2	0.87	-	-
	θ3	0.295	-	-
	θ4	1.21	-	-
	$V/F = \theta_5 \times (\frac{BW}{25})^{\theta_6} \times (\frac{AGE}{8})^{\theta_7}$	-	IIV on V	11.7%
	θ5	17.8	-	-
	θ6	0.678	-	-
	θ7	0.199	-	-

Residual	30.9%	-	-

Figure 11 Age Effect and Body Weight Effect on Clearance



(A) (B)

Note: A.) = Age Effect on Clearance
B.) = Clearance vs. Body Weight [Age ≥ 3 Yr]

3.3.3.2.3 *Evaluation of Different Dosing Regimens*

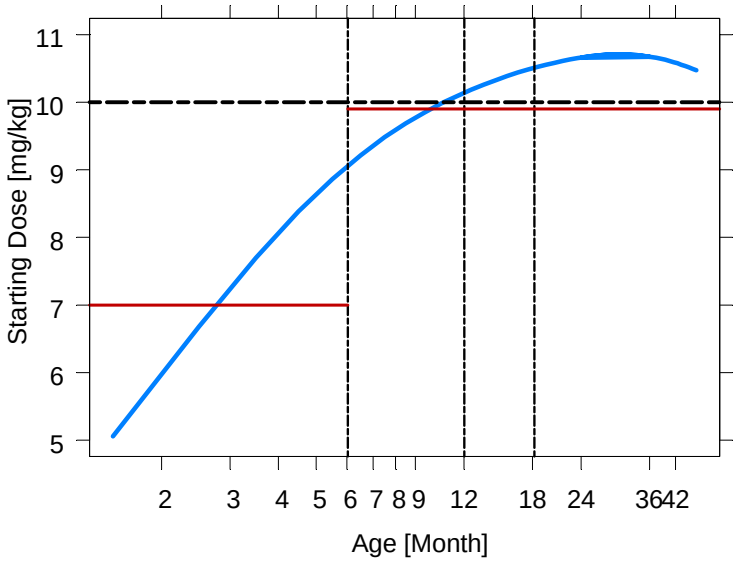
We defined the median steady state AUC for pediatric patients at 4-7 years old as the target exposure. This exposure represented the lowest exposure following the approved dose. We firstly generated the continuous nomogram that best matches the median steady state AUC at different age with the target exposure. Then, we compared AUC, C_{max}, and C_{min} distribution under different doses including a continuous nomogram, a fixed body weight adjusted dose, and a two-step dose, which were illustrated in Table 18 and graphically presented in Figure 12.

Table 18 Proposed Doses for Evaluation

Regimen	Age	Starting Dose * #	Maintenance Dose * #
Fixed Body-Weight Adjusted Dose	1 month - 4 years	10 mg / kg	30 mg / kg
Continuous Nomogram	1 month - 4 years	(Doses shown in Figure 12)	(3-fold higher than doses shown in Figure 12)
Two-Step Dose	1 month - 6 month 6 month - 4 years	7 mg/kg 10 mg / kg	21 mg/kg 30 mg / kg

*: Tevetiracetam is given twice daily.
#: Maintenance dose is assumed to be 3-fold higher than the starting dose in the current evaluation

Figure 12 Different Proposed Starting Dose *



Note: *: This plot demonstrates starting dose only. The maintenance dose is 3-fold higher than the starting dose in the current evaluation.

Black line = Fixed body-weight adjusted dose at the target dose (10 mg/kg)
Blue line = Continuous nomogram determined dose
Red line = Two-step dose: 7 mg/kg for pediatric patients aged 1 month – 6 month
10 mg/kg for pediatric patients aged 6 month – 4 years

3.3.3.2.3.1 Generation of Continuous Nomogram Dose

A fixed body weight adjusted dose is not adequate, and additional dose adjustment based on age is necessary from the simulation results. A simulation was conducted to obtain the levetiracetam exposure (i.e. steady state AUC) over different age groups for patients 1 month to 4 years of age. The simulation was performed based on the individual estimated clearance. Assuming each subject received 10 mg/kg, the exposure-age relationship was demonstrated in Figure 13. Clearly, under the same body weight adjusted dose (i.e. 10 mg/kg), the levetiracetam exposure decreased as the patient age decreased. However, for patients younger than 2-3 years of age, the exposure started to increase as the patient age decreased. It is to note the predicted median exposure for pediatric patients aged 1month old was about 65% higher than the median exposure of the 4-year-old pediatric patients. Therefore additional dose-adjustment was necessary for pediatric patients within the age of 1 month – 4 years, rather than use a fixed body weight adjusted dose (e.g. 10 mg/kg)

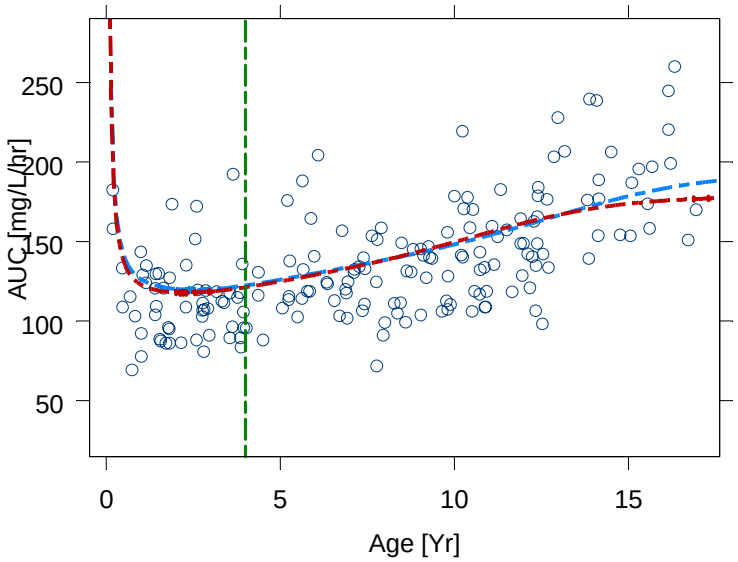
Continuous nomogram dose was generated to best match the target exposure. We chose the median steady state AUC under 10 mg/kg of 4-7 year old pediatric patients, which is the lowest exposure under approved starting dose, as the target starting exposure. We then calculated the fraction of the dose needed in order to best match the median of target AUC. The dose and age relationship can be described by using the following equation (Equation 5). The matching starting dose and age relationship was illustrated in Figure 12. The maintenance dose was

assumed to be 3-fold higher than the starting dose. The 3 – fold was chosen because the maintenance dose is 3-fold higher than starting dose in the approved patient population, including adults and pediatric patients 4 to 16 years of age.

$$Dose_{adj} = Dose_{\text{Re } ference} \times \frac{1.89 \times (\frac{BW}{25})^{0.655} \times (\frac{AGE}{AGE + 0.295}) \times BW_{\text{Re } ference}}{CL_{median(\text{Re } ference)} \times BW} \qquad \text{(Equation 5)}$$

Where Dose $_{adj}$ is the dose after the adjustment in order to match with the target exposure, Dose $_{ref}$ is the reference dos. In the current simulation study, the reference dose is 10 mg/kg. AGE is the age of the pediatric patient within the range of 1 month – 4 years. For a given age within this age group, BW represents the correspondent median body weight. BW $_{reference}$ and CL $_{reference}$ are the median body weight and median clearance for pediatric patients 4-7 years of age.

