CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-872

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-872
Drug:	Levetiracetam Injection 100 mg/mL
Trade Name:	Keppra®
Sponsor:	UCB Pharma
Indication:	Adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy
OND Clinical Division:	Division of Neurology Drug Products (HFD-120)
OCPB Division:	DCPB 1 (HFD-860)
Submission Type:	Standard (New Formulation)
Submission Dates:	12/20/04, 5/20/05, 7/14/05, 7/20/05, 8/1/05, 8/23/05, 9/1/05, 9/15/05, 10/24/05, 11/3/05, 11/4/05
PM Reviewer:	Leslie Kenna, Ph.D.
PM Team Leader:	Jogga Gobburu, Ph.D.
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

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1. Executive Summary

1.1. Recommendations

Based on the data submitted to the Human Pharmacokinetics and Bioavailability Section of NDA 21-872, the application is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). OCPB supports a recommendation for approval.
OCPB Labeling recommendations are provided in Section 3.1

1.2. Phase 4 Commitments

There are no Phase 4 commitments recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Background: Keppra™ oral 250, 500 and 750 mg oral tablets and 100 mg/mL oral solution are approved as adjunctive treatment of partial onset seizures in adults and children (4- 16 years) with epilepsy. The sponsor has developed an intravenous (IV) solution as an alternative for patients when oral administration is temporarily not feasible. The proposed indication and dosing regimen are the same as that already approved for oral tablets and solution. The Keppra injection NDA is based on the results from two clinical studies: 1) A comparative bioavailability and bioequivalence study and 2) A Safety and tolerability study.

Bioequivalence: Levetiracetam 1500 mg injection (3 x 500 mg/5 mL ampoules) diluted in 100 mL 0.9% saline solution and infused over 15 minutes was demonstrated to be bioequivalent to 1500 mg (3 x 500 mg) levetiracetam oral tablets.

Table 1: Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate[a]	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.7 ± 88.6	378.6 ± 73.2	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.9 ± 89.6	392.4 ± 71.2	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.5 ± 18.8	103.7	91.6 -117.4

[a]Point Estimate and 90% CI for the expected test/reference geometric mean ratio (%).

Analyses with subject 0007 eliminated

The primary bioequivalence study (N01077) was inspected by the Division of Scientific Investigations (DSI). DSI reported one subject (0007) received 1200 mg instead of 1500 mg dose because one of the ampoules was under-filled. The subject was not included in the bioequivalence analysis (Table 1). DSI reported that it was not accurately reported in the original submission that this under-dosing was due to an under-filled ampoule. The sponsor, subsequent to the DSI report updated the final study report to indicate that subject 0007 was dosed with an under-filled ampoule.

Analyses with subjects 0001, 0002, 0007 eliminated

DSI reported that the QC samples included in the analytical run for samples for subjects 0001 and 0007 in the primary bioequivalence study did not meet the acceptance criteria. However, a review of the sponsor's response with this deficiency indicated that by the sponsor's SOP, the runs met the acceptance criteria [redacted] Therefore, analytical procedure for subjects 0001 and 0002 was acceptable. Nonetheless, the data was recalculated eliminating subjects 0001, 0002 and 0007 both by the sponsor and the reviewer. The results of the reviewer's calculations were consistent with the sponsor's calculations. Table 2 below provides the results of the calculations.

Table 2: Pharmacokinetic Parameters of Levetiracetam after a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (0001, 0002, 0007 omitted)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate	90% CI
AUC(0-t) (µg*h/mL)	414.6 ± 82.6	376.40 ± 66.40	91.4	87.5 – 95.4
AUC (µg*h/mL)	427.0 ± 83.0	389.73 ± 63.31	92.0	88.4 – 95.7
Cmax (µg/mL)	47.9 ± 13.1	50.90 ± 20.0	103.3	92.6 – 116.1

Analysis that randomly eliminated 3 subjects at a time

The sponsor reported a [redacted] rejection rate at release of the ampoules that were manufactured. The reviewers calculated the bioequivalence data by randomly eliminating 3 subjects at a time to reflect the possibility that 3 out 18 subjects [redacted] may have received defective levetiracetam injection ampoules due to the [redacted] rejection rate. Both reviewer's and the sponsor's calculations indicated that levetiracetam 1500 mg IV infusion was bioequivalent to 1500 mg oral tablet. The 90% confidence interval around the point estimate for both AUC and Cmax were contained within the regulatory limit of 80% to 125% for declaring two formulations to be bioequivalent.

The following is a sample table obtained from the analysis that randomly eliminated 3-subjects at a time.

Table 3: Mean Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in Healthy Subjects (Randomly eliminated Subjects 0006, 0007, 0018)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (μg*h/mL)	413.13 ± 93.83	376.93 ± 77.75	92.3	88.6 – 96.1
AUC (μg*h/mL)	426.20 ± 95.28	390.73 ± 75.70	91.7	87.8 – 95.8
Cmax (μg/mL)	47.12 ± 13.79	50.53 ± 19.93	104.8	92.4 – 118.8

Safety Profiles: In the pivotal bioequivalence study, the sponsor reported that both the IV and oral formulations were well tolerated. The sponsor reported that safety assessments did not reveal any unexpected risks following the administration of levetiracetam. The incidence of TEAE was reported by the sponsor to be 72.2% for LEV tablet and 88.9% for LEV IV. After administration of the oral and IV formulations, the most commonly reported adverse event were somnolence, dizziness and headache. The sponsor also evaluated the safety and tolerability of a single dose IV infusion of levetiracetam up to 4000 mg in 15 minutes and up to 2500 mg in 5 minutes (Study 1165). The sponsor concluded that the intravenous infusion of levetiracetam up to 4000 mg in 15 minutes and up to 2500 in 5 minutes was safe and well tolerated. Safety profiles were reported by the sponsor to be similar after single ascending administration of LEV IV and at a faster infusion rate. Please refer to the medical officer's review for the assessment of the safety profile for the IV formulation.

Dosing Recommendation in Adults: The proposed dosing regimen is similar to that approved for the tablets and oral solution.

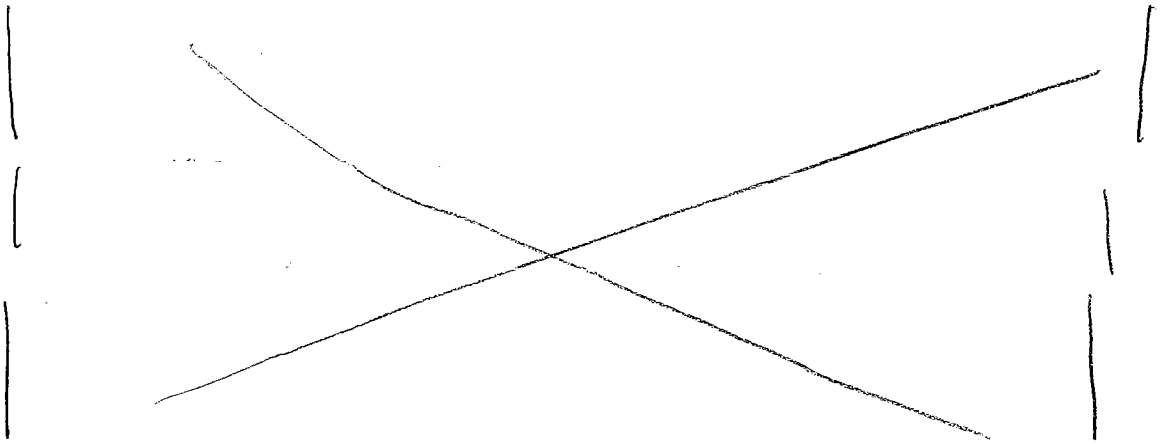
Keppra® Injection is an alternative for patients when oral administration is temporarily not feasible. Keppra® Injection is for intravenous use only and must be diluted prior to administration. [redacted] should be diluted in at least 100 mL of a compatible diluent and administered intravenously as a 15-minute I.V. infusion.

Product with particulate matter or discoloration should not be used.

Treatment should be initiated with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg BID). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. Doses greater than 3000 mg/day have been used in open-label studies with Keppra® tablets for periods of 6 months and longer. There is no evidence that doses greater than 3000 mg/day confer additional benefit.

Use of IV in Pediatric Patients

The purpose of the pediatric review



2. Question-Based Review (QBR)

2.1. General Attributes of the Drug

Keppra™ oral 250, 500 and 750 mg oral tablets and 100 mg/mL oral solution are approved as adjunctive treatment of partial onset seizures in adults with epilepsy. The sponsor has developed an intravenous (IV) solution as an alternative for patients when oral administration is temporary not feasible. The proposed indication is the same as that already approved for oral tablets and solution: adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. At the pre-NDA meeting in December, 2003, the agency agreed that an efficacy study would not be needed. The Keppra injection NDA would be based on the results from two clinical studies: 1) A comparative bioavailability and bioequivalence study and 2) Safety and tolerability study. The studies included in the NDA focused on the bioequivalence for oral and intravenous formulations, and safety of the IV formulation.

2.1.1. What are the highlights of the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Levetiracetam is an antiepileptic drug (AED). Levetiracetam is a pyrrolidone derivative and is chemically designated (S)-alpha-ethyl-2-oxo-1- pyrrolidone acetamide and has a molecular weight of 170.21 and molecular formula of $C_{18}H_{14}N_2O_2$. Its water solubility is 1.04 g/mL and the partition coefficient (octanol/water) is [redacted] Keppra IV (levetiracetam injection) 100 mg/mL is a sterile, clear colorless solution. Each vial contains 500 mg of levetiracetam as a 100 mg/mL preservative free solution. Keppra IV will be supplied commercially as a 100 mg/mL sterile solution of levetiracetam in a 5 mL glass vial.

2.1.2. What is the mechanism of action and therapeutic indication?

Keppra is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. The precise mechanism by which levetiracetam exerts its antiepileptic effect is unknown.

2.1.3. What are the proposed dosage and route of administration?

Levetiracetam is therapeutically active when dosed daily at 1000 mg and if needed, the daily dose can be increased to a total daily dose of 3,000 mg. The proposed total daily dose for Keppra IV is 1000 to 3000 mg levetiracetam. The proposed dosing regimen is 1000 mg to 3000 mg daily, administered intravenously in two divided doses (b.i.d.)

