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Human Medicines Development and Evaluation

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/P46/079

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Introduction

On October 12 2015, the MAH submitted the final clinical study report for study NO1375, 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 NO1375 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

The study medication was provided as levetiracetam (LEV) 250 mg and 500mg tablets.

1.3. Clinical aspects

1.3.1. Description of the study

Title:

“An open-label, randomized, multicenter study to evaluate the efficacy and safety of Levetiracetam used as monotherapy in newly or recently diagnosed epilepsy patients aged older than or equal to 16 years with partial seizures”

Methods

Objective(s): The primary objective of N01375 was to evaluate the efficacy of levetiracetam (LEV) used as monotherapy, with efficacy measured as 6-month seizure freedom at the final evaluated dose in the LEV 1000 to 2000mg/day group, in subjects with newly or recently diagnosed epilepsy.

The secondary objectives of this study were the following:

- To evaluate the 1-year efficacy of LEV used as monotherapy at the final evaluated dose in the LEV 1000mg/day to 2000mg/day group
- To evaluate the efficacy of LEV used as monotherapy in subjects in the LEV 3000mg/day group
- To evaluate the long-term safety of LEV used as monotherapy

Study design

Methodology: N01375 was designed as a Phase 3, open-label, randomized, 2-arm, multicenter study for LEV monotherapy. After subjects were screened at Visit 1, eligible subjects were randomized in a 6:1 ratio to 1 of 2 treatment groups: LEV 1000 to 2000mg/day or LEV 3000mg/day. All subjects started LEV treatment at 1000mg/day regardless of the treatment group.

Regardless of the frequency of seizures during the Stabilization Period, subjects were allowed to enter the 6-month (26-week) Evaluation Period and continued the initial dose of

LEV 1000mg/day or LEV 3000mg/day for the efficacy evaluation during 3 consecutive study periods, the Evaluation Period, the Maintenance Period, and the Follow-Up Period, unless a seizure occurred.

In principle, the LEV dose had to be unchanged to continue LEV monotherapy, unless a seizure occurred. If a seizure occurred, the LEV dosage was allowed to increase using the protocol-specified methods.

Prior to entering the Follow-Up Period at Visit 9, informed consent was obtained for those subjects who agreed to continue participating in N01375. During the Follow-Up Period, the LEV dosage could be adjusted to the subject's best benefit at the investigator's discretion from a minimum of 1000mg/day to a maximum of 3000mg/day. The rate of increase or decrease had to be no faster than 1000mg/day per 2 weeks. Decreases in dosage and subsequent increases back to the previous dosage were permitted as frequently as the subjects needed to maintain the subject's safety while controlling seizures.

Duration of treatment: The total study duration by subject was up to 3.2 years and the study period included a 3- to 28-day Screening Period, 4-week Up-Titration Period (only for subjects in the LEV 3000mg/day group), 1-week Stabilization Period, 6-month (26-week) Evaluation Period, 6-month (26-week) Maintenance Period, Follow-Up Period (until approval of LEV monotherapy for POS in adults on 20 Feb 2015), and 6-week Withdrawal Period (included down-titration for 2 to 4 weeks and safety follow up for 2 weeks).

Study population /Sample size

Number of subjects (planned and analyzed):

Planned: 70 subjects in total to be enrolled

- 60 subjects in the LEV 1000 to 2000mg/day group
- 10 subjects in the LEV 3000mg/day group

Analyzed number: 71 subjects in total (included in Safety Set [SS])

- 61 subjects in the LEV 1000 to 2000mg/day group
- 10 subjects in the LEV 3000mg/day group

A total of 101 subjects provided informed consent and were screened. A total of 71 subjects were eligible to enter N01375 and received at least 1 LEV dose.

Diagnosis and main criteria for inclusion: Key inclusion criteria included the following:

- Subjects with newly or recently diagnosed epilepsy having experienced unprovoked partial onset seizures (POS) (IA, IB, IC) that were classifiable according to the International League Against Epilepsy (ILAE) 1981 classification of epileptic seizures
- Subjects with at least 2 unprovoked seizures separated by a minimum of 48 hours in the year prior to registration, of which, at least 1 unprovoked seizure occurred in the 3 months prior to Visit 1

Treatment

Oral tablets of LEV (250mg and 500mg) were used in this study. Subjects received 2 equal doses of the LEV oral tablets per day, 1 in the morning and 1 in the evening.

