London, 07 August 2006
Product name: **Keppra**
Procedure No. **EMEA/H/C/277/II/63**

SCIENTIFIC DISCUSSION

1. Introduction

Epilepsy is one of the most common and challenging neurological disorders. It has been estimated that there are over 50 million people affected worldwide. However, there are few antiepileptic drugs (AEDs) licensed for initial use as monotherapy in subjects with newly or recently diagnosed epilepsy. The first-line drugs for the treatment of partial and generalized tonic-clonic seizures are carbamazepine (CBZ), phenytoin (PHT) and valproate (VPA). In the 2001 International League Against Epilepsy guidelines, the first choice of treatment for partial seizures is CBZ. Established AEDs may not always be an ideal first choice regarding, in particular, their propensity to cause neurotoxicity, idiosyncratic reactions and pharmacokinetic interactions.

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. It is also authorized as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. Based on the results of a well-conducted comparative monotherapy study in patients with newly or recently diagnosed epilepsy and suffering from partial or generalized tonic-clonic, the MAH applied to extend the current indication as follows:

"Keppra is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy."

In addition to section 4.1 of the SPC, the MAH proposed to update sections 4.2 and 4.8 to reflect the new data generated by the pivotal study and to introduce an improvement to the wording of section 4.5. 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. In 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 a pivotal comparative monotherapy study (N01061).

Extended treatment was possible in 3 follow-up studies, all of which were ongoing at the time of the submission of this application:

- Study N01093, a double-blind long-term follow-up study to N01061in which subjects who benefited from their randomized treatment are able to continue to receive the same study drug, to evaluate the long-term safety of LEV and CBZ in monotherapy.

- Two open-label follow-up studies, N01091 (a Named Patient program) and N01127, intended to allow subjects from N01061 or N01093 to continue to receive LEV (and, although no subject did so, before N01061 unblinding, subjects previously exposed to CBZ who converted to LEV were also eligible).

One additional study is ongoing, N01175, a phase IIIb therapeutic confirmatory, open-label, multicenter, randomized, community-based trial investigating the efficacy and safety of LEV compared to VPA and CBZ as monotherapy in subjects with newly diagnosed epilepsy.

Main study N01061: Phase III, multicenter, double-blind, randomized, parallel-group, positive-controlled, non-inferiority, monotherapy study

METHODS

Objectives

- Primary objective: to prove that monotherapy treatment with LEV 1000 to 3000 mg/day is non-inferior to monotherapy with CBZ 400 to 1200 mg/day in achieving 6-month seizure freedom as primary end-point, in adults (≥16 years) with newly or recently diagnosed epilepsy, suffering from partial or generalized tonic-clonic seizures.
- Secondary objective: To compare the safety and tolerability of both drugs in the same population.
- Exploratory objective: To compare the direct and indirect cost parameters between both drugs.

Study Participants

Inclusion criteria
Among the inclusion criteria were:

- Subjects with newly or recently diagnosed epilepsy having experienced unprovoked partial seizures (IA, IB, IC with clear focal origin), or generalized tonic-clonic seizures (without clear focal origin), that were classifiable according to the International Classification of Epileptic Seizures. The discrimination between IC and IIE was not requested for inclusion.
- Subjects with at least 2 unprovoked seizures separated by a minimum of 48 hours in the year preceding randomization, of which, at least 1 unprovoked seizure occurred in the 3 months preceding randomization.
- Male/female subjects (≥ 16 years). Inclusion was limited to subjects ≥ 18 years at one site in Poland.
- Minimum body weight of 40 kg.

Exclusion criteria:
The exclusion criteria included known allergic reaction, intolerance to CBZ derivatives and/or excipients, known skin rash or allergic reaction with any other drug, known alcohol or drug addiction or abuse within the last two years, clinical or EEG finding suggestive of idiopathic generalized epilepsy (IGE) at randomization, history or presence of known pseudo-seizures, and previous AED treatment except for acute and subacute seizure treatment with a maximum of 2 week duration.

Treatments

The study drug was LEV 250 mg tablets at daily dose of 1000 to 3000 mg divided in two equal oral intakes.

The comparator was CBZ controlled release (CBZ CR) tablets at daily dose of 400 to 1200 mg divided in two equal oral intakes.

All LEV, CBZ and placebo capsules were made identical in shape, size, weight and colour by the over-encapsulation process to ensure the blinding of the study.

