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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/P46/083

Note

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

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Introduction

On March 21 2016, the MAH submitted the final clinical study report for study NO1364, 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 NO1364 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

The study medications were **levetiracetam (LEV) 1000 mg/day** and **carbamazepine immediate-release (CBZ-IR) 400mg/day.**

1.3. Clinical aspects

1.3.1. Description of the study

Title:

"A Multicenter, Open-Label, Randomized, Parallel-Group, Active-Controlled Study Comparing the Efficacy and Safety of Levetiracetam to Carbamazepine Used as Monotherapy in Subjects (≥16 Years) Newly or Recently Diagnosed as Suffering from Epilepsy and Experiencing Partial Seizures."

Methods

Objectives

The primary objective of this study was to demonstrate the non-inferiority of the efficacy of LEV (1000mg/day) versus CBZ-IR (400mg/day) used as monotherapy for at least 6 months. Efficacy was measured as a primary variable by 6-month seizure freedom in adult subjects (≥16 years of age) who were newly or recently diagnosed with epilepsy and were experiencing POS with or without secondarily generalized seizures.

The secondary objective was to compare the safety and tolerability of both drugs in the same population.

Study design

This was a Phase 3, multicenter, open-label, randomized, parallel-group, active-controlled study comparing the efficacy and safety of LEV to CBZ-IR as monotherapy in adult subjects (≥16 years of age) newly or recently diagnosed with epilepsy and experiencing POS. Subjects were randomized in a 1:1 ratio to treatment with LEV 1000mg/day or CBZ-IR 400mg/day.

The study consisted of the following periods:

☐ **Screening Period** (up to 1 week): The Screening Period allowed the Investigator to evaluate subjects for suitability for study enrollment. It was acceptable for this visit to be conducted on more than 1 day, although it should not have extended over a period longer than 1 week.

☐ **Up-Titration Period (**2 weeks): The Up-Titration Period started with Visit 2. At this time, subjects were randomized in a 1:1 ratio to their drug treatment (LEV 1000mg/day or CBZ-IR 400mg/day). The randomization was stratified by the number of seizures in the 3-month period prior to Visit 1 (≤2 seizures and >2 seizures). Subjects started receiving study drug at half the randomized target dose (LEV 250mg bid or CBZ-IR 200mg once daily [qd]). At the end of the Up-Titration Period, subjects started receiving the full target dose (LEV 500mg bid or CBZ-IR 200mg bid). Subjects who did not reach or tolerate the target dose were withdrawn.

☐ **Stabilization Period** (1 week): 1 Stabilization Visit was conducted at the end of the Stabilization Period, 1 week after the end of the Up-Titration Period.

☐ **Evaluation Period** (26 weeks): Following completion of the Stabilization Period, subjects began the Evaluation Period. Two Interim Evaluation Visits (IEVs) were conducted 8 weeks apart. A Full Evaluation Visit (FEV) was conducted 10 weeks after the second IEV.

A subject continued to be treated in the Evaluation Period for up to 26 weeks unless a seizure occurred or the subject needed to be withdrawn from the study. In these cases, the subject had an Early Discontinuation Visit (EDV). If a seizure occurred during the Evaluation Period and the subject was entering the Named Patient Program (NPP), a dose titration was planned. If the subject was withdrawn, the dose was down-titrated at the discretion of the Investigator.

☐ **Named Patient Program**: Subjects in the LEV treatment group who were seizure free during the 26-Week Evaluation Period or who had a seizure and needed further dose titration had the opportunity to continue taking LEV in the NPP until the monotherapy indication was approved in China or until UCB terminated the development of this indication in China. Patients may have had their dose up-titrated to 3000mg/day (refer to the NPP Guidance Book for details). Visits were planned according to the routine clinical practice.

Subjects in the CBZ-IR treatment group who were seizure free at the end of the Evaluation Period, or who had a seizure and needed further dose titration, had the opportunity to participate in the NPP for a maximum of 6 months. Subjects may have had their dose up-titrated to 1600mg/day (refer to the NPP Guidance Book for details). After 6 months, subjects switched to prescribed marketed CBZ-IR at the discretion of the Investigator.

Subjects who did not enter the NPP entered the Down-Titration Period and stopped

randomized study drug treatment.

