London, 13 September 2005
Product name: **Keppra**
Procedure No. **EMEA/H/C/277/II/44**

SCIENTIFIC DISCUSSION

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1. Introduction

This application relates to new data submitted by the MAH to extend Keppra's indication to children from 4 years of age as adjunctive therapy in the treatment of partial onset seizures.

Levetiracetam (UCB L059), the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide is currently indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age. The recommended dose-range is 1000-3000 mg/day in a BID regimen. This type II variation proposes to extend the indication to children from 4 years of age. Since epilepsy in children differs from that in adults, and adverse events of anti-epileptic drugs (AEDs) may significantly impact the maturing CNS, separate clinical studies are needed in children (see Note for Guidance on AEDs).

The proposed dosing regimen for children is a twice-daily target dose of between 20 and 60 mg/day. This will be titrated from a twice-daily starting dose of 20 mg/day with the maintenance dose being selected on an individual patient clinical response basis. Dosage in children 40 kg or greater is proposed to be the same as in adults. Maximum dosage in children is 60 mg/kg/day. The already approved formulations (tablets of 250 mg and oral solution of 100 mg/ml) will be used for this extension to the adult adjunctive therapy indication. The other formulations approved in the EU are tablets of 500, 750 and 1000 mg.

Levetiracetam derived from a research effort originally orientated toward the discovery of GABAergic compounds with potential application in various cerebral disorders and only commenced development as an AED in the early 1990s. Data from a large number of pharmacodynamic investigations, pharmacokinetic, safety pharmacology and toxicology have previously been evaluated (original MA Application 1999; EMEA/H/C/277). For this extension application, further efficacy and safety studies have been undertaken, with particular focus on the safety in neonatal and/or juvenile rats and dogs to assess the effects on maturation processes and subsequent reproductive potential of the drug.

2. Chemical, pharmaceutical and biological

Not applicable

3. Toxico-pharmacological

The excipients used in the final formulation are all pharmacopoeial materials (except Opadry and Grape Flavour) and pose no safety concerns. The limits set for impurities in the drug substance comply with ICH guidelines inasmuch the 2 major impurities, 2-pyrrolidone-N-butyric acid (known as UCB L057, itself the main human metabolite of levetiracetam) and the R-enantiomer of levetiracetam (known as UCB L060), representing <0.3% and <1%, respectively, have been qualified (as detailed in the Quality Overall Summary) and present no safety concerns. The threshold for all other impurities is ≤0.05%. The limits for residual organic solvents are compliant with the corresponding ICH guideline.

The pharmacokinetic profile of ucb L059 is uncomplicated and similar in all species investigated including man. The metabolism is minor and approximately 60% of the substance is excreted unchanged in urine, which is the main route of excretion in both humans and animals. The extent of the major metabolite in man, L057, is somewhat lower in animals compared to man. No major differences in metabolism between children in the target age and adults have been identified.

To support the paediatric indication, the MAH submitted four studies: a preliminary 2-week repeated dose toxicity study in juvenile beagles (dosage-range finding), a 4-week repeated dose toxicity study in juvenile beagles followed by a 4-week recovery period, a 7-week oral gavage toxicity study in neonatal/juvenile Sprague Dawley rats and a study in Rhesus monkeys focused on gross behavioural observations of acute CNS effects and intravenous self-administration.

In the original MAA for Keppra, in non-clinical toxicity studies carried out with adult animals the main target organs were kidney, liver and the CNS. With respect to the kidney, it was demonstrated

that levetiracetam induced accumulation of hyaline droplets through α2-microglobulin accumulation specifically in male rats. This effect was also seen to be reversible upon cessation of treatment and was considered as non-relevant to humans.

Concerning the liver effects in the adult rat, treatment-related changes consisted of increased weights, centrilobular hypertrophy, fatty infiltration, and increased serum enzymes. After long-term exposure in the rat, the effects were observed at clinical exposure levels. The changes were attributed to an adaptive change generally associated with microsomal enzyme induction, a finding demonstrated in the rodent with several compounds, and not regarded as an adverse effect of treatment. There were no neoplastic changes in the carcinogenicity studies. The relevance for humans is considered unknown and section 5.3 of the SPC reflects the liver effects.

The MAH conducted single dose toxicity studies in neonatal rats and in juvenile dogs and repeat dose toxicity studies have been conducted in neonatal rats (up to 7 weeks) and in juvenile dogs up to 4-weeks in order to support the paediatric indication.

Single dose toxicity studies in neonatal rats and juvenile dogs show a very low order of acute toxicity, which is similar to that seen in adult animals of the same species. The liver was the same target organ in neonatal rats as it was in the adult rat with mild hypertrophy of centrilobular hepatocytes, attributed to proliferation of smooth endoplasmic reticulum.

The kidney of neonatal male rats showed mild hyaline droplet nephropathy linked to the short-term nature of drug administration. As with adult rats there was no effect of treatment on the kidneys of female neonatal rats. The pathogenesis of hyaline droplet nephropathy has been documented extensively as a lesion that is unique to the male rat with no predictive value with regard to the extrapolation of risk to man.

In the dog, transient CNS signs were generally associated with high oral dose levels. No target organ was identified at histopathology in juvenile dogs.

Reproduction toxicity parameters in neonatal rats and juvenile dogs did not identified any effects of levetiracetam that could be associated with adverse effects upon maturation processes or subsequent reproductive performance.

In neonatal rats and juvenile dogs, levetiracetam appeared to be well absorbed as the plasma levels and exposure were similar to those observed in adult animals at equivalent doses. Trough levels of levetiracetam declined with age in neonatal rats. As levetiracetam is cleared mainly by excretion of unchanged compound into the urine, this finding is consistent with lower glomerular filtration rates in neonatal rats, which are low in 10-day old rats but approach adult values by 7 weeks of age. In the juvenile dog, no trends were observed with age for trough concentrations of levetiracetam. At doses used in toxicology studies, levetiracetam generally displayed linear pharmacokinetics after single or repeated administration in the neonatal rat. In the juvenile dog while pharmacokinetics were generally linear following a single-dose, there was a hypo-proportional increase in exposure with dose following repeated administration suggesting auto-induction.

The NOAEL was considered to be 450 mg/kg/day for males (with a $C_{1.5h}$ value of 244-450 µg/mL) and 1800 mg/kg/day for females (with a $C_{1.5h}$ value of 664-1569 µg/mL). For children receiving the maximum dosage, 60 mg/kg/day, the C_{max} and $AUC_{(0-24h)}$ is 73 µg/mL and 427 µg/mL, respectively. Using the NOAEL levels, the margin to human exposure in the 4-week dog study was approximately 8 when comparing C_{max} and 11 when comparing AUC-levels. In the 7-week rat study, the margin to human exposure based on AUC-levels was approximately 2 and 9 for male and female rats, respectively.

In conclusion, the newly performed neonatal studies demonstrate that levetiracetam presents a low risk of causing adverse effects upon developmental and maturation processes in children at the proposed therapeutic doses, and support the following statement added to section 5.3 of the SPC for this extension of indication of Keppra:

Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day corresponding to 30 times the maximum recommended human dose.

The MAH agreed with the CHMP conclusions and provided Annexes amended accordingly.

4. Clinical aspects

4.1 Clinical pharmacology

The MAH proposed that as a result of new data on pharmacokinetics included in this application, the SPC be revised to insert wording relating to paediatric patients in three main areas, as follows:

- treatment in children from the age of four years;
- a statement on interactions in section 4.5 and information about pharmacokinetic characteristics in paediatric patients older than 1 month in section 5.2;
- In addition, information on the relationship between saliva and plasma concentrations is proposed for inclusion in section 5.2.

Pharmacokinetic characteristics
Levetiracetam has a fast and almost complete absorption, no food-interaction, low protein binding, moderate volume of distribution, and a terminal half-life of 6-8 hours. The drug is eliminated through renal excretion, including active secretion (66% of CL) and through metabolism catalysed by amidases/esterases to the inactive carboxylic acid metabolite ucb L057. Clearance in adults has been estimated to approximately 80 ml/min (4.8 L/min).

Pharmacokinetic documentation in support of the suggested SPC changes
Three standard pharmacokinetic studies have been submitted where the pharmacokinetics is investigated in children between 2.3 months and 12 years of age (Studies N01052, N151 and N01010). In addition, sparse sampling was performed in two clinical studies, (N157, N159) and all available data (from the five studies) were included in a population pharmacokinetic analysis (N01139). Also results from a study of the correlation between plasma and saliva concentrations in adults have been submitted. A significant correlation between saliva and plasma concentrations has been shown in adults and children. The MAH states that the ratio of saliva/plasma concentrations ranged from 1 to 1.6 for oral tablet formulation and (after 4 hours post-dose) for oral solution formulation.

Population pharmacokinetic analysis
Levetiracetam concentrations vs. time profiles were available for 228 patients between 1 month and 18 years of age. For the basic model a one-compartment model with first order absorption and first order elimination was found to best characterise the plasma concentration-time profile for levetiracetam, with interindividual variability on each primary parameter and inter-occasion variability on Ka, and proportional residual error. The modelling was performed on log-transformed concentrations. The report was clear and both the analysis procedure and results were adequately presented and discussed. The covariate found for CL/F were (in ranking order): body weight, followed by age and BMI, CL_{CR} and dose. The resulting model is defined by the equation: $CL/F=K * 2.17(Bw/30)^{0.640} * (Dose/500)^{0.0443} * (CL_{CR}/100)^{0.111}$ where K=1 for children not receiving inducing AED and K=1.22 if children receive at least one dose of a concomitant inducer. There was also an association between Ka and age: $Ka=1.46*(age/10)^{0.27}$ and a statistically significant relation between V/F and bodyweight (BW); $V/F=21.5*(Bw/30)^{0.901}$.

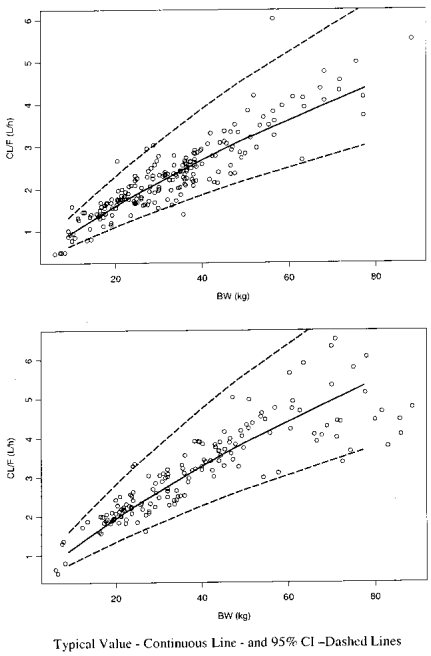
Concomitant intake of other antiepileptic drugs increased CL/F by a mean of 22% and this was believed to be an underestimation.

To evaluate the relative influence of the covariates, contribution factors were calculated based on the characteristics of the patients in the dataset, divided in six groups. The effect of bodyweight was much larger than the influence of dose and CL_{CR}. Therefore, these factors were removed creating a reduced model. The influence on clearance by age was lower than the influence of bodyweight. Age was not

included in the reduced model. However, it is not clear whether the performance of a model including both age and bodyweight was tested. The covariates for Vd/F were age and body surface area (BSA). As BSA has a strong correlation with BW and the effect of BSA was very similar to BW, the latter was chosen. The final reduced model was defined by: CL/F=K * 2.18(Bw/30)$^{0.753}$.

Figure. 1. Population prediction of CL/F at the first visit.

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



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

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

There was no simulation including the variability of the estimates. It is possible that the variability is higher in children of certain weight ranges than in other children and adults. In the presentation of the simulations, a typical paediatric value is compared with the exposure range observed in adults.

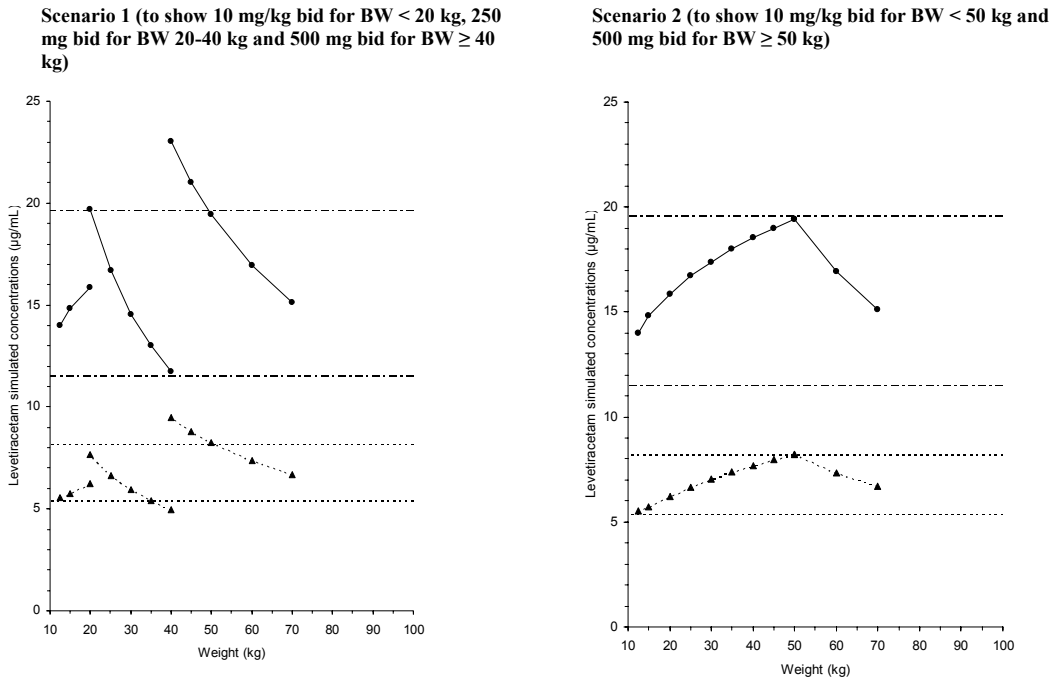
The effect of levetiracetam on the pharmacokinetics of other AEDs was studied by repeated measures covariance analysis. No effect on the steady state trough concentrations of carbamazepine or valproic acid was observed. Too few data was available for the other antiepileptic drugs to obtain reliable statistics.

After their first assessment of the documentation submitted by the MAH, a number of concerns were identified by CHMP in the area of pharmacokinetics. The MAH were therefore requested to provide clarifications on aspects of the PK data submitted. Due to their significance, these PK-related concerns (text *in italics*) and the MAH's answers to them are discussed individually below:

- *As the submitted pharmacokinetic documentation appeared to support that the mean exposure of levetiracetam is similar in adults and in children from the age of 4 years (with the exception of children with body weights between 40 and 50kg which are predicted to have a higher mean exposure), the MAH was requested to discuss the results of the simulations taking into account the expected variability in children. Based on the simulations of typical patient curves, as the dose is titrated and due to clinical indications that the exposure may be unnecessarily high, it was proposed by CHMP that a bodyweight cut-off of 50 kg instead of 40 kg be used. Furthermore, the MAH was requested to comment on the fact that the initial adult dose (1000mg) corresponds to a weight of 50 kg at 20 mg/kg/day, and not 40 kg, and adapt the recommended dosage and weight accordingly.*

The MAH argued that the final model of population pharmacokinetic analysis was used to simulate plasma concentrations that would be achieved using the recommended dosing scheme based on available tablet strengths and the oral solution (Module 5, Vol. 9, Section 5.3.3.5 - N01139, page 36). The aim of the simulation is to get similar plasma concentrations as in adults after 500 mg bid (the recommended starting dose). Four scenarios were simulated. Two of these were finally selected and are presented in Figure 2 below.

Figure 2 **Simulated Levetiracetam Steady State C_{min} (Dotted Line, Triangles) and C_{max} (Continuous Line, Circles) in Children Receiving a Possible Body Weight (BW) Based Dosage Regimen. Horizontal Lines Represent the Simulated C_{min} (Dotted) and C_{max} (Dashed) Ranges in Adults.**



Because of the flexibility of dosing with a solution, a recommendation of 10 mg/kg bid (20 mg/kg/day) for children weighing less than 50 kg, and 500 mg tablet bid, similar to adults, above 50 kg, appears to be an adequate dose adaptation rule since predicted steady-state C_{min} and C_{max} values are within the range observed in adults receiving 500 mg bid. This scenario (#2) has the disadvantage of requiring administration of a solution to children weighing up to 50 kg (i.e. age of 14 years).

Scenario 1 making use of the tablet strengths available predicts most steady-state C_{min} and C_{max} values within the ranges observed in adults. However, if the cut-off to switch from 250mg tablet bid to 500 mg tablet bid is set at 50 kg, the 250 mg tablet bid is predicted to result in lower C_{min} and C_{max} values for children weighing more than 40 kg than those obtained in adults receiving 500 mg bid. The actual dose administered for 40 kg would be 12.5 mg/kg/day, decreasing to 10 mg/kg/day as the weight increases to 50 kg, i.e. half the targeted dose of 20 mg/kg/day. Consequently, the cut-off for the 500 mg tablet bid was extended to children weighing 40 kg (which is equivalent to 25 mg/kg/day for 40 kg, decreasing to 20 mg/kg/day as weight increase). With this scenario, steady-state C_{min} and C_{max} values were within the ranges observed in adults in most children. But, as expected, children weighing between 40 and 50 kg were predicted to have steady-state C_{min} and C_{max} values at most 20% higher than those simulated in adults receiving 500 mg bid. However, the safety of levetiracetam is very good and much higher concentrations have been well tolerated in studies N159 and N157. Furthermore, the inter-subject variability for the different parameters of the model, leads to a range of concentrations of at least 2 fold whatever the dose. Therefore, the slight increase observed for the children above 40 kg is not significant.