The study consisted of several periods, with a maximal duration of 121 weeks for an individual subject (see Figure 1):

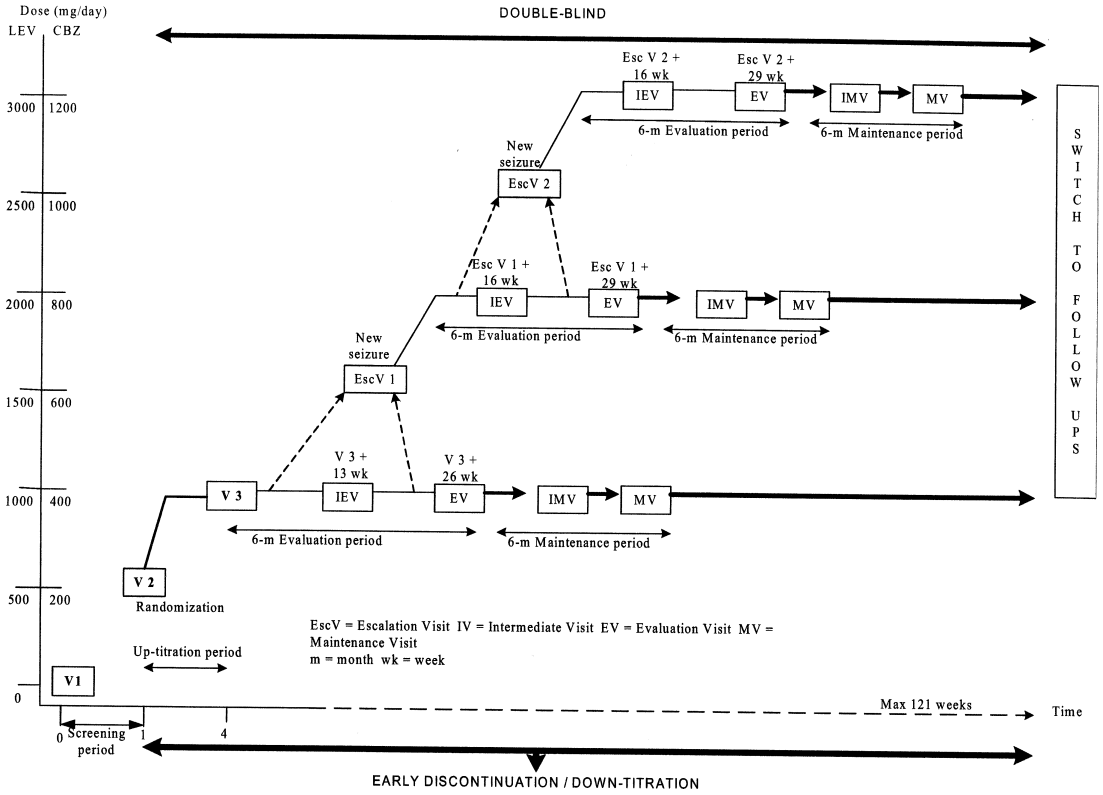
- Screening period: 1 week.
- Up-titration period: 2 weeks: CBZ CR 200mg/day or LEV 500mg/day (250mg bid).
- Stabilization period: 1 week: CBZ CR 400mg/day or LEV 1000mg/day (Dose level 1).
- Evaluation period: 26 weeks.
- Maintenance period: 26 weeks.
- Conversion (2 to 6 weeks) to open label LEV or down-titration (3 to 7 weeks) or switch to a double-blind LEV/CBZ follow-up study.

If a seizure occurred during the evaluation period, a 2-week dose escalation period to the second target daily dose (CBZ CR 800mg/day or LEV 2000mg/day) was followed by a 1-week stabilization period, a 26-week evaluation period and a 26-week maintenance period. The same was true if a seizure occurred during the evaluation period at the second dose level with an escalation to the third target daily dose (CBZ CR 1200mg/day or LEV 3000mg/day).

At the end of the study the subject had three options:

- To continue in an open-label LEV treatment (named patient program N01091) after a double-blind 2 to 6-week conversion period, or
- To continue with double-blind LEV/CBZ treatment (study N01093) until database lock and unblinding of study N01061, or
- To discontinue the study drug after a 3 to 7-week down-titration period.

Figure 1. Overview of study N01061 design



Randomisation and sample size

A total number of 619 subjects were screened, from which 579 were randomized, 291 in the CBZ group and 288 in the LEV group. The ITT population totalled then 576 subjects, 291 in the CBZ group and 285 in the LEV group. The randomization list was generated by the Central Randomization Centre

and Drug Supply Management Centre. A central randomization process was selected because of the high number of centres to be included and the expected small number of subjects per centre. The seizure type was considered as potentially influencing the 6-month seizure-freedom rate and was thus included as a stratification factor in the randomization, in order to guarantee the appropriate balance between treatment groups.

Endpoints

Primary efficacy variable

The primary efficacy variable was the proportion of the per-protocol (PP) subjects with 6-month seizure freedom at the last evaluated dose.

