# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-285**

# MEDICAL REVIEW(S)

# CLINICAL REVIEW

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| Application Type | NDA |
| Submission Number | 22-285 |
| Letter Date | November 13, 2007 |
| Stamp Date | November 14, 2007 |
| PDUFA Goal Date | September 14, 2008 |
| Reviewer Name | Martin S. Rusinowitz, M.D. |
| Review Completion Date | September 5, 2008 |
| Established Name | Levetiracetam |
| (Proposed) Trade Name | Keppra XR |
| Therapeutic Class | Anticonvulsant |
| Applicant | UCB, Inc. |
| Priority Designation | S |
| Formulation | Tablet |
| Dosing Regimen | Once Daily |
| Indication | Seizures |
| Intended Population | [redacted] – 70 years b(4) |

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

I recommend approval for Keppra XR 500 mg as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents 16 years of age and older with epilepsy.

## 1.2 Recommendation on Postmarketing Actions

None

### 1.2.1 Risk Management Activity

None

### 1.2.2 Required Phase 4 Commitments

I agree with the recommendations of Dr. Gilbet Burckart, clinical pharmacologist, that the Sponsor will conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions. For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters.

### 1.2.3 Other Phase 4 Requests

As originally proposed by Dr. Gilbert Burckart, clinical pharmacologist, I agree that the Sponsor should [redacted] b(4)

2. Perform a pharmacokinetic study in geriatric patients with Keppra XR to provide specific dosing information.

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Levetiracetam, a pyrrolidone derivative, is an antiepileptic drug (AED) which is structurally unrelated to any known antiepileptic drug. The drug provides broad-spectrum seizure protection in animal models of epilepsy but lacks anticonvulsant activity in conventional models. Levetiracetam does not modulate any of the three main mechanisms accounting for the antiepileptic action of classical AEDs. Its action may be linked to a novel mechanism of action, based on the binding of the drug to the synaptic vesicle protein SV2A. No other known anticonvulsant binds to SV2A. The compound has been granted marketing approval for an oral tablet and solution (KEPPRA) as well as a parenteral I.V. injection.

The extended release product is proposed in order to facilitate convenience of dosing and patient compliance. The total daily dose of the extended release formulation (LEV XR) is felt to be similar to that of KEPPRA with a dosage range of 1,000 to 3,000 mg/day. This NDA is for approval to market LEV XR 500 mg as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents.

In total, five studies have been conducted in the development of levetiracetam extended release tablet 500 mg (LEV XR). One efficacy and safety study (N01235) recruited patients ages 12 years of age and older with epilepsy, experiencing partial onset seizures. Three clinical pharmacology studies (N01140, N01160, and N01260) were conducted in healthy volunteers to investigate the bioavailability of the extended release tablet 500 mg as compared to the immediate release tablet 500 mg, the food effect, and the dose proportionality over the approved 1000 mg to 3000 mg dose range for immediate release KEPPRA. Data from these four studies includes a total of 137 unique subjects who have been exposed to levetiracetam extended release tablet 500 mg, including 77 patients with epilepsy and not including 79 patients exposed to placebo in the efficacy and safety study (N01235).

In addition, a pharmacoscintigraphic study (N01173) to investigate the regional absorption of levetiracetam (250 mg) delivered using the [redacted] capsule in 3 different sites of the gastrointestinal tract in comparison with the levetiracetam immediate release tablet 250 mg was also performed to investigate the feasibility of the development of the extended release tablet formulation. The total exposure does not include the 9 subjects from study N01173, since the levetiracetam extended release tablet was not used in the study. b(4)

### 1.3.2 Efficacy

Study N01235 was a randomized, double-blind, placebo-controlled, efficacy and safety study of LEV XR administered as 2 x 500 mg once daily (1000 mg/day) as add-on therapy in subjects from 12 to 70 years old with refractory epilepsy suffering from partial onset seizures, POS. During the 8-week Baseline Period, the subject had to have experienced at least 8 partial seizures with or without secondary generalization and at least 2 partial seizures in each 4-week interval of the Baseline Period. Furthermore, subjects were to be on a stable dose of at least 1 and no more than 3 concomitant AEDs.

After an 8 week baseline period, qualified subjects were randomized to the 12 week Treatment Period to receive either LEV XR 2 x 500 mg/day or 2 matching placebo tablets, to be taken each evening. Out of the 188 subjects screened, 158 (59 females; 99 males) aged between 12.2 and 67.9 years (mean [SD]: 33.17 [13.00]) were randomized into the study (79 in the placebo group [PBO]; 79 in the LEV XR group); they constituted the ITT population. One hundred forty-three (143) subjects (72 PBO; 71 LEV XR) completed the study.

The primary endpoint of this study was the median percent reduction in partial onset seizure frequency per week over the Treatment Period in the LEV XR vs. PBO group. An important secondary endpoint was the responder rate (the proportion of subjects who have a $\geq$ 50% reduction in seizure frequency per week from baseline) for partial onset seizures and for total seizures over the treatment period. There were no problems or issues with the choice of endpoint, choice of control, adequacy of blinding, conduct of the studies or appropriateness of statistical analyses. Baseline demographic values, including age race, weight, gender and seizure types were generally well matched between treatment groups.

This study demonstrated a reduction in partial seizures when Keppra XR was used as a once daily add-on therapy in adult patients ($\geq$ 16 years of age) with refractory epilepsy. There were inadequate numbers of adolescent patients in this study [redacted] A pharmacokinetic study of adolescents (ages 12 to 16 years) with partial onset seizures intended to establish dosing of Keppra XR in this population is recommended. b(4)

### 1.3.3 Safety

Adverse events were coded using MedDRA (Version 9.0). Two sources of information are described, the double-blind, placebo-controlled study N01235 and the three pharmacology studies. 158 patients with epilepsy were randomized in Study N01235, 79 to LEV XR (one subject was excluded because drug was not dispensed, while another was excluded because she returned all the tablets received at the site). The ITT population comprised all the randomized patients. Although this population was the primary subset for the analysis of efficacy data, the Safety population comprised all subjects who were dispensed medication. The three pharmacology studies included only healthy volunteers. There were a total of 60 subjects exposed to LEV XR in the 3 clinical pharmacology studies.

There were, therefore, 137 unique exposures to LEV XR. No pooling of safety data occurred; safety from the efficacy and clinical pharmacology studies is described separately. No Serious Adverse Events were reported in any of the three clinical pharmacology studies, neither pre-treatment nor treatment emergent. No important difference in the nature and the number of TEAEs reported in the PBO and LEV XR groups was observed. However, after aggregating asthenia and fatigue, it appeared that these events were more frequently reported in the LEV XR group than in the PBO group.

In the safety population, two subjects in the PBO group and five in the LEV XR group reported at least one SAE, two of which had sequelae: one of ischemic stroke and one of brain trauma. There was one death of a subject in the LEV XR group. None of these appeared to be causally related to LEV XR.

### 1.3.4 Dosing Regimen and Administration

The only dosage studied was 2x500mg LEVXR tablets once daily. This is at the low end of the approved daily dosing for Keppra which is 1,000mg to 3,000 mg daily.

### 1.3.5 Drug-Drug Interactions

*In vitro* data on metabolic interactions indicate that levetiracetam is unlikely to produce, or be subject to, pharmacokinetic interactions. Levetiracetam and its major metabolite, at concentrations well above $C_{max}$ levels achieved within the therapeutic dose range, are neither inhibitors of, nor high affinity substrates for, human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. Levetiracetam circulates largely unbound (< 10% bound) to plasma proteins. Clinically significant interactions with other drugs through competition for protein binding sites are therefore unlikely. Potential pharmacokinetic interactions were assessed in clinical pharmacokinetic studies (phenytoin, valproate, oral contraceptive, digoxin, warfarin and probenecid) and through pharmacokinetic screening in the placebo-controlled clinical studies in epilepsy subjects. The following reflect the conclusions as currently stated in the most recently approved labeling (KEPPRA tablets and oral solution labeling, rev. March 2007).

KEPPRA (3000 mg daily) had no effect on the pharmacokinetic disposition of phenytoin in subjects with refractory epilepsy. Pharmacokinetics of levetiracetam were also not affected by phenytoin. KEPPRA (1500 mg twice daily) did not alter the pharmacokinetics of valproate. Valproate 500 mg twice daily did not modify the rate or extent of levetiracetam absorption or its plasma clearance or urinary excretion. There also was no effect on exposure to and the excretion of the primary metabolite, ucb L057. Potential drug interactions between KEPPRA and other AEDs (carbamazepine, gabapentin,lamotrigine, phenobarbital, phenytoin, primidone and valproate) were also assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo controlled clinical studies. These data indicate that levetiracetam does not influence the plasma concentration of other AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.

In children, there was about a 22% increase of apparent total body clearance of levetiracetam when it was co-administered with enzyme-inducing AEDs. Dose adjustment is not recommended. Levetiracetam had no effect on plasma concentration of carbamazepine,valproate, topiramate or lamotrigine.

KEPPRA (500 mg twice daily) did not influence the pharmacokinetics of an oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel, or of the luteinizing hormone and progesterone levels, indicating that impairment of contraceptive efficacy is unlikely. Co-administration of this oral contraceptive did not influence the pharmacokinetics of levetiracetam. KEPPRA (1000 mg twice daily) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Co-administration of digoxin did not influence the pharmacokinetics of levetiracetam. KEPPRA (1000 mg twice daily) did not influence the pharmacokinetics of R and S warfarin. Prothrombin time was not affected by levetiracetam. Co-administration of warfarin did not affect the pharmacokinetics of levetiracetam. Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg twice daily. $C_{max}$ of the metabolite, ucb L057, was approximately doubled in the presence of probenecid while the fraction of drug excreted unchanged in the urine remained the same. Renal clearance of ucb L057 in the presence of probenecid decreased 60%, probably related to competitive inhibition of tubular secretion of ucb L057. The effect of KEPPRA on probenecid was not studied.

### 1.3.6 Special Populations

None studied.

## 2 Introduction and Background

### 2.1 Product Information

Keppra is an anticonvulsant that is presently marketed in the United States and labeled as adjunctive therapy for partial onset seizures in adults and children ≥ 4 years of age, adjunctive therapy in the treatment of myoclonic seizures in adults and children ≥ 12 years with juvenile myoclonic epilepsy (JME), adjunctive therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures in adults and children ≥ 6 years with idiopathic generalized epilepsy, adjunctive therapy for partial onset seizures in adults with epilepsy, adjunctive therapy for myoclonic seizures in adults with JME.

The approved drug formulations of levettiracetam in the U.S., taken from the Sponsor's Original Application, are listed below.

| Drug Formulation | Dose Strength | Approval Year |
|---|---|---|
| IR Tablet | 250 mg, 500 mg, 750 mg | 1999 |
| Oral Solution | 100 mg/mL | 2003 |
| IR Tablet | 1000 mg | 2005 |
| I.V. Injection | 500 mg / 5 mL | 2006 |

### 2.2 Currently Available Treatment for Indications

There are many AEDs available as adjunctive therapy in the treatment of partial onset seizures, but few in a once daily preparation.

## 2.3 Availability of Proposed Active Ingredient in the United States

See 2.1 above.

## 2.4 Important Issues with Pharmacologically Related Products

No safety or effectiveness concerns have arisen in other members of this pharmacologic class. The pharmacokinetics and pharmacodynamics of levetiracetam have been studied extensively with different drug formulations. The information from these studies was summarized in detail in the previous NDA / sNDA submissions (NDAs 21-035, 21-505 and 21-872)

## 2.5 Pre-submission Regulatory Activity

*Pre-IND Meeting*

A Pre-IND meeting with the Division of Neurology Products to discuss the development plan for levetiracetam extended release tablet 500 mg was held on April 19, 2006. The recommendations and agreements from this meeting are reproduced below:

b(4)

- Proposed stability acceptable, i.e., 12 months data on 3 pilot scale batches of [redacted] tablets and 6 months data for one batch of red tablets; photostability testing to be included; comparative dissolution acceptable; proposal to satisfy commitment to place first 3 commercial batches on stability with data from first 3 validation (full scale) batches acceptable; plan to maintain use of EP excipients with commitment to perform periodic testing as approved for [redacted] manufacture of KEPPRA immediate release tablets (NDA 21-035/S-048) acceptable. b(4)
- Plan to not conduct additional nonclinical studies acceptable, provided there were no new impurities or degradants in the extended release formulation of particular concern (i.e., genotoxic) or exceed the qualification threshold per ICH guidance for impurities.
- Proposals for clinical pharmacology data from single and multiple dose bioequivalence with food effect acceptable; should also calculate 90% CI for Cmin values for multiple dose; proposal to add 90% CI for Cmin at steady state, T75%Cmax at steady state, and PK dose proportionality for 1000 mg, 2000 mg and 3000 mg acceptable.
- After discussing with the Division the rationale for a bioequivalence approach and different proposals as to the design of an efficacy study and dose effect, it was agreed that UCB would conduct a single and multiple dose (BE/BA) study with 1000 mg, an efficacy study with 1000 mg dose as adjunctive therapy in patients 12 years and older experiencing partial onset seizures, and a dose proportionality study with 1000, 2000 and 3000 mg.
- A population pharmacokinetic (PK) analysis would be performed based on sampling from the efficacy study, the BA/BE study and the dose proportionality study.
- Dose dumping with alcohol would be evaluated with in vitro dissolution studies in various concentrations of alcohol (e.g., 5, 10, 20 and 40%).
- Labeling for the proposed daily dose range of 1000 mg to 3000 mg, approved for KEPPRA, dependent upon the dose proportionality data for 1000 mg to 3000 mg doses.
- Sponsor should consider developing higher strengths of the extended release dosage form in order to avoid the administration of multiple units to achieve higher doses.
- [redacted] b(4)
- [redacted] b(4)

*Pre-NDA Meeting*

A Pre-NDA meeting with the Division of Neurology Products to discuss the NDA for KEPPRA XR was held as videoconference on October 1, 2007. The recommendations and agreements from this meeting are reproduced below:

- Quality information proposed and release tests for drug product specifications adequate. Facility information for drug substance manufacturing and testing and a summary table for drug substance specifications requested. Proposal to satisfy commitment to place first 3 commercial batches on stability with data from first 3 validation (full scale) batches acceptable.
- Nonclinical information was agreed not to be required unless needed to support any proposed labeling change.
- Clinical data from clinical pharmacology studies and efficacy study agreed adequate.
- Population pharmacokinetic meta-analysis plan was acceptable, population PK datasets must be provided in SAS XPORT transport format, version 5.
- Proposal for integrated summary of safety acceptable; narratives requested for deaths, SAEs and discontinuations related to seizures. Discontinuations due to seizures (loss of efficacy) should be analyzed for comparison with prior adjunctive studies at similar dose, understanding that cross-study comparisons must be interpreted with caution. Proposal to report adverse events with a cutoff at 2% for efficacy study and 5% for PK studies was acceptable. ISS to include pertinent elements as described in the Appendix from the Pre-sNDA meeting for pediatric exclusivity held on 17 September 2007.
- Proposal to not include an integrated summary of efficacy was acceptable. In lieu of a PK/PD analysis of dose response with previous adjunctive studies, the proposal to provide descriptives for exposure response was acceptable; the clinical study report would include comparative tables for efficacy at similar doses in previous adjunctive studies, understanding that cross-study comparisons must be interpreted with caution.
- Proposals for the 120-day safety update were acceptable.
- Proposed document mapping was acceptable for the electronic NDA in CTD format; if the submission were received after 31 December 2007, a waiver from the requirement for eCTD format must be requested. PDF files must be version 1.4.
- Proposals for CRFs acceptable; CRFs for SAEs also requested. Datasets must be delivered in SAS XPORT transport format, version 5. SAS programs in ASCII and/or PDF format acceptable.
- Proposal for CRTs adequate; all datasets to be submitted in SAS transport V5 format.
- [redacted] levetiracetam extended release tablet 750 mg strength, the key study will be a single dose bioequivalence study with 2 x 750 mg fasted versus 3 x 500 mg fasted, with a 2 x 750 mg fed arm for food effect. A multiple dose study is not necessary. [redacted] b(4)
- Additional clinical pharmacology request to provide a summary using the template provided as Appendix for Clinical Pharmacology and Biopharmaceutics Review Aid; can be provided in Module 2 with the clinical summary or as a review aid in Module 5.

## 2.6 Other Relevant Background Information

None

# 3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

## 3.1 CMC

The most recent CMC review (15 AUG 2008) for NDA 22-285 recommended that this application be approved on receipt of an overall acceptable recommendation from the Office of Compliance. Such a recommendation was received on September 9, 2008. All outstanding CMC issues have now been resolved.

## 3.2 Animal Pharmacology/Toxicology

In animal studies, levetiracetam produced evidence of developmental toxicity at doses similar to or greater than human therapeutic doses.

*Carcinogenesis*
Rats were dosed with levetiracetam in the diet for 104 weeks at doses of 50, 300 and 1800 mg/kg/day. The highest dose corresponds to 6 times the maximum recommended daily human dose (MRHD) of 3000 mg on a $mg/m^2$ basis and it also provided systemic exposure (AUC) approximately 6 times that achieved in humans receiving the MRHD. There was no evidence of carcinogenicity. A study was conducted in which mice received levetiracetam in the diet for 80 weeks at doses of 60, 240 and 960 mg/kg/day (high dose is equivalent to 2 times the MRHD on a $mg/m^2$ or exposure basis). Although no evidence for carcinogenicity was seen, the potential for a carcinogenic response has not been fully evaluated in that species because adequate doses have not been studied.

*Mutagenesis*
Levetiracetam was not mutagenic in the Ames test or in mammalian cells *in vitro* in the Chinese hamster ovary/HGPRT locus assay. It was not clastogenic in an *in vitro* analysis of metaphase chromosomes obtained from Chinese hamster ovary cells or in an *in vivo* mouse micronucleus assay. The hydrolysis product and major human metabolite of levetiracetam (ucb L057) was not mutagenic in the Ames test or the *in vitro* mouse lymphoma assay.

*Impairment Of Fertility*
No adverse effects on male or female fertility or reproductive performance were observed in rats at doses up to 1800 mg/kg/day (approximately 6 times the maximum recommended human dose on a $mg/m^2$ or exposure basis).

# 4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

## 4.1 Sources of Clinical Data

Clinical efficacy is solely based upon one multicenter trial (N01235).

Pooled safety data consists of 137 subjects who have been exposed to levetiracetam extended release tablets 500 mg. These include 77 LEV XR randomized patients in trial N01235 and 60 healthy volunteers in three clinical pharmacology studies (N01140, N01160, and N01260).

## 4.2 Tables of Clinical Studies, reproduced from the Sponsor's Original Application

| Type of Study | Study Identifier (Country) Year | Location of the Study Report | Study Objectives | Study Design / Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects (Age [Years] Range) | Healthy Subjects or Diagnosis of Patients | Treatment Duration | Study Status / Type Report |
|---|---|---|---|---|---|---|---|---|---|
| | 2007 | | single dose bioavailability from 1000 mg, 2000 mg, and 3000 mg LEV XR | 3-way cross-over, open label, randomized | 2 x 500 mg; 4 x 500 mg; and 6 x 500 mg fasting | 12 F] (18-55) | female subjects | with 1 week between Day 1 of consecutive periods | RRCE07D2417 |

| Type of Study | Study Identifier (Country) Year | Location of the Study Report | Study Objectives | Study Design / Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects (Age [Years] Range) | Healthy Subjects or Diagnosis of Patients | Treatment Duration | Study Status / Type Report |
|---|---|---|---|---|---|---|---|---|---|
| BA/BE | N01140 (France) 2005 | Module 5.3.1.2.1 | Pilot BA/BE study to compare PK profile of LEV 500 mg oral dose from 3 test XR formulations with LEV IR reference and to assess food effect on one LEV 500 mg test XR formulation | Single center, 4-way cross-over, open label, randomized fasted with LEV IR as reference; single dose test XR fed | LEV IR 500 mg oral tablet and 3 test XR formulations of LEV 500 mg oral tablets single dose fasting; 1 test XR formulation of LEV 500 mg tablet single dose fed | 12 M (18-55) | Healthy male subjects | 4 periods of 3 days with 1 week between Day 1 of consecutive periods | Complete ICH report RRCE05A3106 |
| BA/BE | N01160 (France) 2006 | Module 5.3.1.2.2 | Pivotal BA/BE study to compare single dose bioavailability of LEV XR 2 x 500 mg *o.d.* and LEV IR 500 mg *b.i.d.*; to compare multiple dose bioavailability of LEV XR 2 x 500 mg *o.d.* with LEV IR 500 mg *b.i.d.*; to assess food effect on LEV XR 2 x 500 mg | Single center, 3-way cross-over, open label, randomized | LEV XR 2 x 500 mg oral tablets *o.d.* single dose fasting Day 1 with repeated *o.d.* administration Day 3 to Day 9; LEV IR 500 mg oral tablet *b.i.d.* fasting on Day 1 with repeated administration b.i.d. from Day 3 to Day 9; LEV XR 2 x 500 mg oral tablet single dose after high fat breakfast | 24 [12 M / 12F] (18-55) | Healthy male and female subjects | 3 periods of a maximum of 11 days; with 2 week between Day 1 of consecutive periods | Complete ICH report RRCE06D1006 |

| Type of Study | Study Identifier (Country) Year | Location of the Study Report | Study Objectives | Study Design / Type of Control | Test Product(s); Dosage Regimen; Route of Administration | No. of Subjects (Age [Years] Range) | Healthy Subjects or Diagnosis of Patients | Treatment Duration | Study Status / Type Report |
|---|---|---|---|---|---|---|---|---|---|
| Efficacy and Safety | N01235 (Brazil, Finland, India, Mexico, Russian Federation, Ukraine, South Africa) 2006 - 2007 | Module 5.3.5.1.1 | Pivotal efficacy and safety study with LEV XR 2 x 500 mg once daily as add-on therapy in refractory epilepsy patients ages 12-70 years with partial onset seizures | Multi-center, double-blind, placebo-controlled, randomized efficacy and safety | LEV XR 2 x 500 mg oral tablets once daily vs. matching placebo | 156 M/F (12-70 years) | Refractory male and female patients with partial seizures | 8-week baseline period followed by 12-week treatment period | Complete ICH report RRCE06E0505 |

### 4.3 Review Strategy

One pivotal efficacy/safety study (N01235) and three PK studies ((N01140, N01160, and N01260) were reviewed. All trials were used in the integrated safety analysis. Efficacy was determined only by study N01235. Literature was not relied upon to support safety or efficacy.

