London, 27 April 2006
Product name: **Keppra**
Procedure No. **EMEA/H/C/277/II/61**

SCIENTIFIC DISCUSSION

1. Introduction

Myoclonus is the hallmark of the myoclonic epilepsies, which encompass some of the idiopathic, symptomatic and cryptogenic generalized epilepsies. The myoclonic epilepsies consist of benign myoclonic epilepsy of infancy, epilepsy with myoclonic-astatic seizures (Dose syndrome), and Juvenile Myoclonic Epilepsy (JME). In addition, myoclonic seizures can be observed in some other types of epilepsy such as Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE) and Grand Mal seizures on awakening as well as in other syndromes such as Lennox-Gastaut Syndrome (LGS), Early Myoclonic Encephalopathy, Severe Myoclonic Epilepsy in Infancy and Progressive Myoclonic Epilepsy (PME).

Juvenile myoclonic epilepsy (JME) is an epilepsy syndrome that accounts for 5-10% of all epilepsies. It belongs to the group of idiopathic generalised epilepsies (IGE). JME typically starts at the age of 12-18 years, and is characterized by myoclonic jerks and infrequent primary generalised tonic-clonic seizures. Absences occur infrequently in one third of the patients. Valproate is the treatment of choice and renders 80-90% of patients with JME completely seizure free. However significant adverse drug reactions reported with valproate, such as weight gain, tremor and hair loss, occur in one third of the patients, and the teratogenic potential of valproate is of concern in women of childbearing age. If valproate does not render the patient seizure free, or has unacceptable side effects, other options are lamotrigine, which may worsen the myoclonic jerks, or a benzodiazepine.

Keppra (levetiracetam – LEV) is currently authorized as an adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy.

Based on the results of a well-controlled study, with possible extended treatment in an open-label long-term extension, conducted in patients who have IGE with myoclonic seizures, the MAH applied to extend the current indication by including the *"adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy."*

In addition to section 4.1 of the SPC, the MAH proposed to update section 4.8 to include the new safety data generated by study N166. The Package Leaflet (PL) was revised accordingly.

2. Quality aspects

Not applicable

3. Non-clinical aspects

Not applicable

4. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP, as stated by the MAH. Tin addition, the MAH confirmed that the ethical requirements of the clinical trial directive 2001/20/EC were applied for clinical trials conducted outside the EU.

Clinical efficacy

The clinical efficacy programme was based on one placebo-controlled study (N166) and its open-label extension study (N167). An overview of the clinical studies providing clinical data in this application is shown in Table I.

Table I.

Study No.	No. Enrolled (Exposed to levetiracetam (LEV)	Population (Target Age Range)	Dosing
Controlled Study Pertinent to the Indication			
N166	122 (66)	Patients with idiopathic generalized epilepsy with myoclonic seizures (ages 12 to 65 years)	3000 mg/day LEV or placebo adjunctive therapy × 16 weeks (500 mg tablets b.i.d.)
Uncontrolled Long-Term Exposure Study			
N167 (ongoing study)	92(a) (42 previously treated with PBO in N166)	Patients entering long-term follow-up from studies in patients with primary generalized seizures (ages 4 to 65 years)	Open-label, individualized doses up to a maximum of 4000 mg/day (~80 mg/kg/day for children and adolescents less than 50 kg) adjunctive therapy (166, 250 or 500 mg tablets b.i.d.)

(a) Total enrollment is 199, with the balance of the patients enrolling from N164 (N162), N01057, and N129; 58 ITT evaluable in the interim analysis of N167 (i.e. those who completed more than the first visit in N167 and had study drug exposure data available).

Main study N166: Phase III, double-blind, randomized, placebo-controlled add-on study

METHODS

Objectives

The objective of the study was to assess the efficacy of adjunctive treatment with levetiracetam (LEV) 3000 mg/day in reducing myoclonic seizures in adolescents (≥ 12 years) and adults (≤ 65 years) suffering from IGE, and to evaluate the safety and tolerability of LEV in the same population.

Study Participants

Inclusion criteria

Among the inclusion criteria were:

- Confirmed diagnosis consistent with idiopathic generalized epilepsy with myoclonic seizures (IIB) that were classifiable according to the International Classification of Epileptic Seizures. To ensure an idiopathic generalized epilepsy population, only those subjects with the diagnosis of JME, JAE or epilepsy with generalized tonic-clonic seizures on awakening were to be included.