Subjects dropping out of the evaluation period (by definition without having achieved 6-month seizure freedom) were counted as non-seizure free.
For each subject, a 6-month period was defined as starting at the latest of the three following dates:

- Visit 3 date
- Escalation visit 1 date + 21 days
- Escalation visit 2 date + 21 days

The end date of the 6-month seizure-freedom evaluation period was equal to the start date + 181 days, so that the number of evaluated days was 182.

Secondary efficacy variables

- Proportion of subjects from the intention-to-treat (ITT) population with 6-month seizure freedom at the last evaluated dose.
- Proportion of subjects from a subset of the per-protocol (SPP) population with 6-month seizure freedom at the last evaluated dose. The subset (SPP) excluded subjects who dropped out for reasons not linked to efficacy before achieving 6-month seizure freedom.
- Proportion of subjects from the PP population with 1-year seizure freedom at the last evaluated dose.
- Time to first seizure at the last evaluated dose in the PP population.
- Time to withdrawal at the last evaluated dose in the PP population.

Exploratory variables

- Direct cost parameters for concomitant medications, medical procedures, additional physician visits, emergency room visits and hospitalizations.
- Indirect cost parameters: number of school or working days lost.

Statistical methods

The subject populations for analysis were the following:

- The ITT population was defined as all randomized subjects who took at least one dose of either trial medication.
- The PP population was defined as the subset of the intention-to-treat population, consisting of those subjects who had no major protocol deviations affecting the efficacy variables. This subset was defined during a pre-analysis data review meeting before the trial was unblinded.
- The SPP population was defined as the subset of the primary efficacy analysis PP. It excluded all subjects discontinuing the study before having reached 6 months of seizure-freedom for any reason not linked to efficacy.

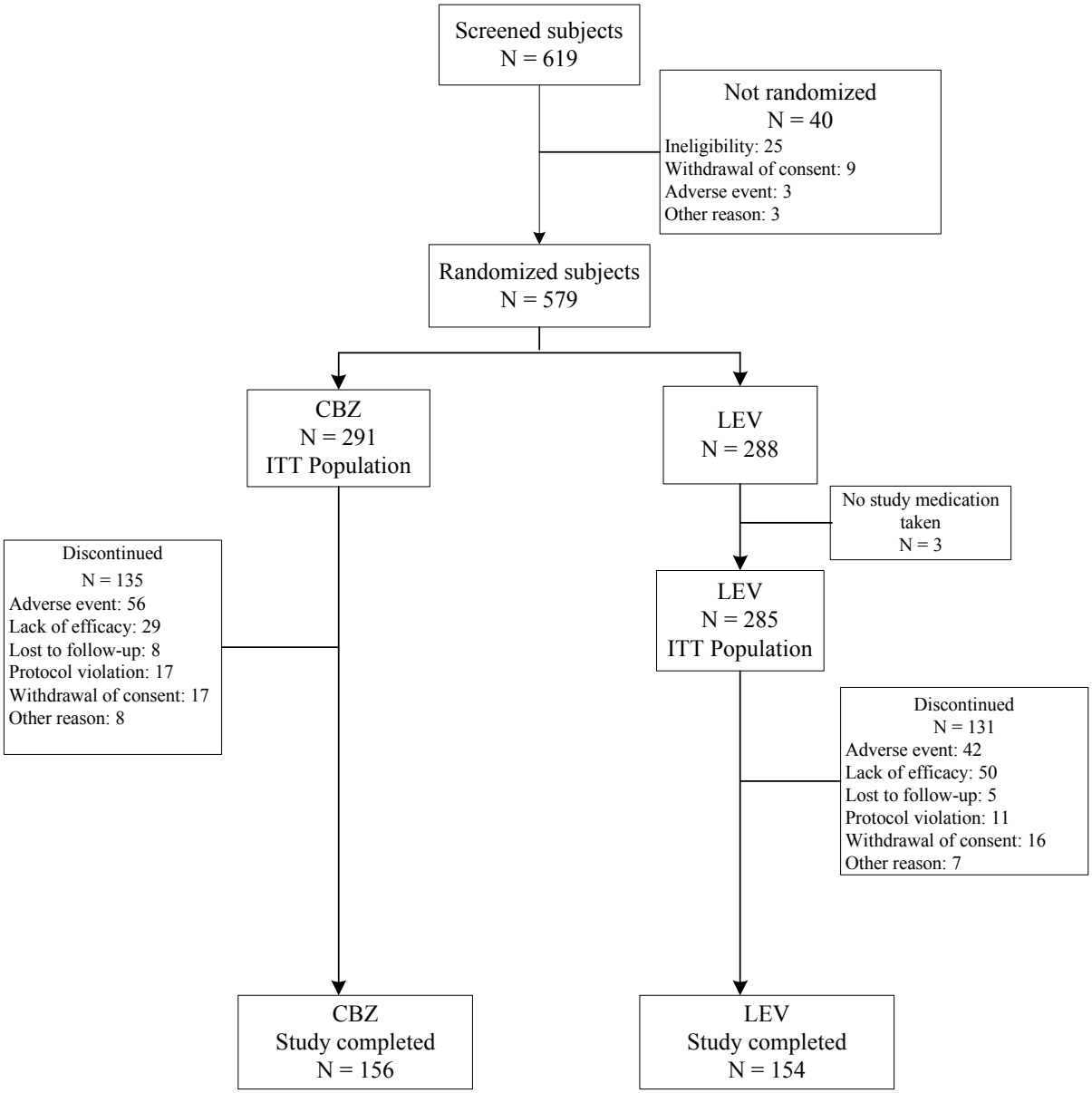
- The primary efficacy variable was defined as the proportion of subjects from the PP population with 6-month seizure freedom at the last evaluated dose. The analysis was performed by the mean of a logistic regression model, including as factors, the treatment (CBZ vs LEV) and the seizure type category as last assessed (IA/IB/IC with clear focal origin vs IC/IIE generalized tonic–clonic seizures without clear focal origin). The parameters estimated from this model were used to derive an adjusted absolute difference (LEV – CBZ) and its 95 % two-sided confidence interval. This confidence interval was thus compared to the non-inferiority limit set to –15 % in order to define if LEV could be considered as non-inferior to CBZ on the primary efficacy variable.