### 4.4 Data Quality and Integrity

There were no DSI audits.

### 4.5 Compliance with Good Clinical Practices

Studies were carried out in accordance with ICH E6 Guidance on Good Practice.

### 4.6 Financial Disclosures

A list of investigators has been provided who certify no financial compensation based on the outcome of the study as defined in 21 CFR 54.

## 5 CLINICAL PHARMACOLOGY

### 5.1 Pharmacokinetics

In adult pharmacokinetic studies, KEPPRA is rapidly and almost completely absorbed after oral intake. Peak plasma levels are generally reached within 1 hour, and steady state concentrations are reached after 2 days of twice daily (b.i.d.) treatment. The volume of distribution of KEPPRA is approximately 0.7 L/kg, which is approximately the volume of distribution of total body water. KEPPRA does not significantly bind to plasma proteins (< 10%) and is therefore unlikely to interfere with the protein binding (PB) of other medications. Approximately 66% of the administered dose of KEPPRA is excreted unchanged in the urine over 48 hours, and approximately 24% of the dose is eliminated as an acidic metabolite (L057) produced by hydrolysis of the acetamide group. The half-life of KEPPRA is 7.2 ± 1.1 hours in healthy adults and 10 – 11 hours in elderly healthy volunteers (> 65 years) . Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is not dependent on any liver cytochrome P450 isoenzymes. The major metabolic, the carboxylic acid derivative ucb 057, is the product of enzymatic hydrolysis of the acetamide group [via amidase(s) / serine-type esterases(s) present in blood, liver, and probably also other tissues]. The major metabolite is inactive in mouse seizure models. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no enantiomeric interconversion of levetiracetam or its major metabolite.

The disposition of levetiracetam was studied in subjects with varying degrees of renal function. Total body clearance of levetiracetam is reduced in subjects with impaired renal function by 40% in the mild group (CLcr = 50 - 80 mL/min), 50% in the moderate group (CLcr = 30 - 50 mL/min) and 60% in the severe renal impairment group (CLcr < 30 mL/min).

Clearance of levetiracetam is correlated with creatinine clearance. In anuric (end-stage renal disease) subjects, the total body clearance decreased 70% compared to normal subjects (CLcr > 80mL/min). Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4 - hour hemodialysis procedure. The clearance of LEV XR in subjects with impaired renal function was not studied. It was expected to be similar to that of KEPPRA. Subjects with clinically significant renal function impairment were excluded from the

placebo-controlled study. No renal function impairment was noted for any of the three clinical pharmacology studies.

In subjects with mild (Child-Pugh A) to moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of levetiracetam were unchanged. In patients with severe hepatic impairment (Child-Pugh C), total body clearance was 50% that of normal subjects, but decreased renal clearance for most of the decrease.

Population pharmacokinetic analysis modeling and simulation suggested that $C_{max}$ and AUC following LEV XR administration in a typical patient is similar as to those following KEPPRA administration. As consistently observed in study N01160, the $C_{min}$ was lower with LEV XR than with KEPPRA. The modeling and simulation also illustrate that, as expected, $C_{min}$ is generally reduced in case of non-compliance during one dosing interval, and to a lesser extent if the missed dose is taken later during the same day. Also, $C_{max}$ is slightly decreased (about 7%) when the dose is taken late and nearly doubled with the double rescue dose. However, the model predicts that a return to the initial peak and trough conditions takes place the following day. Seventy-seven (77) subjects were exposed LEV XR 2 x 500 mg/day once daily for up to 12 weeks in the controlled efficacy and safety study in epilepsy patients with partial onset seizures. Intake of a high fat, high calorie breakfast before the administration of the LEV XR tablets resulted in a higher peak concentration, and longer median time to peak. However, food intake did not modify the pharmacokinetics of LEV XR in a clinically relevant way. The pharmacokinetics (AUC and $C_{max}$) were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mg LEV XR.

Overall, female subjects had a slightly higher AUC and $C_{max}$ in both LEV XR and KEPPRA.

The Sponsor's table below shows the main PK parameters under fasting conditions by gender in study N01260.

| | **Levetiracetam dose** | | | | | |
|---|---|---|---|---|---|---|
| | **2 x 500 mg(a)** | | **4 x 500 mg(a)** | | **6 x 500 mg(a)** | |
| Parameter | Males (N=12) | Females (N=12) | Males (N=12) | Females (N=12) | Males (N=12) | Females (N=12) |
| Cmax (µg/mL) | 14.2 (12.8) | 18.5 (18.5) | 28.7 (20.1) | 34.6 (12.0) | 40.9 (12.8) | 52.2 (19.7) |
| tmax (h) | 4.50 (2.00-7.00) | 4.50 (3.00-8.00) | 5.00 (3.00-10.00) | 4.00 (2.00-6.00) | 5.00 (3.00-8.00) | 4.00 (2.00-10.00) |
| AUC(0-t) (µg.h/mL) | 258 (13.3) | 304 (17.9) | 518 (14.0) | 604 (16.6) | 803 (12.9) | 876 (18.0) |
| AUC (µg.h/mL) | 264 (13.3) | 309 (18.2) | 529 (14.1) | 614 (17.0) | 822 (13.1) | 889 (18.3) |
| t½ (h) | 7.73 (10.7) | 6.82 (10.4) | 7.76 (5.22) | 6.92 (17.7) | 7.53 (7.30) | 6.78 (15.7) |
| CL/F (mL/min) | 63.1 (13.3) | 54.0 (18.2) | 63.0 (14.1) | 54.3 (17.0) | 60.9 (13.1) | 56.2 (18.3) |
| Vz/F (L) | 42.3 (19.1) | 31.9 (14.2) | 42.3 (15.0) | 32.5 (18.3) | 39.7 (12.6) | 33.0 (18.2) |

The main PK parameters under fasting conditions by gender in study N01160, provided by the Sponsor, is shown below.

| Parameter | Both Sexes (N=24) | | Males (N=12) | | Females (N=12) | |
|---|---|---|---|---|---|---|
| | IR tablet(a) | XR tablet(a) | IR tablet(a) | XR tablet(a) | IR tablet(a) | XR tablet(a) |
| Cmax (µg/mL) | 19.7 (17.1) | 17.4 (17.9) | 18.7 (20.3) | 15.1 (12.6) | 20.7 (11.7) | 20.2 (6.21) |
| tmax (h)[b] | 0.88 (0.50-3.03) | 4.00 (2.00-10.00) | 0.88 (0.50-2.00) | 4.00 (2.00-6.00) | 0.88 (0.50-3.03) | 4.00 (3.00-10.00) |
| AUC(0-t) (µg.h/mL) | 317 (13.9) | 307 (15.1) | 292 (11.4) | 279 (12.5) | 345 (10.8) | 338 (10.5) |
| AUC (µg.h/mL) | 325 (13.8) | 313 (15.1) | 300 (11.5) | 285 (12.7) | 353 (11.0) | 344 (10.7) |
| t½ (h) | 7.28 (12.1) | 7.60 (10.0) | 7.60 (11.4) | 7.82 (7.35) | 6.97 (11.6) | 7.39 (11.8) |

## 5.2 Pharmacodynamics

Experimental models suggest a mode of action for levetiracetam consisting of selective interference with abnormal neuronal activity. The nearly equal potency in efficacy models following p.o., i.p. or i.v. dosing and the slightly higher potency following i.c.v. administration supported the view that the site of action was within the CNS; further support was provided by studies demonstrating specific binding and selective inhibition of neuronal activity in the CNS. Most recently, a specific binding site for levetiracetam, the synaptic vesicle protein SV2A, unique for an AED, has been identified.

Potential adverse pharmacological effects with levetiracetam appear to be limited. Seizure suppression is obtained with a high safety margin between the doses inducing seizure protection and CNS adverse effects (indeed, the therapeutic index has been shown to be markedly higher for levetiracetam compared to other AEDs). Pharmacological effects on gastrointestinal and renal function were minimal to non-existent. It did not prolong cardiac action potential duration in vitro nor QT corrected for heart rate in dogs at up to 600 mg/kg p.o.. These latter findings were supported by a lack of effect on ECG in repeat dose toxicity studies in the dog at up to 600 mg/kg p.o. and 600 mg/kg i.v..

## 5.3 Exposure-Response Relationships

The mean daily dose and duration of treatment for subjects in the double-blind, placebo-controlled study of LEV XR-N01235 safety population is shown below. Mean daily dose and duration of treatment were consistent with protocol instructions (PBO or LEV XR 2x500 mg/day o.d. for 12 weeks); no relevant differences between groups were noted in this table provided by the Sponsor.

| Treatment Period | Statistics | PBO (N=79) | LEV XR (N=77) |
|---|---|---|---|
| Mean daily dose (g) | n | 78[a] | 77 |
| | Mean (SD) | 0.99 (0.04) | 0.98 (0.10) |
| | Median | 1.00 | 1.00 |
| | Q1 – Q3 | 1.00 – 1.00 | 1.00 – 1.00 |
| Duration of treatment (day) | n | 78[a] | 77 |
| | Mean (SD) | 80.47 (15.43) | 81.70 (15.51) |
| | Median | 84.00 | 84.00 |
| | Q1 – Q3 | 83.00 – 85.00 | 83.00 – 85.00 |

# 6 INTEGRATED REVIEW OF EFFICACY

## 6.1 Indication

The Sponsor seeks approval to market levetiracetam extended release tablet 500 mg as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents [redacted] years of age and older with epilepsy, under the trade name KEPPRA XR. b(4)

### 6.1.1 Methods

Clinical data from a single trial was submitted to obtain approval for the above indication. Study N01235: A double-blind, placebo-controlled, randomized efficacy and safety study of levetiracetam extended release formulation (LEV XR), administered as 2 x 500 mg LEV XR tablets once daily as add-on therapy in subjects from 12 to 70 years with refractory epilepsy suffering from partial onset seizures.

### 6.1.2 General Discussion of Endpoints

***Primary Efficacy Endpoint, reproduced from the Sponsor's Original Application***

The primary efficacy variable was the partial seizure frequency per week over the treatment Period. The log-transformed partial onset seizure frequency per week calculated from the Treatment Period was compared between LEV XR and placebo using an ANCOVA model. Descriptive statistics for the partial seizure frequency per week over the Baseline and Treatment Periods, its reduction and percent reduction from baseline over the Treatment Period by visit and period were computed. ANCOVA of (log-) partial seizure frequency per week over Treatment Period, using the (log-) baseline seizure frequency per week as a covariate were provided. The percent reduction of LEV XR over placebo, its 2-sided 95% CI, and the p-value were presented. The seizure types and counts by day of presence during the Baseline and Treatment Periods for individual subjects were listed. Efficacy parameters based on partial seizures were listed by visit and period over the Baseline and Treatment Periods.

***Secondary Efficacy Endpoint, reproduced from the Sponsor's Original Application***

- The total seizure frequency per week over the Treatment Period.

- The absolute and percentage (%) reduction from baseline in partial onset seizure frequency per week over the Treatment Period.

- The absolute and percentage (%) reduction from baseline in total seizure frequency per week over the Treatment Period.

- The responder rate (the proportion of subjects who have a $\geq$ 50% reduction in seizure frequency per week from baseline) for partial onset seizures and for total seizures over the Treatment Period.

- The categorical response to treatment: percent reduction from baseline in partial onset seizure and in total seizure frequency per week grouped into six categories (< -25%, - 25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100% and 100%) over the Treatment Period.

***Exploratory Endpoints, reproduced from the Sponsor's Original Application***

• The global evaluation of disease evolution using a Global Evaluation Scale (GES) assessed by the Investigator at the end of the Treatment Period.

• The number of seizure free days over the Baseline and Treatment Periods.

• The medical resources used over the Baseline and Treatment Periods, including concomitant medications, medical procedures and hospitalizations.

### 6.1.3 Study Design

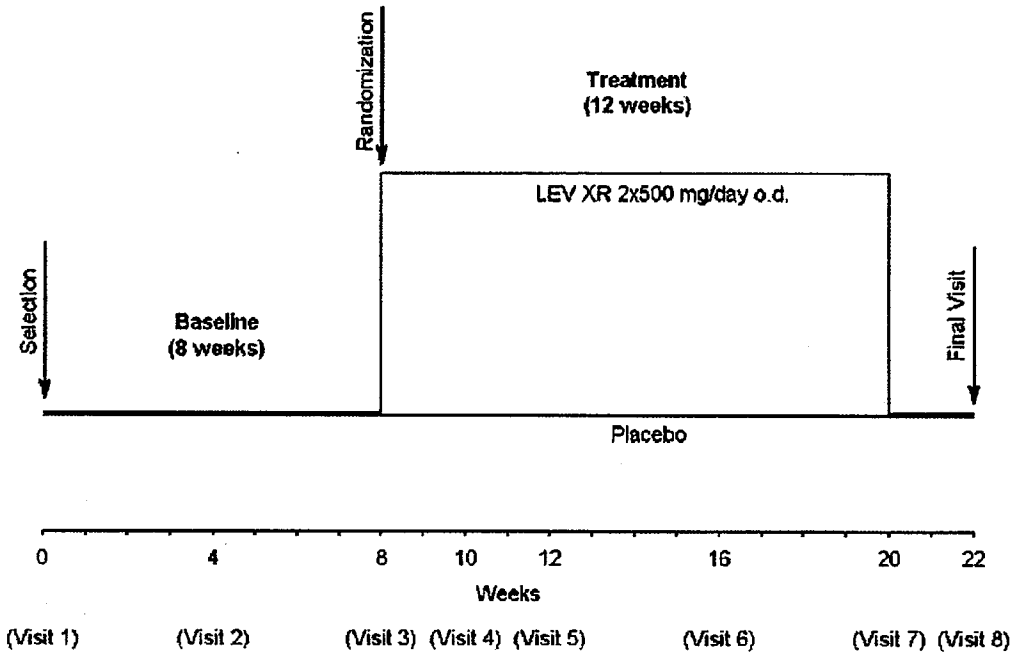
***General Design***

This was a multicenter, double-blind, randomized (1:1), parallel group, placebo-controlled, add-on study.

***Study Objective***

The objective of this study was to assess the efficacy and safety of levetiracetam extended release formulation (LEV XR), administered as 2 x 500 mg LEV XR tablets once daily as add-on therapy in subjects from 12 to 70 years with refractory epilepsy suffering from partial onset seizures. The study was conducted at 34 investigative sites across 7 countries. To qualify for the study, subjects had to have been diagnosed with epilepsy for at least 6 months prior to the Selection Visit. During the 8-week Baseline Period, the subject had to have experienced at least 8 partial seizures with or without secondary generalization and at least 2 partial seizures in each 4-week interval of the Baseline Period. Furthermore, subjects were to be on a stable dose of at least 1 and no more than 3 concomitant AEDs. AED treatment was required to be stable for at least 4 weeks prior to Visit 1. If Vagal Nerve Stimulator (VNS) was in place, the setting had to have been stable for at least 3 months prior to Visit 1; VNS was counted as one AED. Potential subjects were excluded if they had a history of status epilepticus within the 3 months prior to Visit 1. Other exclusion criteria included neoplasia, progressive cerebral disease or any other progressive neurodegenerative disease; presence of another clinical disease (e.g., cardiovascular, hepatic, renal, auto-immune or associated with hematology, neurology, or psychiatry) or other disease which could interfere with the absorption, distribution, metabolism or excretion of the study medication; current ketogenic diet; history of pseudoseizures; use of felbamate.

*Study Schedule, reproduced from the Sponsor's Original Application*




The trial consisted of the following periods:

**Baseline Period (8 weeks)**

A Selection Visit occurred on Visit 1 to ensure that the subject qualified to go into the Baseline Period. Once it was verified that the subject was suitable, the subject was given a Daily Record Card (DRC) to document the number of seizures experienced during the 8 weeks following the Selection Visit. Subjects returned to the clinic after 4 weeks baseline (Visit 2) to verify that he/she completed the DRC correctly and was still qualified for the study. At the end of the 8-week period (Visit 3) the subject returned to assess their eligibility for entry into the study and continuation into the Treatment Period. Subjects had to experience at least eight partial seizures with or without secondary generalization during the 8-week Baseline Period and at least 2 partial seizures in each 4-week interval of the Baseline Period in order to qualify for study participation.

**Treatment Period (12 weeks)**

The Treatment Period was 12 weeks in duration. Since the targeted dose of LEV XR was 2x500 mg/day, the recommended daily dose for Keppra immediate release formulation, there was no up-titration period. Subjects returned to the clinic four times during this period for efficacy and safety assessments (Visits 4, 5, 6, and 7, respectively). At the end of the Treatment Period, subjects who wanted to continue with LEV treatment were converted to LEV IR, either by prescription or by named patient program in countries where LEV IR was not marketed or fully reimbursed.

**Final Visit (2 weeks after Visit 7 or 2 weeks after Early Discontinuation Visit)**

Subjects who discontinued the study prematurely or completed the Treatment Period but decided not to convert to LEV IR returned for the final study visit two weeks after the last dose of study medication for follow-up.

Details of Study Schedule provided by the Sponsor are shown in the table below.

| Study Periods | Selection | Baseline | | Treatment | | | | Early Discontinuation Visit[a] | Final Visit[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | 8 Weeks | | 12 Weeks | | | | | |
| Week | 0 | 4 | 8 | 10 | 12 | 16 | 20 | | 22 |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | | 8 |
| Written Informed Consent | X | | | | | | | | |
| Eligibility Criteria Assessment | X | X | X | | | | | | |
| Demographics | X | | | | | | | | |
| Medical and Surgical History | X | | | | | | | | |
| Epilepsy History | X | | | | | | | | |
| Epilepsy Treatment History | X | | | | | | | | |
| Physical Examination | X | | X | | | | X | X | X |
| Neurological Examination | X | | X | | | | X | X | X |
| Vital Signs[c] | X | X | X | X | X | X | X | X | X |
| Daily Record Card[d] / Seizure Count | X | X | X | X | X | X | X | X | |
| Global Evaluation Scale | | | | | | | X | X | |
| Laboratory Assessments[e] | X | | X | | | | X | X | X |
| Urine Pregnancy Test | X | | X | | X | X | X | X | X |
| ECG | X | | X | | | | X | X | X |
| EEG[d] | X | | | | | | | | |
| MRI or CT Scan[e] | X | | | | | | | | |
| Randomization | | | X | | | | | | |
| Adverse Event Assessment | X | X | X | X | X | X | X | X | X |
| Previous & Concomitant Medications | X | X | X | X | X | X | X | X | X |
| Drug Dispensing | | | X | X | X | X | | | |
| Drug Return / Accountability | | | | X | X | X | X | X | |
| Patient Trial Card | X | | | | | | | | |

Appears This Way
On Original

| Study Periods | Selection | Baseline | | Treatment | | | | Early Discontinuation Visit[a] | Final Visit[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | 8 Weeks | | 12 Weeks | | | | | |
| Week | 0 | 4 | 8 | 10 | 12 | 16 | 20 | | 22 |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | | 8 |
| Study Medication Administration | | | | X | X | X | X | | |
| Drug Monitoring for Study Medication | | | | | X | X | X | X | |
| Medical Procedures | | X | X | X | X | X | X | X | X |

[a] If subject discontinued at visit 4, 5, 6, or 7, Early Discontinuation Visit had to be completed.
[b] Only subjects not switching to Keppra® IR completed this visit.
[c] Vital Signs included measurement of weight, height, blood pressure (BP), and pulse rate. Height was only recorded at Visit 1.
[d] At Visit 1, historical seizure frequency for the past 4 weeks was collected. Afterwards subjects were required to complete the Daily Record Card for seizure count each day.
[e] Including blood chemistry and hematology.
[f] Required during the Selection period only if no previous electroencephalogram (EEG) had been performed to confirm the diagnosis of partial onset seizures.
[g] Only for subjects who (1) had not had a CT Scan or MRI confirming the absence of a progressive lesion since being diagnosed with epilepsy, or (2) had changes on physical examination suggested a lesion had occurred since the last imaging procedure.

***Inclusion Criteria, reproduced from the Sponsor's Original Application***

• Signed and dated written informed consent. Signed and dated written assent if applicable.

