15 December 2016
EMA/CHMP/769369/2016
Human Medicines Evaluation 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/P46/085

## Note

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

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# Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

On September 21st 2016, UCB submitted dossier EMEA/H/C/000277 , containing the final clinical study report (study 01361) ) in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended (Feb 2014), which requires UCB to report new study results in paediatric subjects treated with levetiracetam.

The submission included: - Cover Letter; - Information about the Expert (Clinical); - Information Relating to Clinical Trials - Short critical Clinical Overview and - Clinical Study Report

### *1.1. Steps taken for the assessment*

| | |
|---|---|
| Submission date: | 21 September 2016 |
| Start of procedure: | 17 October 2016 |
| CHMP Rapporteur's preliminary assessment report circulated on: | 21 November 2016 |
| CHMP Rapporteur's updated assessment report circulated on: | n/a |
| CHMP opinion: | 15 December 2016 |

# 2. Assessment of the post-authorisation measure PAM P46 085

# Scientific discussion

### *Information on the development program*

N01361 was designed as an open-label, long-term, and multicenter study conducted in Japan to provide subjects who completed either N01159 or N01363, or who discontinued N01159 due to lack of efficacy, with the opportunity to continue LEV treatment in an open-label manner. This study was planned to be conducted until the date of market approval (i.e., 29 Feb 2016) or completion of development of LEV for the GTC seizure indication. As soon as an approval for the GTC seizure indication was granted, all subjects were to complete a Closeout Visit and to fulfil all obligations of the protocol-defined activities in order to formally bring closure to the study at the institution. The Closeout Visit was to be made within 3 months from the approval date.

### *Information on the pharmaceutical formulation used in the study*

Levetiracetam for oral administration was as follows:

Table 3–1: Study medication in N01361

| Study medication | Active ingredient | Batch number |
|---|---|---|
| Dry syrup 50% | LEV 0.5g in 1g dry syrup | BX1004616 |
| | | LV1361001 |
| | | LV1361002 |
| | | LV1361003 |
| | | LV1361004 |
| 250 mg tablets | LEV 250mg | Not applicable, as no subjects had received any 250mg tablets |
| 500mg tablets | LEV 500mg | 18809/1 |
| | | 18809/2 |
| | | 58862/1 |
| | | 58862/2 |
| | | 121054/1 |
| | | 121054/2 |

LEV=levetiracetam

## *Clinical aspects*

## Description of the study

## Title:

"An open-label, multicenter, long-term follow-up study in Japan to evaluate the safety, tolerability, and efficacy of adjunctive treatment with oral L059 (levetiracetam) in epilepsy subjects with generalized tonic-clonic (GTC) seizures

Sponsor protocol number: N01361"

## Methods

### *Objectives*

The primary objectives of the study were the following:

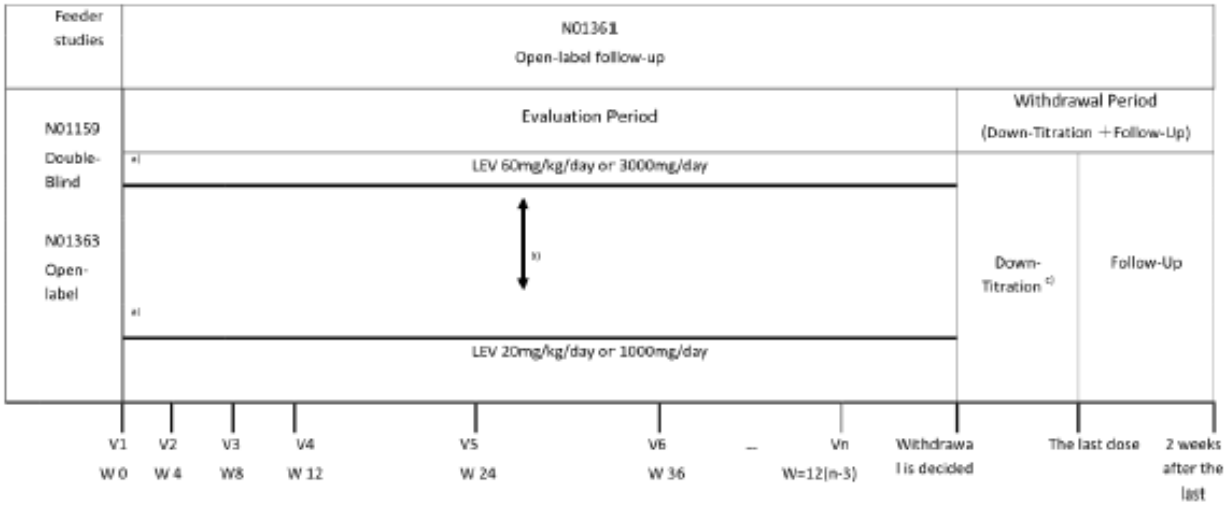
- To provide the LEV treatment to epilepsy subjects in Japan who were judged to benefit from continued treatment with LEV by the investigators and who were willing to continuously receive this drug.
- To evaluate **the safety and tolerability** of long-term administration of LEV at doses up to 60mg/kg/day or 3000mg/day in subjects with epilepsy in Japan who had completed N01363 (This study included Japanese pediatric subjects aged ≥4 to <16 years with uncontrolled GTC seizures; note from the Rapporteur) or N01159 (This study included epilepsy patients aged ≥16 years with generalized tonic-clonic (GTC) seizures; note from the Rapporteur) or had discontinued N01159, due to lack of efficacy.

The secondary objectives were the following:

- To evaluate **the efficacy** of long-term administration of LEV at doses up to 60mg/kg/day or 3000mg/day in subjects with epilepsy in Japan who had completed N01159 or N01363 or who had discontinued N01159 due to lack of efficacy.

***Study design***

**Figure 3–1: Schematic diagram**




LEV=levetiracetam; V=visit; W=week

[a] The individual starting dose for each subject was the same dose prescribed during the Evaluation Period of N01159 or N01363.

[b] The LEV dosage for each subject during the Evaluation Period was decided by his/her age and weight.

- Subjects ≥16 years of age: 1000mg/day to 3000mg/day
- Subjects weighing ≥50kg and <16 years of age: 1000mg/day to 3000mg/day
- Subjects weighing <50kg and <16 years of age: 20mg/kg/day to 60mg/kg/day

If a dose adjustment became necessary, the investigator increased or decreased the dose for a 2-week interval or longer. Each increase or decrease in the dose was not to exceed 20mg/kg/day or 1000mg/day for the 2-week interval.

[c] When the subject needed to discontinue LEV treatment or to terminate the study participation, in principle, the LEV dose was down-titrated for a 2-week interval or longer and the dose decrement was not to exceed 20mg/kg/day or 1000mg/day.

N01361 was an open-label follow-up of N01159 and N01363 and was designed to assess the long-term safety and efficacy of oral LEV in Japanese subjects aged ≥4 years with GTC seizures. This study consisted of the following periods:

☐ Evaluation Period

A visit was scheduled every 12 weeks. However, Visits 1 through 4 occurred at 4-week intervals for the subjects from N01159 to ensure subjects' safety. The dose and duration of exposure to LEV in the subjects from N01159 were not disclosed at the time of entry in this study, due to blinding of N01159. Visit 2 and Visit 3 allowed the subjects from N01159 to be monitored by the investigators. The subjects from N01363 did not have to complete Visit 2 and Visit 3.