The treatment by seizure type and treatment by country interactions on the primary efficacy variable were assessed. A sensitivity analysis on the primary efficacy variable was also performed including aetiology as an additional factor in the logistic regression model.

- The proportion of subjects from the ITT and SPP populations with 6-month seizure freedom at the last evaluated dose and the proportion of subjects from the PP population with 1-year seizure freedom at the last evaluated dose were all analyzed using the same logistic regression model as for the primary efficacy analysis.
- The time to first seizure and the time to withdrawal were both computed at the last evaluated dose and analyzed by the Kaplan-Meier survival method for the PP population. For both variables, the median time to event and its 95 % two-sided confidence interval were presented for each treatment arm together with the hazard ratio of LEV/CBZ and its 95 % two-sided confidence interval. No non-inferiority comparison was performed on these variables.
- Safety parameters were listed and analyzed descriptively by treatment group.

RESULTS

The participant flow is displayed in Figure 2 below.



Recruitment

The first subject was enrolled on 20 June 2002 and the last subject was enrolled on 12 July 2005.

Baseline data

Demographic characteristics for the LEV and CBZ groups are shown in Table I.

Table I. Demographics of the study population in Study N01061

	Descriptive statistics	**CBZ N=291**	**LEV N=285**	**Overall N=576**
Age (years)	Mean (SD)	39.04 (15.83)	39.79 (16.60)	39.41 (16.21)
	Min - Max	15.9 - 82.5	15.1 - 81.3	15.1 - 82.5
Age class				
< 16	n (%)	1 (0.3)	2 (0.7)	3 (0.5)
16 - < 65	n (%)	269 (92.4)	257 (90.2)	526 (91.3)
≥65	n (%)	21 (7.2)	26 (9.1)	47 (8.2)
Gender				
Male	n (%)	171 (58.8)	146 (51.2)	317 (55.0)
Female	n (%)	120 (41.2)	139 (48.8)	259 (45.0)
Race				
Caucasian	n (%)	268 (92.1)	262 (91.9)	530 (92.0)
African / American	n (%)	10 (3.4)	5 (1.8)	15 (2.6)
Asian / Pacific Islander	n (%)	4 (1.4)	1 (0.4)	5 (0.9)
Other	n (%)	9 (3.1)	17 (6.0)	26 (4.5)
Weight (kg)	Mean (SD)	73.62 (15.20)	73.65 (16.75)	73.63 (15.97)
	Min - Max	39.0 - 133.0	42.0 - 134.0	39.0 - 134.0
Height (cm)	Mean (SD)	171.1 (9.7)	170.0 (9.7)	170.6 (9.7)
	Min - Max	143 - 203	140 - 198	140 - 203
BMI (kg/m²)	Mean (SD)	25.11 (4.61)	25.45 (5.17)	25.27 (4.89)
	Min - Max	14.6 - 47.7	14.8 - 45.3	14.6 - 47.7

As the primary efficacy analysis was performed on the PP population, a summary of the history of epilepsy and of the etiologies of epilepsy at last available assessment is presented for the PP population in Table II and III respectively.