• Subjects suffering from partial onset seizures according to the International League against Epilepsy (ILAE) classification of epileptic seizures, whether or not secondarily generalized.

• Subjects with diagnosed epilepsy for a minimum of 6 months prior to the selection visit.

• An EEG was to be present in the subject's hospital file but it might be normal if taken interictaly.

• Presence of the following during the eight weeks of the Baseline Period: at least eight partial seizures with or without secondary generalization and at least two partial seizures in each 4-week interval of the Baseline Period.

• Subjects reliable and mentally capable of adhering to the protocol, according to the Investigator's judgment.

• Male/female subjects, 12 to 70 years of age inclusive, weighing at least 50 kg at Visit 1. The lower age and body weight limit of 12 years old and 50 kg was based on the approved labeling for Keppra. In the Dosage and Administration section of Keppra labeling, the weight - based dosing guide for children indicates that children weighing more than 50 kg should be dosed as an adult. A child weighing 50 kg would generally correspond to approximately 12 years old of age.

• Female subjects without childbearing potential were eligible. Female subjects with childbearing potential were eligible if they used a medically accepted contraceptive method. The subjects had to understand the consequences and potential risks of inadequately protected sexual activity, be educated about and understood the proper use of contraceptive method, and undertook to inform the Investigator of any potential change in status.

• Subjects on a stable dose for at least four weeks before the Selection Visit (Visit 1) of at least one and no more than three other concomitant AEDs. Benzodiazepines were considered as one AED if taken at an average frequency greater than once a week; whatever the indication.

• Vagal Nerve Stimulator (VNS), as long as the settings were stable for at least 3 months prior to Visit 1. The VNS was counted as one AED.

• If past epilepsy surgery, documentation of failure of surgery outcome.

• Previous CT scan or MRI confirmed the subject's free of neoplasia, progressive cerebral disease or any other progressively neurodegenerative disease.

***Exclusion Criteria, reproduced from the Sponsor's Original Application***

• Females lactating or pregnant.

• Known alcohol or drug addiction or abuse.

• Known allergic reaction or intolerance to pyrrolidine derivatives (such as piracetam, succinimide, proline and rolitetracycline) and/or excipients (not exclusively, but principally to lactose, corn starch, cellulose).

• History of status epilepticus within the three months prior to the Selection Visit.

• History or current neoplasia, progressive cerebral disease or any other progressive neurodegenerative disease.

• Subjects whose seizures could not be reliably counted on a regular basis due to their fast and repetitive occurrence (clusters or flurries).

• Use of any medication (other than the concomitant AED) influencing the central nervous system (CNS) unless on a stable regimen for at least 4 weeks prior to the Selection Visit. Antidepressants (except amitriptyline, mianserin and fluoxetine), anxiolytics and hypnotics were allowed.

• Neuroleptics and traditional herb AEDs were not allowed.

• Subjects on felbamate.

• Subjects on ketogenic diet.

• Presence of another clinical disease (cardiovascular, hepatic, renal, auto-immune or associated with hematology, neurology or psychiatry) or any other disease which could interfere with the absorption, distribution, metabolism or excretion of the investigational product or with the subjects' ability to reliably complete the daily record card.

• History of recurrent psychotic or major affective disorder or suicide attempts.

• History or presence of pseudoseizures.

• Clinically significant abnormal laboratory values as assessed by the Investigator.

• History of poor compliance with visit schedule or medication intake.

• Subjects taking part in another clinical/pharmacological study in the 30 days prior to Visit 1.

• Subjects having already been treated with an adequate dose of LEV (at least 1000 mg/day) for more than 4 weeks and discontinued due to reasons related to lack of efficacy or due to tolerability problems.

• Subjects with any medical or surgical condition that might interfere with the subject's study participation i.e., scheduled elective surgery, etc.

*Dosage*

The only dosage studied was 2x500mg LEV XR tablets once daily. This is at the low end of the approved daily dosing for Keppra which is 1,000mg to 3,000 mg daily.

*Concomitant Medication*

Patient's needed to be on at least one and no more than three other AEDs. Benzodiazepines were considered as one AED if taken at an average frequency greater than once a week; whatever the indication. Vagal Nerve Stimulator (VNS) was counted as one AED. The use of any medication (other than the concomitant AED) influencing the central nervous system (CNS), unless on a stable regimen for at least 4 weeks prior to the Selection Visit, were not allowed. Antidepressants (except amitriptyline, mianserin and fluoxetine), anxiolytics and hypnotics were allowed. Neuroleptics, felbamate and traditional herb AEDs were not allowed.

Any medication, including over-the-counter products, other than the investigated drugs taken during the study had to be recorded in the source documentation and the Case Report Form. These records had to include the name of the drug, the dose, the date(s) and time of administration, and the indication for use.

The number (%) of subjects by the number of AEDs taken in each Analysis Period, as provided by the Sponsor, is displayed below.

| Number of AEDs | PBO N=79 n (%) | LEV XR N=79 n (%) |
|---|---|---|
| 0 | 1 (1.3) | 0 |
| 1 | 17 (21.5) | 27 (34.2) |
| 2 | 38 (48.1) | 36 (45.6) |
| 3 | 22 (27.8) | 12 (15.2) |
| > 3 | 1 (1.3) | 4 (5.1) |

The concomitant AEDs used by at least 5% of Subjects during the baseline period (ITT Population) are shown in the Sponsor's table reproduced below.

| AED Generic Name | PBO N=79 n (%) | LEV XR N=79 n (%) |
|---|---|---|
| Carbamazepine | 42 (53.2) | 42 (53.2) |
| Clobazam | 5 (6.3) | 11 (13.9) |
| Clonazepam | 7 (8.9) | 5 (6.3) |
| Ergenyl Chrono[a] | 2 (2.5) | 5 (6.3) |
| Gabapentin | 0 | 4 (5.1) |
| Lamotrigine | 18 (22.8) | 12 (15.2) |
| Oxcarbazepine | 7 (8.9) | 6 (7.6) |
| Phenobarbital | 7 (8.9) | 8 (10.1) |
| Phenytoin | 13 (16.5) | 8 (10.1) |
| Topiramate | 21 (26.6) | 10 (12.7) |
| Valproic acid | 30 (38.0) | 28 (35.4) |

Concomitant non-AEDs used by >5% of the subjects in one group during the baseline period for the double-blind, placebo-controlled study of LEV XR - N01235 ITT population are listed in the Sponsor's table shown below. No relevant imbalance between treatment groups was found in the concomitant non-AEDs medications used during the Baseline Period.

| Main Group<br>Therapeutic Group | PBO N=79 n (%) | LEV XR N=79 n (%) |
|---|---|---|
| Alimentary Tract and Metabolism | | |
| Stomatological Preparations | 2 (2.5) | 4 (5.1) |
| Blood and Blood Forming Organs | | |
| Vitamin B12 and Folic Acid | 4 (5.1) | 7 (8.9) |
| Cardiovascular System | | |
| Cholesterol and Triglyceride Reducers | 0 | 4 (5.1) |
| Musculo-Skeletal System | | |
| Antiinflammatory/Antirheumatic Prod., non-Steroids | 5 (6.3) | 5 (6.3) |
| Topical Products for Joint and Muscular Pain | 6 (7.6) | 7 (8.9) |
| Nervous System | | |
| Other Analgesics and Antipyretics | 14 (17.7) | 14 (17.7) |
| Sensory Organs | | |
| Antiinflammatory Agents | 2 (2.5) | 4 (5.1) |
| Various | | |
| All Other Therapeutic Products | 7 (8.9) | 2 (2.5) |

b(4)

*Analysis*

Populations considered for the efficacy analysis were the Intention-to-Treat population (consisting of the 79 subjects randomized to PBO and the 79 subjects randomized to LEV XR) and the PP population consisting of the 137 subjects in the ITT population (69 in the PBO group and 68 in the LEV XR group) without major

protocol deviation. The primary efficacy analysis was carried out on both the ITT and the PP populations as there were more than 10% subjects with major protocol deviations.

***Primary Endpoints, reproduced from the Sponsor's Original Application***

The primary endpoint of the study was to evaluate the efficacy of LEV XR in reducing the partial onset seizures frequency per week over a 12-week Treatment Period.

***Secondary Endpoints, reproduced from the Sponsor's Original Application***

• The total seizure frequency per week over the Treatment Period.

• The absolute and percentage (%) reduction from baseline in partial onset seizure frequency per week over the Treatment Period.

• The absolute and percentage (%) reduction from baseline in total seizure frequency per week over the Treatment Period.

• The responder rate (the proportion of subjects who have a $\geq$ 50% reduction in seizure frequency per week from baseline) for partial onset seizures and for total seizures over the Treatment Period.

• The categorical response to treatment: percent reduction from baseline in partial onset seizure and in total seizure frequency per week grouped into six categories (< -25%, - 25% to < 25%, 25% to < 50%, 50% to < 75%, 75% to < 100% and 100%) over the Treatment Period.

***Exploratory Endpoints, reproduced from the Sponsor's Original Application***

• The global evaluation of disease evolution using a Global Evaluation Scale (GES) assessed by the Investigator at the end of the Treatment Period.

• The number of seizure free days over the Baseline and Treatment Periods.

• The medical resources used over the Baseline and Treatment Periods, including concomitant medications, medical procedures and hospitalizations.

***Protocol Deviations***

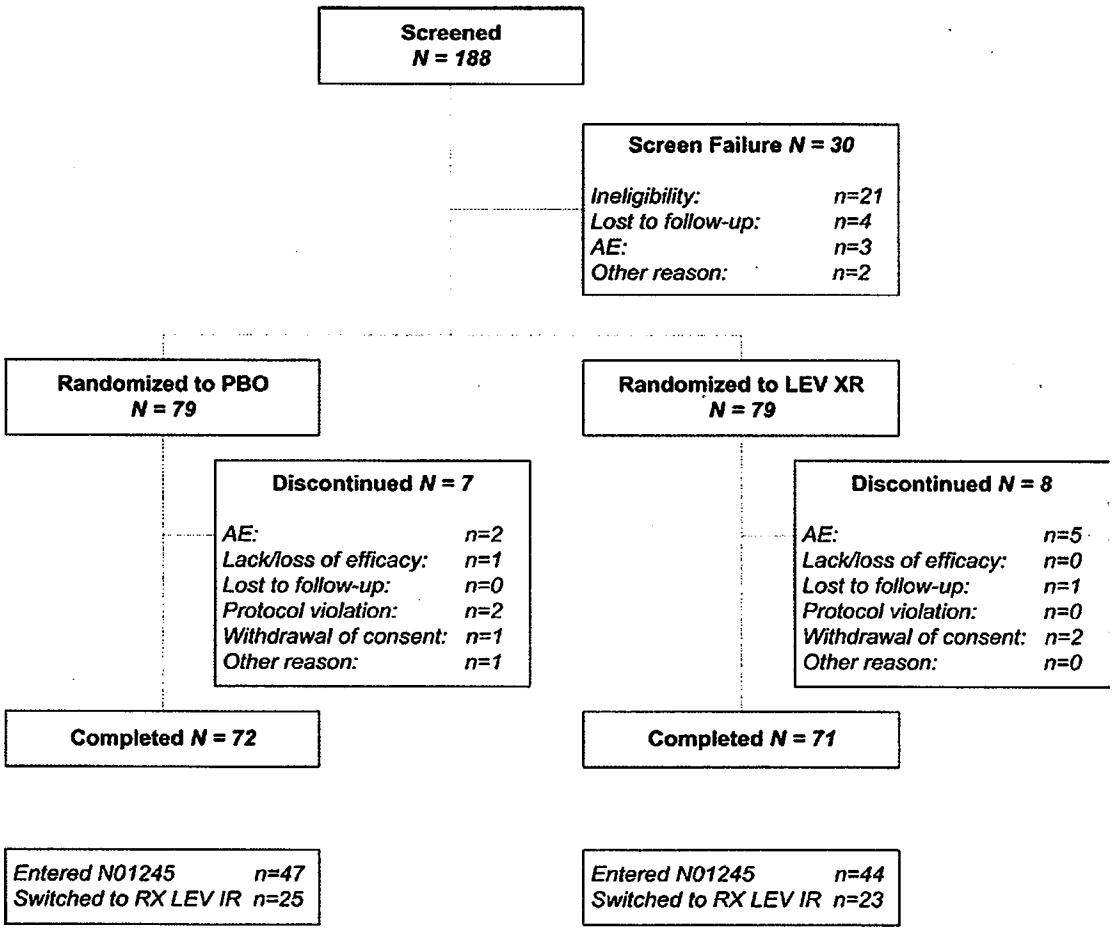
The number of subjects with at least one major protocol deviation leading to the exclusion from the Per Protocol (PP) population is listed in the Sponsor's table below.

| Categories | PBO N=79 n(%) | LEV XR N=79 n(%) |
|---|---|---|
| Compliance study medication: intake too low | 5 (6.3) | 5 (6.3) |
| Study medication: no intake | 1 (1.3) | 1 (1.3) |
| Deviation(s) in general | 0 | 1 (1.3) |
| Ineligibility in general | 4 (5.1) | 5 (6.3) |
| Total | 10 (12.7) | 11 (13.9) |

### 6.1.4 Efficacy Findings

*Disposition*

Subject Disposition is described in the Sponsor's figure below for study N01235. More subjects in the LEV XR group discontinued due to adverse events than in the PBO group, but the differences were not considered clinically relevant.




The disposition of the number of subjects (%) by country (%), as provided by the Sponsor, is presented in the table below.

| Country | Investigators N | PBO N=79 n(%) | LEV XR N=79 n(%) |
|---|---|---|---|
| Brazil | 1 | 0 | 1 (1.3) |
| Finland | 3 | 2 (2.5) | 2 (2.5) |
| India | 10 | 26 (32.9) | 25 (31.6) |
| Mexico | 4 | 16 (20.3) | 15 (19.0) |
| Russian Federation | 9 | 19 (24.1) | 19 (24.1) |
| South Africa | 2 | 4 (5.1) | 4 (5.1) |
| Ukraine | 5 | 12 (15.2) | 13 (16.5) |

The number of subjects per center was too small to allow a meaningful investigation of the consistency of treatment effect across centers. At the end of the recruitment and before unblinding, pooling of the centers was done based on the country and number of subjects in each center. Pooling 1: all centers from India; Pooling 2: all centers from Brazil, Mexico and South Africa; Pooling 3: all centers from the Russian Federation and Pooling 4: all centers from Ukraine and Finland. The percent reduction from baseline in partial seizure frequency per week by pooled countries and by country is provided in the Sponsor's table below and summarized by pooled countries.

| Pooled Countries | Statistics | PBO N=79 | LEV XR N=79 |
|---|---|---|---|
| India | n | 26 | 24 |
| | Mean (SD) | 19.44 (59.81) | 31.76 (63.10) |
| | Median | 35.31 | 39.73 |
| | Q1 - Q3 | -6.63 - 54.17 | 7.15 - 75.38 |
| | Min - Max | -199 - 100 | -210.5 - 100.0 |
| Brazil, Mexico, South Africa | n | 19 | 17 |
| | Mean (SD) | 18.71 (49.37) | 53.28 (46.79) |
| | Median | 33.60 | 67.18 |
| | Q1 - Q3 | -4.54 - 51.81 | 23.81 - 93.94 |
| | Min - Max | -102.4 - 91.0 | -51.7 - 100.0 |
| Russian Federation | n | 19 | 18 |
| | Mean (SD) | 9.74 (52.65) | 43.29 (30.44) |
| | Median | 26.74 | 33.73 |
| | Q1 - Q3 | -46.41 - 51.81 | 27.87 - 64.04 |
| | Min - Max | -73.5 - 82.0 | -26.3 - 100.0 |
| Ukraine, Finland | n | 14 | 15 |
| | Mean (SD) | 32.98 (37.88) | 47.28 (41.85) |
| | Median | 30.41 | 55.54 |
| | Q1 - Q3 | -0.38 - 51.78 | 15.30 - 70.01 |
| | Min - Max | -22.2 - 100.0 | -44.4 - 100.0 |

***Demographics***

The demographic characteristics for the ITT population are listed in the table below. The four subjects in the PBO group with weights below the inclusion criterion weights were considered as minor protocol deviations. There were only six adolescents in the LEV XR group, as detailed in the Sponsor's table reproduced below.

| Characteristics | PBO N=79 | LEV XR N=79 |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 32.38 (12.60) | 33.97 (13.41) |
| Min - Max | 13.3 – 67.9 | 12.2 – 67.9 |
| Median | 29.61 | 33.71 |
| **Gender** | | |
| Male (n%) | 47 (59.5) | 52 (65.8) |
| Female (n%) | 32 (40.5) | 27 (34.2) |
| **Race** | | |
| White | 35 (44.3) | 37 (46.8) |
| Asian / Pacific Islander | 1 (1.3) | 0 |
| Hispanic | 15 (19.0) | 15 (19.0) |
| Indian / Pakistani | 27 (34.2) | 27 (34.2) |
| Other | 1 (1.3)[a] | 0 |
| **Weight (kg)** | | |
| Mean (SD) | 67.80 (15.55) | 70.21 (15.66) |
| Min – Max | 48.0 – 134.0 | 50.0 – 118.0 |
| Median | 64.00 | 69.00 |
| **Height (cm)** | | |
| Mean (SD) | 165.7 (9.8) | 168.1 (10.3) |
| Min – Max | 138 - 189 | 150 - 188 |
| Median | 165.0 | 170.0 |
| **BMI (kg/m²)** | | |
| Mean (SD) | 24.60 (4.55) | 24.76 (4.71) |
| Min – Max | 16.8 – 38.6 | 17.6 – 47.1 |
| Median | 23.70 | 23.78 |

A Sponsor's summary of the history of epilepsy for the double-blind, placebo-controlled study of LEV XR - N01235 ITT Population-is listed below.

| | PBO N=79 | LEV XR N=79 |
|---|---|---|
| Epilepsy Duration at Randomization Visit (years) | | |
| Mean (SD) | 16.43 (11.93) | 13.11 (10.87) |
| Min - Max | 0.7 – 53.5 | 0.8 – 42.6 |
| Age at time of Epilepsy Diagnosis (years) | | |
| Mean (SD) | 15.95 (11.51) | 20.86 (15.18) |
| Min - Max | 0.1 – 47.9 | 0.3 – 61.5 |

Individual data on the etiology of epilepsy, as provided by the Sponsor, in the ITT population are provided in the table below.

| | PBO N=79 n (%) | LEV XR N=79 N (%) |
|---|---|---|
| Unknown | 35 (44.3) | 43 (54.4) |
| Genetic origin or idiopathic | 2 (2.5) | 0 |
| Congenital malformation | 3 (3.8) | 1 (1.3) |
| Asphyxia during birth | 8 (10.1) | 6 (7.6) |
| Complications due to pregnancy | 1 (1.3) | 1 (1.3) |
| Intra-uterine viral infection | 1 (1.3) | 0 |
| Cranial trauma | 14 (17.7) | 7 (8.9) |
| Primary degenerative lesion | 1 (1.3) | 0 |
| Cerebrovascular accident | 1 (1.3) | 6 (7.6) |
| Cerebral infection | 7 (8.9) | 12 (15.2) |
| Other | 8 (10.1) | 5 (6.3) |

The Sponsor's information regarding the ILAE classification of epileptic syndromes for the subjects who participated in N01235 is summarized in the table below.

| | PBO N=79 n (%) | LEV XR N=79 n (%) |
|---|---|---|
| Epileptic syndrome unknown | 4 (5.1) | 7 (8.9) |
| Confirmed / suspected syndromes | 75 (94.9) | 72 (91.1) |
| Localization-related - Idiopathic | 7 (8.9) | 4 (5.1) |
| Localization-related - Symptomatic | 44 (55.7) | 38 (48.1) |
| Localization-related - Cryptogenic | 20 (25.3) | 25 (31.6) |
| Generalized - Idiopathic | 1 (1.3) | 4 (5.1) |
| Generalized - Symptomatic | 2 (2.5) | 2 (2.5) |
| Epilepsies and syndromes undetermined (whether or not focal or generalized) | 4 (5.1) | 2 (2.5) |

Information from the Sponsor regarding the classification of epileptic seizures recorded at the Screening Visit for the subjects who participated in N01235 is summarized below.

| Seizure Type (ILAE Classification)<br>Seizure Subtype | PBO<br>N=79<br>n (%) | LEV XR<br>N=79<br>n (%) |
|---|---|---|
| **Partial Seizures** | 79 (100.0) | 79 (100.0) |
| Simple Partial Seizures (IA) | 33 (41.8) | 36 (45.6) |
| Complex Partial Seizures (IB) | 53 (67.1) | 52 (65.8) |
| Partial seizures Secondarily Generalized (IC) | 66 (83.5) | 56 (70.9) |
| **Generalized Seizures (II)** | 1 (1.3) | 2 (2.5) |
| Absence Seizures (IIA1) | 1 (1.3) | 1 (1.3) |
| Tonic-Clonic Seizures (IIE) | 1 (1.3) | 1 (1.3) |

Individual precipitating factors of seizures are provided in the Sponsor's table below.