All subjects initially received open-label LEV treatment at the prescribed dose of the feeder studies, N01159 or N01363.

Once the dose and mode of administration of the concomitant AED(s) were stable for the 4 consecutive weeks prior to the Evaluation Period, the AED was to be continued at the same dose and then the dose of LEV was adjusted at the investigator's discretion in the range from 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day during this period. The investigators increased or decreased the dose for a 2-week interval or longer, when a dose adjustment was necessary. Each increase or decrease in the dose was not to exceed 20mg/kg/day or 1000mg/day for the 2-week interval.

☐ Withdrawal Period

A subject entered the Withdrawal Period when the subject or investigators decided to discontinue treatment with LEV. This period consisted of a Down-Titration Period and a Follow-Up Period.

☐ Down-Titration Period

The dose of LEV was reduced as gradually as possible to ensure the subject's safety. The recommended dose decrement was 1000mg/day or 20mg/kg/day for a 2-week interval or longer as follows. The 3000mg/day or 60mg/kg/day dosage was decreased to 2000mg/day or 40mg/kg/day for the first 2 weeks and then the dosage was decreased again to 1000mg/day or 20mg/kg/day for 2 additional weeks. The 2000mg/day or 40mg/kg/day dose was decreased to 1000mg/day or 20mg/kg/day for 2 weeks, and then LEV treatment was discontinued. The 1000mg/day or

20mg/kg/day dose was immediately discontinued without down-titration at the time the discontinuation was decided.

☐ Follow-Up Period (2 weeks)

The subject entered the Follow-Up Period, when the last dose of LEV was administered. A final visit was required for all subjects at any time during the 2 weeks after the last dose of LEV.

The planned study duration was from May 2011 until the date of approval of LEV treatment for the GTC seizure indication and until the time when the sponsor decided to discontinue the development for the GTC seizure indication.The study duration for each subject varied depending on the date when the individual subject received the first LEV dose in this study.

**Table 3–4: Schedule of study assessment for subjects**

| Assessments \ Study Period | Evaluation | | | | | | | | | Withdrawal | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 0 | 4 | 8 | 12 | 24 | 36 | 48 | 60 | … | Down-Titration | | Follow-Up |
| Visit | 1 | 2 [a] | 3 [a] | 4 | 5 | 6 | 7 | 8 | … | | | |
| A visit window (days) | - | ±7 | ±7 | ±14 [b] | ±14 | ±14 | ±14 | ±14 | | EDV [c] (Start of Down-Titration) | Stopped Treatment | SFV after 2 weeks |
| Informed consent [d] | X | | | | | | | | | | | |
| Inclusion-exclusion criteria | X | | | | | | | | | | | |
| Childbearing potential [e] | X | | | | | | | | | | | |
| Vital signs | X [f] | X | X | X | X | X | X | X | X | X | X | X |
| Body weight | X [f] | X | X | X | X | X | X | X | X | X | X | X |
| Height [g] | X | | | | X | | X | | X | | | X |
| ECG [h] | X [i] | | | | X | | X | | X [k] | X | | X |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X |
| Seizure event recording | X [f] | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X |
| Medical procedures | X | X | X | X | X | X | X | X | X | X | X | X |
| Laboratory tests (including hCG) | X [f] | X | X | X | X | X | X | X | X | X | X | X |
| IMP dispense/retrieval | X | X | X | X | X | X | X | X | X | X | X [j] | |
| Compliance check | | X | X | X | X | X | X | X | X | X | X | |
| DRC dispense/retrieval | X [k] | X | X | X | X | X | X | X | X | X | X [l] | X |

DRC=daily record card; ECG=electrocardiogram; EDV=Early Discontinuation Visit; hCG=human chorionic gonadotropin; IMP=investigational medicinal product; SFV=Safety Follow-Up Visit

[a] Visits for subjects from N01159 only.

[b] A visit window was ±7 days for only the subjects from N01159.

[c] Early Discontinuation Visit. A subject on the LEV at 60mg/kg/day or 3000mg/day was to undergo a 4-week down-titration and a 2-week follow-up at the Withdrawal Period. A subject on the LEV at 40mg/kg/day or 2000mg/day was to undergo a 2-week down-titration and a 2-week follow-up at the Withdrawal Period. A subject on the LEV at 20mg/kg/day or 1000mg/day was to undergo a 2-week follow-up at the Withdrawal Period.

[d] Informed consent must have been obtained during the Evaluation Period of N01159.

[e] When a subject was reported to have the first menstruation during the study, the pregnancy test was performed.

[f] The measurements obtained at the last visit of N01159 (Visit 10) or N01363 (Visit 9) were used as the data for Visit 1 in this study.

[g] For subjects from N01159, height was measured at Visit 1 and at the last visit if the subject prematurely discontinued (14 days after the LEV was discontinued). For subjects from N01363, height was measured at the last visit of N01363 was used as the data for the Visit 1 in this study and the height was measured every 24 weeks.

[h] An ECG was performed for all subjects who entered this study at 24-week intervals.

[i] For subjects from N01159, the ECG was performed at Visit 1. For subjects from N01363, the ECG performed at Visit 9 in N01363 was used in the data for Visit 1 in this study. If a clinical abnormality was detected in the data from N01363, a repeat of the ECG test was performed at an unscheduled visit in this study.

[j] The unused IMP was only returned.

[k] The DRC was only dispensed.

[l] The DRC was only retrieved.

***Study population /Sample size***

The planned number of subjects for N01361 was the number of the Japanese subjects who had completed either N01159 or N01363 in Japan, or who had discontinued N01159 in Japan due to lack of efficacy (N01159 included Chinese and Japanese subjects). The number of sites for N01361 approximately matched the number of sites that enrolled subjects who participated in either N01159 or N01363.

**Inclusion criteria**:

**To be eligible** to participate in this study, all of the following criteria were to be met:

1. For the subjects from N01159: an IRB-approved written ICF was signed and dated by the subject. If the subject was a minor or mentally retarded, the parent(s)/legal representative signed and dated the

consent form. A patient who was a minor or mentally retarded, but judged by the investigator as capable of consenting personally signed and dated the ICF or a specific IRB-approved assent form. For the subjects from N01363: an IRB-approved written informed consent was signed and dated by the patient's parent or legal representative. The consent form or a specific IRB-approved assent form was signed and dated by the patient if the investigators judged that the subject was capable of consenting.
2. The subject in Japan completed either N01159 or N01363 or discontinued N01159 due to lack of efficacy.
3. The subject who was judged to benefit from continued treatment with LEV by the investigators.
4. Female subjects of childbearing potential (without a history of hysterectomy or bilateral oophorectomy) were eligible if they used a medically accepted contraceptive method for the duration of the study participation. They must have understood and accepted that pregnancy was to be avoided during participation in the study. Also, they were to provide a negative pregnancy test result at all Visits to confirm the absence of pregnancy. Female subjects not of childbearing potential (no occurrence of the first menstruation, bilateral oophorectomy, tubal ligation, or complete hysterectomy) were eligible.
5. The subject and parent(s)/legal representative were considered reliable and capable of adhering to the protocol (e.g., able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the investigator.