Table II. History of Epilepsy - PP Population

	Descriptive statistics	**CBZ N=235**	**LEV N=237**	**Overall N=472**
History of withdrawal seizures	n (%)	0	0	0
History of convulsive status epilepticus	n (%)	0	0	0
History of non-convulsive status epilepticus	n (%)	0	0	0
N of seizures in the past year	n	232	237	469
	Median	3.0	4.0	3.0
	Q1 - Q3	2.0 - 10.0	2.0 - 10.0	2.0 - 10.0
N of seizures in the past year categories				
< 2	n (%)	2 (0.9)	0	2 (0.4)
≥ 2 - < 5	n (%)	144 (61.3)	138 (58.2)	282 (59.7)
≥ 5 - < 15	n (%)	42 (17.9)	52 (21.9)	94 (19.9)
≥ 15	n (%)	44 (18.7)	47 (19.8)	91 (19.3)
Unknown	n (%)	3 (1.3)	0	3 (0.6)
N of seizures in the last 3 months	n	233	237	470
	Median	2.0	2.0	2.0
	Q1 - Q3	1.0 - 4.0	1.0 - 4.0	1.0 - 4.0
N of seizures in the last 3 months categories				
< 1	n (%)	3 (1.3)	2 (0.8)	5 (1.1)
≥ 1 - < 4	n (%)	163 (69.4)	154 (65.0)	317 (67.2)
≥ 4 - < 10	n (%)	35 (14.9)	45 (19.0)	80 (16.9)
≥ 10	n (%)	32 (13.6)	36 (15.2)	68 (14.4)
Unknown	n (%)	2 (0.9)	0	2 (0.4)
Epilepsy duration (years)	Median	0.73	0.77	0.75
	Q1 - Q3	0.33 - 2.36	0.29 - 2.24	0.31 - 2.30
Age at onset (years)	Median	32.28	34.79	33.48
	Q1 - Q3	20.62 - 49.13	21.57 - 49.22	21.22 - 49.17
Duration since last seizure (days)	Median	10.0	9.0	10.0
	Q1 - Q3	4.0 - 28.0	3.0 - 23.0	3.0 - 24.0

Table III. Etiology of Epilepsy at Last Available Assessment - PP Population

	CBZ N=235 n (%)	**LEV N=237 n (%)**	**Overall N=472 n (%)**
Unknown	149 (63.4)	147 (62.0)	296 (62.7)
Idiopathic (genetic origin, familial history of epilepsy)	1 (0.4)	1 (0.4)	2 (0.4)
Congenital malformation	10 (4.3)	7 (3.0)	17 (3.6)
Asphyxia during birth	6 (2.6)	9 (3.8)	15 (3.2)
Complication due to prematurity	4 (1.7)	1 (0.4)	5 (1.1)
Cranial trauma	36 (15.3)	27 (11.4)	63 (13.3)
Cerebral neoplasm	1(0.4)	2 (0.8)	3 (0.6)
Brain surgery	2 (0.9)	2 (0.8)	4 (0.8)
Primary degenerative lesion	2 (0.9)	0	2 (0.4)
Cerebrovascular accident	16 (6.8)	26 (11.0)	42 (8.9)
Cerebral infection	2 (0.9)	11 (4.6)	13 (2.8)
Other	8 (3.4)	9 (3.8)	17 (3.6)

Outcomes and estimation

Primary efficacy variable:

One hundred seventy three (73.0%) of the PP subjects in the LEV arm were seizure-free for at least 6 months at the last evaluated dose, compared to 171 (72.8%) of the PP subjects in the CBZ arm. The adjusted absolute difference between LEV and CBZ (95% two-sided CI) obtained from a logistic regression model (including a factor for the seizure type category as last assessed) equalled 0.2% (-7.8%; 8.2%). The lower limit of the confidence interval (-7.8%) was thus above the non-inferiority limit set by protocol at -15%. Results are summarized in Table IV.

Table IV. Six month seizure freedom at the last evaluated dose – PP population

Statistics	**CBZ N=235**	**LEV N=237**
n (%)	171 (72.8%)	173 (73.0%)
Adjusted Difference (LEV-CBZ) 95% two-sided CI	0.2% (-7.8%; 8.2%)	

A sensitivity analysis on the primary efficacy variable and including aetiology was also performed. The adjusted absolute difference between LEV and CBZ (95% two-sided CI) obtained from a logistic regression model including the additional aetiology factor as last assessed equalled 0.1% (-7.6%; 7.8%), a comparable outcome to the one obtained without including the aetiology factor. In addition, when evaluating the potential interactions between treatment and seizure type, or between treatment and country, no significant differences were observed.

