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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Keppra

levetiracetam

Procedure no: EMEA/H/C/000277/P46/078

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On April 2nd 2015, the MAH submitted the final clinical study report for study NO1367, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical clinical overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study NO1367 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

The study medication was provided as levetiracetam (LEV) 500mg tablets.

1.3. Clinical aspects

1.3.1. Description of the study

Title:

“A Multi-center, Open-label, Randomized Study to Evaluate the Long Term Effectiveness of Levetiracetam as Monotherapy in Comparison with Oxcarbazepine in Subjects With Newly or Recently Diagnosed Partial Epilepsy”

Methods

Objectives

The primary objective was to evaluate the long-term effectiveness of levetiracetam (LEV) monotherapy on treatment failure rate in subjects with newly diagnosed partial onset seizures with or without secondarily generalized seizures, compared with oxcarbazepine (OXC) monotherapy, over 50 weeks from the first dose of study medication and to demonstrate that monotherapy with LEV (1000 to 3000mg/day) was noninferior to monotherapy with OXC (900 to 2400mg/day).

The secondary objectives were:

- To evaluate the efficacy of LEV monotherapy on time to first seizure in subjects with newly diagnosed partial onset seizures with or without secondarily generalized seizures compared with OXC monotherapy
- To evaluate the efficacy of LEV monotherapy on 24-week seizure freedom rate for 24 consecutive weeks during the Treatment Period at any time and 48-week seizure freedom rate during the Treatment Period
- To evaluate the safety and tolerability of LEV monotherapy in subjects with newly diagnosed partial onset seizures with or without secondarily generalized seizures compared with OXC monotherapy

Study design

Methodology: After the 1-week Screening Period, subjects were randomized to the LEV or OXC treatment group in a 1:1 ratio. During the Treatment Period, if the seizures were not controlled, the dose of LEV was titrated up to 3000mg/day and the dose of OXC was titrated up to 2400mg/day at the investigator's discretion based on the subject's response of seizure control and tolerability.

If an intolerable adverse event (AE) related to study medication occurred, after up-titration to the first dose level (LEV 1000mg/day or OXC 900mg/day), a single step dose down-titration (limited to 1 time) was permitted. This case was evaluated as a treatment failure, but the subjects were not discontinued from the study if the subjects' seizures were well controlled with the down-titrated dose.

If subjects discontinued the study during the Treatment Period, an Early Discontinuation Visit occurred. Subjects who discontinued prematurely, or completed the study and chose not to continue receiving commercial LEV or OXC, were gradually tapered off study medication (Down-titration Period). A faster or slower taper was permitted if medically necessary. The following were the recommendations for down-titration:

- LEV: Decreased by 1000mg/day every 2 weeks from the last dose the subject was on, down to zero
- OXC: Decreased by 600mg/day weekly from the last dose the subject was on, down to zero

Subjects who chose not to continue receiving commercial LEV or OXC after study termination should have returned for a Safety Follow-up (SFU) Visit approximately 2 weeks after their last administration of study medication.

Subjects who chose to continue receiving commercial LEV or OXC after the completion of this study were not required to taper study medication or return for an SFU Visit.

Study population /Sample size

Number of subjects (planned and analyzed): It was planned that 352 subjects would be enrolled in the study and randomized in a 1:1 ratio to LEV or OXC. A total of 353 subjects were randomized in N01367, 175 subjects to the LEV treatment group and 178 subjects to the OXC treatment group.

Diagnosis and main criteria for inclusion: Subjects included in this study were male or female, 16 to 80 years of age, inclusive, with newly or recently diagnosed epilepsy, having experienced at least 2 unprovoked seizures separated by 48 hours in the year preceding randomization out of which at least 1 unprovoked seizure occurred in the 6 months preceding randomization. Subjects were not to have received treatment with antiepileptic drugs (AEDs) in the 6 months preceding the study. Female subjects were to have had a negative pregnancy test at Visit 1, have been without childbearing potential, surgically sterile, or using a medically acceptable method of birth control for the duration of study participation.