| | PBO<br>N=79<br>n (%) | LEV XR<br>N=79<br>n (%) |
|---|---|---|
| No precipitating factor | 54 (68.4) | 56 (70.9) |
| At least one precipitating factor | 25 (31.6) | 23 (29.1) |
| Alcohol or drug withdrawal | 3 (3.8) | 3 (3.8) |
| Stress | 14 (17.7) | 12 (15.2) |
| Hyperventilation | 1 (1.3) | 0 |
| Sleep deprivation | 9 (11.4) | 8 (10.1) |
| Hormonal changes | 5 (6.3) | 1 (1.3) |
| Photic stimulation | 1 (1.3) | 2 (2.5) |
| Other | 10 (12.7) | 8 (10.1) |

The seizure counts during the 8-week baseline period are provided by the Sponsor in the table below. Seizure counts during the four weeks before the Screening visit did now show relevant differences between treatment groups.

| Seizure Counts | Statistics | PBO N=79 | LEV XR N=79 |
|---|---|---|---|
| Type I | n | 79 | 78 |
| | Mean (SD) | 30.3 (52.6) | 39.7 (66.3) |
| | Median | 18 | 15 |
| | Q1 - Q3 | 11 - 27 | 9 - 33 |
| | Min - Max | 8 - 428 | 0 - 378 |
| Type (IA) | Missing n(%) | 1 (1.3) | 1 (1.3) |
| | 0 n(%) | 42 (53.2) | 36 (45.6) |
| | 0 - 8 n(%) | 14 (17.7) | 18 (22.8) |
| | 9 - 16 n(%) | 7 (8.9) | 9 (11.4) |
| | >16 n(%) | 15 (19.0) | 15 (19.0) |
| Type (IB) | Missing n(%) | 0 | 0 |
| | 0 n(%) | 24 (30.4) | 25 (31.6) |
| | 0 - 8 n(%) | 14 (17.7) | 19 (24.1) |
| | 9 - 16 n(%) | 24 (30.4) | 20 (25.3) |
| | >16 n(%) | 17 (21.5) | 15 (19.0) |
| Type (IC) | Missing n(%) | 0 | 0 |
| | 0 n(%) | 34 (43.0) | 43 (54.4) |
| | 0 - 8 n(%) | 35 (44.3) | 31 (39.2) |
| | 9 - 16 n(%) | 5 (6.3) | 4 (5.1) |
| | >16 n(%) | 5 (6.3) | 1 (1.3) |
| All Types | n | 79 | 79 |
| | Mean (SD) | 30.6 (52.5) | 40.7 (66.0) |
| | Median | 18 | 17 |
| | Q1 - Q3 | 11 - 27 | 9 - 36 |
| | Min - Max | 8 - 428 | 8 - 378 |

Three clinical pharmacology studies were completed for LEV XR development. The following table from the Sponsor summarizes the subject demographics from these studies. All subjects in these studies were healthy volunteers.

| Characteristics | N01140 (N=12) | N01160 (N=24) | N01260 (N=24) |
|---|---|---|---|
| **Age** | | | |
| Mean (SD) | 30.49 (11.13) | 30.81 (10.28) | 33.51 (8.92) |
| Range (years) | 19.6 – 56.0 | 18.6 – 51.9 | 22.0 – 52.4 |
| Median | 26.70 | 27.56 | 33.44 |
| **Sex** | | | |
| Male | 12 | 12 | 12 |
| Female | 0 | 12 | 12 |
| **Race** | | | |
| Caucasian | 8 (66.7%) | 21 (87.5%) | 20 (83.0%) |
| Black / African American | 3 (25.0%) | 2 (8.3%) | 4 (17.0%) |
| Other | 1 8.3%) | 1 (4.2%) | 0 |
| Asian / Pacific Islander | 0 | 0 | 0 |
| **Height (cm)** | | | |
| Mean (SD) | 175.7 (6.98) | 168.8 (8.0) | 170.6 (8.7) |
| Range (cm) | 165 - 189 | 154 - 181 | 158 – 186 |
| Median | 177.5 | 169.5 | 170.0 |
| **Weight (kg)** | | | |
| Mean (SD) | 72.67 (10.76) | 66.3 (7.7) | 65.8 (10.6) |
| Range (kg) | 56.0 – 89.0 | 51.0 – 79.0 | 50.0 – 90.5 |
| Median | 71.5 | 68.3 | 64.5 |

***Primary Endpoint, as taken from the Sponsor's Original Application***

The primary endpoint was the partial seizure frequency per week over the treatment Period. The log-transformed partial onset seizure frequency per week calculated from the Treatment Period was compared between LEV XR and placebo using an ANCOVA model. Descriptive statistics for the partial seizure frequency per week over the Baseline and Treatment Periods, its reduction and percent reduction from baseline over the Treatment Period by visit and period were computed. ANCOVA of (log-) partial seizure frequency per week over Treatment Period, using the (log-) baseline seizure frequency per week as a covariate were provided. The percent reduction of LEV XR over placebo, its 2-sided 95% CI, and the p-value were presented. The seizure types and counts by day of presence during the Baseline and Treatment Periods for individual subjects are listed.

The estimated percent reductions over PBO in partial onset seizure frequency per week over the Treatment Period was 18.6% in the PP population; this reduction over PBO was statistically significant at the 2-sided 5% significance level ($p = 0.003$).

| Partial onset seizure (Type I) frequency per week | PBO N=69 | LEV XR N=68 |
|---|---|---|
| n | 69 | 67 |
| Log- transformed value | | |
| LS Mean (SE) | 1.119 (0.048) | 0.914 (0.049) |
| 2-sided 95% CI (LEV XR – PBO) | | 0.070 - 0.341 |
| Inverse-transformed value | | |
| Percentage of reduction of LEV XR over PBO | | 18.6% |
| 2-sided 95% confidence interval of the % reduction | | 6.7% - 28.9% |
| p-value | | 0.003 |

***Secondary Endpoints, as taken from the Sponsor's Original Application***

*Total Seizure Frequency per Week over the Treatment Period*

The estimated percent reductions over PBO in total seizure frequency per week over the Treatment Period was 14.7% in the ITT population; this reduction over PBO was statistically significant at the 2-sided 5% significance level (p = 0.034).

*Absolute and Percent (%) Reduction from Baseline for Partial Onset Seizure Frequency per Week over the Treatment Period*

The Hodges-Lehmann estimator and its 2-sided 95% CI of the median of the differences between the treatment groups on the percent reduction from baseline in partial (Type I) onset seizure frequency per week over the Treatment Period was 21.9% (7.3% - 36.7%). The difference between treatment group on the percent reduction from baseline was statistically significant (p = 0.002) at the 5% significance level as detailed below.

*Absolute and Percentage (%) Reduction from Baseline for Total Seizure Frequency per Week over the Treatment Period*

The Hodges-Lehmann estimator and its 2-sided 95% CI of the median of the differences between the treatment groups on the reduction from baseline in total seizure frequency per week over the Treatment Period was 0.5 (0.1 - 0.9). The difference between treatment group on the reduction from baseline was statistically significant (p = 0.012) at the 5% significance level.

*Responder Rates*

A responder was defined as a subject having at least 50% reduction in seizure frequency per week from baseline in partial onset seizures over the Treatment Period in the ITT Population. Subjects with missing or unknown count during the Treatment Period were considered as non-responder in the analyses on responder rate. The proportion of responders over the Treatment Period was higher after LEV XR (43.0%) than after PBO (29.1%); this difference in favor of LEV XR was not statistically significant (p = 0.070) at the 5% significance level.

Similarly, the proportion of responders in total seizure frequency per week over the Treatment Period in the ITT Population was higher after LEV XR (43.0%) than after PBO (30.4%); this difference in favor of LEV XR was not statistically significant (p = 0.100) at the 5% significance level.

*Categorical Response*

Percent reductions from baseline over the Treatment Period in partial onset and in total seizures frequency per week were grouped into five categories (< -25%, -25% to < 25%, 25% to < 75%, 75% to < 100% and 100% - the initially foreseen categories 25% to < 50% and 50% < 75% being merged. Subjects with missing or unknown counts during the Treatment Period were considered as worsening (< -25%) in the analyses on categorical response. The categorized responses in partial onset seizure frequency per week over the Treatment Period showed that a larger number of subjects had a very positive response(≥ 75%) after LEV XR than after PBO [19 (24.1%) vs. 9 (11.4%), respectively]. The distribution difference in categorized responses was statistically significant (p = 0.033) at the 5% significance level.

***Exploratory Endpoints***

Results, on a Global Evaluation Scale (GES), of the Investigator's global evaluation of disease evolution at the end of the Treatment Period in the ITT population are provided in the table below. The proportion of subjects with a marked improvement was larger in the LEV XR group than in the PBO group (27.6% vs. 15.6%). No relevant differences between groups were observed in the other classes of the global evaluation scale, as provided by the Sponsor in this table.

| Global Evaluation Scale | PBO N=79 n(%) | LEV XR N=79 n(%) |
|---|---|---|
| n | 77 | 76 |
| Marked worsening | 1 (1.3) | 0 |
| Moderate worsening | 2 (2.6) | 1 (1.3) |
| Slight worsening | 6 (7.8) | 4 (5.3) |
| No change | 19 (24.7) | 16 (21.1) |
| Slight improvement | 16 (20.8) | 13 (17.1) |
| Moderate improvement | 21 (27.3) | 21 (27.6) |
| Marked improvement | 12 (15.6) | 21 (27.6) |
| p-value [a] | | 0.109 |

### 6.1.5 Efficacy Conclusions

After an 8-week qualifying Baseline Period, 158 refractory epileptic subjects (79 PBO; 79 LEV XR) (ITT population) aged 12 to 70 years and suffering from partial onset seizures were randomized in this placebo-controlled, double-blind study conducted in 34 investigative sites across 7 countries. After randomization, subjects received LEV XR 2x500 mg/day or 2 matching placebo tablets once daily every evening during a 12-week period (Treatment Period). Demographic and baseline characteristics of both treatment groups were well matched. In this study, approximately one-third of the subjects were taking 3 concomitant AEDs. The median percent reductions in partial onset seizure frequency per week over the Treatment Period from Baseline were 46.1% in LEV XR vs. 33.4% in PBO. The primary efficacy, the percent reductions over PBO in partial onset seizure frequency per week over the Treatment Period was 14.4% in the ITT population; this reduction over

PBO was statistically significant at the 2-sided 5% significance level (p = 0.038). This percent reduction increased to 18.6% (p = 0.003) after excluding the subjects with major protocol deviations [10 subjects (12.7%) in the PBO group; 11 (13.9%) in the LEV XR group]. The absolute and percent reduction from baseline in either partial onset or total seizure frequency per week over the Treatment Period yielded similar results in favor of LEV XR over PBO, all significant at the 2-sided 5% significance level. The absolute and median percentage of reduction from baseline in partial onset seizure frequency per week were consistently higher in LEV XR than in PBO in all the pooled countries. The proportion of responders in partial onset seizure frequency per week (at least 50% reduction from baseline over the Treatment Period) was higher in LEV XR (43.0%) than in PBO (29.1%); this difference was; however, not statistically significant (p = 0.070). Eight subjects (10.1%) in the LEV XR group and 2 subjects (2.5%) in the PBO group reported 100% reduction in partial onset seizure frequency per week during the Treatment Period from the Baseline Period. Among these 10 subjects, all subjects in the LEV XR group and one subject in the PBO group completed the 12-week Treatment Period; one subject in the PBO group discontinued the study at Visit 4. Although the placebo response is higher than expected, the efficacy observed in this study appears similar to what was observed in two previous studies of Keppra with 1000 mg dosed as 500 mg, b.i.d. (N051 and N132). The proportion of subjects with a marked improvement was larger in LEV XR than in PBO (27.6% vs. 15.6%) according to the Investigators' evaluation (GES scale).

This study has demonstrated a reduction in partial seizures when Keppra XR was used as a once daily add-on therapy in adult patients with refractory epilepsy. There were inadequate numbers of adolescent patients (ages 12 to 16 years) in this study [redacted] b(4)

# 7 INTEGRATED REVIEW OF SAFETY

## 7.1 Methods and Findings

Adverse events were coded using MedDRA (Version 9.0). Two sources of information are described, the double-blind, placebo-controlled study N01235 and the three pharmacology studies. 158 patients with epilepsy were randomized in Study N01235, 79 to LEV XR, of which only 77 subjects were exposed to LEV XR (one subject was excluded because drug was not dispensed, while another was excluded because she returned all the tablets received at the site). A total of 143 (90.5%) subjects completed the study; 72 (91.1%) in the placebo group and 71 (89.9%) in the LEV XR group. 60 subjects were exposed to LEV XR in the 3 clinical pharmacology studies. The ITT population comprised all the randomized patients. Although this population was the primary subset for the analysis of efficacy data, the Safety population comprised all subjects who were dispensed medication. The three pharmacology studies included only healthy volunteers. There were a total of 60 Subjects. Therefore there were 137 unique exposures to LEV XR. No pooling of safety data occurred; safety from the efficacy and clinical pharmacology studies is described separately. Therefore, the safety population included those subjects exposed to drug in the following studies. The details of these studies are provided by the Sponsor in table form and reproduced below.

| Study No. | No. Randomized (Exposed to XR) | Dates of Conduct / Countries | Overview of Design |
|---|---|---|---|
| **Subjects with Partial Onset Seizures** | | | |
| N01235 | 158 (77) | 21-Aug-2006 – 30-May-2007 / Brazil, Finland, India, Mexico, Russian Federation, South Africa, Ukraine | Double-blind, placebo-controlled, randomized, 1000 mg once daily, as add-on therapy in patients 12 – 70 years of age with refractory epilepsy with POS; 8-week baseline followed by 12 weeks of treatment. |
| **Healthy Volunteers** | | | |
| N01140 | 12 (12) | 16-Mar-2005 – 25-May-2005 / France | Single dose, open-label pilot study to compare the pharmacokinetics of LEV 500 mg from 3 XR test formulations with the IR reference formulation in healthy volunteers and to assess the influence of food on one of the test formulations. (Bioequivalence study) |
| N01160 | 24 (24) | 04-Jul-2006 – 02-Sep-2006 / France | Randomized, open-label, three-way crossover study of LEV XR (1000 mg, once daily) and LEV IR (500 mg B.I.D.). Single and multiple dose bioequivalence and assessment of food effect on LEV XR in healthy volunteers. |
| N01260 | 24 (24) | 05-Jan-2007 – 26-Feb-2007 / France | Randomized, open-label, single dose, three-way crossover dose proportionality study of LEV XR 1000 mg, 2000 mg, and 3000 mg, in healthy volunteers. |

Although adverse events (AEs) were coded using MEDRA (version 9), some modifications were made by the Sponsor. These included the remapping of some Preferred Terms from the MedRA Primary System Organ Class (SOC) to a UCB SOC and the creation of UCB Grouping Terms. Thus "increased liver enzymes" where moved from "investigations" to "Hepatobiliary Disorders." This change also included placed some accepted psychiatric terms into a more appropriate higher level group (e.g. restlessness under anxiety disorders).

The Sponsor considered an AE as drug-related when the relationship to study drug was assessed by the Investigator as possible, probable or highly probable. AEs with missing relationships were also considered as drug-related. Sixteen subjects (20.3%) in the PBO group and 18 (23.4%) in the LEV XR group had at least one drug-related TEAE. The incidence of drug-related TEAEs was similar in both treatment groups. The TEAEs in Gastrointestinal Disorders, and General Disorders UCB SOC were, however, more frequent in the LEV XR group. A similar imbalance between treatment groups was observed for headache (reported in six subjects [7.6%] under PBO and in one subject [1.3%] under LEV XR), and for somnolence (reported in one subject [1.3%] under PBO and in six subjects [7.8%] under LEV XR).

An AE was classified as pre-treatment if its onset date was before first study drug intake. Twenty-six (32.9%) subjects in the PBO group, and 25 (32.5%) in the LEV XR group reported at least one pre-treatment AE. For study N01235, the pre-treatment AEs with the highest incidences (above 2% within group) were reported in the "Cardiac Disorders", "Gastrointestinal Disorders", "General Disorders and Administrative Site Conditions", "Infections and Infestations", "Musculoskeletal and Connective Tissue Disorders", "Nervous System Disorders", and "Psychiatric Disorders" UCB SOC. The highest incidences of events were reported in the SOCs of Infections and Infestations, and Nervous System Disorders. No important differences in the nature and the number of pre-treatment AEs reported in the PBO and LEV XR groups were observed. No pre-treatment SAEs were reported in the three safety population studies.

An AE was classified as treatment-emergent (TEAE) if its onset date was on or after first study drug intake; post-treatment AEs were also classified as TEAEs. A similar number of subjects in the PBO and LEV XR groups experienced at least one TEAE. The number of subjects with severe or serious TEAEs was small in both groups but larger in the LEV XR group. With the exception of headache, reported more frequently under PBO, and influenza, irritability, and somnolence reported more frequently under LEV XR, no important difference in the nature and the number of TEAEs reported in the PBO and LEV XR groups was observed. However, after aggregating asthenia and fatigue, it appeared that these events were also more frequently reported in the LEV XR group than in the PBO group. Anxiety and nervousness were reported 2.5% in the PBO group but none in the LEV XR group.

### 7.1.2 Serious Adverse Events and Death

A serious adverse event (SAE) was defined as any untoward medical occurrence that, at any dose, resulted in death, was life threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly/birth defect. The Sponsor's table below summarizes the treatment emergent SAEs which occurred during the controlled clinical trial.

| Subject | Treatment | TTE [DOE] | Verbatim / MedDRA PT | Severity | Relationship | Outcome |
|---|---|---|---|---|---|---|
| 4003/0008 | PBO | 32 [3]H | Stupor / Stupor | Severe | Possible | Resolved |
| 5006/0003 | PBO | 27 [2]H | Series epileptic seizures with secondary generalization (N4) / Partial seizures with secondary generalization | Moderate | Unlikely | Resolved |
| | | 42 [3]H | Epilepsy aggravated / Epilepsy | Moderate | Unlikely | Resolved |
| 3002/0007 | LEV XR | 65 [6]H | Acute respiratory failure due to pulmonary bronchiecteis (single comprehensive medical event) / Respiratory failure | Severe | Unlikely | Fatal |
| 3009/0002 | LEV XR | 17 [1] | Epilepsy aggravated / Epilepsy | Severe | Possible | Resolved |
| 3010/0007 | LEV XR | 2 [1]H | Skin Rash / Rash | Moderate | Possible | Resolved |
| 5004/0001 | LEV XR | 59 [12]H | Ischemic stroke / Ischaemic stroke | Severe | Possible | Sequalae |
| 5004/0003 | LEV XR | 25 [2] | Repeating simple seizures / Simple partial seizures | Severe | Possible | Resolved |
| 5004/0005 | LEV XR | 8 [24]H | Mild traumation brain injury (concussion) / Concussion | Severe | None | Sequalae |

One subject in the LEV XR group died during study. The subject, a 64.8 year old Male Indian, in the LEV XR treatment group had an "acute respiratory failure due to pulmonary bronchiecteis (single comprehensive medical event)" (Investigator's verbatim). This subject had a medical history of "breathlessness" (treated with theophylline 200 mg BID and another illegible drug 150 mg daily within 30 days before Visit 1, apparently discontinued during the study). The event began 65 days after first study drug administration and was considered by the investigator as unlikely related to the study drug. On day 65 the patient presented with breathlessness and a bloody cough and was admitted to a local hospital and then transferred to another hospital. The study drug was discontinued on that day. The patient improved with "treatment" on that first day but four days later had an "episode of severe dyspnea" and died. At the time of the event, the patient was not taking any other concomitant non-AEDs. His concomitant AED treatment included Valproic acid and Oxatomide. Based on my review of the clinical data available, I feel this event is not likely related to the study drug.

One subject randomized in the LEV XR group who did not take study drug medication (and was, therefore, excluded from the safety population) reported two SAEs. This 21.7 year old Hispanic Female had severe, continuous epileptic status (Investigator's verbatim); the event resolved after four days. The same subject also reported a moderate, continuous urinary tract infection (Investigator's verbatim) resolving after eight days. In the safety population, two subjects (2.5%) in the PBO group and 5 subjects (6.5%) in the LEV XR group (excluding the subject who died) reported at least one SAE. All SAEs reported were transient and 2 had sequelae: 1 of ischemic stroke and 1 of brain trauma.

Based on my review of the available clinical data, I feel these remaining SAEs were not likely related to the study drug.

In the safety population, two subjects (2.5%) in the PBO group and 5 subjects (6.5%) in the LEV XR group (excluding the subject who died) reported at least one SAE. The narratives of all of the remaining severe AEs were reviewed, with the exception of 4003/0008, 5004/0003 and 5004/0005 which could not be located. Subject 5006/0003 had an increase in epileptic seizures and withdrew his consent after 51 days on PBO. Review of the clinical data does not suggest any relationship to study drug. The death of subject 3002/0007 is reviewed above. Subject 3009/0002 developed recurrent simple partial seizures, with secondary generalization, 17 days after being randomized to LEV XR. The subject withdrew from the study. Review of the clinical data available does not suggest any relationship to study drug. Subject 3010/0007 developed a diffuse skin rash with mouth ulcerations about eight hours after her first dose of LEV XR. The subject had a history of allergic reactions to at least two previous AEDs. After hospitalization and symptomatic treatment, there was complete resolution of the rash. Review of this time course with the Division of Dermatology and Dental Products did not suggest the potential for a Stevens-Johnson Syndrome. Review of the available clinical data suggests that this was likely related to study drug. Subject 5004-0001 developed a recurrent ischemic stroke 59 days after being randomized to LEV XR. Given the subjects multiple risk factors for ischemic stroke (previous ischemic stroke, myocardial infarction, non-insulin-dependent diabetes mellitus and obesity), along with review of available clinical data, this event is felt to be unlikely related to study drug. LEV XR was continued and the patient completed the study and then discontinued levetiracetam intake.