☐ **Down-Titration Period** (including Safety Follow-Up [SFU] Visit): Following the EDV, subjects who did not enter the NPP entered a Down-Titration Period over a maximum of 3 weeks. An SFU Visit was scheduled 2 weeks after the last study drug intake.

Study duration per subject

The maximum duration of study participation per subject was expected to be up to 33 weeks including the Screening Period (up to 1 week), Up-Titration Period (2 weeks), Stabilization Period (1 week), Evaluation Period (26 weeks), and Down-Titration Period (up to 3 weeks).

The end of the study was defined as the date of the last visit of the last subject in the Evaluation Period or Down-Titration Period.

Planned number of subjects and sites

Approximately 550 subjects were planned to be enrolled in the study at approximately 28 sites in order to randomize 436 subjects.

Anticipated regions and countries

The study was conducted in mainland **China**.

Selection of study population

Inclusion criteria

To be eligible to participate in this study, all of the following criteria must have been met:

1. An IRB/IEC approved written ICF was signed and dated by the subject or by the parent(s) or legal representative. The ICF or a specific Assent form, where required, was signed and dated by minors.

2. Subject/legal representative was considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.

3. Subject was male or female, and ≥16 years of age.

4. Subject was of Chinese origin.

5. Female subject of childbearing potential (without a history of hysterectomy, tubal ligation, or bilateral oophorectomy) was eligible if she used a medically accepted contraceptive method for the duration of the study participation. She must have understood and accepted that pregnancy was to be avoided during participation in the study. A negative result from the pregnancy test at all visits was necessary to confirm the absence of pregnancy. Female subjects without childbearing potential (bilateral oophorectomy or tubal ligation, complete

hysterectomy) were eligible.

6. Subject weighed at least 40kg.

7. Subject was newly or recently diagnosed with epilepsy, having experienced unprovoked POS (IA, IB, IC with clear focal origin) that were classifiable according to the ILAE Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981).

8. Subject had experienced at least 2 unprovoked seizures (separated by a minimum of 48 hours) in the year preceding randomization, out of which at least 1 unprovoked seizure occurred in the 3 months preceding randomization. In case of simple partial seizures, only those with motor signs were counted.

9. Subject had an electroencephalogram (EEG) and a brain computed tomography (CT) scan or brain magnetic resonance imaging (MRI) scan consistent with a diagnosis of epilepsy with POS according to the ILAE Classification of Epileptic Seizures (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). If the EEG and brain CT scan or brain MRI were not performed within 1 year prior to the Screening Visit, the assessment needed to be completed and results must have been available prior to randomization.

Exclusion criteria

Subjects were not permitted to enroll in the study if any of the following criteria was met:

1. Subject had previously participated in this study or subject had previously been assigned to treatment in a study of the medication under investigation in this study.

2. Subject had participated in another study of an investigational medicinal product (IMP) (or a medical device) within the previous 2 months or was currently participating in another study of an IMP (or a medical device).

3. Subject tested positive for human leukocyte antigen major histocompatibility complex, class I, B (HLA-B)* 1502 allele.

4. Subject was pregnant or nursing.

5. Subject had a history or presence of seizures of other types than POS (IA, IB, IC, with clear focal origin).

6. Subject had only experienced type IA nonmotor seizures.

7. Subject had a history or presence of seizures occurring only in clustered patterns, defined as repeated seizures occurring over a short period of time (ie, <20 minutes) with or without function regained between 2 ictal events.

8. Subject had a history of clinical or EEG findings suggestive of Idiopathic Generalized Epilepsy prior to randomization, according to the ILAE Classification of Epilepsies and Epileptic Syndromes (Commission on Classification and Terminology of the International League Against Epilepsy, 1989).

9. Subject had current or previous diagnosis of pseudoseizures, conversion disorders, or other nonepileptic ictal events that could have been confused with seizures.

10. Subject had a history of status epilepticus.

11. Subject had any medical or psychiatric condition that, in the opinion of the Investigator, could have jeopardized or would have compromised the subject's ability to participate in this study.

12. Subject had a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt) or had suicidal ideation in the past 6 months.

13. Subject had a history of chronic alcohol or drug abuse within the previous 2 years.

14. Subject had a known hypersensitivity to any components of the study drug or comparative drugs as stated in the protocol.