**Exclusion criteria:**

Subjects with multiple protocol deviations during N01159 or N01363, such as missing laboratory data, and low or noncompliance with the study medication, and who the investigator considered not to have the potential to have deviations stopped were ineligible to participate in this study. Subjects meeting any of the withdrawal criteria (see Removal of subjects from therapy or assessment) were also ineligible.

Removal of subjects from therapy or assessment

Subjects were free to withdraw from the study at any time, without prejudice to their continued care. Subjects were to be withdrawn from the study if any of the following events occurred:

1. The subject or parent(s)/legal representative withdrew consent to participate in the study for any reason.
2. The subject developed an illness or worsened laboratory test findings that would have led to noncompliance with the study procedures or medications.
3. The subject was found to be ineligible in terms of the efficacy and safety evaluations after the start of the study.
4. The subject developed an adverse event (AE) that would have interfered with his/her continued participation.
5. Confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
6. The subject became lost to follow-up, which would have stopped his/her continued participation.
7. The subject was noncompliant with the protocol for reasons other than those mentioned above.
8. The investigators requested withdrawal of the subject at their discretion.

***Treatment***

Tablets and dry syrup for oral administration were used as study treatment. The individual starting dose in this study was the same dose prescribed at the end of the Evaluation Period of N01159 or N01363. Once the dose and mode of administration of the concomitant AED(s) were stable for the 4 consecutive weeks prior to the Evaluation Period, the AED was to be continued at the same dose and then the LEV dose was increased or decreased at the investigator's discretion in the dose ranges provided in Table 3−2. A minimum interval of 2 weeks was required for a change in the LEV dose and increase or decrease in the LEV dose was not to exceed 20mg/kg/day or 1000mg/day for each 2-week interval. Subjects from N01363 who weighed <20kg continued receiving the LEV dry syrup at 20mg/kg/day to 60mg/kg/day and those who weighed ≥20kg were allowed to choose one of the formulations: LEV dry syrup 20mg/kg/day to 60mg/kg/day or LEV tablet 1000mg/day to 3000mg/day. The dosage for the dry syrup was determined using the subject's weight at each visit (please see Table

3–2). The daily dose for the tablet was determined based on the equivalent dosage to dry syrup dosage (please see Table 3–3).

**Table 3–2: Dosage by subject's weight**

| Age | Weight | Dosage |
|---|---|---|
| ≥16 years | – | 1000mg/day, 2000mg/day, or 3000mg/day |
| ≥4 and <16 years | ≥50kg | 1000mg/day, 2000mg/day, or 3000mg/day |
| | <50kg | 20mg/kg/day, 40mg/kg/day, or 60mg/kg/day |

Data source: N01361 Protocol Amendment 2 Table 7-2

**Table 3–3: Daily dose of the tablet equivalent to dry syrup determined by weight at the time of change in the use of tablet (twice daily)**

| Equivalent dosage / Weight | Dry syrup 20mg/kg/day | Dry syrup 40mg/kg/day | Dry syrup 60mg/kg/day |
|---|---|---|---|
| ≥20kg to <30kg | 250mg tablet × 2 | 250mg tablet × 4<br>or<br>500mg tablet × 2 | 250mg tablet × 6<br>or<br>250mg tablet × 2 and<br>500mg tablet × 2 |
| ≥30kg to <40kg | 250mg tablet × 2 | 250mg tablet × 6<br>or<br>250mg tablet × 2 and<br>500mg tablet × 2 | 250mg tablet × 8<br>or<br>500mg tablet × 4 |
| ≥40kg to <50kg | 250mg tablet × 4<br>or<br>500mg tablet × 2 | 250mg tablet × 8<br>or<br>500mg tablet × 4 | 250mg tablet × 10<br>or<br>250mg tablet × 2 and<br>500mg tablet × 4 |
| ≥50kg | 250mg tablet × 4<br>or<br>500mg tablet × 2 | 250mg tablet × 8<br>or<br>500mg tablet × 4 | 250mg tablet × 12<br>or<br>500mg tablet × 6 |

Data source: N01361 Protocol Amendment 2 Table 7-3

The mode of administration was as follows:

- Tablets

  Subjects received 2 equal oral doses of LEV tablets in the morning and evening.

- Dry syrup

  Subjects received 2 equal doses of the LEV dry syrup 50% dissolved in water, 1 in the morning and 1 in the evening. The subjects were encouraged to take the LEV dry syrup 50% dissolved in the smallest volume of water necessary, if possible, followed by a glass of water.

Please refer to the body text for the study directives regarding concomitant medications.(p20-21).

Duration of treatment

The study duration for each subject varied depending on the date when the individual subject received the first LEV dose in this study. The study began with an Evaluation Period, which consisted of visits at

12-week interval starting from the time of the first LEV dose until the time of determination to discontinue LEV treatment or to terminate study participation. The Evaluation Period was followed by the Withdrawal Period (2 to 6 weeks), comprising the Down-Titration Period (0 to 4 weeks depending on the LEV dose received during the Evaluation Period) and the Follow-Up Period (2 weeks).

The mean overall duration of exposure to study medication for the Safety Set (SS) was 1098.8 days.

***Outcomes/endpoints***

Safety: The following safety information was collected during the study:

Adverse events (AEs)
Serious adverse events,

The following AEs must have been reported immediately: SAE:
- AE that the investigator classified as serious by the definition of a SAE (see body text)
regardless of causality
-Suspected transmission of an infectious agent via a medicinal product

Laboratory measurements: parameters of hematology, blood biochemistry, and urinalysis
Other safety measurements: 12-lead electrocardiograms, vital signs, body weight and height
Efficacy: The efficacy variable was the percentage reduction in GTC seizure frequency per week over the Evaluation Period from either of the Combined Baseline Periods of the previous studies (N01159 or N01363).

The epileptic seizures were classified according to (Commission on Classification and Terminology of the International League Against Epilepsy [ILAE], 1981).

The subject, parent(s)/family member, or other people (eg, a legal representative, school teacher, or child caregiver, etc) was to commit to recording the following information on the DRCs: date/time of the seizure onset, frequency, and symptoms of the seizure, the use of LEV treatment, concomitant AEDs, and concomitant non-AEDs, including as-needed medication use and any other symptoms to assess the presence of any AEs. The investigator discussed any written information in the DRCs with the subject and/or the parent(s)/legal representative at each visit, in order to determine and indicate if recorded events were to be considered AEs. As a result of the discussion, the investigator confirmed the assessment of the seizure written in the DRCs as well as in any of the source documentation, such as medical charts, in addition to entering it into the eCRF.