No Serious Adverse Events were reported in any of the three clinical pharmacology studies, neither pre-treatment nor treatment emergent.

### 7.1.3 Adverse events associated with dropouts

Adverse events that led to discontinuation in dose are listed in the Sponsor's table reproduced below. Two subjects (2.5%) in the PBO group and 4 subjects (5.2%) in the LEV XR group reported TEAEs leading to permanent study drug discontinuation. Subject 7002/0006 withdrew from the study 18 days after being randomized to PBO. The Investigator assessed the event to be highly probably related to study drug and the subject withdrew from the study. Based on review of available clinical data, this event is not likely related to study drug. Subject 3001/0003 experienced asthenia 73 days after being randomized to LEV XR. Based on review of available clinical data, this event is unlikely to be related to LEV XR.

| Subject # | Group | TTE [DOE] | Verbatim / MedDRA PT | Severity | Relation-ship | Outcome |
|---|---|---|---|---|---|---|
| 4003/0008 | PBO | 32 [3]H | Stupor / Stupor | Severe | Possible | Resolved |
| 7002/0006 | PBO | 18 [13] | Psychomotor agitation / Psychomotor hyperactivity | Moderate | Highly probable | Resolved |
| 3001/0003 | LEV XR | 73 [5] | Asthenia / Asthenia | Mild | Possible | Resolved |
| 3002/0007 | LEV XR | 65 [6]H | Acute respiratory failure due to pulmonary bronchiecteis (single comprehensive medical event) / Respiratory failure | Severe | Unlikely | Fatal |
| 3009/0002 | LEV XR | 17 [1] | Epilepsy aggravated / Epilepsy | Severe | Possible | Resolved |
| 3010/0007 | LEV XR | 2 [1]H | Skin rash / Rash | Moderate | Possible | Resolved |
| | | 2 [5] | Mouth ulcer / Mouth ulceration | Moderate | Possible | Resolved |

One subject (1.3%) in the PBO group and 2 subjects (2.6%) in the LEV XR group reported TEAEs leading to temporary study drug discontinuation are shown in the Sponsor's table below.

| Subject # | Group | TTE [DOE] | Verbatim / MedDRA PT | Severity | Relation-ship | Outcome |
|---|---|---|---|---|---|---|
| 6002/0001 | PBO | 2 [13] | Diplopia / Diplopia | Mild | Possible | Resolved |
| | | 2 [13] | Headache / Headache | Mild | Possible | Resolved |
| | | 2 [13] | Forgetfulness / Memory impairment | Moderate | Probable | Resolved |
| | | 2 [13] | Emotional lability / Affect lability | Mild | Unlikely | Resolved |
| | | 2 [13] | Episodic confusion / Confusional state | Moderate | Probable | Resolved |
| | | 2 [13] | Orthostatic hypotension / Orthostatic hypotension | Mild | Probable | Resolved |
| | | 2 [90] | Dizziness / Dizziness | Mild | Highly probable | Sequalae |
| | | 2 [90] | Sleepiness / Somnolence | Moderate | Probable | Sequalae |
| 5004/0003[a] | LEV XR | 25 [2]H | Repeating simple seizures / Simple partial seizures | Severe | Possible | Resolved |
| 5004/0004 | LEV XR | 26 [5] | Constipation / Constipation | Severe | Possible | Resolved |



No subjects in either the PBO or LEV XR groups reported any TEAEs leading to study drug dose increase. One subject (1.3%) in the PBO group and one subject (1.3%) in the LEV XR group reported at least one TEAE

leading to study drug dose decrease. No adverse events (pre-treatment nor treatment emergent), as shown in the Sponsor's table below, led to complete or temporary dose change or interruption.

| | PBO (N=79) n (%) | LEV XR (N=77) n (%) |
|---|---|---|
| Total number of AEs | 125 | 118 |
| Subjects with at least one AE | 43 (54.4) | 41 (53.2) |
| Subjects with AEs leading to permanent study drug discontinuation | 2 (2.5) | 4 (5.2) |
| Subjects with AEs leading to temporary study drug discontinuation | 1 (1.3) | 2 (2.6) |
| Subjects with AEs leading to dose decreased | 1 (1.3) | 1 (1.3) |
| Subjects with AEs that led to hospitalization or prolongation of hospitalization | 2 (2.5) | 4 (5.2) |
| Subjects with drug-related AEs | 16 (20.3) | 18 (23.4) |
| Subjects with severe AEs | 2 (2.5) | 6 (7.8) |
| | | |
| Subjects with SAEs | 2 (2.5) | 6 (7.8) |
| Subjects with drug-related SAEs | 1 (1.3) | 4 (5.2) |
| | | |
| Number of deaths | 0 | 1 (1.3) |

Since one of the common concerns of extended release formulations is "breakthrough" seizures. In order to further evaluate the safety profile of LEV XR, subjects who discontinued the study due to lack/loss of efficacy or reported any adverse events relating to "seizure" or "epilepsy" were reviewed. One subject in the PBO group and none in the LEV XR group discontinued the study prematurely due to lack/loss of efficacy. One subject reported an episode of status epilepticus prior to randomization. This subject was randomized to LEV XR but no study drug was dispensed due to this event and the subject was excluded from the safety population. All "seizure" or "epilepsy" related TEAEs reported during the study are summarized in the Sponsor's table below.

| Subject # | Group | TTE [DOE] | Verbatim / MedDRA PT | Severity/SAE | Relation-ship | Outcome |
|---|---|---|---|---|---|---|
| 3008/0007 | PBO | 81 [1] | Seizure aggravation / Convulsion | Moderate / No | Unlikely | Resolved |
| 5006/0003 | PBO | 27 [2] H | Series epileptic seizures with secondary generalization (N4) / Partial seizures with secondary generalization | Moderate / Yes | Unlikely | Resolved |
| | | 42 [3] H | Epilepsy aggravated / Epilepsy | Moderate / Yes | Unlikely | Resolved |
| 3009/0002 | LEV XR | 17 [1] | Epilepsy aggravated / Epilepsy | Severe / Yes | Possible | Resolved |
| 5004/0003 | LEV XR | 25 [2] | Repeating simple seizures / Simple partial seizures | Severe / Yes | Possible | Resolved |

Patient 3008/0007 was a 41-year-old Indian / Pakistani male who was randomized to PBO. He experienced a moderate increase in seizures 81 days after initiation of study drug. The duration of the event was one day and study drug was not changed. The investigator rated the event as unlikely related to study drug. The patient completed the study 4 days later.

Patient 5006/0003 was a 21-year old Caucasian male who was randomized to PBO. He experienced moderate, continuous partial seizures with secondary generalization 27 days after first study drug intake. That morning he had three seizures with secondary generalization. The first seizure occurred at 5:50 and started with jerking of his arms, the second occurred at 9:40. The subject vomited after taking valproic acid (1000 mg). A third seizure occurred at 12:10 and the patient was hospitalized. A fourth seizure occurred at 14:10. He received IM diazepam (10 mg), after which the seizures were controlled. A second dose of diazepam (10 mg, IV) was given in the evening. Study drug was temporarily discontinued. He was discharged from the hospital the next day. Sixteen days later (i.e., 42 days after first study drug intake), the patient experienced moderate, continuous aggravated seizures. Four stereotyped seizures with secondary generalization occurred. The first seizure at 5:40 started with jerking of his arms. The second seizure started at 7:40, during which he bit his tongue after which he vomited. The subject took oral valproic acid (750 mg) and IM diazepam (20 mg). After having two more seizures at 8:40 and at 13:40, he was hospitalized. In the hospital, he received IM diazepam (20 mg), metoclopramide and pyridoxine along with intravenous magnesium sulfate. No laboratory examinations or diagnostic tests were performed. He recovered 2 days after the event began. Study medication was permanently discontinued 1 week later. The Investigator assessed the events as unlikely related to study drug.

Patient 3009/0002 was a 14-year old Indian / Pakistani male who experienced severe, intermittent aggravated epilepsy 17 days after randomization to LEV XR. He presented with severe, recurrent simple partial seizures that developed into generalized seizures. He was administered 750 mg intravenous fosphenytoin and treatment with phenytoin (200 mg, BID) was initiated. The subject experienced post-ictal confusion for approximately 2 weeks. He was then asymptomatic for approximately 1 month after the event began. The Investigator assessed the event as possibly related to study drug. Study drug was discontinued due to the event.

Patient 5004/0003 was a 26-year old Caucasian male who was randomized to LEV XR and experienced severe, intermittent simple partial seizures 25 days after first study drug intake. These occurred in the evening for 2-3 hours. The next morning he again experienced a series of simple partial seizures. The study drug was temporarily discontinued. Emergency services administered IM diazepam (20 mg) as corrective treatment. He recovered the same day and refused hospitalization. Blood tests performed 2 days later showed AST = 56 U/L

(range 0-37) and GGT = 76 U/L (range 0-51). Study drug was restarted the same day. The Investigator assessed the event as possibly related to study drug. The patient subsequently completed the study and after study participation continued on prescription KEPPRA.

### 7.1.4 Common Adverse Events

Two hundred forty-three treatment-emergent AEs (TEAEs) (125 in the PBO group; 118 in the LEV XR group) were reported; the intensity of most was mild to moderate. The incidence of the TEAEs was similar in both treatment groups; 43 subjects (54.4%) in the PBO group and 41 (53.2%) in the LEV XR reported at least one TEAE. With the exception of headache, reported more frequently under PBO, influenza (3 subjects [3.8%] in PBO and 6 subjects [7.8%] in LEV XR), irritability (0 in PBO and 5 subjects [6.5%] in LEV XR), and somnolence (2 subjects [2.5%] in PBO and 6 subjects [7.8%] in LEV XR), no important differences in the nature and the number of TEAEs reported in the PBO and LEV XR group were observed. Similarly, 16 subjects (20.3%) in the PBO group and 18 (23.4%) in the LEV XR group had at least one drug-related TEAE. The larger imbalances between treatment groups in drug related TEAEs were observed for headache (reported by 6 subjects [7.6%] in the PBO group and by 1 subject [1.3%] in the LEV XR group) and for somnolence (1 [1.3%] PBO; 6 [7.8%] LEV XR). Six subjects (2 [2.5%] in the PBO group and 4 [5.2%] in the LEV XR group) permanently discontinued the study due to TEAEs. Nine treatment-emergent SAEs were reported by 8 subjects (2 [2.5%] in the PBO group and 6 [7.8%] in the LEV XR group). One subject under LEV XR died 65 days after study drug initiation due to severe pulmonary bronchiecteis. The event was considered by the Investigator as unlikely related to the study drug. One subject in the PBO group and none in the LEV XR group discontinued the study prematurely due to lack/loss of efficacy. One subject (4003/0005) reported an episode of status epilepticus before randomization. Although this subject was randomized into LEV XR, no study drug was dispensed due to this event and the subject was excluded from safety population. The incidence of psychiatric / behavioral TEAEs was similar in LEV XR (7 subjects [9.1%]) and PBO (8 subjects [10.1%]). The incidence of seizure or epilepsy related TEAEs was similar in LEV XR (2 subjects [2.6%]) and PBO (2 subjects [2.5%]). There was no signal of "breakthrough" seizures with LEV XR treatment.

A general overview of the TEAEs recorded during the study, classified by UCB SOC, is displayed below in the Sponsor's table reproduced below.

| Safety Results | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| Subjects with at least one TEAE, n(%) | 43 (54.4) | 41 (53.2) |
| **Subjects with at least one TEAE by UCB System Organ Class** | **n(%) [n considered drug-related by the Investigator]** | |
| Blood and Lymphatic System Disorders | 5 (6.3) [0] | 3 (3.9) [1] |
| Cardiac Disorders | 1 (1.3) [0] | 1 (1.3) [1] |
| Ear and Labyrinth Disorders | 2 (2.5) [1] | 1 (1.3) [0] |
| Eye Disorders | 1 (1.3) [0] | 2 (2.6) [1] |
| Gastrointestinal Disorders | 9 (11.4) [2] | 10 (13.0) [7] |
| General Disorders and Administration Site Conditions | 7 (8.9) [1] | 10 (13.0) [5] |
| Hepatobiliary Disorders | 0 | 1 (1.3) [0] |
| Immune System Disorders | 2 (2.5) [0] | 0 |
| Infections and Infestations | 18 (22.8) [0] | 21 (27.3) [1] |
| Injury, Poisoning and Procedural Complications | 3 (3.8) [0] | 5 (6.5) [0] |
| Metabolism and Nutrition Disorders | 2 (2.5) [1] | 0 |
| Musculoskeletal and Connective Tissue Disorders | 4 (5.1) [1] | 3 (3.9) [0] |
| Nervous System Disorders | 22 (27.8) [13] | 16 (20.8) [11] |
| Psychiatric Disorders | 8 (10.1) [4] | 7 (9.1) [5] |
| Respiratory, Thoracic and Mediastinal Disorders | 3 (3.8) [0] | 2 (2.6) [1] |
| Skin and Subcutaneous Tissue Disorders | 1 (1.3) [0] | 3 (3.9) [3] |
| Vascular Disorders | 2 (2.5) [1] | 3 (3.9) [0] |
| **Death, SAEs, and Other Significant AEs** | | |
| Death, n (%) | 0 | 1 (1.3) [0] |
| Subjects with at least one SAE, n (%) | 2 (2.5) | 6 (7.8) |
| **Subjects with at least one treatment-emergent SAE by UCB System Organ Class** | **n(%) [n considered drug-related by the Investigator]** | |
| Injury, Poisoning and Procedural Complications | 0 | 1 (1.3) [0] |
| Nervous System Disorders | 2 (2.5) [1] | 3 (3.9) [3] |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 1 (1.3) [0] |
| Skin and Subcutaneous Tissue Disorders | 0 | 1 (1.3) [1] |
| **Subjects with TEAEs leading to permanent study drug discontinuation, n(%)** | **2 (2.5)** | **4 (5.2)** |
| **Subjects with TEAEs leading to permanent study drug discontinuation by UCB System Organ Class** | **n(%) [n considered drug-related by the Investigator]** | |
| Gastrointestinal Disorders | 0 | 1 (1.3) [1] |
| General Disorders and Administration Site Conditions | 0 | 1 (1.3) [1] |
| Nervous System Disorders | 2 (2.5) [2] | 1 (1.3) [1] |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 1 (1.3) [0] |
| Skin and Subcutaneous Tissue Disorders | 0 | 1 (1.3) [1] |
| **Subjects with TEAEs leading to temporary study drug discontinuation, n(%)** | **1 (1.3)** | **2 (2.6)** |

| Safety Results | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| **Subjects with TEAEs leading to temporary study drug discontinuation by UCB System Organ Class** | **n (%) [n considered drug-related by the Investigator]** | |
| Gastrointestinal Disorders | 0 | 1 (1.3) [1] |
| Nervous System Disorders | 1 (1.3) [1] | 1 (1.3) [1] |
| Psychiatric Disorders | 1 (1.3) [1] | 0 |
| Vascular Disorders | 1 (1.3) [1] | 0 |
| **Subjects with TEAEs leading to dose decreased, n(%)** | 1 (1.3) | 1 (1.3) |
| **Subjects with TEAEs leading to dose changes by UCB System Organ Class** | **n(%) [n considered drug-related by the Investigator]** | |
| General Disorders and Administration Site Conditions | 0 | 1 (1.3) [1] |
| Nervous System Disorders | 1 (1.3) [0] | 0 |
| **Subjects with TEAEs leading to hospitalization or prolongation of hospitalization, n(%)** | 2 (2.5) | 4 (5.2) |
| **Subjects with TEAEs leading to hospitalization or prolongation of hospitalization by UCB System Organ Class** | **n(%) [n considered drug-related by the Investigator]** | |
| Injury, Poisoning and Procedural Complications | 0 | 1 (1.3) [0] |
| Nervous System Disorders | 2 (2.5) [1] | 1 (1.3) [1] |
| Respiratory, Thoracic and Mediastinal Disorders | 0 | 1 (1.3) [0] |
| Skin and Subcutaneous Tissue Disorders | 0 | 1 (1.3) [1] |

There were no Serious Adverse Events nor any deaths reported in these pharmacokinetic studies. None of the reported adverse events led to permanent or temporary discontinuation of study drug. The Sponsor's table below summarizes the TEAEs for studies N01140, N01160 and N01260. The TEAEs reported were consistent with those usually reported with levetiracetam. All TEAEs in the clinical pharmacology studies were mild to moderate in severity. Relationship to study drug was consistent with previous reports in levetiracetam.

| Primary SOC<br>MedDRA Preferred Term | N01140 (N=12) n (%) | N01160 (N=24) n (%) | N01260 (N=24) n (%) |
|---|---|---|---|
| Number of Subjects with at least 1 Drug-related TEAE | 9 (75.0%) | 20 (83.3%) | 17 (70.8%) |
| Nervous System Disorders | 8 (66.7%) | 8 (33.3%) | 12 (50.0%) |
| Disturbance in Attention | 0 | 3 (12.5%) | 0 |
| Dizziness | 0 | 1 (4.2%) | 4 (16.7%) |
| Headache | 7 (58.3%) | 2 (8.3%) | 1 (4.2%) |
| Somnolence | 7 (58.3%) | 5 (20.8%) | 9 (37.5%) |
| Musculoskeletal and Connective Tissue Disorders | 0 | 0 | 3 (12.5%) |
| Muscle Spasms | 0 | 0 | 3 (12.5%) |
| General Disorders and Administration Site Conditions | 4 (33.3%) | 17 (70.8%) | 7 (29.2%) |
| Asthenia | 3 (25.0%) | 17 (70.8%) | 7 (29.2%) |
| Feeling Drunk | 1 (8.3%) | 0 | 0 |

| Primary SOC<br>MedDRA Preferred Term | N01140<br>(N=12)<br>n (%) | N01160<br>(N=24)<br>n (%) | N01260<br>(N=24)<br>n (%) |
|---|---|---|---|
| Eye Disorders | 1 (8.3%) | 0 | 0 |
| Visual Disturbance | 1 (8.3%) | 0 | 0 |
| Ear and Labyrinth Disorders | 1 (8.3%) | 0 | 0 |
| Vertigo | 1 (8.3%) | 0 | 0 |
| Psychiatric Disorders | 0 | 5 (20.8%) | 0 |
| Insomnia | 0 | 2 (8.3%) | 0 |
| Nightmare | 0 | 4 (16.7%) | 0 |

### 7.1.5 Additional analyses and explorations

None

### 7.1.6 Laboratory Finding

#### 7.1.6.1 Overview of laboratory testing in the development program

Criteria for identifying subjects with potential treatment-emergent possibly clinically significant (PCST) values are presented by parameter, age category and gender (whenever appropriate). PCST assessments are based on the subject's age at the time of the assessment. These values are reproduced below from the Sponsor's Original Application.

| Parameter | PCST values | |
|---|---|---|
| | S.I. Units | Conventional Units |
| White blood cells (WBC) | < 17 yrs: ≤ 3.0 or ≥ 20 × 109/L<br>≥ 17 yrs: ≤ 2.8 or ≥ 16 × 109/L | < 17 yrs: ≤ 3.0 or ≥ 20 × 109/L<br>≥ 17 yrs: ≤ 2.8 or ≥ 16 × 109/L |
| Lymphocytes | 2 – < 12 yrs: ≤ 1.5 or ≥ 7.5 × 109/L<br>≥ 12 - 17 yrs: ≤ 0.5 or ≥ 5.5 × 109/L<br>≥ 17 yrs: ≤ 0.5 or ≥ 4.5 × 109/L | 2 – < 12 yrs: ≤ 1.5 or ≥ 7.5 × 109/L<br>≥ 12 - 17 yrs: ≤ 0.5 or ≥ 5.5 × 109/L<br>≥ 17 yrs: ≤ 0.5 or ≥ 4.5 × 109/L |
| Monocytes | ≥ 1.5 × 109/L | ≥ 1.5 × 109/L |
| Neutrophils | ≤ 1.0 × 109/L | ≤ 1.0 × 109/L |
| Eosinophils | ≥ 0.7 × 109/L | ≥ 0.7 × 109/L |
| Basophils | ≥ 0.4 × 109/L | ≥ 0.4 × 109/L |
| Red blood cells (RBC) | < 17 yrs: ≤ 2.5 × 1012/L<br>≥ 17 yrs: M: ≤ 2.5 × 1012/L<br>F: ≤ 2.0 × 1012/L | < 17 yrs: ≤ 2.5 ×106/mm3<br>≥ 17 yrs:<br>M: ≤ 2.5 ×106/mm3<br>F: ≤ 2.0 ×106/mm3 |
| Hemoglobin | ≥ 6 mo. - < 12 yrs: ≤ 100 g/L<br>≥ 12 yrs: M: ≤ 115 g/L<br>F: ≤ 95 g/L | ≥ 6 mo. - < 12 yrs: ≤ 10.0 g/dL<br>≥ 4 yrs: M: ≤ 11.5 g/dL<br>F: ≤ 9.5 g/dL |
| Hematocrit | ≥ 4 yrs: M: ≤ 0.37<br>F: ≤ 0.32 | ≥ 4 yrs: M: ≤ 37%<br>F: ≤ 32% |
| Mean corpuscular volume (MCV) | N/A | N/A |
| Mean corpuscular hemoglobin (MCH) | N/A | N/A |
| Mean corpuscular hemoglobin concentration (MCHC) | N/A | N/A |
| Platelet count | ≤ 75 or ≥ 700 × 109/L | ≤ 75 or ≥ 700 × 109/L |

There were no clinically relevant changes from baseline in hematology, biochemistry, and vital signs. Few treatment-emergent results were found in laboratory parameters; no clinically relevant differences were found between groups

### 7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The ISS presented by the Sponsor concentrates on hematology and blood chemistries in all four studies. Urinalysis was not completed in study N01235.