Outcomes/endpoints

Efficacy: The primary efficacy variable was seizure freedom for 6 consecutive months (26 weeks) of treatment following stabilization during the Evaluation Analysis Period at the final evaluated dose for each subject in the LEV 1000 to 2000mg/day group. The primary efficacy variable was calculated as the proportion of subjects who were seizure free for 6 months using the Full Analysis Set (FAS). The primary efficacy result was considered positive if the lower limit of the exact confidence interval (CI) was greater than the predefined reference value of 40%. To verify the robustness of the results of the primary efficacy analysis, the primary variable was analyzed on the Per Protocol Set (PPS), which included all subjects from the FAS without any important protocol deviations that might have had an impact on the validity of the efficacy data.

The secondary efficacy variables included seizure freedom for 6 months (26 weeks) in the LEV 3000mg/day group, seizure freedom for 1 year (52 weeks), time to the first seizure at the final evaluated dose, and time to withdrawal.

Safety: Safety was assessed by collecting information on adverse events (AEs), clinical laboratory results, electrocardiograms (ECGs), vital sign measurements, and body weight.

Statistical Methods

Statistical methods: This final CSR presents the analyses of all data from the study (including data from the first and second interim analyses).

During the course of the study, 3 study parts were defined:

- Part 1 included the Up-Titration Period, Stabilization Period 1, Evaluation Period 1, Stabilization Period 2, Evaluation Period 2, and Withdrawal Period. The first interim data cut (17 Oct 2013) was performed when all subjects had the opportunity to complete the Evaluation Period on their final evaluated dose; the data for analysis of the primary efficacy variable were available for all subjects.
- Part 2 included the Maintenance Period and Withdrawal Period. At the time of the second interim data cut (17 Apr 2014), all subjects had the opportunity to complete the Maintenance Period. The results of the Part 2 data analyses were considered final in the second interim analyses (second data cut)
- Part 3 included the Follow-Up Period and Withdrawal Period.

For the primary efficacy variable, a statistical test was performed. The hypothesis H_0: p=0.4 was to have been formally rejected in favor of H_1: p>0.4, if the lower confidence limit for p was greater than 0.4. An accompanying exact p-value of the 2-sided statistical test at level of α=5% was calculated using the binomial distribution.

For categorical parameters, the number and percentage of subjects in each category were presented. For continuous parameters, descriptive statistics were presented (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). For continuous efficacy parameters, descriptive statistics may have also included the 25th percentile (Q1) and the 75th percentile (Q3), depending on the distribution.

Results

Subject disposition

A total of 71 subjects in the Randomized Set started the study; 61 subjects in the LEV 1000 to 2000mg/day group and 10 subjects in the LEV 3000mg/day group. A total of 29 subjects (40.8%) discontinued from the study; the most frequently reported reasons for discontinuation were consent withdrawn (12 subjects [16.9%]), and AEs and lack of efficacy (7 subjects [9.9%] each).

Paediatric subjects

A total of 6 subjects were <18 years old at study entry (4 subjects were 17 years old; 2 were 16 years old). Two of these subjects were female; 4 were male. All 6 subjects were randomized to LEV 1000mg/day to 2000mg/day (Table 4–1).

Table 4–1: Subjects less than 18 years old at study entry in N01375

Subject ID	Age (years)	Sex	Treatment	Subject disposition
001/04037	17	M	1000mg/day to 2000mg/day	Completed
001/04049	17	M	1000mg/day to 2000mg/day	Completed
001/04067	16	F	1000mg/day to 2000mg/day	Discontinued due to lost to follow-up
008/04042	17	M	1000mg/day to 2000mg/day	Completed
013/04071	16	F	1000mg/day to 2000mg/day	Completed
029/04045	17	M	1000mg/day to 2000mg/day	Completed

F=female; M=male
Data sources: N01375 CSR Listing 1.1, N01375 CSR Listing 2.1.1

One subject (Subject 001/04067) discontinued due to lost to follow-up; the other 5 subjects completed the study (N01375 CSR Listing 1.1).