Figure 13 Levetiracetam Exposure-age Relationship



Note: Assume each subject receives 10 mg / kg
Blue open cycle = Simulated AUC for each individual in the epilepsy patients
Blue line = median AUC for male subjects based on the median body weight and age relationship derived from American population (NCHS dataset)
Red line = median exposure for female subjects based on the median body weight and age relationship derived from American population (NCHS dataset).
Green dashed line = 4 years

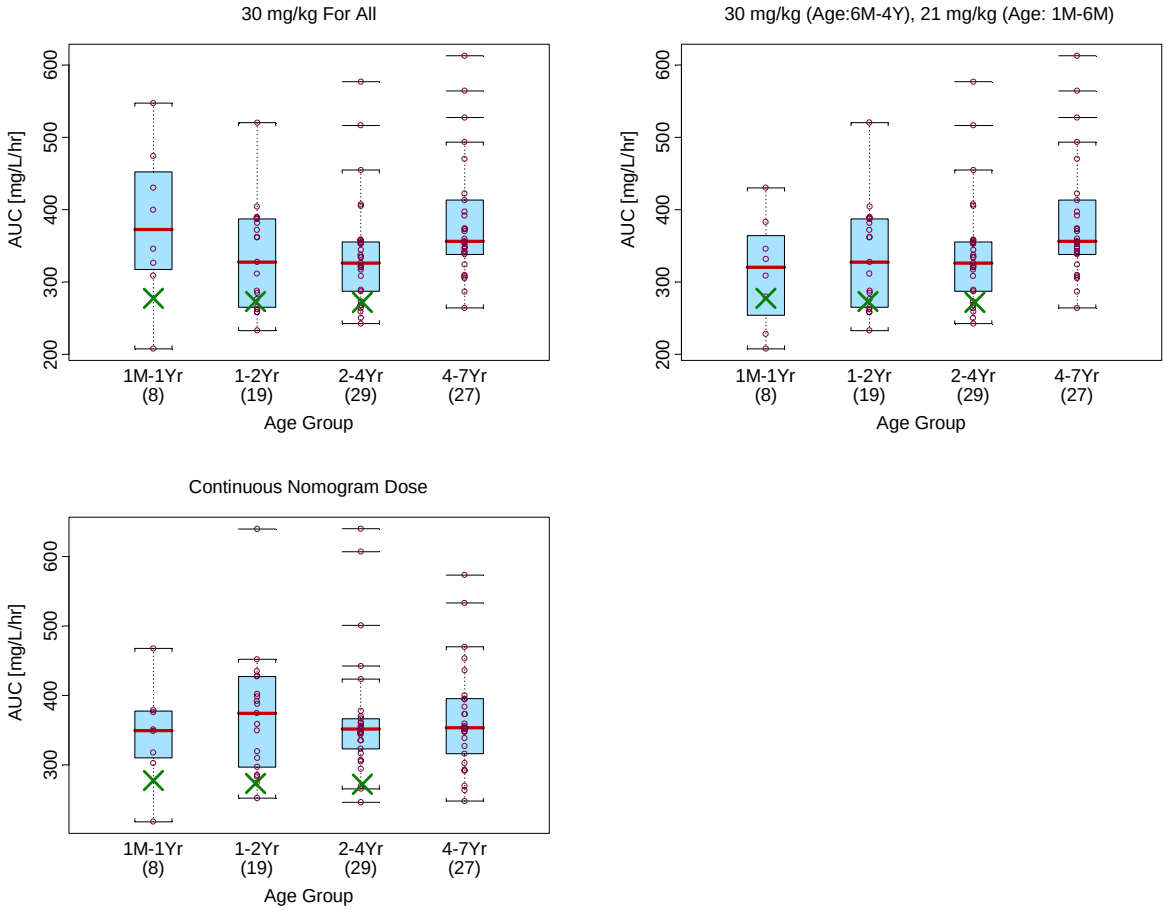
3.3.3.2.3.2 Comparison of Exposure Distribution under Different Maintenance Doses

We compared the exposure distributions under different proposed maintenance doses. Exposure under maintenance dose, rather than under starting dose, was compared because in the pivotal efficacy and safety trial, the observed effectiveness was mainly driven by the maintenance dose,

and the starting dose was given for only 1 day. The exposure at maintenance dose in the pivotal trial was used to evaluate the selected dose.

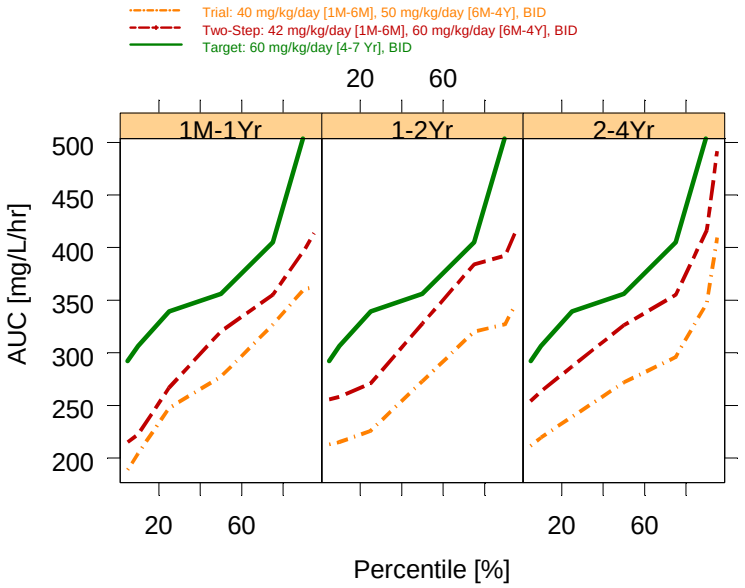
We firstly compared the steady state AUC following different maintenance doses. The comparison was necessary because we previously demonstrated that steady state AUC drives the effectiveness of levetiracetam. The goal was to ensure that the AUC under different proposed maintenance doses yield adequate AUC in order to maintain effectiveness. The comparison of AUC values following a fixed body weight adjusted dose, a two-step dose, and a continuous nomogram dose could be found in Figure 14. A detailed comparison of AUC distribution of two-step dose with the target exposure and clinical tested exposure was shown in Figure 15.