Hence, the initial recommendation of the 40 kg cut-off was based on the fact that the switch from 250 mg tablet bid to 500 mg tablet bid with a 50 kg cut off leads to typical predicted concentrations that are slightly below the observed concentrations at 1000 mg per day in adults. However, further to the CHMP comment, it is understood that the body weight cut-off for the recommended dose should be based on the switch from a prescription by mg/kg/day to mg/day, as in adult, and therefore should be 50 kg.

The dose adjustment will be made on individual titration to the optimal dose and the clinician will decide on the most appropriate dosage formulation for the patient.

As suggested by the CHMP, the above population PK simulations show that a posology of 10 mg/kg bid for BW < 50 kg and 500 mg bid for BW ≥ 50 kg yields the best results as compared to adult PK data. In the light of the fact that the MAH agreed to the CHMP's proposal and that the Posology has been adapted in the SPC/PL, this issue is resolved. Updated Product Information has been provided accordingly.

- *In adults, elimination half-life is known to be 7 ± 1 hours after single or repeated administration. Elimination half-life was 6 hours after single administration of 20 mg/kg BW in children aged 6 to 12 years and only approximately 5 hours after repeated administration of 20 to 60 mg/kg BW in children aged 4 to 12 years. Thus, the MAH was asked to discuss if (especially younger) children could benefit from a more frequent than twice-daily administration. TID could give less adverse events and better efficacy than BID.*

The MAH responded that, as the elimination half life (t½) of a drug usually determines the administration frequency, and since the t½ for levetiracetam in children is around 5−6 hours, it would be expected that a three times daily (TID) regimen would be warranted for levetiracetam. However, throughout the clinical trials evaluation program of levetiracetam, a highly efficacious and sustainable effect was observed with twice daily (BID) administration. These findings are further supported by the following data.

- Levetiracetam pharmacokinetics in the cerebrospinal fluid (CSF) and brain extracellular fluid of rats, and CSF of human. It appears that the efflux of levetiracetam from both the extracellular fluid (ECF) and CSF compartments is restricted, with t½ values that are approximately 50% and 100% longer, for ECF and CSF respectively, than that observed in serum. A study in four patients showed that peak levels of levetiracetam are achieved rapidly in both the serum and CSF after a single oral loading dose. Levetiracetam CSF t½ is twice as long as that of levetiracetam in serum. This may in part explain the substantial clinical efficacy of levetiracetam during BID dosing.

- A study in 12 patients with photosensitive epilepsy who were administered a single oral dose (250-1000 mg) of levetiracetam. In the nine patients who experienced a suppression of photosensitivity, the effect occurred within 1 hour after drug ingestion and was associated with blood concentrations of 40–170 µmol/L. Of particular note, however, is that suppression lasted > 6 hours (24 – 30 hours in two patients), by which time plasma levetiracetam concentrations were very low (< 18 µmol/L).

- A transcranial magnetic stimulation study of levetiracetam in a series of six healthy subjects aged 25-38 years. Transcranial magnetic stimulation provides a non-invasive test to assess the effect of AEDs on corticospinal excitability. After a single oral dose of levetiracetam 3000 mg a time-dependent suppression of motor-evoked potentials amplitude was observed in all six subjects. The effect became distinct at 1 hour and was still present at 24 hours post dose.

Thus, the MAH consider that there are compelling data to support that levetiracetam has a long duration of action that outlasts its blood concentration. These are the basis of BID dosing strategy of levetiracetam in clinical development. The efficacy data in clinical studies confirmed that BID is the most appropriate frequency of dosing. Furthermore, the MAH considered that changing the dosing regimen from BID to TID might decrease the compliance, and also lead to fluctuations due to the fact

that, from a practical point of view, it would be difficult to give 3 doses separated by 8 hours in children. Finally, the MAH believe that this may potentially lead to confusion when the children would be switched from TID to BID.

In summary, UCB considers BID dosing the most appropriate dosing recommendation based on the following:

- Efficacy seems to be appropriate with BID due to an apparent disconnection between plasma t½ and duration of efficacy in the brain (possibly due to a longer t½ in the brain).
- Safety does not seem to be an issue with BID.
- Strict TID (i.e. every 8 hours) is unlikely to be achieved, and, added to the potential decrease in compliance, would also lead to fluctuation.
- Change from TID to BID might lead to confusion and errors in prescription.

The CHMP endorsed the MAH's summary and justification of the BID posology, although the scientific data provided to support a long duration of action of levetiracetam outlasting its blood concentration are all related to adults. Significant differences may exist between adults and children in this regard, so this information has limited value. Nevertheless, the efficacy data outweigh the PK data and a BID regimen is probably preferable for practical reasons. CHMP therefore considered this issue resolved.

- *The MAH was asked to submit the pharmacokinetic report of study N151 and verify which dose the reported pharmacokinetic parameters were related to. The MAH was also asked to present plots on AUC vs. age and Cmax vs. age for giving a clearer view of the results and the effect of age on the pharmacokinetics of levetiracetam and its metabolite.*

The pharmacokinetic report of study N151 was submitted. Graphs on AUC vs. age and Cmax vs. age were attached for levetiracetam and its metabolite. The pharmacokinetic results were related to a dose of about 20 mg/kg (range 12.8-29.1 mg/kg). The report also displayed graphs on clearance and t½ vs. age. No correlations between age and the pharmacokinetic parameters were observed. This is expected, as a clear correlation between age and body weight was demonstrated (coefficient of correlation = 0.895) and the doses were adjusted according to the body weight.

CHMP considered that no trends between age and AUC, Cmax, t½ and clearance were observed for levetiracetam. For the metabolite, no correlation between age and AUC or age and Cmax was demonstrated. CHMP therefore considered this issue resolved.

- *The MAH was requested to disclose the co-medications used in the pivotal PK study N01052.*
  The MAH advised that summary statistics of concomitant medications used in study N01052 were provided in the submission (Module 5, Vol. 5, Section 5.3.3.3 – Study N01052, pp 87-93: Table 14.1.3.1, and Table 14.1.3.2). Out of 13 patients, 7 took benzodiazepines, 4 phenobarbital, 4 valproic acid or vigabatrin, and 8 other AEDs (hydantoins, oxcarbazepine, gabapentin, lamotrigine, topiramate). CHMP therefore considered this issue resolved.

- *The information regarding children between 1 month and 4 years should be further discussed. The MAH is requested to submit the results of study N01052 as plots of Cmax, AUC and t½ vs. age as continuous variable.*

Scatter plots of Cmax, AUC and t½ vs. age as continuous variable for levetiracetam using data from study N01052 were provided. In this study no effect of age was demonstrated based on either Cmax or AUC after administration of levetiracetam at the dose of 20 mg/kg.

CHMP considered that no trends between age and any of the pharmacokinetic parameters were observed. This issue was therefore considered resolved.

- *In study N01052, 4 treatment-emergent ADRs were reported for 3 subjects. Nausea, vomiting, lethargy and eczema were reported for 1 patient each. The ADRs were of mild or moderate intensity and were considered by the investigators not to be related to study drug*

administration. However, as nausea, diarrhoea and lethargy could be related to some degree of fructose intolerance, the MAH was requested to investigate the risk of undiagnosed fructose intolerance and to clearly indicate this risk in the warnings section of the SPC for the solution.

The MAH pointed out that, as part of the recent 5-Year Renewal procedure, according to the Guideline "Excipients in the label and package leaflet of medicinal products for human use (July 2003)", the following statements, added in Keppra's Product Information, were approved by CHMP (Positive Opinion in April 2005):

- *In Section 4.4, "Special Warnings and Special Precautions for Use" of the SPC:*
  "(...) It also includes maltitol; patients with rare hereditary problems of fructose intolerance should not take this medicine."
- *In Section "Important information about some of the ingredients of Keppra" of the Package leaflet*
  "If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product."

It was therefore the opinion of the MAH that no additional statement is to be added in the Product Information. The CHMP noted the MAH comments and considered this issue resolved.

- *The "rigid" titration of 20 mg/kg/day every 2 weeks has been used in regulatory studies, but it is meaningless in clinical practice where lower increment and longer periods between changes are recommended for both safety and practical reasons. The MAH should comment.*

The MAH explained that the current dosing recommendations for titration in the initially proposed SPC were written based on the titration schedules used in the pivotal safety and efficacy study N159. The MAH agreed that this "rigid" titration schedule may have to be adapted in clinical practice. Therefore they modified the dosage recommendations as follows:

<u>Children aged 4 to 11 years and adolescents (12 to 17 years) of less than 50 kg</u>

The initial therapeutic dose is 10 mg/kg twice daily.
Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increments of 20 mg/kg/day every two weeks.
Dosage in children and adolescents 50 kg or more is the same as in adults.
The physician should prescribe the most appropriate pharmaceutical form and strength according to weight and dose.

Table 1: Dosage recommendations for children and adolescents:

Weight	*Starting dose:* *10 mg/kg twice daily*	*Maximum dose:* *30 mg/kg twice daily*
15 kg [(1)]	*150 mg twice daily*	*450 mg twice daily*
20 kg [(1)]	*200 mg twice daily*	*600 mg twice daily*
25 kg	*250 mg twice daily*	*750 mg twice daily*
From 50 kg [(2)]	*500 mg twice daily*	*1500 mg twice daily*

[(1)] Children 20 kg or less should preferably start the treatment with Keppra 100 mg/ml oral solution.
[(2)] Dosage in children and adolescents 50 kg or more is the same as in adults.

This amended posology section of the SPC is considered satisfactory by the CHMP. However, considering that no formal dose-response was established, the following sentence should be added: "*The lowest effective dose should be used*." The MAH agreed with the CHMP conclusions and provided Annexes amended accordingly. The CHMP considered this issue resolved. (see page 23)

- *An interaction with topiramate (TPM) could not be excluded. Moreover, the data concerning lamotrigine were not sufficient to exclude interactions.*

As requested by CHMP, the potential interaction with topiramate and lamotrigine was evaluated by the MAH.

Topiramate
To assess the potential pharmacodynamic interaction between levetiracetam and topiramate, percentage change from baseline in partial onset seizure frequency per week over the treatment period was calculated for patient taking topiramate or not and the results are summarised below (Table 2). Similar percentages of patients were taking topiramate in levetiracetam group and placebo group (29/101, 28.7% versus 31/97, 31.6%). In the levetiracetam group, the baseline media seizure frequency was higher in patients not taking topiramate (5.1 versus 3.7); while the opposite was observed in the placebo (4.4 versus 6.8). For the levetiracetam group, whether patients were taking topiramate or not, the partial seizure percentage reduction from baseline was similar, with median around 40%. However, it is very interesting that patients taking topiramate had much lower placebo response than patients not taking the drug (median 0.3% increase versus 20.7% reduction). Therefore, it seems that levetiracetam in combination with topiramate could provide better efficacy benefit when compared to topiramate patients taking placebo, suggesting a potential synergetic effect between levetiracetam and topiramate. However, there may be other factors contributing to this observation since the study was not stratified for topiramate intake. It is also important to note that very few patients were on topiramate monotherapy at baseline.

Table 2 Percentage Change from Baseline in Partial Onset Seizure Frequency per Week over the Treatment Period in Patients Taking or not Taking Topiramate - N 159 ITT Population

		Levetiracetam		Placebo	
		Taking Topiramate?		Taking Topiramate?	
		Yes	No	Yes	No
Baseline Seizure Frequency	N	29	72	31	66
	Mean (SD)	12.26 (22.87)	22.49 (83.63)	11.93 (14.19)	21.52 (60.87)
	Median	3.7	5.1	6.8	4.3
	Q1 - Q3	2.4 - 8.1	2.8 - 16.4	2.6 - 17.4	2.2 - 13.2
	Min - Max	0.8 - 113.5	0.0 - 696.1	1.0 - 53.3	0.0 - 466.6
% Change from Baseline	N	29	71	31	65
	Mean (SD)	- 41.95 (43.70)	-32.15 (51.55)	8.25 (59.11)	-14.31 (55.38)
	Median	-40.7	-45.1	0.3	-20.7
	Q1 - Q3	-77.7 - - 22.9	-62.3 - -12.8	-30.5 - 21.4	-52.2 - 9.6
	Min - Max	-100.0 - 98.6	-100.0 - 159.7	-53.4 - 263.0	-100.0 - 156.3

In conclusion, the MAH believe that patients whose seizures were not controlled by topiramate will still respond to levetiracetam. There was a higher percentage of seizure reduction in patients receiving concomitant levetiracetam and topiramate treatments.

Lamotrigine

Results are shown below in Table 3. Similar percentage of patients was taking lamotrigine in levetiracetam group and placebo group (23/101, 22.8% versus 20/97, 20.6%). For both levetiracetam and placebo groups, the baseline median seizure frequency was similar in patients taking or not taking lamotrigine. Efficacy of levetiracetam was demonstrated in all patients, whether it was combined with lamotrigine or not. The placebo response was similar in both subgroups of patients taking or not taking lamotrigine. In levetiracetam group, patients taking lamotrigine had a slightly higher median percentage of seizure reduction (51.6% versus 40.7%).

Table 3 Percentage Change from Baseline in Partial Onset Seizure Frequency per Week over the Treatment Period in Patients Taking or not Taking Lamotrigine - ITT Population

		Levetiracetam		Placebo	
		Taking Lamotrigine?		Taking Lamotrigine?	
		Yes	No	Yes	No
Baseline Seizure Frequency	N	23	78	20	77
	Mean (SD)	7.76 (10.20)	23.03 (81.14)	38.91 (105.22)	13.15 (19.16)
	Median	4.7	4.8	5.5	5.3
	Q1 - Q3	1.6 - 9.5	2.6 - 15.4	2.6 - 13.0	2.2 - 14.1
	Min – Max	0.7 - 46.7	0.0 - 696.1	1.2 - 466.6	0.0 - 110.9
% Change from Baseline	N	23	77	20	76
	Mean (SD)	-50.83 (36.96)	-30.27 (51.80)	-14.48 (31.19)	-5.07 (62.39)
	Median	-51.6	-40.7	-14.6	-16.5
	Q1 - Q3	-80.5 - -23.4	-62.3 - -10.8	-30.4 - 5.5	-43.2 - 23.0
	Min – Max	-100.0 - 28.8	-100.0 - 159.7	-73.7 - 49.1	-100.0 - 263.0

In conclusion, the MAH believes that patients whose seizures were not controlled by lamotrigine will still respond to levetiracetam. There was a slightly higher percentage of seizure reduction in patients receiving concomitant levetiracetam and lamotrigine treatments.

In the light of the MAH's responses, the CHMP considered that no negative pharmacodynamic interaction between levetiracetam and lamotrigine or topiramate was observed. On the contrary, in this small group of patients, a tendency for a synergistic effect of levetiracetam and topiramate was noted. The CHMP considered this issue resolved.

The above question was linked to concerns over the fact that in Study N151 all four patients receiving TPM had to reduce TPM doses for adverse events related to TPM. This trend also exists in clinical practice. Furthermore, TPM might be involved as a co-medication in the occurrence of the frequent adverse event anorexia. For a complete discussion of this question and the answer to it provided by the MAH please refer to section on Clinical Safety

Conclusion on pharmacokinetics

The preclinical package included newly performed neonatal and juvenile animal studies suggesting that levetiracetam presents a low risk of causing adverse effects upon developmental and maturation processes in children at the proposed therapeutic doses. The MAH provided satisfactory answers to all of the PK-related questions posed to them as part of the requests for supplementary information. PK data are sufficient to support the dose selection.

4.2 Clinical efficacy

Main studies
The primary basis for the demonstration of efficacy in children is study N159. The extension study N157 is ongoing, so data have been submitted until a cut-off date of 30 April 2004. Limited supportive data are also available from two open-label pharmacokinetic studies, N151 and N01010. An overview of the designs of the four studies contributing efficacy data is provided in Table 4 below.