The other efficacy variables were as follows:

1. GTC seizure frequency per week by 12-week window over the Evaluation Period
2. The percentage reduction from either of the Combined Baseline Periods of the previous studies (N01159 or N01363) in GTC seizure frequency per week by 12-week window over the Evaluation Period
3. GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from either of the Combined Baseline Periods of the previous studies (N01159 or N01363 in the frequency of GTC seizures) by 12-week window during the Evaluation Period
4. GTC seizures 75% responder rate (the proportion of subjects with 75% or more reduction from either of the Combined Baseline Periods of the previous studies [N01159 or N01363] in the frequency of GTC seizures) by 12-week window during the Evaluation Period.
5. The cumulative probability of a subject being continuously seizure-free since the beginning of this study by 12-week window during the Evaluation Period
6. The percentage of subjects with 12-week seizure freedom duration at any time during the study
7. Responder rate in myoclonic seizure days per week. A responder was defined as a subject with a >50% reduction in myoclonic seizure days (equal to day[s] with myoclonic seizure[s]) per week from

either of the Prospective Baseline Periods of the previous studies (N01159 or N01363) to the Evaluation Period in this study.

8. All seizure days per week by 12-week window over the Evaluation Period.

9. The percentage reduction from either of the Prospective Baseline Periods of the previous studies (N01159 or N01363) in all seizure days per week by 12-week window over the Evaluation Period

### *Statistical Methods*

Descriptive statistics were used to provide an overview of the primary, secondary, and other variable results.

For categorical parameters, the number and percentage of subjects in each category were presented. The denominator for percentages was based on the number of subjects that was appropriate for the purpose of analysis.

For continuous parameters, descriptive statistics included the number of subjects, mean, standard deviation, median, interquartile range (QI [25th percentile] to Q3 [75th percentile]), minimum, and maximum.

Baseline values for the safety and efficacy analyses in N01361 were the data collected at Baseline of the feeder studies, N01159 and N01363.

All enrolled subjects who signed and dated the informed consent form were included in the ES.

All safety analyses were performed on the SS. Safety data were presented for subjects by feeder study, N01159 or N01363, and for all subjects who enrolled in N01361.

All efficacy analyses were performed in a descriptive manner for FAS, which was a subset of the SS that consisted of all subjects with evaluable Baseline and post-Baseline values of GTC seizure frequency as the efficacy analysis. Efficacy data were presented overall and by feeder study for the safety analyses as well as by the treatment groups of N01159 (ie, N01159 LEV, N01159 Placebo [PBO]).

Descriptive statistics for exposure duration and mean daily dose of LEV were presented overall, by period, and by 12-week window.

The safety of LEV was the primary endpoint in this study and was assessed via AEs, including ADRs, laboratory data, ECG parameters, vital signs, body weight, and height.

Analysis sets:

All subjects screened: This set consisted of subjects who signed and dated the ICF and were screened for eligibility for this study.

Enrolled Set (ES): The ES consisted of subjects who enrolled in this study.

Safety Set (SS): The SS consisted of subjects who received at least 1 (partial) dose of LEV.

Full Analysis Set (FAS): The FAS was a subset of the SS, consisting of all subjects with evaluable Baseline and post-Baseline values of GTC seizure frequency as the efficacy analysis, and excluded those who seriously violated GCP. The FAS was used for the efficacy analyses.

## Results

### *Subject disposition*

A total of 44 subjects enrolled in N01361, including 33 subjects from N01159 and 11 subjects from N01363. Of the 44 subjects who enrolled in N01361, a majority of subjects reached Week 144 (range across Weeks 24 through 144: 68.2% to 95.5%) and approximately half reached Week 168 (52.3%). A total of 34 subjects (77.3%) completed the study, and 10 subjects (22.7%) discontinued the study. Of the 10 subjects who discontinued, 4 subjects (9.1%) discontinued due to an adverse event (AE), 4 subjects (9.1%) withdrew consent, and 2 subjects (4.5%) discontinued for other reasons (‘subject moves a long distance from hospital’ and ‘withdrawal criteria #3’). Of the subjects who discontinued

due to an AE, 3 subjects (9.1%) from N01159 and 1 subject (9.1%) from N01363 discontinued due to non-serious, nonfatal AEs. Two additional subjects, withdrew their informed consents to participate in N01361 during the feeder study (N01159) and were regarded as feeder study non-completers, who did not meet inclusion criterion #2.

A total of 14 subjects were <18 years old at study entry. Five of these subjects were female; 9 were male. All subjects received LEV.

**Table 4–1: Subjects less than 18 years old at study entry in N01361**

| Age (years) | Sex | Feeder study and treatment group | Subject disposition |
|---|---|---|---|
| 17 | F | N01159 PBO | Completed |
| 4 | M | N01363 | Completed |
| 12 | F | N01363 | Completed |
| 17 | M | N01159 LEV | Completed |
| 12 | M | N01363 | Completed |
| 17 | M | N01159 LEV | Completed |
| 8 | F | N01363 | Completed |
| 14 | F | N01363 | Completed |
| 4 | M | N01363 | Completed |
| 15 | M | N01363 | Discontinuation due to adverse event |
| 13 | F | N01363 | Completed |
| 4 | M | N01363 | Completed |
| 6 | M | N01363 | Completed |
| 9 | M | N01363 | Discontinuation due to consent withdrawn |

F=female; LEV=levetiracetam; M=male; PBO=placebo

Note: All subjects initially received open-label LEV treatment at the prescribed dose of the feeder studies, N01159 or N01363. The dose of LEV was adjusted at the investigator's discretion during the Evaluation Period.

Data sources: N01361 CSR Listing 1.3, N01361 CSR Listing 2.1

***Safety results***

Overall, a total of 44 subjects received at least 1 LEV dose ranging from 786.8mg/day to 3000mg/day. The safety results for this study are as follows:

The **mean overall duration of exposure to study medication** was 1098.8 days, and was higher for subjects from N01363 (1163.2 days) compared with subjects from N01159 (1077.4 days). The longest exposure to LEV in this study was 1708 days (approximately 4.7 years). The mean daily dose of LEV overall was 2126.75mg/day, with a lower mean daily dose for paediatric subjects from N01363 (1723.85mg/day), who were dosed by weight, compared with adult subjects from N01159 (2261.05mg/day).

A total of 15 subjects (34.1%) reported **pre-treatment** AEs (11 subjects [33.3%] from N01159 and 4 subjects [36.4%] from N01363). The only pre-treatment AE by PT reported by >1 subject overall was somnolence (reported by 4 subjects [9.1%]).

Overall, 43 subjects (97.7%) reported a total of 626 TEAEs **during the study**, including 32 subjects (97.0%) from N01159 and 11 subjects (100%) from N01363. Of the individual TEAEs with an incidence of ≥10% overall, the most frequently reported were nasopharyngitis (35 subjects [79.5%]), convulsion (16 subjects [36.4%]), and dental caries (11 subjects [25.0%]). There was no clear pattern of onset by 12-week window overall or by feeder study for any TEAE with an overall incidence of ≥10% across the study duration, with the exception of somnolence (10 subjects [22.7%]) and convulsion. During the first 12 weeks of the study, 5 of 10 subjects had the onset of somnolence and 4 of 16

subjects had the onset of convulsion. Four of the 5 subjects who had somnolence and 0 of 4 subjects who experienced convulsion during the first 12 weeks of the study had their first exposure to LEV in this study (ie, had received PBO during N01159).