Treatment

Oral tablets of LEV (250mg and 500mg), as the test product and oral tablets of OXC (150mg and 300mg), as the reference product were used in this study.

Outcomes/endpoints

Efficacy: The primary efficacy variable was the treatment failure rate, defined as the percentage of subjects who dropped out due to treatment failure at the maximum tolerated dose (MTD), after 50 weeks from the first dose of study medication.

Treatment failure was defined as meeting at least 1 of the following treatment failure criteria:

- Lack of efficacy; the occurrence of a seizure at the MTD
- Need for the addition of another AED
- The occurrence of an intolerable AE related to study medication

The secondary efficacy variables were:

- Time to the first seizure, defined as the time from the first dose of medication to the occurrence of the first seizure during the Treatment Period
- 24-week seizure freedom (rate), defined as the number and percentage of subjects who achieved seizure freedom for 24 consecutive weeks at any time during the Treatment Period
- 48-week seizure freedom (rate), defined as the number and percentage of subjects who achieved seizure freedom during the Treatment Period

The exploratory variables were:

- Change of the QOLIE-31-P score from Baseline through the end of the Treatment Period
- Change of the ESS score from Baseline through the end of the Treatment Period

Safety: The safety variables were:

- Number and percentage of subjects with treatment-emergent adverse events (TEAEs), severe TEAEs, drug-related TEAEs, and serious TEAEs reported during the whole study period
- Time from randomization to drug discontinuation due to AEs
- Discontinuation (rate) due to an AE: the number and percentage of subjects who dropped out due to AEs after the first dose of study medication

Statistical Methods

Statistical methods: In general, summaries were presented by treatment group (LEV, OXC) and for all subjects (ie, across both treatment groups), where applicable. For categorical parameters, the number and percentage of subjects in each category were presented. For continuous parameters, descriptive statistics included number of subjects, mean, standard deviation, median, minimum, and maximum.

As the first dose of study medication was taken after randomization and randomization occurred after the assessments at Visit 2, data obtained at this visit were used as Baseline data. In case of missing data at Visit 2, the last data collected before administration of the first dose of study medication were used.

Presentation of the primary efficacy data was based on the Per Protocol Set (PPS). Presentation of secondary efficacy data was based on the Full Analysis Set (FAS). Presentation of disposition data was based on the Enrolled Set and the Randomized Set. Demographics and other baseline characteristics were presented for the Safety Set (SS). Safety and exposure data were presented for the SS. For the sensitivity analysis, the primary efficacy analysis was repeated for the FAS, the secondary efficacy analyses were repeated for the subjects who completed the study, and the safety analyses were repeated for the subjects who completed the study.

The primary analysis of this study aimed to demonstrate that LEV was noninferior to OXC with respect to the treatment failure rate in the PPS. The noninferiority margin was 15%.

The null hypothesis:

$$H_0: p_{LEV} > p_{OXC} + 0.15$$

was statistically tested against the alternative hypothesis:

$$H_1: p_{LEV} \leq p_{OXC} + 0.15$$

where p_{LEV} denoted the treatment failure rate in the LEV group and p_{OXC} denoted the treatment failure rate in the OXC group.

If LEV was demonstrated to be noninferior to OXC in the PPS, an exploratory analysis was to be performed to determine whether LEV was superior to OXC in the PPS.

The null hypothesis:

$$H_0: p_{LEV} \geq p_{OXC}$$

was statistically tested against the alternative hypothesis:

$$H_1: p_{LEV} < p_{OXC}$$

The primary analysis was repeated for the FAS and the Per Protocol Set 2 (PPS2; ie, subjects in the FAS without any important protocol deviations that may have influenced the validity of the data, including subjects who discontinued the study before Week 50 for any reason other than treatment failure).

Time to treatment failure was analyzed using log-rank methodology.