Table 4. Overview of studies contributing efficacy data for levetiracetam in children

Study No.	Dates of Conduct (Country(ies))	Children Exposed (Boys / Girls)	Mean Age (Range)	Overview of Design
Studies in Pooled Efficacy Database (ITT Population)				
N159	9/99 – 3/03 (U.S. and Canada)	101 (54 / 47)	10.2 yrs (4.1 – 17 yrs)	Randomized, double-blind, placebo controlled, 28-week (8-week baseline, 4-week titration, 10-week evaluation, 6-week withdrawal) efficacy and safety study of flexible escalating doses of 20, 40, 60 mg/kg/day
N157	2/98 ongoing (International)	80 *de novo* (44 / 36)	9.7 yrs (0.2 –17 yrs)	Open-label, long-term follow-up study (20 – 99 mg/kg/day)
Supportive Studies				
N151	9/97 – 9/98 (U.S.)	24 (15 / 9)	9.5 yrs (5.6 – 12.7 yrs)	Open-label, single and multiple dose PK, safety and efficacy study of escalating doses of 10, 20, 40 mg/kg/day)
N01010	1/02 - 7/03 (U.S., Mexico)	21 (12 / 9)	9.8 yrs (4.5 – 12.8 yrs)	Open label, multiple dose, 6-week, PK study of escalating (every 2 weeks) doses of 20, 40, 60 mg/kg/day as well as bi-directional AED interactions

4.2.1 Pivotal study, Study N159

[Evaluation of the Efficacy and Tolerability of Levetiracetam Add-on Treatment in Refractory Pediatric Patients with Partial Onset Seizures: A 28-Week Double-Blind, Placebo-Controlled Multi-centre Trial]

Design: Randomised, double-blind, placebo-controlled, 28-week efficacy and safety study of flexible escalating doses of levetiracetam 20, 40, 60 mg/kg/day. The study was performed at 49 study centres in the US and 10 study centres in Canada. Data from one site that enrolled 16 patients were excluded from analyses due to significant protocol and GCP violations.
Patients: The ITT population consisted of 198 patients (100 male), 97 randomized to placebo and 101 randomised to levetiracetam. The age range was from 3 to 17 years of age, mean age 10 years. About 70% were Caucasian. No important differences were noted between treatment groups for demographic or socio-demographic characteristics.
Inclusion criteria: Age 4-14 years and diagnosis of epilepsy with uncontrolled partial onset seizures, whether or nor secondarily generalised. At least 4 partial onset seizures in the 4 weeks prior to screening were required, as well as at least 4 partial onset seizures in each of the 4-week periods during the 8-week baseline.
Exclusion criteria: Patients who required concomitant administration of more than two AEDs (except for intermittent and infrequent use of benzodiazepines) or had seizures that were too close to count accurately.
Treatment: The initial dose level of levetiracetam was 20 mg/kg/day for the first two weeks, followed by a dose level of 40 mg/kg/day for two weeks. If these doses were well tolerated, the levetiracetam dose was increased to 60 mg/kg/day for the remaining 10 weeks.
Evaluation criteria: The primary efficacy variable was the partial onset seizure frequency per week during the Treatment period (4-week Titration and 10-week Evaluation Periods) versus baseline. Secondary efficacy variables included response rate (50 % reduction in seizure frequency from baseline), number of patients in 6 categories (from ≤ 25% to 100% seizure reduction), total seizure

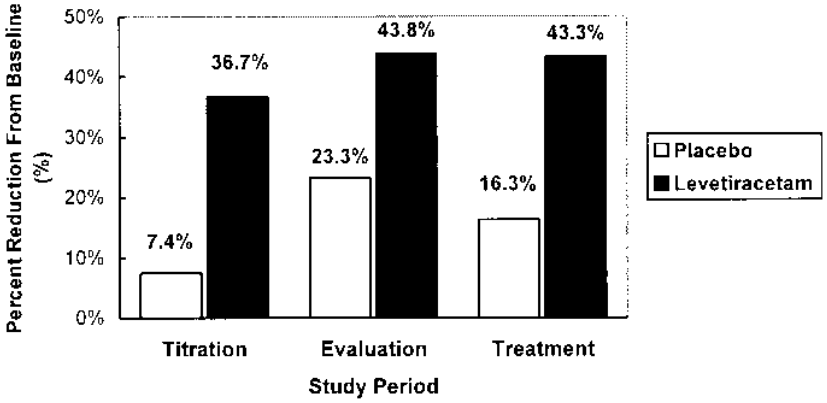
frequency, number of seizure-free days, and comparison of titration and evaluation periods. Exploratory variables analysed different aspects of QoL and severity scale of seizures.

Results

Primary efficacy variable: The median percent reduction of partial (Type I) seizure frequency from baseline was 43.3% in the levetiracetam group and 16.3% on the placebo group over the entire 14-week titration and evaluation periods. The difference between groups corresponds to a 26.8% reduction of partial seizure frequency per week in the levetiracetam group over placebo (p=0.0002). The median reduction from baseline in partial seizure frequency per week in the levetiracetam group was -1.6 in the levetiracetam group and -0.7 in the placebo group.

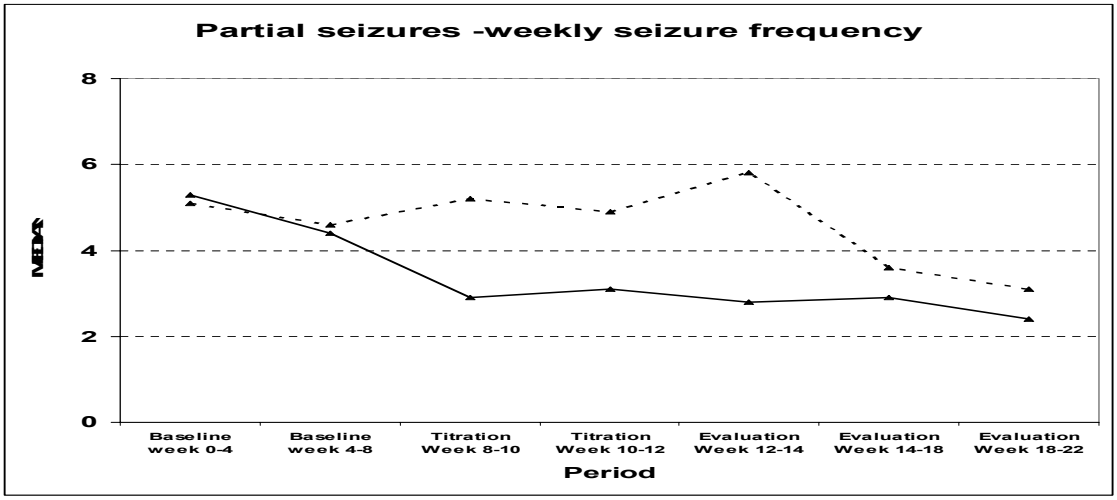
The percent reduction in weekly seizure frequency is illustrated in Fig. 3. The Treatment Period represents the entire time on study drug, *i.e.*, up-titration (Titration) + stable dose period (Evaluation).

Figure 3. Median percent reduction from baseline in partial onset seizure frequency per week by study period (ITT population)



These results appear straightforward; however, questions have been raised concerning the robustness of the results for the primary endpoint, mostly because of the relatively high, though somewhat delayed, placebo response. In fact, as shown in Fig. 4, the placebo group had a similar improvement compared to the active treatment arm after week 14. Only 2/97 patients in the placebo group withdrew due to lack of efficacy, as compared with 0/101 in the active treatment group. The unexpected behaviour of the placebo group raises the question whether the right patients were included, and whether the results can be extrapolated to the whole population of subjects with partial onset seizures between 4 and 16 years of age.

Figure 4. Median weekly seizure frequency over treatment episodes indicated (data from Table 11.10 of the study report).



Secondary efficacy variables

The *Response rate*, defined as the percent of patients experiencing at least a 50% reduction from baseline in the partial onset seizure frequency per week during the Treatment Period, was significantly larger for levetiracetam (45 patients, 44.6 %) than for placebo (19 patients, 19.6 %) [p = 0.0002]. Seven patients (7 %) randomised to levetiracetam were seizure-free during the entire treatment period compared with 1 patient (1 %) randomised to placebo. On-treatment, the mean seizure-free interval was 18.4 days for patients randomised to levetiracetam (as compared to 4.2 days during the baseline period) and 10.6 days for patients randomised to placebo (as compared to 5.5 days during the baseline period). Twenty patients randomised to levetiracetam (20%) had a 75% or greater reduction in seizures as compared to 5 placebo patients (5%).

After their first assessment of the data from study N159, CHMP identified the robustness of the results for the study's primary endpoint as an area of concern that required clarification, mostly because the response to placebo improved significantly with time during the whole treatment period.

To address the above concern, the MAH further evaluated the following three aspects of study N159:

- *Baseline characteristics of patients in N159*
- *placebo responses in N159; and*
- *maintenance of efficacy of levetiracetam.*

- *Baseline characteristics of Patients in N159*

The demographic and baseline characteristics of patients enrolled in study N159 were reviewed. Their summary is shown in table 5. No difference between levetiracetam-treated and placebo-treated patients was observed.

Table 5. Summary of Demographic Characteristics (ITT Population In N159)

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

[(a)] Each percent is the number of randomized patients in the treatment group

In summary, the demographic characteristics, epilepsy history, baseline seizures and concomitant AEDs of patients enrolled in study N159 were similar between levetiracetam and placebo treatment groups and were the targeted population as specified by the study protocol.

To ensure that the right patients were included in the study N159, the inclusion/exclusion criteria, and the study design of study N159 were compared to those in the published clinical studies in children with other four second generation AEDs, Topiramate (TPM), Lamotrigine (LTG), Gabapentin (GBP) and Oxcarbazepine (OXC). These AEDs are approved in epilepsy children with partial onset seizure. As shown in table 6 the age range, numbers of concomitant AEDs and main inclusion/exclusion criteria in levetiracetam study (N159) were very similar to the efficacy and safety studies of other new AEDs in children. This suggests that the patients enrolled in study N159 were typical patients seen in this population, the refractory epilepsy patients with partial onset seizure aged 4 - 16 years old, the targeted population for the proposed claim.

Table 6 Main Inclusion/Exclusion Comparison

	Age Range (Years)	Number of AEDs	Inclusion Criteria	Exclusion Criteria
Levetiracetam (LEV)	4 - 16	1 - 2	≥ POS / 8 wk	Lennox-Gastaut, Cluster, status in 3 months
Topiramate (TPM)	2 - 16	1 - 2	≥ POS / 8 wk	Lennox-Gastaut, Cluster only, status in 3 months
Lamotrigine (LTG)	2 - 16	1 - 2	≥ POS / 4 wk	PGS, status in 12 weeks
Gabapentin (GBP)	3 - 12	1 - 3	≥ POS / 6 wk	Absence seizure, Seizure related to drugs, alcohol or acute illness
Oxcarbazepine (OXC)	3 - 17	1 - 2	≥ POS/ 8 wk	seizure of metabolic, neoplastic or active infection, status in 6 months

- *Placebo Responses in Study N159*

To evaluate whether or not the placebo response was higher in N159 than expected, placebo response for the primary efficacy end point, median percent seizure reduction from baseline, and responder rate in N159 were compared to those in the above-mentioned studies with other four new AEDs, with similar population and design. As shown in table 7, the placebo response observed in N159 was similar to that in studies with other new AEDs.

Table 7 Percent Reduction in Partial Onset Seizure Frequency and Percent Responders (≥ 50% Reduction) with LEV and Other New AEDs used in Children

		Median % Seizure Reduction from Baseline		% Responder	
	N (age range)	Active	Placebo	Active	Placebo
Levetiracetam (LEV)	198 (4 - 16 years)	43	16	45	20
Topiramate (TPM)	86 (2 - 16 years)	33	11	39	20
Lamotrigine (LTG)	199 (2 - 16 years)	36	7	42	16
Gabapentin (GBP)	247 (3 - 12 years)	17	7	21	18
Oxcarbazepine (OXC)	267 (3 - 17 years)	35	9	41	22

As the CHMP pointed out, the mean weekly seizure frequency in the placebo group seems to decrease through the study. However, as discussed further below, mean is not the most suitable method to present seizure data due to the non-normal distribution of seizure frequency. Non-parametric

parameters, e.g. median, are more stable and recommended by the International League against Epilepsy (ILAE). In addition, non-responders tend to drop out of studies earlier and further complicate the issue. Reviewing the data indicated that 10 of 14 prematurely discontinued patients in the placebo group were dropped out of study N159 between Visit 4 and Visit 6, and all these 10 patients had an increase or no change in their seizure frequency from baseline. Therefore, it is likely that drop-out of non-responding patients with higher seizure frequencies led to improved summary statistics on seizure frequency on the remaining patients in later visits.

The Last Observation Carry Forward (LOCF) approach takes into account drop-outs in later visits to correct for this phenomenon. As shown in table 8, summary statistics with LOCF approach showed similar median weekly seizure frequency across all visits, including baseline visit, for placebo group (4.3-5.9), while seizure frequency was consistently reduced from baseline to Visit 7 in the levetiracetam group (from 4.7 to 2.7). This confirmed the hypothesis that improved placebo response was an artefact of non-responders discontinuing from study N159, in addition to non-normal distribution of seizure data leading to skewed means.

Table 8. Partial Onset Seizure Frequency per Week by Visit - N159 ITT Population

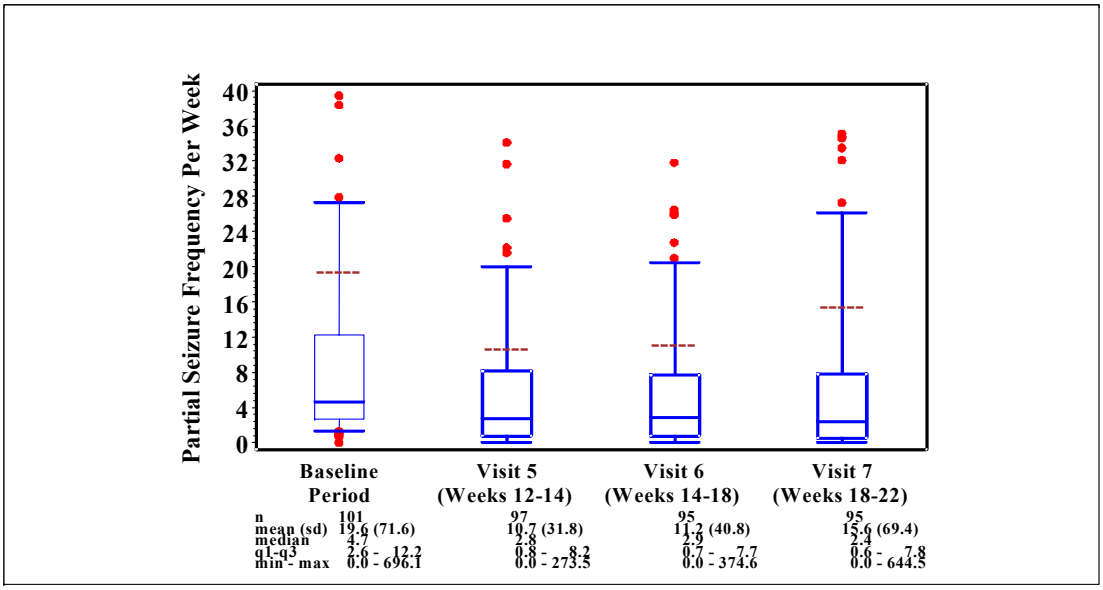
		LOCF		Non LOCF*	
		Levetiracetam (N = 101)	Placebo (N = 97)	Levetiracetam (N = 101)	Placebo (N = 97)
Bsl (V 1 - V 2)	n	101	97	101	97
Mean (SD)		19.6 (71.6)	18.5 (50.9)	19.6 (71.6)	18.5 (50.9)
Median (Q1 - Q3)		4.7 (2.6 - 12.2)	5.3 (2.5 - 14.1)	4.7 (2.6 - 12.2)	5.3 (2.5 - 14.1)
Min - Max		0.0 - 696.1	0.0 - 466.6	0.0 - 696.1	0.0 - 466.6
Visit 5	n	101	96	97	91
Mean (SD)		11.5 (32.2)	12.1 (17.2)	10.7 (31.8)	12.4 (17.7)
Median (Q1 - Q3)		2.9 (0.9 - 8.4)	5.9 (1.5 - 13.6)	2.8 (0.8 - 8.2)	5.8 (1.5 - 16.0)
Min - Max		0.0 - 273.5	0.0 - 75.7	0.0 - 273.5	0.0 - 75.7
Visit 6	n	101	97	95	87
Mean (SD)		11.9 (40.4)	12.3 (18.9)	11.2 (40.8)	11.8 (18.5)
Median (Q1 - Q3)		2.9 (0.9 - 8.3)	5.1 (1.5 - 14.0)	2.9 (0.7 -7.7)	3.6 (1.2 - 14.2)
Min - Max		0.0 - 374.6	0.0 - 86.7	0.0 - 374.6	0.0 - 86.7
Visit 7	n	101	97	95	85
Mean (SD)		**16.1** (67.8)	11.2 (18.0)	**15.6** (69.4)	10.5 (17.6)
Median (Q1 - Q3)		2.7 (0.6 - 8.8)	4.3 (1.2 - 11.8)	2.4 (0.6 - 7.8)	3.1 (0.9 - 11.8)
Min - Max		0.0 - 644.5	0.0 - 85.9	0.0 - 644.5	0.0 - 85.9

*Analysis included in the main text of study report
Source: N159 study Table 14.2.1:7 (LOCF) and Table 14.2.1:6 (non-LOCF) (Module 5, Vol.15, pages 210-2107 and 202-209)

- *Maintenance of Efficacy of Levetiracetam*

The efficacy of levetiracetam was maintained throughout study N159 and the long-term follow-up study N157. The increase in mean seizure frequency at Visit 7 (to 15.6 or 16.1 [depending on the non-LOCF/LOCF method], highlighted in the Table) was due to outliers, as confirmed by the median, which tended to decrease. Almost all of the increase in mean seizure frequency in the levetiracetam group (3.8 of 4.4) was contributed by two patients with extremely high seizure frequencies. One subject had weekly seizure frequency 121 at Visit 6, and 209 at Visit 7; a second subject had weekly seizure frequency 374 at Visit 6 and 644 at Visit 7. As shown in Figure 5, based on the non-parametric summary statistics, median and Q1-Q3, efficacy of levetiracetam is maintained over the stable dosing period (between Visit 5 and Visit 7), with median weekly seizure frequency even further reduced from 2.9 to 2.4 between Visit 6 and Visit 7, while mean seizure frequency increased from Visit 6 to Visit 7 due to these two outliers. If these two outliers are removed, the mean seizure frequency at Visit 7 would be very similar to that in Visit 6 (11.8 vs. 11.2).

Figure 5 Levetiracetam Weekly Partial Seizure Frequency at Baseline Period, Visit 5, 6, and 7, N = 101



The long-term follow-up study N157 showed that the effect of levetiracetam was maintained for at least 63 weeks.

- *Summary*

In summary, the study design and inclusion/exclusion criteria of N159 were similar to those in other AED studies in children. The placebo responder rate in N159 was also similar to that in other AED studies in children. The seizure frequencies in the placebo group artificially improved over time due to non-responding early discontinuation patients not being taken into account in the summary statistics of the later visits and the misleading nature of mean seizure frequency due to the non-normal seizure frequency distribution. Efficacy in the levetiracetam group is stable over the treatment period and shows a highly significant treatment benefit over placebo over time. There was no progressive loss of efficacy of levetiracetam when observed over more than 1 year.