No **deaths** occurred during the study. A total of 13 subjects (29.5%) reported 29 SAEs during the study, 1 of which was considered related to study medication by the investigator (ADR of breast adenoma). The only SAE by PT that was reported by >1 subject was influenza (reported by 2 subjects [4.5%]; 1 subject from each feeder study).

Four subjects (9.1%) **discontinued the study due to** 5 **TEAEs**. The only TEAE by PT that led to discontinuation of >1 subject was aggression (reported by 2 subjects [4.5%]; 1 subject from each feeder study). The TEAEs of aggression, logorrhea, and gait disturbance were considered related to study medication by the investigator.

A total of 22 subjects (50.0%) reported ADRs during the study, including 17 subjects (51.5%) from N01159 and 5 subjects (45.5%) from N01363. The only **ADRs reported by >1 subject** overall were somnolence (8 subjects [18.2%]), electrocardiogram QT prolonged (3 subjects [6.8%]), and aggression, weight increased, and headache (2 subjects [4.5%] each). The incidence of ADRs occurring in >1 subject was low, making it difficult to interpret the onset of ADRs by 12-week window. Nevertheless, 5 of the 8 subjects who reported the most frequent ADR of somnolence did so within the first 12 weeks.

☐ The majority of **TEAEs** were **mild** (42 subjects [95.5%]) or **moderate** (23 subjects [52.3%]) in intensity. A total of 4 subjects (9.1%) reported 7 severe TEAEs during the study, all of which were **serious**, and none were considered by the investigator to be related to study medication.

All **ADRs** were **mild** (20 subjects [45.5%]) or **moderate** (7 subjects [15.9%]) in intensity. No severe ADRs were reported during the study.

A total of 8 subjects (18.2%) reported other significant TEAEs in the Psychiatric disorders SOC; 4 of these TEAEs were considered to be related to study medication (ADRs of aggression [2 events], irritability, and logorrhea). Aggression and stress were reported by 2 subjects (4.5%) each, while adjustment disorder, insomnia, irritability, logorrhea, nightmare, and sleep disorder were each reported by 1 subject (2.3%). The TEAEs of aggression and logorrhea led to discontinuation from the study. None of these TEAEs were serious or severe.

**Clinical laboratory evaluation:** Changes from Baseline in mean and median hematology and blood chemistry values did not show any clinically meaningful trends over time and were generally similar across feeder studies. Few subjects had hematology or blood chemistry values that shifted from not PCS at Baseline to PCS during the study. There were few TEAEs related to abnormal hematology, abnormal blood chemistry, or urinalysis values.
Hematology
neutrophil count decreased in 1 subject from N01159, and 2 events of white blood cell count decreased in 1 subject from N01363 (Table 10.4) were considered related to study medication by the investigator.
Blood chemistry
hepatic function abnormal was considered related to study medication by the investigator.

**Vital sign measurements over time:** Changes from Baseline in mean and median vital sign values (systolic and diastolic blood pressure, pulse rate, body weight, height, and body temperature) were generally small. Few shifts in vital sign results from not possibly clinically significant (PCS) at Baseline to possibly clinically significant post-Baseline were reported. Few TEAEs related to vital signs were reported. The most frequently reported TEAEs related to abnormal vital signs were pyrexia (8 subjects

[18.2%]) and weight increased (5 subjects [11.4%]). Of these TEAEs, all were mild in intensity, nonserious, did not lead to discontinuation, were considered not related to study medication by the investigator, and resolved, with the exception of a TEAE of weight increased in 1 subject that was reported as not resolved, and TEAEs of weight increased in 2 subjects that were considered related to study medication.

**Electrocardiogram findings:** Two subjects from N01363 and 1 subject from N01159 had shifts from normal ECG values at Baseline to abnormal, clinically significant post-Baseline ECG values. These were all reported as TEAEs (electrocardiogram QT prolonged) and were mild in intensity, nonserious, did not lead to discontinuation, were considered related to study medication by the investigator, and resolved.

***Efficacy results***

**Percentage reduction in GTC seizure frequency per week over the Evaluation Period:** The median frequency of GTC seizures per week improved between the Combined Baseline Period and the Evaluation Period in N01361 overall and by feeder study.

**Table 9–1: Percentage reduction in GTC seizure frequency per week over the Evaluation Period from the Combined Baseline Periods of the feeder studies for N01361 subjects overall (FAS)**

| Statistic | GTC seizure frequency per week | | Percentage reduction (%) |
|---|---|---|---|
| | Combined Baseline | Evaluation Period | |
| **N01159 N=32** | | | |
| n | 32 | | |
| Mean (SD) | 0.76 (0.51) | 0.29 (0.51) | 72.08 (39.37) |
| Median | 0.60 | 0.04 | 94.73 |
| 95% CI for median | 0.51, 0.76 | 0.01, 0.20 | 75.27, 97.48 |
| Q1, Q3 | 0.48, 0.76 | 0.01, 0.39 | 49.36, 98.59 |
| Min, max | 0.38, 2.67 | 0.00, 2.03 | -41.24, 100.00 |
| **N01363 N=11** | | | |
| n | 11 | | |
| Mean (SD) | 5.94 (10.94) | 5.38 (12.81) | 54.45 (43.95) |
| Median | 1.63 | 0.75 | 64.12 |
| 95% CI for median | 0.75, 13.74 | 0.01, 11.87 | 13.00, 99.80 |
| Q1, Q3 | 0.75, 3.69 | 0.01, 1.42 | 13.00, 99.21 |
| Min, max | 0.50, 36.88 | 0.00, 42.58 | -15.48, 100.00 |
| **N01361 N=43** | | | |
| n | 43 | | |
| Mean (SD) | 2.08 (5.82) | 1.59 (6.66) | 67.57 (40.80) |
| Median | 0.64 | 0.05 | 92.07 |
| 95% CI for median | 0.51, 0.86 | 0.02, 0.46 | 64.64, 97.16 |
| Q1, Q3 | 0.50, 1.19 | 0.01, 0.71 | 38.40, 99.21 |
| Min, max | 0.38, 36.88 | 0.00, 42.58 | -41.24, 100.00 |

CI=confidence interval; FAS=Full Analysis Set; GTC= generalized tonic-clonic; max=maximum; min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation
Note: The information of Combined Baseline presented was taken from the feeder studies (N01159, N01363).
Note: 'N01159' and 'N01363' denote subjects previously enrolled in the respective feeder study.
Data source: Table 8.1.1

The median percentage reduction in GTC seizure frequency per week over the Evaluation Period from either of the Combined Baseline Periods of the feeder studies (N01159 or N01363) was 92.07%; the median percentage reduction was higher in subjects from N01159 (94.73%) compared with subjects from N01363 (64.12%). Subjects from N01363 had a higher median Baseline seizure frequency (1.63 seizures/week) compared with subjects from N01159 (0.60 seizures/week).