15. Subject had a history of severe anaphylactic reaction or serious blood dyscrasias.

16. Subject had a history of skin rash or allergic reaction to any other drug.

17. Subject had an acute or subacute progressive CNS disease.

18. Subject had a medical condition that might have reasonably been expected to have interfered with drug absorption, distribution, metabolism, or excretion (including presence of mild, moderate, and severe renal impairment).

Subject had ever been treated for any indication with LEV or CBZ in the past.

20. Subject had been treated for epilepsy with any AED in the 6 months before Visit 1. However, acute and subacute seizure treatment was accepted with a maximum duration of 2 consecutive weeks and if treatment was stopped at least 1 week before Visit 1, and the use of benzodiazepines as rescue therapy for epilepsy was allowed if taken at a maximum frequency of once per week prior to Visit 1.

21. Subject had taken Chinese traditional medicine for epilepsy within 6 months prior to Visit 1.

22. Subject had received treatment with phenobarbital or primidone within 28 days prior to Visit 1.

23. Subject was taking any drug with possible CNS effects. However, antidepressants (with the exception of amitriptyline, fluoxetine, and mianserine) use was allowed if the medication and dose had been stable for at least 6 months prior to study entry and was kept stable for the entire study duration.

24. Subject had experienced seizure(s) while treated with any AED for an indication other than epilepsy.

25. Subject had levels of ≥2x the upper limit of normal (ULN) at Visit 1 for alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, or had alkaline phosphatase levels ≥3x ULN at Visit 1.

26. Subject had platelets ≤100,000/μL or neutrophils ≤1800/μL.

Withdrawal criteria

Subjects were free to withdraw from the study at any time, without prejudice to their continued care.

Subjects must have been withdrawn from the study if any of the following events occurred:

1. Subject developed an illness that would have interfered with his/her participation.

2. Subject took prohibited concomitant medication as defined in this protocol

3. Subject did not reach or did not tolerate the target dose.

4. Subject experienced a seizure during the 26-Week Evaluation Period.

5. Subject experienced emergence of a new seizure type (ie, other than POS or generalized

tonic-clonic seizures) or occurrence of status epilepticus, or for any other safety reason.

6. There was confirmation of a pregnancy, as evidenced by a positive pregnancy test.

7. Subject withdrew his/her consent.

8. The Sponsor or a regulatory agency requested withdrawal of the subject.

Subjects may have been withdrawn from the study if any of the following events occurred:

1. Subject required a medication that was not permitted.

2. Subject was noncompliant with the study procedures or medications in the opinion of the Investigator.

Treatment

The study medications were Oral tablets of LEV (250mg and 500mg) and oral tablets of CBZ-IR (200 mg).

Outcomes/endpoints

Efficacy

The primary efficacy variable was the proportion of subjects remaining seizure free during the 6-month (26 weeks) Evaluation Period.

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

Results

Subject disposition

A total of 436 subjects in the Randomized Set started the study; 220 subjects in the LEV group and 216 subjects in the CBZ-IR group. A total of 218 subjects (50.0%) discontinued from the study; 127 subjects (57.7%) in the LEV group and 91 subjects (42.1%) in the CBZ-IR group. The most frequently reported reasons for discontinuation in all subjects were lack of efficacy (LOE) (135 subjects [31.0%]), adverse events (AEs) (33 subjects [7.6%]), and consent withdrawn (not due to AE) (30 subjects [6.9%]). More subjects in the LEV group discontinued from the study due to LOE compared with the CBZ-IR group (94 subjects [42.7%] vs 41 subjects [19.0%], respectively), and fewer subjects discontinued from the study due to AEs in the LEV group compared with the CBZ-IR group (7 subjects [3.2%] vs 26 subjects [12.0%], respectively). A total of 337 subjects (77.3%) entered the NPP; 179 subjects (81.4%) in the LEV group and 158 subjects (73.1%) in the CBZ-IR group.

Paediatric subjects

A total of 28 subjects were <18 years old at study entry (19 subjects were 17 years old; 9 were 16 years old). Twelve of these subjects were female; 16 were male. Fourteen subjects were randomized to LEV 1000mg/day, and 14 subjects were randomized to CBZ-IR 400mg/day (Table 4–1).