CHMP agreed with the considerations in the *summary* of the MAH's response. In particular, it agreed that baseline characteristics were similar in the active group and placebo group. Yet, it is surprising that "genetic origin (familial epilepsy)" was cited as one of the most common aetiologies. True familial epilepsy accounts for less than 1% of all epilepsies (familial frontal lobe epilepsy with nocturnal seizures for example). In most cases, some family members have fever seizures or epilepsy. Children would then fall into the "idiopathic epilepsies" category, which is not the target population for this study. Finally, some familial diseases such as Bourneville disease have a high incidence of epilepsy. In that case, the disease is genetic, not the epilepsy.

The MAH was therefore requested to clarify why "genetic origin" was cited as one of the most common aetiologies of epilepsy in study N159, and whether this meant that an inappropriate targeted population had been selected.

The MAH therefore, to further elucidate the meaning of "genetic origin (familial epilepsy)" in the N159 study population, reviewed the medical history of all patients reported as having either suspected or confirmed aetiology of epilepsy as "genetic origin (familial epilepsy)".

The outcome was that there is no suggestion of case of true familial epilepsy. Actually, several of them had a clear focal lesion. The higher percentage of "genetic origin" aetiology of epilepsy may be related to the way the data was collected and the poor definition of the recorded aetiologies. In particular:

- The patients with "genetic origin (familial epilepsy)" included patients with both suspected and confirmed aetiologies. Some of these patients had clear focal lesions;

- Review of the medical history did not suggest any case of true familial epilepsy. Therefore, it is likely that this finding is the result of a poor definition of the aetiology. There is no evidence that this has resulted in inappropriate inclusion of "idiopathic epilepsy" as suggested by the CHMP. The study population in N159 was the appropriate target population, i.e. patients with partial onset seizures;

- There was no difference in the type of seizures between levetiracetam and placebo groups. On a clinical point of view, it is nearly impossible to make the difference between simple and complex partial seizures under the age of 5-7 years or in mentally handicapped patients. For that reason, it is more accurate to analyse partial and secondarily generalised seizures only. However, grouping the patients as such would not create any difference between groups.

Therefore, in the opinion of the MAH, the study population in N159 is appropriate for the target population

The MAH explanations were acceptable to the CHMP, and the issue was considered resolved.

Concerning the types of seizures, the MAH states there were 10.9% and 11.3% of patients with clusters of seizures in the levetiracetam and placebo groups, respectively, but in Table 6, cluster is mentioned as an exclusion criterion. The MAH was therefore requested to clarify why about 10% of patients in study N159 exhibit clusters of seizures if this was considered as an exclusion criterion.

The MAH pointed out that the precise wording of exclusion criteria in study N159 was "Patient has seizures too close together to accurately count (i.e. the patient's seizures must be countable)" – i.e. the clinical definition of "cluster seizures". However, the definition of cluster seizure during data collection in study N159 is slightly different. According to seizure coding guideline for N159, "Any seizure that is 30 minutes or longer in duration should automatically be coded as a Type IV (cluster) seizure". Therefore, patients who reported Type IV (cluster) seizures during the 8-week prospective baseline could still meet the inclusion/exclusion criteria if the serial seizures were countable.

The percentage of patients with a history of cluster seizures history was similar in levetiracetam and placebo group (10.9% in the levetiracetam group and 11.3% in the placebo group). Therefore, any impact should be balanced between the two treatment groups. To assess whether or not cluster seizure affected the efficacy assessment, patients with more than 20% of their partial seizures classified as Type IV (cluster) seizures were excluded from per protocol (PP) population analysis, together with other patients who had major protocol violations. There were 6 levetiracetam-treated patients and 9 placebo-treated patients excluded from the PP analysis for having cluster seizures. The efficacy results with PP population were included in the N159 study report (Tables 14.2.1:3, 14.2.1:5, 14.2.1:8, 14.2.1:11, 14.2.1:19, 14.2.1:23, and 14.2.1:25). The primary efficacy endpoint and the responder rate were analyzed using both the ITT and PP populations and the efficacy results were very similar.

In conclusion:
- Although about 10% of N159 patients reported a history of cluster seizures, the percentages of patients were similar in the levetiracetam and placebo group. The percentage of patients actually presenting cluster seizures during the 4-week retrospective baseline was much smaller (about 3%). The percentage of patients with cluster seizures during the 8-week prospective baseline period was 6.9% and 9.3% for the levetiracetam and placebo group, respectively;
- Due to the definition of Type IV (cluster) seizure used in study N159, patients reporting cluster seizures during the prospective baseline could still meet the inclusion/exclusion criteria since these seizures were countable;
- The sensitivity analysis using the PP population (which excluded patients with more than 20% of partial seizures classified as Type IV seizures or other major protocol violations) showed similar efficacy as in the ITT population.

The MAH explanations were acceptable to the CHMP, and the issue was considered resolved.

With regard to the placebo response in N159, it is agreed that non-responders tend to drop out of studies earlier, and that a reanalysis of the data using the LOCF approach showed similar median weekly seizure frequency across all visits for placebo group (4.3-5.9), while median seizure frequency was consistently reduced in the levetiracetam group (from 4.7 to 2.7). The seemingly increased mean seizure frequency at Visit 7 in that group was due to two outliers.

Thus, the apparently improved placebo response over time was at least in large part an artefact due to non-normal distribution of seizure data and early discontinuation of non-responders, while the effect of levetiracetam was maintained throughout the study, except for two outliers at the end of the observation period. These two outliers represent treatment failures, but their relative importance should not be over-emphasized. This issue is therefore considered resolved by the CHMP.

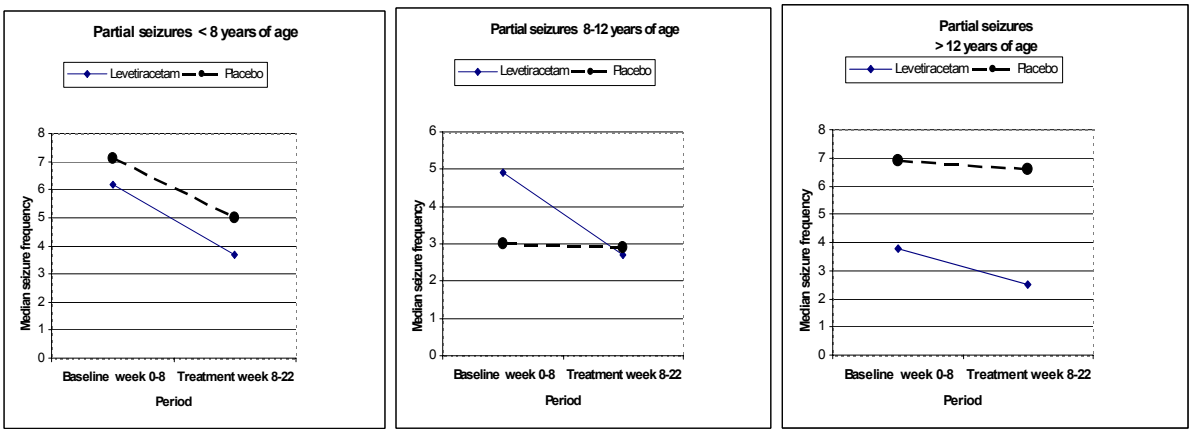
Response in different age categories
In their submission dossier for this variation, the MAH presented this in Table 9 and Fig. 6 (see below)

Table 9. Distribution of age and efficacy by age as provided in the study report.

Age category	4 - < 8 years		8 - <12 years		>= 12 years	
	Levetiracetam	Placebo	Levetiracetam	Placebo	Levetiracetam	Placebo
Responders[a]	n/N (%) 7/25 (28.0%)	n/N (%) 9/32 (28.1%)	n/N (%) 25/46 (54.3%)	n/N (%) 9/42 (21.4%)	n/N (%) 13/30 (43.3%)	n/N (%) 1/23 (4.3%)
Seizure[b]	Median	median	median	median	median	median
Baseline over week 0-8	6.2	7.1	4.9	3	3.8	6.9
Treatment over week 8-22	3.7	5	2.7	2.9	2.5	6.6

[a] Subjects with 50% reduction in seizure frequency as compared to baseline
[b] Seizure frequency/week

Figure. 6. Median seizure frequency for baseline and treatment period by age categories.



CHMP considered that, in terms of responders, only limited effect was observed in the 4- 8 years age group (n=57). Moreover, the effect size seems to increase with increasing age category, suggesting potential effect modification. Most importantly, results with respect to responders are not reflected in seizure frequency. All these analyses indicate substantial heterogeneity between age categories, suggesting that the age category subjects are not comparable.

This issue was identified by CHMP as a major concern after their first assessment of the data submitted by the MAH, who were therefore requested, as part of the RfSI, to provide explanations and

to perform a subgroups analysis per age category, discussing also the implications for the Product Information.

To address this CHMP's concern, the MAH performed a sensitive analysis to assess whether or not age is a prognostic factor for Keppra efficacy. In addition, scatter plots of percentage of partial seizure frequency reduction from baseline as a continuous variable *vs* age as a continuous variable in both levetiracetam and placebo groups were generated. These approaches were chosen since the International League against Epilepsy (ILAE) Commission Report on outcome measurement in epilepsy indicated that seizure frequency as a continuous variable is by far the most sensitive measure of efficacy and should be used whenever possible. Responder rate, defined as ≥ 50% reduction from baseline represents the extreme of data reduction, and being binary is a blunt measure of outcome. Because dichotomy at 50% reduction is arbitrary important differences between treatments may be missed.

The same rationale is valid for the categorisation of age into (<8y; 8–<12y; ≥12y). The grouping of patients in 3 age categories based on the arbitrary selection of cut-off points at 8 and 12 years may lead to loss of important information. In addition, sample sizes are small in each age group. Study N159 was powered on the entire cohort not the subgroup analysis.

To assess whether or not age is a prognostic factor for Keppra efficacy, a sensitivity analysis to the primary efficacy analysis was performed adding age as a continuous variable to the model. The results indicate that age is not an explanatory variable (p = 0.6380). Scatter plots of percentage of partial seizure reduction from baseline as a continuous variable vs. age as a continuous variable were generated for both Keppra and Placebo groups. Patients above the horizontal "0" line show a reduction in seizure frequency compared to baseline. As shown in Figure 7, percent seizure reduction for Keppra for most patients was above the "0" line and evenly distributed throughout the whole age range. The distribution of scatter plot for placebo (Figure 8) was also evenly distributed through the whole age range, and also evenly distributed above and below the "0" line.

In conclusion, the MAH believes that these data demonstrate a clear response to Keppra, which is stable across the whole age range of 4-16 years old, as already demonstrated in the sensitivity analysis.

Figure 7 Scatter Plot of % Partial Seizure Reduction from Baseline vs. Age - Keppra Group

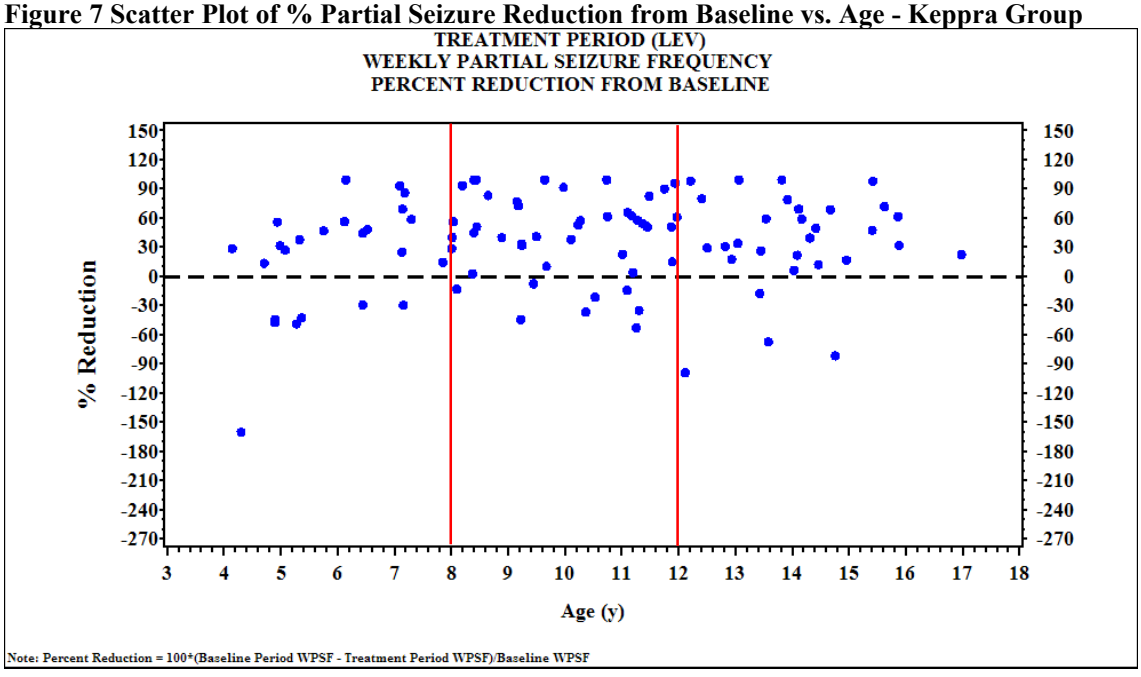
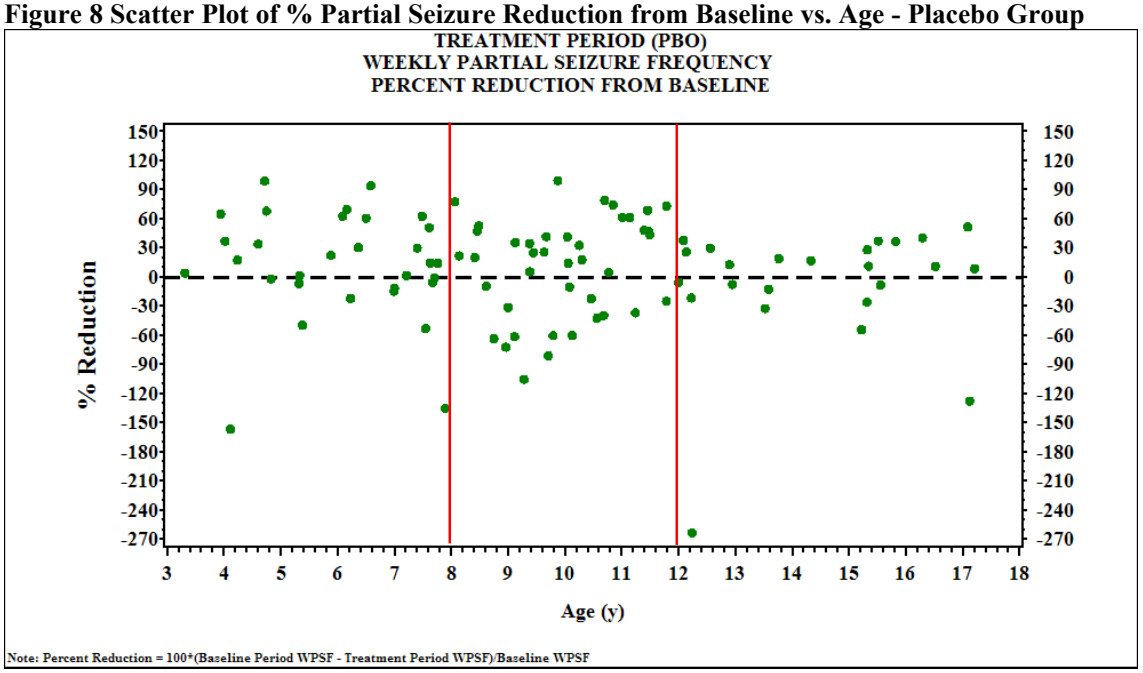


Figure 8 Scatter Plot of % Partial Seizure Reduction from Baseline vs. Age - Placebo Group



CHMP considered that the MAH's presentation of seizure reduction rates *vs* age as continuous variables shows that there is no real concern about the effect of levetiracetam across the whole age range from 4 to 17 years. It appears from these plots, and from data already submitted, that the placebo response is clearly higher for children <8 years of age than for the other two age categories. Although no real explanation for this behaviour can be provided, some kind of parental effect may be evoked. This observation would mean that it is not possible, based on the small numbers of children in each category, to determine if the effect of levetiracetam is significantly different from placebo in the youngest children, but the study was not powered in such a way.

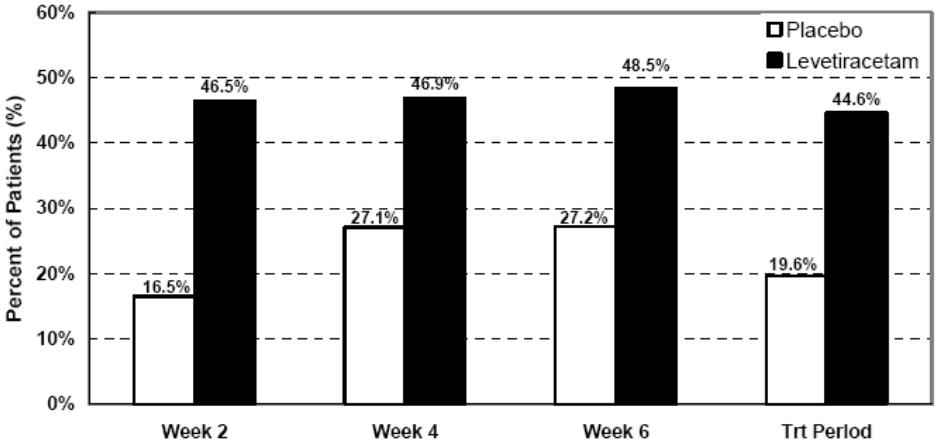
Therefore, as both age categorisation itself as well as the better placebo response in the youngest children may have created a disproportionate impression of heterogeneity in response between age groups, this issue was considered resolved by the CHMP.

