European Medicines Agency

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ASSESSMENT REPORT FOR KEPPRA

International Nonproprietary Name: levetiracetam

Procedure No. EMEA/H/C/000277/II/0097

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. EXECUTIVE SUMMARY

I.1. About the product and Problem statement

Levetiracetam (LEV), is a pyrrolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic drug substances.

Keppra is authorised under several pharmaceutical forms: Film-coated tablets 250 mg, 500 mg, 750 mg and 1000 mg, oral solution 100mg/ml, and concentrate for solution for infusion (5 ml vials).

The mechanism of action of Keppra remains to be fully elucidated but appears to be different from the mechanisms of current anti-epileptic drugs (AEDs). *In vitro* and *in vivo* experiments suggest that LEV does not alter basic cell characteristics and normal neurotransmission. In vitro studies show that LEV affects intraneuronal Ca2+ levels by partial inhibition of N-type Ca2+ currents and by reducing the release of Ca2+ from intraneuronal stores. In addition, it partially reverses the reductions in GABA- and glycine-gated currents induced by zinc and beta-carbolines. Furthermore, LEV has been shown in *in vitro* studies to bind to a specific site in rodent brain tissue. The biding site is the synaptic vesicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. LEV and related analogues show a rank order of affinity for binding to the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. This finding suggests that the interaction between LEV and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the drug.

Keppra is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy. Keppra is also indicated as adjunctive therapy:

- In the treatment of partial onset seizures with or without secondary generalization in adults and children from 4 years of age with epilepsy
- In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy
- In the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalized Epilepsy

The initial therapeutic dose authorised is 500 mg b.i.d in adults or 10 mg/kg b.i.d. in children. Depending upon the clinical response and tolerance, the daily dose can be increased up to 1500 mg b.i.d. in adults or 30 mg/kg b.i.d. in children. Adjustment of the dose is recommended in patients with renal impairment and in elderly patients with decreased renal function.

This type II variation proposes to extend the age range to children from 1 month to 4 years old in the indication of adjunctive treatment of partial onset seizures with or without secondary generalization. Two new presentations, a bottle of 150 ml with a 3 ml syringe and a bottle of 150 ml with a 1 ml syringe are introduced with an adaptor for the syringes. In order to keep consistency between the 2 pack sizes of Keppra oral solution (syringe graduated in ml, use of an adaptor, way to remove the product) and above all to avoid any confusion for the patients, the MAH also proposes a new 10 ml syringe with an adaptor for the syringe for the already authorised 300 ml bottle of Keppra 100 mg/ml oral solution. The 100 mg/ml concentrate for solution for infusion is not considered to be within the extension of the indication from the age of 1 month.

Finally, the MAH also takes this opportunity to update the available in-use stability data and to extend the in-use shelf life from 2 months to 4 months. The qualitative and quantitative composition, the manufacturing process, the batch size and the specifications of the drug product remain unchanged.

I.2. The development programme

The pharmaceutical development is detailed in section II.1 Quality aspects. An overview of the clinical development is provided in the table below.

Overview of clinical studies

Study Number/ Design	Population	Objective	Dosage and Dosage Form	Duration of Study/Status	Previously Submitted[a]
Studies in Subjects Aged 1 Month to <4 Years					
N01052 Multicenter, Open-Label, Single-Dose, PK	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=13)	Pharmacokinetic evaluation in infants and children aged <4 years	20 mg/kg Oral solution	3 weeks/ Completed	Yes
N01009 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (1 month to <4 years) (N=116)	Efficacy and safety	20 mg/kg/day to 50 mg/kg/day Oral solution	34 days/ Completed	No
Studies in Subjects Aged 4 to 16 Years					
N01010 Multicenter, Open-Label, PK	Pediatric epileptic subjects with refractory partial onset seizures (4 to 12 years) (N=21)	Pharmacokinetic linearity and bidirectional evaluation of 2 AEDs and LEV	20 to 40 to 60 mg/kg/day Tablets	12 weeks/ Completed	Yes
N151 Multicenter, Open-Label, PK	Pediatric epileptic subjects with partial onset seizures (5 to 12 years) (N=24)	Pharmacokinetic, efficacy, and safety	10 to 40 mg/kg/day Tablets	22 weeks/ Completed	Yes
N159 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects with refractory partial onset seizures (4 to 16 years) (N=216)[b]	Efficacy and safety	20 to 40 to 60 mg/kg/day Tablets	28 weeks/ Completed	Yes
N01103 Multicenter, Randomized, Double-Blind, Placebo-Controlled, Add-on	Pediatric epileptic subjects (4 to 16 years) (N=99)	Monitor cognitive and neuropsychiatric effects and safety of LEV	20 to 60 mg/kg/day Tablets or Oral solution	19 weeks/ Completed	No

N157 Multicenter, Long-Term Open-Label	Pediatric epileptic subjects who completed N151, N159, N01010, or N01052 (1 month to 16 years) (N=238)[b, c]	Long-term safety follow-up	20 to 99 mg/kg/day Tablets or Oral solution	Open/ Completed	No
Studies in Subjects Aged 1 Month to 16 Years					
N01148 Multicenter, Long-Term Open-Label	Pediatric epileptic subjects[d] from N01009 or N01103 and de novo (1 month to 16 years) (N=255; 1m to <4y: N=152; 4y to 16y: N=103)	Long-term safety follow-up	20 to 80[e] mg/kg/day Tablets or Oral solution	48 weeks/ Ongoing[f]	No

AED=antiepileptic drug; m=months; PK=pharmacokinetic; y=years

[a] Previously submitted in type II variation file EU/H/C/00277/II/044.

[b] One site was excluded from the analysis for both N159 (n=16) and N157 (n=15). In N159, 2 additional subjects discontinued prior to taking any study medication, resulting in a total of 198 subjects. In N157, a total of 223 subjects were included in the intent-to-treat analysis.

[c] Because the number of subjects younger than 4 years old was very small (n=14), their data were not analyzed separately from the data for subjects 4 years and older; therefore, all results are presented in the overall population aged 1 month to 16 years.

[d] Including screen failures from N01103 and N01009.

[e] Doses >80 mg/kg/day to be discussed with Sponsor before implementation.

[f] An interim report with data as of the 18-Sep-2007 cut-off date is included in Module 5, Section 5.3.5.4.2.

I.3. General comments on compliance with GMP, GLP, GCP

The MAH confirmed that all studies were conducted in accordance with applicable regulatory and International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved, as well as the ICH Tripartite Guidelines, Guideline for GCP, January 1997.

II. SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Drug substance

The drug substance documentation is not affected by this variation.

Drug Product

Description and composition of the product
The product composition is not affected by this variation. The composition of the oral solution is:

	mg/ml	Function	Reference to standards
Active substance			
LEV	100 mg	drug substance	In house
Excipients			
Sodium citrate		buffer agent	Ph. Eur.
Citric acid monohydrate		buffer agent	Ph. Eur.
Methylparahydroxybenzoate		antimicrobial preservative	Ph. Eur.
Propylparahydroxybenzoate		antimicrobial preservative	Ph. Eur.
Ammonium glycyrrhizinate		flavouring agent	In house
Glycerol 85%		viscosity agent	Ph. Eur.
Maltitol		sweetener, viscosity agent	Ph. Eur.
Acesulfam potassium		sweetener	Ph. Eur.
Grape flavour Firmenich 501040A		flavouring agent	In house
Purified water		vehicle	Ph. Eur.

The oral solution is packed in amber glass bottles (type III of the Ph.Eur.) closed by a polypropylene white child-resistant closure.
Three presentations will be available, namely:

- 300 ml bottle (already available on the market) with a 10 ml graduated oral syringe per 0.25 ml and a syringe adaptor, suitable for children from 4 years
- 150 ml bottle with a 3 ml oral syringe graduated per 0.1 ml and a syringe adaptor, suitable for younger children (from 6 months to less than 4 years)
- 150 ml bottle with a 1 ml oral syringe graduated per 0.05 ml and a syringe adaptor, suitable for younger children (1 month to less than 6 months).

Pharmaceutical development
The 100 mg/ml oral solution was developed to provide a convenient dosage form for patients who have difficulty in swallowing and for paediatric use.

- Most of the existing documentation on the development of the oral solution is not affected by this variation application.

The main objective of this variation is the extension of indication of Keppra to infants and young children from 1 month to 4 years.

- In infants from 1 month to less than 6 months, the proposed initial therapeutic dose is 7 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 21 mg/kg twice daily.

- In infants aged 6 to 23 months and children, the proposed 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.

In the framework of the extension of indication, a new presentation and an amendment to the current presentation are proposed.

- The new presentation consists of a 150-ml bottle size with a 3-ml syringe and an adaptor that is fixed to the bottle by the patient at first use. The 3-ml syringe is graduated per 0.1 ml (from 0.3 ml). The adaptor facilitates removal of the oral solution of the bottle since it allows the bottle to be turned upside down after fixing the syringe. In addition, there is also a 150 ml bottle with a 1 ml syringe graduated per 0.05 ml and a syringe adaptor, suitable for younger children (1 month to less than 6 months).

- In order to ensure consistency between the current and proposed pack sizes and to avoid confusion at the patient level, the applicant also proposes a new 10 ml syringe and the addition of an adaptor for the existing 300-ml bottle. The 10-ml syringe is graduated per 0.25 ml (from 1 ml).
  It is noted that the current syringe for the 300-ml bottle is marked in mg. However, mg marked devices may be used by the patient for other drugs at different concentrations and lead to overdose. Therefore, ml-marked syringes are proposed both for the 150-ml and 300-ml presentations.

- A validation of the graduation of the 1, 3 and 10 ml syringes was performed in order to demonstrate the accuracy of the dosing syringe for the drug product in the complete posology range. The results were evaluated according to Ph.Eur. 2.9.27.

Manufacture
The manufacturing process is not affected by this variation.

Control of excipients
The excipients remain unchanged and their control is not affected by this variation.

Control of the drug product
Control of the drug product is not documented as it is stated to be unchanged.

Reference standards or materials
Not affected by this variation.