Figure 14 Comparison of AUC under Different Maintenance Doses



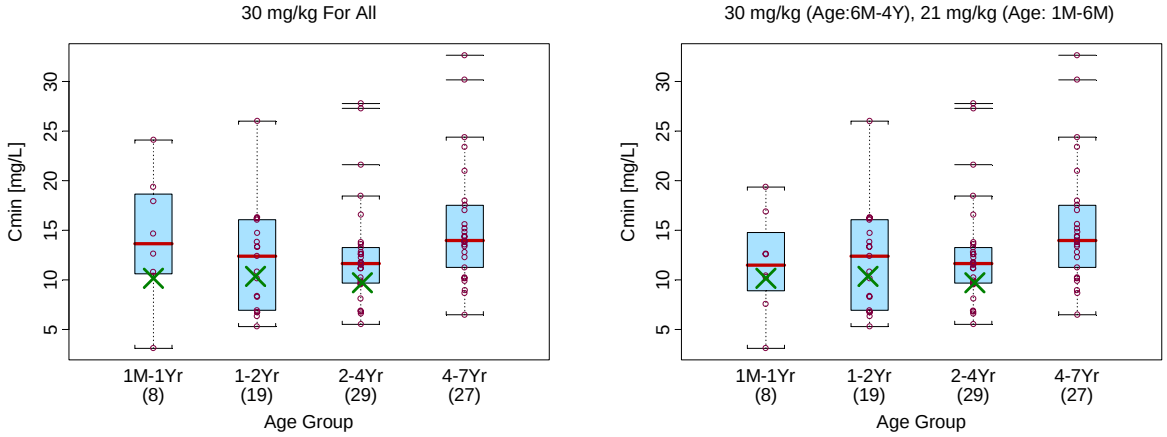
Note: Open circle = simulated AUC for each individual
Cross = median AUC being evaluated in the pivotal trial

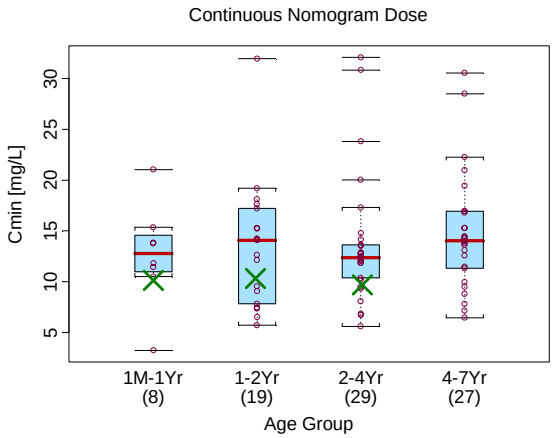
Figure 15 Comparison of Steady State AUC Distribution under Two-Step Maintenance Dose with Target Exposure and Clinical Tested Exposure



We then examined the steady state trough concentration distributions. It is generally believed that antiepileptic drug trough concentration should be above adequate level in order to ensure the effectiveness. A comparison of steady state trough concentration under different does and the trough concentration plot was presented in Figure 16. A detailed comparison of C min distribution of two-step dose with the target exposure and clinical tested exposure was shown in Figure 17.

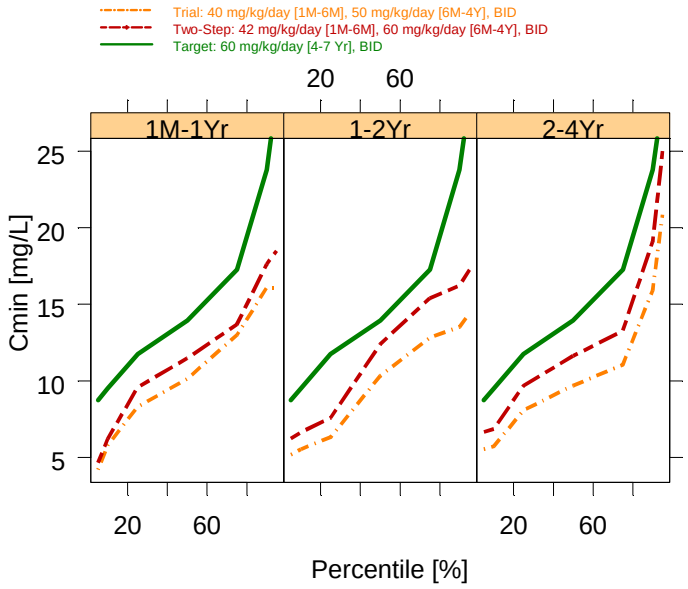
Figure 16 Comparison of Steady State Cmin under Different Maintenance Doses





Note: Open circle = simulated AUC for each individual
Cross = median AUC being evaluated in the pivotal trial

Figure 17 Comparison of Steady State Cmin Distribution under Two-Step Dose with the Target Exposure and the Clinical Tested Exposure



Thirdly, we compared the maximum steady state concentration under different maintenance doses. The maximum concentration is typically associated with adverse effects. Therefore, the maximum concentration needs to be controlled. The comparison of the maximum concentration under different maintenance doses was presented in Figure 18. A detailed comparison of the Cmax distribution under two-step dose and target exposure and clinical tested exposure can be found in Figure 19.