Dose-response

For the 101 evaluable patients randomised to levetiracetam in N159, the mean dose during the 10-week evaluation period was 51.6 mg/kg/day [range 16.5 to 79.2 mg/kg/day]. In comparison, mean and median doses for adults in the studies that supported the original approval were 34 and 35 mg/kg/day, respectively. This is consistent with the differences in clearance between children and adults. Since patients were forced to escalate the dose every 2 weeks from 20 to 40 to 60 mg/kg/day, regardless of response, the lowest effective dose and dose response could not be determined reliably. Efficacy analyses were performed based on data from the first double-blind visit when all patients had received a dose of 20 mg/kg/day for 2 weeks. Patients randomised to levetiracetam had statistically significantly greater reduction in the number of seizures than those randomised to placebo and significantly more patients met criteria for response, indicating that this is already an effective dose in many patients. Response based on percentage responders for each two-week interval during the first 6 weeks of the treatment period was relatively constant irrespective of dose (Fig. 9). However, there was a trend towards progressive improvement in the placebo group between visit 3 and 5, as discussed above.

Figure 9.

:5 Percentage Of Patients With At Least 50% Reduction Of Seizure Frequency Per Week During First 6 Weeks Of The Treatment Period (ITT Population in N159)



Levetiracetam seems already effective during titration at 20mg/kg/day, and therefore CHMP considered that the dose-response relationship in children had been insufficiently characterised, and it was not clear if a further dose increase from the initial dose 20mg/kg/day increases efficacy. There is some data suggesting a better efficacy at 40mg/kg/day than at 60mg/kg/day. On the other hand, lower doses have not been explored except in study N151, an open exploratory study with a final responder rate of 52.2% (see below). Overall, a more cautious dose titration (for both up-titration and down-titration) than initially proposed in the SPC is suggested, except in emergency situations. This issue was also identified by CHMP as a major concern after their first assessment of the data submitted by the MAH, and led to formulation of a specific question from the CHMP.

In their answers to the RfSI, the MAH agreed that no dose-response relationship of levetiracetam as adjunctive therapy in the treatment of generalised partial onset seizures has been established in children. The dosage initially proposed therefore reflected: a) similar plasma concentrations in children receiving 20 to 60 mg/kg/day as compared to adults receiving 1000 to 3000 mg/day; b) efficacy in the proposed indication as demonstrated in the pivotal study N159.

CHMP, however, considered that adult "therapeutic" plasma level ranges are only a guide and not an "aim", and should not necessarily be extrapolated to children due to several factors such as maturity of the mechanisms of action and permeability of the blood-brain-barrier.

Based on the limited clinical evidence obtained by the MAH in children treated with levetiracetam, the optimal dose is difficult to establish. However, it should be taken into account that for children, more than for adults, the lowest effective dose is the best. Therefore, treatment should be started with 20 mg/kg/day and increased only in case of insufficient efficacy. It is also difficult to interpret the relatively high mean doses (54 mg/kg/day) used in the open-label long-term studies.

The SPC, however, reflects the need for dose adjustment. Moreover, more cautious regimens for up- and down-titration have been introduced by the MAH as a consequence of CHMP comments, to reflect the concepts expressed above. As already discussed the CHMP considered that addition of the sentence "*the lowest effective dose should be used*" was necessary.

The MAH agreed with the CHMP and provided amended Product Information, as requested.

The CHMP also sought clarification on a last point with regards to study N159, requesting the MAH to provide efficacy data for study N159 separately for all seizure types included in partial epilepsy, i.e. simple partial, complex partial and secondary generalized seizures.

In the MAH's response to this point, primary efficacy and responder rate were analysed for all seizure types included in partial epilepsy in N159 separately. As shown below in Table 10, all patients in N159 had a history of partial onset seizures. The distribution of seizure types was similar in the two treatment groups.

Table 10. Partial seizure history (ITT population)

Seizure Type	Levetiracetam n(%)	Placebo n (%)	Total n (%)
Partial seizures (Type I)	101 (100.0)	97 (100.0)	198 (100.0)
Simple Partial (IA)	26 (25.7)	27 (27.8)	53 (26.8)
Complex Partial (IB)	88 (87.1)	86 (88.7)	174 (87.9)
Partial Secondary Generalized (IC)	56 (55.4)	50 (51.5)	106 (53.5)

The number (%) of patients having Type IA, IB and IC partial seizures over the baseline and treatment periods is shown in Table 11. The percentage of patients with each subtype or partial seizures in levetiracetam and placebo groups is similar.

Table 11. Number (%) or patients presence of partial seizure by subtype over the baseline and treatment periods (ITT population).

	Levetiracetam N = 101 n (%)	Placebo N=97 n (%)
Baseline period		
Simple partial (IA)	20 (19.8)	25 (25.8)
Complex partial (IB)	78 (77.2)	77 (79.4)
Partial Secondary Generalized (IC)	38 (37.6)	29 (29.9)
Treatment period		
Simple partial (IA)	17 (16.8)	24 (24.7)
Complex partial (IB)	70 (69.3)	75 (77.3)
Partial secondary generalised (IC)	34 (33.7)	29 (29.9)

The primary efficacy parameter, reduction of the weekly seizure frequency per week over placebo during the treatment period was analysed. For Type IB seizures, there was a statistically significant weekly seizure frequency reduction over placebo (31.2 %, 95 % CI = 16.8, 43.0 %, p=0.0001). For Type IA and IC seizures, there was a numerical reduction over placebo but the difference did not reach statistical significance (For IA 15.6 %, 95 % CI = -19.4 %, 40.4 %, p=0.3286; for IC 16.4 %, 95 % CI -8.8 %, 35.7 %, p=0.1787). This may be related to the smaller sample size and the higher variability of the response for these subtypes. The study was not powered to compare the treatment effect on the seizure subtypes.

The responder rate by partial seizure subtype during treatment period was analysed. Similar to the primary efficacy, the levetiracetam group had a statistically significant higher responder rate than placebo for Type IB seizure (50 % versus 19.2 %, p<0.0001). The difference between levetiracetam and placebo for Type IC seizures was also statistically significant (39.5 % versus 16.1 %, p=0.0386). For Type IA seizures, there was no statistically significant difference in responder rate between the levetiracetam and placebo groups (61.9 % versus 48.0 %, p=0.3474). This may be due to the smaller sample size for Type IA seizures and to the fact that this seizure subtype is more sensitive to any treatment effect, including placebo effect, than the other two subtypes.

In conclusion, Type IB was the subtype that occurred in the largest percentage of the patients. For Type IB, both the treatment effect presented as levetiracetam reduction of seizure frequency per week over placebo and the responder rate were statistically higher in the levetiracetam group than under placebo. In the opinion of the MAH, the result of the same efficacy analysis for the two other subtypes, with smaller number of subjects, showed that levetiracetam was more efficacious than placebo. The difference in responder rate between levetiracetam and placebo for Type IC seizures was also statistically significant.

The CHMP agreed that complex partial seizures (type IB) was the most common subtype of partial seizures in the study. For this type of seizures, a statistically significant reduction of seizure frequency over placebo was demonstrated during the treatment period, and the proportion of 50% responders was also significantly higher than for placebo. For Type IA and IC seizures, there was a numerical trend for seizure reduction, but no statistically significant differences *vs* placebo. However, this is considered acceptable, as the study was not powered to show treatment effects on seizure subtypes. The issue was considered resolved by the CHMP.

4.2.2 Extension study - N157

[A multi-centre, open-label long-term follow-up study of the safety and efficacy of levetiracetam in children with epilepsy]
Children who had participated in the previous levetiracetam studies N151, N159, N1010 or N01052 could enter N157, an open-label extension study. Long-term seizure frequency was analysed in 180 patients. Most of these patients, 103, remained on treatment for more than 1 year. The mean dose during the patient's entire treatment was 52.0 mg/kg/day; most patients were escalated to target doses of 60 mg/kg/day and appeared to remain at that dose for the duration of their study participation.
Patients: A total of 238 patients were enrolled, of which 223 were included in the ITT population. As of the clinical cut-off 30 Apr 2004, of the 223 enrolled ITT patients, 101 (45.3 5 %) were continuing study participation, and 122 (54.7 %) had discontinued. The reasons for discontinuation were lack of efficacy (25) protocol violation (17), withdrew consent (15), adverse events (119, lost to follow-up (3), UCB decision (1) and other (50). Other discontinuation included 23 patients with loss of efficacy and 8 patients who discontinued because the site was ending participation in the study.
Treatment. N157 consisted of a Screening phase, an up to 6 week Titration phase for patients entering from the double-blind study, and a Maintenance phase during which patients could take open-label levetiracetam.
Efficacy variables: The primary efficacy parameter was defined as the percentage change from baseline in weekly seizure frequency over time including the Treatment period.
Secondary efficacy variables included:

- the absolute change from baseline in weekly seizure frequency over time during the Treatment Period;
- responder rate defined as the number of patients experiencing at least a 50% reduction from baseline in the weekly seizure frequency during the Treatment Period;
- the maximum seizure-free interval (periods of greater than 1 week with no seizure activity);

Efficacy result: At study entry, approximately 42% of the ITT population had been randomised to the placebo group of the double-blind multi-centre study (N159) or had received a single oral dose of levetiracetam during a PK study (N01052). The other 58% of the ITT population had received up to 98 days of open label levetiracetam treatment prior to entry into N157. As a result, approximately two-thirds of the patients entering N157 were seizure free at the Screening visit. During treatment with levetiracetam, the median seizure frequency per week decreased from baseline for both partial onset seizures and total seizures. Approximately one-third (32.7%) of the patients experienced a reduction from baseline in seizure frequency per week of at least 50% for partial onset and total seizures. For the ITT population, the mean (SD) percent change from baseline was an increase of 51.3% (453.6) for partial onset seizures and 68.3% (466.0) for total seizures. These results are, however, likely to result from a skewed distribution due to extreme outliers. The median values, unaffected by extreme outliers, were decreases of -20.5% and -20.7%, respectively.
For the ITT population, the mean (SD) and median absolute changes from baseline were -2.3 (23.7) and -0.5, respectively, for partial onset seizure frequency per week and -3.1 (28.2) and -0.6, respectively, for total seizure frequency per week. The response rate for the ITT population was 31.8% for partial onset seizures and 32.7% for total seizures. The highest and lowest response rates for partial onset seizures were observed in patients treated with placebo during N159 (40.5%) and patients entering N157 from N01052 (7.1%), respectively.

In summary, extension study N157 is still ongoing and the results are preliminary. The preliminary data do not seem to indicate development of tolerance with long-term treatment, but the final results

should be awaited before a definite conclusion can be drawn. Notably, 48 patients ended the study for loss (23) or lack (25) of efficacy, representing in total approximately 40% of patients ending the study.

CHMP therefore expressed their concern over the difficulty in interpreting the results of study N157 in which two-thirds of the patients were seizure-free at inclusion and according to the definitions they could not have any reduction in seizure frequency (probably explaining part of the results showing an increase in mean seizure frequency and a decrease in median seizure frequency). In addition, it was unclear how seizure reduction was calculated for patients that were seizure-free at inclusion but had seizures during follow-up. Therefore, CHMP requested that for patients included in N159, seizure reduction (ITT) would be calculated in study N157 using the original baseline from study N159 (Weeks 1 to 8).

In their response, the MAH argued that for patients included in N159, seizure reduction had been calculated in study N157 using the original baseline from study N159 and had been included in the initial submission. However, the relevant information was summarised again, as follows: The analysis of long-term efficacy data is based on only those patients in study N157 who entered from study N159. All study N159 data from Site 55 (N157 Site 419), however, were excluded based on UCB Quality Assurance recommendations.

Data for 180 patients who received levetiracetam in the extension study were pooled. Of the 180 patients entering the extension study, 101 patients had received levetiracetam during their initial double-blind study and 79 had received placebo.

Measurements of the percentage change from baseline show that seizure control was maintained during the extended treatment period. The median percentage reduction from baseline of Type I (partial onset seizure) seizure frequency in ISE analysis population patients with at least 63 weeks of levetiracetam exposure is in Figure 10. The majority of patients remained on levetiracetam for more than 1 year.

The proportion of patients responding to levetiracetam remained high over time and patient attrition was relatively low. As could be expected, patients who responded tended to remain in the long-term extension study as evidenced by the increased proportion of responding patients over time. That levetiracetam contributed to the maintenance of efficacy is further supported by the decrease in the proportions of patients who respond when they are down-titrated off drug (see Table 12).

Figure 10 Percent Reduction of Type I Seizure Frequency from Baseline by Analysis Interval - ISE Analysis Population Patients with at least 63 Weeks of Levetiracetam Exposure

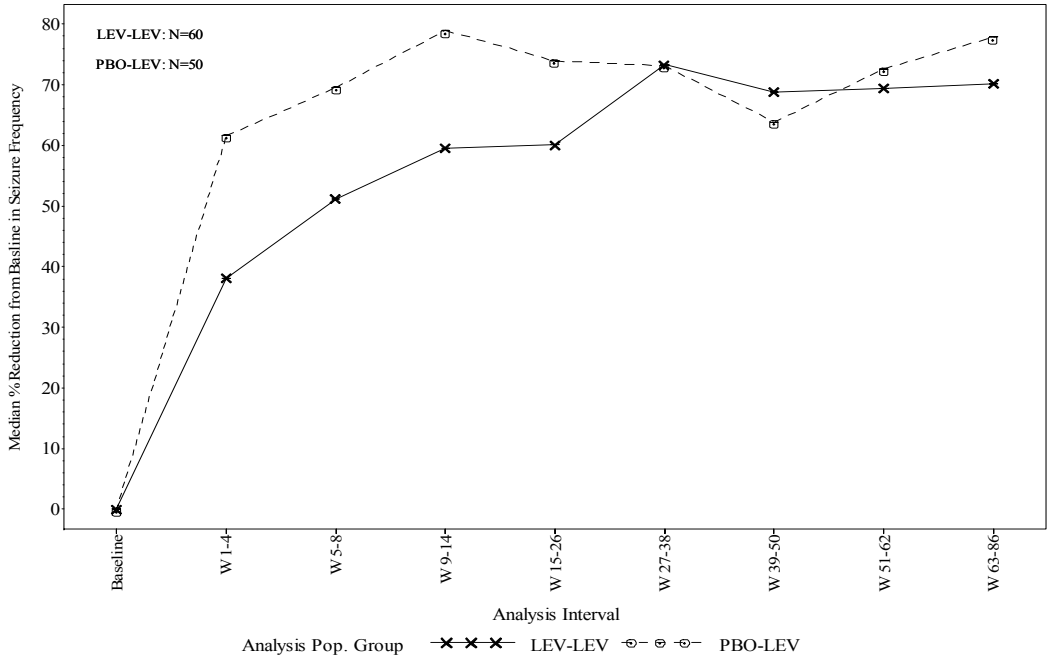


Table 12 Number (%) Patients with 50% Reduction in Seizure Frequency by Duration of Levetiracetam Exposure (ISE Analysis Population)

Analysis Interval	N	N (%) with 50% Reduction in Seizure Frequency
Week 1 - 4	180	91 (50.6%)
Week 5 - 8	176	97 (55.1%)
Week 9 - 14	169	93 (55.0%)
Week 15 - 26	166	99 (59.6%)
Week 27 - 38	149	98 (65.8%)
Week 39 - 50	135	89 (65.9%)
Week 51 - 62	124	79 (63.7%)
Week 63 - 86	112	70 (62.5%)
Week 87 - 110	71	51 (71.8%)
Week 111 - 134	54	39 (72.2%)
Week 135 - 158	45	30 (66.7%)
Week 159 - 206	34	28 (82.4%)
Week 207 - 254	9	9 (100%)
Down-titration	38	17 (44.7%)

Further to this new presentation of data from the long-term extension, CHMP considered that there was a tendency to support the conclusion that the efficacy of levetiracetam was maintained in a sufficient way.

4.2.3 Study N151

[A multi-centre, open label, exploratory study of levetiracetam in children 6-12 years old with partial onset seizures]

Design, treatment: An open-label primarily pharmacokinetic study of 24 male and female patients aged 6 to 12 years with partial onset seizures whose past or current AED treatment was unsatisfactory. A maximum of one concomitant AED was allowed. After at least four weeks of monotherapy on their

concomitant AED (Baseline phase), patients received increasing doses of levetiracetam with stepwise dose titration at 10-20 to 40 mg/kg/day (6 weeks) in addition to their concomitant AED. The Evaluation phase lasted for 8 weeks at a dose of approximately 40 mg/kg/day. Efficacy was assessed by the number of responders, the The Hague Seizure Severity Scale and the Global Evaluation Scale. Safety was assessed by adverse event monitoring, clinical laboratory assessments and clinical assessments.
Results for efficacy: The responder analysis showed that 52.2 % of the patients were responders in the intent-to-treat analysis (N=23). The majority of seizures experienced by patients during the study were complex partial seizures. The total partial seizure frequency per week was reduced by a median of 53%. Only one patient experienced clusters during the study; the clusters were characterized by predominately simple partial seizures. The majority of the patients successfully titrated up to the valuable dose level of levetiracetam. The Per Protocol Population analysis (N=l9; those patients who were on a dose of 40 mg/kg/day during the entire eight week Evaluation phase as well as those who stayed on 20 mg/kg/day due to a good response to levetiracetam) showed that 63.2 % of patients responded. Patients showed an overall improvement in the Hague Seizure Severity Scale at Day 98 from Baseline (mean change from Baseline, -2.7). For the Global Evaluation Scale, the median rating on Day 98 from both the investigator and the parent was a 3, showing that half the patients showed no change from Day 70.