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

Two primary studies were conducted to demonstrate that levetiracetam 1500 mg infused intravenously over 15 minutes is bioequivalent to the levetiracetam 1500 mg oral tablet. And, to demonstrate that there is a similar safety profiles between the oral and the intravenous formulations and to describe the safety profile.

The bioequivalence study (Part A) was a randomized, single dose, fasted, open-label, two way cross-over bioavailability comparison trial of LEV 1500mg administered as 15 minute infusion and LEV 1500 mg orally as 3 x 500 mg tablets (N01077). Part B of the study was a randomized, double-blind, placebo-controlled, safety, tolerability and pharmacokinetic parallel trial of levetiracetam 1500mg 15 minute intravenous infusion during 4 days of twice a day dosing. The safety and tolerability study was a randomized, single-blind, placebo-controlled, safety study of ascending doses of LEV administered in 15-minute intravenous infusions (up to 4000 mg) and in 5-minute intravenous infusions (up to 2500 mg) (N01165).

2.2.2. Are the safety profiles for the IV formulations similar to that of the oral formulation?

In the pivotal bioequivalence study, the sponsor reported that both the IV and oral formulations were well tolerated. The sponsor reported that safety assessments did not reveal any unexpected risks following the administration of levetiracetam. The incidence of TEAE was reported by the sponsor to be 72.2% for LEV tablet and 88.9% for LEV IV. After administration of the oral and IV formulations, the most commonly reported adverse event were somnolence, dizziness and headache.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure relationships?

Yes, the active moiety (levetiracetam) was appropriately identified. (See Analytical Section). The metabolite (ucb L057) was also assayed.

2.2.4. What are the pharmacokinetic characteristics of the drug and its major metabolite after intravenous administration?

Cmax of LEV IV was higher after repeated administration (71.7 ± 21.3 µg/mL) than after a single dose administration (52.4 ± 22.3 µg/mL). Minimal concentration (Cmin) averaged 14.1 ± 3.75 µg/mL. Steady state was reached from 24 h onwards. AUC and AUC_T were similar after single or multiple dose administration of LEV IV (389.4 vs 371.9 µg*h/mL for single and multiple doses of LEV, respectively). There was no significant difference in the metabolites after IV and oral administration of LEV.

The PK profile of levetiracetam 1500 mg IV infusion during repeated dosing (4 days b.i.d.) was assessed using descriptive statistics on all available PK parameters. Eighteen randomized subjects received, under fasting conditions the following treatments: Either LEV 1500 mg (500 mg/mL ampoule) administered as a 15-minute intravenous infusion and diluted in 100 mL 0.9% saline solution (n= 12). Or saline solution (3 ampoules) added to 100 mL 0.9%, administered as a 15-minute IV infusion (n = 6). These treatments were administered every 12 hours during 4.5 days (from Day 3 to Day 7 in the morning). On Day 7, plasma samples were collected before and up to 12 hours post-dose.

Table 4: The following table provides a comparison of the pharmacokinetic parameters for LEV IV after single dose and multiple dose administration.

Parameter	Levetiracetam 1500 mg IV single dose (Day 1)	Levetiracetam 1500 mg IV multiple dose (Day 7)
	Mean ± SD	
AUC_T (µg*h/mL)	389.4 ± 77.6	371.9 ± 80.9
Cmax (µg/mL)	52.4 ± 22.3	71.7 ± 21.3
Tmax (h)	0.25 (0.22 – 2.0)	0.25 (0.20 – 0.27)
Cmin (µg/mL)	-	14.1 ± 3.75
Rmax	-	1.51 ± 0.48

Tmax: median (range)

The following table provides a comparison of the parameters of ucb L057 after administration of the IV and tablet formulations.

Table 5: Pharmacokinetic Parameters of ucb L057 (metabolite) After Administration of LEV Tablet and IV Formulations

ucb L057 Parameters	Levetiracetam 3 x 500 mg tablet	Levetiracetam 1500 mg IV
	Mean ± SD	
AUC (0-t) (µgEq LEV *h/mL)	18.8 ± 4.43	17.2 ± 4.30
AUC (µgEq LEV*h/mL)	19.1 ± 4.34	18.3 ± 5.33
Cmax (µg Eq LEV/mL)	1.02 ± 0.183	0.946 ± 0.189
T max (h)	6.05 (6.0 – 12.0)	6.00 (3.0 – 9.0)
T ½ (h)	8.50 ± 1.09	8.37 ± 1.09

Tmax values are median (range)

2.3. Intrinsic

The studies were not designed to adequately evaluate the effect of intrinsic factors after IV administration.

2.4. Extrinsic Factors

Extrinsic factors were not evaluated in this application. However, the effect of extrinsic factors (e.g. drug-drug interactions) have been evaluated and available in the approved label.

2.5. General Biopharmaceutics

2.5.1. What is the composition of levetiracetam intravenous solution?

Keppra (levetiracetam injection), 100 mg/mL is a sterile, clear colorless solution for intravenous administration. Each single use vial contains 500 mg of levetiracetam as 100 mg/mL preservative free solution. The following is the composition of Keppra IV

Table 6: Composition of Keppra IV (100 mg/mL)

Ingredient	Unit of Quantity	Function
Levetiracetam	0.100 g	Active Ingredient
Sodium Acetate Trihydrate		Buffering Agent
Sodium Chloride		
Glacial Acetic Acid as Solution	As needed for pH adjustment	pH adjustment
Water for Injection		Drug vehicle

2.5.2. Is Levetiracetam injection infused over 15 mins bioequivalent to an equal dose of the tablet?

Levetiracetam 1500 mg IV infused over 15 minutes was found to be bioequivalent to levetiracetam 1500 mg (3 x 500 mg) oral tablets after single dose administration.

The sponsor conducted a randomized, monocenter, open-label, two-way cross over bioavailability comparison trial of levetiracetam 1500 mg administered as a 15-minute intravenous infusion and levetiracetam 3 x 500 mg oral tablet. Eighteen randomized subjects (mean age and weight were 35 ± 9.28 years and 73.3 ± 14.2 kg, respectively) received, under fasting conditions, either levetiracetam 1500 mg diluted in 100 mL 0.9% saline solution administered as a 15 minute intravenous infusion in Period I followed by 3 x 500 mg of levetiracetam oral tablet in Period 2 after a 7 day wash out period. Or 3 x 500 mg of levetiracetam oral tablet (Period 1) followed by levetiracetam 1500 mg diluted in 100 mL 0.9% saline solution administered as a 15 minute intravenous infusion (Period 2) after 7-day wash-out period.

Pharmacokinetic analysis was conducted on seventeen subjects. The data for one subject was not used because the subject received 1200 mg instead of 1500 mg. The pharmacokinetic parameters and the 90% confidence interval (CI) are provided in the following table

Table 7: Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.7 ± 88.6	378.6 ± 73.2	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.9 ± 89.6	392.4 ± 71.2	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.5 ± 18.8	103.7	91.6 -117.4

Cmax for the two formulations were similar after administration of LEV tablet and IV and the 90% CI was contained within the regulatory limit of 80% - 125% for bioequivalence. AUCs were similar after administration of the two formulations and the 90% CI are contained within the regulatory limit of 80% to 125% for bioequivalence

Analysis with Subject 0007 eliminated

The pivotal bioequivalence study (N01077) was inspected by the Division of Scientific Investigations (DSI). DSI and the sponsor reported that subject 0007 received 1200 mg instead of 1500 mg dose because one of the ampoules was under-filled. Subject 0007 was therefore omitted from the analysis (Table 7). The reviewer re-calculated the data and the results and conclusions are consistent with that of the sponsor. The results of the reviewer's calculations are provided below.

Table 8: Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects (Reviewer's calculations).

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.2 ± 88.6	378.1 ± 73.3	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.4 ± 89.7	392.0 ± 71.1	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.4 ± 18.8	103.7	91.6 -117.4

Analysis with subjects 0001, 0002, 0007 eliminate.

DSI reported that the analytical run for samples from subjects 0001 and 0002 included QC samples that did not meet the acceptance criteria. In response to the DSI report, the sponsor indicated that according to the SOP. [redacted] and hence are acceptable. The reviewer and DSI in reviewing the response to DSI inspection report accepted the sponsor's explanation. Therefore the QC samples met the acceptance criteria. Nonetheless, the bioequivalence data was recalculated with subjects 0001, 0002 and 0007 omitted. The results of that analysis is provided in the table below.

Table 8: Pharmacokinetic Parameters of Levetiracetam after a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Subjects 1, 2, 7) (Sponsor's calculations)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate	90% CI
AUC(0-t) (µg*h/mL)	414.6 ± 82.6	376.40 ± 66.40	91.4	87.5 – 95.4
AUC (µg*h/mL)	427.0 ± 83.0	389.73 ± 63.31	92.0	88.4 – 95.7
Cmax (µg/mL)	47.9 ± 13.1	50.90 ± 20.0	103.3	92.6 – 116.1

Table 9: Pharmacokinetic Parameters of Levetiracetam after a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Subjects 1, 2, 7) (Reviewer's calculations)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate	90% CI
AUC(0-t) (µg*h/mL)	414.1 ± 82.6	376.4 ± 66.40	91.4	87.5 – 95.4
AUC (µg*h/mL)	426.5 ± 83.0	389.73 ± 63.31	92.0	88.4 – 95.7
Cmax (µg/mL)	47.9 ± 13.1	50.90 ± 20.0	103.3	92.0 – 116.1

Eliminating subjects 1, 2 and 7 did not alter the conclusions of the study. Levetiracetam 1500 mg infused over 15 mins was bioequivalent 1500 mg oral tablet. The 90% confidence interval around the point estimate for Cmax and AUC were contained within the regulatory criteria of 80 to 125%.

Analysis by randomly eliminating 3 subjects at a time

The sponsor reported a [redacted] rejection rate at release of the ampoules that were manufactured.