Container closure system
Description:
- The oral solution is packed in an amber glass bottle (Ph.Eur. type III) containing either 300 ml or 150 ml of solution.
- Both bottle-sizes are closed by the same white, polypropylene child-resistant closure system. The closure is composed of four parts, the outer shell, the inner shell, the tamper evident ring and the liner. The outer and the inner shell are both injection-moulded from polypropylene while tamper evident ring and liner are made of polyethylene. The liner is the only part of the stopper that comes into contact with the product.
- The bottle is housed in a cardboard box which also contains a dosing syringe, an adaptor for the syringe and the patient information leaflet.
- The 300 ml bottle is supplied with a 10 ml syringe (graduated per 0.25 ml) while the 150 ml is supplied with a 3 ml syringe (graduated per 0.1 ml) or a 1 ml syringe (graduated per 0.05 ml).

Specifications:

- Appropriate specifications are presented for the glass bottles and stoppers, for the syringes and the adaptors As well as representative Certificates of Analysis are included in the dossier.
- Materials used for the container closure systems comply with PhEur and relevant European Food Legislation.

The dosing syringe is a class I medical device according to the European Directive 93/42/EC, annex V. The CE marking of conformity was affixed by the supplier after assessment of its quality system with the Notified Body Systems & Services Certification (SGS United Kingdom Limited – Notified Body number 0120).

In-use stability

- In-use stability simulating the conditions of use for the product were carried out on two pilot batches (200 litres) and two industrial batches (2000 litres) of product in the 300 ml bottles and using the current syringe (graduated from 100 mg to 1000 mg LEV). For the pilot batches, in-use stability testing was repeated after storage of 12, 24 and 36 months in the closed packaging. In-use testing was also repeated on the industrial scale batches after storage.

There are no significant trends observed and all results are in compliance with the specifications. Preservative efficacy (Ph.Eur. 5.1.3) is confirmed at the different test points.

- In-use testing on product in the proposed 150-ml bottles and using the proposed 3-ml syringe is planned on two batches. During the in-use study, 0.3 ml of product will be removed twice daily. Samples will be tested according to the shelf life specifications and the Ph.Eur. preservative efficacy test after 60, 120, 150, 180 and 210 days. The applicant commits to provide the results of the in-use study as soon as available and the applicant committed to perfom in-use stability studies on batches at the end of their shelf-life. Out-of-specification results will be immediately reported.

Since the new 10-ml syringe for the 300-ml bottles consists of the same materials, results obtained with 3-ml syringe are considered representative.

II.2 NON CLINICAL ASPECTS

Pharmacology / Pharmacokinetics

Not applicable.

Toxicology

The MAH did not submit new toxicology data.

In the absence of AUC data, the CHMP observed that section 5.3 of the SPC should be reworded to express human exposure levels on a mg/m2 basis. In addition, in view of the new population authorised for Keppra treatment, results of the reproductive toxicity, peri- and post natal studies have been provided in more details in the SPC.

A full environmental risk assessment has not been provided. The MAH committed to provide further assessment for the need or not for a full ERA, in accordance with the Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/447/00, June 2006.

II.3 CLINICAL ASPECTS

Pharmacokinetics (PK)

LEV is rapidly and almost completely absorbed after oral administration and all formulations studied in adults have been demonstrated to be bioequivalent and dose proportional. Co-administration with food, while resulting in a delayed time to peak concentration, has no relevant effect on AUCs. Renal clearance of LEV is less than glomerular filtration rate, indicating that re-absorption is larger than secretion.

Three studies have been performed to assess LEV PK and metabolism in the paediatric population:
- N01052 where LEV was administered as a 10% oral solution to children <4 years of age.
- N151 where LEV was administered as tablets to children from 5 to 12 years.
- N01010 where LEV was administered as tablets to children from 4 to 12 years.

In addition, plasma concentrations were monitored in studies N159, N01009, N01103, N157, and N01148.

Data from study N151, N01010 and N01052, together with study N01009, N01103, and N01148 was included in the population analysis, referred to as population N01288. Any subject with at least one valid plasma concentration and valid dosing record was included in the population PK analysis. The primary objectives of the analysis were:

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

Population

Demographic and Baseline Characteristics are summarized in the following tables.

Demographic and Baseline Characteristics (Continuous) for Children Included in the Population Pharmacokinetics of LEV, per Study and Overall

Studies Variable	Statistics	N151	N01010	N1052	N01009	N01103	N01148	Overall [a]
	N	24	19	13	19	42	80	197
Age (years)	Mean (SD)	9.52 (2.19)	9.63 (2.45)	1.68 (1.18)	2.47 (1.04)	10.75 (3.64)	7.57 (4.71)	7.80 (4.56)
	Median	10.02	10.24	1.44	2.60	10.98	7.39	7.77
	Min-max	5.62-12.67	4.50-12.86	0.20-3.87	0.69-3.94	5.06-16.95	0.19-16.72	0.19 – 16.95
Weight (kg)	Mean (SD)	33.2 (11.8)	33.2 (11.3)	10.1 (3.5)	11.5 (3.1)	40.6 (19.3)	30.2 (20.1)	29.9 (18.9)
	Median	31.5	32.0	9.4	11.5	33.5	24.8	25.2
	Min-Max	17-54	19-68	6-18	6-17	18-86	6-93	5.5 – 93.2
BSA (m^2)	Mean (SD)	1.10 (0.26)	1.11 (0.23)	0.47 (0.11)	0.53 (0.10)	1.24 (0.38)	0.99 (0.44)	0.99 (0.42)
	Median	1.07	1.09	0.45	0.52	1.12	0.93	0.94
	Min-Max	0.7-1.6	0.8-1.7	0.3-0.7	0.4-0.7	0.8-2.1	0.3-2.1	0.3 – 2.1
CL_{CR} (mL/min)	Mean (SD)	87.76 (25.03)	91.90 (20.14)	36.90 (12.04)	42.64 (10.62)	92.81 (32.74)	78.66 (35.85)	77.83 (34.40)
	Median	83.18	87.88	33.12	44.88	87.96	75.99	75.02
	Min-Max	50.4-136.9	59.5-144.7	15.9-60.5	28.6-60.1	46.2-181.1	13.8-173.5	13.8 – 181.1

[a] unique children (each child is counted once from the first study with evaluable sample)

BSA is calculated as $BSA = 0.024265 * BW^{0.5378} * HT^{0.3964}$ [15], BW on kg, HT in cm

CLCR (mL/min) is calculated as:

$$CL_{CR} = \frac{ks * HT}{S_{CR}} * \frac{BSA}{1.73}$$, HT in cm, Scr in mg/dL , where *ks*=0.45 for infants;

ks=0.55 for 1 to 12 years children and adolescent girls (13 years onward); *ks*=0.7 for adolescent boys (13 years onward) [16]

Source: Section 13

Studies Variables	N151 N=24	N01010 N=19	N01052 N=13	N01009 N=19	N01103 N=42	N01148 N=80	Overall[a] N=197
Gender							
Male	15	11	7	10	22	47	112
Female	9	8	6	9	20	33	85
Race							
Asian	0	0	0	0	2 (4.8%)	19 (15.2%)	21 (10.7%)
American Indian/ Alaskan	0	0	0	4 (21.1%)	0	2 (1.6%)	6 (3.0%)
Black	3 (12.5%)	2 (10.5%)	3 (23.1%)	0	8 (19.0%)	12 (9.6%)	28 (14.2%)
Caucasian	21 (87.5%)	7 (36.8%)	6 (46.2%)	14 (73.7%)	28 (66.7%)	35 (28.0%)	111 (56.3%)
Hispanic	0	8 (42.1%)	4 (30.8%)	0	0	0	12 (6.1%)
Other/ Mixed race	0	2 (10.5%)	0	1 (5.3%)	4 (9.5%)	12 (9.6%)	19 (9.6%)
Number of AEDs							
1	24	18	6	1	31	35	115
2	0	0	7	17	10	34	68
3	0	0	0	1	1	5	7
4	0	0	0	0	0	6	6
None	0	1	0	0	0	0	1
AED class							
Neutral (1)	11 (45.8%)	1 (5.3%)	4 (30.8%)	2 (10.5%)	12 (28.6%)	10 (12.5%)	40 (20.3%)
Inducer (2)	7 (29.2%)	10 (52.6%)	2 (15.4%)	2 (10.5%)	5 (11.9%)	21 (26.3%)	47 (23.9%)
Inhibitor (3)	6 (25.0%)	8 (42.1%)	6 (46.2%)	12 (63.2%)	24 (57.1%)	33 (41.3%)	89 (45.2%)
Other (4)	0	0	1 (7.7%)	3 (15.8%)	1 (2.4%)	16 (20.0%)	21 (10.7%)

[a] unique children (each child is counted once from the first study with evaluable sample)
Source: Section 13

Analytical methods

The objectives were achieved through population PK modeling of LEV concentration-time data, using a non-linear mixed-effects model. LEV plasma concentrations from 197 subjects were used for non-linear mixed effects modeling by extended least squares regression using NONMEM version VI with PdxPop interface version 2 (Globomax Corp.).

The strategy analysis was as follows:

1. Select a base model, and perform both a univariate and a multiple forward selection analyses to get a full model including covariates.
2. Backward elimination analysis.
3. Sensitivity analysis to check if any of the statistically significant covariates were not clinically relevant.
4. Validation of the model using the posterior predictive check technique.
5. Application of the model to perform some simulations to establish dose adjustment, if any, for children below 4 years of age.

Statistical analysis

- *Base model:*

A 1-compartment model with first-order absorption and first-order elimination was found to best characterize the plasma concentration-time profile for LEV, with inter-individual variability on absorption rate constant (KA), CL/F and V/F. As is common practice given the wide age range investigated, BW was included a priori as a covariate in the structural model on both CL/F and V/F. On the base model with BW, the exponents for CL/F and V/F were as expected based on allometric scaling, i.e., 0.75 for CL/F and 1 for V/F.