**Percentage reduction in GTC seizure frequency per week by 12-week window over the Evaluation Period** : The median frequency of GTC seizures per week improved between the Combined Baseline Period and the Evaluation Period in N01361 by each 12-week window, overall and by feeder study. The median percentage reduction in GTC seizure frequency per week was ≥83.63% in

N01361 subjects overall across all 12-week windows during the Evaluation Period.(cf. Table 9.2, CSRp.94)

Table 9-2: Percentage reduction in GTC seizure frequency per week by 12-week window over the Evaluation Period for N01361 subjects overall (FAS)

| Statistic | GTC seizure frequency per week | | Percentage reduction (%) |
|---|---|---|---|
| | Combined Baseline | Evaluation Period | |
| | N01361 Total N=43 | | |
| **Day 1 to ≤12 weeks (n=43)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.19) | 0.08 (0.00, 0.75) | 83.63 (36.79, 100.00) |
| **>12 weeks to ≤24 weeks (n=41)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.08 (0.00, 0.42) | 83.63 (50.89, 100.00) |
| **>24 weeks to ≤36 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.08 (0.00, 0.33) | 89.09 (62.59, 100.00) |
| **>36 weeks to ≤48 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.00 (0.00, 0.42) | 100.00 (51.53, 100.00) |
| **>48 weeks to ≤60 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.08 (0.00, 0.42) | 89.09 (61.11, 100.00) |
| **>60 weeks to ≤72 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.00 (0.00, 0.50) | 100.00 (72.38, 100.00) |
| **>72 weeks to ≤84 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 0.91) | 0.00 (0.00, 0.33) | 100.00 (65.70, 100.00) |
| **>84 weeks to ≤96 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 0.91) | 0.00 (0.00, 0.17) | 100.00 (75.69, 100.00) |
| **>96 weeks to ≤108 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 0.91) | 0.00 (0.00, 0.33) | 100.00 (68.82, 100.00) |
| **>108 weeks to ≤120 weeks (n=36)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.03) | 0.00 (0.00, 0.21) | 100.00 (74.75, 100.00) |
| **>120 weeks to ≤132 weeks (n=34)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.00 (0.00, 0.50) | 100.00 (72.91, 100.00) |
| **>132 weeks to ≤144 weeks (n=31)** | | | |
| Median (Q1, Q3) | 0.64 (0.50, 1.15) | 0.00 (0.00, 0.33) | 100.00 (73.26, 100.00) |
| **>144 weeks to ≤156 weeks (n=28)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.18) | 0.00 (0.00, 0.38) | 100.00 (73.31, 100.00) |
| **>156 weeks to ≤168 weeks (n=24)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.00) | 0.00 (0.00, 0.46) | 100.00 (72.19, 100.00) |

| Statistic | GTC seizure frequency per week | | Percentage reduction (%) |
|---|---|---|---|
| | Combined Baseline | Evaluation Period | |
| | N01361 Total N=43 | | |
| **>168 weeks to ≤180 weeks (n=21)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.15) | 0.00 (0.00, 0.00) | 100.00 (100.00, 100.00) |
| **>180 weeks to ≤192 weeks (n=17)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.63) | 0.00 (0.00, 0.25) | 100.00 (84.62, 100.00) |
| **>192 weeks to ≤204 weeks (n=17)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.63) | 0.00 (0.00, 0.50) | 100.00 (70.65, 100.00) |
| **>204 weeks to ≤216 weeks (n=13)** | | | |
| Median (Q1, Q3) | 0.63 (0.51, 1.15) | 0.00 (0.00, 0.08) | 100.00 (92.72, 100.00) |
| **>216 weeks to ≤228 weeks (n=12)** | | | |
| Median (Q1, Q3) | 0.61 (0.50, 0.95) | 0.00 (0.00, 0.38) | 100.00 (85.07, 100.00) |
| **>228 weeks to ≤240 weeks (n=10)** | | | |
| Median (Q1, Q3) | 0.57 (0.50, 1.15) | 0.00 (0.00, 0.92) | 100.00 (74.71, 100.00) |
| **>240 weeks to ≤252 weeks (n=5)** | | | |
| Median (Q1, Q3) | 0.50 (0.38, 0.63) | 0.00 (0.00, 0.00) | 100.00 (100.00, 100.00) |

FAS=Full Analysis Set; GTC=generalized tonic-clonic; Q1=25th percentile; Q3=75th percentile
Note: The information of Combined Baseline presented was taken from the feeder studies (N01159, N01363).
Note: 'N01159' and 'N01363' denote subjects previously enrolled in the respective feeder study.
Data source: Table 8.1.2

**50%Responder rate in GTC seizures by 12-week window during the Evaluation Period:** The GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from either of the Combined Baseline Periods of the feeder studies [N01159 or N01363] in the frequency of GTC seizures) was ≥67.4% in N01361 subjects overall across all 12-week windows during the Evaluation Period. (cf. Table 9.3, CSRp.98)

Table 9-3: 50%responder rate in GTC seizures by 12-week window during the Evaluation Period (FAS)

| Statistic | N01159 Total N=32 | N01363 N=11 | N01361 Total N=43 |
|---|---|---|---|
| **>156 weeks to ≤168 weeks** | | | |
| n/Nobs | 12/16 | 8/8 | 20/24 |
| Rate (%) | 75.0 | 100 | 83.3 |
| Exact 95% CI | 47.6, 92.7 | 63.1, 100 | 62.6, 95.3 |
| **>168 weeks to ≤180 weeks** | | | |
| n/Nobs | 12/14 | 7/7 | 19/21 |
| Rate (%) | 85.7 | 100 | 90.5 |
| Exact 95% CI | 57.2, 98.2 | 59.0, 100 | 69.6, 98.8 |
| **>180 weeks to ≤192 weeks** | | | |
| n/Nobs | 10/12 | 5/5 | 15/17 |
| Rate (%) | 83.3 | 100 | 88.2 |
| Exact 95% CI | 51.6, 97.9 | 47.8, 100 | 63.6, 98.5 |
| **>192 weeks to ≤204 weeks** | | | |
| n/Nobs | 10/12 | 5/5 | 15/17 |
| Rate (%) | 83.3 | 100 | 88.2 |
| Exact 95% CI | 51.6, 97.9 | 47.8, 100 | 63.6, 98.5 |
| **>204 weeks to ≤216 weeks** | | | |
| n/Nobs | 9/10 | 3/3 | 12/13 |
| Rate (%) | 90.0 | 100 | 92.3 |
| Exact 95% CI | 55.5, 99.7 | 29.2, 100 | 64.0, 99.8 |
| **>216 weeks to ≤228 weeks** | | | |
| n/Nobs | 9/10 | 2/2 | 11/12 |
| Rate (%) | 90.0 | 100 | 91.7 |
| Exact 95% CI | 55.5, 99.7 | 15.8, 100 | 61.5, 99.8 |
| **>228 weeks to ≤240 weeks** | | | |
| n/Nobs | 7/8 | 1/2 | 8/10 |
| Rate (%) | 87.5 | 50.0 | 80.0 |
| Exact 95% CI | 47.3, 99.7 | 1.3, 98.7 | 44.4, 97.5 |

| Statistic | N01159 Total N=32 | N01363 N=11 | N01361 Total N=43 |
|---|---|---|---|
| **>240 weeks to ≤252 weeks** | | | |
| n/Nobs | 3/4 | 1/1 | 4/5 |
| Rate (%) | 75.0 | 100 | 80.0 |
| Exact 95% CI | 19.4, 99.4 | 2.5, 100 | 28.4, 99.5 |