Figure 18 Comparison of Steady State Cmax under Different Maintenance Doses

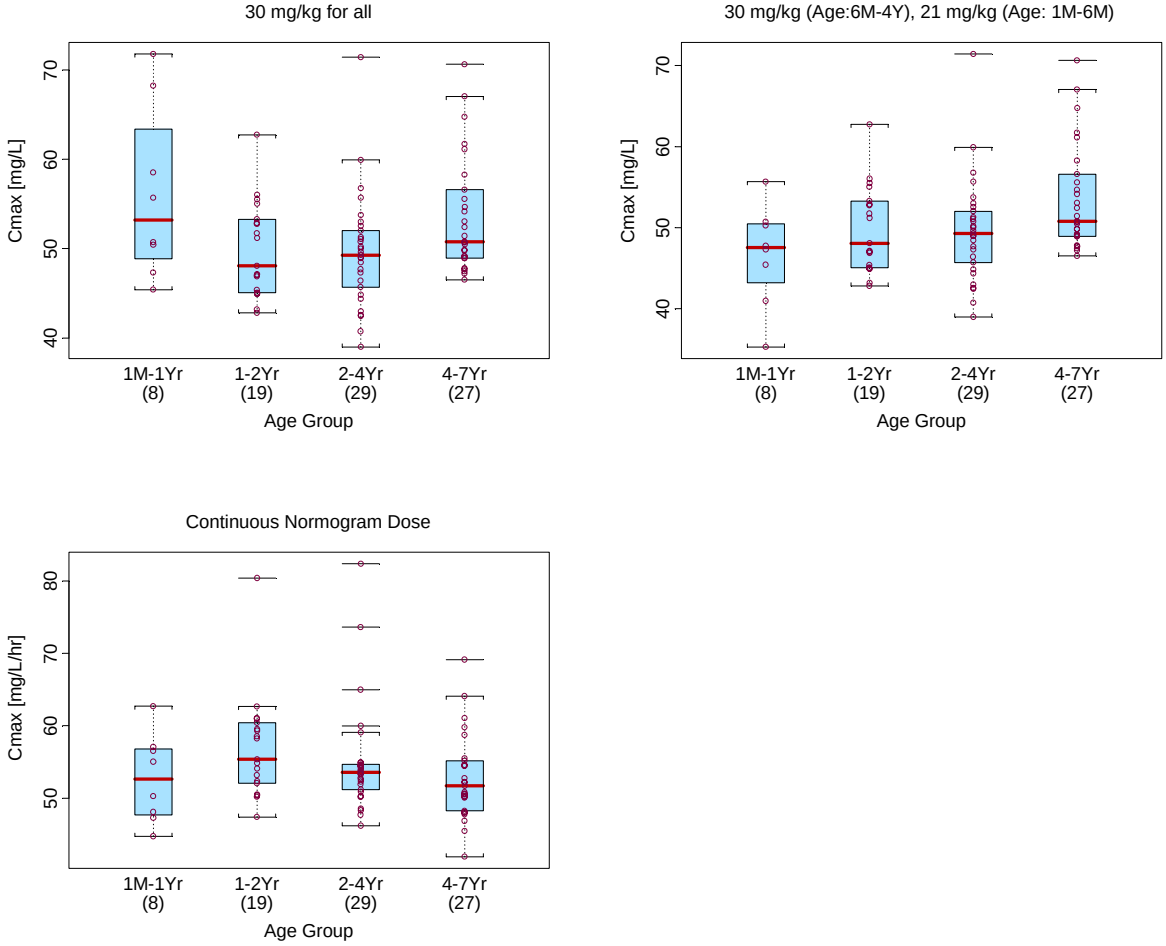


Figure 19 Comparison of Cmax Distribution under Two-Step Dose with the Target Exposure and Clinical Tested Exposure

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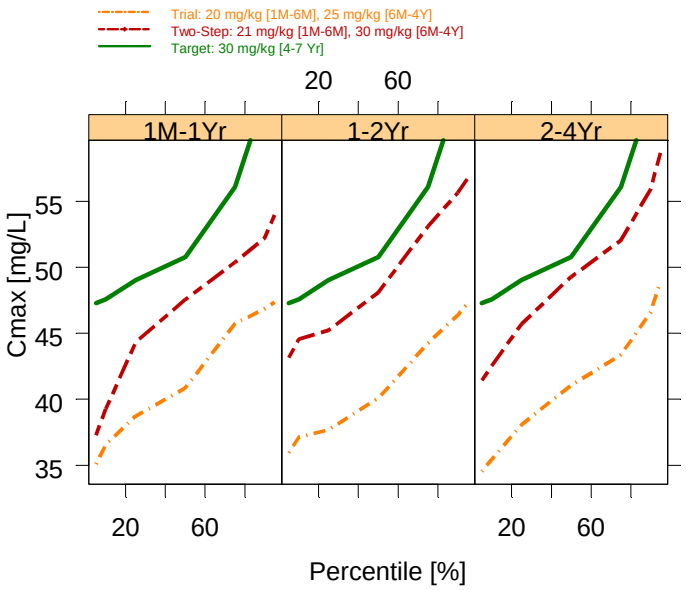


In summary, two-step dose appears to be optimal compared to the two other doses based on the evaluation of simulated AUC, C_{max} and C_{min} distribution. Even though, nomogram provides better match on AUC values, the C_{max} produced by nomogram is consistently higher than the target exposure. This can related to higher risk of adverse effect. A fixed body-weight dose raises more concern in pediatric patients aged 1month – 6 month, because all AUC, C_{min} and C_{max} values are higher than the target exposure. The two-step dose results in lower than the target C_{max} distribution, thus lower risk of adverse effect is expected. Even though the C_{min} and AUC are slightly lower than the target exposure, they are indeed higher than the exposure in the pivotal efficacy and safety study in which levetiracetam demonstrated significant treatment effect as compared to placebo.

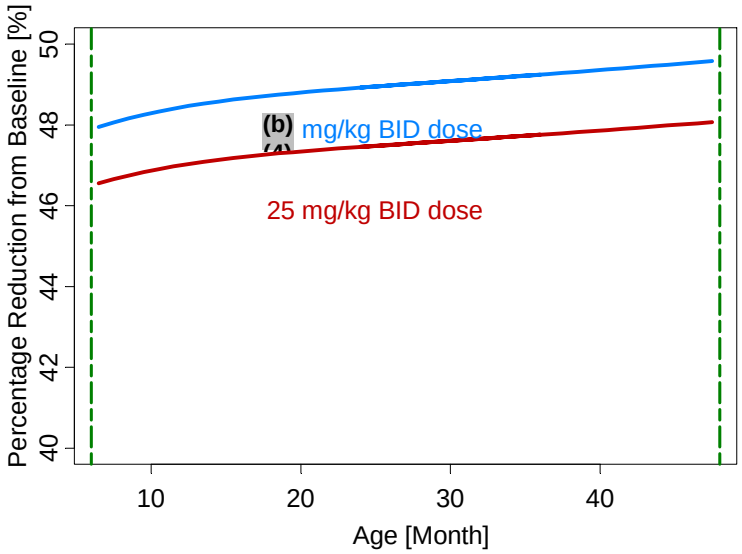
3.3.3.2.3.3 Evaluation of Maintenance Dose in Pediatric Patients 6 Month – 4 Years of Age

In the previous section (Section 3.3.3.2.3.2), we assumed that the maintenance dose is 3 –fold higher than the starting dose, (b) (4) and approved dose. However, under current assumption, the maintenance dose is (b) (4) mg/kg/day (BID), (b) (4) than the maintenance dose being tested in the pivotal clinical trial for patients aged 6 month – 4 years. Additional analysis was thus performed to compare the response difference between 50 mg/kg/day dose and (b) (4) mg/kg/day dose.