According to an amendment of the protocol, other idiopathic generalised epilepsy syndromes were considered on a case by case basis.

- Presence of at least eight days with at least one myoclonic seizure (IIB) per day during the eight weeks of the baseline period.
- Absence of brain lesion documented on a CT scan or MRI performed during the baseline period or within five years before Visit 1.

- Presence of EEG features consistent with IGE on an EEG recorded during the baseline period or no more than one year before Visit 1.
- Subject or parent/legal guardian able to understand and complete daily record card.
- Male/female children ≥12 years of age or adult ≤ 65 years of age at Visit 1. Minimum body weight of 40 kg (88.2 lbs).
- Subject on a stable dose of one standard anti-epileptic drug (AED) for at least four weeks before Visit 1.

Exclusion criteria

The exclusion criteria included previous exposure to LEV, history of partial onset seizures, chronic illness, signs of progressive brain lesion, subject taking vigabatrin or tiagabine, subject on felbamate with less than 18 months exposure, and subject under vagal nerve stimulation or ketogenic diet.

Treatments

Study N166 was a phase III, double-blind, randomized 1:1, parallel group, placebo-controlled add-on, multi-centre study.

For each subject, the maximum study duration was 30 weeks. The study consisted of 4 phases:

- An 8-week placebo single-blind baseline.
- A 4-week double-blind up-titration by dose increment of 1000 mg/two weeks up to a total dose of 3000 mg/day.
- A 12-week double-blind evaluation (During the first week in the evaluation period, patients were allowed a dose reduction to 2000 mg/day if necessary).
- A 6-week double-blind conversion to an open-label follow-up study (study N167), or progressive double-blind down-titration for withdrawal. Only subjects who completed the last evaluation visit (Visit 8) were given the opportunity to enter the long-term follow-up study N167.

An overview of mean daily dose and duration of exposure during the evaluation period in N166 is given below in table II.

Table II.		
	PBO (N = 60)	LEV (N = 60)
No. with Dose Information	58	56
Dose (mg/day) Mean ± S.D. (Range)	2974.9 ± 67.9 (2613-3000)	2935.0 ± 225.9 (2000-3000)
Duration (days) Mean ± S.D. (Range)	81.7 ± 14.8 (29 - 101)	84.3 ± 10.2 (21 - 99)

Concomitant therapy

One standard AED, with the exception of tiagabine or vigabatrin, was to be taken concomitantly. Felbamate use of less than 18 months duration was excluded. The concomitant AED was to remain stable during the study period unless a change was necessary for safety. Benzodiazepine use was excluded if taken at a higher frequency than an average of once a week, unless counted as the concomitant AED.

The use of two concomitant AEDs was originally an exclusion criterion. However, to facilitate patient recruitment, it was decided during an Investigator Meeting to allow the inclusion of patients taking two AEDs, provided one of them was given at sub-therapeutic doses. The decision was to be made for each patient individually through a waiver procedure. The therapeutic doses were defined according to published AED dosing guidelines.

Randomisation and sample size

After an 8-week, single-blind, placebo baseline, patients were randomised and up-titrated to LEV 3000 mg/day or matching placebo. Randomisation occurred centrally by IVRS with randomisation stratified by region: Europe/Australia/New Zealand and North America.
Target enrolment was 116 patients (58 per treatment group); this sample size was to be adequate to have a power of 90% to detect a difference of 30% in responder rate of LEV over placebo, assuming a responder rate of 20% for placebo patients and of 50% for LEV patients, and using a 5% two-sided significance level.

Endpoints

Primary efficacy variable
The primary endpoint is the responder rate in myoclonic (type IIB) seizure days. A responder is defined as a subject with ≥ 50% reduction in myoclonic seizure days [= day(s) with myoclonic seizure(s)] per week from the baseline period as compared to the treatment period (up-titration + evaluation periods).