4.2.4 Study N01010

[An open-label, multi-centre, repeated dose pharmacokinetic study of 20, 40 and 60 mg/kg/day of levetiracetam in children (4 - 12 years of age inclusive) with partial onset seizures.]
Design, treatment: N01010 was an open-label, multicentre pharmacokinetic (PK) study in children with partial onset seizures. Efficacy was also evaluated. N01010 consisted of a 2-week Selection Period to determine subject eligibility, a 6-week titration period, a 4-week withdrawal period, and a final visit two weeks after the last intake of levetiracetam, for a total of up to 14 weeks of study participation.
The primary objectives of this study were: to document the pharmacokinetics of 20, 40 and 60 mg/kg/day of both levetiracetam and its metabolite ucb L057 in children (ages 4 - 12 years inclusive) with partial onset seizures; to evaluate the potential interaction of carbamazepine (CBZ) and valproate (VPA) on the pharmacokinetics of levetiracetam; and to evaluate the potential interaction of levetiracetam on the plasma levels of CBZ and VPA. The exploratory objective was to document the relationship between levetiracetam levels in plasma and saliva.
Efficacy parameters: The primary efficacy parameter was the responder rate, defined as the percent of subjects experiencing at least a 50% reduction from baseline in the standardized seizure frequency during the Titration Period. Secondary efficacy variables included the absolute change and percent change from baseline in the standardized partial seizure frequency and total seizure frequency during the Titration Period and global assessments by the parent/guardian and the investigator using a Global Evaluation Scales (GES) ranging from 1 (marked improvement) to 7 (marked worsening). The subject provided a global assessment using a visual analogue scale ranging from 0 (marked worsening) to 10 (marked improvement).
Results for efficacy: Only partial seizures were observed during the study. For the ITT population, the partial seizure frequency per week decreased from baseline by at least 50% for 9 subjects, a responder rate of 42.9%. The responder rate was 30.8% for subjects treated with CBZ and 62.5% for subjects treated with VPA. The reduction from baseline was larger at 40 mg. In CBZ subjects, the median change from baseline was 0, -0.7, and -0.5 and in VPA subjects, the median change from baseline was 0.9, -1.2, and -0.3 at Visits 3, 4, and 5, respectively.
The global evaluations of the subjects' epilepsy showed marked or moderate improvement for 16/20 (80%) subjects when rated by the investigator and for 15/20 (75%) subjects when rated by the subject's parent/guardian. The subject's global evaluation was ≥ 8 for 7/8 (87.5%) CBZ subjects and 8/8 (100%) VPA subjects who completed the evaluation.

- *Why was maximal efficacy in Study N01010 reached at 40 mg/kg/day?*

Study N01010 was a pharmacokinetic study and inclusion/exclusion criteria was mainly based on the need for PK objectives. It was not required that patients have partial seizure at baseline to enter study N01010. Therefore, *study N01010 was not designed for assessing efficacy.* The median percent change

of partial seizure from baseline is presented in Table 13. As shown, the efficacy was similar between 40 mg/kg and 60 mg/kg in both Carbamazepine (CBZ) and Valproic acid (VPA) groups.

Table 13 Median Percent Change of Partial Seizure from Baseline in Study N01010

Treatment	LEV Dose (mg/kg/day)	N[(a)]	n[(b)]	Median % Change of Partial Seizure from Baseline
CBZ	40 (Visit 3)	13	11	- 88.4%
	60 (Visit 4)	13	7	- 70.0%
VPA	40 (Visit 3)	8	5	- 100.0%
	60 (Visit 4)	8	5	- 100.0%

[(a)] N is the number of subjects in the treatment group
[(b)] n is the number of subjects with data at both baseline and the visit

- *Seizure worsening*

After assessment of the data deriving from Study N01010, CHMP considered that there was not enough information about the population with seizure worsening, and in particular it was not possible to establish whether seizure worsening was dose-related. Additionally, as in Study N01010 maximum efficacy is noted for 40 mg/kg/day, the MAH was asked to clarify whether this was related to specific co-medication, and finally to clarify whether levetiracetam clearance increased by 22% in association with enzyme-inducer medication.

To answer CHMP's questions, additional analyses were performed in patients with seizure worsening. Seizure worsening is defined as either an increase from baseline in total seizure frequency per week over treatment period > 25% or at least one treatment emergent adverse event with the following COSTART preferred terms: Convulsion, Grand Mal Convulsion, Status Epilepticus NOS, or Status Epilepticus Partial. The dose of study medication during treatment period, whether or not taking enzyme inducing AEDs, whether or not taking non-AEDs potentially worsening seizures were analyzed for patients with seizure worsening.

- *Is seizure worsening dose-related?*

Study N159 was not designed to look at the dose-response relationship since all patients were to be titrated up to a stable dose of 60 mg/kg/day. Fewer patients on levetiracetam met the criteria of seizure worsening as compared to placebo: respectively 21/101 (20.8%) and 32/97 (33.0%), indicating that *levetiracetam at high doses does not increase the risk of seizure worsening versus placebo*. In addition, Table 14 shows the dose of levetiracetam and placebo during treatment period in patients with and without seizure worsening. There is no difference between the doses administered in the patients with or without seizure worsening.

Table 14 Average Daily Study Drug Dose over Treatment Period for Subjects with Seizure Worsening[(a)] – N159 ITT Population

	Levetiracetam		Placebo	
Descriptive Statistics	No Seizure Worsening	Seizure Worsening	No Seizure Worsening	Seizure Worsening
n	80	21	65	32
Mean (SD)	43.47 (10.08)	44.09 (9.17)	42.67 (10.11)	41.68 (9.83)
Median	45.7	45.3	43.1	44.1
Q1-Q3	38.9 - 49.2	40.1 - 49.7	39.1 - 50.1	36.0 - 49.8
Min-Max	13.6 - 67.8	18.6 - 58.3	9.8 - 59.8	9.7 - 55.0

[(a)] Increase from baseline in total seizure frequency per week over the treatment period > 25% or treatment emergent AE: Convulsion, Grand Mal Convulsion, Status Epilepticus NOS, and Status Epilepticus Partial

- *What is the effect of enzyme-inducing AEDs?*

To address CHMP's concern, percent change of partial seizure from baseline in patients who received levetiracetam with and without enzyme inducers in study N159 was analyzed. As shown in Table 15, the efficacy is similar in patients received enzyme inducers or not.

Table 15 Median Percent Change of Partial Seizure from Baseline over Treatment Period in Levetiracetam Treated Patient – N159 ITT Population

Enzyme Inducer?	N	Median Baseline Seizure Frequency	Median Percent Change from Baseline
No	54	4.0	- 48.2%
Yes	47	6.2	- 40.1%

The relationship between *seizure worsening and intake of enzyme inducing AEDs* was also explored. The results are presented in Table 16. The percentage of patients with enzyme inducing AEDs was similar in the levetiracetam and placebo group (47/101, 46.5% versus 43/97, 44.3%). As expected, more patients in the placebo group were classified as having seizure worsening than in the levetiracetam group (33.0% *vs* 20.8%, respectively). In the subgroup "not taking an enzyme-inducing AED", the percentage of patients reporting seizure worsening is much higher in the placebo group than in the levetiracetam group. In the other subgroup "taking an enzyme-inducer" the difference is smaller but is still in favour of levetiracetam (25.5% *vs* 30.2%, respectively). However, since the samples are small and this study was not stratified according to concomitant AEDs, some other factors may also contribute to this observation.

Table 16 Relationship between Seizure Worsening[(a)] and Intake of Enzyme Inducing AEDs[(b)] – N159 ITT Population

Any AE or Eff sign of seizure worsening?	Levetiracetam		Placebo	
	Enzyme Inducer?		Enzyme Inducer?	
	No	Yes	No	Yes
No	45 83.3%	35 74.5%	35 64.8%	30 69.8%
Yes	9 16.7%	12 25.5%	19 35.2%	13 30.2%
Total	54	47	54	43

[(a)] Increase from baseline in total seizure frequency per week over the treatment period >25% or treatment emergent AE: Convulsion, Grand Mal Convulsion, Status Epilepticus NOS, and Status Epilepticus Partial
[(b)] Intake of enzyme inducers (with or without inhibitors) during the treatment period

Are there other potential pro-seizure medications?
Some non-AEDs are known to potentially worsening seizures. To assess whether or not there is a relationship between seizure worsening and intake of *pro-seizure drugs*, additional analysis was conducted and results are summarized in Table 17. Since the use of these drugs was prohibited by the study protocol, the number of patients with these medications was very low and the results were inconclusive.

Table 17 Relationship between Seizure Worsening[(a)] and Intake of Potentially Pro-Seizure Drugs[(b)] – N159 ITT Population

Any AE or Eff sign of seizure worsening?	Levetiracetam		Placebo	
	Pro-Seizure Drugs?		Pro-Seizure Drugs?	
	No	Yes	No	Yes
No	75 79.0%	5 83.3%	61 66.3%	4 80%
Yes	20 21.0%	1 16.7%	31 33.7%	1 20%
Total	95	6	92	5

[(a)] Increase from baseline in total seizure frequency per week over the treatment period > 25% or treatment emergent AE: Convulsion, Grand Mal Convulsion, Status Epilepticus NOS, and Status Epilepticus Partial
[(b)] Intake of non-AED with potential pro-convulsive effect sometime during the study drug intakes.

Summary
In summary, the MAH responses to these aspects can be summarised as follows:

- The percentage of seizure worsening is lower under the high doses of levetiracetam compared to placebo.
- The efficacy of levetiracetam 40 mg/kg/day is similar to that of 60 mg/kg/day in the PK study N01010, although this study was not intended to assess efficacy as inclusion criteria differed.
- The efficacy of levetiracetam is similar in patients who received concomitant enzyme inducer AEDs or not. Therefore, there is no evidence that the slightly increased clearance of levetiracetam, associated with the use of enzyme-inducing AEDs, results in less seizure control.
- The percentage of seizure worsening is lower under levetiracetam than in the placebo group in both the subgroups with and without concomitant enzyme inducer AEDs. The treatment difference is less pronounced in the subgroup "with enzyme inducer AED". However due to the low sample size in the subgroups and since the study was not stratified for this factor, these results need to be interpreted with caution.
- The assessment of potential effect of concomitant pro-seizure drugs was not conclusive because of the very low number of subjects who received these compounds.

The CHMP endorsed the MAH's summary. However, the MAH were asked to clarify the rate of seizure worsening (as per the proposed section 4.4 of the SPC with this application) in the levetiracetam group (20.8%), as although lower than in placebo (33%), remains relatively high compared to other novel AEDs. The percentages for increase seizure frequency were then checked and found correct by the MAH. The percentages quoted by the CHMP are for "Seizure worsening" which includes increase in seizure frequency plus seizure related adverse events; e.g. seizure worsening, convulsions, etc. The corresponding paragraph in section 4.4 of the SPC is therefore considered correct by the MAH, who believed that it should not be changed. The CHMP considered the MAH's explanations acceptable.

4.3 Clinical safety

Safety results are primarily based on the pivotal placebo-controlled study N159, with additional information from the open-label extension study. Other safety information includes that derived in pharmacokinetic studies, ongoing studies, and post-marketing use. As of August 2004, approximately 515,000 patient-years of marketed Keppra tablet use are estimated. Paediatric use is estimated to represent less than 10% of this figure.

Patient exposure
A total of 239 children with partial onset seizures have received levetiracetam in 5 completed studies. Of these, 124 were boys and 115 were girls; about two-thirds were Caucasian. The mean age was approximately 9 years with patients ranging in age from 2 months to 17 years; 16 patients were between the ages of 1 month and < 4 years; 63 patients were between 4 and < 8 years; 104 patients were between 8 and < 12 years; and 56 patients were between 12 and < 18 years. Additional safety information was reviewed for 58 children who participated in other studies.

Adverse events
In study N159, the majority of the patients experienced at least one treatment-emergent adverse event (TEAE): 88.1% in the levetiracetam group and 91.8% in placebo patients. These TEAE were considered related to the drug in 55.4 % in the active group and 40.2 % in the placebo group, respectively. Adverse events that were more common among patients randomised to levetiracetam than to placebo were somnolence, accidental injury, hostility, nervousness, asthenia, pain, cough increased, rhinitis and anorexia. TEAEs that occur with an incidence of >1% in the patients randomised to levetiracetam are presented in Table 18.

Table 18.

Incidence of Treatment Related TEAEs Summarized by COSTART Body System and Preferred Term for TEAEs Reported >1% of Patients in the Levetiracetam Treated Group (ITT Population)

	Levetiracetam N=101	Placebo N=97
Bold System/Preferred Term	n (%)	n (%)
Body As A Whole		
Accidental injury	2 (2.0)	2 (2.1)
Asthenia	7 (6.9)	1 (1.0)
Headache	5 (5.0)	2 (2.1)
Infection	3(3.0)	3 (3.1)
Digestive System		
Anorexia	10 (9.9)	5 (5.2)
Diarrhea	2 (2.0)	4 (4.1)
Nausea	2 (2.0)	1 (1.0)
Vomiting	3 (3.0)	4 (4.1)
Nervous System		
Agitation	5 (5.0)	0 (0.0)
Convulsion	3 (3.0)	7 (7.2)
Dizziness	4 (4.0)	0 (0.0)
Emotional lability	5 (5.0)	4 (4.1)
Hostility	10 (9.9)	6 (6.2)
Hyperkinesia	3 (3.0)	1 (1.0)
Insomnia	2 (2.0)	3 (3.1)
Nervousness	8 (7.9)	1 (1.0)
Personality disorder	6 (5.9)	6 (6.2)
Somnolence	17 (16.8)	7 (7.2)
Thinking abnormal	2 (2.0)	4 (4.1)
Respiratory System		
Cough increased	2(2.0)	1(1.0)
Skin and Appendages		
Rash	2(2.0)	1(1.0)

Ref Table 14.3.1:9

Some of these adverse events, whatever the relationship with the treatment, are clearly dose-related: vomiting, from 3.4% for <29mg/kg/day to 12.2% for ≥50mg/kg/day; hostility, from 2.6% for <29mg/kg/day to 9.9% for ≥50mg/kg/day; and convulsion, from 3.4% for <29mg/kg/day to 10.3% for ≥50mg/kg/day. Some of these adverse events could be secondary to pharmacodynamic interactions between levetiracetam and co-medications. For example, anorexia is often described in children, who receive more often topiramate compared to adults. Some of these children received psychotropic drugs for their behavioural problems and again some interactions are possible. Finally, several dose-related TEAEs persisted after 48 weeks of treatment.

Behavioural and other psychiatric events have been associated with levetiracetam in adults. There was a similarly elevated risk for these events in children, especially children with neurological problems. The individual terms for which there was a two-fold or greater relative risk in levetiracetam-treated patients as compared to placebo (without consideration for treatment relationship) were, in decreasing order of incidence, agitation, nervousness, and depression. Hostility (the COSTART term for aggressive behaviour, aggression, angry outbursts, *etc.*) also occurred with a greater relative risk in patients randomised to levetiracetam. Overall, these were more common in children.

A total of 126 of 239 (52.7%) children exposed to levetiracetam experienced CNS-related adverse events that can be considered disturbances of behaviour and/or mood. The behavioural events were most commonly described as hostility (10.9%) and nervousness (10.5%). Twenty patients either discontinued as a result or had a dose reduction and the event either resolved or diminished. A total of 18 patients had behavioural events that were severe in intensity, including 7 of the patients with dose decreases or discontinuation. None were serious adverse events (SAE). The mood disorders were described with terms consistent with depression, sadness, and suicidal ideation. Five of these cases either required hospitalisation (in 1 patient in which the event was reported as an SAE), resulted in discontinuation (2 patients, with resultant resolution of the events), required dose reduction (1 patient), or were severe in intensity (1 patient).

Eight patients experienced psychotic episodes while on levetiracetam. Four of these patients had histories of behaviour problems or ADHD, one of whom also had a history of prior psychotic events in association with seizures. Four of the cases were SAEs. One child experienced psychotic depression after about 3 years on levetiracetam and withdrew from study as a result. The event continued despite discontinuation of treatment. There were three cases of psychotic episodes, described more consistently as hostility and aggressive behaviours than true psychoses, and one of schizoaffective disorder. All occurred roughly within the first year of treatment. The patients were all hospitalized at some time for psychiatric reasons and treated with antipsychotic and/or antidepressant medication. There were three cases of hallucinations; none of these was classified as SAEs.

Overall however, few patients discontinued due to adverse events. In the placebo-controlled trial (N159), 5 patients randomised to levetiracetam (5.0%) discontinued due to an adverse event versus 9 patients (9.3%) in the placebo group. Convulsion was a common reason for discontinuation, more so in the placebo group than in the levetiracetam group: 3 patients on placebo (3.1%) and 1 patient randomised to levetiracetam (1.0%). The remaining reasons for discontinuation amongst patients randomised to levetiracetam (single patients each, 1.0%) were ataxia, depression, hostility, and hyperkinesia. The remaining reasons amongst patients randomised to placebo were ataxia, depression, emotional lability, hallucinations, hostility, and sleep disorder (in 1 patient each, 1.0%). In the remaining studies, including the extension study, 13 patients discontinued levetiracetam due to an adverse event. The reasons were hostility (2 patients for a total of 1.3%), convulsion (1 case for a total of 0.8%), and single cases of asthenia, headache, left ventricular hypertrophy, vomiting, nervousness, psychotic depression, status epilepticus, and rash. One patient also discontinued to receive a therapeutic procedure. With respect to worsening of seizures, 20 patients randomised to placebo (20.6%) and 14 patients randomised to levetiracetam (13.9%) experienced a 25% or greater increase in weekly seizure frequency in N159. Similarly, more patients randomised to placebo (17 patients or 17.5%) had seizures reported as an adverse event as compared to levetiracetam (10 patients or 9.9%). Across all studies, 54 patients treated with levetiracetam (22.6%) had seizures reported at least once as an adverse event, described either as increase in frequency or intensity. Nine patients were hospitalised (SAEs).