- *Covariate model*

Age, sex, dose, race, concomitant AEDs, CL_{CR} and maturation factor on CL/F and age and sex on V/F respectively were tested for statistical significance in a Univariate analysis. Covariates which were found significant were subsequently tested in forward inclusion and backwards elimination procedure. The statistically significant covariates after backwards elimination were subsequently tested for clinical relevance, except for BW as it was part of the structural model.

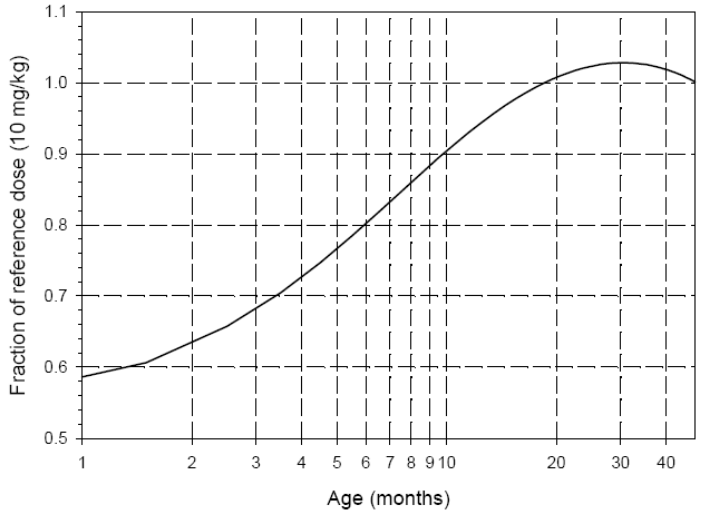
All scatter plots of population and individual predicted vs. observed concentrations were evenly distributed around the line of unity. In addition, conditional weighted residuals were evenly distributed around zero when plotted against time and population predicted concentrations. The plots per subject showed a good agreement between the observed concentrations and the individual prediction.

The final model was validated with the posterior predictive check, which showed that the model could predict the central tendency and variability of the data. The final parameter estimates could be used to predict LEV plasma concentration-time profiles to support dosing recommendations. The inter-individual variability was estimated to be less than 20% for both CL/F and V/F. The final model included BW, AEDC and age through a maturation factor on CL/F, and age on V/F.

- *Simulation of dose adjustments using the validated model*

The model was further used for simulations of exposure in children from 1 month to 4 years to evaluate the necessity of a dose adjustment to obtain the same typical exposure as a 4 year old patient receiving 10mg/kg per intake (20 mg/kg/day), and to establish a nomogram. A dose of 10 mg/kg per intake was chosen as this is the currently recommended starting dose for children 4 to 16 years old. The nomogram is applicable whatever the dose as the PK of LEV is dose proportional. The nomogram is presented in Figure 1.

Figure 1. Dose adjustment factor in pediatric age 4 years or younger



The following dose recommendations are suggested by the MAH:

Age range (months)	1-6	Above 6
Recommended starting dose (mg/kg b.i.d.)	7	10
Recommended level 2 dose (mg/kg b.i.d.)	14	20
Recommended level 3 dose (mg/kg b.i.d.)	21	30

The MAH provided further explanation for the choice of the dose recommendations, as requested by the CHMP, as detailed thereafter.

In the most recent population PK analysis (N01288), conducted in children ranging in age from 1 month to 16 years, there was a statistically significant association between age and both clearance and volume of distribution. The effect of age on both parameters decreases as age increases, to become negligible around 4 years.

The MAH presented simulations using the proposed dosing strategy in a 1 month child with a very low body weight and a 6 month child with a high body weight to evaluate the necessity of a dose adjustment. The calculated fraction of dose required to achieve the same exposure as a 4-year-old was 0.58 for a 1-month-old. This substantially exceeded a change of 20% which was deemed the minimum threshold necessitating a dose adjustment. Therefore, the dose was adjusted in order to avoid unnecessarily high exposure to the drug. The decision to put the cut-off at 6 months was based on the fact that the nomogram shows an inflection point at 6 months with the fraction of the reference dose equal to 0.8, ie in the middle of the 0.58 to 1 interval. Besides, LEV is entirely eliminated via the kidneys, mostly as the unchanged compound, and it has been consistently demonstrated in the recent literature that the maturation of glomerular filtration is essentially complete by the age of 6 to 12 months. Furthermore, the dosing adjustment proposed is simple and the cut-off age of 6 months is convenient and easy to remember, thereby limiting the risk of error for the physician in his clinical practice.

Children 1 to 6 months of age would require about 70 %, and children aged from 6 months onward 100% of the dose of children aged 4 years to reach the same exposure. The highest dose level 42mg/kg/day (21mg/kg b.i.d.) recommended based on PK analysis is consistent with the 40mg/kg/day dose used in the efficacy study N01009. Therefore, based on the efficacy and safety results from short-term and long-term clinical studies, and population PK analysis (N01288), the dose recommendation for pediatric patients 1 month to <6 month is to initiate the treatment with a daily dose of 14mg/kg/day (7mg/kg b.i.d.) that can be increased up to 42mg/kg/day (21mg/kg b.i.d.). Although rapid titration (over 1 day in inpatient) was well tolerated in N01009 a slower dose adjustment is preferred in an outpatient setting and dose changes should not exceed increments or decrements of 14mg/kg/day (7mg/kg b.i.d.) every 2 weeks.

There is very limited PK data in infants below 1 year of age (8 patients in total, the youngest subject being 2.3 months old). This posed the question of whether the model can be predictive enough for this age group, particularly given the extensive heterogeneity in epilepsy syndromes in this age group. The MAH performed some additional analysis (e.g. visual predictive checks stratified by age and weight, Goodness of fit plots tagged with aged or weight) showing that the model is indeed predictive enough for this age group from a PK perspective. Using this model, LEV concentrations were similar for all age groups when normalized to 10mg/kg dose. The dosing recommendations were supported by simulations using the proposed dosing strategy in a 1 month child with a very low body weight and a 6 month child with a high body weight. Thus, the proposal appears reasonable from a PK perspective, if aiming for a similar exposure.

Pharmacodynamics

Not applicable.

Clinical efficacy

To support the current application, the MAH submitted one pivotal safety and efficacy study in children down to 1 month of age (N01009), a safety study examining cognitive and neuropsychological functioning in children 4 to 16 years of age (N01103), and a long-term follow-up study (N01148), as summarised in the table below.

Overview of studies providing efficacy data

Study No.	LEV Dose(s)	Actual Maximum Study Drug Duration	Children Exposed (Male / Female)	Children Exposed to LEV	Mean age (Range)	Overview of Design
Primary Efficacy Study (1 month to <4 years)						
N01009	20 mg/kg/day, 25 mg/kg/day, 40 mg/kg/day, 50 mg/kg/day	21.5 days	116 (57 / 59)	60	23.43 months (1.0 to 47 months)	Randomized, DB, PC
Short-Term Study (4 to 16 years)						
N01103[a]	20 to 60 mg/kg/day	138 days	98 (56 / 42)	64	10.47 years (4.1 to 16.7 years)	Randomized, DB, PC non-inferiority study of cognitive and neuropsychological effects
Supporting Long-Term Studies (1 month to 16 years)						
N01148	Up to 80 mg/kg/day[b]	511.5 days	255 (139 / 116)	255	5.28 years (0.1 to 16.7 years)	OL, LT FU
1m to <4y			152 (78 / 74)	152	23.46 months (1 to 47 months)	
4y to 16y			103 (61 / 42)	103	10.14 years (4.1 to 16.7 years)	
N157[c]	Up to 80 mg/kg/day or 3000 mg/day	2,340 days	223 (118 / 105)	223	9.7 years (0.2 to 17.5 years)	OL, LT, FU
			14[e] (7 /7)	14[e]		
			209 (111 / 98)	209		

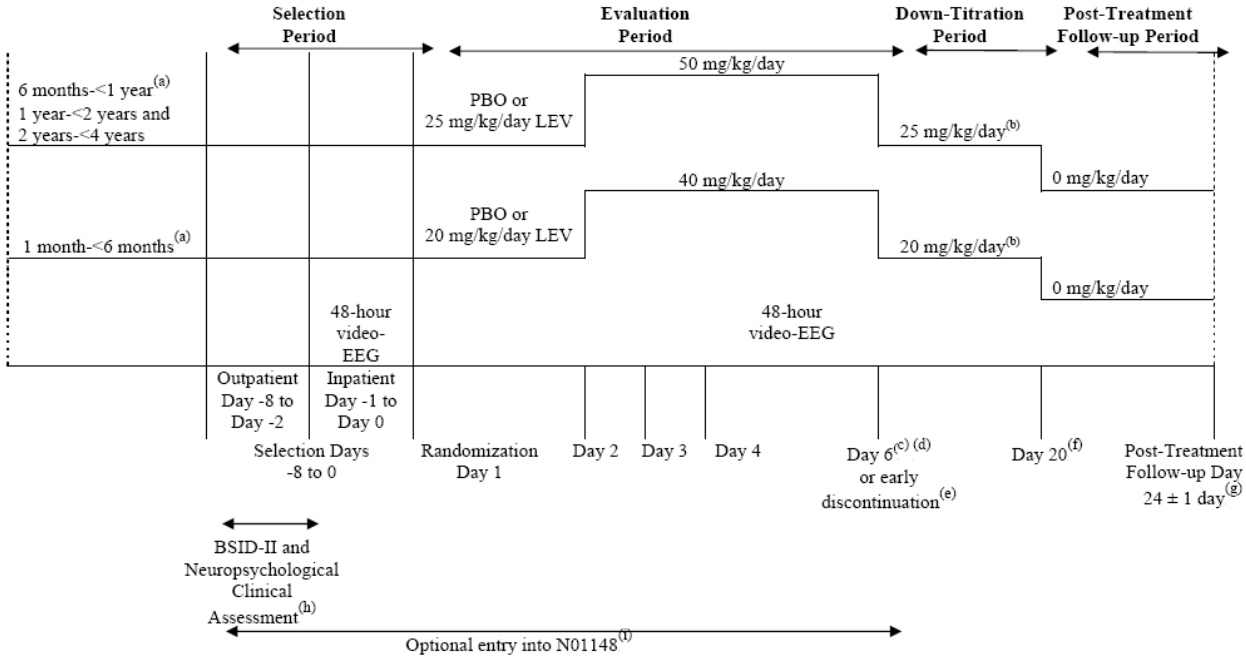
DB=double-blind; FU=follow-up; LT=long term; OL=open-label; PC=placebo-controlled
[a] N01103 had 99 subjects randomized; however, 1 subject did not receive study drug
[b] Doses >80 mg/kg/day to be discussed with Sponsor before implementation.
[c] Majority of the data (interim analysis) included in a previous submission.
[d] Because the number of subjects younger than 4 years old was very small (n=14) and their Baseline seizure information was not collected, their data were not analyzed separately from the data for subjects 4 years and older; therefore, all results are presented in the overall population aged 1 month to 16 years.
[e] A total of 14 subjects aged 1 month to <4 years were enrolled in N157. Thirteen of these subjects were enrolled in N01052. An additional subject was screened but not enrolled in N01052 because enrollment had been completed. This subject was enrolled in N157.