Results

Subject disposition

Overall, a total of 353 subjects were randomized in N01367 (175 subjects to LEV and 178 subjects to OXC) and 243 subjects (68.8%) completed the study. Of the 110 subjects (31.2%) who discontinued from the study, the most common reasons for discontinuation were consent withdrawn (40 subjects

[11.3%]) and AEs (31 subjects [8.8%]). Subjects in each treatment group discontinued from the study at a similar incidence; however, slightly higher percentages of subjects in the OXC group discontinued due to consent withdrawn and AEs compared with the LEV group (14.0% and 11.2% vs 8.6% and 6.3%, respectively).

Paediatric subjects

A total of 14 subjects were <18 years old at study entry (8 subjects were 17 years old; 6 were 16 years old). Eight of these subjects were female; 6 were male. Eight subjects were randomized to LEV and 6 to OXC.

Table 4–1: Subjects less than 18 years old at study entry in N01367

Subject ID	Age (years)	Sex	Treatment	Subject disposition
002-03058	17	F	LEV	Completed
002-03080	17	F	OXC	Completed
003-03106	16	F	LEV	Completed
003-03107	17	M	LEV	Completed
004-03151	17	M	OXC	Completed
004-03189	17	F	LEV	Completed
007-03307	17	F	LEV	Discontinued due to protocol violation
007-03320	17	F	OXC	Discontinued due to withdrawal of consent

Subject ID	Age (years)	Sex	Treatment	Subject disposition
009-03417	16	M	LEV	Discontinued due to withdrawal of consent
009-03420	16	F	OXC	Discontinued due to lack of efficacy
010-03452	16	F	OXC	Discontinued due to AE
010-03462	16	M	LEV	Discontinued due to withdrawal of consent
013-03637	17	M	OXC	Completed
014-03664	16	M	LEV	Discontinued due to lack of efficacy

AE=adverse event; F=female; LEV=levetiracetam; M=male; OXC=oxcarbazepine
Data sources: N01367 CSR Listing 1.3, N01367 CSR Listing 1.4

In the LEV group, 2 subjects discontinued due to withdrawal of consent, 1 subject discontinued due to a protocol violation, and 1 subject discontinued due to lack of efficacy; the other 4 subjects who received LEV completed the study. In the OXC group, 1 subject discontinued due to withdrawal of consent, 1 subject discontinued due to lack of efficacy, and 1 subject discontinued due to AE; the other 3 subjects in the OXC group completed the study.

Efficacy results

The efficacy results are summarized as follows:

- For the PPS, 15 subjects (12.7%) in the LEV group were considered treatment failures compared with 30 subjects (23.4%) in the OXC group. The absolute difference in the treatment failure rates of LEV vs OXC was -10.7% (95% confidence interval [CI]: -20.2%, -1.2%). The upper limit of the 2-sided 95% CI (-1.2%) did not exceed the selected noninferiority margin of +15% for absolute treatment failure rate difference vs OXC, indicating that treatment with LEV was noninferior to treatment with OXC in this study. Since LEV was demonstrated to be noninferior to OXC in the PPS, an exploratory analysis was performed to determine whether LEV was superior to OXC in the PPS. Because the upper limit of the 2-sided 95% CI (-1.2%) for the absolute difference in treatment failure rates of LEV vs OXC was less than zero, it may be concluded that LEV was superior to OXC for treatment failure rate in the PPS. Similar supportive results were observed for the PPS2.
  - Analysis of the FAS also showed that LEV was noninferior to OXC, but did not show superiority of LEV over OXC as the upper limit was greater than zero (absolute difference in treatment failure rates of LEV vs OXC: -7.1% [95% CI: -14.6%, 0.3%]).
- For the analysis of time to treatment failure in the FAS, the hazard ratio of LEV vs OXC was 0.6 (95% CI: 0.3, 1.0), indicating a 40% reduction in hazard of treatment failure for subjects in the LEV group compared with subjects in the OXC group (log-rank test p-value=0.0658).
  - Results of the time to treatment failure analyses performed for the PPS and the PPS2

were similar to those observed for the FAS.