Because of the reported ≻≺ rejection rate in the release of the IV formulation, upon request of the medical reviewers, the data was re-analyzed by the OCPB reviewers by randomly eliminating ≻≺ of the subjects (3 subjects at a time). Results from 3 random samples are provided in the following tables

Table 10: Mean Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in Healthy Subjects (Randomly eliminated Subjects 0006, 0007, 0018)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	413.13 ± 93.83	376.93 ± 77.75	92.3	88.6 – 96.1
AUC (µg*h/mL)	426.20 ± 95.28	390.73 ± 75.70	91.7	87.8 – 95.8
Cmax (µg/mL)	47.12 ± 13.79	50.53 ± 19.93	104.8	92.4 – 118.8

Table 11: Mean Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Randomly eliminated Subjects 7, 11, 15)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	410.93 ± 93.58	375.53 ± 77.86	91.8	88.8 – 96.3
AUC (µg*h/mL)	410.93 ± 93.58	389.53 ± 75.45	92.5	87.9 – 96.0
Cmax (µg/mL)	48.7 ± 14.03	52.2 ± 19.26	105.1	91.3 – 120.9

Table 12: Mean Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in Healthy Subjects (Randomly eliminated Subjects 3, 7, 17)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	425.7 ± 87.9	390.8 ± 66.6	92.5	88.9 – 96.1
AUC (µg*h/mL)	439.5 ± 88.49	404.3 ± 64.9	92.7	89.2 – 96.4
Cmax (µg/mL)	47.7 ± 47.8	51.5 ± 19.3	105.6	93.7 – 119

Randomly eliminating 3 subjects at a time from the bioequivalence analysis did not alter the conclusions. Levetiracetam 1500 mg infused over 15 minutes was determined to be bioequivalent to 1500 mg oral tablet.

2.6. Analytical Method

2.6.1. What bioanalytical methods are used to assess concentrations?

Levetiracetam and ucb L057 were determined in plasma using a validated gas chromatographic method [redacted] The limit of quantitation (LOQ) of the assay for LEV in plasma is [redacted] and the calibration curves ranging from [redacted] The mean of relative deviations of LEV in QC samples were 3.6, -0.4 and 0.0% at nominal concentrations of 1, 8 and 30 µg/mL, respectively. Concentrations of the metabolite (ucb L057) in plasma was measured by high performance liquid chromatography to electrospray mass spectrometry (LC/ESI/MS). The LOQ of the assay for ucb L057 in plasma is [redacted] ng Eq LEV/mL and the calibration curves ranging from [redacted] Eq LEV/mL. The mean of relative deviations of ucb L057 in QC samples were 7.3, 5.1, and 10.3% at nominal concentrations of 60, 200 and 1000 ng-Eq LEV/mL, respectively.

The accuracy of QC samples for LEV represented 3.6%, -0.4% and -0.0% at effective concentrations of 1.01, 8.08 and 30.3 µg/mL. The precision of the validated assay was as follows: The intra-run precision on QC samples, %RSD ≤ 2.6, Inter-run precision on QC samples %RSD ≤ 2.4. The total precision (%RSD) and accuracy were ≤ 3.5% and ≤ | 3.1 |. The limit of detection (LOD) was approximately [redacted] for LEV in plasma extracts. The accuracy of measurement of the analyte in plasma samples was not affected by 100-fold dilution with [redacted] The mean relative deviation between expected and measured concentrations in diluted samples was 6.2%.

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CC: NDA: 21-872, HFD-120, HFD-860 (Mehta, Baweja, KumiK), HFD-850 (Gobburu, Kenna)

CPB Briefing Date and Attendees: December 21, 2005, Sang Chung, Jim Wei, Shiew-Mei Huang, Joga Gobburu, Leslie Kenna, Kofi Kumi, Hank Malinowski, Mehul Mehta, Yaning Wang, Raman Baweja, John Feeney, Norman Hershokowitz, Courtney Calder

23 Page(s) Withheld

_____ Trade Secret / Confidential

__✓__ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 1

3.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Study N01077

Title (Protocol RRCE03H2602, Study N01077): Randomized, Monocenter, Open-Label, Two-Way Cross Over Bioavailability Comparison Trial of Levetiracetam 1500 mg (500 mg/5 mL ampoules) Administered as a 15 Minute Intravenous Infusion and Levetiracetam 3 x 500 mg Oral Tablet (Part A); and a Randomized, Double-Blind, Placebo-Controlled (12:6), Safety, Tolerability and Pharmacokinetic Parallel Trial of Levetiracetam 1500 mg 15 Minute Intravenous Infusion During 4 Days of b.i.d. Dosing (Part B) in 9 Male and 9 Female Healthy Volunteers

Objectives: 1) Compare the single dose bioavailability of levetiracetam 1500 mg 15-min IV infusion with levetiracetam 1500 mg (3 x 500 mg) Oral tablet 2) Assess Pharmacokinetic Profile of Levetiracetam 1500 mg IV infusion during repeated dosing (4 days b.i.d.) 3) To document the safety and tolerability of levetiracetam 1500 mg 15 min IV infusion during repeated dosing (4 days b.i.d.)

Study Design: The study was divided into two parts. Part A was conducted as an open label, randomized, two-way cross over, monocenter, single dose trial. It consisted of 2 treatment periods of 3 days separated by a 7-day wash out period. Part B followed directly the second treatment period of Part A. It was a double-blind, randomized, placebo-controlled, monocenter, repeated dose trial. Part B consisted of one treatment period of 4.5 days, with b.i.d administration from Day 3 to Day7 morning, taking day 1 of the 4th treatment period of Part A as the single dose reference.

During Part A, 18 randomized subjects (mean age and weight were 35 ± 9.28 years and 73.3 ± 14.2 kg, respectively) received, under fasting conditions, either levetiracetam 1500 mg (500 mg/5 mL ampoule) administered as a 15 minute intravenous infusion and diluted in 100 mL 0.9% saline solution in Period I followed by 3 x 500 mg of levetiracetam oral tablet in Period 2 after a 7 day wash out period. Or 3 x 500 mg of levetiracetam oral tablet (Period 1) followed by levetiracetam 1500 mg (500 mg/5 mL ampoule) administered as a 15 minute intravenous infusion and diluted in 100 mL 0.9% saline solution (Period 2) after 7-day wash-out period.

Each single dose (either IV or p.o.) was administered on Day 1 of each treatment period after an overnight fast. Plasma samples were collected before and up to 36 hours post-dose for the determination of the concentrations of levetiracetam.

Part B of the study was a double blind, randomized, placebo-controlled, parallel, monocenter, repeated dose trial. Eighteen randomized subjects received, under fasting conditions the following treatments: Either LEV 1500 mg (500 mg/mL ampoule) administered as a 15-minute intravenous infusion and diluted in 100 mL 0.9% saline solution. Or saline solution (3 ampoules) added to 100 mL 0.9%, administered as a 15-minute IV infusion. These treatments were administered every 12 hours during 4.5 days (from Day 3 to Day 7 in the morning). On Day 7, plasma samples were collected before and up to 12 hours post-dose.

Analytical Method: Levetiracetam and ucb L057 were determined in plasma using a validated gas chromatographic method [redacted] The limit of quantitation (LOQ) of the assay for LEV in plasma is [redacted] and the calibration curves ranging from [redacted] The mean of relative deviations of LEV in QC samples were 3.6, -0.4 and 0.0% at nominal concentrations of 1, 8 and 30 µg/mL, respectively. Concentrations of the metabolite (ucb L057) in plasma was measured by high performance liquid chromatography to electrospray mass

spectrometry (LC/ESI/MS). The LOQ of the assay for ucb L057 in plasma is [redacted] Eq LEV/mL and the calibration curves ranging from [redacted] ng Eq LEV/mL. The mean of relative deviations of ucb L057 in QC samples were 7.3, 5.1, and 10.3% at nominal concentrations of 60, 200 and 1000 ng-Eq LEV/mL, respectively.

Data Analysis: The bioequivalence of the two administrations was assessed regarding the following pharmacokinetic parameters: AUC, AUC (0-t) and Cmax, using the standard 90% CI for the ratio of the geometric means between the two administrations. For all other PK parameters, only descriptive statistics were reported. The PK profile of LEV 1500 mg IV infusion during repeated dosing (4 days b.i.d.) was assessed and descriptive on all available PK parameters provided.

The sponsor reported that due to some further increase in drug levels after the end of infusion in several subjects, Cmax instead of C_{15} was used as maximal concentration for the intravenous 15-minute infusion.

The following deviations from infusion duration (theoretical: 15 minutes) were reported by the sponsor: Subject 001/001, infusion lasted 28 min for period 3 (= part B; repeat dosing) Day 3 (P3D3); 20 min for P3D4; and 17 min for P3D6. Subject 001/002, infusion lasted 33 min for P3D3 and 16 min for P3D5. Subject 001/003 infusion lasted 16 min for P3D3. Subject 001/007, infusion lasted 20 minutes for P3D5. Subject 001/005, infusion lasted 20 min for P3D4. Also, due to administration problems, the sponsor reported that subject 001/007 received 1200 mg instead of 1500 mg of study drug in Part A for Day 1 of the period 1. The subject was excluded and seventeen subjects were submitted to the PK analysis for Part A of the study.

The sponsor reported that several time deviations representing difference between 7% and 140% (21 min for Day 4 at 15 min post-dose for subject 001/002) were observed in most of the subjects (mainly on period 3). Also due to poor availability of veins, two blood samples were not collected: subjects No. 001/0014 (Day 7 at 5 min post-dose) and No. 001/006 (Day 7 at 10 min post-dose).

The bioavailability of levetiracetam 1500 mg administered as a 15-minute intravenous infusion was compared to levetiracetam 1500 mg administered as 3 x 500 mg oral tablet. The bioequivalence of the two administrations (test = levetiracetam 1500 mg administered as a 15-minute intravenous infusion, reference = levetiracetam 1500 mg administered as 3 x 500 mg tablet) was assessed.

The PK profile of levetiracetam 1500 mg IV infusion during repeated dosing (4 days b.i.d.) was assessed using descriptive statistics on all available PK parameters. After Ln-transformation, AUCt after the last IV dose was compared to AUC after the first dose using a paired t-test with treatment (single/repeated dosing) and subject as factors and a 90% CI for the geometric mean ratio was computed.