Table 4–1: Subjects less than 18 years old at study entry in N01364

Subject ID	Age (years)	Sex	Treatment	Subject disposition
[redacted]	17	M	LEV 1000mg/day	Discontinued due to lack of efficacy
	17	M	CBZ-IR 400mg/day	Completed
	17	M	CBZ-IR 400mg/day	Discontinued due to consent withdrawn (not due to adverse event)
	17	F	LEV 1000mg/day	Completed
	17	M	CBZ-IR 400mg/day	Discontinued due to lack of efficacy
	17	F	CBZ-IR 400mg/day	Completed
	16	F	LEV 1000mg/day	Discontinued due to lack of efficacy
	16	F	CBZ-IR 400mg/day	Completed
	17	F	LEV 1000mg/day	Completed
	16	F	LEV 1000mg/day	Discontinued due to lack of efficacy
	16	M	CBZ-IR 400mg/day	Completed
	16	F	LEV 1000mg/day	Completed
	17	M	CBZ-IR 400mg/day	Completed
	16	M	CBZ-IR 400mg/day	Discontinued due to adverse event
	17	F	CBZ-IR 400mg/day	Discontinued due to adverse event
	17	M	LEV 1000mg/day	Discontinued due to lack of efficacy
	17	F	LEV 1000mg/day	Discontinued due to lack of efficacy
	17	M	LEV 1000mg/day	Discontinued due to lack of efficacy
	16	M	LEV 1000mg/day	Discontinued due to lack of efficacy
	17	F	CBZ-IR 400mg/day	Completed
	17	M	LEV 1000mg/day	Completed
	17	M	LEV 1000mg/day	Completed
	17	M	LEV 1000mg/day	Discontinued due to lack of efficacy
	16	M	CBZ-IR 400mg/day	Discontinued due to adverse event
	17	F	CBZ-IR 400mg/day	Discontinued due to lack of efficacy
	17	F	LEV 1000mg/day	Completed
	17	M	CBZ-IR 400mg/day	Discontinued due to lack of efficacy
	16	M	CBZ-IR 400mg/day	Completed

CBZ-IR=carbamazepine immediate release; F=female; LEV=levetiracetam; M=male

Data sources: N01364 CSR Listing 1.3, N01364 CSR Listing 2.1

Fifteen subjects discontinued the study: 8 in the LEV group and 7 in the CBZ-IR group. The most common reason for discontinuation in the LEV group was LOE (8 subjects, compared with 3 subjects in the CBZ-IR group). The most common reasons for discontinuation in the CBZ-IR group were adverse event and LOE (3 subjects each in the CZB-IR group, compared with no subjects in the LEV group). Thirteen subjects completed the study, 6 subjects in the LEV group and 7 subjects in the CBZ-IR group

Efficacy results

The analysis of the primary efficacy variable, the proportion of subjects remaining seizure free during the 6-month Evaluation Period, indicated that fewer subjects in the LEV group reached 6 months of seizure freedom compared with the CBZ-IR group (88 subjects [47.3%] vs 117 subjects [68.4%]). The adjusted 6-month seizure freedom rate was 47.7% for LEV and 70.6% for CBZ-IR with an adjusted difference of -22.9%; the 95% confidence interval (CI) was -33.1% to -12.6%. The lower bound of the 95% CI of this difference was not above the noninferiority margin of -20%, indicating that noninferiority of LEV compared with CBZ-IR could not be established at the administered doses.

The results of the sensitivity analyses of the primary efficacy variable, conducted on the Full Analysis Set (FAS), were similar to the primary analysis results observed for the Per Protocol Set (PPS). The adjusted 6-month seizure freedom rate was 46.9% for the LEV group and 68.8% for the CBZ-IR group with an adjusted difference of -21.9%; the 95% CI was -32.0% to -11.9%. A similar result was observed in both of the historical seizure count strata (≤2 seizures, >2 seizures), with fewer subjects achieving 6 months of seizure freedom in the LEV group compared with the CBZ-IR group.

A smaller proportion of subjects were retained in the study for the 30-week period in the LEV group (90 subjects [48.4%]) compared with the CBZ-IR group (120 subjects [70.2%]).

Safety results

Overall, the mean duration of exposure to LEV for subjects in the LEV group was 128.7 days (range: 1 to 226 days). The mean duration of exposure to CBZ-IR for subjects in the CBZ-IR group was 148.0 days (range: 1 to 241 days).