- For the analysis of time to first seizure during the Treatment Period in the FAS, the hazard ratio of LEV vs OXC was 1.2 (95% CI: 0.9, 1.7; log-rank p-value=0.1643). For subjects in the LEV group, the median time to first seizure was 7.556 months; for subjects in the OXC group, the median time to first seizure was not estimable since <50% of the subjects had a seizure.
- Similar percentages of subjects in the LEV and OXC groups were 24-weeks seizure free during the study (53.8% and 58.5%, respectively). A slightly lower percentage of subjects in the LEV group (34.7%) was 48-weeks seizure free during the study, compared with subjects in the OXC group (40.9%). The absolute difference between the LEV vs OXC treatment groups for 24-weeks seizure freedom was -4.7% (95% CI: -15.2%, 5.8%; 2-proportion Z-test p=0.3775) and for 48-weeks seizure freedom rate was -6.3% (95% CI: -16.5%, 4.0%; 2-proportion Z-test p=0.2317).
- Subjects in the LEV and OXC treatment groups had moderate improvements in the QOLIE-31-P subscales of energy, mood, daily activities, cognition, and overall quality of life; large improvement was observed for both groups in the subscale of seizure worry. The differences in the mean change from Baseline for the LEV group vs the OXC group were small for the subscales of energy, mood, daily activities, cognition, seizure worry, and overall quality of life. Subjects in the LEV group showed slightly greater improvements from Baseline vs subjects in the OXC group for the subscales of energy (Visit 9 and Last Visit), mood (Visit 9), and cognition (Visit 9 and Last Visit). Of note, change from Baseline for the total score could only be calculated for a few subjects due to the fact that only newly diagnosed subjects were included in the study.

Safety results

The safety results are summarized as follows:

- The mean durations of exposure to study medication were similar between the LEV and OXC treatment groups (279.19 and 273.21 days, respectively). The mean daily dose of LEV and OXC overall was 1170.23 and 996.91mg/day, respectively.
- During the study, a total of 344 TEAEs were reported by 117 subjects (67.6%) in the LEV group, and a total of 407 TEAEs were reported by 130 subjects (74.7%) in the OXC group. The incidence of serious TEAEs and severe TEAEs was similar between the LEV and OXC treatment groups. Discontinuations due to TEAEs, TEAEs requiring dose

change, and adverse drug reactions (ADRs) were reported with lower incidence in the LEV group compared with the OXC group.

- Treatment-emergent AEs were most commonly reported in the system organ class (SOC) of Nervous system disorders by subjects in the LEV and OXC treatment groups. By preferred term (PT), the most common TEAEs in the LEV and OXC treatment groups were dizziness, headache, and somnolence. The incidence of TEAEs was similar between treatment groups with the exception of dizziness, headache, and rash, which were reported with lower incidence by subjects in the LEV group compared with subjects in the OXC group.
- The majority of TEAEs were mild or moderate in intensity and were reported at a similar incidence in the LEV and OXC treatment groups. During the study, 6 subjects (3.5%) in the LEV group reported a total of 7 severe TEAEs, and 8 subjects (4.6%) in the OXC group reported a total of 13 severe TEAEs. All of the severe TEAEs were reported by only 1 subject in either treatment group, with the exceptions of cardiac arrest and headache that were each reported by 2 subjects, both in the OXC treatment group.
- Fifty-three subjects (30.6%) in the LEV group and 67 subjects (38.5%) in the OXC group reported ADRs during the study. Treatment-emergent ADRs were most frequently reported in the SOC of Nervous system disorders by subjects in the LEV and OXC treatment groups. Adverse drug reactions were reported at a similar incidence in the other SOCs for the LEV and OXC treatment groups with the exceptions of Psychiatric disorders (6.9% and 1.1%, respectively) and Skin and subcutaneous tissue disorders (2.9% and 9.2%, respectively). By PT, the ADRs most commonly reported by subjects in the LEV and OXC treatment groups were dizziness and somnolence. The incidence of ADRs by PT was similar between the LEV and OXC treatment groups with the exceptions of dizziness and rash that were lower in the LEV group compared with the OXC group.