Secondary efficacy variables
The secondary endpoints included:

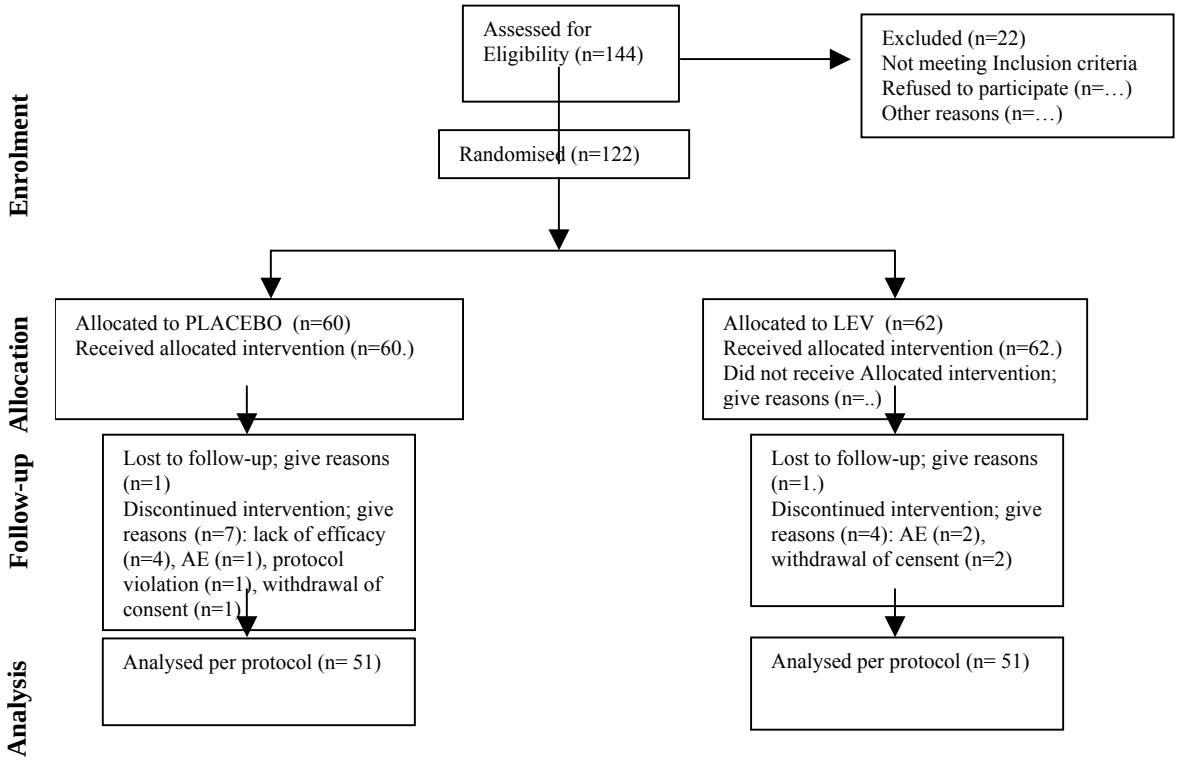
- The responder rate in myoclonic (IIB) seizure frequency per week over the treatment period.
- The responder rate in seizure days per week for all (I + II + III) seizures over the treatment period.
- The absolute and percent reduction from baseline in myoclonic seizure days per week over the treatment period.
- The absolute and percent reduction from baseline in all seizure days per week over the treatment period.
- The categorized response in myoclonic and all seizure days per week over the treatment period.
- Seizure-freedom in myoclonic and all seizure types over the evaluation period.
- The percent reduction from baseline to treatment in primary generalized tonic-clonic (PGTC) seizure frequency per week.

Statistical methods

The treatment groups were compared with respect to the primary efficacy endpoint using logistic regression analysis. The model included treatment group as factors, and the baseline myoclonic seizure days per week as covariate. The analysis was based on the ITT population (i.e. all randomized subjects who took at least one dose of randomized study medication). An estimate and 95% confidence interval for the treatment odds ratio was presented. For the primary efficacy endpoint, treatment-by-covariate interaction and, geographical unit and treatment-by-geographical unit interaction was investigated.
Statistical methods used for other efficacy variables were as follows: logistic regression (responder rates variables) and Cochran-Mantel-Haenszel test (response to treatment variables).
An analysis by other seizure types was also performed. Patients have been categorised by seizure type present at baseline and/or during the treatment period in N166. The denominators in these analyses are restricted to those patients with the seizure type during this period(s).

RESULTS

Participant flow



Recru

The first subject was enrolled on 03 September 2001 and the last subject completed the study on 13 December 2004.

Baseline data

The history and aetiology of epilepsy for the ITT population is displayed in Table III below.