The discrimination between IC (partial onset seizures with secondary generalisation) and IIE (primary generalised tonic-clonic seizures) was not requested for inclusion. At the request of the CHMP, the MAH provided a supplementary analysis of efficacy in patients with Type IC seizures. Seventy-three subjects (12.7%) of the ITT population were classified at their last available assessment in the "IC/IIE without clear focal origin" category and it was therefore impossible to separate subjects with seizures IC from those with seizures IIE within this subset. Within the 503 (87.3%) ITT subjects classified at their last available assessment in the category "IA/IB/IC with clear focal origin", it was possible to

identify those reporting partial seizures Type IC). The efficacy results for this subset are presented in table V below.

Table V. Six-month seizure freedom at the last evaluated dose in the entire population and in the subset of subjects reporting some IC seizures –ITT and PP populations

Population	**Statistics**	**Entire Population**		**Subset of Subjects Reporting Some IC Seizures**	
		CBZ	LEV	CBZ	LEV
PP	n seizure free / N (%)	171 / 235 (72.8%)	173 / 237 (73.0%)	113 / 145 (77.9%)	110 / 139 (79.1%)
	Adjusted Difference (LEV-CBZ) 95% 2-sided CI	-	0.2 (-7.8; 8.2)	-	1.2 (-8.3; 0.8)
ITT	n seizure free / N (%)	194 / 291 (66.7%)	190 / 285 (66.7%)	126 / 177 (71.2%)	118 / 166 (71.1%)
	Adjusted Difference (LEV-CBZ) 95% 2-sided CI	-	0.1 (-7.4; 7.5)	-	-0.1 (-9.7;9.5)

Secondary efficacy endpoints

- Proportion of subjects from the intention-to-treat (ITT) population with 6-month seizure freedom at the last evaluated dose (see Table VI).

TableVI. Six month seizure freedom at the last evaluated dose – ITT

Statistics	**CBZ N=291**	**LEV N=285**
n (%)	194 (66.7%)	190 (66.7%)
Adjusted Difference (LEV-CBZ) 95% two-sided CI	0.1% (-7.4%; 7.5%)	

When using the SPP population, the adjusted absolute difference between LEV and CBZ (95% two-sided CI) equalled -2.1% (-8.1%; 3.9%).

- Proportion of subjects from the PP population with 1-year seizure freedom at the last evaluated dose (see Table VII).

Table VII. One year seizure freedom at the last evaluated dose – PP population

Statistics	**CBZ**	**LEV**
	N=224	**N=228**
n (%)	131 (58.5%)	129 (56.6%)
Adjusted Difference (LEV-CBZ) 95% two-sided CI	-1.8% (-10.8%; 7.2%)	

- Time to first seizure and time to withdrawal at the last evaluated dose in the PP population.

The Kaplan-Meier analysis on time to first seizure and time to withdrawal at the last evaluated dose both confirmed the similarity of efficacy observed in the two treatment groups.

Disposition of patients and reasons for discontinuations

More subjects discontinued the study because of adverse events in CBZ group (19.3 %) than in the LEV group (14.7 %), while more subjects discontinued the study because of lack of efficacy in the LEV group (17,5 %) than in the CBZ group (10.0 %), as shown in Table VIII.

Table VIII**.** Reasons for discontinuations in study N01061

	CBZ (N = 291) n (%)	**LEV (N = 285) n (%)**
Completed	156 (53.6%)	154 (54.0%)
Discontinued	135 (46.4%)	131 (46.0%)
Adverse event	56 (19.2%)	42 (14.7%)
Lack of efficacy	29 (10.0%)	50 (17.5%)
Lost to follow-up	8 (2.7%)	5 (1.8%)
Protocol violation	17 (5.8%)	11 (3.9%)
Withdrawal of consent	17 (5.8%)	16 (5.6%)
Other reason	8 (2.7%)	7 (2.5%)

The subject disposition by visit from randomization visit to evaluation visit in the ITT population showed that more patients on CBZ could remain on dose level 1 till the end of the study whilst more patients in the LEV group had to escalate to dose level 2 (28.8 % for LEV vs. 18.9 % for CBZ), and also to dose level 3 (15.8 % for LEV vs. 8.2 % for CBZ). At dose level 3, 31 patients in the LEV group discontinued due to lack of efficacy versus 13 for CBZ.

DISCUSSION ON CLINICAL EFFICACY

The clinical efficacy programme was based on a pivotal non-inferiority active controlled monotherapy study. The design of the study and the primary endpoint are in accordance with the recommendations in the CHMP epilepsy guideline. The choice of CBZ as comparator and the choice of doses for LEV and CBZ are considered adequate.