Pivotal study (N01009) to evaluate efficacy and safety of LEV used as adjunctive treatment in paediatric subjects aged 1 month to <4 years with refractory partial onset seizures.

- *Study design and treatment*

N01009 was a Phase III, double-blind, randomized, parallel-group, multicenter, placebo-controlled, add-on study in children aged 1 month to < 4 years (Figure 2).

Figure 2. Study diagram



- *Inclusion criteria*

Patients included in the study were paediatric subjects (aged 1 month to <4 years) diagnosed with refractory partial onset seizures, whether or not secondarily generalized. Subjects were required to be on a stable regimen of at least 1, but no more than 2 other AEDs for 2 weeks prior to entering the study. Subjects had to have experienced at least 2 partial onset seizures with or without secondary generalization during each 7-day period during the 2 weeks prior to entering the study. Subjects aged 1 month to <6 months had to have at least 2 partial onset seizures (i.e., seizures with focal paroxysmal discharges of 10 or more seconds), whether or not secondarily generalized, during the 48-hour video-EEG performed prior to randomization. These seizures did not need to be accompanied by a corresponding clinical event. Subjects aged 6 months to <4 years had to have at least 2 partial onset seizures (i.e., seizures with focal paroxysmal discharges of 10 or more seconds), whether or not secondarily generalized, during the 48-hour video-EEG performed prior to randomization. These seizures had to be accompanied by a corresponding clinical event as noted on video or as reported by a qualified observer. Video-EEG data was interpreted by the central reader in a blinded manner and was used for all seizure-based analyses.

- *Data sets analyzed*

1) <u>ITT population</u>

The ITT population consisted of all the randomized subjects who took at least one dose of study drug and included 116 subjects; 56 in the PBO group and 60 in the LEV group.

2) <u>Modified ITT (mITT) population</u>

The mITT population consisted of all intent to treat (ITT) subjects who had at least 24 hours of usable selection video-EEG time (as determined by a central reader). Furthermore, subjects were included if they met the following criteria:

• At least 24 hours of usable Evaluation video-EEG time, or

• If < 24 hours of usable Evaluation video-EEG time (including zero time available) and withdrawal from the study with reasons linked to lack or loss of efficacy. These subjects were deemed non-responders (for the primary endpoint).

Usable selection video-EEG time was defined as total video-EEG time minus total un-interpretable time.

The mITT population included 109 subjects; 51 in the PBO group and 58 in the LEV group.

3) PP population

The PP population consisted of all subjects in the mITT population without major protocol violations that affected the primary efficacy variable and included 99 subjects; 47 in the PBO group and 51 in the LEV group.

ITT Population demographic characteristics by treatment group

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

Source: Table 14.1.2:1

The aetiology of epilepsy is shown in the following table.

Aetiology of epilepsy.

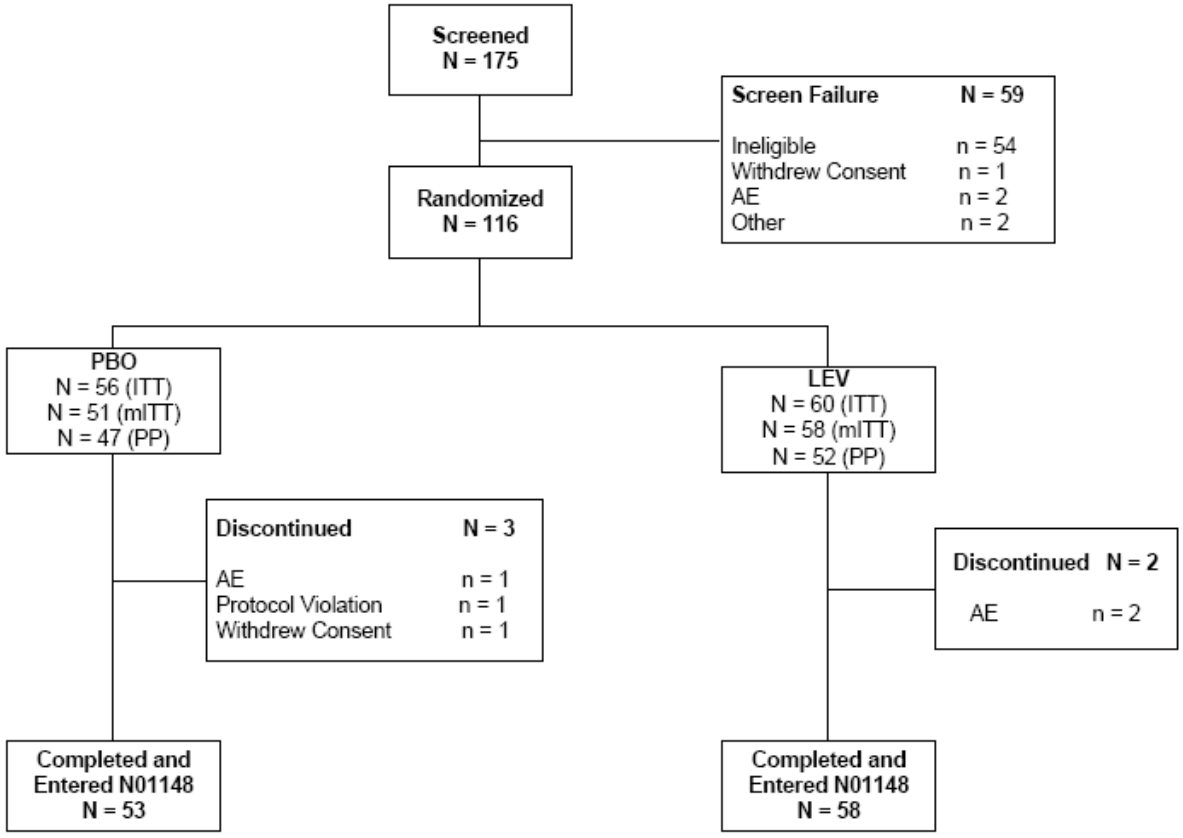
	PBO (N=56) n (%)	LEV (N=60) n (%)	Overall (N=116) n (%)
Unknown	14 (25.0%)	16 (26.7%)	30 (25.9%)
Genetic Origin (Familial Epilepsy)	3 (5.4%)	3 (5.0%)	6 (5.2%)
Congenital Malformation	17 (30.4%)	16 (26.7%)	33 (28.4%)
Perinatal Events	8 (14.3%)	18 (30.0%)	26 (22.4%)
Cranial Trauma	6 (10.7%)	2 (3.3%)	8 (6.9%)
Brain Surgery	1 (1.8%)	0	1 (0.9%)
Primary Degenerative Lesion	1 (1.8%)	1 (1.7%)	2 (1.7%)
Cerebrovascular Accident	2 (3.6%)	2 (3.3%)	4 (3.4%)
Cerebral Infection	4 (7.1%)	4 (6.7%)	8 (6.9%)
Other	11 (19.6%)	6 (10.0%)	17 (14.7%)

Source: Table 14.1.3:2

- *Disposition of subjects*

The disposition of subjects in study N01009 is summarised in figure 3. In addition, seven subjects (5 on placebo and 2 on LEV) were excluded from the mITT population. Of these 7 subjects, 5 (4 on placebo and 1 on LEV) had completely missing video EEG seizure data for the following reason: subject withdrew due to adverse event (2), subject withdrew due to protocol violation (1), lost data (2).

Figure. 3. Disposition of subjects in study N01009



Source: Table 14.1.1:1, and Listing 16.2.1:3

- *Primary efficacy endpoint results*

The primary efficacy endpoint was the responder rate, for total partial onset seizures (Type I) for subjects in all age groups. This was defined as the number of subjects with a ≥ 50% reduction from baseline in their average daily frequency (ADF) divided by the total number of subjects. ADF was computed from the 48-hour Evaluation video-EEG (post-baseline) and the 48-hour Selection video-EEG (baseline).

The primary efficacy analysis was based on the mITT population. The same analysis on the PP population and ITT population resulted in consistent results.

Responder rate in ADF for partial onset seizures adjusted for age and subgroup analyses by age group - mITT population.

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

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

Supportive study N01103 to characterize potential cognitive and neuropsychological effects of LEV (20 to 60 mg/kg/day) as adjunctive treatment in children aged 4 to 16 years with partial onset seizures as non-inferior when compared to adjunctive treatment with PBO.

- *Study design and treatment*

Study N01103 was a phase II, 19-week, randomized, double-blind, multicenter, placebo-controlled safety study in children (4 to 16 years old) with partial onset seizures with or without secondary generalization.
The study consisted of a baseline period (up to 7 days), a 12-week evaluation period, and a 6-week withdrawal period for subjects not enrolling in the open-label extension study N01148. The evaluation period included 4 weeks of up-titration followed by 8 weeks of maintenance treatment. The randomization was 2:1 (LEV: placebo), and the final randomized sample had 65 LEV subjects and 34 PBO subjects. Seventy-nine subjects completed the study (PBO 85.3%; LEV 78.1%).