- There were 3 deaths during the study (1 subject in the LEV group and 2 subjects in the OXC group), all of which occurred posttreatment due to TEAEs considered not related to study medication (upper airway obstruction, cardiac arrest, and respiratory failure).
- There were 4 randomized subjects with positive pregnancy tests reported during the Treatment Period that resulted in their discontinuation from the study.
- Serious TEAEs were reported at a similar incidence between the LEV and OXC treatment groups. Serious TEAEs were reported by no more than 1 subject in either treatment group, with the exceptions of cardiac arrest and convulsion. Three serious ADRs were reported

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during the study, each by 1 subject (hyponatremia, convulsion, and status epilepticus).

- Both TEAEs leading to discontinuation and ADRs leading to discontinuation were reported at a lower incidence by subjects in the LEV group compared with the OXC group. The TEAEs and ADRs leading to discontinuation that were reported by more than 1 subject in the LEV or OXC treatment groups were dizziness, lethargy, somnolence, rash, and urticaria.
- Eleven subjects in the LEV group and 20 subjects in the OXC group discontinued from the study due to AEs. Based upon Kaplan-Meier estimates, the hazard ratio of LEV vs OXC was 0.6 (95% CI: 0.275, 1.125), indicating a 40% reduction in hazard of discontinuation due to AE for subjects in the LEV group compared with subjects in the OXC group (log-rank p-value=0.1027).
- In the LEV group, 4 out of the 157 subjects who entered the Treatment Period (2.5%) had a reduction of study medication on or before the end of the Treatment Period. Fourteen out of 159 subjects (8.8%) in the OXC group had a reduction on or before the end of the Treatment Period.
- There was no evidence of any effect of LEV treatment on laboratory parameters, vital signs, ECG evaluations, or neurological examinations.

Paediatric subjects

Eight of the 14 subjects <18 years old (4 subjects in the OXC group and 4 subjects in the LEV group) had TEAEs. Most TEAEs were mild or moderate in intensity, not related to study medication, and resolved.

There were no deaths or SAEs in subjects aged <18 years. One subject (Subject 010-03452) in the OXC group discontinued due to an AE of rash; no subjects in the LEV group discontinued due to an AE. A full narrative for this subject is provided in Section 12 of the N01367 CSR.

Conclusion

- LEV monotherapy treatment at doses from 1000mg/day to 3000mg/day was noninferior to OXC monotherapy at doses from 900mg/day to 2400mg/day with respect to long-term effectiveness in Korean subjects aged ≥16 years recently diagnosed with partial onset seizures.
- The evaluation of the safety data demonstrated that LEV was well tolerated. No new safety concerns were identified in this study.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

Results from N01367 show that LEV monotherapy treatment at doses from 1000mg/day to 3000mg/day was noninferior to OXC monotherapy at doses from 900mg/day to 2400mg/day with respect to long-term effectiveness in Korean subjects aged ≥16 years recently diagnosed with partial onset seizures.

The evaluation of the safety data demonstrated that LEV was well tolerated. No new safety concerns were identified in this study.

The MAH considers that no changes to the approved EU Product Information for Keppra are proposed following the completion of this study.

At this time, the MAH considers that the standard immediate-release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU. This study was solely submitted in accordance with Article 46 of the Paediatric Regulation.

Recommendation

The Rapporteur endorses the submission of this study in accordance with Article 46 of the Paediatric Regulation and confirms that there is no impact on either the Product Information or on the benefit-risk balance of the EU authorized formulations.

☒ Fulfilled:

No regulatory action required