Results: For the evaluation of bioequivalence (Part A), pharmacokinetic analysis was conducted on seventeen subjects.

The mean plasma concentration of levetiracetamn is provided in the attachments. The pharmacokinetic parameters and the 90% confidence interval (CI) are provided in the following table

Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration

of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate[b]	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.7 ± 88.6	378.6 ± 73.2	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.9 ± 89.6	392.4 ± 71.2	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.5 ± 18.8	103.7	91.6 -117.4
Tmax (h)[c]	0.75 (0.5– 2.0)	0.25 (0.2-2.0)		
T ½ (h)	7.22 ± 1.16	7.16 ± 1.13		
CL (L/h)	3.65 ± 0.77	3.95 ± 0.75		
V (L)	38.3 ± 11.4	41.1 ± 11.5		

[a]Point Estimate and 90% CI for the expected test/reference geometric mean ratio (%) ;
[c]Median (range).

Cmax for the two formulations were similar after administration of LEV tablet and IV. The 90% CI was contained within the regulatory limit of 80% - 125% for bioequivalence. AUCs were similar after administration and the 90% CI are contained within the regulatory limit of 80% to 125% for bioequivalence.

The pharmacokinetics of the major metabolite (ucb L057) was similar after both the IV and oral tablet administration. The following table provides pharmacokinetic parameters for the metabolite after the IV and oral administration.

Pharmacokinetic Parameters of ucb L057 After Administration of LEV Tablet and IV Formulations

ucb L057 Parameters	Levetiracetam 3 x 500 mg tablet	Levetiracetam 1500 mg IV
	Mean ± SD	
AUC (0-t) (µgEq LEV *h/mL)	18.8 ± 4.43	17.2 ± 4.30
AUC (µgEq LEV*h/mL)	19.1 ± 4.34	18.3 ± 5.33
Cmax (µg Eq LEV/mL)	1.02 ± 0.183	0.946 ± 0.189
T max (h)	6.05 (6.0 – 12.0)	6.00 (3.0 – 9.0)
T ½ (h)	8.50 ± 1.09	8.37 ± 1.09

Tmax values are median (range)

Part B (Multiple Dosing): The pharmacokinetic analysis included all twelve subjects receiving levetiracetam 1500 mg b.i.d. by intravenous infusion administration repeated during 4 days. The other 6 subjects received placebo b.i.d. by intravenous infusion administration repeated during 4 days and all levetiracetam concentration results were reported as none detected. The following table provides a comparison of the pharmacokinetic parameters for LEV IV after single dose and multiple dose administration.

Pharmacokinetics of Levetiracetam Injection After Single and Repeat Dose Administration.

Parameter	Levetiracetam 1500 mg IV single dose (Day 1)	Levetiracetam 1500 mg IV multiple dose (Day 7)
	Mean ± SD	
AUC_T (µg*h/mL)	389.4 ± 77.6	371.9 ± 80.9
Cmax (µg/mL)	52.4 ± 22.3	71.7 ± 21.3
Tmax (h)	0.25 (0.22 – 2.0)	0.25 (0.20 – 0.3)
Cmin (µg/mL)	-	14.1 ± 3.75
Rmax	-	1.51 ± 0.48

Tmax: median (range)

Cmax of LEV IV was higher after repeated administration (71.7 ± 21.3 µg/mL) than after a single administration (52.4 ± 22.23 µg/mL). Minimal concentration (Cmin) averaged 14.1 ± 3.75 µg/mL. Steady state was reached from 24 h onwards. AUC and AUC_T were similar after administration of LEV IV single or multiple doses (389.4 vs 371.9 µg*h/mL) of LEV, respectively. Inter-subject variability of Cmax and AUCt after multiple doses of LEV IV was less than 30%.

Descriptive pharmacokinetic parameters of ucb L057 after repeated administrations of 1500 mg levetiracetam IV infusion (4 days b.i.d) are provided in the following table

Average Pharmacokinetic Parameters of ucb L057 After Multiple Doses of Levetiracetam 1500 mg IV infusion in 12 Healthy Subjects, PP Population

Parameter	ucb L057[a]
Cmax (µgEq. LEV/mL)	1.66 ± 0.45
Tmax (h)	3.0 (2.0 – 3.0)
Cmin (µg Eq. LEV/mL)	0.89 ± 0.34

Values are arithmetic means ± SD, Tmax values are median (range)

Summary and Conclusions

AUCs were similar after single administration of LEV oral and intravenous infusions. The 90% confidence intervals for AUC, AUC(0-t) and Cmax were contained within the regulatory criteria of 80% - 125%.

Cmax of LEV IV was higher after multiple than after a single administration and median Tmax was same to that observed after a single IV administration. The comparison between the AUC and AUC_T indicated that the 90% confidence interval of AUC was contained within the 80% - 125% regulatory criteria.

Adverse Events: The sponsor reported that treatment emergent adverse events were 72.2% for LEV tablet and 88.9% with the LEV IV during Part A of the study. The sponsor reported that no serious adverse events were observed. The most frequent treatment emergent adverse events that were reported were somnolence, dizziness and headache. The frequency was 83.3% vs 66.7% for LEV IV and tablet, respectively. The sponsor reported all adverse events had resolved by the end of the trial. During Part B, the proportion of subjects who experienced at least one TEAE was higher with LEV IV (66.7% compared to 33.3% of subjects with placebo IV).

Conclusions: Levetiracetam 1500 mg IV infusion over 15 minutes was found to be bioequivalent to levetiracetam 1500 mg (3 x 500 mg) oral tablets after single dose administration. Safety

profiles were reported by the sponsor to be similar between the IV and oral LEV administrations and adverse event profile reported for the two administration conditions are consistent with the known adverse event profile of levetiracetam.

Reviewer's Comments:

This study (N01077) was inspected by the Division of Scientific Investigations. Some infractions were reported by DSI. Subject number 001/0007 received 1200 mg instead of 1500 mg dose because one of the ampoules was under-filled. It was not accurately reported in the original submission that this under-dosing was due to an under-filled ampoule. The sponsor subsequent to the DSI report updated the final study report to indicate that this subject was dosed with an under-filled ampoule. This subject was therefore eliminated from the pharmacokinetic analysis. The sponsor reported a < rejection rate at release of the ampoules that were manufactured. DSI initially reported that some of the QC samples included in the analytical run for some samples that did not meet the acceptance criteria. This run included samples from subjects 1 and 2. The sponsor indicated that by the SOP, the runs met the acceptance criteria of [redacted] and hence are acceptable. The sponsor's explanation was adequate and acceptable. Nonetheless, the data was recalculated with subjects 1 and 2 omitted.

The reviewers re-analyzed the data in the following way:

1) With subject 7 omitted
2) With subjects 1, 2, 7 omitted
3) Randomly eliminating 3 subjects to reflect the < rejection rate

The following are the results of the calculations with subject 0007 omitted.

Computations with subject 0007 omitted
Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects (Subject 0007 omitted- *Sponsor's calculations)*

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate[b]	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.7 ± 88.6	378.6 ± 73.2	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.9 ± 89.6	392.4 ± 71.2	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.5 ± 18.8	103.7	91.6 -117.4
Tmax (h)[c]	0.75 (0.5– 2.0)	0.25 (0.2-2.0)		
T ½ (h)	7.22 ± 1.16	7.16 ± 1.13		
CL (L/h)	3.65 ± 0.77	3.95 ± 0.75		
V (L)	38.3 ± 11.4	41.1 ± 11.5		

[a]Point Estimate and 90% CI for the expected test/reference geometric mean ratio (%) ;
[c]Median (range).

Pharmacokinetic Parameters of Levetiracetam (LEV) After a Single Administration of a 3 x 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects *(Reviewer's re-calculation)*.

Parameter	Reference: Levetiracetam 3 x 500 mg tablet	Test: Levetiracetam 1500 mg IV	Point Estimate[b]	90% CI
	Mean ± SD			
AUC(0-t) (µg*h/mL)	414.2 ± 88.6	378.1 ± 73.3	91.7	88.3 – 95.3
AUC (µg*h/mL)	427.4 ± 89.7	392.0 ± 71.1	92.2	89.0 – 95.6
Cmax (µg/mL)	47.7 ± 13.5	50.4 ± 18.8	103.7	91.6 -117.4

The results from the reviewer's calculations are similar to that of the sponsor's.

Computations with subject 0001, 0002, 0007 omitted

The inspection report indicated that quality control (QC) (1.01 µg/mL) injections for subjects 0001 and 0002 samples did not meet the acceptance criteria and recommended the subjects be excluded.

Consistent with the procedures detailed in the SOP, [redacted] the sponsor recalculated the bioequivalence of the IV formulation by excluding data from subjects 0001 and 0002. The following table contains the pharmacokinetic parameters with subjects 1, 2 and 7 excluded

Pharmacokinetic Parameters of Levetiracetam after a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Subjects 1, 2, 7 Omitted- *Sponsor's Analysis*)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate	90% CI
AUC(0-t) (µg*h/mL)	414.6 ± 82.6	376.40 ± 66.40	91.4	87.5 – 95.4
AUC (µg*h/mL)	427.0 ± 83.0	389.73 ± 63.31	92.0	88.4 – 95.7
Cmax (µg/mL)	47.9 ± 13.1	50.90 ± 20.0	103.3	92.6 – 116.1
Tmax (h)	0.75 (0.5 – 2.0)	0.25 (0.2 – 2.0)		
T ½ (h)	7.09 ± 1.18	7.00 ± 1.09		
CL (L/h)	3.64 ± 0.71	3.95 ± 0.69		
V (L)	37.5 ± 10.7	40.2 ± 10.3		

Tmax values are median (range)

The reviewer also recalculated the pharmacokinetic data with subjects 1, 2, and 7 out. The following table is the recalculation.

Pharmacokinetic Parameters of Levetiracetam after a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Subjects 1, 2, 7) *(Reviewers re-calculation)*

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate	90% CI
AUC(0-t) (µg*h/mL)	414.1 ± 82.6	376.4 ± 66.40	91.4	87.5 – 95.4
AUC (µg*h/mL)	426.5 ± 83.0	389.73 ± 63.31	92.0	88.4 – 95.7
Cmax (µg/mL)	47.9 ± 13.1	50.90 ± 20.0	103.3	92.0 – 116.1

Computations with 3 subjects omitted randomly at a time

The following tables provide sample Pharmacokinetic Parameters after randomly eliminating (jackknife) 3 subjects from the data analysis.