- *Inclusion criteria*

Subjects enrolled were 4 to 16 years of age and had inadequately controlled epilepsy with a low baseline seizure frequency. The majority of subjects had epilepsy of unknown aetiology, and were treated with only 1 concomitant AED. Up to 2 concomitant AEDs were allowed during the study.

- *Study efficacy endpoints and results*

In this study, efficacy evaluation for partial onset seizure frequency was only exploratory as the primary endpoint was safety. Results for the median absolute change from the baseline period to the evaluation period in partial onset seizure weekly frequency are presented in the table below.

Summary of partial onset seizure weekly frequency at baseline and during the evaluation period (ITT population).

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

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

In addition, the percentage of subjects showing response to treatment (defined as at least 50% reduction from Baseline in partial onset seizure weekly frequency) was greater in the LEV group (40/64 subjects; 62.5%) than in the PBO group (14/34 subjects; 41.2%). The percentage of subjects who were seizure-free was also greater in the LEV group (30/64 subjects; 46.9%) than in the PBO group (3/34 subjects; 8.8%).

Few subjects in N01103 study had Type II or Type III seizures. Therefore, the results of all analyses of total seizures were nearly identical to those for partial onset (Type I) seizures. Results obtained with the GES, a measure of the change in severity of illness, indicated greater improvement in the LEV group than the PBO group, regardless of whether the raters were investigators, subjects, or parents/legal guardians (see table below).

Number (%) of subjects by global evaluation scale ratings at week 12 (or Early Discontinuation), as rated by investigators, subjects, and parents/legal guardians (ITT population).

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

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

Supportive study N01148 to obtain long-term descriptive safety and efficacy data in paediatric epileptic subjects with partial onset seizures receiving long-term treatment with LEV at individualized doses of up to 80 mg/kg/day.

- *Study design and treatment*

Study N01148 was a multi-centre, open-label, long-term, follow-up study of the safety and efficacy of LEV in children with partial onset seizures. Subjects received LEV at individualized doses and, if required, their existing antiepileptic drugs for 48 weeks. The dose was flexible and optimized within the range of 20 to 80 mg/kg/day. After a titration/conversion phase of up to 8 weeks to open-label LEV, subjects entered the maintenance phase at Visit 3. The visits during the maintenance phase occurred approximately every 8 to 10 weeks ± 4 days for the first 6 months and then at 12 week intervals for the next 6 months. A final visit was scheduled approximately 2 weeks ± 4 days after the final dose of LEV had been taken or earlier if the subject was continuing on LEV after completion of Visit 7 (Week 48).

- *Inclusion criteria*

Paediatric subjects with partial onset seizures whose parents or legally authorized representative gave consent to participate in the previous LEV paediatric studies (N01009 and N01103), and paediatric subjects between 1 month and 16 years of age with partial onset seizures whose parents or legally authorized representative gave consent to participate in this study as direct enrollers, and for whom LEV treatment was considered to be of possible benefit.

- *Baseline characteristic sand disposition*

The baseline characteristics differed between the age groups 1m – 4years and 4 – 16 years old. In the 1m – <4year group, the baseline seizure frequency was higher (median = 17.25 seizures per week) than for subjects in the 4year – 16year group (median = 1.17 seizures), the majority had symptomatic/cryptogenic epilepsy, and most were treated with 2 concomitant AEDs. The majority of subjects in the 4year – 16year group had a lower baseline seizure frequency than the 1m – < 4year group, and the majority had epilepsy of unknown aetiology and were treated with only 1 concomitant AED.

Subject Disposition by Age Group and Overall

	1m - <4y n (%)	**4y - 16y n (%)**	**Overall n (%)**
Screened Subjects[(a)]	152	104	256
ITT Population	152	103	255
Enrolled from Prior Study	111 (73.0)	80 (77.7)	191 (74.9)
Screen Failed from Prior Study	33 (21.7)	1 (1.0)	34 (13.3)
Directly Enrolled in N01148	8 (5.3)	22 (21.4)	30 (11.8)
Completed Study	97 (63.8)	83 (80.6)	180 (70.6)
Discontinued from the Study	55 (36.2)	20 (19.4)	75 (29.4)
Adverse Event	13 (8.6)	5 (4.9)	18 (7.1)
Lack/Loss of Efficacy	23 (15.1)	7 (6.8)	30 (11.8)
Lost to Follow-up	2 (1.3)	3 (2.9)	5 (2.0)
Withdrawal of Consent	6 (3.9)	2 (1.9)	8 (3.1)
Other	9 (5.9)	2 (1.9)	11 (4.3)
Protocol Violation	2 (1.3)	1 (1.0)	3 (1.2)
Intake of prohibited concomitant medication	1 (0.7)	0	1 (0.4)
Failure to meet inclusion criteria	1 (0.7)	1 (1.0)	2 (0.8)

[(a)] Direct enrolled Subject 803/9001 screen failed for reason "ineligibility."

Efficacy variables and results

The primary efficacy results are summarised in the following tables.

Summary of partial onset seizure weekly frequency at baseline and during the maintenance period - ITT population.

	Statistic	1m - <4y (N=152)	4y - 16y (N=103)	Overall (N=255)
Combined Baseline[a]	n	148	103	251
	Mean (SD)	47.90 (99.76)	7.49 (31.06)	31.32 (81.50)
	Median	17.25	1.17	6.00
	Q1 - Q3	5.00 – 45.75	0.40 – 4.00	1.00 – 28.00
	Min - Max	0.0 – 1030.0	0.0 – 295.1	0.0 – 1030.0
Maintenance Phase Weekly Seizure Frequency	n	138	95	233
	Mean (SD)	88.06 (600.72)	3.29 (9.81)	53.50 (463.55)
	Median	6.39	0.14	1.49
	Q1 - Q3	0.41 – 38.96	0.00 – 1.91	0.07 – 17.89
	Min - Max	0.0 – 7023.3	0.0 – 75.9	0.0 – 7023.3
Maintenance Phase Absolute Reduction from Baseline	n	134	95	229
	Mean (SD)	-35.41 (616.41)	4.37 (28.19)	-18.91 (471.55)
	Median	3.44	0.39	0.93
	Q1 - Q3	-1.07 – 18.61	0.09 – 1.53	-0.33 – 8.99
	Min - Max	-7020.3 – 943.1	-21.4 – 264.9	-7020.3 – 943.1
Maintenance Phase Percent Reduction from Baseline[b]	n	132	94	226
	Mean (SD)	-1768.32 (20369.20)	31.55 (136.39)	-1019.70 (15568.06)
	Median	55.97	86.41	68.87
	Q1 - Q3	-10.93 – 92.84	23.20 – 100.0	-3.60 – 96.61
	Min - Max	-234011.1 – 100.0	-875.6 – 100.0	-234011.0 – 100.0

[a] Includes the combined Historical and Prospective Period Baselines.
[b] 1m – <4y subjects 507/2001 and 515/1001 and 4y – 16y subject 715/3005 had a zero Baseline SFPW; thus, their percent reduction from Baseline could not be calculated.

Number and percent of subjects who responded to treatment (partial onset seizures) - ITT population

Visit		1m - <4y (N=152)	4y - 16y (N=103)	Overall (N=255)
Visit 4 (Weeks 4-14, 6-15, or 8-16)	n	131	93	224
	Median	54.17	88.64	69.88
	Q1 - Q3	-16.94 – 95.29	37.50 – 100.0	2.55 – 100.0
Visit 5 (Weeks 14-24, 15-24, or 16-24)	n	117	89	206
	Median	67.97	91.67	79.99
	Q1 - Q3	-6.38 – 99.47	48.44 – 100.0	4.07 – 100.0
Visit 6 (Weeks 24-36)	n	105	87	192
	Median	75.78	100.00	82.92
	Q1 - Q3	16.78 – 100.0	35.71 – 100.0	25.62 – 100.0
Visit 7 (Weeks 36-48)	n	98	83	181
	Median	81.54	100.00	89.20
	Q1 - Q3	23.91 – 100.0	58.06 – 100.0	36.46 – 100.0

Amount of Subjects who responded (with response defined as a reduction in partial onset seizure weekly frequency that was ≥50%), to treatment (Partial Onset Seizures) - ITT

Study Phase and Visit	1m - <4y (N=152) n (%)	4y - 16y (N=103) n (%)	Overall (N=255) n (%)
Up-Titration/Conversion Phase	62/146 (42.5)	63/101 (62.4)	125/247 (50.6)
Maintenance Phase	71/132 (53.8)	65/94 (69.1)	136/226 (60.2)
Visits 3-4[a]	71/131 (54.2)	63/93 (67.7)	134/224 (59.8)
Visits 4-5[b]	70/117 (59.8)	65/89 (73.0)	135/206 (65.5)
Visits 5-6 (Weeks 24-36)	68/105 (64.8)	63/87 (72.4)	131/192 (68.2)
Visits 6-7 (Weeks 36-48)	66/98 (67.3)	64/83 (77.1)	130/181 (71.8)

Note: A responder is a subject with a ≥ 50% reduction in seizure weekly frequency from Baseline. Responder rate is calculated as number of responders divided by number of subjects with non-missing, non-zero Baseline and non-missing post-Baseline seizure frequency/week.

Supportive study N157 to obtain standardized descriptive safety and efficacy data in paediatric subjects during long-term treatment with LEV at individualized doses and who had participated in a previous LEV study

- *Study design and treatment*

Study N157 was a Phase III, open-label, multicentre, non-randomized, long-term follow-up trial in children with epilepsy who had completed a previous paediatric LEV study. The trial consisted of four phases: a screening phase (Visit 1), a blinded titration phase lasting up to 6 weeks (for subjects in prior study N159), a maintenance phase, and a withdrawal phase lasting up to 6 weeks. A preliminary report of this study was assessed in the application for extension of indication to children from 4 years of age (EMEA/H/C/227/II/44).

- *Inclusion criteria*

Subjects were eligible for inclusion in N157 if they were males or non-pregnant, non-nursing females; had participated in a previous LEV study (N159, N01010 + N151, or N01052); and might have benefited from further treatment with LEV.