A total of 135 subjects (61.9%) in the LEV group reported 464 treatment-emergent adverse events (TEAEs) and 146 subjects (67.9%) in the CBZ-IR group reported 469 TEAEs. The incidence of serious TEAEs and severe TEAEs was similar between the LEV and CBZ-IR groups (4.1% vs 5.1% and 4.6% vs 5.6%, respectively). Discontinuations due to TEAEs, permanent withdrawal of study drug due to TEAEs, TEAEs requiring dose change, and adverse drug reactions (ADRs) were reported with lower incidence in the LEV group (12 subjects [5.5%], 12 subjects [5.5%], 22 subjects [10.1%], and 61 subjects [28.0%], respectively) compared with the CBZ-IR group (29 subjects [13.5%], 29 subjects [13.5%], 43 subjects [20.0%], and 80 subjects [37.2%], respectively).

In general, the pattern observed when TEAEs were assessed by study period was similar to the pattern observed for TEAEs overall.

The most frequently reported TEAEs by preferred term (PT) in the LEV group were nasopharyngitis (40 subjects [18.3%]), dizziness (33 subjects [15.1%]), and somnolence (20 subjects [9.2%]). The most frequently reported TEAEs in the CBZ-IR group were nasopharyngitis (32 subjects [14.9%]), dizziness (18 subjects [8.4%]), upper respiratory tract infection, and headache (both 16 subjects [7.4%]). By PT, the incidences of TEAEs were similar between treatment groups with the exceptions of GGT increased, white blood cell count decreased, and liver function test abnormal which were reported at lower incidences by subjects in the LEV group (0.9%, 0.5%, and 0, respectively) compared with the CBZ-IR group (5.1%, 5.1%, and 4.2%, respectively). Dizziness and somnolence were reported at higher incidences by subjects in the LEV group (15.1% and 9.2%, respectively) compared with the CBZ-IR group (8.4% and 3.3%, respectively).

The majority of TEAEs were mild or moderate in intensity and were reported at a similar incidence in the LEV group (58.3% and 8.3%, respectively) and CBZ-IR group (61.4% and 13.5%, respectively). During the study, 10 subjects (4.6%) in the LEV group reported a total of 15 severe TEAEs and 12 subjects (5.6%) in the CBZ-IR group reported a total of 17 severe TEAEs. All of the severe TEAEs were reported by only 1 subject each per group, with the exceptions of status epilepticus, reported by 2 subjects in the LEV group, and abortion induced reported by 2 subjects in the CBZ-IR group.

Sixty-one subjects (28.0%) in the LEV group and 80 subjects (37.2%) in the CBZ-IR group reported ADRs during the study; 158 events were reported in each group. By PT, the ADRs most commonly reported were dizziness and somnolence (9.6% and 9.2%, respectively) in the LEV group, and dizziness (6.0%) in the CBZ-IR group. The incidence of ADRs was slightly lower in the LEV group compared with the CBZ-IR group with the exceptions of dizziness (9.6% vs 6.0%, respectively) and somnolence (9.2% vs 2.8%, respectively), which were higher in the LEV group compared with the CBZ-IR group.

The majority of adverse drug reactions (ADRs) were mild or moderate in intensity; ADRs that were mild in intensity were reported at similar incidences in the LEV and CBZ-IR groups (27.1% and 30.7%, respectively).

One death occurred during the study. One subject in the LEV group had a single TEAE of epilepsy on Day 132 during the Evaluation Period; the event was considered not related to study drug by the investigator. A full narrative for this subject is provided in N01364 CSR Section 12.

Serious TEAEs were reported at similar incidences between the LEV group (9 subjects [4.1%]) and the CBZ-IR group (11 subjects [5.1%]). Serious TEAEs by PT were reported by no more than 1 subject in either treatment group, with the exceptions of status epilepticus (2 subjects [0.9%] in the LEV group and 1 subject [0.5%] in the CBZ-IR group) and abortion induced (1 subject [0.5%] in the LEV group and 2 subjects [0.9%] in the CBZ-IR group). No subjects in the LEV group and 4 subjects (1.9%) in the CBZ-IR group reported serious ADRs.

Overall, TEAEs leading to discontinuation were reported at a lower incidence by subjects in the LEV group (12 subjects [5.5%]) compared with the CBZ-IR group (29 subjects [13.5%]). Similarly, ADRs leading to discontinuation were reported at a lower incidence by subjects in the LEV group (5 subjects [2.3%]) compared with the CBZ-IR group (25 subjects [11.6%]).