Table III	N166 ITT Population	
	PBO (N = 60)	LEV (N = 61)
Epileptic Syndrome Classification n (%)		
JME	59 (98.3%)	54 (88.5%)
JAE	1 (1.7%)	7 (11.5%)
Epilepsy History		
Mean Age (yrs) at onset ± S.D. (Range)	12.7 ± 5.4 (<1-30)	13.1 ± 4.3 (<1-21)
Mean epilepsy duration (yrs) ± S.D. (Range)	14.1 ± 11.3 (<1-51)	11.8 ± 8.5 (<1-51)
Seizure Type and Subtype n (%)		
Generalized seizures (II)	60 (100%)	61 (100%)
Absence seizures (IIA1)	21 (35.0%)	28 (45.9%)
Atypical absence seizures (IIA2)	0	1 (1.6%)
Myoclonic seizures (IIB)	60 (100%)	61 (100%)
Tonic-clonic seizures (IIE)	40 (66.7%)	41 (67.2%)
Atonic seizures (IIF)	0	1 (1.6%)
Clusters (IV)	6 (10.0%)	2 (3.3%)
Myoclonic seizures (IIB)	5 (8.3%)	2 (3.3%)
Unknown	1 (1.7%)	0

All patients in the study experienced myoclonic seizures, as also specified in the inclusion criteria. The classification of epileptic seizures is presented in table IV.

Table IV	N166 PBO N = 60	N166 LEV N = 61
Seizure Days per Week		
Myoclonic		
n	60	61
Mean (SD)	2.6 (2.0)	2.3 (1.6)
Median	1.6	1.8
Q1 - Q3	1.1 - 3.8	1.2 - 2.9
Min - Max	0 - 7	0 - 7
All Seizure		
n	60	61
Mean (SD)	2.8 (2.0)	2.8 (1.8)
Median	2.0	2.5
Q1 - Q3	1.2 - 3.8	1.3 - 3.8
Min - Max	0 - 7	0 - 7
Seizure Frequency per Week		
Myoclonic		
n	60	61
Mean (SD)	8.6 (15.3)	6.3 (9.3)
Median	3.7	2.7
Q1 - Q3	1.5 - 7.7	1.5 - 5.5
Min - Max	0 - 78	0 - 41

Primary Generalized Tonic Clonic		
n	20	22
Mean (SD)	0.6 (1.0)	0.4 (0.7)
Median	0.2	0.2
Q1 - Q3	0.1 - 0.5	0.0 - 0.4
Min - Max	0 - 4	0 - 3

Outcomes and estimation

Primary efficacy endpoint

Thirty-five of 60 patients randomized to LEV (58.3%) had a 50% or greater decrease in the number of myoclonic seizure days per week over the treatment period (up-titration and evaluation periods), compared to 14 of 60 patients randomized to placebo (23.3%). For the primary efficacy analysis, the treatment odds ratio (LEV versus placebo) that was obtained with a logistic regression adjusting for baseline myoclonic seizure days per week equalled 4.77 (95% confidence interval [CI] 2.12 to 10.77) and was statistically different from "1" (p=0.0002) (Table V). A sensitivity analysis of the primary efficacy analysis limiting the period to the evaluation period only, when patients are on a stable dose of study drug, has been performed and is also reflected in Table V.

Table V**.** 50 % responder rate in myoclonic seizure days per week over the treatment period and the evaluation period. Study N166, ITT population

	Treatment period		**Evaluation period**	
	PBO N=60 n (%)	**LEV N=60** n (%)	**PBO N=60** n (%)	**LEV N=60** n (%)
Non-responders Responders	46 (76.7) 14 (23.3)	25 (41.7) 35 (58.3)	39 (65.0) 21 (35.0)	20 (33.3) 40 (66.6)
Odds ratio (LEV vs PBO)	4.77		4.294	
(95% CI)	(2.12, 10.77)		(1.93, 9.54)	
p-value	0.0002		0.0003	

The results were also reported by response category for Myoclonic Seizure Days per Week over the Treatment Period in N166 ITT population in table VI below.

Table VI	N166 ITT Population Myoclonic Seizure Days per Week	
	PBO N = 60 n (%)	LEV N = 60 n (%)
< -25%	10 (16.7)	4 (6.7)
-25% to < 25%	24 (40.0)	10 (16.7)
25% to < 75%	18 (30.0)	24 (40.0)
75% to 100%	8 (13.3)	22 (36.7)
p-value	0.0001	

Secondary efficacy endpoints

The same conclusions could be drawn from similar analyses performed on seizure days per week and on seizure frequency per week for myoclonic seizures and for all seizures aggregated (see table VII).