Serious adverse events and deaths
In N159, 8 patients (7.9%) randomised to levetiracetam group and 9 patients (9.3%) randomised to placebo experienced a serious adverse event (SAE). None were considered by the Investigator to be possibly related to study drug other than one case of convulsion in a patient randomised to placebo. Across all of the studies, a total of 66 patients exposed to levetiracetam (58 in addition to the 8 that occurred in N159) had one or more SAEs. All but one of these occurred in N157; 1 patient in N151 had an overdose. The most common pertained to the nervous system (convulsion, status epilepticus NOS, personality disorder, depression, and psychosis), reported for 32 patients overall (13.4%). Procedures requiring hospitalisation were reported for 23 patients (9.6%). The latter were, however, mostly diagnostic or therapeutic procedures related to epilepsy, and if they are not taken into consideration (since these are not related to treatment with levetiracetam), there were 50 patients with treatment-emergent SAEs. One SAE had a fatal outcome. A 15-year old Caucasian girl had received levetiracetam for a total of approximately 1 year, first in N159 and then in N157. In the 2 months before her death, she was noted to have serious worsening of behaviour problems. She was admitted to the hospital for status epilepticus, thought to be fever-induced. She had symptoms of respiratory infection as was being treated. On the way to the hospital, she experienced a respiratory arrest and

subsequently went into cardiopulmonary arrest. Ultimately, she experienced multi-organ failure due to massive ischemic insult. The death was judged by the investigator to be unrelated to study drug.

Laboratory findings
Levetiracetam causes small, but statistically significant decreases in white blood cell (WBC) and neutrophil counts (relative to placebo in N159). These effects have also been reported in adults. During long-term exposure, the magnitude of decrease was similar, *i.e*., there was no trend towards a progressive worsening or greater risk with longer treatment. A total of 39 patients who received levetiracetam in any clinical trial (16.3%) had a WBC and/or neutrophil count that was significantly low and/or reported as an adverse event. The values generally normalized despite continued treatment and no clinical sequelae were reported. Low white counts were reported as adverse events in 9 patients (3.8%). None had concomitant clinical manifestations nor resulted in dose change or discontinuation. There is a trend for lower platelets in LEV group compared to placebo. Two patients had thrombocytopenia reported as an adverse event, but neither had clinically significantly low platelets or clinical consequences.

On continued open-label treatment, there were small increases in transaminases, but clinical consequences were not reported. There was a total of 6 patients with possibly clinically significant elevations in liver function tests (other than GGT), reported as adverse events in 3. AST and/or ALT were elevated to between one and three times the upper limit of normal in 4 patients: 2 continued on treatment and the values normalized, 1 value was observed at the final study visit in 1 patient with no further follow-up, and one occurred 2 weeks after the last dose of drug. In the two latter patients, alkaline phosphatase was also increased. Two additional patients had increased alkaline phosphatase as the only possibly clinically significant value, one of whom had substantial increases (worst value 3439 U/L) with no identifiable cause despite extensive work-up. The patients' alkaline phosphatase was within normal limits at the next scheduled visit, approximately 3 months later with continued treatment. However, it is frequent to observe high alkaline phosphatase in children and teenagers, these being the reflection of growth.

Eighteen children had adverse events described as urinalysis abnormalities. Three children, all of whom were receiving topiramate, had kidney stones. The remaining 15 had mild to moderate urinalysis abnormalities (described as WBCs in the urine, ketones, calcium, leukocyte esterase, and nitrites, glucose, and bilirubin), judged not related to treatment in all but 3 cases.

ECGs were obtained at the local site and results entered into the CRF. A centralised ECG reading was not performed and measurements were relatively infrequent (end of the placebo controlled trial and after 1 year in the open-label extension study). These were not timed to peak plasma concentrations. The analysis of ECGs did not show evidence that levetiracetam has an effect on the ECG in children. However, one case of prolonged QT was described when receiving high levetiracetam doses (>99mg/kg/day) (ISS Nos. 5202).

Paediatric post-marketing experience
The post-marketing experience of levetiracetam in children and adolescents aged between 1 month and less than 16 years was reviewed by the MAH. A total of 236 cases were identified. These 236 cases involve 459 adverse events. Upon review of the post-marketing safety information, no specific safety signal was identified. There were nine fatalities. One child died due to status epilepticus with acute circulatory failure, one child with a congenital dilated cardiomyopathy died due to heart failure during a seizure, and four cases were suggestive for sudden unexplained death in epilepsy. Of the other three fatalities, one completed suicide, one died due to pneumonia and one died due to sudden hepatic insufficiency subsequently to a blood pressure drop due to hypoxia in relation with an inhalation pneumopathy.

The most frequently reported adverse events were related to psychiatric disorders (29%), including, aggression, abnormal behaviour, hallucination, crying, anger, psychotic disorder and anxiety. There were four cases of suicidal behaviour. All 4 patients were concomitantly treated with other AEDs. In one case of completed suicide the patient had a history of difficult social situation, psychosis years ago and attention deficit hyperactivity disorder. In one case of suicide attempt, the patient became

depressed and attempted suicide by stepping into the street. There was no previous history of depression or suicidal ideation. In one case of suicidal ideation, the patient had a history of learning disability. After starting levetiracetam he was seizure free and presented with behaviour disorder. In another case of suicidal ideation, the patient presented with aggression after starting levetiracetam. There was no data on psychiatric history and seizure control. In the latter two cases the events resolved while levetiracetam was continued at a reduced dosage.

The second most frequently reported adverse events were related to nervous system disorder (17%), including convulsions, somnolence and psychomotor hyperactivity. The reported events in the paediatric population are comparable to these reported in the adult population, with the exception of psychomotor hyperactivity, which is more frequently reported in the paediatric population.

In summary, adverse events linked to the treatment with levetiracetam in children were frequent, as expected for this type of medication. Safety results in paediatric patients are largely consistent with the safety profile in adults. However, the occurrence of neuropsychiatric adverse events in children was identified by CHMP as a matter of concern after their first assessment of the data submitted by the MAH. The MAH was requested to clarify if the side effects were dose-related, and if risk factors for the development of levetiracetam-induced psychiatric side effects can be identified in the paediatric population. CHMP suggested that 'Suicide' and 'suicidal ideation' should be added to the SPC as undesirable effects in post-marketing experience, and requested that the MAH looked into this issue.

This and other safety-related concerns, and the MAH responses to them are listed (text *in italics*) and discussed individually below

- *The most frequently reported adverse events in children were CNS-related disorders, and included hostility, aggression, abnormal behaviour, anger, psychotic disorder and anxiety on one hand, and somnolence and dizziness on the other hand. A more detailed description of patients at risk for psychiatric AEs would be useful. The MAH should clarify whether risk factors for the development of levetiracetam-induced psychiatric side effects can be identified in the paediatric population with epilepsy. For instance: mental handicap, pre-existing behavioural problems, hyperkinesia, etc. A warning should be added in Section 4.4 of the SPC.*

The MAH pointed out that a detailed description of the relative risk of different patients for psychiatric AEs had been presented in their submission, in the Integrated Safety Summary (Module 5, Vol.27, Section 5.3.5.3 – ISS – p.1). Further to the CHMP request, however, these data have been extracted and presented below:

<u>Relative risks of CNS adverse events in adults and children</u>
The relative risk of psychiatric/behavioural events between levetiracetam and placebo was estimated based on study N159 and compared to adult data (from adequate and well controlled studies from the original adult partial onset seizure submission of levetiracetam). As shown in Table 19 and Table 20 below, although the incidence of psychiatric/behavioural AEs in children with refractory partial seizure who are treated with levetiracetam is 38.6% versus 18.6% in adults, *the relative risk (RR) is similar in adults and children*, as there is also a higher incidence of such AEs in children treated with placebo as compared to adults (27.8% vs. 10.5%). The modestly elevated RR for psychiatric/behavioural AEs in children is 1.39 (95% CI: 0.93-2.08); while that in adults is 1.77 (95% CI: 1.30-2.42). The majority of these AEs in children are in the category of non-psychotic mood/anxiety/behavioural symptoms, RR of 2.03 [95% CI: 1.25 - 3.30]. Those individual terms for which there was a two-fold or greater RR in levetiracetam treated paediatric patients as compared to placebo were *agitation* (5.76; 95% CI: 0.71-46.99), *nervousness* (4.32; 95% CI: 0.96-19.50), and *depression* (2.88; 95% CI: 0.30-27.23). *Hostility* also tended to occur with a greater RR (1.92; 95% CI: 0.75-4.91) in paediatric patients randomized to levetiracetam.

Table 19 Number of Patients with at Least One Treatment-Emergent Psychiatric / Behavior Adverse Events by UCB Grouping Term (Overall Population Exposed to levetiracetam)

	N159			
	Placebo (N = 97)	LEV (N = 101)	Rel. Risk (LEV/PBO)	95% CI
All Psychiatric / Behaviour	27 (27.8%)	39 (38.6%)	1.39	0.93 - 2.08
Thinking Abnormal	5 (5.2%)	4 (4.0%)	0.77	0.21 - 2.78
Non-Psychotic Mood / Anxiety / Behaviour	18 (18.6%)	38 (37.6%)	2.03	1.25 - 3.30
Agitation	1 (1.0%)	6 (5.9%)	5.76	0.71 - 46.99
Anxiety	1 (1.0%)	0		
Apathy	1 (1.0%)	1 (1.0%)	0.96	0.06 - 15.14
Depersonalization	1 (1.0%)	0		
Depression	1 (1.0%)	3 (3.0%)	2.88	0.30 - 27.23
Emotional Lability	4 (4.1%)	6 (5.9%)	1.44	0.42 - 4.95
Hostility	6 (6.2%)	12 (11.9%)	1.92	0.75 - 4.91
Hyperkinesia	3 (3.1%)	3 (3.0%)	0.96	0.20 - 4.64
Nervousness	2 (2.1%)	9 (8.9%)	4.32	0.96 - 19.50
Neurosis	1 (1.0%)	0		
Personality Disorder	7 (7.2%)	8 (7.9%)	1.10	0.41 - 2.91
Psychotic Symptoms	1 (1.0%)	1 (1.0%)	0.96	0.06 - 15.14
Hallucinations	1 (1.0%)	0		
Psychosis	0	1 (1.0%)		
Self Aggressive Symptoms	1 (1.0%)	0		
Overdose	1 (1.0%)	0		
Sleep Symptoms	6 (6.2%)	4 (4.0%)	0.64	0.19 - 2.20
Insomnia	6 (6.2%)	4 (4.0%)	0.64	0.19 - 2.20

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Table 20 Number of Adults with at Least One Treatment-Emergent Psychiatric / Behavior Adverse Events by UCB Grouping Term (Adequate and Well Controlled Trials)

	Placebo (N = 439)	LEV (N = 769)	Rel. Risk (LEV/PBO)	95% CI
All Psychiatric /Behaviour	46 (10.5%)	143 (18.6%)	1.77	1.30 - 2.42
Non-Psychotic and Behavioural Symptoms	27 (6.2%)	102 (13.3%)	2.16	1.43 - 3.24
Agitation	1 (0.2%)	6 (0.8%)	3.43	0.41 - 28.36
Antisocial Reaction	0	1 (0.1%)		
Anxiety	5 (1.1%)	14 (1.8%)	1.60	0.58 - 4.41
Apathy	1 (0.2%)	2 (0.3%)	1.14	0.10 - 12.56
Depersonalization	1 (0.2%)	2 (0.3%)	1.14	0.10 - 12.56
Depression	10 (2.3%)	31 (4.0%)	1.77	0.88 - 3.57
Emotional Lability	1 (0.2%)	13 (1.7%)	7.42	0.97 - 56.54
Euphoria	1 (0.2%)	2 (0.3%)	1.14	0.10 - 12.56
Hostility	4 (0.9%)	18 (2.3%)	2.57	0.87 - 7.54
Hyperkinesia				
Nervousness	8 (1.8%)	30 (3.9%)	2.14	0.99 - 4.63
Neurosis	0	1 (0.1%)		
Personality Disorder	1 (0.2%)	7 (0.9%)	4.00	0.49 - 32.37
Screaming Syndrome				
Psychotic Symptoms	1 (0.2%)	5 (0.7%)	2.85	0.33 - 24.35
Hallucinations	0	2 (0.3%)		
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Paranoid Reaction	1 (0.2%)	0		
Psychosis	0	2 (0.3%)		
Psychotic Depression	0	1 (0.1%)		
Auto-Aggressive Behaviour	0	4 (0.5%)		
Suicide Attempt	0	4 (0.5%)		
Sleep Disorders	11 (2.5%)	28 (3.6%)	1.45	0.73 - 2.89
Abnormal Dreams	0	2 (0.3%)		
Insomnia	11 (2.5%)	24 (3.1%)	1.25	0.62 - 2.52
Sleep Disorder	0	3 (0.4%)		

Risk factors for CNS adverse events

To assess whether or not certain pre-existing medical conditions and seizure responses are risk factors of developing psychiatric/behaviour AEs, explorative analyses were conducted.

The neuropsychiatric history of each of the 239 patients in the pooled database was reviewed. The review focused on the investigator verbatim for each medical history term as it provided a more reliable and accurate description than the ICD coding. The neuropsychiatric history verbatim terms were therefore re-classified according to the Diagnostic Criteria from the DSM-IV-TR published by the American Psychiatric Association, 2000.

The RR (levetiracetam/placebo) of psychiatric events for patients with or without psychiatric histories was calculated. There is *no greater risk of psychiatric behavioural events in patients with psychiatric histories* (RR = 1.05, 95% CI = 0.63, 1.72). The incidence of these events in levetiracetam-treated patients is similar whether or not they have a prior history (39.2% vs. 38.0%, for with and without, respectively) and the RRs of emotional lability (RR = 2.94 vs 0.94), hostility (RR = 3.43 vs 1.18), and personality disorder (RR = 3.92 vs. 0.63) are higher in patients without a history (probably attributable to a lower incidence amongst placebo patients).

The cognitive status of each N159 patient in the pooled database was also reviewed, again using the investigator verbatim for each medical history term rather than the ICD coding. Eighty-two of the patients (41.4%) had a significant history of cognitive impairment in the medical history, i.e., mental retardation, cognitive delay or impairment, encephalopathy, and/or global developmental delay. More events were reported in patients without known cognitive impairment history and the expected pattern of events with increased risk was seen in that group. This could, in part, be attributed to the difficulty in rating severely impaired children. *A history of cognitive impairment does not seem to be a risk factor* for the appearance of these behavioural adverse events.

Adverse events reported in patients in N159 or receiving levetiracetam in the pooled database with and without *a given medical history* were compared for six ICD-Level 2 categories that pertain to the nervous system: mental and behavioral disorders, behavioral/emotional disorders with childhood onset, disorders of psychological development, congenital malformations of the nervous system, mental retardation, and organic mental disorders. There are *no predominant trends* in adverse events occurring in combination with any medical condition. The only observation is that cognitive adverse events tended not to be reported in patients with mental retardation and organic mental disorders. The latter group had relatively few nervous system adverse events reported.

A past neuropsychiatric history, obtained in 41.4% patients receiving levetiracetam, was not a predictive factor for CNS adverse events.

Psychiatric adverse events have been reported to occur following improvement of seizure control, a phenomena known as “alternative psychosis” or “forced normalization”. Therefore, the patients in N159 were also categorized into those who responded (defined as at least a 50% reduction from baseline in weekly seizure frequency) and those who did not meet the criterion. There are relatively few patients randomized to placebo in N159 who met responder criteria; nonetheless, there does not appear to be a preponderance of events in either response category.

Summary

- These additional analyses confirm a modestly elevated risk for psychiatric and behavioural events, in the category of non-psychotic mood/anxiety/behavioural symptoms, in children with refractory partial onset seizure disorder who are treated with levetiracetam.

- Even though the overall incidence of psychiatric and behavioural events appears higher in children as compared to adults, the relative risks are comparable.
- There is no greater risk of psychiatric behavioural events in patients with psychiatric histories. The incidence of these events in levetiracetam-treated patients is similar whether or not they have a prior history and the relative risks of emotional lability, hostility, and personality disorder are paradoxically higher in patients without a history (attributable to a lower incidence amongst placebo patients).

A history of cognitive impairment or organic mental disorders does not seem therefore to be a risk factor for the appearance of these behavioural adverse events.

SPC changes

In accordance with this reply, since there is no real warning sign, the MAH proposed to include the information in section 4.8 ("Undesirable effects") instead of section 4.4:

"*Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk is similar in children as compared to adults as there was also a higher incidence of behavioural psychiatric adverse events in the placebo group in children as compared to adults (27.8% versus 10.5%)*."

The MAH's assessment of the relative risk of CNS adverse events in children receiving levetiracetam is acceptable to the CHMP. The RR is similar in adults and children. No risk factor has been identified. Therefore, the CHMP agreed to the MAH's proposal to include this information in section 4.8 of the SPC.

The wording, however, needs to be simplified, as follows:

"*Safety results in paediatric patients were consistent with the safety profile of levetiracetam in adults except for behavioural psychiatric adverse events which were more common in children than in adults (38.6% versus 18.6%). However, the relative risk is similar in children as compared to adults*".

The MAH agreed with the CHMP and provided amended Product Information, as requested.

- *The incidence of somnolence and loss of appetite, if persisting, may interfere with the normal development. The MAH should assess this risk.*

The MAH explained that body weight was one of the indicators for development and was measured multiple times during levetiracetam treatment. To address the concern of CHMP regarding potential risk of somnolence and loss of appetite that may interfere with normal development, patients with PCS "abnormal weight change" and with reported adverse events related to weight, somnolence and loss of appetite are reviewed below:

In the double-blind study N159, ***somnolence*** was more commonly reported among patients randomised to levetiracetam than to placebo (22.8% vs 11.3%). In the ISS pooled safety database, 29.7% patients treated with levetiracetam reported somnolence. These findings are similar to those found in adults exposed to levetiracetam. The events were generally mild or moderate in intensity but were reported as severe in 5 patients. The onset ranged from within 1 day of starting treatment to more than 3 years after. The duration ranged from 1 day to 870 days, with a median duration of 30 days.