A summary of the changes in hematology from Baseline Visit to Visit 7 in study N01235 are shown below, as reproduced from the Sponsor's Original Application. None appeared to be clinically significant. Few treatment-emergent PCST results were observed in hematology parameters. No relevant differences between treatment groups were found.

| Parameters (Unit) | LEV XR (N = 77) | | | Placebo (N = 79) | | |
|---|---|---|---|---|---|---|
| | n | Mean ± SD | Median | n | Mean ± SD | Median |
| Hematocrit (%) | 65 | - 0.41 ± 2.67 | - 0.60 | 69 | 0.53 ± 2.78 | 0.50 |
| Hemglobin (g/L) | 65 | - 3.1 ± 6.6 | - 2.0 | 69 | 0.1 ± 9.0 | - 1.0 |
| RBCs (E12/L) | 65 | - 0.13 ± 0.22 | - 0.13 | 69 | - 0.04 ± 0.29 | - 0.05 |
| MCH (pg) | 65 | 0.25 ± 0.82 | 0.40 | 69 | 0.30 ± 1.20 | 0.30 |
| MCHC (g/L) | 65 | - 4.0 ± 12.7 | - 5.0 | 69 | - 3.8 ± 11.3 | - 4.0 |
| MCV (fL) | 65 | 1.8 ± 3.8 | 1.3 | 69 | 1.9 ± 4.0 | 2.0 |
| WBCs (E9/L) | 65 | - 0.09 ± 1.84 | - 0.20 | 69 | 0.06 ± 2.0 | - 0.04 |
| Neutrophils (E9/L) | 65 | - 0.11 ± 1.64 | 0.01 | 69 | 0.13 ± 1.74 | 0.05 |
| Lymphocytes (E9/L) | 65 | 0.01 ± 0.51 | 0.10 | 69 | - 0.06 ± 0.60 | - 0.08 |
| Monocytes (E9/L) | 65 | 0.01 ± 0.16 | 0 | 69 | 0.01 ± 0.23 | 0 |
| Eosinophils (E9/L) | 65 | - 0.03 ± 0.13 | - 0.01 | 69 | - 0.03 ± 0.34 | 0 |
| Basophils (E9/L) | 65 | 0 ± 0.05 | 0 | 69 | 0 ± 0.05 | 0 |
| Platelets (E9/L) | 63 | - 2.9 ± 47.3 | - 4.0 | 69 | - 29.3 ± 104.1 | - 8.0 |

A summary of the changes in blood chemistry from Baseline Visit to Visit 7, in study N01235, is displayed in the Sponsor's table below. The changes were not clinically relevant.

| Parameters (Unit) | LEV XR (N = 77) | | | Placebo (N = 79) | | |
|---|---|---|---|---|---|---|
| | n | Mean ± SD | Median | n | Mean ± SD | Median |
| Total bilirubin (µmol/L) | 69 | - 0.4 ± 3.2 | 0 | 68 | - 0.3 ± 2.8 | 0 |
| AST (U/L) | 70 | - 0.5 ± 8.8 | 0 | 69 | 1.7 ± 10.4 | 0 |
| ALT (U/L) | 69 | 0.1 ± 9.3 | 1.0 | 67 | 0.3 ± 16.8 | - 1.0 |
| GGT ( U/L) | 70 | - 3.1 ± 22.5 | - 3.0 | 69 | - 0.9 ± 14.7 | 0 |
| Alkaline phosphatase (U/L) | 63 | - 3.7 ± 18.9 | - 3.0 | 66 | 2.0 ± 13.3 | 2.0 |
| Creatinine (µmol/L) | 70 | 3.3 ± 9.5 | 0.5 | 70 | 2.1 ± 9.6 | 1.9 |
| BUN (mmol/L) | 70 | 0.01 ± 1.45 | - 0.12 | 70 | - 0.13 ± 1.22 | - 0.12 |
| Uric acid (µmol/L) | 69 | 1.9 ± 47.4 | 2.0 | 68 | 2.6 ± 38.1 | 0.5 |
| Glucose (mmol/L) | 70 | 0.03 ± 1.05 | 0.11 | 69 | 0.11 ± 2.01 | 0 |
| Total Protein (g/L) | 70 | - 0.7 ± 4.6 | 0 | 70 | - 0.3 ± 4.7 | - 0.5 |
| Albumin (g/L) | 70 | - 0.4 ± 2.6 | - 0.9 | 70 | - 0.3 ± 2.6 | 0 |
| Sodium (mmol/L) | 69 | - 0.6 ± 3.4 | 0 | 68 | - 0.2 ± 3.8 | 0 |
| Potassium (mmol/L) | 63 | 0.02 ± 0.46 | 0.04 | 65 | - 0.01 ± 0.48 | 0 |
| Calcium (mmol/L) | 63 | - 0.02 ± 0.11 | - 0.01 | 66 | 0.01 ± 0.12 | 0 |
| Phosphorus (mmol/L) | 70 | 0.01 ± 0.22 | 0.04 | 70 | 0.02 ± 0.21 | 0.04 |

Eight subjects (5 in the PBO group and 3 in the LEV XR group) had at least one treatment emergent PCS result above range in hematology parameters. Eleven subjects (5 in the PBO group, 6 in the LEV XR group) had at least one treatment-emergent PCS result below range in hematology parameters. With the exception of two subjects in the PBO group, and four subjects in the LEV XR group, all the PCS results found during or after the Treatment Period were already present at baseline. These details are provided below, reproduced from the Sponsor's Original Application.

| Treatment Group | Subject Number Age/Gender | Parameter (Unit) | Visit [a] | Baseline Value[b] | PCS Value[b] | Last Value[b] |
|---|---|---|---|---|---|---|
| PBO | 3001/0001 22.5/M | Eosinophil count (E9/L) | V7 | 1.450 H | 1.400 H | 1.400 H |
| | | Eosinophil count (relative) (fraction of 1) | V7 | 0.220 H | 0.250 H | 0.250 H |
| PBO | 3002/0006 23.7/M | Platelet count (E9/L) | V7 | 150 | 64 L | 64 L |
| PBO | 3002/0008 33.4/M | Eosinophil count (relative) (fraction of 1) | V7 | 0.060 | 0.110 H | 0.110 H |
| PBO | 3007/0001 41.7/M | Haematocrit (fraction of 1) | V7 | 0.326 L | 0.335 L | 0.335 L |
| | | Haemoglobin (g/L) | V7 | 104 L | 102 L | 102 L |
| PBO | 3008/0006 22.9/F | Eosinophil count (E9/L) | V7 | 0.950 H | 0.870 H | 0.870 H |
| | | Eosinophil count (relative) (fraction of 1) | V7 | 0.110 H | 0.110 H | 0.110 H |
| PBO | 3010/0002 18.1/F | Eosinophil count (E9/L) | V7 | 1.710 H | 2.110 H | 2.110 H |
| | | Eosinophil count (relative) (fraction of 1) | V7 | 0.180 H | 0.270 H | 0.270 H |
| PBO | 3011/0003 36.1/F | Haematocrit (fraction of 1) | AV | 0.288 L | 0.309 L | 0.336 |
| PBO | 3011/0005 25.7/M | Haematocrit (fraction of 1) | V7 | 0.343 L | 0.338 L | 0.338 L |
| | | Haemoglobin (g/L) | V7 | 107 L | 100 L | 100 L |
| | | Eosinophil count (E9/L) | V7 | 1.580 H | 1.100 H | 1.100 H |
| | | Eosinophil count (relative) (fraction of 1) | V7 | 0.220 H | 0.190 H | 0.190 H |
| PBO | 5006/0004 48.2/F | Haematocrit (fraction of 1) | AV | 0.310 L | 0.310 L | 0.426 |
| LEV XR | 2003/0001 56.9/M | Haematocrit (fraction of 1) | V7 | 0.378 | 0.370 L | 0.398 |
| LEV XR | 3001/0003 54.0/M | Haematocrit (fraction of 1) | EDV | 0.323 L | 0.330 L | 0.323 L |
| | | | V8 | 0.323 L | 0.323 L | 0.323 L |
| | | Haemoglobin (g/L) | EDV | 101 L | 98 L | 96 L |
| | | | V8 | 101 L | 96 L | 96 L |
| LEV XR | 3004/0001 41.6/M | Eosinophil count (E9/L) | EDV | 1.080 H | 1.310 H | 0.840 H |
| | | | V8 | 1.080 H | 0.840 H | 0.840 H |

| Treatment Group | Subject Number Age/Gender | Parameter (Unit) | Visit [a] | Baseline Value[b] | PCS Value[b] | Last Value[b] |
|---|---|---|---|---|---|---|
| | | Eosinophil count (relative) (fraction of 1) | EDV | 0.120 H | 0.150 H | 0.110 H |
| | | | V8 | 0.120 H | 0.110 H | 0.110 H |
| LEV XR | 3009/0002 14.2/M | Eosinophil count (E9/L) | EDV | 0.820 H | 1.440 H | 1.150 H |
| | | | V8 | 0.820 H | 1.150 H | 1.150 H |
| | | Eosinophil count (relative) (fraction of 1) | EDV | 0.080 | 0.140 H | 0.120 H |
| | | | V8 | 0.080 | 0.120 H | 0.120 H |
| LEV XR | 3010/0004 39.4/F | Haematocrit (fraction of 1) | V7 | 0.313 L | 0.306 L | 0.306 L |
| | | Haemoglobin (g/L) | V7 | 96 | 95 L | 95 L |
| LEV XR | 3010/0007 25.6/F | White blood cell count (E9/L) | EDV | 6.400 | 17.100 H | 17.100 H |
| | | Lymphocyte count (relative) (fraction of 1) | EDV | 0.250 | 0.090 L | 0.090 L |
| LEV XR | 3011/0004 38.6/M | Haematocrit (fraction of 1) | V7 | 0.399 | 0.344 L | 0.344 L |
| LEV XR | 5004/0001 48.3/F | White blood cell count (E9/L) | AV | 5.700 | 2.700 L | 6.780 |

Eight other TEAEs related to the "Blood and Lymphatic System Disorders" UCB SOC were reported in six subjects (4 PBO and 2 LEV XR) in the N01235 study. All of these TEAEs, including those for subjects 5006/0004 (PBO) and 5004/0001 (LEV XR), are summarized in the Sponsor's table below. These AEs are graded by the sponsor as mild and moderate in severity, however, I was unable to locate explicit definitions for these terms.

| Subject # | Group | TTE [DOE] | Verbatim / MedDRA PT | Severity | Relation-ship | Outcome |
|---|---|---|---|---|---|---|
| 5006/0003 | PBO | 50 [>16] | Monocytosis / Monocytosis | Mild | Unlikely | Ongoing |
| 5006/0004 | PBO | 6 [4] | Anemia (iron deficiency) / Iron deficiency anaemia | Moderate | None | Sequalae |
| | | 6 [4] | Leukopenia / Leukopenia | Moderate | None | Sequalae |
| 5009/0001 | PBO | 1 [57] | Platelets decreasing to 141 / Platelet count decreased | Mild | None | Resolved |
| 5009/0004 | PBO | 1 [57] | Lymphocyte count decreased / Lymphocyte count decreased | Mild | None | Resolved |
| 6003/0001 | PBO | 85 [>14] | Anemia / Anaemia | Mild | None | Ongoing |
| 5004/0001 | LEV XR | 29 [29] | Decrease in a level of WBC, abs. neutrophils (blood analysis) / Neutrophil count decreased | Mild | Possible | Resolved |
| 5009/0005 | LEV XR | 98 [>1] | High level of leucocitis / Leukocytosis | Mild | None | Ongoing |
| | | 98 [>1] | Lymphocyte count decreased / Lymphocyte count decreased | Mild | None | Ongoing |
| 5009/0007 | LEV XR | 99 [>1] | High level platelet / Platelet count increased | Mild | None | Ongoing |

With the exception of patients 5006/0004 and 5004/0001, no other subject noted had any abnormal hematology values that met PCS criteria. Patient 5006/0004, a 48-year-old Caucasian Female had PCS low hematocrit (0.310) at baseline. The values remained below the normal range throughout the trial without any impairment. Patient 5004/0001, also a 48-year-old Caucasian Female had PCS WBC (2.77) 28 days post-baseline during an unscheduled visit. Subsequent values were lower than normal limits throughout the study, but were not considered PCS. No adverse event of "infection" was reported. The WBC increased to within normal limits at time of study completion

The change between screening and discharge for the hematology laboratory results in the three clinical pharmacology studies are shown in the table below, reproduced from the Sponsor's Original Application.

| Parameter (unit) | Visit | N01140 Mean (SD) | N01160 Mean (SD) | N01260 Mean (SD) |
|---|---|---|---|---|
| Hematocrit (fraction of 1) | Screening | 0.4467 (0.0265) | 0.4151 (0.0347) | 0.4071 (0.0293) |
| | Discharge | 0.4378 (0.0265) | 0.3900 (0.0356) | 0.3842 (0.0381) |
| | Change | -0.0088 (0.0138) | -0.0251 (0.0222) | -0.0229 (0.0206) |
| Hemoglobin (g/L) | Screening | 149.7 (9.4) | 140.6 (12.2) | 137.6 (11.0) |
| | Discharge | 145.0 (9.9) | 131.6 (12.2) | 131.2 (13.9) |
| | Change | -4.7 (3.4) | -9.0 (7.7) | -6.5 (7.3) |
| RBC (E12/L) | Screening | 5.2233 (0.383) | 4.6871 (0.3984) | 4.7325 (0.4038) |
| | Discharge | 5.1158 (0.46) | 4.4038 (0.4124) | 4.4724 (0.4864) |
| | Change | -0.1075 (0.1513) | -0.2833 (0.2571) | -0.2600 (0.2461) |
| MCV (fL) | Screening | 85.8 (7.0) | 88.6 (4.4) | 86.2 (4.6) |
| | Discharge | 86.0 (7.3) | 88.7 (4.3) | 86.1 (4.6) |
| | Change | 0.2 (1.1) | 0.0 (1.0) | -0.1 (1.0) |
| WBC (E9/L) | Screening | 5.1333 (0.95) | 6.9375 (1.8747) | 5.7375 (1.3091) |
| | Discharge | 5.375 (0.7569) | 6.7792 (1.4261) | 5.7958 (1.7409) |
| | Change | 0.2417 (0.6259) | -0.1583 (1.8900) | 0.0583 (1.1669) |
| Neutrophil Count (E9/L) | Screening | 2.745 (0.9909) | 4.1517 (1.5839) | 3.3579 (1.0743) |
| | Discharge | 2.9917 (0.8617) | 3.7229 (1.2812) | 3.3700 (1.5828) |
| | Change | 0.2467 (0.6678) | -0.4288 (1.5445) | 0.0121 (1.1259) |
| Lymphocyte Count (E9/L) | Screening | 1.8058 (0.3796) | 1.9442 (0.6414) | 1.8000 (0.4848) |
| | Discharge | 1.7592 (0.3697) | 2.2275 (0.4215) | 1.8146 (0.3656) |
| | Change | -0.0467 (0.2364) | 0.2833 (0.6119) | 0.0146 (0.2739) |
| Monocyte Count (E9/L) | Screening | 0.3767 (0.1022) | 0.5675 (0.1965) | 0.4608 (0.1304) |
| | Discharge | 0.4158 (0.1213) | 0.5579 (0.2061) | 0.4604 (0.1522) |
| | Change | 0.0392 (0.1199) | -0.0096 (0.2047) | -0.0004 (0.1116) |
| Eosinophil Count (E9/L) | Screening | 0.1692 (0.1476) | 0.2421 (0.3917) | 0.1071 (0.0735) |
| | Discharge | 0.1683 (0.1122) | 0.2429 (0.1345) | 0.1438 (0.0930) |
| | Change | -0.0008 (0.1097) | 0.0008 (0.3200) | 0.0367 (0.0536) |
| Basophil Count (E9/L) | Screening | 0.035 (0.0271) | 0.0317 (0.0373) | 0.0125 (0.0251) |
| | Discharge | 0.0392 (0.0243) | 0.0275 (0.0373) | 0.0092 (0.0210) |
| | Change | 0.0042 (0.0345) | -0.0042 (0.0374) | -0.0033 (0.0218) |
| Platelet Count (E9/L) | Screening | 230 (31.4) | 263.2 (40.4) | 268.3 (46.9) |
| | Discharge | 237.7 (38.9) | 242.9 (77.8) | 274.8 (47.2) |
| | Change | 7.7 (22.8) | -20.3 (73.7) | 6.5 (29.2) |

In study N01260, one female subject (0020) presented with a slight decrease in Hb, Hc, RBC, MCV and MCH values at discharge visit (Hb: 101 g/L, normal range: 115-160 g/L; Hc: 0.309, normal range: 0.370-0.470; RBC: 3.99, normal range: 4.00-5.00; MCV: 77 fL, normal range: 80-100 fL; MCH: 24.9 pg, normal range: 27.0-33.0 pg). These abnormal results were initially considered to be not clinically significant at the discharge visit and

the laboratory parameters were to be retested. After 1 week, similar results were obtained. After 2 weeks, the hematological lab results were lower than those previously obtained and considered clinically relevant by the Investigator (Hb: 96 g/L; Hc: 0.294; RBC: 3.85; MCV: 76 fL; MCH: 24.9 pg). Mild anemia was reported as an AE starting 18 days after the last study drug intake and assessed as not related to the study drug. The subject's anemia was still ongoing at the date of database lock but resolved within 6 weeks. No clinically relevant hematology results were noted in studies N01160 or N01140. PCST criteria were not applied to the clinical pharmacology studies.

Fourteen subjects (7 in the PBO group, 7 in the LEV XR group) had at least one treatment emergent PCS result above range in biochemistry parameters. Three subjects (1 in the PBO group, 2 in the LEV XR group) had at least one treatment-emergent PCS result below range in biochemistry parameters. Individual data of the PCS results observed post-randomization in biochemistry parameters are displayed in the Sponsor's table below.

| Treat-ment Group | Subject Number Age/Gender | Parameter (Unit) | Visit [a] | Baseline Value[b] | PCS Value[b] | Last Value[b] |
|---|---|---|---|---|---|---|
| PBO | 3002/0004 29.6/F | Aspartate aminotransferase (U/L) | V3 | 15 | 490 H | 49 |
| | | Alanine aminotransferase (U/L) | V3 | 8 | 153 H | 27 |
| | | Blood uric acid (umol/L) | V3 | 137 | 625 H | 250 |
| PBO | 4003/0001 28.9/M | Blood glucose (mmol/L) | V7 | 4.88 | 1.28 L | 1.28 L |
| PBO | 4006/0001 55.0/M | Blood glucose (mmol/L) | V7 | 8.38 | 11.93 H | 11.93 H |
| PBO | 4006/0008 17.8/M | Gamma-glutamyltransferase (U/L) | V7 | 120 | 142 H | 142 H |
| PBO | 5004/0002 46.5/M | Blood potassium (mmol/L) | V7 | 5.60 | 5.80 H | 5.20 |
| PBO | 6003/0001 34.5/M | Blood creatinine (umol/L) | V8 | 57 | 217 H | 57 |
| PBO | 7001/0003 41.3/M | Blood glucose (mmol/L) | V7 | 5.70 | 18.90 H | 24.00 H |
| | | | AV | 5.70 | 24.00 H | 24.00 H |
| PBO | 7001/0004 58.5/F | Blood urea nitrogen (mmol/L) | AV | 10.50 | 11.20 H | 13.10 H |
| | | | V7 | 10.50 | 13.10 H | 13.10 H |
| | | Blood glucose (mmol/L) | AV | 14.90 | 12.70 H | 17.20 H |
| | | | V7 | 14.90 | 17.20 H | 17.20 H |
| | | Blood potassium (mmol/L) | V7 | 5.10 | 5.80 H | 5.80 H |
| LEV XR | 1007/0001 43.6/M | Blood urea nitrogen (mmol/L) | V7 | 10.35 | 17.14 H | 17.14 H |
| LEV XR | 2003/0001 56.9/M | Blood urea nitrogen (mmol/L) | V7 | 7.60 | 11.30 H | 10.20 |
| LEV XR | 3002/0009 34.2/M | Protein total (g/L) | V7 | 74 | 90 H | 90 H |
| LEV XR | 3010/0004 39.4/F | Blood glucose (mmol/L) | V7 | 4.38 | 2.78 L | 2.78 L |
| LEV XR | 3011/0004 38.6/M | Blood glucose (mmol/L) | V7 | 11.04 | 10.16 H | 10.16 H |
| LEV XR | 4001/0004 14.6/F | Blood uric acid (umol/L) | V7 | 565 | 583 H | 583 H |
| LEV | 4003/0007 | Blood calcium (mmol/L) | V7 | 2.22 | 1.68 L | 1.68 L |

| Treat-ment Group | Subject Number Age/Gender | Parameter (Unit) | Visit [a] | Baseline Value[b] | PCS Value[b] | Last Value[b] |
|---|---|---|---|---|---|---|
| XR | 30.6/F | | | | | |
| LEV XR | 5001/0001 34.0/M | Blood potassium (mmol/L) | V7 | 5.40 | 5.90 H | 4.70 |
| LEV XR | 6002/0002 35.4/M | Gamma-glutamyltransferase (U/L) | V7 | 174 | 310 H | 295 H |
| | | | V8 | 174 | 295 H | 295 H |
| | | Blood uric acid (umol/L) | AV | 670 | 650 H | 540 |
| | | | V7 | 670 | 600 H | 540 |

Only one of the treatment-emergent PCS results were reported as a TEAE. Subject 7001/0003 was a 41-year-old Caucasian male with an ongoing history since 1995 of diabetes mellitus. His Visit 1 and Visit 3 blood glucose values of 6.60 mmol/L and 5.70 mmol/L, respectively, were within normal limits. At Visit 7, the value increased to 18.90 mmol/L; however, the investigator did not consider the increase as a TEAE until a post-study repeat blood test result of 24.0 mmol/L was noted. No other TEAEs related to biochemistry results were reported. PCST criteria were not applied to the clinical pharmacology studies. Overall, no clinically significant findings /changes were noted.