Table VII.	**Myoclonic Seizure days per week**		**All Seizure days per week**	
	PBO N=60	**LEV N=60**	**PBO N=60**	**LEV N=60**
Baseline				
n	60	60	60	60
Mean (SD)	2.57 (1.96)	2.37 (1.59)	2.81 (2.00)	2.88 (1.83)
Median	1.64	1.76	2.04	2.53
Q1 - Q3	1.05-3.82	1.22-2.99	1.22-3.82	1.35-3.79
Min -Max	0.1-7.0	0.3-6.9	0.1-7.0	0.8-6.9
Treatment				
n	60	60	60	60
Mean (SD)	2.34 (2.16)	1.22 (1.40)	2.55 (2.17)	1.59 (1.86)
Median	1.65	0.87	1.73	0.94
Q1 - Q3	0.61-3.83	0.12-1.86	0.76-3.97	0.12-2.32
Min -Max	0.0-7.0	0.0-7.0	0.0-7.0	0.0-7.0
Absolute reduction from baseline				
n	60	60	60	60
Mean (SD)	0.23 (1.04)	1.15 (1.51)	0.27 (1.05)	1.29 (1.45)
Median	0.28	0.93	0.26	0.99
Q1 - Q3	-0.26-0.75	0.53-1.49	-0.26-0.75	0.60-1.58
Min -Max	-4.6-3.09	-2.84-6.82	-4.67-3.09	-1.96-6.82

Examination of subgroups

- Primary Generalized Tonic-Clonic (PGTC)
  The PGTC subgroup consists of all subjects who had at least 1 tonic-clonic seizure during baseline or treatment. Twenty subjects in the placebo group and 22 subjects in the LEV group presented tonic-clonic seizures during baseline or treatment. The median percent reduction on tonic-clonic seizure frequency was 48% in the placebo group and 84% in the LEV group (not statistically significant (p=0.1228)).

Table VIII. Categorized Response for Tonic-Clonic Seizure Days per Week over the Treatment Period - ISE Analysis Population (Patients Exposed to LEV)

Response Category	Overall LEV (N=46) n (%)
< -25%	18 (39.1)
-25% to < 25%	2 (4.3)
25% to < 50%	2 (4.3)
50% to < 75%	5 (10.9)
75% to <100%	13 (28.3)
100%	6 (13.0)

- Absence seizures

Seventeen patients (28.3 %) in the placebo group and 19 (31.1 %) in the LEV group had generalised absence seizures at baseline. No differences between treatment groups were observed during the treatment period. There was no worsening from baseline.

Exploratory efficacy variables

The investigator's and patient's global evaluation scores showed improvement (slight, moderate, or marked) since starting study medication for 72.9% (43/59) and 77.8% (42/54) of the patients in the LEV group, respectively, compared to 55.2% (32/58) and 63.6% (35/55) of the patients in the placebo group, respectively. Investigators noted a slight worsening for 1 out of 59 patients in the LEV group and a slight or moderate worsening for 5 out of 58 patients in the placebo group (no marked worsening in any group). There were 4 out of 54 patients in the LEV group and 5 out of 55 patients in the placebo group who reported a worsening (slight, moderate or marked) since starting study medication.

Open-label Extension study N167

The applicant has submitted an interim report which presents analyses performed on data from subjects enrolling into study N167 only from study N166, as collected until 28 February 2005 (clinical cut off date). Male/female children, adolescents and adults experiencing myoclonic seizures and having completed the final visit of the double-blind study N166 were included.

Of the 58 subjects included in the ITT population, 51.7% had a 6 month period of myoclonic seizure freedom. During the entire Evaluation period, 31% of the subjects reported complete myoclonic seizure freedom until the time they dropped from the study or the interim clinical cut off date. Nineteen percent of the subjects reported complete freedom from all seizures during the entire evaluation period, until the time they dropped from the study or the interim clinical cut off date.

The drop in myoclonic and all seizure days per week and myoclonic and all seizure frequency per week as compared to the N166 baseline was maintained over time (Analysis intervals). Only 6 subjects (10.3%) discontinued due to lack of efficacy.

DISCUSSION ON CLINICAL EFFICACY

The clinical efficacy programme was based on one placebo-controlled study (N166) and its open-label extension study (N167).