In the double-blind study N159, ***anorexia*** (loss of appetite) was more commonly reported among patients randomised to levetiracetam than to placebo (12.9% vs 8.2%). In the ISS pooled safety database, 15.5% patients treated with levetiracetam reported anorexia. The events were generally mild or moderate in intensity but were reported as severe in 2 patients. The onset ranged from within 1 day of starting treatment to more than 5 years after. The duration ranged from 1 day to 578 days, with a median duration of 55 days.

Body weight was measured several times throughout the studies N159 and N157. There was a small mean increase in body weight during the total 22-week period from baseline to the final on-treatment visit in N159 as illustrated in table 21 The change was similar in the placebo- and levetiracetam-treated group (p = 0.4909, Kruskal-Wallis test).

Table 21 Change in Body Weight (kg) from Baseline to the Last On-Treatment Visit - N159

	Levetiracetam (N = 101)			Placebo (N = 97)		
	n	Mean ± S.D.	Median	n	Mean ± S.D.	Median
Body Weight (kg)	101	1.1 ± 2.0	0.9	96	1.3 ± 1.9	1.0

In analysing the body weights in the overall pooled safety database, the 50th percentile of the normal growth curve was used as the marker for change, since increase in body weight is expected in children. In children between 4 to < 8 years of age, there was a mean increase of 2.5 kg and in children 8 to < 12 and 12 to < 18 years of age, there was a 4.3 to 5.7 kg mean increase, respectively. Therefore, it appears that levetiracetam treatment *would not affect the normal weight gain or growth curve in children*.

Further analysis performed by the MAH *did not reveal any clear relationship between weight change and somnolence* and thus did not suggest that somnolence will interfere with normal development in children. However, if anorexia is induced and persists, this may alter normal weight gain in children. Overall, since the mean body weight change in levetiracetam treated patients was similar to placebo treated patients, there is no clear relationship between levetiracetam treatment and weight loss.

CHMP considered that body weight is a rather crude method to assess growth BMI and head circumference in younger children would have been valuable additional parameters. However, CHMP agreed that there is no apparent relationship between somnolence and weight or growth changes. The issue is therefore considered resolved.

However, according to the 'Note for Guidance on clinical investigation of medicinal products in the treatment of epileptic disorders' (16 November 2000, CPMP/EWP/566/98/rev), development of AED in children should include short and long term studies designed to detect possible impact on growths (amongst others). Thus, CHMP requested that the MAH would amend the protocol of the ongoing long-term follow up study NO1148 so that body height be not only measured at visit 1, but also at the final study visit.

- *It should be clarified if the side effects of levetiracetam in children are dose-related and if they persist over time as suggested by the present data.*

In addition to the data presented with their submission dossier for this variation, to further explore whether AE persisted over time, the MAH derived the AE duration. When a subject reported more than one episode of the same event, the maximum duration would be used. After the merging, AEs reported by ≥ 20 subjects and the following events: agitation, hyperkinesia and weight loss, were evaluated (31 events in total). Results are presented in the form of histograms and scatter plots in the MAH's response. No trend is apparent. In addition, the Pearson and Spearman *correlation coefficients between AE duration and daily dose at onset* have been calculated. Most of the correlations were low in magnitude. Only the following events showed moderate correlations: *agitation* (Pearson = 0.545, Spearman = 0.629 and both were significant at 5% level); *emotional lability* (Pearson = 0.396, Spearman = 0.427 and the latter was significant at 5% level); and *flu syndrome, with a negative correlation* (Pearson = - 0.395, Spearman = - 0.604 and the latter was significant at 1% level). The significance test here was merely used to highlight some "interesting" results out of many evaluations. In fact the numbers of subjects for these 3 events were all pretty small: 15, 24, and 20, respectively.

The CHMP considered that there was no clear trend with respect to time of onset or dose for any of the AEs, except for *agitation* and *emotional lability* in relation to dose (relatively low coefficient of correlation). When AEs are categorised by the dose at onset, the incidence of *nervousness* tended to increase with increased dose and there was a weak trend for hostility and personality disorder to occur at higher doses. There was one case of QT prolongation in a child treated with a very high dose. No other case of QT prolongation has been described so far, even in overdoses; the preclinical data did not raise concern in that respect; and levetiracetam does not inhibit, nor is it metabolised by, CYP450 enzymes.

When it comes to prolonged adverse events, it is difficult to determine from study N159 which effects would persist longer since this was a relatively short-term, dose-escalating study. According to the new analyses provided by the MAH, agitation, hostility, hyperkinesia, nervousness, and personality

disorder could be present for prolonged periods, while somnolence is especially mentioned at the beginning of the treatment.

In summary, CHMP considered that the safety data are reassuring in terms of duration of AEs, reversibility, and a lack of clear dose-relationship for any effect (with a possible exception for nervousness, agitation and emotional lability). The SPC correctly describes these aspects.

- *According to the CHMP guideline for clinical investigation of medicinal products in epileptic disorders, the development of AEDs in children should include short-term and long-term studies to detect possible impact on learning, intelligence, growth, endocrine functions, puberty, and childbearing potential. Have such studies been included in the paediatric developmental plan for Keppra? Before getting these results, a warning should be added to the SPC to clearly specify that long-term effects remain unknown.*

The MAH explained that in the current paediatric development program, growth, puberty, and childbearing potential were assessed and the results are briefly summarized. A study specifically assessing any possible impact on learning and intelligence, cognitive and behaviour of levetiracetam is *ongoing* (N01103, long term follow-up N01148; both protocols had been included by the MAH). The results should be available in 2008. Endocrine function was not specifically assessed although blood glucose was measured several times during the study and no clinically significant findings were identified.

Growth

Body weight was measured several times throughout the study N159 and its long-term extension study N157. There was a small mean increase in body weight during the total 22-week period from baseline to the final on-treatment visit in N159. Based on the data of body weight, it did not suggest that levetiracetam treatment would impact the growth of children.

Puberty and childbearing potential

The Tanner Staging Scale was to be used in N157 in patients for whom it was applicable. There was variable compliance with completing this assessment. Some sites completed it for all patients regardless of whether it was applicable, e.g., site 380 completed it for virtually all patients, even those less than 4 years of age. Some sites did not complete the form at all (e.g., sites 368, 389, and 395). Finally, for some patients, the staging either was not performed despite seemingly being applicable based on age (≥ 14 years of age) or was performed but not consistently at all visits. By reviewing the listing and adverse events, there is no clear signal that levetiracetam treatment will impact the puberty and childbearing potential of children.

Learning and intelligence: ongoing study N01103-N01148

The potential effects of levetiracetam in learning and intelligence will be evaluated in the currently ongoing Study N01103 and its long-term follow-up Study N01148. Study N01103 is a 19-week, randomized, double-blind, multi-centre, placebo-controlled safety study to evaluate the cognitive and neuropsychological effects of levetiracetam 20-60 mg/kg/day, divided in twice daily dosing, as adjunctive treatment in children 4-16 years old with refractory partial onset seizures. The objectives of this study are also to generate additional double-blind, placebo-controlled safety and efficacy data for levetiracetam (20-60 mg/kg/day), as compared to placebo, in this population. Subjects will be titrated to a maximum tolerated and effective dose, up to 60 mg/kg/day, during the Evaluation Period. Neurocognitive and behavioral testing will be performed at Baseline and at the end of the Evaluation Period (Week 12). The primary cognitive and neuropsychological safety variable is the change from baseline to the end of the Evaluation Period (Week 12) in the Leiter-R AM Memory Screen Composite Score. The secondary cognitive and neuropsychological safety variables are the changes from baseline to the end of the Evaluation Period (Week 12) in the Wide Range Assessment of Memory and Learning-2 (WRAML-2) General Memory Index, Visual Memory Index, Verbal Memory Index, and Learning Index (ages 5-16). The exploratory safety variables are change from baseline to the end of the Evaluation Period (Week 12) in the Leiter-R Examiner's Rating, Achenbach Child Behavior Checklist (CBCL) Activities, Social, School, and Total Competence (Activities + Social + School) raw scores, and Child Health Questionnaire (CHQ-PF50). The details can be found in the study

protocol of study N01103 and N01148. These two studies are currently ongoing. The MAH committed to submit the final reports upon completion.

Endocrine Function
No special endocrine function tests were included in the paediatric development program. However, blood glucose was monitored during all studies. As shown in table 22, the mean and median changes from baseline to the last on-treatment visit for glucose were small and comparable for both treatment groups in N159. Differences between treatments were neither clinically relevant nor statistically significant.

Table 22 Summary of Change in Blood Chemistry Parameters from Baseline to Last On-Treatment Visit (ITT Population in N159)

	Levetiracetam (N = 101)		Placebo (N = 97)		p-value (Kruskall-Wallis)
Parameter	Mean ± S.D.	Median	Mean ± S.D.	Median	Test
Glucose, non-fasting (mg/dL)	0.3 ± 15.6	1.0	1.1 ± 19.6	3.5	0.3844

Similar results were obtained for the pooled database. There were 8 unique patients with possible clinically significant glucose abnormalities, all but one being single transient episodes of hypoglycemia. There was one case of new onset, insulin-dependent diabetes mellitus, which was considered not to be related to study medication by the Investigator.

Proposed changes to the SPC
The MAH proposed that the following wordings are added in Section 4.4 Special Warning and special precautions:
"*Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown*."

The CHMP considered that growth did not seem to be affected based on changes in weight. The assessment of puberty and childbearing potential was not performed adequately, so no conclusion on this aspect can be reached. It was agreed, however, that until valid data are generated in ongoing studies to be reported in 2008, a warning should be added to the SPC section 4.4. It is strongly recommended that thyroid function be measured in study N01103-48; such tests could not be found in the study protocol as provided.

In summary, the CHMP considered acceptable to wait for the results of the ongoing double-blind randomised safety study in order to assess the risk towards growth, learning, intelligence, endocrine function, puberty and childbearing potential in children. Until then, a warning is added to section 4.4 of the SPC. However, the MAH is requested to amend the protocol of the ongoing N01103 safety study to include thyroid tests in it.

- *Anorexia is often reported as an adverse event. Was topiramate a co-medication in these cases?*

The MAH responded that, in pooled database, there were 37 of 239 (15.5%) patients reporting anorexia. To evaluate whether or not there is a relationship between anorexia and topiramate co-medication, an exploratory analysis was conducted. As shown in table 23, in pooled safety database, among patients not concomitantly treated with topiramate, the incidence of anorexia was 12.6% (21 of 167 patients). However, for patients with topiramate as a concomitant medication, the incidence of anorexia was 22.2% (16 of 72 patients), higher than that in patients not receiving topiramate. The Chi-Square test is approaching significant level (p = 0.0585). The odds ratio was 1.99 with 90% CI of 0.97 - 4.08.

Table 23 Relationship between Anorexia and Topiramate

Anorexia	Topiramate		Total
	No (N = 167) n (%)	Yes[(a)] (N = 72) n (%)	(N = 239) n (%)
No	146 (87.4)	56 (77.8)	202 (84.5)
Yes*	21 (12.6)	16 (22.2)	37 (15.5)

[(a)] Yes = Anorexia occurred when patients took Topiramate concomitantly at same time. Subjects 4894, 5228, and 5351 were excluded from "yes" since they had the anorexia and took Topiramate, but the TEAE did not occur concomitantly with Topiramate intake.

If one does not consider whether or not anorexia and topiramate administration occurred concomitantly, then the incidences of anorexia for patients without or with topiramate as concomitant medication were 10.8% and 26.4%, respectively. This difference is statistically significant (p = 0.0022). The odds ratio is 2.97 with 90% CI of 1.45 - 6.08. For 37 patients who reported anorexia, 19 of them also received topiramate treatment. In the double blind, placebo controlled study N159, the incidence of anorexia in placebo group was 8.2%. In conclusion, it is the MAH belief that co-medication of *topiramate did increase the risk of developing anorexia* in children treated with levetiracetam.

CHMP considered that anorexia is a well-known AE of topiramate. The current data cannot determine whether co-administration of levetiracetam and topiramate increases the risk of anorexia over and above that of topiramate alone. However, it should be mentioned in the SPC that anorexia is more frequent when topiramate is coadministered with levetiracetam.

Therefore, the issue is considered resolved by CHMP, provided the MAH adds the following text under the heading 'Metabolism and nutrition disorders' in section 4.8 of the SPC:
"The risk of anorexia is higher when topiramate is co-administered with levetiracetam".

The MAH agreed with the CHMP and provided amended Product Information, as requested.

- *In paediatric studies, in 16.3% of patients there is a slight but significant decrease in white blood cell and neutrophil counts. This is reported as an adverse event in 3.8% of patients. What is the co-medication? Carbamazepine? Is there a pharmacodynamic interaction? There is also a small decrease in platelet count: is it due to valproate as co-medication? The applicant should answer these questions.*

The MAH answer was divided in the following two points:

Leukopenia and use of carbamazepine or other AEDs
In pooled safety database, there were 39 unique patients (16.9%) with either possible clinically significant abnormality of one or more WBC indices (WBC counts and WBC differential counts) and/or those with adverse events suggestive of hematological disorders. These cases were reviewed.
In *N159*, more children randomized to levetiracetam (3 vs 0 in the placebo group) had a *possible clinically significant decrease in total WBC* value; however, there was *no apparent difference between treatment groups with respect to neutrophil counts* (decreased in 5.0% and 4.2% of levetiracetam and placebo patients, respectively). Slightly higher values were found in the pooled safety database for levetiracetam (n=237). Most of these possible clinically significant abnormal WBC indices were transient.
For all patients with WBC changes, co-medications were reviewed. They were found to be similar, in type and frequency, in patients with possible clinically significant abnormal WBC indices and/or adverse events compared to those in the population of pooled safety database. There is no clear relationship between certain AED use and decrease in white cell and neutrophil counts or leukopenia. There is no indication of pharmacodynamic interaction.

- *Decrease in platelet count and use of valproate*

An explorative analysis was conducted. No clear relationship between valproate use and decrease of platelet counts could be established.

In summary, after reanalysing the pooled safety database and the results of the double-blind N159 study, the MAH concluded there is no sign of a pharmacodynamic interaction with any other AED that could increase the risk of leukopenia or thrombocytopenia in children treated with levetiracetam. CHMP considered the MAH arguments satisfactory.

4.4 SPC changes

A number of comments were raised on the SPC wording initially proposed by the MAH. Additionally, various adjustments became necessary after provision of additional data as part of the MAH's answers to the RfSI. These SPC-related issues have been discussed in details individually as part of the appropriate sections of this document. For clarity, however, the full SPC and PL as eventually approved by CHMP are provided in Attachment 1 to this assessment report.

The agreed changes to the Therapeutic Indication (4.1) section of the SPC are presented below:

Therapeutic indications

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in ~~patients~~ adults and children from 4 years of age with epilepsy.

4.5 Discussion and risk/benefit assessment

At the time of the application to support this extension of the indication to children aged 4 years and older, Keppra (levetiracetam) was approved for use as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents from 16 years of age.

Clinically, the application was primarily based on one placebo-controlled study (N159) for demonstration of efficacy in the proposed indication/population. The efficacy of levetiracetam in children from 4 years of age for the adjunctive treatment of partial seizures has been globally demonstrated in this short-term study.

Numerous concerns were identified by CHMP after the first assessment of the dossier. These led to the adoption of a Request for Supplementary Information (RfSI). (See Attachment 5 for complete list) In addition, a number of comments were raised on the initially proposed SPC wording.

The MAH provided their answers to the RfSI on 10 June 2005.

In conclusion, the MAH has provided satisfactory answers to all of the clinical questions posed to them as requests for supplementary information. The MAH acknowledged limited available data on dose-response relationship. A more cautious dose titration (for both up-titration and down-titration) is now proposed in the SPC and the use of the lowest efficient dose is stressed. The robustness of the results of the primary endpoint of study N159 has been supported in a more convincing way and the responses to both levetiracetam and placebo have been reanalysed taking into account non-parametric distribution and differential drop-outs. The response to levetiracetam appears identical across all ages. No risk factors have been found for CNS adverse events, the relative risk of which appears similar in children and adults. The coadministration of topiramate increases the risk of anorexia and maybe of other AEs. For an overview of the outcome of the discussions over the SPC.

Therefore, based on the review of safety and efficacy, and following the MAH's responses, the benefit-risk balance for levetiracetam as adjunctive therapy in the treatment of partial onset seizures in children from 4 to 16 years of age with epilepsy has been sufficiently demonstrated.

V. Conclusion

On 27 July 2005 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments:

Follow-up measures undertaken by the Marketing Authorisation Holder

Area[1]	Description	Due date[2]
Clinical	Close monitoring of seizure worsening in children. A special section in the PSUR should be devoted to this.	Alongside PSUR submissions (next due date for PSUR is January 2006)
Clinical	The MAH is requested to include thyroid tests in the protocol for the ongoing safety studies N01103 / N01148.	Immediate effect
Clinical	According to the 'Note for Guidance on clinical investigation of medicinal products in the treatment of epileptic disorders', 16 November 2000 (CPMP/EWP/566/98/rev), development of AED in children should include short and long term studies designed to detect possible impact on growths (amongst others). Thus, the MAH is requested to modify the protocol of the long-term follow up study NO1148, so that body height is not only measured at visit 1, but also at the final study visit.	Immediate effect
Clinical	Provide the results of the ongoing long-term safety studies N01103 / N01148.	Upon completion, estimated finalisation dates 4Q 2007 and 3Q 2009, respectively.

1. Quality, Non-clinical, clinical, pharmacovigilance

2. Due date for the FUM or for the first interim report if a precise date cannot be committed to. Please specify whether theses SOs or FUMs have been fulfilled.

The MAH agreed with the CHMP conclusions, and provided a Letter of Undertaking committing to comply with the CHMP's requests.