The proportion of patients who were seizure-free for at least 6 months at their last evaluated dose was similar in the two groups in the primary analysis with an adjusted absolute difference between LEV and CBZ of 0.2% (-7.8%; 8.2%). The choice of -15 % as non-inferiority limit might be considered too high, but the observed lower limit of the confidence interval was well above -15 %. In addition, the MAHs' supplementary analysis of efficacy in patients with partial onset seizures with secondary generalisation has shown that the results are consistent with those observed in the entire population.

The efficacy data show that control of seizures was achieved at dose level 1 in a slightly higher percentage of patients in the CBZ group than in the LEV group. However, these differences were relatively small and the total proportion of patients with 6 months seizure freedom for all 3 dose levels was similar for LEV and CBZ. The CHMP considered that the posology used in the study for Keppra was adequate.

Based on the above elements, it can be concluded that the pivotal study comparing LEV (1000 to 3000 mg/day) to CBZ (400 to 1200 mg/day) has demonstrated the non-inferiority of LEV as compared to CBZ in reaching 6-month seizure freedom in monotherapy in newly or recently diagnosed subjects with epilepsy experiencing partial or generalized tonic-clonic seizures.

Clinical safety

PATIENT EXPOSURE

The safety data are primarily derived from subjects who participated in the pivotal study N01061. A total of 576 subjects were included in the ITT population, 291 in the CBZ group and 285 in the LEV group. A total of 426 subjects were exposed to the study drug for at least 6 months.

The mean duration of exposure to treatment with CBZ and LEV were 302 and 316 days, respectively. The mean actual dose was similar in the ITT and PP populations. The mean daily doses in the ITT population were 434.1 mg in the CBZ group and 1170.4 in the LEV group. These means are only slightly higher than dose level 1 due to the fact that the majority of subjects remained at dose level 1.

ADVERSE EVENTS

Overall, during the randomized treatment period (dose finding, evaluation and maintenance periods), 235 (80.8%) subjects in the CBZ group and 227 (79.6%) subjects in the LEV group experienced at least one treatment emergent adverse event (TEAE). The intensity of most TEAEs was mild or moderate.

The most common TEAEs (≥ 5%) in the CBZ group were headache (25.4%), fatigue (14.1%), dizziness (13.7%), nausea (10.7%), nasopharyngitis (9.6%), somnolence (9.3%), influenza (8.6%), back pain (6.9%), diarrhoea (6.5%), weight increased (6.5%) and rash (5.5%).

The most common TEAEs (≥ 5%) in the LEV group were headache (20.7%), fatigue (16.5%), somnolence (11.2%), dizziness (10.9%), nasopharyngitis (9.1%), influenza (8.6%), diarrhoea (7.4%), nausea (7.0%), depression (6.3%), insomnia (6.0%) and vertigo (5.3%).

The most common TEAEs (≥ 5% in one treatment group) with different incidences (based on a difference of ≥ 3%) between both treatment groups are presented in Table IX.

Table IX. Most common (≥5 % in one treatment group) TEAEs with different (≥ 3 %) incidences between both treatment groups – ITT.

MedDRA Preferred term	**CBZ N=291 n (%)**	**LEV N=285 n (%)**
Back pain	20 (6.9)	8 (2.8)
Depression	6 (2.1)	18 (6.3)
Headache	74 (25.4)	59 (20.7)
Insomnia	7 (2.4)	17 (6.0)
Nausea	31 (10.7)	20 (7.0)
Weight increased	19 (6.5)	9 (3.2)

SERIOUS ADVERSE EVENTS/DEATHS/OTHER SIGNIFICANT EVENTS

A total of 47 subjects, 29 (10.0%) subjects in the CBZ group and 18 (6.3%) subjects in the LEV group experienced at least one serious adverse event (SAE) during the randomized treatment period. The numbers of SAEs by SOC were similar in both treatment groups; 8 SAEs were reported in the UCB SOC Psychiatric disorders, 4 in each treatment group; 1 SAE was reported in the UCB SOC Skin and subcutaneous tissue disorders, in the CBZ group.

There were a total of 5 deaths in the studies. Two deaths were reported during study N01061, both in the CBZ group, 1 as outcome of a lung neoplasm and 1 as outcome of a gun shot wound. One subject of the LEV group died 2.5 months after stopping the study drug. This patient had at study entry multiple diseases which included diabetes mellitus, hypertension, hypercholesterolemia, atherosclerosis, obesity and several strokes / brain haemorrhages. Considering the patient's medical history, it appears likely that the status epilepticus was related to the patients cerebrovascular disease and that the causal relationship with the study drug is unlikely.