The responses in terms of median percentage reduction from baseline in the responder patient population are similar between 50 mg/kg and (b) (4) mg/kg dose. We obtained the body weight and age relationship from NCHS. By applying this relationship, the median clearance and subsequently steady state AUC under 50 mg/kg or (b) (4) mg/kg can be simulated. The median response rates were calculated based on the exposure-response relationship established in section 3.3.3.1.2 using the AUC under 50 mg/kg or (b) (4) mg/kg dose. The response and age relationship following 50 mg/kg and (b) (4) mg/kg doses were illustrated in Figure 20. It appeared that across

different age sub-groups, the simulated response rate is about 2% lower under 50 mg/kg dose as compared to (b) (4) mg/kg dose.

Figure 20 Response-Age Relationship Following 50 mg/kg or (b) (4) mg/kg Dose (6 Month – 48 Month)



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4 DETAILED LABELING RECOMMENDATIONS

(b) (4)

(b) (4)

5 APPENDICES

5.1 Individual Study Review

The sponsor provided one population PK report and one exposure-response report. They were summarized in Table 19.

Table 19 Summary of Population PK and Exposure-Response Analyses Study Reports

Type	Study Number	Report	Population
Pop-PK	N01288	Retrospective population pharmacokinetic analysis of levetiracetam in pediatric patients with epilepsy aged 1 month to 16 years.	Pediatric Patients aged 1 month to 17 year
Dose-Response	N01308	Levetiracetam exposure-response analysis in children with partial onset seizures.	Pediatric Patients aged 1 month to 16 year and adult patients

5.1.1 Population Pharmacokinetics of Levetiracetam in Pediatric Subjects, Study Report Number: N01288

Objectives

Objectives of the population PK analysis were the following:

1. To characterize the pharmacokinetics of levetiracetam (LEV) in pediatric patients, including estimation of the inter- and intra-patient variability in the main pharmacokinetic parameters, using data pooled from six clinical studies.
2. To assess the linearity of levetiracetam pharmacokinetics on the investigated dose range.
3. To identify relevant demographic and/ or physiologic determinants of levetiracetam disposition, including if possible a potential influence of concomitant anti-epileptics drugs (AEDs) in that population.
4. To simulate optimal dosing regimens as a function of the relevant covariates.

Clinical Studies Overview:

The population PK analysis was based on the PK observations from 6 clinical trials. The clinical trials were summarized in Table 20. The pharmacokinetic samples were connected at various time points in these trials (Table 21).

Table 20 Summary of Clinical Trials

Trials	Patient Age	Dose Range	Formulation	Duration	Comedication
N0151	5.6 Year - 12.7 Year	10 mg/kg/day - 40 mg/kg/day	Tablet	Up to 18 Wks	A single AED
N01010	4.5 Year - 12.9 Year	20, 40, 60 mg/kg/day	Tablet	Up to 10 Wks	Two AEDs at most
N01052	2.3 Month - 3.9 Year	20 mg/kg Single dose	Solution	Single Dose	Two AEDs at most

N01009	1.0 Month - 3.9 Year	20 mg/kg/day to 50 mg/kg/day	Solution	Up to 20 days	Two AEDs at most
N01103	4.8 Year - 16.7 Year	up to 60 mg/kg/day	Tablet and Solution	Up to 18 Wks	Two AEDs at most
N01148	1 Month - 16 Year	20 mg/kg/day to 60 mg/kg/day	Tablet and Solution	Up to 48 Wks	Two AEDs at most

Table 21 Summary of Blood Samples Schedules

Study N°	Sample collection times
N151	Day 1: Pre-dose, 1 h, 2 h, 4 h, 9 h, 12 h, 16 h, and 24 h post-dose; Titration Visits (days 14, 28 and 42): Pre-dose and 1 post-dose sample taken between 1 and 7 h post-dose
N01010	Pre-dose, 15 min, 30 min, 1 h, 3 h, 6 h, and 12 h post-dose on days 14, 28 and 42.
N01052	Pre-dose, 1 h, 2 h, 4 h, 9 h, 12 h, 16 h, and 24 h post-dose
N01103	One sample at day 84
N01009	One sample at day 6
N01148[a]	One sample at each visit during the titration phase (on day 0, week 2, week 4, week 6), Visit 5 (week 24), and Visit 7 (week 48)

[a] samples on weeks 2 and 4 were only taken from de novo subjects and from those who had received doses higher than 20/25 mg/kg/day in studies N01009 and N01103.

Data for Analysis:

Data from 197 epileptic children with 1182 plasma concentrations were used for this population analysis. There were 112 males and 85 females (56% were Caucasians, 14% Blacks, 11% Asians, other races represented less than 10% each), with the following median (range) demographic covariates: age 7.77(0.19-16.95) years, body weight 25.2 (5.5 – 93.2) kg, body surface area 0.94 (0.3 – 2.1) m², and creatinine clearance 75.0 (13.8 - 181) mL/min.

Major Covariates included age, gender, body weight, dose, body surface area, serum creatinine, AED comedication,

Analysis Method:

These objectives were achieved through population pharmacokinetic modeling of levetiracetam concentration time data, using a non-linear mixed-effects model. Levetiracetam plasma concentrations from 197 subjects were used for non-linear mixed effects modeling by extended least squares regression using NONMEM. The analysis strategy was first to select a base model, then to perform both a univariate and a multiple forward selection analyses to get a full model including covariates. The association between the following potential covariates and clearance and distribution volume was examined: age, body weight, body surface area, gender, ethnicity, creatinine clearance, a renal maturation factor, concomitant AEDs, and dose. Dose and age were also tested on the absorption rate. The potential formulation effect was not tested as it was confounded with an age effect (almost only the youngest children received the solution).
This was followed then by a backward elimination analysis. A sensitivity analysis was performed to check if any of the statistically significant covariates were not clinically relevant. The model was then validated using the posterior predictive check technique. Once validated, it was used to perform some simulations to establish dose adjustment, if any, for children below 4 years of age.

RESULTS:

The structure model for the final base model was one-compartment model with first-order absorption and first-order elimination, including log-normally distributed inter-individual variability on Ka, CL/F, and V/F. Both CL/F and V/F were described as functions of body weight. The residual was described by the proportional error model. The model parameter

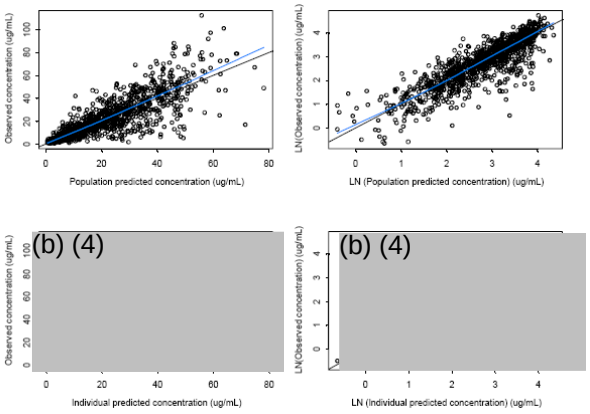
estimates were summarized in Table 22 and the major goodness-of-fit plots were shown in Figure 21.