The change between screening and discharge for the biochemistry laboratory results in the three clinical pharmacology studies are listed below in the Sponsor's table.

| Parameter (unit) | Visit | N01140 Mean (SD) | N01160 Mean (SD) | N01260 Mean (SD) |
|---|---|---|---|---|
| Total Blood Bilirubin (umol/L) | Screening | 13.1 (5.0) | 10.6 (5.1) | 9.1 (4.2) |
| | Discharge | 10.3 (3.3) | 6.9 (2.7) | 9.5 (4.1) |
| | Change | -2.8 (4.2) | -3.7 (4.4) | 0.4 (3.1) |
| Blood Bilirubin Conjugated (umol/L) | Screening | 1.4 (0.5) | 1.5 (0.6) | 1.3 (0.5) |
| | Discharge | 1.3 (0.5) | 1.1 (0.3) | 1.2 (0.4) |
| | Change | -0.3 (0.5) | -0.4 (0.6) | -0.1 (0.3) |
| SGOT (U/L) | Screening | 21.8 (6.2) | 17.3 (2.7) | 20.2 (5.1) |
| | Discharge | 24.8 (9.8) | 15.5 (3.3) | 19.5 (9.4) |
| | Change | 3 (7.3) | -1.9 (1.9) | -0.7 (8.0) |
| SGPT (U/L) | Screening | 23.3 (11.3) | 14.2 (6.4) | 18.8 (8.6) |
| | Discharge | 29 (17.5) | 13.4 (5.7) | 18.2 (11.6) |
| | Change | 5.8 (13.9) | -0.8 (4.0) | -0.5 (11.6) |
| GGT (U/L) | Screening | 31.3 (15.4) | 17.4 (7.3) | 20.6 (7.4) |
| | Discharge | 31.3 (17.9) | 15.6 (8.4) | 20.9 (13.9) |
| | Change | 0.1 (5.2) | -1.8 (3.8) | 0.3 (10.2) |
| Alkaline Phosphatase (U/L) | Screening | 80.8 (37.1) | 54.9 (19.6) | 57.0 (18.4) |
| | Discharge | 77 (31.4) | 53.5 (20.1) | 57.5 (23.4) |
| | Change | -3.8 (10.9) | -1.3 (7.3) | 0.5 (10.2) |
| Blood Lactate Dehydrogenase (U/L) | Screening | 150.9 (25.0) | N/A | N/A |
| | Discharge | 153.3 (20.3) | | |
| | Change | 2.3 (15.2) | | |
| Creatinine Kinase U/L) | Screening | 134.1 (68.4) | N/A | N/A |
| | Discharge | 134.2 (82.3) | | |
| | Change | 0.1 (50.1) | | |
| Blood Creatinine (U/L) | Screening | 76.5 (10.8) | 68.5 (12.3) | 65.9 (16.0) |
| | Discharge | 74.8 (12.5) | 69.1 (13.7) | 70.4 (18.2) |
| | Change | -1.7 (5.5) | 0.6 (6.1) | 4.5 (8.1) |
| Blood Urea (mmol/L) | Screening | 4.338 (1.082) | 4.590 (1.295) | 4.195 (1.060) |
| | Discharge | 4.138 (0.781) | 4.600 (1.235) | 4.849 (1.039) |
| | Change | -0.2 (0.824) | 0.010 (1.066) | 0.655 (1.071) |
| Blood Uric Acid (umol/L) | Screening | 344.4 (61.4) | N/A | N/A |
| | Discharge | 339.8 (43.3) | | |
| | Change | -4.6 (33.3) | | |
| Blood Glucose (mmol/L) | Screening | 4.682 (0.392) | 4.398 (0.360) | 4.467 (0.390) |
| | Discharge | 4.453 (0.39) | 4.735 (0.376) | 4.524 (0.341) |
| | Change | -0.228 (0.355) | 0.337 (0.317) | 0.057 (0.308) |
| Total Protein (g/L) | Screening | 74.9 (5.5) | 78.8 (4.5) | 75.4 (4.5) |
| | Discharge | 75 (4.6) | 72.0 (4.9) | 73.2 (4.5) |
| | Change | 0.1 (3.4) | -6.8 (4.7) | -2.2 (4.8) |
| Blood Albumin (g/L) | Screening | 48.6 (1.5) | 45.9 (3.4) | 46.4 (5.5) |
| | Discharge | 48.6 (2.1) | 40.2 (4.5) | 40.1 (3.5) |
| | Change | 0 (2.3) | -5.8 (3.7) | -6.3 (5.0) |

| Parameter (unit) | Visit | N01140 Mean (SD) | N01160 Mean (SD) | N01260 Mean (SD) |
|---|---|---|---|---|
| Blood Sodium (mmol/L) | Screening | 139 (1.5) | 138.8 (1.8) | 138.0 (1.9) |
| | Discharge | 139.2 (1.4) | 141.3 (2.1) | 138.6 (1.4) |
| | Change | 0.2 (1.4) | 2.5 (2.4) | 0.5 (2.4) |
| Blood Potassium (mmol/L) | Screening | 4.075 (0.122) | 3.896 (0.149) | 3.996 (0.274) |
| | Discharge | 4.117 (0.374) | 4.138 (0.286) | 3.938 (0.287) |
| | Change | 0.042 (0.434) | 0.242 (0.308) | -0.058 (0.380) |
| Blood Calcium (mmol/L) | Screening | 2.443 (0.116) | 2.403 (0.078) | 2.378 (0.080) |
| | Discharge | 2.376 (0.079) | 2.235 (0.108) | 2.380 (0.097) |
| | Change | -0.067 (0.131) | -0.168 (0.098) | 0.002 (0.110) |
| Blood Chloride (mmol/L) | Screening | 100 (1.6) | 101.0 (2.2) | 101.4 (1.5) |
| | Discharge | 99.3 (1.6) | 105.7 (2.0) | 101.4 (2.0) |
| | Change | -0.7 (1.6) | 4.8 (2.7) | 0.0 (1.8) |
| Blood Phosphorus (mmol/L) | Screening | 0.97 (0.095) | 0.884 (0.119) | 0.958 (0.117) |
| | Discharge | 0.884 (0.155) | 1.079 (0.167) | 1.059 (0.147) |
| | Change | -0.086 (0.107) | 0.195 (0.160) | 0.100 (0.144) |

Only one subject in the 3 clinical pharmacology studies had a clinically significant abnormal urinalysis. One female patient in study N01160 had blood and leukocytes in the urine with burning micturition. This AE was not felt to be likely related to the study medication.

### 7.1.7 Vital Signs

No clinically relevant changes from the baseline were observed in the vital signs and body weight parameters in placebo controlled study N01235 as reproduced from the Sponsor's Original Application.

| Parameters (Unit) | Visit | LEV XR (N = 77) | | | Placebo (N = 79) | | |
|---|---|---|---|---|---|---|---|
| | | n | Mean ± SD | Median | n | Mean ± SD | Median |
| Systolic BP (mm Hg) | 4 | 76 | - 0.2 ± 13.1 | 0 | 76 | 0.7 ± 10.0 | 0 |
| | 5 | 74 | - 1.1 ± 11.4 | 0 | 75 | 0 ± 11.1 | 0 |
| | 6 | 73 | - 3.0 ± 9.2 | - 3.0 | 72 | - 2.2 ± 12.1 | - 3.0 |
| | 7 | 71 | - 1.5 ± 10.9 | - 1.0 | 72 | - 1.3 ± 9.5 | 0 |
| Diastolic BP ( mm Hg) | 4 | 76 | - 1.0 ± 7.9 | 0 | 76 | - 0.1 ± 10.2 | 0 |
| | 5 | 74 | - 0.5 ± 8.2 | 0 | 75 | - 0.1 ± 8.9 | 0 |
| | 6 | 73 | - 1.9 ± 7.9 | 0 | 72 | - 0.7 ± 9.4 | 0 |
| | 7 | 71 | - 0.9 ± 9.2 | 0 | 72 | - 0.2 ± 9.7 | 0 |
| Heart Rate (bpm) | 4 | 76 | - 0.2 ± 6.6 | 0 | 76 | 0.1 ± 8.5 | 2.0 |
| | 5 | 74 | - 1.1 ± 6.3 | - 0.5 | 75 | - 0.7 ± 8.9 | - 1.0 |
| | 6 | 73 | - 2.5 ± 8.0 | - 2.0 | 72 | - 2.0 ± 10.1 | - 2.0 |
| | 7 | 71 | - 0.6 ± 8.4 | 0 | 72 | - 1.1 ± 10.2 | 0 |
| Body Weight (kg) | 4 | 76 | 0.19 ± 0.96 | 0 | 76 | 0.02 ± 1.14 | 0 |
| | 5 | 74 | - 0.13 ± 1.63 | 0 | 75 | 0.03 ± 1.15 | 0 |
| | 6 | 73 | - 0.09 ± 1.68 | 0 | 72 | - 0.09 ± 2.13 | 0 |
| | 7 | 71 | 0.05 ± 2.02 | 0 | 72 | 0.09 ± 2.07 | 0.1 |

Five TEAEs, related to blood pressure, graded mild and moderate, were reported in four subjects (1 PBO and 3 LEV XR); summarized in the Sponsor's table below. I do not believe these are clinically significant.

| Subject # | Group | TTE [DOE] | Baseline Value (Visit 3) | Verbatim / MedDRA PT | Severity | Relation-ship | Outcome |
|---|---|---|---|---|---|---|---|
| 7003/ 0003 | PBO | 50 [10] | 130/80 | Elevated arterial pressure / Blood pressure increased | Moderate | None | Resolved |
| | | 73 [2] | 130/80 | Elevated arterial pressure / Blood pressure increased | Mild | None | Resolved |
| 5004/ 0005 | LEV XR | 21 [1] | 115/80 | Increase of arterial pressure (135/76) / Blood pressure increased | Mild | Unlikely | Resolved |
| 5009/ 0007 | LEV XR | 35 [1] | 120/80 | High blood pressure (150/100) / Hypertension | Moderate | None | Resolved |
| 7004/ 0003 | LEV XR | 65 [6] | 130/85 | Hypertension / Hypertension | Mild | None | Resolved |
| TTE: Time to Event (days on drug) [DOE]: Duration of Event (days) | | | | | | | |

The Sponsor's table, reproduced below, summarizes the change between screening and discharge for blood pressure and heart rate in the three clinical pharmacology studies as the summary of change between screening and discharge for blood pressure and heart rate.

| Parameter (unit) | Visit | N01140 Mean (SD)[b] | N01160 Mean (SD)[c] | N01260 Mean (SD)[c] |
|---|---|---|---|---|
| Systolic Blood Pressure | Screening | 128.6 (14.0) | 116.0 (8.1) | 120.4 (9.6) |
| | Discharge | 124.3 (12.3) | 110.3 (10.9) | 120.8 (11.3) |
| | Change | -4.3 (10.8) | -5.7 (8.5) | 0.4 (7.5) |
| Diastolic Blood Pressure | Screening | 76.1 (13.6) | 68.4 (5.6) | 72.3 (6.4) |
| | Discharge | 73.8 (12.8) | 63.8 (5.8) | 72.4 (7.9) |
| | Change | -2.3 (5.1) | -4.6 (6.7) | 0.1 (5.2) |
| Heart Rate | Screening | 67.7 (10.8) | 59.9 (8.3) | 65.8 (9.5) |
| | Discharge | 81.3 (13.2) | 60.0 (6.9) | 68.2 (5.7) |
| | Change | 13.6 (12.2) | 0.1 (7.8) | 2.3 (6.6) |

Body weight and height measurements were obtained only at the screening visit in the three clinical pharmacology studies. Therefore, change from baseline / screening could not be assessed. However, no adverse events regarding weight increase or decrease or events involving appetite change were reported in any of the studies.

### 7.1.8 Electrocardiograms (ECGs)

Standard 12-lead ECGs were recorded: study-specific equipment was not provided. In the double-blind study (N01235), a qualified physician and/or the Investigator determined whether the results of the ECG were normal or abnormal. The incidence of abnormalities in ECG is given, for Baseline and Treatment Periods, in the Sponsor's table below.

| Period | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| Baseline | | |
| n[a] | 79 | 76 |
| Abnormal (%) | 33 (41.8%) | 29 (38.2%) |
| Clinically Significant | 0 (0%) | 0 (0%) |
| Treatment Emergent | | |
| n[a] | 76 | 76 |
| Abnormal (%) | 25 (32.9%) | 27 (35.5%) |
| Clinically Significant Worsening from Baseline | 0 (0%) | 0 (0%) |

None of the ECG abnormalities found were considered clinically significant by the Investigators. No clinically significant worsening of the preexistent ECG abnormalities was observed during the study. The investigators did not consider any of the findings to be clinically significant. There were also no significant changes from baseline. No clinically significant ECG abnormalities were noted in any of the three clinical pharmacology studies. A definitive QTc study was completed using KEPPRA; the conclusions were that KEPPRA had no effect on QTc or other ECG parameters.

### 7.1.9 Additional analyses and explorations

The incidence of abnormalities in physical examinations, during baseline and treatment periods, are shown in the table below, reproduced from the Sponsor's Original Application, as the number (%) of subjects with at least one abnormality in physical examinations during the baseline and treatment emergent periods in the double-blind, placebo-controlled study N01235.

| Period | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| Baseline | | |
| n[a] | 79 | 77 |
| Abnormal (%) | 12 (15.2%) | 15 (19.5%) |
| Clinically Significant | 1 (1.3%) | 3 (3.9%) |
| Treatment Emergent | | |
| n[a] | 77 | 76 |
| Abnormal (%) | 9 (11.7%) | 9 (11.8%) |
| Clinically Significant Worsening from Baseline | 0 (0%) | 2 (2.6%) |

In the LEV XR group, as assessed by the investigators, a clinically significant worsening of the physical abnormalities found during the study was observed in two subjects: In subject 3001/0002 (Indian Female aged 35.3 years), a mild, continuous fungal infection, starting 83 days after the first study drug intake and lasting 11 days, worsened. The event resolved spontaneously and was reported as a TEAE. In subject 6003/0005 (Indian Male aged 50.4 years), a mild continuous influenza starting 96 days after the first study drug intake and lasting 4 days worsened; the event resolved spontaneously. The event was reported as a TEAE. In the same subject, tenderness in right hypochondrium worsened at V8 (98 days after V3); this worsening was not reported as TEAE.

The incidence of abnormalities in neurological examinations is given, during baseline and treatment periods, in the Sponsor's table below. It shows the number (%) of subjects with at least one abnormality in neurological examinations during the baseline and treatment emergent periods in the double-blind, placebo-controlled study N01235.

| Period | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| Baseline | | |
| n[a] | 79 | 77 |
| Abnormal (%) | 26 (32.9%) | 22 (28.6%) |
| Clinically Significant | 3 (3.8%) | 8 (10.4%) |
| Treatment Emergent | | |
| n[a] | 77 | 76 |
| Abnormal (%) | 23 (29.9%) | 16 (21.1%) |
| Clinically Significant Worsening from Baseline | 1 (1.3%) | 1 (1.3%) |

In two subjects (1 PBO; 1 LEV XR), a clinically significant worsening of the neurological abnormalities was observed. Subject 2003/0002 (PBO; Caucasian Male aged 54.1 years) developed intermittent diplopia which was already present at V1 worsened at the end of the study. The event was felt to possibly be related to the study drug and was reported as a TEAE. In subject 5004/0001 (LEV XR; Caucasian Female aged 48.3 years), a central monoparesis of the left hand, already present at V1, worsened at the end of the study (V7 and V8). This event was not reported as a TEAE. No significant findings for physical and neurological findings over time were noted in the clinical pharmacology studies.

The incidences of concurrent medical procedures, provided in the Sponsor's table below, shows the number (%) of subjects with at least one concomitant medical procedure during the baseline and treatment emergent periods in the double-blind, placebo-controlled study N01235.

| Period | PBO (N=79) | LEV XR (N=77) |
|---|---|---|
| Baseline | | |
| No Medical Procedure | 64 (81.0%) | 69 (87.3%) |
| 1 Medical Procedure | 8 (10.2%) | 3 (3.8%) |
| 2 Medical Procedures | 7 (8.9%) | 5 (6.3%) |
| ≥ 3 Medical Procedures | 0 | 2 (2.5%) |
| n | 79 | 79 |
| Mean (SD) | 0.3 (0.6) | 0.2 (0.7) |
| Median | 0.0 | 0.0 |
| Q1 – Q3 | 0.0 – 0.0 | 0.0 – 0.0 |
| Min - Max | 0 – 2 | 0 – 3 |
| Treatment | | |
| No Medical Procedure | 71 (91.0%) | 67 (87.0%) |
| 1 Medical Procedure | 2 (2.6%) | 6 (7.8%) |
| 2 Medical Procedures | 4 (5.1%) | 0 |
| ≥ 3 Medical Procedures | 1 (1.3%) | 4 (5.2%) |
| n | 78 | 77 |
| Mean (SD) | 0.2 (0.6) | 0.4 (1.2) |
| Median | 0.0 | 0.0 |
| Q1 – Q3 | 0.0 – 0.0 | 0.0 – 0.0 |
| Min - Max | 0 – 4 | 0 - 6 |

Seven subjects (8.9%) in the PBO group, ten subjects (13.0%) in the LEV XR group had at least one concurrent medical procedure during the study. Concurrent medical procedures associated, or not, to the study disease showed no relevant differences between groups. The number (%) of patients with at least one concurrent medical procedure by primary SOC, and preferred term, in study N01235 are reproduced from the Sponsor's Original Application and shown below.

| Primary System Organ Class<br>Preferred Term | PBO<br>(N = 79)<br>n (%) | LEV XR<br>(N = 77)<br>n (%) |
|---|---|---|
| Number of Subjects with at least 1 concurrent medical procedure | 7 (8.9%) | 10 (13.0%) |
| Investigations | 6 (7.6%) | 8 (10.4%) |
| Blood Test | 0 | 2 (2.6%) |
| Colonoscopy | 0 | 1 (1.3%) |
| Computerized tomogram | 0 | 1 (1.3%) |
| Drug level decreased | 1 (1.3%) | 0 |
| Electrocardiogram | 0 | 2 (2.6%) |
| Electroencephalogram | 2 (2.5%) | 3 (3.9%) |
| Neurological examination | 0 | 2 (2.6%) |
| Nuclear magnetic resonance imaging | 0 | 2 (2.6%) |
| Nuclear magnetic resonance imaging brain | 2 (2.5%) | 0 |
| Oesophagogastroduodenoscopy | 0 | 1 (1.3%) |
| Ophthalmological examination | 0 | 1 (1.3%) |
| Physical examination | 1 (1.3%) | 3 (3.9%) |
| Ultrasound abdomen | 0 | 1 (1.3%) |
| Ultrasound scan | 0 | 1 (1.3%) |
| X-ray | 1 (1.3%) | 0 |
| X-ray limb | 1 (1.3%) | 0 |
| | | |
| Surgical and Medical Procedures | 3 (3.8%) | 5 (6.5%) |
| Dental treatment | 0 | 1 (1.3%) |
| Enema administration | 0 | 1 (1.3%) |
| Hospitalization | 0 | 1 (1.3%) |
| Joint stabilization | 1 (1.3%) | 0 |
| Polypectomy | 0 | 1 (1.3%) |
| Psychotherapy | 1 (1.3%) | 0 |
| Septoplasty | 1 (1.3%) | 0 |
| Suture insertion | 0 | 1 (1.3%) |
| Therapy regimen changed | 0 | 1 (1.3%) |

Fifteen subjects (eight in the PBO group, seven in the LEV XR group) reported at least one TEAE in the "Psychiatric Disorders" in the double-blind, placebo-controlled study N01235 as shown in the Sponsors table reproduced below.