There were 4 pregnancies reported during the study; 3 subjects discontinued the study and 3 subjects (1 subject in the LEV group and 2 subjects in the CBZ-IR group) reported induced abortions.

There was no evidence of clinically relevant effects of LEV treatment on laboratory parameters, vital signs, ECG evaluations, or neurological examinations. Laboratory abnormalities related to CBZ-IR included PCS GGT values in 2 subjects and TEAEs of drug induced liver injury related to elevated AST and ALT in 1 subject. Few relevant effects of CBZ-IR treatment on vital signs, ECG evaluations, or neurological examinations were observed.

Paediatric subjects

Of the 28 subjects aged <18 years, 21 subjects reported 101 TEAEs; 11 subjects in the LEV group reported 47 TEAEs, and 10 subjects in the CBZ-IR group reported 54 TEAEs. Most TEAEs were mild or moderate. One subject in the LEV group had an SAE (seizure); 1 subject in the CBZ-IR group had 2 SAEs (lung infection and rash). The event of rash was considered drug related; the other SAEs were considered not related to study drug by the Investigator. All SAEs were severe and resolved. One subject in the LEV group and 4 subjects in the CBZ-IR group discontinued due to an AE (N01364 CSR Listing 7.2). The AEs that led to discontinuation were seizure in the LEV group, and pruritus, 2 events of rash, and seizure in the CBZ-IR group. The events of pruritus and rash in the CBZ-IR group were considered drug related. No subjects aged <18 years died during the study.

Conclusion of the MAH

Results from N01364 show that non-inferiority of monotherapy LEV 1000mg/day compared with CBZ-IR 400mg/day could not be established with respect to effectiveness in Chinese subjects ≥16 years of age recently diagnosed with epilepsy with POS. However, UCB believes that the result of the benefit risk consideration of the monotherapy indication of Keppra in adolescents (aged 16 and 17 years) is positive.

Previous studies have demonstrated that over the complete dose range, LEV is as efficacious as CBZ; however, this could not be demonstrated in N01364 due to the study design, where only the lowest efficacious daily doses of LEV (1000mg) and CBZ-IR (400mg) were assessed. At 1000mg/day, the 6-month seizure freedom rate of LEV in N01364 (47.3%) was lower than in the European PBO-controlled noninferiority study N01061 (59.1%), but very similar to the one (49.2%) seen in the open-label Japanese study N01375. The safety results from the current study support the results from previous LEV studies. Levetiracetam has a good safety profile and is better tolerated than CBZ-IR, with a lower incidence of TEAEs leading to discontinuation and ADRs in N01364.

UCB has investigated possible explanations for why the primary objective was not met in N01364 and concluded that it is likely due to different aspects of the study design. The open-label design includes several sources of potential bias that might have impacted efficacy. Only the lowest efficacious daily doses of LEV and CBZ-IR were assessed in this study, and uptitration was not allowed if a subject experienced a seizure during the Evaluation Period. The criterion excluding subjects who tested positive for human leukocyte antigen major histocompatibility complex, class I, B (HLA-B)* 1502 allele may have biased the results toward CBZ. Subjects with this genotype and randomized to CBZ would have been more likely to

discontinue the study due to hypersensitivity reactions (ie, rash). In addition, the difference in seizure freedom at the dose of LEV 1000mg/day comparing studies N01364 and N01061 might be caused by a higher average disease severity of subjects in N01364, as indicated by slightly higher historical 1-year and 3-month seizure counts for the N01364 study population when compared with the N01061 population.

No changes to the approved EU Product Information for Keppra are proposed following the completion of this study.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

Although the results from N01364 show that non-inferiority of monotherapy LEV 1000mg/day compared with CBZ-IR 400mg/day could not be established with respect to effectiveness in Chinese subjects ≥16 years of age recently diagnosed with epilepsy with POS, the evaluation of the safety data demonstrated that LEV was well tolerated and that the safety profile for LEV monotherapy was similar to the known data. No new safety concerns were identified in this study.

Consequently, the rapporteur agrees with the MAH that no changes to the approved EU Product Information for Keppra are proposed following the completion of this study since no new safety concern appeared in 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