Efficacy results

The analysis of the primary efficacy variable, 6-month seizure freedom for subjects in the Full Analysis Set (FAS) in the LEV 1000 to 2000mg/day group was achieved by 73.8% of subjects, which resulted in a positive outcome as the lower limit of the 95% confidence interval (CI) (60.9%) was greater than the predefined value of 40% and the result was statistically significant (p-value <0.0001). The supportive and sensitivity analyses of the primary efficacy variable repeated using the Per Protocol Set (PPS) confirmed the robustness of the positive results of the primary efficacy analysis on the FAS.

Twelve-month seizure freedom in the FAS in the LEV 1000 to 2000mg/day group was achieved by 59.0% of subjects and the exact 95% CI was 45.7% to 71.4%. In the analysis repeated using the PPS, 12-month seizure freedom was achieved by 61.4% of subjects and the exact 95% CI was 47.6% to 74.0%.

The efficacy of LEV monotherapy for up to 6 months and up to 12 months was confirmed in subjects who received LEV doses ranging from 1000 to 2000mg/day.

Of the 9 subjects in the FAS in the LEV 3000mg/day group, 2 subjects (22.2%) achieved 6-month seizure freedom and 1 subject (11.1%) achieved 12-month seizure freedom.

The efficacy of LEV monotherapy was also observed during the Follow-Up Period in subjects who had the LEV dose escalated. Of the 14 subjects in the LEV 1000 to 2000mg/day group who received LEV 3000mg/day during the Follow-Up Period, 3 subjects (21.4%) achieved 6-month seizure freedom after the LEV dose was increased to 3000mg/day.

Overall, efficacy of LEV monotherapy for the treatment of POS at doses ranging from 1000 to 3000mg/day was observed in this study.

Safety results

During the overall study (Parts 1+2+3), the mean (SD) duration of exposure to LEV for all subjects was 735.7 (361.4) days (range: 14 to 1176 days). The mean (SD) duration of exposure to LEV for subjects in the LEV 1000 to 2000mg/day group was 783.2 (332.5) days (range: 31 to 1148 days) and for subjects in the LEV 3000mg/day group was 445.9 (412.3) days (range: 14 to 1176 days).

During the overall study (Parts 1+2+3), a total of 68 subjects (95.8%) reported 638 TEAEs and 45 subjects (63.4%) reported 101 ADRs. A total of 7 subjects (9.9%) reported 11 TEAEs that led to discontinuation from the study and 10 subjects (14.1%) reported 20 serious TEAEs. A total of 7 subjects (9.9%) reported 11 severe TEAEs. A total of 7 subjects (9.9%) reported 7 TEAEs that required changes in the LEV dose. No deaths were reported during the study.

During Parts 1 and 2, the most frequently reported TEAE was nasopharyngitis (37 subjects [52.1%]) followed by somnolence (25 subjects [35.2%]), malaise (8 subjects [11.3%]), dizziness (8 subjects [11.3%]), and headache (6 subjects [8.5%]). Other AE preferred terms (PTs) were reported in ≤5 subjects (7.0%) each

During the overall study (Parts 1+2+3), the incidences of the most frequently reported TEAE PTs were similar to those reported during Parts 1 and 2 with the exception of nasopharyngitis, which was reported in 51 subjects (71.8%). Other frequently reported TEAE PTs were somnolence (26 subjects [36.6%], malaise (12 subjects [16.9%]), headache (11 subjects [15.5%]), diarrhoea (10 subjects [14.1%]), and dizziness (9 subjects [12.7%]).

During the overall study (Parts 1+2+3), the most frequently reported ADR PT was somnolence (24 subjects [33.8%]). Other ADR PTs of malaise, irritability, dizziness, hypoaesthesia, and eczema were reported in ≤4 subjects (5.6%) each.

A total of 10 subjects (14.1%) reported 20 serious AEs (SAEs) during the overall study (Parts 1+2+3). A total of 6 subjects (8.5%) reported 12 SAEs during Parts 1 and 2. Four subjects (5.6%) reported 6 SAEs during Part 1; 3 subjects (6.5%) reported 6 SAEs during Part 2; and 5 subjects (8.2%) reported 8 SAEs during Part 3. The SAEs were irritability, pyelonephritis, Kaposi's varicelliform eruption, suicide attempt, meniscus removal, postictal psychosis, postictal state, alcohol withdrawal syndrome, status epilepticus, agitation, anaphylactic reaction, syncope, cystitis, convulsion, and epilepsy (aggravated). All SAEs were judged as not related to LEV by the investigator, with the exception of irritability and postictal psychosis. All SAEs resolved.

During the overall study (Parts 1+2+3), a total of 7 subjects (9.9%) reported 11 TEAEs leading to study discontinuation. Treatment-emergent AEs leading to study discontinuation were reported in 7.0% of subjects who discontinued during Part 1, 4.3% of subjects who discontinued during Part 2, and 1.6% of subjects who discontinued during Part 3. Of the 11 TEAEs leading to study discontinuation, 5 events were SAEs: irritability, postictal psychosis, suicide attempt, postictal state, and status epilepticus. The other 6 TEAEs leading to study discontinuation were agitation, vertigo positional, 2 events of somnolence, overdose (reported term: drug overdose of Nelurolen), and nausea. All events were judged as related to LEV by the investigator with the exception of overdose, suicide attempt, postictal state, and status epilepticus. All TEAEs leading to study discontinuation resolved.

Treatment-emergent AEs in the Psychiatric disorders system organ class (SOC) were given special consideration and termed other significant TEAEs in this study. During the overall study

(Parts 1+2+3), a total of 10 subjects (14.1%) reported 18 TEAEs in the Psychiatric disorders SOC: 2 events each of agitation, depression, nightmare, suicide attempt, and alcohol withdrawal syndrome; and 1 event each of anxiety, postictal psychosis, somatic hallucination, stress, alcoholism, depressed mood, attention deficit/hyperactivity disorder, and insomnia.. The incidence of TEAEs in the Psychiatric disorders SOC was 1 subject each with the exception of depression and agitation that were reported in 2 subjects each. No new safety concerns were noted.

Overall, there were no clinically relevant findings in clinical laboratory evaluations, vital signs, and ECG findings. The majority of the post-Baseline possibly clinically significant (PCS) clinical laboratory values during each study part were reported at an incidence of ≤8.7% of subjects with the exception of triglycerides too high (14.1% and 18.0% of subjects during Part 1 and Part 3, respectively), bilirubin too high (10.9% and 11.5% of subjects during Part 2 and Part 3, respectively), and occult blood (20.3%, 15.6%, and 21.7% of subjects during Part 1, Part 2, and Part 3, respectively). Although post-Baseline PCS bilirubin too high was reported in 5.6% of subjects during Part 1, and triglycerides too high was reported in 6.5% of subjects during Part 2, overall post-Baseline PCS clinical laboratory values did not show any clinically relevant increases or decreases during the study. No specific trends in post-Baseline PCS values were noted.

Overall, the safety evaluation indicated that LEV monotherapy for up to 3.2 years was safe and well tolerated in subjects with newly or recently diagnosed epilepsy.

Paediatric subjects

All 6 subjects <18 years old had TEAEs. Most TEAEs were mild in intensity and resolved; the majority of TEAEs were considered not related to study medication (N01375 CSR Listing 7.2).

There were no deaths, SAEs, or discontinuations due to AEs in subjects aged <18 years.

Conclusion

- The efficacy of monotherapy with LEV 1000mg/day to 2000mg/day in Japanese subjects aged ≥16 years with newly or recently diagnosed epilepsy was demonstrated by the measurements of 6-month and 12-month seizure freedom.
- The safety profile for LEV monotherapy was similar to the known data and appeared to be safe and well tolerated in subjects.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

Results from N01375 show efficacy of monotherapy with LEV 1000mg/day to 2000mg/day in Japanese subjects aged ≥16 years with newly or recently diagnosed epilepsy as measured by 6-month and 12-month seizure freedom.

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.

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