- *Baseline characteristic and disposition*

Only 15 children of a total of 223 were aged 1 month to 4 years. The vast majority were older than 4 years. The demographic characteristics and patient disposition are summarised in the tables below.

Demographic characteristics in study N157

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Characteristic	Descriptive Statistics	N159 PBO/LEV (N=79)	N159 LEV/LEV (N=89)	N01010+N151 LEV/LEV (N=41)	N01052 LEV/LEV (N=14)	Overall (N=223)
Age (years) (a)	n	79	89	41	14	223
	Mean (SD)	9.88(3.46)	10.61(3.24)	10.07(2.20)	1.62(1.16)	9.68(3.72)
	Median	9.9	11.0	10.7	1.4	10.1
	Q1 - Q3	7.5 - 11.8	8.4 - 12.8	8.2 - 12.0	0.7 - 2.3	7.3 - 12.2
	Min-Max	3.6 - 17.5	4.4 - 17.3	5.9 - 13.0	0.2 - 3.9	0.2 - 17.5
Age Class						
=> 1 month < 4 y	n (%)	1 (1.3%)	0 (0.0%)	0 (0.0%)	14 (100.0%)	15 (6.7%)
=> 4 and < 8 y	n (%)	26 (32.9%)	20 (22.5%)	10 (24.4%)	0 (0.0%)	56 (25.1%)
=> 8 and < 12 y	n (%)	33 (41.8%)	38 (42.7%)	21 (51.2%)	0 (0.0%)	92 (41.3%)
=> 12 and < 17 y	n (%)	18 (22.8%)	30 (33.7%)	10 (24.4%)	0 (0.0%)	58 (26.0%)
=> 17 y	n (%)	1 (1.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
Sex						
Male	n (%)	36 (45.6%)	50 (56.2%)	25 (61.0%)	7 (50.0%)	118 (52.9%)
Female	n (%)	43 (54.4%)	39 (43.8%)	16 (39.0%)	7 (50.0%)	105 (47.1%)

Note: %=(n/N)x100
Note: y=year(s), 1y=360 days, PBO=Placebo, LEV=Levetiracetam
(a) Age (years) at the Screening visit

Disposition of subjects in study N157

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

Source: Table 14.1.1:1 and Listing 16.2.1:1

- *Efficacy variables and results*

The primary efficacy variable was the percentage change from the prior study of enrolment baseline in partial onset (and total) seizure frequency per week. All efficacy and safety analyses for this study were performed on the intention-to-treat (ITT) population.

The primary analysis and the responder analyses were conducted on the 203 subjects with baseline seizure counts. The mean and median exposures in N157 were approximately 2 years; maximum exposure was approximately 7.5 years. A median percentage reduction from baseline above 50% in partial onset seizure frequency per week was maintained above 50% over the entire treatment period. Of the 154 subjects exposed to LEV ≥1 year, 53 (34.4%) had at least one continuous interval of seizure freedom lasting at least 6 months and 34 (22.1%) had at least one continuous interval of seizure freedom lasting at least 1 year, at some time during the study. Because the number of subjects younger than 4 years old was very small (n=14) and their baseline seizure information was not collected, their data were not analyzed separately from the data for subjects 4 years and older; therefore, all results are presented in the overall population aged 1 month to 16 years.

Clinical safety

Exposure

Overall, 285 individual paediatric and adolescent subjects received LEV in the MAH-sponsored studies included in the pooled safety database in this submission. An overview of these studies is presented in the table below.

Overview of enrolment in MAH-Sponsored clinical studies included in the pooled analyses in the current application

Study	Total	PBO	LEV	Unique exposures to LEV
	Number of Subjects			
1 Month to <4 Years Pool[a]	168	N/A	168	168
4 Years to 16 Years Pool[b]	117	N/A	117	117
N01009 (1 month to <4 years)	116	56	60	60
N01103 (4 to 16 years)	99[c]	34	64	64
N01148	255	N/A	255	147
1 month to <4 years	152	N/A	152	94
4 years to 16 years	103	N/A	103	53
N157 (N01052) (1 month to 16 years)	223	N/A	223	14[d]

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

Safety pools analysed

Two data pools based on subject age group (1 month to <4 years and 4 years to 16 years) were defined for the pooled analyses of AEs, specific laboratory evaluations, specific vital sign measurements, and ECG data.

Three safety pools based upon subject age and assessment were defined for the cognitive and neuropsychological safety endpoints. These 3 data pools are described below:

- Bayley Scales of Infant Development-II (BSID-II) (1 Month to <4 Years) Safety Pool
  All subjects who provided BSID-II data in either N01009 or N01148 were included in this safety pool. This pool contains 53 subjects treated with LEV.

- Leiter International Performance Scale-Revised (Leiter-R) and Achenbach Child Behavior Checklist (CBCL) (4 Years to 16 Years) Safety Pool
  All subjects who provided Leiter-R or CBCL data in either N01103 or N01148 were included in this safety pool. Not all subjects had data for both the Leiter-R and CBCL assessments (e.g., CBCL assessments were not done for a majority of the 4- and 5-year-old subjects). This pool contains 121 subjects treated with LEV.

- CHQ-PF50 (4 years to 16 years) Double-Blind, Placebo-Controlled Safety Pool
  All subjects who provided CHQ-PF50 data in either N01103 or N159 were included in this pooled sample. This pool contains 118 subjects treated with PBO and 149 subjects treated with LEV.

Children from 1 month to <4 Years Safety Pool

Exposure by mean daily dose by duration of exposure is shown in the following table.

Exposure by mean daily dose by duration of exposure (1 month to < 4 years pool).

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

LEV=levetiracetam
Source: ISS Table 16.3.1:9

Almost all subjects from this group had partial onset seizures. The age of onset of epilepsy was approximately 6 months on average, and the epilepsy duration at first study entry was approximately 17 months. They were on 1 or 2 AEDs at Baseline to which LEV was added as adjunctive therapy. The most commonly used concomitant AEDs were phenobarbital, valproic acid, topiramate, oxcarbazepine, and diazepam.

Overall, the mean age of subjects in the 1 Month to <4 Years Pool was 22.9 months. There was a relatively even distribution of male (50.6%) and female (49.4%) subjects. Most subjects were Caucasian (76.8%). The majority of subjects were taking 2 concomitant AEDs at Baseline. In the 1 month to <4 years Pool, 38.1% of subjects discontinued prematurely. The most common reasons for premature discontinuations were lack or loss of efficacy (13.1%) and AE (10.7%). Most discontinuations occurred in the first 24 weeks of LEV exposure.

- *Adverse events*

The most frequent common treatment-emergent adverse events (TEAEs) occurring in ≥5% of subjects in the 1 month to <4 years Pool are summarized by preferred term in the table below.

Common TEAEs occurring in ≥5% of Subjects Overall (1 Month to <4 Years Pool)

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

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

- *Serious adverse events and deaths*

Three deaths were reported in the 1 Month to <4 years Pool. One child died of brain oedema; one died of malignant brain oedema; and the last subject died of intermittent obstructive airways disorder. The events of brain oedema were considered unlikely to be related to study drug by the investigator; the event of obstructive airways disorder was considered not related to study drug by the investigator. Serious AEs reported for ≥2 subjects overall are summarized in table below.

Treatment-Emergent Serious Adverse Events Reported for ≥2 Subjects overall (1 Month to <4 Years Pool)

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

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

- *Psychiatric adverse events*

Psychiatric disorders SOC are summarised in the table below.

Table 3:2 TEAEs in the psychiatric disorders SOC occurring in ≥3% of patients overall (1 Month to <4 Years Pool)

UCB SOC/MedDRA PT	Overall (N=168) n (%)
Patients with at least 1 event	158 (94.0)
Psychiatric disorders	52 (31.0)
Irritability	26 (15.5)
Insomnia	7 (4.2)
Sleep disorder	7 (4.2)
Aggression	6 (3.6)
Restlessness	5 (3.0)
Agitation	5 (3.0)
Crying	3 (1.8)
Anxiety	2 (1.2)
Decreased activity	2 (1.2)
Food aversion	2 (1.2)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Sorted by descending frequency overall by PT within SOC.

Preferred terms coded using MedDRA dictionary Version 9.0.

Source: ISS Table 16.4.1:5

- *Nervous system adverse events*

Nervous system disorders SOC are summarised in the table below.

Table 3:1 TEAEs in the nervous system disorders SOC occurring in ≥3% of patients overall (1 Month to <4 Years Pool)

UCB SOC/MedDRA PT	Overall (N=168) n (%)
Patients with at least 1 event	158 (94.0)
Nervous system disorders	72 (42.9)
Convulsion	29 (17.3)
Somnolence	22 (13.1)
Coordination abnormal	7 (4.2)
Psychomotor hyperactivity	7 (4.2)
Status epilepticus	7 (4.2)
Headache	6 (3.6)
Hypotonia	5 (3.0)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Sorted by descending frequency overall by PT within SOC.

Preferred terms coded using MedDRA dictionary Version 9.0.

Source: ISS Table 16.4.1:5

- *Cognitive and Neuropsychological assessments*

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

Safety in subjects aged 4 years to 16 years

Cumulative LEV exposure by time is summarized below.

Summary of cumulative LEV exposure by time (4 Years to 16 Years Pool)

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

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

The age of onset of epilepsy in this group was approximately 4.7 years on average, and the epilepsy duration at first study entry was approximately 5.5 years. They were on 1 or 2 AEDs at Baseline to which LEV was added as adjunctive therapy. The most commonly used concomitant AEDs were oxcarbazepine, carbamazepine, lamotrigine, and valproic acid. Overall, the mean age of subjects in the 4 Years to 16 Years Pool was 10.2 years. The majority of subjects were male (59.8%); 40.2% were female. The highest percentage of subjects was Caucasian (49.6%). Twenty-two of 23 screen failure/direct enrollment (SF/DE) subjects were enrolled at sites in India; these subjects had lower mean weight and mean body mass index (BMI).

The percentage of subjects in the 4 years to 16 years Pool who discontinued prematurely was 27.4%. The most common reason for premature discontinuations was AE (9.4%). Most discontinuations occurred in the first 24 weeks of LEV exposure.