The benefit of Keppra in the claimed indication was supported by the primary endpoint with a 50% responder rate in myoclonic seizure days per week of 35/60 (58.3%) for the subjects in the LEV group compared to 14/60 (23.3%) for the subjects in the placebo group. The odds ratio (LEV v placebo) were 4.77 times higher on LEV than on placebo. This difference was statistically significant (p=0.0002). These results were confirmed by the sensitivity analysis on the PP population. The CHMP Note for Guidance on clinical investigation of medicinal products in the treatment of epilepsy recommends that the analysis of efficacy should be based on the period when patients are established on a fixed dose of the study drug. In study N166, the comparison was between the baseline and the treatment period (including both up-titration and evaluation periods). This primary endpoint was defined in the original protocol, the finalisation of which preceded the current CHMP guideline. However, the MAH provided a supplementary analysis for the primary efficacy parameter based on the evaluation period only, which showed similar responder rates as in the primary analysis. The efficacy of Keppra in the treatment of myoclonic seizures was also supported by secondary endpoints, including those analyses performed on seizure days per week and on seizure frequency per week for myoclonic seizures and for all seizures aggregated. The primary endpoint was determined as the purpose of the study was to demonstrate the effect of LEV on myoclonic seizures in patients with idiopathic generalised epilepsy. As virtually all of the subjects (93.4%) included in study N166 were diagnosed with JME, the present extension of indication is limited to JME.

A therapeutic benefit of LEV in the reduction of myoclonic seizure frequency was already observed during the first 2 weeks of treatment at a daily dose of 1000 mg. Thirteen (21.7%) subjects in the LEV group were seizure free during the evaluation period compared to 2 (3.4%) subjects in the placebo group. Eight (13.3%) of these subjects in the study drug group were seizure free for the entire treatment period (up-titration + evaluation) compared to 1 (1.7%) subject in the placebo group. Most subjects on LEV with a high number of myoclonic seizure days during baseline substantially improved during treatment. Although study N166 was not designed as a dose-response study, these elements suggest that LEV was efficient in reducing myoclonic seizures already at the doses of 1000 and 2000 mg/day.

During the discussion, the MAH also provided supplementary analysis to show that the subject's gender and the concomitant use of valproate was not prognostic for response to treatment with respect to the primary efficacy endpoint. More than 57% of subjects were concomitantly administered valproate. The MAH clarified that the proportion of patients with concomitant valproate was similar in both treatment groups (LEV and placebo) and so was the dose of valproate received. The proportion of subjects responding to LEV as compared to placebo was approximately 2:1 (52.8% v 27.3%) for the subset of subjects concomitantly receiving valproate and approximately 3:1 for those who were not, both similar to the overall statistically significant results (58.3% of subjects randomized to LEV responded as compared to 23.3% of subjects randomized to placebo).

With regards to the subgroups (PGTC and absence seizures), the median percent reduction in tonic-clonic seizure frequency was 48% in the placebo group and 84% in the LEV group, suggesting an improvement in PGTC seizures. However, as study N166 was designed to assess the efficacy of LEV versus placebo on myoclonic seizures and was not powered to assess the effect on PGTC and absence seizures, no statistically significant differences between treatment groups were observed regarding a reduction in PGTC and absence seizure frequency.

Clinical safety

PATIENT EXPOSURE

Safety data are derived from two sources, a pooled safety database (consisting of study N166 and its open-label extension study N167), and three studies in patients with idiopathic generalised epilepsy, referred to as "other studies". In the controlled study N166, 120 patients provide safety data, 60 patients randomised to LEV and 60 to placebo. Ninety-two of these patients continued to receive LEV in N167, the open label extension study. In total 108 patients were exposed to LEV in one or both of these studies and have safety data available.

ADVERSE EVENTS

In the placebo-controlled study N166, 40 patients randomized to placebo (66.7%) and 45 patients randomized to LEV (75.0%) experienced one or more treatment-emergent adverse events (AEs), considered related to treatment in about one-half of the cases (18 patients randomized to placebo (30.0%) and 20 patients randomized to LEV (33.3%). The most frequently reported AEs during the double-blind study was headache, which occurred in 23.3% of patients in both the LEV and placebo groups. Headache was judged possibly related to treatment in 13.3% of the patients randomized to LEV and 6.7% of the patients randomized to placebo.

Among all patients exposed to LEV 81 patients (75 %) had one or more treatment-emergent AE. The most common events overall were headache (25,9 %), somnolence (13.9 %), dizziness (10.2%), nasopharyngitis (9.3%), fatigue (6.5%), and pharyngitis (6.5%).