Random Sample 9: Mean Pharmacokinentic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in 15 Healthy Subjects (Randomly eliminated Subjects 7, 11, 15)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	410.93 ± 93.58	375.53 ± 77.86	91.8	88.8 – 96.3
AUC (µg*h/mL)	410.93 ± 93.58	389.53 ± 75.45	92.5	87.9 – 96.0
Cmax (µg/mL)	48.7 ± 14.03	52.2 ± 19.26	105.1	91.3 – 120.9

Table 12: Mean Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test) in Healthy Subjects (Randomly eliminated Subjects 3, 7, 17)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	425.7 ± 87.9	390.8 ± 66.6	92.5	88.9 – 96.1
AUC (µg*h/mL)	439.5 ± 88.49	404.3 ± 64.9	92.7	89.2 – 96.4
Cmax (µg/mL)	47.7 ± 47.8	51.5 ± 19.3	105.6	93.7 – 119

Random Sample 20: Pharmacokinetic Parameters of Levetiracetam After a Single Oral Administration of 3 x 500 mg Oral Tablets (Reference) or a 1500 mg IV (Test)

in Healthy Subjects (Randomly eliminated Subjects 0006, 0007, 0018)

Parameter	LEV 1500 mg oral Tablet (Ref)	LEV 1500 mg I.V. (Test)	Test/Reference Ratio	
			Point Estimate (%)	90% CI
AUC(0-t) (µg*h/mL)	413.13 ± 93.83	376.93 ± 77.75	92.3	88.6 – 96.1
AUC (µg*h/mL)	426.20 ± 95.28	390.73 ± 75.70	91.7	87.8 – 95.8
Cmax (µg/mL)	47.12 ± 13.79	50.53 ± 19.93	104.8	92.4 – 118.8

In all of the random sample analysis conducted, the 90% confidence interval around the point estimate for AUC and Cmax for the Test (IV) versus Reference (p.o.) were contained within the regulatory 80% to 125% criteria for bioequivalence. The IV formulation infused over 15 minutes was found to be bioequivalent to the oral formulation.

Reviewer's conclusion: Levetiracetam 1500 mg IV infused over 15 minutes was demonstrated to be bioequivalent to 1500 mg levetiracetam oral tablets. Eliminating the subject 7 who was under-dosed and also eliminating subjects 1 and 2 did not change the overall conclusions.

Figure 11:2 Average Plasma Concentrations of Levetiracetam Over Time After a Single Administration of Levetiracetam 3 x 500 mg Oral Tablet (Reference) or Levetiracetam 1500 mg IV Infusion (Test) in 17 Healthy Subjects, PP Population. Values Are Arithmetic Means ± SD. Inset: 0-4 Hour Interval

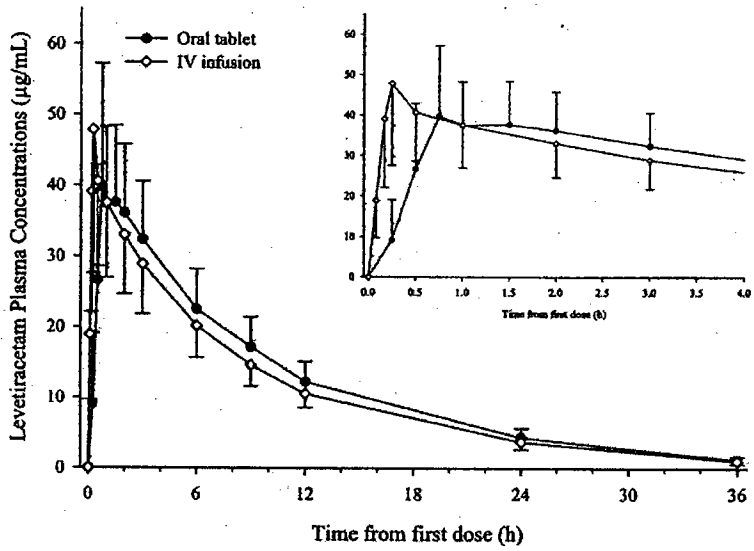
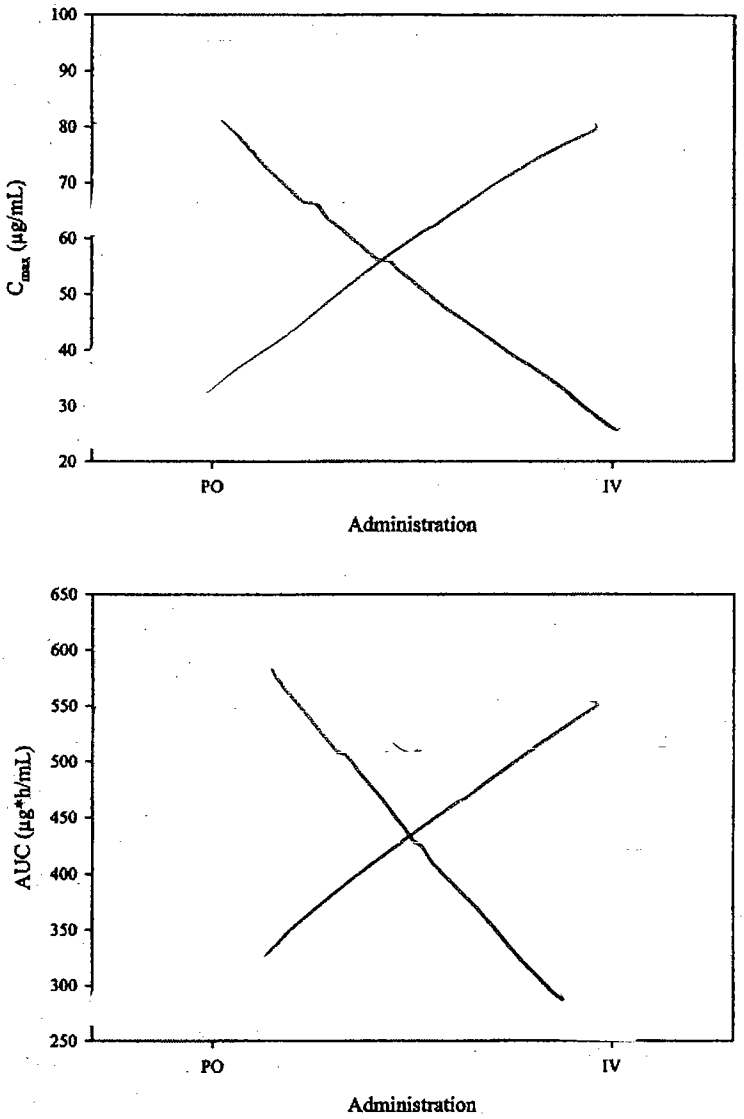
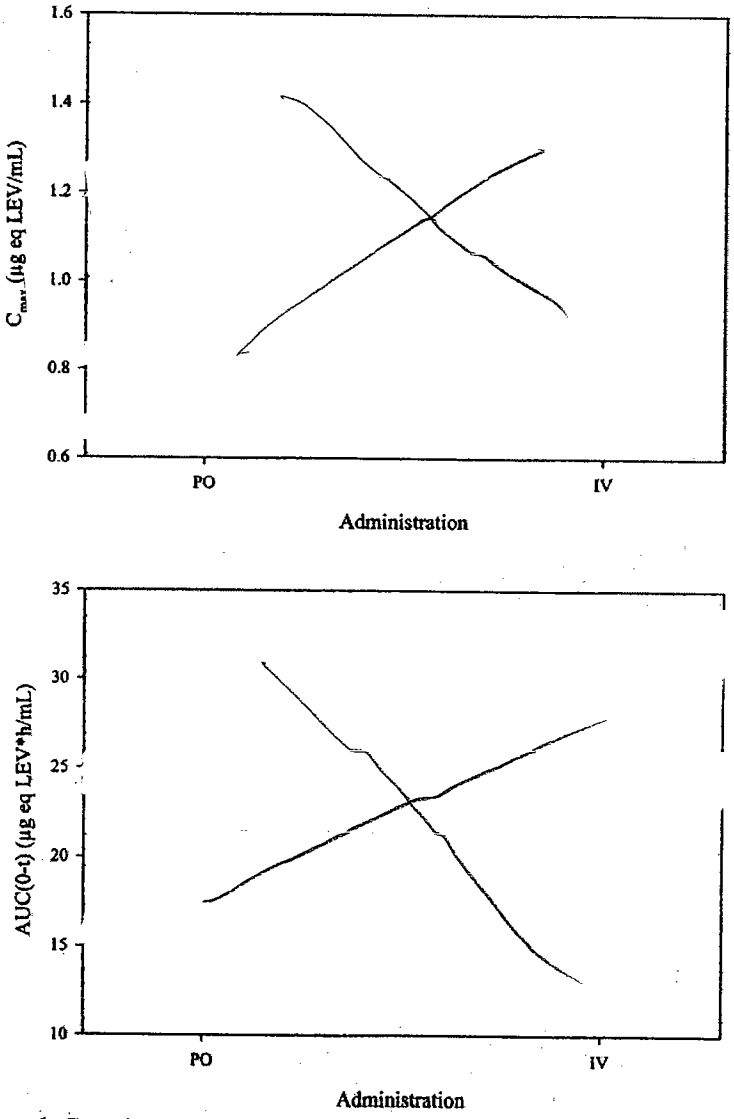


Figure 11:3 Individual Levetiracetam Pharmacokinetic Parameters, C_{max} and AUC by Administration, PP population



Upper panel: C_{max}; lower panel: AUC. PO: *per os*; IV: intravenous; open symbol: female; closed symbol: male.