Table 22 Levetiracetam Base Population PK Model Parameter Estimates

Parameter	Estimate [95% CI]	Precision (%CV)[a]
KA= Θ_{KA} Θ_{KA} (h^{-1})	3.03 [1.99-4.07]	17.6%
CL/F = Θ_{CL} *(BW/25)**(0.75*$\Theta_{BW,CL}$) Θ_{CL} (L/h) $\Theta_{BW,CL}$	1.92 [1.84-2.00] 0.989 [0.897-1.08]	2.11% 4.72%
V/F = =Θ_V*(BW/25)**(1*$\Theta_{BW,V}$) Θ_V (L) $\Theta_{BW,V}$	16.7 [15.7-17.7] 0.966 [0.878-1.05]	3.19% 4.64%
Variability	**Estimate in %CV[b]**	**Precision (%CV)[a]**
Inter-individual variability in KA	97.5%	31.9%
Inter-individual variability in CL/F	20.5%	14.4%
Inter-individual variability in V/F	13.0%	49.7%
Residual variability in concentrations	30.0%	8.16%

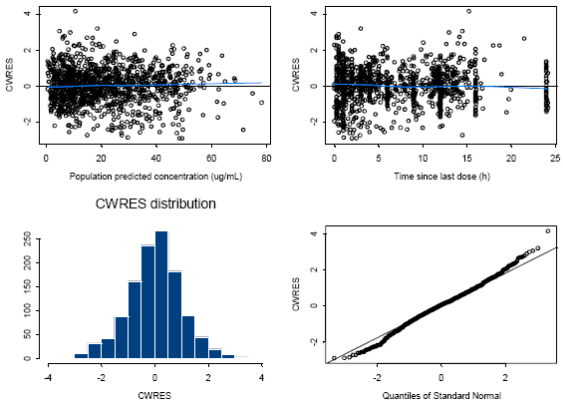
[a] Precision was calculated as s.e. divided by the parameter estimate x 100.
[b] The %CV for both inter-individual and residual variability is an approximation taken as the square root of the variance x 100.

Figure 21 Goodness-of-fit Plots for Levetiracetam Base Population PK Model Derived from Trial SP640



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

(A)



(B)

Note: (A) is observed versus population predicted and observed versus individual predicted in both regular scale and log-transformed scale

(B) is conditional weighted residual versus population predicted, time, the distribution of conditional residual.

The final model was selected from the base model chosen with the same inter-individual variability and residual error structure. The covariate effects were described as following:

CL/F was expressed by the following equation:

$$CL/F = \Theta_{CL} * (\frac{BW}{25})^{0.75 x \Theta_{BW,CL}} x \Theta_{AEDC,CL} * \frac{(AGE*12+9)^{2.5}}{\Theta_{MF,CL}{}^{2.5} + (AGE*12+9)^{2.5}}$$

where:

Θ_{CL} is the typical value of CL/F in L/h

$\Theta_{BW,CL}$ is the power exponent of the body weight relationship

$\Theta_{AEDC,CL}$ is a multiplicative factor for the influence of the inducing AEDs on CL/F. It is equal to 1 for subject not taking inducing AEDs and to 1.19 for subject receiving at least one inducing AED.

$\frac{(AGE*12+9)^{2.5}}{\Theta_{MF,CL}{}^{2.5} + (AGE*12+9)^{2.5}}$ is overall a relation taking into account the maturation of the renal function (maturation factor). $\Theta_{MF,CL}$ is multiplicative factor of MF.

AGE is in years

V/F was expressed by the following equation:

$$V/F = \Theta_{V} * (\frac{BW}{25})^{1*\Theta_{BW,V}} * (\frac{AGE}{8})^{\Theta_{AGE,V}}$$

where:

Θ_{V} is the typical value of V/F in L

$\Theta_{BW,V}$ is the power exponent of the body weight relationship

$\Theta_{AGE,V}$ is the power exponent of the age relationship

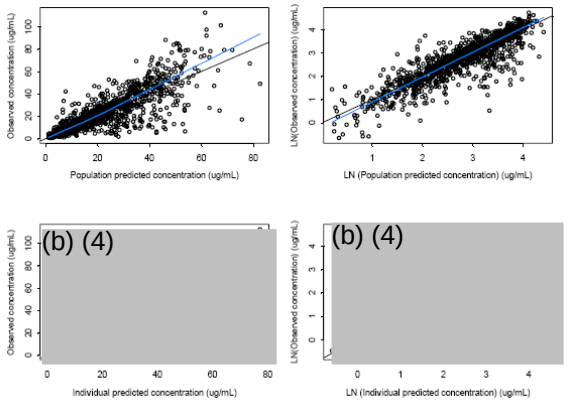
The final parameter estimates were summarized in Table 23. Goodness-of-fit plots were shown in Figure 22.

Table 23 Parameter Estimates for the Final Model for Levetiracetam

Parameter	Estimate [95% CI]	Precision (%CV)[a]
Absorption		
Θ_{ka} (h-1)	4.24 [2.93 – 5.55]	15.8
Clearance		
Θ_{CL} (L/h)	1.86 [1.76 – 1.96]	2.84
$\Theta_{BW,CL}$	0.904 [0.795 – 1.01]	6.13
$\Theta_{AEDC,CL}$	1.19 [1.09 – 1.29]	4.42
$\Theta_{MF,CL}$	12.3 [9.67 – 14.9]	10.9
Volume		
Θ_{V} (L)	17.8 [16.5 – 19.1]	3.58
$\Theta_{BW,V}$	0.684 [0.482 – 0.886]	15.1
$\Theta_{AGE,V}$	0.198 [0.0851 – 0.311]	29.1
Variability	**Estimate (%CV)[b]**	**Precision (%CV)[a]**
Inter-subject variability in ka	64.3	39.0
Inter-subject variability in CL/F	19.5	15.9
Inter-subject variability in V/F	12.5	48.3
Residual variability in concentration	30.7	7.96

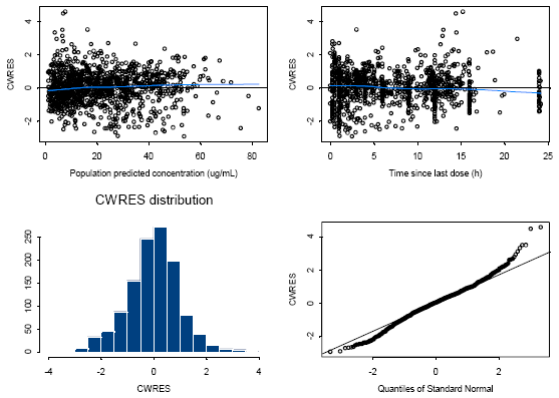
[a] Precision was calculated as the s.e. divided by the parameter estimate × 100.
[b] The %CV for both inter-subject and residual variability is an approximation taken as the square root of the variance × 100.