Nervous system events, including behavioural and other psychiatric events, have been associated with LEV in children and in adults. In Study N166, adverse events coded to Non-Psychotic Behavioral Disorders, Non-Psychotic Mood Disorders, and Sleep Disorders and Disturbances occurred with at least twice the incidence in LEV-treated patients compared with those in the placebo. Based on all 108 patients exposed to LEV, a total of 10 patients exposed to LEV (9.3%) had adverse events that were categorized as consistent with anxiety disorders; none of these 10 had similar events while on placebo during the N166 Baseline Period. Study drug was discontinued in 2 patients on LEV, as well as 1 patient on placebo, and the dose modified (not increased above 2000 mg/day or decreased) in the 2 patients on LEV. In one of those patients who discontinued, the anxiety occurred in conjunction with depression. There were no reports of suicide in any patient in the pooled database or completed supportive study. There is one SAE report of depression and suicide attempt in the on-going study N01057, but the study remains blinded. The number and percentages of patients with at least one treatment-emergent psychiatric
adverse event in study N166 and overall LEV-exposed subjects is shown in Table IX.

Table IX. Number (%) of patients with at least one treatment-emergent psychiatric AE by UCB High Level Grouping Term and MedDRA Preferred Term - ISS Analysis Population

UCB High Level GroupingTerm/MedDRA Preferred Term	**N166**		**Overall LEV (N=108) n (%)**
	Placebo (N=60) n (%)	**LEV (N=60) n (%)**	
Anxiety Disorders	**6 (10.0%)**	**4 (6.7%)**	**10 (9.3%)**
Agitation	0	0	1 (0.9%)
Anxiety	2 (3.3%)	2 (3.3%)	5 (4.6%)
Nervousness	4 (6.7%)	2 (3.3%)	5 (4.6%)
Stress Symptoms	0	1 (1.7%)	3 (2.8%)
Cognition/Mental Acuity Disorders	**3 (5.0%)**	**2 (3.3%)**	**3 (2.8%)**
Amnesia	1 (1.7%)	1 (1.7%)	1 (0.9%)
Bradyphrenia	1 (1.7%)	0	2 (1.9%)
Confusional state	0	0	1 (0.9%)
Disturbance in attention	1 (1.7%)	1 (1.7%)	1 (0.9%)
Non-psychotic Behavioral Disorders	**1 (1.7%)**	**3 (5.0%)**	**5 (4.6%)**
Aggression	0	2 (3.3%)	2 (1.9%)
Irritability	0	1 (1.7%)	3 (2.8%)
Staring	1 (1.7%)	0	0
Non-psychotic Mood Disorders	**2 (3.3%)**	**4 (6.7%)**	**7 (6.8%)**
Affect lability	0	0	1 (0.9%)
Apathy	0	0	1 (0.9%)
Depressed mood	0	1 (1.7%)	2 (1.9%)
Depression	1 (1.7%)	3 (5.0%)	4 (3.9%)
Mood swings	1 (1.7%)	0	0
Sleep Disorders and Disturbances	**1 (1.7%)**	**4 (6.7%)**	**8 (7.4%)**
Insomnia	1 (1.7%)	2 (3.3%)	6 (5.6%)
Sleep disorder	0	2 (3.3%)	2 (1.9%)

SERIOUS ADVERSE EVENT/DEATHS/OTHER SIGNIFICANT EVENTS

There were no deaths in the study program for myoclonic seizures. Among all patients exposed to LEV, 9 patients (8.3%) had serious adverse events (SAEs) while on LEV (including 3 patients with such events while in the double-blind study N166). The most frequent SAEs were three reports of grand mal convulsion (2.8%), one of which was judged possibly related. The only other SAE that was judged possibly related to treatment was the arrhythmia/atrial fibrillation that occurred in 1 patient. No serious adverse events (SAEs) occurred in the placebo group in N166.

LABORATORY FINDINGS

Small decreases in white blood cell (WBC) and neutrophil counts may occur with LEV treatment. With expanded commercial use, there have been reports of leukopenia, neutropenia, and pancytopenia (with or without bone marrow depression) and these are labeled adverse reactions. There have also been reports of thrombocytopenia. In this pooled population, an effect on haematology parameters, WBC indices, red blood cell indices, and platelet count, was not detectable based on descriptive statistics. There were no clinically significant treatment-related findings on clinical chemistry, including parameters reflective of liver and kidney function. One patient had a possibly clinically significant treatment-emergent blood urea value, with a worst on-treatment value slightly above the normal limit at the final measurement. There were no reports of adverse events related to decreased renal function test results.