- *Adverse events*

The frequency of the most frequent common TEAEs which occurred in ≥5% of subjects overall is summarized in the table below.

Common TEAEs Occurring in ≥5% of Subjects Overall (4 Years to 16 Years Pool)

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

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

- *Serious adverse events and death*

One death occurred in subjects aged 4 to 16 years. A 14-year-old Caucasian female died during N157. This event was reported in the previous submission (Variation II/044). Overall, 2 subjects (1.7%) in the 4 Years to 16 Years Pool had at least 1 treatment-emergent SAE each. Both subjects were in the LEV group by original treatment assignment. One subject had an SAE of neutropenia; the other had an SAE of abdominal pain. The percentage of subjects with at least 1 SAE in the 1 Month to <4 Years Pool was higher than in the 4 Years to 16 Years Pool. Differences in SAEs between the pools may possibly be related to the severity of disease and the general medical condition in the younger subjects.

- *Psychiatric adverse events*

disorders SOC are summarised in the table below.

Table 3:4 TEAEs in the psychiatric disorders SOC occurring in ≥3% of patients overall (4 Years to 16 Years Pool)

UCB SOC/MedDRA PT	Overall (N=117) n (%)
Patients with at least 1 event	105 (89.7)
Psychiatric disorders	48 (41.0)
Aggression	13 (11.1)
Irritability	11 (9.4)
Abnormal behaviour	10 (8.5)
Insomnia	6 (5.1)
Depression	5 (4.3)
Anxiety	4 (3.4)
Mood altered	4 (3.4)
Disturbance in attention	4 (3.4)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SF/DE=screen failure/directly enrolled; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Sorted by descending frequency overall by PT within SOC.

Preferred terms coded using MedDRA dictionary Version 9.0.

Source: ISS Table 16.4.1:6

- *Nervous system adverse events*

Nervous system disorders SOC are summarised in the table below.

Table 3:3 TEAEs in the nervous system disorders SOC occurring in ≥3% of patients overall (4 Years to 16 Years Pool)

UCB SOC/MedDRA PT	Overall (N=117) n (%)
Patients with at least 1 event	105 (89.7)
Nervous system disorders	60 (51.3)
Headache	37 (31.6)
Somnolence	14 (12.0)
Dizziness	10 (8.5)
Psychomotor hyperactivity	7 (6.0)
Convulsion	6 (5.1)
Lethargy	5 (4.3)
Migraine	4 (3.4)
Tremor	4 (3.4)

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Sorted by descending frequency overall by PT within SOC.

Preferred terms coded using MedDRA dictionary Version 9.0.

Source: ISS Table 16.4.1:6

- *Cognitive and Neuropsychological Assessments*

Study N01103

Study 1103 was a double-blind, randomized, multicentre, placebo-controlled trial to evaluate the safety of LEV compared with PBO, as adjunctive treatment for poorly controlled partial onset seizures with or without secondary generalization in children. The study was designed to determine whether

LEV was non-inferior to PBO after 12 weeks of treatment with regard to the major safety variables measures of cognitive and neuropsychological functioning.

The study included children (ages 4-16 years) with partial onset seizures who were taking AEDs. After collection of historical baseline seizure data and a prospective baseline period of up to 7 days, subjects received LEV or PBO (in either oral tablet or oral solution form) as add-on treatment. The randomization ratio was 2 (LEV) to 1 (PBO). Doses were titrated up to a maximum of 60 mg/kg/d over 4 weeks. Subjects continued at their maximum dose for 8 weeks. Cognitive and neuropsychological testing, as well as other safety and efficacy assessments, were performed at baseline and at the end of the Evaluation Period (Week 12).

The primary cognitive and neuropsychological safety variable was change from baseline (Visit 2) to the end of the Evaluation Period (Week 12 or the Early Discontinuation Visit [EDV]) in the Leiter International Performance Scale-Revised (Leiter-R) Attention and Memory (AM) Battery's Memory Screen Composite Score. The change score was similar in the PBO group (LS mean=5.17) and the LEV group (LS mean=5.36) in the primary PP population. LEV was declared non-inferior to PBO because the lower bound of the 2-sided 90% CI (-4.69) was contained in the critical interval for determining non-inferiority (-9, ∞). The LS mean difference was 0.19 and the 2-sided 90% CI was (-4.69, 5.08). Similar results were obtained in the ITT population.

Leiter-R AM Memory Screen Composite Scores and Change from Baseline to Week 12 or Early Discontinuation (PP Population)

Study Visit Statistic	PBO (N=27)		LEV (N=46)		LEV-PBO
	Value	Change at Week 12/EDV	Value	Change at Week 12/EDV	
Visit 2 (Baseline/Day 0)					
n	27		46		
Mean (SD)	87.11 (15.92)		89.57 (18.80)		
Median	90.00		90.00		
Q1 – Q3	71.00 – 96.00		71.00 – 106.00		
Min – Max	62.00 – 122.00		56.00 – 131.00		
Visit 6 (Day 84/Week 12)					
n	27	27	46	46	
Mean (SD)	92.48 (17.17)	5.37 (11.15)	94.80 (20.79)	5.24 (12.79)	
Median	87.00	9.00	94.50	4.50	
Q1 – Q3	81.00 – 103.00	-3.00 – 13.00	81.00 – 109.00	0.00 – 12.00	
Min – Max	62.00 – 122.00	-28.00 – 19.00	56.00 – 134.00	-44.00 – 38.00	
LS Mean for Change from Baseline (Std Err)		5.17 (2.33)		5.36 (1.78)	0.19 (2.93)
2-sided 90% CI					(-4.69, 5.08)

Note: Only subjects with non-missing values for both Visit 2 and Visit 6 are included.

Source: Table 14.3.8:1

Exploratory neuropsychological safety variables related to behavioural and emotional functioning were measured with the Achenbach Child Behavior Checklist (CBCL). For each of the competence scores, a larger value indicates better performance. On the CBCL syndrome scores, the treatment group differences reached statistical significance on the Aggressive Behaviour (LS mean=3.07; p=0.0126; 95% CI: 0.68, 5.46), Externalizing Syndromes (LS mean=3.94; p=0.0114; 95% CI: 0.92, 6.96), and Total Problems scores (LS mean=11.54; p=0.0203; 95% CI: 1.85, 21.23) in the PP population. The pattern of mean performance for these scores showed improvement in the PBO group, and worsening in the LEV group. When compared with the placebo group, there were at least 20 % more LEV children who worsened on the following syndrome scores: Withdrawn/Depressed, Aggressive Behavior, Internalizing Syndromes, Externalizing Syndromes, and Total Problems.

On the CBCL competence scores (Activites, School, and Social), there were no major group differences, but a greater percentage of children worsened on the Total Competence score in the placebo group (placebo 36.8 %, LEV 17.6 %). An overview of the Achenbach Child Behaviour Checklist scores is shown in the table below.

Achenbach Child Behavior Checklist Categorical Level of Change from Baseline to Week 12 or Early Discontinuation (PP Population)

CBCL Scale/Score	PBO (N=27)[a]			LEV (N=46)[b]		
	Improved n (%)	Stable n (%)	Worsened n (%)	Improved n (%)	Stable n (%)	Worsened n (%)
Competence Scores						
Activities	2 (9.1%)	14 (63.6%)	6 (27.3%)	5 (12.2%)	30 (73.2%)	6 (14.6%)
Social	4 (18.2%)	12 (54.5%)	6 (27.3%)	5 (12.2%)	25 (61.0%)	11 (26.8%)
School	5 (26.3%)	13 (68.4%)	1 (5.3%)	6 (17.1%)	25 (71.4%)	4 (11.4%)
Total	4 (21.1%)	8 (42.1%)	7 (36.8%)	7 (20.6%)	21 (61.8%)	6 (17.6%)
Syndrome Scores						
Anxious/ Depressed	4 (18.2%)	17 (77.3%)	1 (4.5%)	10 (23.3%)	28 (65.1%)	5 (11.6%)
Withdrawn/ Depressed	7 (31.8%)	14 (63.6%)	1 (4.5%)	8 (18.6%)	23 (53.5%)	12 (27.9%)
Somatic complaints	8 (36.4%)	13 (59.1%)	1 (4.5%)	13 (30.2%)	21 (48.8%)	9 (20.9%)
Social problems	6 (27.3%)	11 (50.0%)	5 (22.7%)	10 (23.3%)	24 (55.8%)	9 (20.9%)
Thought problems	8 (36.4%)	12 (54.5%)	2 (9.1%)	9 (20.9%)	25 (58.1%)	9 (20.9%)
Attention problems	3 (13.6%)	14 (63.6%)	5 (22.7%)	15 (34.9%)	18 (41.9%)	10 (23.3%)
Rule-breaking	4 (18.2%)	16 (72.7%)	2 (9.1%)	7 (16.3%)	24 (55.8%)	12 (27.9%)
Aggressive behavior	5 (22.7%)	15 (68.2%)	2 (9.1%)	10 (23.3%)	16 (37.2%)	17 (39.5%)
Internalizing syndromes	10 (45.5%)	11 (50.0%)	1 (4.5%)	14 (32.6%)	17 (39.5%)	12 (27.9%)
Externalizing syndromes	5 (22.7%)	15 (68.2%)	2 (9.1%)	6 (14.0%)	19 (44.2%)	18 (41.9%)
Total problems	9 (40.9%)	12 (54.5%)	1 (4.5%)	13 (30.2%)	15 (34.9%)	15 (34.9%)

NOTE: "Improved" is an increase in raw score of > 2 times the standard error of the mean. "Stable" is change in raw score that is within 2 times above or below the standard error of the mean. Worsened is a decrease in raw score of > 2 times the standard error of the mean.
[a] Because only subjects with non-missing values at baseline and Week 12 were included, the PBO group n varied across scales from 19 to 22.
[b] Because only subjects with non-missing values at baseline and Week 12 were included, the LEV group n varied across scales from 34 to 43.
Source: Table 14.3.11:16, Table 14.3.11:17, Table 14.3.11:18, Table 14.3.11:19, Table 14.3.11:20, Table 14.3.11:21, Table 14.3.11:22, Table 14.3.11:23, Table 14.3.11:24, Table 14.3.11:25, Table 14.3.11:26, Table 14.3.11:27, Table 14.3.11:28, Table 14.3.11:29, and Table 14.3.11:30

Study N01148

Study N01148 was a phase III multi-center, open-label, long-term follow-up study of the safety and efficacy of LEV in children with partial onset seizures. It was designed for peadiatric patients between 1 month and 16 years of age with partial onset seizures, who participated in the previous LEV pediatric exclusivity studies (N01009 or N01103) as well as N01148 direct enrollers who could benefit from LEV treatment, whom would undergo LEV treatment.