Figure 22 Goodness-of-fit Plots for Levetiracetam Final Population PK Model



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

(A)



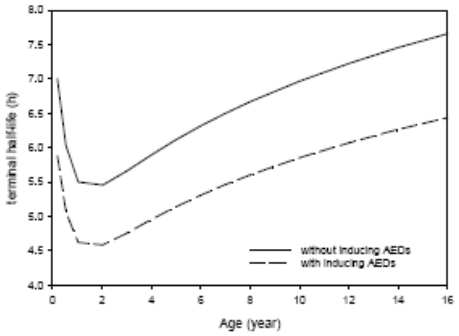
(B)

Note: (A) is observed versus population predicted and observed versus individual predicted in both regular scale and log-transformed scale
(B) is conditional weighted residual versus population predicted, time, the distribution of conditional residual.

Model validation was performed using the posterior predictive check method. Although strictly speaking more than 10% of the points were outside the PI, the majority of those were close to the PI margins, indicating that the model slightly underestimate the variability in the data. Given that this deviation was not deemed serious and that there was no systematic bias, the model was considered to be validated.

Based on the final model, the variation in the terminal half-life was not monotonous as shown in the Figure 23. For children taking concomitant inducing AED, whether alone or not, the shape of the curve was the same but had to be shifted downward by approximately 20%.

Figure 23. Age and Terminal Half-life Relationship



The effect of age on both CL/F and V/F decreases as age increases. Its influence on CL/F through the maturation factor becomes negligible after the age of 2 years and on V/F becomes negligible around 4. This was substantiated when the clinical significance was tested: although age was significant, its effect was much more pronounced over the lower age range simulated (7 months to 2 years) than over the higher age range (2 to 5.5 years). This is likely due to the major changes that occur in the first years of life with regards to the maturation of the renal function and to the body composition, mainly decrease in total body water and increase in body fat.

In the previous population PK analysis (N01139) the age effect was not significant on volume of distribution and was not tested through the renal maturation factor on CL/F due to the age range in the population. However, when CL/F, V/F and t½ are calculated from 6 years onward with the 2 models (N01139 and N01288), the values are very similar differing in most cases by less than 10% .

Simulations of exposure in children from 1 month to 4 years were performed to evaluate the necessity of a dose adjustment, and to establish if necessary a nomogram. A dose of 10 mg/kg per intake was chosen as this is the currently recommended starting dose. The nomogram is applicable whatever the dose as the pharmacokinetics of LEV is dose proportional.

The simulations showed that the dose should be reduced by a factor that depends on age to obtain en exposure equivalent to that observed in a 4 year old (Figure 24). Children aged one to 6

months would require about (b) (4) and children aged from 6 months onward 100% of the dose of children aged 4 years to reach the same exposure.

As an example, to get a similar exposure to that observed in a 4 year old receiving the recommended 10 mg/kg per intake starting dose, (b) (4) mg/kg per intake, the following doses would be recommended (Table 24):

Figure 24 Dose Adjustment Nomogram

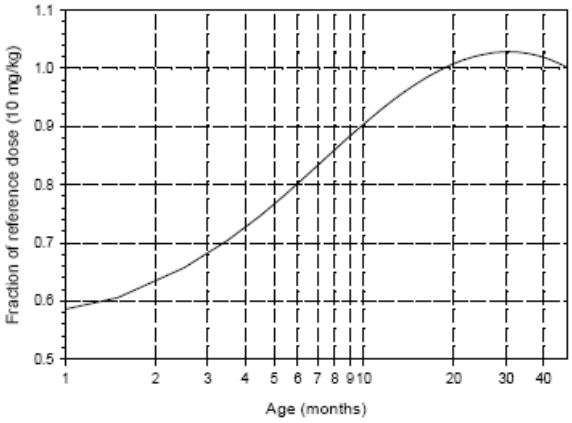


Table 24. Recommended Dose at Different Age Groups

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

Conclusion:

The pharmacokinetics of levetiracetam, including interindividual variability, was characterized in children aged from 1 month to 17 years inclusive. The major covariates explaining the intersubject variability were BW on both CL/F and V/F, followed by inducing AEDs on CL/F, and a factor based on age taking into account the renal maturation, as well as age on V/F. The dose was not a significant covariate in the model, confirming the dose proportionality of levetiracetam pharmacokinetics. A nomogram was established to help with dose adjustment in children from 1 month to 4 years. Dose reduction is suggested for the 1 to 6 month children, to (b) (4) of the dose of older children.

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5.1.2 Exposure-Response of Levetiracetam in Pediatric Subjects, Study Report Number: N01308

Objectives:

- To develop an exposure-response model for levetiracetam in adults and children using non-linear mixed-effects modeling based on seizure frequency data of individual subjects with refractory epilepsy suffering from partial onset seizures as obtained in the four phase-III studies of levetiracetam in adults combined with the studies of levetiracetam in children.

- To undertake simulations based on the exposure-response model of levetiracetam in adults and children to aid in providing a rationale for an optimal dosing scheme of levetiracetam in children.

Clinical Study Overview:

Clinical observations from 6 clinical trials were included in the population exposure-response analysis. They were summarized in Table 25.

Table 25 Summary of Clinical Studies included in the Exposure-Response Analysis

Population	Age	Study	Dose	Treatment Duration
Adult	NA	N501	500 mg, 1000 mg, BID and Placebo	12 Weeks
	NA	N502	1000 mg, 2000 mg, BID and Placebo	24 Weeks
	NA	N132	500 mg, 1500 mg, BID and Placebo	14 Weeks
	NA	N138	1500 mg, BID and Placebo	12 Weeks
Children	4 - 16 yr	N 159	60 mg/kg/day and Placebo	14 Weeks
	1 month - 4 yr	N01009	20 - 50 mg/kg/day	Up to 20 days

(Summarized from P-4, Synopsis)

Data for Analysis:

There were 950 subjects in the four combined adult trials, 195 subjects aged 4 – 16 years, and 106 subjects aged 1 month to 4 years were included in the analysis dataset.

The influence of continuous and categorical covariates was evaluated using graphical exploration. No covariates were formally tested in the model.