Figure 11:5 Individual ucb L057 Pharmacokinetic Parameters, C_{max} and AUC(0-t) by Administration, PP Population

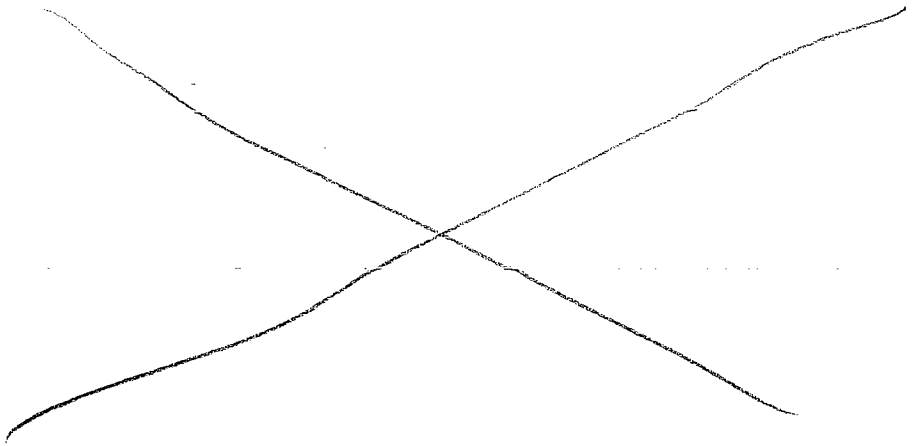


Upper panel: C_{max}; lower panel: AUC(0-t). PO: *per os*; IV: intravenous; open symbol: female; closed symbol: male.

Table 14.2.1:3 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam 1500 mg Oral Tablet by Gender and Overall -Part A- PP Population

Subject (Sequence)
Final

	Cmax [mcg/ml]	tmax [h]	AUC(0-t) [mcg*h/ml]	AUC [mcg*h/ml]	Lz [1/h]	t1/2 [h]	CL/f [l/h]	Vz/f [l]
001/0001 (Tablet/iv)								
001/0002 (iv/Tablet)								
001/0003 (Tablet/iv)								
001/0004 (iv/Tablet)								
001/0005 (Tablet/iv)								
001/0006 (iv/Tablet)								
001/0007 (iv/Tablet)								
001/0008 (Tablet/iv)								
001/0009 (Tablet/iv)								
001/0010 (iv/Tablet)								
001/0011 (Tablet/iv)								
001/0012 (iv/Tablet)								
001/0013 (Tablet/iv)								
001/0014 (iv/Tablet)								
001/0015 (iv/Tablet)								
001/0016 (Tablet/iv)								
001/0017 (iv/Tablet)								
001/0018 (Tablet/iv)								



* : Subject excluded from PP population

Table 14.2.1:3 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam 1500 mg Oral Tablet by Gender and Overall -Part A- PP Population

Overall
Final

22OCT2003 at 11:00

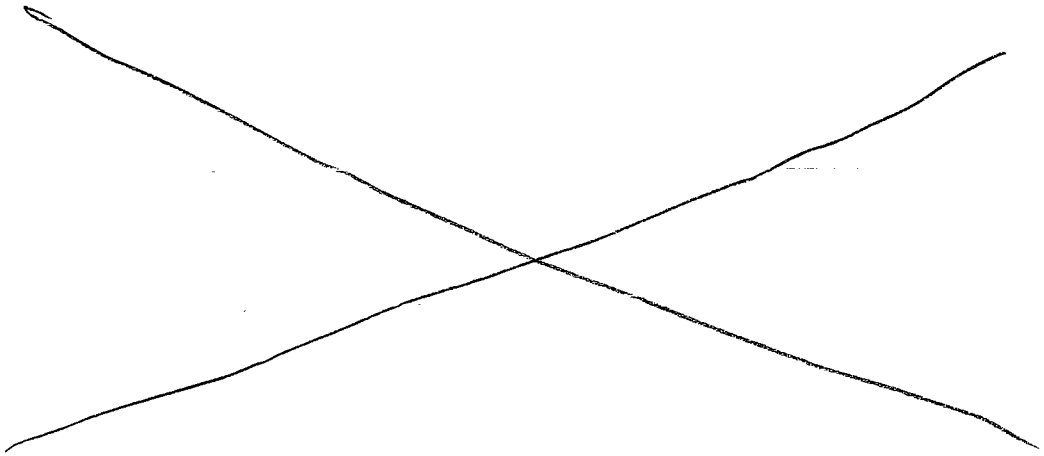
	Cmax [mcg/ml]	tmax [h]	AUC(0-t) [mcg*h/ml]	AUC [mcg*h/ml]	Lz [1/h]	t1/2 [h]	CL/f [l/h]	Vz/f [l]
N (non zero values)	17	17	17	17	17	17	17	17
Geometric mean	45.87	0.88	405.92	419.21	0.10	7.13	3.58	36.78
Exp(mean-SD,ln-data)	34.28	0.56	327.56	339.91	0.08	6.04	2.90	27.41
Exp(mean+SD,ln-data)	61.38	1.38	503.02	517.03	0.11	8.41	4.41	49.36
N	17	17	17	17	17	17	17	17
Arithmetic mean	47.69	0.97	414.74	427.94	0.10	7.22	3.65	38.32
SD	13.47	0.46	88.61	89.64	0.02	1.16	0.77	11.44
CV(%)	28.25	47.18	21.37	20.95	16.93	16.06	21.09	29.86
Minimum	26.2	0.5	277.8	288.8	0.1	5.3	2.4	23.1
Median	44.43	0.75	411.07	420.66	0.09	7.65	3.57	35.41
Maximum	74.6	2.0	607.7	621.7	0.1	8.7	5.2	58.6

* : Subject excluded from PP population

Table 14.2.1:4 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam 1500 mg iv by Gender and Overall -Part A- PP Population

Subject (Sequence)
Final

	Cmax [mcg/ml]	tmax [h]	AUC(0-t) [mcg*h/ml]	AUC [mcg*h/ml]	Lz [1/h]	t1/2 [h]	CL [l/h]	Vz [l]	AUCtau [mcg*h/ml]
001/0001 (Tablet/iv)									
001/0002 (iv/Tablet)									
001/0003 (Tablet/iv)									
001/0004 (iv/Tablet)									
001/0005 (Tablet/iv)									
001/0006 (iv/Tablet)									
001/0007 (iv/Tablet)									
001/0008 (Tablet/iv)									
001/0009 (Tablet/iv)									
001/0010 (iv/Tablet)									
001/0011 (Tablet/iv)									
001/0012 (iv/Tablet)									
001/0013 (Tablet/iv)									
001/0014 (iv/Tablet)									
001/0015 (iv/Tablet)									
001/0016 (Tablet/iv)									
001/0017 (iv/Tablet)									
001/0018 (Tablet/iv)									



* : Subject excluded from PP population

Table 14.2.1:4 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam 1500 mg iv by Gender and Overall -Part A- PP Population

Overall
Final

22OCT2003 at 11:01

	Cmax [mcg/ml]	tmax [h]	AUC(0-t) [mcg*h/ml]	AUC [mcg*h/ml]	Lz [1/h]	t1/2 [h]	CL [l/h]	Vz [l]	AUCtau [mcg*h/ml]
N (non zero values)	17	17	17	17	17	17	17	17	17
Geometric mean	47.50	0.40	371.75	386.27	0.10	7.07	3.88	39.63	260.90
Exp(mean-SD,ln-data)	33.22	0.20	304.85	320.97	0.08	6.04	3.23	29.88	208.78
Exp(mean+SD,ln-data)	67.91	0.81	453.33	464.85	0.11	8.29	4.67	52.55	326.04
N	17	17	17	17	17	17	17	17	17
Arithmetic mean	50.49	0.53	378.55	392.44	0.10	7.16	3.95	41.13	267.01
SD	18.80	0.48	73.18	71.18	0.02	1.13	0.75	11.52	58.73
CV(%)	37.24	90.89	19.33	18.14	15.90	15.74	19.00	28.02	22.00
Minimum	27.1	0.2	243.7	263.1	0.1	5.6	2.9	24.3	181.8
Median	47.95	0.25	378.30	395.83	0.09	7.30	3.79	36.31	275.72
Maximum	92.8	2.0	504.4	519.1	0.1	8.9	5.7	64.7	378.8

* : Subject excluded from PP population

Table 14.2.1:11 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after Repeated Doses (day 3 to day 7) of Levetiracetam 1500 mg iv by Gender and Overall - Part B- PP Population

Subject
Final

22OCT2003 at 11:02

	Cmax [mcg/ml]	tmax [h]	Cmin [mcg/ml]	LI	Rmax	RAUC	AUCtau [mcg*h/ml]
001/0002							
001/0003							
001/0004							
001/0005							
001/0008							
001/0009							
001/0010							
001/0011							
001/0013							
001/0014							
001/0017							
001/0018							

Table 14.2.1:11 Individual Values and Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after Repeated Doses (day 3 to day 7) of Levetiracetam 1500 mg iv by Gender and Overall - Part B- PP Population

Overall
Final

	Cmax [mcg/ml]	tmax [h]	Cmin [mcg/ml]	LI	Rmax	RAUC	AUCtau [mcg*h/ml]
N (non zero values)	12	12	12	12	12	12	12
Geometric mean	68.97	0.25	13.61	0.95	1.43	1.41	364.09
Exp(mean-SD,ln-data)	51.49	0.23	10.45	0.85	1.00	1.21	294.09
Exp(mean+SD,ln-data)	92.39	0.26	17.72	1.07	2.04	1.65	450.75
N	12	12	12	12	12	12	12
Arithmetic mean	71.73	0.25	14.05	0.96	1.51	1.43	371.86
SD	21.29	0.02	3.75	0.11	0.48	0.23	80.89
CV(%)	29.68	6.32	26.69	11.85	31.84	16.33	21.75
Minimum	40.9	0.2	8.8	0.8	0.8	1.1	265.6
Median	67.50	0.25	13.61	0.94	1.67	1.38	350.74
Maximum	116.5	0.3	22.0	1.2	2.1	1.9	509.8

Table 12:1 Number of Subjects (%) in Part A with Treatment-Emergent Adverse Events by Primary System Organ Class, and MedDRA Preferred Term, with Respect to the Relationship to the Study Drug - ITT Population