The Leiter-R and CBCL were assessed in subjects aged 4 years to 16 years old and the BSID-II was assessed in subjects aged 1m to <4 years. Results from the Leiter-R, which was administered to subjects aged 4 to 16 years, indicated improvement at 24 and 48 weeks in memory and in cognitive, social, and emotional functioning.

The raw scores for the BSID-II Mental and Motor Development scales and the Behavior Rating scales suggest there was progressive mental development, while motor development and behavioral functioning were relatively static over time in subjects 4 years of age and younger, but due to the absence of a placebo-control group and the small sample size, the results should be interpreted cautiously.

Changes in behavioral and emotional functioning in the group aged 4 to 16 years were monitored using the CBCL. Results indicate that subjects who entered this long-term follow-up study did not experience a worsening on average in their behavioral or emotional functioning. An improvement or stability was seen in the different syndromes, whereas for competence stability was observed on average. These results appear to show somewhat different trends than what was seen in the core

double-blind placebo-controlled study N01103, where the externalizing syndrome score and particularly the aggressive behavior component appeared to be affected negatively by LEV treatment. The differences between these two studies' designs, and the fact that doses in N01148 were adapted to each subject's needs, could have contributed to the differences in trends.

Comparison across age groups for most frequent TEAEs in the nervous system and psychiatric disorders SOCs

The most frequently reported TEAEs in the nervous system disorders SOC and the psychiatric disorders SOC in the 3 age groups are summarized below. Whilst some differences are observed, in particular in the higher incidence of convulsions in the youngest patients (a population with a more severe brain dysfunction and concomitant systemic disorders associated with their uncontrolled epilepsy compared with older patients), overall safety results in paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years and adults.

Table 2:1 Most frequent TEAEs in the nervous system disorders and psychiatric disorders SOCs occurring in ≥10% of patients in any pool

MedDRA Preferred Term	1 Month to <4 Years Pool (N=168) n (%)	4 Years to 16 Years Pool (N=117) n (%)	Adults (N=592) n (%)
Convulsion	29 (17.3)	6 (5.1)	31 (5.2)
Irritability	26 (15.5)	11 (9.4)	0
Somnolence	22 (13.1)	14 (12.0)	61 (10.3)
Aggression	6 (3.6)	13 (11.1)	10 (1.7)
Headache	6 (3.6)	37 (31.6)	73 (12.3)
Sensory disturbance	0	0	61 (10.3)

MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class

Sorted in descending order in the 1 Month to <4 Years Pool.

Preferred terms coded using MedDRA dictionary Version 9.0.

Data source: ISS Table 16.4.1:5, ISS Table 16.4.1:6; Table 1.121; Table 1.125

Post marketing experience

A cumulative safety review of the post-marketing experience in infants and children aged 1 month to <4 years was performed by the MAH, taking into account the safety data for of label use of LEV. Eighty-eight cases were identified in infants and children aged 1 month to <4 years. The 88 cases involve 168 adverse events. To date, there is no evidence of a specific safety signal in this age group.

Risk Management plan (RMP)

Given the limited number of patients aged <1 year old, the heterogeneity of epileptic syndromes in this age group, and the limited long-term safety data available, the MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1 of the RMP presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP (see summary table below).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR). In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached

- At the request of the EMEA

Safety concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed risk minimization Activities
Abnormal behavior	Routine PhV	Currently approved SmPC already includes in the section 4.8 the incidence of psychiatric and behavioural adverse events observed in the clinical trials in "adults and in children". Agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders and thinking abnormal, are included as common undesirable effects pertaining to psychiatric disorders. In addition the approved SmPC highlights in the section 4.8 postmarketing experience of abnormal behaviour..
Blood dyscrasias	Routine PhV	Approved SmPC already includes in the section 4.8 thrombocytopenia as a common adverse event observed in the clinical trials in adults and in children. In addition the section 4.8 of approved SmPC highlights postmarketing experience of leukopenia, neutropenia and pancytopenia..
Seizures worsening	Routine PhV	Approved SmPC already includes in the section 4.4 a warning that increase in seizure frequency of more than 25 % was reported in 14 % of levetiracetam treated adult and paediatric patients (4 to 16 years of age) with partial onset seizures, whereas it was reported in 26 % and 21 % of placebo treated adult and paediatric patients, respectively.
Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children.	Routine PhV	Approved SmPC already includes in the section 4.4 a warning that long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

Limited data are available on safety in patients with different epilepsy syndromes younger than 12 months	1. Routine pharmacovigilance Systematic reviews of adverse events, including lack of efficacy in patients younger than 12 month will be conducted on a monthly basis. 2. Observational Sentinel Sites Study N01357 in Infants Younger than 12 Months, who are Prescribed the Treatment with Keppra (Levetiracetam) in Usual Clinical Practice The data of the patients younger than 11 months old at the start of the treatment with Keppra® in usual clinical practice will be collected in this observational study. The sponsor of the study will ensure to have the patients in the age group between 1 and 6 months. representing at least 30% of the observational study population as to be able to provide a sufficient amount of data on this highly vulnerable group. The data of 100 patients younger than 11 months, including at least 30 patients in the age group between 1 and 6 months will be collected. The data will be collected from Sentinel Sites within the EU.	None

The MAH also committed to submit to 6-monthly specific safety reports for children < 4 years old in between yearly PSURs.

III. BENEFIT RISK ASSESSMENT AND OVERALL CONCLUSION

III.1 Benefits

Although there is limited PK data in infants below 1 year of age the PK model proved to be reasonably predictive down to 1 month of age, and the dose titration proposed has been adequately justified.

For the age group 1 month – 4 years, one major primary efficacy study was performed (N01009) as well as two longer term follow up studies (N01148 and N157). Overall, 226 children between 1 month and 4 years were exposed to Keppra, although some of the 226 children have been enrolled twice.

The results of pivotal study N01009 are convincing, although actual numbers in the different age groups are relatively small, with only 8 children aged < 6 months and 15 children aged from 6 to 12 months. The primary variable results for the mITT population show an overall responder rate of 19.6 % for placebo and 43.1 % for the LEV group which is statistically significant. Due to the small size of the subgroups, none of the individual subgroup analyses gave statistically significant results, but the treatment effect remained consistently large across the age groups.

The limited number of patients < 1 year old is of concern to the CHMP, in particular due to the heterogeneity of epileptic syndromes in this age group (tuberous sclerosis, Sturge-Weber, malformations, cerebral palsy etc…). The MAH recognised that patients enrolled in the pivotal study N01009 presented with a variety of syndromes. However, this study was designed to assess LEV as a

treatment of partial onset seizures associated with various etiologies and epilepsy syndromes and all subjects enrolled were diagnosed with partial onset seizures using video-EEG, the only reliable method to identify and characterize partial onset seizures in infants and young children. The MAH committed to assess the long-term efficacy in this age range through observational sentinel sites study.

Whilst the short-term efficacy of the treatment is demonstrated in the pivotal study N01009, the short double blind phase (5 days) and the 48 hour video-EEG-based endpoint do not permit to extrapolate the results to the long-term treatment. In this respect, the data of the 48 weeks follow-up study N01148 provided good and sustained efficacy results. However, this was an open-label study with baseline characteristics differing between age groups. In the long-term open label extension study N157, efficacy for treatment of partial-onset seizures seemed to be maintained over time.

III.2. Risks

The whole PK modeling/simulation exercise assumes that the same PK/PD relation is valid for children from 1 month to 4 years of age as compared to older children and adults. The CHMP considered that the exposure-response should also be taken into consideration as it might not be the same for children from 1 month to 4 years of age as compared to older children and adults.

Another concern related to the limited safety information gathered for patients aged <1 year old and on the lack of long-term safety data available in this new population.

The MAH thoroughly reviewed the safety profile in children from 1 month to 4 years of age as compared to older children (4 years to 16 years), in particular with regards to nervous system, psychiatric and cognitive disorders. Overall, the safety results in younger paediatric patients were consistent with the safety profile of levetiracetam in older children aged 4 to 16 years and adults.

In the double-blind, placebo-controlled paediatric safety N01103 study assessing the cognitive and neuropsychological effects of Keppra in children 4 to 16 years of age with partial onset seizures, it was concluded that Keppra was non inferior to placebo with regard to the change from baseline of the Leiter-R Attention and Memory, Memory Screen Composite score in the per-protocol population. Whilst results related to behavioral and emotional functioning indicated a worsening in Keppra treated patients on aggressive behavior as measured in a standardized and systematic way using a validated instrument (CBCL – Achenbach Child Behavior Checklist), this was not confirmed in the open-label long-term study N01148.

Overall, levetiacetam as an adjunctive therapy in the treatment of partial onset seizures in children < 4 years old presented a safety profile similar to that of reported in older children and adults. Although no particular safety concern emerged, the limited data in children <1 year old, heterogeneity of epileptic syndromes in this age group, and the lack of robust long-term safety data for the new population prompted the MAH to commit to a thorough RMP as described above. The lack of data in children from 1 month to 4 years of age is also reflected in section 4.4 of the SPC.

III.3. OVERALL CONCLUSION

The overall benefit/risk of Keppra in the adjunctive treatment of partial seizures with or without secondary generalisation in children from 1 month to <4 years old is positive provided that the MAH commits to perform a number of post authorisation follow-up measures to be reported back to the CHMP within predefined timeframes.

IV. CONCLUSION

On 23 July 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

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