Analysis Method:

Data analysis was performed by nonlinear mixed effects modeling using NONMEM VI with the Laplace estimation method.

A Poisson distribution (Equation 1) was used for pooled data (counts per period) where pediatric and historical adult data were combined to allow overall predictions comparing the reduction in seizure frequency between adults and children. A zero-inflated Negative Binomial model including Markovian elements was used for Study N159 where daily seizure counts were

available. A Mixture procedure was used to separate improving and deteriorating subjects (viz., subjects exhibiting reduced or increased seizure frequency from baseline). The drug effect was modeled in improving subjects as a hyperbolic function of dose or plasma exposure (Emax function).

$$P(DV) = \frac{\lambda^{DV}}{DV!}\exp(-\lambda)$$

(Equation 1)

Results

An existing model for the effect of levetiracetam on seizure frequency in refractory epilepsy patients developed for adults was extended to data obtained from two separate pediatric studies. The original model described total seizure counts over a specified period. Application of the total seizure counts per period model to the combined adult and pediatric data revealed that the data were well described by a combined mixture model of improving and deteriorating patients that assumed a Poisson distribution.

The proportions of improving patients (viz., those exhibiting a lower seizure frequency than at baseline) under placebo or levetiracetam were similar between adults and children. The fractional changes in seizure frequency were also similar among the three populations. Despite the large uncertainty, the ED50 in young children (153 mg/day in study N01009) was lower than in older children (217 mg/day in study N159) and lower than in adults (1353 mg/day).

Parameters (CV or 90%CI)	Adults		N159		N01009	
	Improving	Deteriorat.	Improving	Deteriorat.	Improving	Deteriorat.
Placebo sub-populations (fraction)	0.63	0.37 (12%)	0.73	0.27 (19%)	0.63	0.37 (32%)
Placebo fractional change	-0.22 (13%)	0.32 (0.25-0.41)	-0.19 (7%)	0.48 (0.38-0.61)	-0.19 (7%)	0.50 (0.17-1.08)
LEV sub-populations (fraction)	0.76	0.24 (10%)	0.81	0.19 (22%)	0.79	0.21 (33%)
E_{max} (fractional change)	0.55		0.57		0.57	
ED_{50} (mg/day)	1353 (682-2685)		217 (46-1014)		153 (22-1042)	

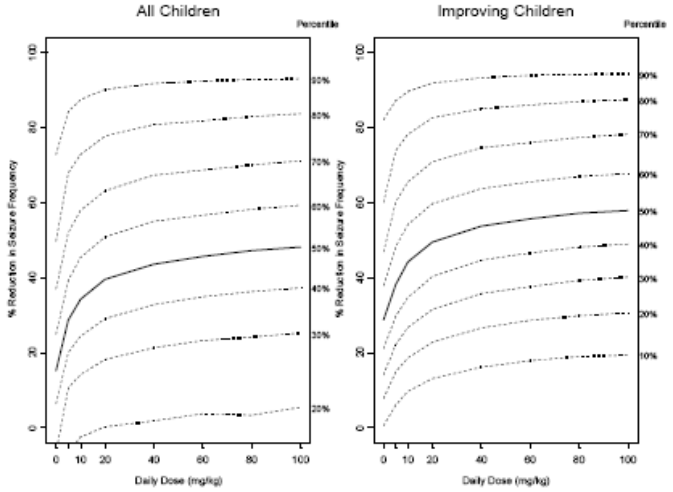
Study N01009 appeared similar to those of study N159. The predictive performance of the model was evaluated using the visual predictive check method: Two thousand clinical trials were simulated for each study, and the distribution of outcomes (median percentage change from baseline and percentage of responders) was well centered on the observed value for each study. Therefore, the results do not indicate a different exposure-response and dosing scheme in children less than 4 years as compared to the recommended dosing scheme of LEV in children older than 4 years of age.

Daily seizure count data were available for one of the pediatric studies (N159), allowing to build a superior model to what had been possible previously. Modeling of daily counts enabled assessment of the adequacy of the traditional Poisson assumption previously used for describing

seizure counts. The data were best described using a zero-inflated Negative Binomial model including Markovian aspects. The ED50 in these 4- 16y children based on the model of the daily seizure counts (287 mg/day) was found to be similar to the ED50 estimated from the counts per period model.

Simulations using the daily seizure count model indicated that a daily dose of 60 mg/kg is predicted to result in a reduction in seizure frequency of ≥ 45% in half of the patients and a reduction of ≥ 55% in half of the improving patients (Figure 25).

Figure 25 Predicted dose-response relationship in children with quantiles of the percentage reduction in seizure frequency from baseline as a function of dose.



Finally, only a minor incremental reduction in seizure frequency (total seizure count) was predicted in improving children for daily levetiracetam doses above 20 mg/kg. As the reduction in seizure frequency in children after a levetiracetam dose of 20-(b) (4) mg/kg/day was predicted to be slightly higher as compared to the recommended dose range of 1000-(b) (4) mg/day in adults, a daily levetiracetam dose of 20-(b) (4) mg/kg is suggested to be optimal as add-on treatment in refractory pediatric patients with partial onset seizures.

Reviewer's Comments on Population Pharmacokinetic Analysis and Dose-Response Analysis

- The sponsor performed population pharmacokinetic analysis in pediatric patients and adult patients. The analysis approach is acceptable. In covariate analysis, the sponsor used equation 5.3.1 to describe the relationship between body weight, age, and co-administration of inducer/others with clearance. We found that the sponsor's covariate model did not account for additional variability in clearance as compared to the simpler model we used. Therefore, we applied equation 5.3.2 in our analysis and further simulation study.

$$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times \theta_4 (AEDC) \times (\frac{AGE \times 12 + 9}{\theta_3 + AGE \times 12})^{2.5} \quad \text{(Equation 5.3.1)}$$

$$CL/F = \theta_1 \times (\frac{BW}{25})^{0.75 \times \theta_2} \times \theta_4 (AEDC) \times (\frac{AGE}{\theta_3 + AGE}) \qquad \text{(Equation 5.3.2)}$$

- In order to select appropriate dose in pediatric patients aged 1 month – 4 years, the sponsor preformed dose-response analysis and simulation based on observation from pediatric patients aged 4 – 16 years (Study N159). We disagree with this approach because our analysis indicate that there are different dose-response relationships for patients aged 1 month – 4 years and patients aged 4 – 16 years. Therefore, the simulation results conducted from one age group should not be extended to another age group.
- Exposure-response, rather than dose-response should be applied in simulation, because our analysis indicates that similar exposure-response relationship can be found across different age groups (i.e. 1month – 4 years, 4 – 16 years, and ≥ 16 years). Therefore, if we can match the exposure in the approved population, then similar treatment effect is expected.

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