System organ class Preferred term	Levetiracetam 3 x 500 mg tablet (N = 18)		Levetiracetam 1500 mg IV (N = 18)		Overall (N = 18)[c]
	Related[a]	Not Related[b]	Related[a]	Not Related[b]	
Gastrointestinal disorders	0	0	0	2 (11.1%)	2 (11.1%)
Flatulence	0	0	0	1 (5.6%)	1 (5.6%)
Loose stools	0	0	0	2 (11.1%)	2 (11.1%)
General disorders and administration site conditions	0	0	2 (11.1%)	2 (11.1%)	4 (22.2%)
Fatigue	0	0	1 (5.6%)	0	1 (5.6%)
Feeling cold	0	0	0	1 (5.6%)	1 (5.6%)
Influenza like illness	0	0	0	1 (5.6%)	1 (5.6%)
Injection site pruritus	0	0	2 (11.1%)	0	2 (11.1%)
Infections and infestations	0	1 (5.6%)	0	0	1 (5.6%)
Nasopharyngitis	0	1 (5.6%)	0	0	1 (5.6%)
Musculoskeletal and connective tissue disorders	0	0	0	1 (5.6%)	1 (5.6%)
Chest wall pain	0	0	0	1 (5.6%)	1 (5.6%)
Nervous system disorders	12 (66.7%)	0	14 (77.8%)	2 (11.1%)	16 (88.9%)
Dizziness	3 (16.7%)	0	1 (5.6%)	0	4 (22.2%)
Dizziness postural	7 (38.9%)	0	3 (16.7%)	0	8 (44.4%)
Headache	1 (5.6%)	0	1 (5.6%)	2 (11.1%)	4 (22.2%)
Somnolence	5 (27.8%)	0	11 (61.1%)	0	11 (61.1%)

[a] Related included possible, probable and highly probable relationship to the study medication according to the Investigator.
[b] Not related included none and unlikely relationship to the study medication according to the Investigator.
If a preferred term was both Related and Not Related for a subject, it was counted as Related.
AEs with a missing relationship to study drug were considered as drug related.
[c] Subjects who experienced at least one adverse event following tablet or IV administration.
Source: Table 14.3.1:2 and Table 14.3.1:4.

Table 12:2 Number of Subjects (%) in Part B with Treatment-Emergent Adverse Events by Primary System Organ Class, and MedDRA Preferred Term, with Respect to the Relationship to the Study Drug - ITT Population

System organ class Preferred term	Placebo IV b.i.d. (N = 6)		Levetiracetam 1500 mg IV b.i.d. (N = 12)		Overall (N = 18)[c]
	Related[a]	Not Related[b]	Related[a]	Not Related[b]	
Gastrointestinal disorders	0	0	2 (16.7%)	1 (8.3%)	3 (16.7%)
Dry mouth	0	0	1 (8.3%)	0	1 (5.6%)
Flatulence	0	0	0	1 (8.3%)	1 (5.6%)
Loose stools	0	0	0	1 (8.3%)	1 (5.6%)
Nausea	0	0	1 (8.3%)	0	1 (5.6%)
General disorders and administration site conditions	0	1 (16.7%)	1 (8.3%)	0	2 (11.1%)
Chest pain	0	1 (16.7%)	0	0	1 (5.6%)
Thirst	0	0	1 (8.3%)	0	1 (5.6%)
Investigations	0	0	2 (16.7%)	0	2 (11.1%)
Blood pressure decreased	0	0	2 (16.7%)	0	2 (11.1%)
Nervous system disorders	1 (16.7%)	0	6 (50.0%)	1 (8.3%)	7 (38.9%)
Disturbance in attention	0	0	1 (8.3%)	0	1 (5.6%)
Dizziness	1 (16.7%)	0	1 (8.3%)	0	2 (11.1%)
Dizziness postural	0	0	3 (25.0%)	0	3 (16.7%)
Headache	0	0	2 (16.7%)	1 (8.3%)	3 (16.7%)
Somnolence	1 (16.7%)	0	4 (33.3%)	0	5 (27.8%)
Psychiatric disorders	1 (16.7%)	0	1 (8.3%)	0	2 (11.1%)
Euphoric mood	1 (16.7%)	0	1 (8.3%)	0	2 (11.1%)

[a] Related included possible, probable and highly probable relationship to the study medication according to the Investigator.
[b] Not related included none and unlikely relationship to the study medication according to the Investigator.
If a preferred term was both Related and Not Related for a subject, it was counted as Related.
AEs with a missing relationship to study drug were considered as drug related.
[c] Subjects who experienced at least one adverse event following placebo or levetiracetam administration
Source: Table 14.3.1:6 and Table 14.3.1:8.

Study 1165

Study Title (Study No. N01165): Randomized, Monocenter, Single-Blind, Placebo-Controlled, Safety Study of Single Ascending Doses of Levetiracetam (500 mg/5 mL Vials) Administered in 15-Minute Intravenous Infusion (up to 4000 mg) and in 5-Minute Intravenous Infusion (up to 2500 mg) in Male and Female Healthy Volunteers

Objective: 1) The primary objective was to document the safety and tolerability of a single dose IV infusion of levetiracetam up to 4000 mg in 15 minutes and up to 2500 mg in 5 minutes. 2) The secondary objective was to assess pharmacokinetics of levetiracetam at all dosing regimens.

Study Design: The trial was a randomized, single- blind, single ascending dose, placebo-controlled trial conducted at one center. A total of 48 healthy subjects were included in the trial in 6 dose groups of 8 subjects. In each dose group, 6 subjects received the active drug and 2 subjects received placebo. In each dose group, 8 subjects were randomized to receive either a single IV infusion of LEV or placebo. Depending on the dose group, the dose of LEV ranged from 2000 to 4000 mg under 15-minute IV infusion and from 1500 mg to 2500 mg under 5-minute IV infusion. The screening visit took place within 3 weeks before administration of the investigational product. Treatment period in the clinical center lasted 3 days from Day -1 to Day 2. The sponsor reported that safety reviews were conducted under blinded conditions during the study. The decision to adjust the dose or to stop the study was based on the tolerability. Blood samples for determination of LEV concentrations were collected at pre-dose, 2, 5, 10, 15, 30 mins and 1, 2, 3, 6, 9, 12 and 24 hours post-dose.

Assay Method: Levetiracetam was determined in plasma samples using a validated gas chromatographic method [redacted] The limit of quantitation (LOQ) of the assay for LEV in plasma was [redacted]. The calibration curve ranged from [redacted] The mean relative deviations of LEV in QC samples were -3.8, -4.5, and -2.2% of nominal concentrations of 1, 8, and 30 µg/mL, respectively.

Data Analysis: The pharmacokinetic parameters were determined using non-compartmental methods. Safety and tolerability assessments were made using adverse event reporting, physical examinations, vital signs, 12-lead ECG and laboratory test results. Descriptive analysis on all pharmacokinetic parameters and for safety and tolerability parameters were conducted.

Results: The mean plasma concentration time profile is provided in the attachment. The descriptive statistics of the pharmacokinetic parameters are provided in the following table.

Pharmacokinetic Parameters of Levetiracetam After a Single Administration of 2000 mg, 3000 mg and 4000 mg IV infusion During 15 min

Parameter	LEV 2000 mg IV	LEV 3000 mg IV	LEV 4000 mg IV
	Mean ± SD (n=6)	Mean ± SD (N=6)	Mean ± SD (N=5)
Cmax (µg/mL)	57.21 ± 16.00	87.51 ± 36.39	148.87 ± 37.29
AUC (0-t) (µg*h/mL)	475.22 ± 84.22	667.74 ± 60.04	1097.14 ± 224.90
AUC (µg*h/mL)	534.77 ± 92.64	755.48 ± 46.68	1258.40 ± 263.82
T ½ (h)	7.75 ± 0.85	7.76 ± 0.94	8.07 ± 1.08
[a]Tmax (h)	0.50 (0.27 – 0.50)	0.375 (0.25 – 2.0)	0.25 (0.25 – 1.0)
CL (L/h)	3.823 ± 0.57	3.98 ± 0.27	3.27 ± 0.56
Vz (L)	42.61 ± 6.96	44.79 ± 7.60	38.03 ± 8.15

[a]Tmax: median (range)

Pharmacokinetic Parameters of Levetiracetam After a Single Administration of 1500 mg, 2000 mg and 2500 mg IV infusion During 5 mins

Parameter	LEV 1500 mg IV	LEV 2000 mg IV	LEV 2500 mg IV
	Mean ± SD (n=6)	Mean ± SD (N=6)	Mean ± SD (N=6)
Cmax (µg/mL)	47.53 ± 8.32	64.52 ± 25.94	99.96 ± 42.37
AUC (0-t) (µg*h/mL)	312.39 ± 17.54	432.84 ± 61.63	532.77 ± 53.45
AUC (µg*h/mL)	348.35 ± 25.49	488.43 ± 72.34	586.80 ± 56.88
T ½ (h)	7.43 ± 0.90	7.77 ± 0.97	7.03 ± 0.84
[a]Tmax (h)	0.09 (.08 – 0.25)	0.125 (0.08 – 0.50)	0.08 (0.08 – 0.17)
CL (L/h)	4.33 ± 0.34	4.17 ± 0.56	4.29 ± 0.40
Vz (L)	46.08 ± 3.80	46.48 ± 7.42	43.55 ± 7.06

[a]Tmax: median (range)

Following 5 and 15 minute infusions, the concentrations increased rapidly. Mean Cmax of 2000 mg/5 min was about 10% higher than mean Cmax of 2000 mg/15 min. However, the AUCs were similar.

Pharmacokinetic conclusions: Primary pharmacokinetic parameters (CL, V, t ½) for LEV were comparable across all dose groups. The overall mean AUC seemed within each dosing regimen appears to increase proportionally with dose.

Safety Summary: The sponsor reported that during the trial, 34 subjects experienced at least one Treatment Emergent Adverse Event (TEAE). The incidence of TEAE was reported to be 25% for placebo and 86.1% for LEV IV groups. The sponsor reported that the most frequently reported TEAEs as well as drug related TEAEs were dizziness and somnolence and headache. The sponsor reported that LEV IV infusion up to 4000 mg in 15 minutes and up to 2500 mg in 5 minutes was safe and well tolerated. The sponsor reported that there was no clear relationship between the incidence of adverse events and LEV IV dose levels or duration of infusions.