| Subject # | Group | TTE [DOE] | Verbatim / MedDRA PT | Severity | Relation-ship | Outcome |
|---|---|---|---|---|---|---|
| 4006/0001 | PBO | 26 [>59] | Exacerbation of anxiety / Anxiety | Moderate | None | Ongoing |
| 5003/0002 | PBO | 30 [29] | Tic / Tic[a] | Moderate | Possible | Resolved |
| 5006/0006 | PBO | 18 [>82] | Insomnia / Insomnia | Moderate | Possible | Ongoing |
| 5009/0003 | PBO | 1 [15] | Anxiety / Anxiety | Mild | None | Resolved |
| | | 31 [1] | Emotional stress / Emotional distress | Mild | None | Resolved |
| | | 34 [3] | Anxiety / Anxiety | Mild | None | Resolved |
| 6002/0001 | PBO | 2 [13] | Forgetfulness / Memory impairment | Moderate | Probable | Resolved |
| | | 2 [13] | Emotional lability / Affect lability | Mild | Unlikely | Resolved |
| | | 2 [13] | Episodic confusion / Confusional state | Moderate | Probable | Resolved |
| 6003/0004 | PBO | 8 [>91] | Depression worse / Depression | Mild | Possible | Ongoing |
| 7003/0003 | PBO | 8 [2] | Nervousness / Nervousness | Severe | None | Resolved |
| | | 22 [7] | Nervousness / Nervousness[a] | Severe | None | Resolved |
| 7005/0003 | PBO | 36 [1] | Nervousness / Nervousness | Mild | Unlikely | Resolved |
| 4001/0001 | LEV XR | 1 [18] | Irritability / Irritability[a] | Mild | Highly probable | Resolved |
| | | 1 [18] | Aggressiveness / Aggression[a] | Mild | Probable | Resolved |
| 4001/0007 | LEV XR | 2 [5] | Irritability / Irritability | Mild | Highly probable | Resolved |
| 5004/0004 | LEV XR | 2 [13] | Emotional irritability / Affect lability | Moderate | Possible | Resolved |
| | | 17 [2] | Insomnia / Insomnia | Moderate | Possible | Resolved |
| | | 28 [3] | Emotional irritability / Affect lability | Moderate | Possible | Resolved |
| 5004/0006 | LEV XR | 30 [>70] | Emotional lability/ Affect lability | Moderate | Possible | Ongoing |
| 6003/0003 | LEV XR | 86 [>14] | Irritable / Irritability | Mild | Unlikely | Ongoing |
| 6003/0005 | LEV XR | 29 [1] | Anger / Anger | Mild | Possible | Resolved |
| | | 15 [>85] | Irritability / Irritability | Mild | Possible | Ongoing |
| 7004/0002 | LEV XR | 53 [1] | Irritability / Irritability | Mild | None | Resolved |

(a) Concomitant medication used to treat event.
TTE: Time to Event (days on drug); [DOE]: Duration of Event (days)

The profile of these "Psychiatric Disorders" TEAEs was not different than that reported with KEPPRA. The majority of the events occurred within the first month of study drug intake and were transient, usually resolving within 15 days. None of the subjects in either group discontinued due to a psychiatric event and only 1 subject (6002/0001) in the PBO group temporarily discontinued study drug for 1 day due to the events. Similarly, only 3 subjects, 2 in PBO and 1 in LEV XR, used a concomitant medication to treat their events.

Of the three clinical pharmacology studies (total N=69), 7 (10%) subjects in study N01160 and study N01260 reported adverse events with a primary SOC related to psychiatric disorders. All events were considered mild in severity. A reproduction of the Sponsor's table below summarizes the psychiatric events reported in the clinical pharmacology studies.

| Study # / Patient I.D. | Age (years) / Sex[a] / Race[b] | Treat-ment Phase[c] | Dose at Onset (mg/day) / Time to Onset | Duration of Event | Verbatim / MedDRA PT | Severity | Action | Related | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| N01260 / 001/0014 | 22.4 / F / B | 3 | 2 x 500 mg LEV XR / 14 hours, 45 minutes | 5 hours | Insomnia / Insomnia | Mild | N/A[d] | Possible | Resolved |
| N01160 / 001/0006 | 32.5 / M / B | 2 | 2 x 500 mg LEV XR with food / 1 day, 18 hours, 5 minutes | 11 days, 20 hours | Insomnia / Insomnia | Mild | No change | Unlikely | Resolved |
| N01160 / 001/0013 | 46.4 / F / C | 2 | 2 x 500 mg LEV XR (fasting) / 9 days, 15 hours, 20 minutes | 5 hours, 30 minutes | Insomnia / Insomnia | Mild | No change | Possible | Resolved |
| | | | | | Nightmare / Nightmare | Mild | No change | Possible | Resolved |
| N01160 / 001/0014 | 25.3 / F / C | 2 | 500 mg b.i.d. LEV IR / 9 days, 15 hours, 18 minutes | 4 days, 22 hours, 30 minutes | Insomnia / Insomnia | Mild | No change | Unlikely | Resolved |
| | | | | | Nightmare / Nightmare | Mild | No change | Possible | Resolved |
| N01160 / 001/0019 | 27.3 / F /C | 2 | 500 mg b.i.d. LEV IR / 10 days, 13 hours, 38 minutes | 1 day, 8 hours | Insomnia / Insomnia | Mild | No change | Possible | Resolved |
| | | | | | Nightmare / Nightmare | Mild | No change | Possible | Resolved |
| N01160 / 001/0020 | 21.3 / F / O | 3 | 500 mg b.i.d. LEV IR / 1 day, 13 hours, 36 minutes | 8 days, 11 hours, 30 minutes | Psychic Slowing Down / Bradyphrenia | Mild | No change | Possible | Resolved |
| N01160 / 001/0023 | 35.2 / F / C | 3 | 2 x 500 mg LEV XR (fasting) / 4 days, 17 hours, 30 minutes | 2 days, 21 hours, 30 minutes | Nightmare / Nightmare | Mild | No change | Possible | Resolved |

Within the double-blind study, one TEAE in each treatment arm was reported with an SOC of cardiac disorders. In the PBO group, subject 5006/0004 reported two episodes of angina pectoris (Preferred Term). Both episodes were considered mild and unrelated to study drug. Both episodes spontaneously resolved with no action taken to study drug, nor concomitant treatment given. In the LEV XR group, subject 5004/0004 experienced moderated, intermittent "exercise induced muscle soreness (stenocaria)" (verbatim term coded to angina pectoris). The event was considered by the Investigator to be possibly related to study drug. The event began 5days after initiation of study drug and was ongoing at the end of the trial. No action was taken with study drug due to the event. No other cardiac events were reported.

Within the three clinical pharmacology studies, no TEAEs were reported with an SOC of cardiac disorders. In study N01160, a TEAE of moderate vasovagal reaction (SOC=Nervous System Disorder) was reported in a 35 year old Female. It was not considered by the Investigator to be related to study drug and resolved after 14 minutes. Additionally in N01160, a TEAE of intermittent, mild hot flushes (SOC=Vascular Disorder) was reported by a 25 year old Female. It was considered unlikely related to study drug and resolved in 4 days.

### 7.1.10 Immunogenicity

No human data is available, but in data supplied by the Sponsor Levetiracetam showed no evidence of immunotoxicity or antigenic potential following evaluation in neonatal or juvenile rats and dogs. The major human metabolite of levetiracetam, ucb L057, [redacted] have been shown to be non-toxic in dose toxicity studies in rats and dogs and to be non-mutagenic. b(4)

### 7.1.11 Human Carcinogenicity

Although no human data is available, data supplied by the Sponsor showed no evidence of carcinogenicity in lifetime studies in rats and mice.

### 7.1.12 Special Safety Studies

None

### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

No reports of abuse or overdose with LEV XR were included in any of the studies reviewed for this application.

### 7.1.14 Human Reproduction and Pregnancy Data

Reproductive toxicity studies in mice, rats and rabbits have not identified any effects of levetiracetam that could be associated with adverse effects upon human fertility, the developing human embryo or in the pre- and post-natal period, at the proposed therapeutic dose levels. Adverse maternal effects were largely restricted to rabbits at 200 mg/kg/day and above and included neuromuscular clinical signs and body weight / food intake effects. The major embryo-fetal findings of a small retardation of fetal weight and bone ossification / skeletal variations, again were observed at the highest study doses in rats (350 mg/kg/day and above) and rabbits (600 mg/kg/day and above). Administration of levetiracetam in pregnant mice did not affect the teratogenic effect of another AED (valproate).

### 7.1.15 Assessment of Effect on Growth

See above.

### 7.1.16 Overdose Experience

According to the current KEPPRA label, the highest known dose of KEPPRA received in the clinical development program was 6000 mg/day. Other than drowsiness, there were no adverse events in the few known cases of overdose in clinical trials. Cases of somnolence, agitation, aggression, depressed level of consciousness, respiratory depression and coma were observed with KEPPRA overdoses in post-marketing use. There is no specific antidote for overdose with KEPPRA. Standard hemodialysis procedures result in significant clearance of levetiracetam (approximately 50% in 4 hours) and may be considered in cases of overdose.

### 7.1.17 Postmarketing Experience

There have been no reports from post-marketing experience, since levetiracetam extended release tablet 500 mg is not marketed. I am not aware of any relevant postmarketing safety concerns with Keppra.

## 7.2 Adequacy of Patient Exposure and Safety Assessments

Keppra has had worldwide exposure and safety assessments with no significant concerns to date. Therefore, even though the patient exposure to Keppra XR is relatively low at 137, the exposure and safety assessment is likely adequate

### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

An overview of the schedule of collection of safety data is given in the table below, as provided by the Sponsor. This is followed by further descriptions of the collection of adverse events, clinical laboratory data, electrocardiograms (ECGs) and vital signs.

| Study #. | Visit Schedule | Adverse Events | Clinical Laboratory Tests / ECG / Physical Exam | Vital Signs |
|---|---|---|---|---|
| N01235 | Selection;<br>8-week Baseline;<br>12-week Treatment Period<br>(4 visits); Final Visit[a] | Each Visit | Selection Visit;<br>End of Baseline Period; End of Treatment Period; Early Discontinuation; Final Visit[a] | Each Visit |
| N01140 | Screening Visit;<br>6-week Treatment Period<br>(5 visits); Discharge Visit | Each Visit | Screening Visit;<br>Discharge Visit | Each Visit |
| N01160 | Screening Visit;<br>3 x 11-day Treatment Period;<br>Discharge Visit | Each Visit | Screening Visit;<br>Discharge Visit | Each Visit |
| N01260 | Screening Visit;<br>3 x 3-day Treatment Periods<br>Discharge Visit | Each Visit | Screening Visit;<br>Discharge Visit | Each Visit |

### 7.2.1.1 Study type and design/patient enumeration

In total, five studies have been conducted in the development of levetiracetam extended release tablet 500 mg (LEV XR). One efficacy and safety study (N01235) recruited patients ages 12 years of age and older with epilepsy, experiencing partial onset seizures. Three clinical pharmacology studies (N01140, N01160, and N01260) were conducted in healthy volunteers to investigate the bioavailability of the extended release tablet 500 mg as compared to the immediate release tablet 500 mg, the food effect, and the dose proportionality over the approved 1000 mg to 3000 mg dose range for immediate release KEPPRA. Data from these four studies includes a total of 137 unique subjects who have been exposed to levetiracetam extended release tablet 500 mg, including 77 patients with epilepsy and not including 79 patients exposed to placebo in the efficacy and safety study (N01235). The fifth study (N01173) was a pharmacoscintigraphic investigation of regional drug absorption using [redacted] capsule in 3 different sites of the GI tractd b(4)

### 7.2.1.2 Demographics

The demographic characteristics for the ITT population are listed in the table below, reproduced from the Sponsor's Original Application. They appear to be well matched between treatment groups. The four subjects in the PBO group with weights below the inclusion criterion weights were considered as minor protocol deviations. There were only six adolescents in the LEV XR group.

| Characteristics | PBO N=79 | LEV XR N=79 |
|---|---|---|
| **Age (years)** | | |
| Mean (SD) | 32.38 (12.60) | 33.97 (13.41) |
| Min - Max | 13.3 – 67.9 | 12.2 – 67.9 |
| Median | 29.61 | 33.71 |
| **Gender** | | |
| Male (n%) | 47 (59.5) | 52 (65.8) |
| Female (n%) | 32 (40.5) | 27 (34.2) |
| **Race** | | |
| White | 35 (44.3) | 37 (46.8) |
| Asian / Pacific Islander | 1 (1.3) | 0 |
| Hispanic | 15 (19.0) | 15 (19.0) |
| Indian / Pakistani | 27 (34.2) | 27 (34.2) |
| Other | 1 (1.3)[a] | 0 |
| **Weight (kg)** | | |
| Mean (SD) | 67.80 (15.55) | 70.21 (15.66) |
| Min – Max | 48.0 – 134.0 | 50.0 – 118.0 |
| Median | 64.00 | 69.00 |
| **Height (cm)** | | |
| Mean (SD) | 165.7 (9.8) | 168.1 (10.3) |
| Min – Max | 138 - 189 | 150 - 188 |
| Median | 165.0 | 170.0 |
| **BMI ($kg/m^2$)** | | |
| Mean (SD) | 24.60 (4.55) | 24.76 (4.71) |
| Min – Max | 16.8 – 38.6 | 17.6 – 47.1 |
| Median | 23.70 | 23.78 |

### 7.2.1.3 Extent of exposure (dose/duration)

79 patients were exposed to LEV XR 1,000 mg daily for 12 weeks. At the end of the Treatment Period, subjects wishing to continue on LEV treatment (specific data not available) could convert to the LEV IR formulation, either by prescription or named patient program in countries where LEV IR is not marketed or fully reimbursed. An additional 60 subjects were briefly exposed to LEV XR during the three PK studies.

### 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

A TEAEs comparison between LEV XR 1000 mg once daily and KEPPRA Tablets 500 mg b.i.d. was made for two studies. Study N051 was a double-blind, placebo controlled, randomized, two-period and crossover study to evaluate the efficacy and tolerability of KEPPRA 500 mg and 1000 mg b.i.d as add-on treatment in refractory epilepsy patients with partial onset seizures Study N132 was a double-blind, placebo controlled, randomized, parallel group study to evaluate the efficacy and tolerability of KEPPRA 500 mg and 1500 mg b.i.d. as add-on treatment in epilepsy patients with partial onset seizures. Overall, LEV XR appeared to have a similar adverse event profile as that of KEPPRA tablets. The incidence of adverse events in LEV XR appears globally lower than that of KEPPRA in the studies compared in particular in the Nervous System and Psychiatric.

### 7.2.3 Adequacy of Special Animal and/or In Vitro Testing

Nonclinical safety information for the levetiracetam extended release tablet 500 mg has been incorporated by reference to approved NDA 21-035 for KEPPRA (levetiracetam) 250 mg, 500 mg, 750 mg and 1000 mg tablets; NDA 21-505 for KEPPRA (levetiracetam) oral solution 100 mg/mL and NDA 21-872 for KEPPRA (levetiracetam) injection 500 mg/5 mL (100 mg/mL). Nonclinical studies has been previously conducted with orally administered levetiracetam, including acute and chronic toxicity, reproductive toxicity, genotoxicity, carcinogenicity and special toxicity studies. Safety pharmacology and toxicology studies have also been conducted with intravenously administered levetiracetam.

### 7.2.4 Adequacy of Routine Clinical Testing

Adequate

### 7.2.5 Adequacy of Metabolic, Clearance, and Interaction Workup

Adequate

### 7.2.6 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Adequate

### 7.2.7 Assessment of Quality and Completeness of Data

Adequate

### 7.2.8 Additional Submissions, Including Safety Update

Provided

## 7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The tolerability and safety profile of LEV XR 1000 mg once daily was consistent with the known safety profile of KEPPRA immediate release tablets. In the present study, the actual rate of TEAEs was lower than that listed in the Investigator's Brochure for levetiracetam . No unexpected safety concerns arose from the reported adverse events, clinical laboratory evaluations, vital signs and body weight, physical and neurological examinations, or ECG monitoring during the course of the study. The double-blind, placebo-controlled study of LEV XR 2 x 500 mg administered once daily during a 12-week period is safe and well tolerated in the treatment of refractory epileptic subjects 16 to 70 years of age suffering from partial onset seizures.

## 7.2 General Methodology

Adverse events were coded using MedDRA (Version 9.0). Two sources of information are described, the double-blind, placebo-controlled study N01235 and the three pharmacology studies. 158 patients with epilepsy were randomized in Study N01235, 79 to LEV XR, of which only 77 subjects were exposed to LEV XR (one subject was excluded because drug was not dispensed, while another was excluded because she returned all the tablets received at the site). A total of 143 (90.5%) subjects

completed the study; 72 (91.1%) in the placebo group and 71 (89.9%) in the LEV XR group. 60 subjects were exposed to LEV XR in the 3 clinical pharmacology studies. The ITT population comprised all the randomized patients. Although this population was the primary subset for the analysis of efficacy data, the safety population comprised all subjects who were dispensed medication. The three pharmacology studies included only healthy volunteers. There were a total of 60 Subjects. Therefore there were 137 unique exposures to LEV XR.

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

No pooling of safety data occurred; safety from the efficacy and clinical pharmacology studies is described separately. Therefore, the safety population included those subjects exposed to drug in the following studies, reproduced from the Sponsor's Original Application.

| Study No. | No. Randomized (Exposed to XR) | Dates of Conduct / Countries | Overview of Design |
|---|---|---|---|
| **Subjects with Partial Onset Seizures** | | | |
| N01235 | 158 (77) | 21-Aug-2006 – 30-May-2007 / Brazil, Finland, India, Mexico, Russian Federation, South Africa, Ukraine | Double-blind, placebo-controlled, randomized, 1000 mg once daily, as add-on therapy in patients 12 – 70 years of age with refractory epilepsy with POS; 8-week baseline followed by 12 weeks of treatment. |
| **Healthy Volunteers** | | | |
| N01140 | 12 (12) | 16-Mar-2005 – 25-May-2005 / France | Single dose, open-label pilot study to compare the pharmacokinetics of LEV 500 mg from 3 XR test formulations with the IR reference formulation in healthy volunteers and to assess the influence of food on one of the test formulations. (Bioequivalence study) |
| N01160 | 24 (24) | 04-Jul-2006 – 02-Sep-2006 / France | Randomized, open-label, three-way crossover study of LEV XR (1000 mg, once daily) and LEV IR (500 mg B.I.D.). Single and multiple dose bioequivalence and assessment of food effect on LEV XR in healthy volunteers. |
| N01260 | 24 (24) | 05-Jan-2007 – 26-Feb-2007 / France | Randomized, open-label, single dose, three-way crossover dose proportionality study of LEV XR 1000 mg, 2000 mg, and 3000 mg, in healthy volunteers. |

#### 7.4.1.1 Pooled data vs. individual study data

As above

#### 7.4.1.2 Combining data

As above

### 7.4.2 Explorations for Predictive Factors

None

#### 7.4.2.1 Explorations for dose dependency for adverse findings

None

#### 7.4.2.2 Explorations for time dependency for adverse findings

None

#### 7.4.2.3 Explorations for drug-demographic interactions

None

#### 7.4.2.4 Explorations for drug-disease interactions

None

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

None

### 8.2 Drug-Drug Interactions

None

### 8.3 Special Populations

None

### 8.4 Pediatrics

b(4)

### 8.5 Advisory Committee Meeting

None

### 8.7 Postmarketing Risk Management Plan

None

# 9 OVERALL ASSESSMENT

## 9.1 Conclusions

This NDA shows that LEV XR 2x500 mg administered once daily was effective, safe and well tolerated in the treatment of refractory epileptic subjects 16 to 70 years of age suffering from partial onset seizures.

## 9.2 Recommendation on Regulatory Action

I recommend approval for Keppra XR 500 mg as adjunctive therapy in the treatment of partial onset seizures in adults and adolescents 16 years of age and older with epilepsy.

## 9.3 Recommendation on Postmarketing Actions

See 9.3.2 below

### 9.3.1 Risk Management Activity

None

### 9.3.2 Required Phase 4 Commitments

I agree with the recommendations of Dr. Gilbet Burckart, clinical pharmacologist, that the Sponsor will conduct an open label, single dose, pharmacokinetic study with Keppra XR in patients with epilepsy, ages 12-16 years, in comparison to adult patients with epilepsy. The patient population can presently be receiving Keppra. The pharmacokinetic study would include at least 6 pharmacokinetic samples. The comparison group will be an equal number of adult patients studied under the same conditions. For each group (adolescents and adults), the mean Cmax and AUC must be estimated with a standard error of 20% or less, and this would be the basis for the original sample size calculation. As study data are evaluated, the sample size can be re-assessed if necessary for precise estimation of these pharmacokinetic parameters.

### 9.3.3 Other Phase 4 Request

As originally proposed by Dr. Gilbert Burkart, clinical pharmacologist, I agree that the Sponsor should

[redacted] b(4)

2. Perform a pharmacokinetic study in geriatric patients with Keppra XR to provide specific dosing information.

## 9.4 Labeling Review

# 1 INDICATIONS AND USAGE

KEPPRA XR™ is indicated as adjunctive therapy in the treatment of partial onset seizures in patients ≥16 years of age with epilepsy.

# 19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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