Three pregnancies occurred during the study, all in the CBZ group. One pregnancy occurred in a subject taking oral contraceptives. Two ended by an induced abortion and 1 by a normal delivery.

DISCONTINUATION DUE TO ADVERSE EVENTS

A total of 97 subjects, 56 (19.2%) in the CBZ group and 41 (14.4%) in the LEV group experienced at least one adverse event that led to permanent study drug discontinuation (PTAE) during the randomized treatment period. The incidence of study drug discontinuations was higher during the dose-finding period than later in the study. PTAEs occurred during the dose finding period in 26/291 (8.9%) subjects in the CBZ group and in 27/285 (9.5%) of the subjects in the LEV group. A total of 44 subjects, 22 in each treatment group, permanently discontinued the study drug during the first 3 weeks of exposure. More subjects in the CBZ group than in the LEV group discontinued the study drug because of AEs classified in UCB SOCs Gastrointestinal disorder (9 subjects, 3.1% versus 3 subjects, 1.1%) and Skin and subcutaneous tissue disorders (17 subjects, 5.8% versus 4 subjects, 1.4%). More subjects in the LEV group than in the CBZ group discontinued the study drug because of adverse events classified in the UCB SOCs Nervous system disorder (12 subjects, 4.2% versus 8 subjects, 2.7%) and Psychiatric disorders (16 subjects, 5.6% versus 11 subjects, 3.8%).

OTHER SAFETY FINDINGS

Abnormal laboratory values were evenly distributed between both treatment groups. No clinical meaningful changes from baseline were observed in blood pressure and pulse rate. Possibly clinically significant weight decreases were observed in 13 (4.7%) subjects in the CBZ group and in 23 (8.6%) subjects in the LEV group. Possibly clinically significant weight increases were observed in 37 (13.4%) subjects in the CBZ group versus 21 (7.8%) subjects in the LEV group. Similar numbers of occurrences of PCST values for ECG QTc interval were reported in both treatment groups. A complete review of the ECG recordings was performed by an external cardiologist for subjects from the LEV group presenting the most important changes. There was no evidence of any issues raising undue concern for findings of significant repolarization abnormalities.

DISCUSSION ON CLINICAL SAFETY

The incidence of TEAEs was similar in the two groups with 80.8 % of the patients in the CBZ group and 79.6 % in the LEV group experiencing at least one TEAE. The spectrum of side effects differs between LEV and CBZ, with a more frequent occurrence of psychiatric adverse events (including depression, nervousness and insomnia) in the LEV group, and a more frequent occurrence of skin reactions and some gastrointestinal events (including rash, pruritus, nausea, vomiting) in the CBZ group. Further to CHMP request, the MAH's review of suicidal ideation as an adverse event in patients exposed to LEV in the monotherapy studies (N01061, N01093, N01091 and N01127) has not provided evidence that, in this limited population, an increased incidence of depression, sleep disturbances, or irritability is linked to increased suicide ideation in patients treated with levetiracetam.

Overall, the safety profile appears slightly more favourable in the LEV group with a lower percentage of patients discontinuing study drug in this group (14.4 % vs. 19.2 % for CBZ), a lower proportion of subjects experiencing at least one SAE during the randomised treatment period in the LEV group (6.3 % vs. 10.0 %) and a lower proportion of subjects reporting at least one AE classified as severe (10.9 %) subjects in the LEV group compared with the CBZ group (15.1%). It should be noted, however,

that a lower initial dose of LEV and a slower rate of dose titration was used in this study than is currently recommended for LEV as adjunctive therapy.

5. Pharmacovigilance

Risk management plan

The CHMP did not require the MAH to submit a risk management plan because the safety profile of Keppra was considered unlikely to be different in monotherapy.

6. Overall conclusions and benefit/risk assessment

The data provided support the efficacy of LEV used in monotherapy for the treatment of partial seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. LEV was shown to be non-inferior to the active comparator CBZ as the proportion of patients who were seizure-free for at least 6 months at their last evaluated dose was similar in the two groups in the primary analysis.

The study also confirmed the safety profile of LEV observed in previous studies in subjects suffering from various epileptic syndromes. Overall, the incidence of treatment-emergent adverse events was similar in both groups, but the spectrum of side effects differed with a more frequent occurrence of psychiatric adverse events (including depression, nervousness and insomnia) in the LEV group, and a higher frequency of some gastrointestinal events and allergic skin reactions including rash and pruritus in the CBZ group.

In light of this favourable benefit/risk profile and the clarifications provided by the MAH, Keppra may be recommended as monotherapy for the treatment of patients with partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy. The CHMP agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.