CI=confidence interval; FAS=Full Analysis Set; GTC=generalized tonic-clonic
Note: Nobs refers to the number of subjects with ≥1 nonmissing measurement during the Evaluation Period.
Note: Generalized tonic-clonic seizures 50% responder rate was defined as proportion of subjects with 50% or more reduction from Combined Baseline Periods of the feeder studies in the frequency of GTC seizures.
Note: 'N01159' and 'N01363' denote subjects previously enrolled in the respective feeder study.
Data source: Table 8.1.3

**Responder rate at 75% in GTC seizures by 12-week window during the Evaluation Period**: The GTC seizures 75% responder rate (the proportion of subjects with 75% or more reduction from either of the Combined Baseline Periods of the feeder studies [N01159 or N01363] in the frequency of GTC seizures) was ≥58.5% in N01361 subjects overall across all 12-week windows during the Evaluation Period.( cf. Table 8.1.4 , tables p149)

**Cumulative probability of seizure freedom by 12-week window during the Evaluation Period:** The cumulative probability of a subject being continuously seizure-free since the beginning of this study by 12-week window during the Evaluation Period decreased from 34.73% at 12 weeks to 14.88% from 108 weeks onward. (cf. Table 8.1.5., tables p155)

N01361

Table 8.1.5
Cumulative Probability of Seizure-Free by 12-week Window during the Evaluation Period
Analysis Set: Full Analysis Set

| Treatment Group<br>Time Window (Relative Day) | Survival Probability | Survival<br>Standard Error | Number at Risk |
|---|---|---|---|
| N01361 Total | | | |
| 0 week (1) | 1.0000 | 0.0000 | 43 |
| 12 week (84) | 0.3473 | 0.0729 | 14 |
| 24 week (168) | 0.2729 | 0.0688 | 11 |
| 36 week (252) | 0.1984 | 0.0620 | 8 |
| 48 week (336) | 0.1984 | 0.0620 | 8 |
| 60 week (420) | 0.1736 | 0.0590 | 7 |
| 72 week (504) | 0.1736 | 0.0590 | 7 |
| 84 week (588) | 0.1736 | 0.0590 | 7 |
| 96 week (672) | 0.1736 | 0.0590 | 7 |
| 108 week (756) | 0.1488 | 0.0555 | 6 |
| 120 week (840) | 0.1488 | 0.0555 | 6 |
| 132 week (924) | 0.1488 | 0.0555 | 5 |
| 144 week (1008) | 0.1488 | 0.0555 | 5 |
| 156 week (1092) | 0.1488 | 0.0555 | 5 |
| 168 week (1176) | 0.1488 | 0.0555 | 5 |
| 180 week (1260) | 0.1488 | 0.0555 | 5 |
| 192 week (1344) | 0.1488 | 0.0555 | 5 |
| 204 week (1428) | 0.1488 | 0.0555 | 3 |
| 216 week (1512) | 0.1488 | 0.0555 | 3 |
| 228 week (1596) | 0.1488 | 0.0555 | 2 |
| 240 week (1680) | 0.1488 | 0.0555 | 2 |
| 252 week (1764) | 0.1488 | 0.0555 | 1 |

Note: Days from initiation of the period (Visit 1= Day 1) to first GTC seizure during the Evaluation period.
Note: Subjects who have not experienced any seizure until the EDV are considered as censored at the last seizure event assessment date in the Evaluation period.
Reference Listing: 6.3

**Subjects with 12-week seizure freedom duration at any time during the study (FAS):** The percentage of subjects with 12-week seizure freedom at any time during the study was 65.1% for N01361 subjects overall; the 12-week seizure freedom percentage was higher in the subjects from N01159 (71.9%) compared with the subjects from N01363 (45.5%).

| Statistic | N01159 Total<br>N=32 | N01363<br>N=11 | N01361 Total<br>N=43 |
|---|---|---|---|
| n/Nobs | 23/32 | 5/11 | 28/43 |
| Rate (%) | 71.9 | 45.5 | 65.1 |
| Exact 95% CI | 53.3, 86.3 | 16.7, 76.6 | 49.1, 79.0 |

CI=confidence interval; FAS=Full Analysis Set
Note: Nobs refers to the number of subjects with ≥1 nonmissing measurement during the period.
Note: "N01159" and "N01363" denote subjects previously enrolled in the respective feeder study.
Data source: Table 8.1.6

**myoclonic seizures 50% Responder rate over the Evaluation Period:** Regarding the responder rate in myoclonic seizure days per week, the 1 subject who experienced myoclonic seizures achieved a 50% reduction in myoclonic seizure days (equal to days with myoclonic seizures) per week from the Prospective Baseline Period of either feeder study (N01159 or N01363) to the Evaluation Period in this study. No subjects from N01363 reported myoclonic seizures. (cf. Table 8.1.7., tables p160)

Table 8.1.7
Myoclonic Seizure 50% Responder Rate over the Evaluation Period
Analysis Set: Full Analysis Set

| Statistic | N01159 LEV N=18 | N01159 PBO N=14 | N01159 Total N=32 | N01363 N=11 | N01361 Total N=43 |
|---|---|---|---|---|---|
| n / Nobs | 1 / 1 | -- | 1 / 1 | -- | 1 / 1 |
| Rate (%) | 100 | -- | 100 | -- | 100 |
| [exact 95% CI] | [2.5, 100] | -- | [2.5, 100] | -- | [2.5, 100] |

CI=confidence interval. '--' = Missing.
Note: Nobs=number of subjects with myoclonic seizure during the baseline period.
Note: Myoclonic seizures 50% responder rate is defined as proportion of subjects with 50% or more reduction from Prospective Baseline Periods of the feeder studies in the seizure days of myoclonic seizures.
Reference Listing: 6.3

**All seizure days per week by 12-week window over the Evaluation Period:** The median frequency of all seizure days per week improved between the Prospective Baseline Period and the Evaluation Period over each 12-week window. The median percentage reduction in all seizure days per week was ≥80.95% across 12-week windows for N01361 subjects overall. .(cf. Table 9.5, CSRp.101)