DISCONTINUATION DUE TO ADVERSE EVENTS

Whether based on the placebo-controlled study or the overall pooled database, the most common events that led to LEV dose adjustment or discontinuation were events relating to anxiety/nervousness, somnolence/sedation/hypersomnia, and depression/depressed mood. Additional events which resulted in dose change in single patients were dizziness, paresthesia, headache, and anxiety. Events which resulted in discontinuation were agitation, arrhythmia, and exanthema.

WORSENING OF SEIZURES

With regard to all seizures combined, or myoclonic seizures specifically, there was no evidence for a worsening (whether calculated as days per week with myoclonic seizures or seizure frequency per week). Roughly twice as many patients randomized to placebo (10 patients or 16.7%) had worsening (exacerbation by 25 % or more) as compared to those randomized to LEV (2 patients with respect to all seizures [3.4%] and 4 patients with respect to myoclonic seizures [6.7%]). However, with respect to tonic-clonic and absence seizures, present at baseline in about 65% and 40% of the patients, respectively, there was a number of patients with increase in seizures. Using ≥ 25% increase from baseline in seizure frequency per week as indicator of worsening, there were 15 patients (36.6%) exposed to LEV who had a worsening of tonic-clonic seizures. In two of these patients, this represented a new seizure type (i.e., not reported in prior history or during the baseline periods). In 1 patient with only one tonic-clonic seizure during the 16-week historical and prospective baseline, the increase in tonic-clonic seizures [14 during the last analysis interval before termination] resulted in discontinuation due to lack of effect. In a total of 4 patients, tonic-clonic seizures were serious adverse events (2 of whom also met the criterion for seizure increase), all of whom had been on LEV for more than 150 days at the time.
With respect to absence seizure frequency per week, there were 6 patients with worsening of absence seizures, 2 of whom had no prior history of absence seizures and 1 who had one such seizure only in the historical baseline. None of these patients discontinued.

DISCUSSION ON CLINICAL SAFETY

Overall, the study N166 results confirm the safety profile of LEV observed in previous well-controlled clinical trials in partial-onset seizures, with few side effects. 33.3% of the patients in the LEV group and 30.0% of the patients in the placebo group experienced undesirable effects that were judged to be related to treatment. The most commonly reported undesirable effects were headache and somnolence.
At the CHMP request, the MAH reviewed the data to determine whether infrequently there could be cases wherein PGTC and absence seizures worsened. A threshold of a 25% or greater increase was used as a means of identifying subjects with possible deterioration. In the double-blind study (N166), there was no difference in the proportions of subjects with increased PGTC seizures (10.0% of placebo subjects and 11.7% of LEV subjects) and no LEV subjects with increase absence seizures (as compared to 11.7% of placebo subjects). In the pooled database (N166 plus N167) of all subjects exposed to LEV (108 subjects), considering only the subjects with documented seizure types, there were 15 such subjects (13.9%) with increased PGTC seizures and 4 subjects (6.7%) with increased

absence seizures. In total, there were only 5 subjects who could be considered noteworthy. None are clearly attributable to LEV given the prior history of the subjects and the time course of the PGTC seizures. Furthermore, this incidence is consistent with what would be expected for this population without the addition of investigational therapy.

5. Pharmacovigilance

Risk Management Plan

The CHMP did not require the MAA to submit a risk management plan because the safety profile of Keppra was considered unlikely to be different in partial seizures or in myoclonic seizures.

6. Overall conclusions and benefit/risk assessment

The data provided support the efficacy of LEV in the reduction of myoclonic seizure frequency. LEV has demonstrated superior efficacy in the 50% responder rate in myoclonic seizure days per week, compared to placebo. No new or unexpected adverse events were reported. The safety profile observed in trial N166 is comparable with those seen in the original application.

In light of this favourable benefit/risk profile and the clarifications provided by the MAH, LEV may be recommended for the treatment of myoclonic seizures in patients with JME. Therefore, the following wording of SPC section 4.1 was agreed by the CHMP, in addition to the currently approved indication in partial onset seizures:

"Keppra is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy."