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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/P46/080

Note

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

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1. Introduction

On November 6 2015, the MAH submitted the final clinical study report for study NO1353, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study NO1353 is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

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

2.3. Clinical aspects

2.3.1. Description of the study

Title:

"A randomized, open-label, parallel group, multicentre, comparative, phase IV trial of Levetiracetam versus Topiramate as adjunctive therapy to evaluate efficacy and safety in subjects with refractory partial onset seizures"

Methods

Objectives:

The primary objective was to assess the long-term effects of levetiracetam (LEV) on the retention rate in subjects with refractory partial onset seizures (POS) that were not fully controlled despite optimal treatment with 1 to 3 concomitant antiepileptic drugs (AEDs), compared to topiramate (TPM) as add-on therapy during the 52-week Treatment Period.

The secondary objectives were:

- To assess the safety and tolerability of LEV in subjects with refractory POS that were not fully controlled despite optimal treatment with 1 to 3 concomitant AEDs, compared to TPM as add-on therapy
- To assess the efficacy of LEV in reducing seizure frequency in refractory subjects with POS that were not fully controlled despite optimal treatment with 1 to 3 concomitant AEDs, compared to TPM as add-on therapy

Study design

After measuring Baseline seizure frequency during 8 weeks by seizure history (retrospective baseline) and 4 weeks after the first visit (prospective baseline), as documented in subjects' seizure diaries, subjects were randomized to either LEV add-on treatment or TPM add-on treatment (1:1 ratio) according to a predefined randomization schedule and entered an Up-Titration Period (4 weeks) and a Dose-Finding Period (20 weeks).

The visit interval during the Up-Titration Period and the Dose-Finding Period was 4 weeks.

Subjects then entered a 28-week Maintenance Period and were maintained at a stable dose. During the Maintenance Period, 1 dose increase to the next higher level or 1 dose decrease to the next lower dose level was allowed by investigator's discretion based on the subject's response of seizure control and tolerability. Between site visits, subjects could have called the investigator in case of any safety question or seizure worsening.

Concomitant AEDs were to be at stable and optimal dosage for at least 1 month before Visit 1, during 4 weeks preceding Visit 2, and throughout the Treatment Period.

After completion of the Treatment Period, which was End of Study or at any time for subjects discontinuing the study, the investigator decided whether the subject should continue the allocated study treatment. Therefore, treatment was either continued with the commercial medication or was discontinued. In the latter case, subjects entered a Down-Titration Period, depending on the last dose level during the study period and a study medication-free period based on the investigator's discretion.

Study population /Sample size

Number of subjects (planned and analyzed): It was planned that 340 subjects (170 per treatment) would be enrolled in the study. A total of 343 subjects were randomized in N01353, 177 subjects to the LEV treatment group and 166 subjects to the TPM 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 confirmed diagnosis of epilepsy with POS classifiable according to the International League Against Epilepsy, having experienced at least 2 POS whether or not secondarily generalized during the 8-week historical Baseline preceding Visit 1 and at least 1 POS whether or not secondarily generalized per 4 weeks preceding Visit 2 (with each interval of POS less than 6 weeks during entire 12 weeks). Subjects were uncontrolled while treated with 1 to 3 concomitant AEDs, that were stable and at optimal dosage for the subject for at least 4 weeks before Visit 1 and during the 4 weeks preceding Visit 2, and were expected to be kept stable during the Treatment Period.

Female subjects were to have been without childbearing potential or using a medically accepted contraceptive method during the study. Female subjects of childbearing potential must have had a negative urine pregnancy test prior to study entry (at Visit 1).

Treatment

Test product: oral tablets of LEV (250mg and 500mg)

Reference product: oral tablets of Topiramate (TPM) (25mg and 100mg)

Outcomes/endpoints

Efficacy:

The primary efficacy variable was the retention rate at 52 weeks of treatment after beginning investigational treatment with LEV compared to TPM, defined as the percentage of subjects continuing the allocated investigational treatment from the first study treatment intake.

The secondary efficacy variables were:

- Median percent reduction in the weekly POS frequency (WPSF) from Baseline during the Treatment Period (combination of the Up-titration, Dose-finding, and Maintenance Periods)
- Responder rate, defined as subjects with at least 50% reduction in the WPSF from Baseline during the Total Treatment Period

The other efficacy variables were:

- 6 months consecutive seizure freedom at any time during the Treatment Period
- Responder rate defined as the proportion of subjects with at least 50% reduction in WPSF as compared to Baseline during the Maintenance Period in subjects who completed the Maintenance Period

- Median percent reduction in the WPSF from Baseline during the Maintenance Period
- Seizure freedom during the Maintenance Period

Safety: The safety variables measured were:

- Adverse events (AEs) reported during the Treatment Period and/or throughout the study
- Time from the first study medication intake to drug discontinuation due to AE
- Significant findings in safety laboratory tests, electrocardiograms (ECGs), and physical and neurological examinations

Statistical Methods

Statistical methods: In general, summaries were presented by treatment group (LEV, TPM) 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 efficacy evaluation was based on the Full Analysis Set (FAS). Presentation of disposition data was based on the Enrolled Set and/or the Randomized Set (RS). 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 Per Protocol Set (PPS).

The primary analysis of this study aimed to demonstrate whether LEV was superior to TPM with respect to retention rate. The analysis was performed on the FAS and was adjusted for center pooling category.

Retention rate was modeled by a logistic regression using treatment group and center pooling category as categorical independent variables.

The null hypothesis of no treatment effect was tested at a significance level of 5% using a likelihood ratio test of the treatment regression coefficient against 0.

The primary analysis was repeated for the PPS and for subjects in the FAS with prescribed maintenance dosing according to label-indicated recommendation.

Results

Subject disposition

Subject disposition: Overall, a total of 343 subjects were randomized in N01353 (177 subjects to treatment with LEV and 166 subjects to treatment with TPM) and 211 subjects (61.5%) completed the study. Similar proportions of subjects in the LEV and TPM groups discontinued from the study (66 subjects [37.3%] and 66 subjects [39.8%], respectively). There was a lower percentage of subjects in the LEV group (14 subjects [7.9%]) who discontinued from the study due to AEs compared with subjects in the TPM group (21 subjects [12.7%]).

Paediatric subjects

One subject was <18 years old at study entry. Subject 016-02123, a 17-year-old female, was randomized to LEV (N01353 CSR Listing 2.1). This subject completed the study (N01353 CSR Listing 1.3). No subjects <18 years old were randomized to TPM.

Efficacy results

For the Full Analysis Set (FAS), the retention rate at Week 52 for subjects in the LEV group was numerically higher than the retention rate for subjects in the TPM group (59.1% and 56.6%, respectively; odds ratio of LEV vs TPM: 1.1; 95% CI: [0.7, 1.7]); this difference was not statistically significant (p=0.7007), therefore, superiority was not shown.

Similar results for the primary efficacy variable were observed for the Per Protocol Set (65.6% and 61.9%, respectively; odds ratio of LEV vs TPM: 1.1; p=0.6815).

For subjects in the FAS with prescribed maintenance dosing according to recommendation, the retention rate at Week 52 for subjects in the LEV group was higher than the retention rate for subjects in the TPM group (59.1% and 42.5%, respectively). The odds ratio for LEV vs TPM was 1.9 (95% CI: [1.2, 3.1]; p=0.0086).

For the FAS, subjects in the LEV group were retained longer, compared with subjects in the TPM group (first quartile for time to event of nonretention: 153.0 and 139.0 days, respectively; p=0.5710) and the estimated percentage of subjects remaining on allocated treatment was higher for subjects in the LEV group compared with subjects in the TPM group from 3 months until the end of the study (12 months).

For the FAS, the median percent reduction from Baseline during the Treatment Period in weekly partial onset seizure frequency (WPSF) was greater in the LEV group compared with the TPM group (74.47% and 67.86%, respectively; p=0.0665).

For the FAS, a similar percentage of subjects had at least a 50% reduction in WPSF from Baseline during the Treatment Period in the LEV and TPM groups (69.0% and 64.8%, respectively; p=0.4205).

For the FAS, a higher percentage of subjects in the LEV group had 6 months of seizure freedom during the Treatment Period compared with subjects in the TPM group (35.8% and 22.3%, respectively; p=0.0061).

For the FAS, the median percent reduction from Baseline during the Maintenance Period in WPSF was greater in the LEV group compared with the TPM group (91.03% and 84.14%, respectively; p=0.0494).

For the FAS, a higher percentage of subjects had at least a 50% reduction in WPSF during the Maintenance Period in the LEV group compared with the TPM group (82.9% and 75.0%, respectively; p=0.1593).

For the FAS, a higher percentage of subjects in the LEV group were seizure free during the Maintenance Period compared with subjects in the TPM group (34.6% and 21.9%, respectively; p=0.0288).

Safety results

The safety results are summarized as follows:

- The mean duration of exposure to study medication was similar for the LEV and TPM groups (278.9 and 267.3 days, respectively). The mean daily dose of LEV and TPM was 1322.42 and 146.12mg/day, respectively.
- During the study, a total of 478 TEAEs were reported by 125 subjects (70.6%) in the LEV group and a total of 426 TEAEs were reported by 128 subjects (77.1%) in the TPM group. Treatment-emergent AEs were most commonly reported in the SOC of Nervous system disorders by subjects in the LEV and TPM groups. By PT, the most common TEAEs in the LEV group were somnolence, dizziness, and nasopharyngitis. The most common TEAEs in the TPM group were decreased appetite, dizziness, and headache. The incidence of TEAEs reported by subjects in either treatment group was similar with the exceptions of weight decreased, decreased appetite, and paraesthesia, which were reported in lower incidence by subjects in the LEV group compared with subjects in the TPM group, and somnolence and tremor, which were reported at higher incidence by subjects in the LEV group compared with subjects in the TPM group.
- The majority of TEAEs were mild or moderate in intensity and were reported at a similar incidence in the LEV and TPM groups. During the study, 7 subjects (4.0%) in the LEV group reported a total of 7 severe TEAEs and 6 subjects (3.6%) in the TPM group reported a total of 9 severe TEAEs. All of the severe TEAEs were reported by only 1 subject, with the exception of seizure that was reported by 2 subjects, 1 subject in each treatment group.

- Sixty-three subjects (35.6%) in the LEV group and 76 subjects (45.8%) in the TPM group reported ADRs during the study. Treatment-emergent ADRs were most frequently reported in the SOC of Nervous system disorders by subjects in both treatment groups. By PT, the most commonly reported ADRs by subjects in the LEV group were somnolence and dizziness, and by subjects in the TPM group were decreased appetite and weight decreased. The incidence of ADRs was similar between the LEV and TPM groups with the exceptions of weight decreased, decreased appetite, and paraesthesia, which were reported in lower incidence by subjects in the LEV group compared with subjects in the TPM group, and somnolence, which was reported at higher incidence by subjects in the LEV group compared with subjects in the TPM group.
- There was 1 subject with a positive pregnancy test during the Treatment Period that resulted in her discontinuation from the study. Twenty-eight days after the TEAE of pregnancy was reported, an SAE of abortion spontaneous occurred that was considered severe and resolved within 5 days.
- Serious TEAEs were reported at a similar incidence by subjects in the LEV group (10 subjects [5.6%]) compared with the TPM group (15 subjects [9.0%]). Serious TEAEs (by PT) were reported by no more than 1 subject in either treatment group, with the exceptions of dizziness (2 subjects [1.1%] in the LEV group and no subjects in the TPM group) and seizure (1 subject [0.6%] in the LEV group and 5 subjects [3.0%] in the TPM group). No subject died during the study.
- Overall, TEAEs leading to discontinuation were reported at a lower incidence by subjects in the LEV group (14 subjects [7.9%]) compared with the TPM group (21 subjects [12.7%]). Treatment-emergent AEs leading to discontinuation were reported by no more than 2 subjects in the LEV or TPM groups with the exceptions of dizziness (5 subjects [2.8%] and 3 subjects [1.8%], respectively); somnolence (3 subjects [1.7%] and no subjects, respectively); weight decreased (no subjects and 3 subjects [1.8%], respectively); fatigue (2 subjects [1.1%] and no subjects, respectively); and vision blurred, asthenia, and seizure (each no subjects and 2 subjects [1.2%], respectively).
- In the LEV group, 5/130 subjects (3.8%) who entered the Maintenance Period had a dose reduction on or before the end of the Maintenance Period. In the TPM group, 1/114 subjects (0.9%) had a dose reduction on or before the end of the Maintenance Period.

- There was no evidence of any effect of LEV treatment on laboratory parameters, vital signs, ECG evaluations, or neurological examinations.

Paediatric subjects

Subject 016-02123 had 1 TEAE (somnolence) during the study. The event of somnolence was mild, not related, and resolved (N01353 CSR Listing 7.2).

Conclusion

- In this study, LEV adjunctive therapy was not superior to TPM adjunctive therapy with regard to efficacy measured by retention in subjects with refractory partial onset seizures.
- There were no new safety concerns for LEV identified in this study and safety data were consistent with the established safety profile of LEV.

3. CHMP's overall conclusion and recommendation

Overall conclusion

Results from N01353, a phase IV study conducted in Korea, show that LEV adjunctive therapy was not superior to TPM adjunctive therapy with regard to efficacy measured by retention in subjects with refractory partial onset seizures. However, the retention rate is of 59.1% at 52 weeks showing effectiveness in these subjects with refractory epilepsy.

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 CHMP 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