Table 9-5: Percentage reduction in all seizure days per week by 12-week window over the Evaluation Period for N01361 subjects overall (FAS)

| Statistic | All seizure days per week | | Percentage reduction (%) |
|---|---|---|---|
| | Prospective Baseline | Evaluation Period | |
| | N01361 Total N=43 | | |
| **Day 1 to ≤12 weeks (n=43)** | | | |
| Median (Q1, Q3) | 0.75 (0.47, 1.56) | 0.08 (0.00, 0.75) | 80.95 (35.71, 100.00) |
| **>12 weeks to ≤24 weeks (n=41)** | | | |
| Median (Q1, Q3) | 0.75 (0.50, 1.17) | 0.08 (0.00, 0.42) | 83.63 (35.71, 100.00) |
| **>24 weeks to ≤36 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.70 (0.47, 1.56) | 0.17 (0.00, 0.42) | 83.93 (56.85, 100.00) |
| **>36 weeks to ≤48 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.70 (0.47, 1.56) | 0.08 (0.00, 0.50) | 91.96 (53.57, 100.00) |
| **>48 weeks to ≤60 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.70 (0.47, 1.56) | 0.08 (0.00, 0.42) | 82.14 (50.00, 100.00) |
| **>60 weeks to ≤72 weeks (n=39)** | | | |
| Median (Q1, Q3) | 0.70 (0.47, 1.56) | 0.08 (0.00, 0.50) | 95.83 (57.14, 100.00) |
| **>72 weeks to ≤84 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.67 (0.47, 1.08) | 0.08 (0.00, 0.42) | 91.96 (54.17, 100.00) |
| **>84 weeks to ≤96 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.67 (0.47, 1.08) | 0.08 (0.00, 0.58) | 91.96 (50.00, 100.00) |
| **>96 weeks to ≤108 weeks (n=37)** | | | |
| Median (Q1, Q3) | 0.67 (0.47, 1.08) | 0.08 (0.00, 0.33) | 91.67 (57.14, 100.00) |
| **>108 weeks to ≤120 weeks (n=36)** | | | |
| Median (Q1, Q3) | 0.66 (0.45, 1.12) | 0.04 (0.00, 0.46) | 97.92 (68.75, 100.00) |
| **>120 weeks to ≤132 weeks (n=34)** | | | |
| Median (Q1, Q3) | 0.73 (0.50, 1.17) | 0.00 (0.00, 0.42) | 100.00 (58.33, 100.00) |
| **>132 weeks to ≤144 weeks (n=31)** | | | |
| Median (Q1, Q3) | 0.75 (0.50, 1.17) | 0.00 (0.00, 0.83) | 100.00 (61.81, 100.00) |
| **>144 weeks to ≤156 weeks (n=28)** | | | |
| Median (Q1, Q3) | 0.73 (0.48, 1.36) | 0.00 (0.00, 0.67) | 100.00 (62.50, 100.00) |
| **>156 weeks to ≤168 weeks (n=24)** | | | |
| Median (Q1, Q3) | 0.66 (0.48, 1.04) | 0.08 (0.00, 0.71) | 91.96 (50.00, 100.00) |
| **>168 weeks to ≤180 weeks (n=21)** | | | |
| Median (Q1, Q3) | 0.70 (0.50, 1.04) | 0.00 (0.00, 0.33) | 100.00 (91.96, 100.00) |
| **>180 weeks to ≤192 weeks (n=17)** | | | |
| Median (Q1, Q3) | 0.75 (0.50, 1.81) | 0.00 (0.00, 0.58) | 100.00 (75.00, 100.00) |
| **>192 weeks to ≤204 weeks (n=17)** | | | |
| Median (Q1, Q3) | 0.75 (0.50, 1.81) | 0.00 (0.00, 0.67) | 100.00 (50.00, 100.00) |
| **>204 weeks to ≤216 weeks (n=13)** | | | |
| Median (Q1, Q3) | 0.75 (0.52, 1.04) | 0.00 (0.00, 0.33) | 100.00 (87.14, 100.00) |
| **>216 weeks to ≤228 weeks (n=12)** | | | |
| Median (Q1, Q3) | 0.73 (0.51, 1.04) | 0.04 (0.00, 0.92) | 95.98 (30.65, 100.00) |
| **>228 weeks to ≤240 weeks (n=10)** | | | |
| Median (Q1, Q3) | 0.63 (0.50, 1.04) | 0.09 (0.00, 0.92) | 91.35 (14.29, 100.00) |
| **>240 weeks to ≤252 weeks (n=5)** | | | |
| Median (Q1, Q3) | 0.52 (0.50, 0.75) | 0.00 (0.00, 0.00) | 100.00 (100.00, 100.00) |

FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile
Note: The information of Prospective Baseline presented was taken from the feeder studies (N01159, N01363).
Note: 'N01159' and 'N01363' denote subjects previously enrolled in the respective feeder study.
Data source: Table 8.1.8

## Conclusion

Based on the study results, the following conclusions were made:

- The **safety and tolerability** of long-term administration of LEV was demonstrated by the safety data for the subjects with exposure to LEV for up to approximately 4.7 years.
- There were no new safety concerns for LEV identified in this study and safety data were consistent with the established safety profile of LEV.
- Long-term administration of LEV at doses up to 60mg/kg/day or 3000mg/day was effective in reducing GTC seizure frequency when used as adjunctive therapy with 1 or 2 other AEDs in Japanese subjects aged ≥4 years.

# 3. Rapporteur's overall conclusion and recommendation

Applicant:

Results from N01361 show that long-term administration of LEV at doses up to 60mg/kg/day or 3000mg/day was effective in reducing GTC seizure frequency when used as adjunctive therapy with 1 or 2 other AEDs in Japanese subjects aged ≥4 years.

There were no new safety concerns for LEV identified in this study and safety data were consistent with the established safety profile of LEV.

Levetiracetam dry syrup is not a registered formulation in the EU, so no changes to the approved EU Product Information for Keppra are proposed following the completion of this study. At this time, UCB considers that the standard immediate-release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU. UCB is submitting this study in accordance with Article 46 of the Paediatric Regulation.

**Recommendation**

At this time, UCB considers that the standard immediate-release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU. UCB is submitting this study in accordance with Article 46 of the Paediatric Regulation.

Rapporteur:

It should be noted that the indication of the present study, i.e. adjunctive treatment with oral levetiracetam in epilepsy patients with generalized tonic-clonic seizures, is not registered in the EU for children > 4 years to 12 years of age, nor is the dry syrup formulation.

It is agreed that at this time, the standard immediate-release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU for the in the EU registered indications.

The Rapporteur endorses the submission of this study in accordance with Article 46 of the Paediatric Regulation, and agrees that there is no impact on the benefit risk balance for the in the in the EU authorized Keppra formulations for the in the EU registered indications.

As regards the **product information**, the following undesirable effects were considered to be related to the study medication in the present study and are not listed in the SmPC:

-breast adenoma
-logorrhea
-gait disturbance
-electrocardiogram QT prolonged.

Specific safety follow-up of these items is recommended to evaluate if addition of these undesirable effects to section 4.8 of the SPC is required.

Therefore, the Rapporteur recommends that you further consider the impact of the available data regarding the undesirable effects

-breast adenoma
-logorrhea
-gait disturbance
-electrocardiogram QT prolonged on the product information.

In addition, It is recommended to add a concise summary of the long term efficacy and safety results of this study to section 5.1 of the SmPC.

☒ PAM fulfilled (all commitments fulfilled) - No further action is required (but is recommended).

Abbreviations:

DRC: daily record card

PCS: potentially clinically significant