Safety Conclusions: The sponsor concluded that the intravenous infusion of levetiracetam up to 4000 mg in 15 minutes and up to 2500 mg in 5 minutes was safe and well tolerated. Safety profiles were reported by the sponsor to be similar after single ascending administration of LEV IV and at a faster infusion rate.

Reviewer comments: *The primary objective of this study was to evaluate the safety and tolerability of different dosing regimens of levetiracetam IV. Refer to the medical review the*

agency's conclusion on the safety and tolerability of the dosing regimens tested in this study. The reviewer agrees with the sponsor's pharmacokinetic conclusions.

Figure 11:1 Mean Plasma Concentrations (Geometric Mean ± SD) of Levetiracetam Versus Time After a Single Administration of Levetiracetam 2000 mg, 3000 mg and 4000 mg IV Infusion During 15 Minutes in 5 or 6 Different Healthy Subjects - PP Population. Inset: 0-1 Hour Interval

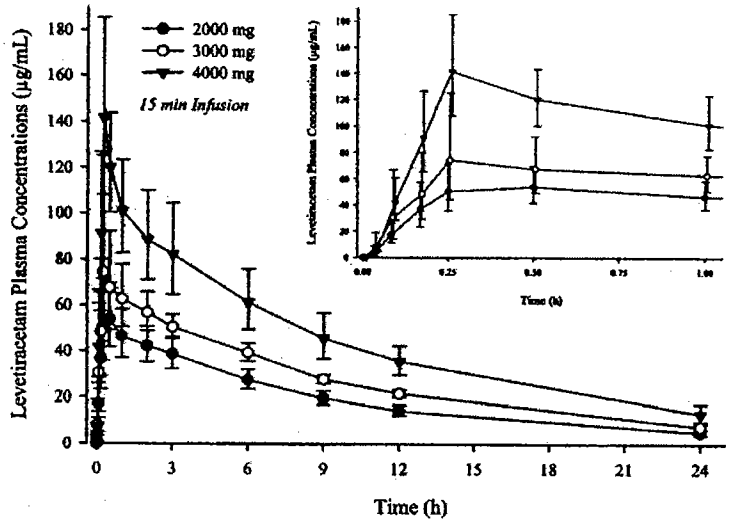


Figure 11:2 Mean Plasma Concentrations (Geometric Mean ± SD) of Levetiracetam Versus Time After a Single Administration of Levetiracetam 1500 mg, 2000 mg and 2500 mg IV Infusion During 5 Minutes in 6 Different Healthy Subjects - PP Population. Inset: 0-1 Hour Interval

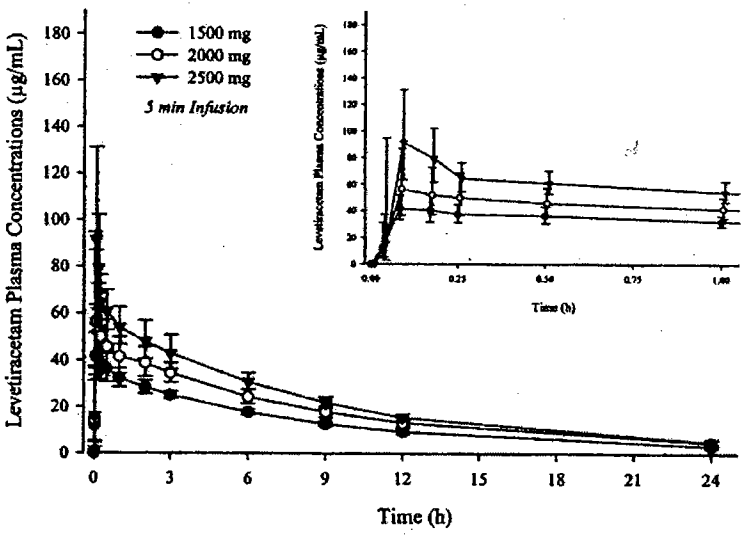


Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2000 mg iv 15 min
Gender: Overall

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Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0001					
001/0003					
001/0004					
001/0025					
001/0026					
001/0027					
N	6	6	6	6	6
Geometric mean	528.706	469.694	50.549	3.783	55.609
Exp(Mean ± SD) (a)	(449.825,621.420)	(399.186,552.656)	(35.675,71.625)	(3.218,4.446)	(43.184,71.610)
Arithmetic mean	534.765	475.218	53.157	3.822	57.213
SD	92.637	84.415	18.664	0.573	16.008
CV(%) (b)	17.323	17.763	35.111	14.985	27.979
Minimum	457.75	409.90	29.69	2.85	41.65
Median	494.962	437.918	49.584	4.041	52.463
Maximum	702.45	636.03	85.32	4.37	87.38

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2000 mg iv 15 min
Gender: Overall

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Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0001				
001/0003				
001/0004				
001/0025				
001/0026				
001/0027				
N	6	6	6	6
Geometric mean	0.090	7.708	0.405	42.067
Exp(Mean ± SD) (a)	(0.081,0.100)	(6.903,8.607)	(0.293,0.561)	(35.037,50.508)
Arithmetic mean	0.090	7.747	0.422	42.614
SD	0.010	0.853	0.120	6.961
CV(%) (b)	11.025	11.016	28.533	16.336
Minimum	0.08	6.60	0.27	29.71
Median	0.091	7.639	0.500	45.397
Maximum	0.10	8.95	0.50	48.46

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 3000 mg iv 15 min
Gender: Overall

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Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0005					
001/0006					
001/0007					
001/0030					
001/0031					
001/0032					
N	6	6	6	6	6
Geometric mean	754.215	665.433	74.335	3.978	81.180
Exp(Mean ± SD) (a)	(707.364,804.168)	(607.036,729.447)	(44.113,125.261)	(3.731,4.241)	(52.892,124.598)
Arithmetic mean	755.476	667.740	82.989	3.985	87.514
SD	46.677	60.004	41.055	0.265	36.393
CV(%) (b)	6.178	8.986	49.470	6.654	41.586
Minimum	667.71	569.98	42.62	3.75	48.05
Median	767.210	668.349	78.995	3.911	82.785
Maximum	800.68	749.37	138.13	4.49	138.13

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 3000 mg iv 15 min
Gender: Overall

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Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0005				
001/0006				
001/0007				
001/0030				
001/0031				
001/0032				
N	6	6	6	6
Geometric mean	0.090	7.708	0.500	44.233
Exp(Mean ± SD) (a)	(0.079,0.102)	(6.764,8.784)	(0.208,1.202)	(37.091,52.750)
Arithmetic mean	0.091	7.761	0.708	44.793
SD	0.012	0.964	0.697	7.603
CV(%) (b)	13.698	12.419	98.360	16.973
Minimum	0.08	6.19	0.25	33.47
Median	0.086	8.086	0.375	45.751
Maximum	0.11	8.68	2.00	55.14

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 4000 mg iv 15 min
Gender: Overall

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Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0010					
001/0011					
001/0012					
001/0034					
001/0035					
001/0036					
N	5	5	5	5	5
Geometric mean	1239.104	1080.728	141.643	3.228	145.327
Exp(Mean ± SD) (a)	(1024.44,1498.74)	(894.762,1305.35)	(108.214,185.400)	(2.669,3.905)	(114.045,185.191)
Arithmetic mean	1258.402	1097.138	145.892	3.272	148.869
SD	263.816	224.900	40.288	0.560	37.288
CV(%) (b)	20.964	20.499	27.615	17.113	25.047
Minimum	1068.25	934.40	108.67	2.33	121.05
Median	1203.720	1010.154	121.092	3.323	123.558
Maximum	1717.43	1477.71	196.46	3.74	196.46

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:3 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 15 min by Gender and Overall - PP Population

Treatment: Levetiracetam 4000 mg iv 15 min
Gender: Overall

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Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0010				
001/0011				
001/0012				
001/0034				
001/0035				
001/0036				
N	5	5	5	5
Geometric mean	0.087	8.005	0.330	37.281
Exp(Mean ± SD) (a)	(0.075,0.100)	(6.927,9.251)	(0.177,0.613)	(29.725,46.758)
Arithmetic mean	0.087	8.069	0.400	38.027
SD	0.014	1.084	0.335	8.146
CV(%) (b)	15.507	13.438	83.853	21.420
Minimum	0.08	6.26	0.25	28.25
Median	0.082	8.408	0.250	43.467
Maximum	0.11	9.15	1.00	44.56

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 1500 mg iv 5 min
Gender: Overall

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Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0014					
001/0015					
001/0016					
001/0038					
001/0039					
001/0040					
N	6	6	6	6	6
Geometric mean	347.535	311.969	41.657	4.316	46.908
Exp(Mean ± SD) (a)	(322.116,374.960)	(294.525,330.447)	(33.548,51.728)	(4.000,4.657)	(39.247,56.065)
Arithmetic mean	348.351	312.393	42.462	4.327	47.525
SD	25.486	17.539	8.914	0.341	8.315
CV(%) (b)	7.316	5.614	20.994	7.890	17.496
Minimum	301.52	281.40	31.43	3.96	36.12
Median	353.104	314.330	42.914	4.248	47.749
Maximum	379.15	329.20	52.49	4.97	58.88

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 1500 mg iv 5 min
Gender: Overall

23JUL2004 at 11:58

Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0014				
001/0015				
001/0016				
001/0038				
001/0039				
001/0040				
N	6	6	6	6
Geometric mean	0.094	7.378	0.116	45.943
Exp(Mean ± SD) (a)	(0.083,0.106)	(6.519,8.350)	(0.073,0.184)	(42.244,49.965)
Arithmetic mean	0.095	7.425	0.128	46.076
SD	0.012	0.900	0.068	3.797
CV(%) (b)	12.577	12.124	53.268	8.240
Minimum	0.08	6.21	0.08	40.00
Median	0.092	7.545	0.092	46.197
Maximum	0.11	8.41	0.25	51.12

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2000 mg iv 5 min
Gender: Overall

23JUL2004 at 11:58

Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0018					
001/0019					
001/0020					
001/0041					
001/0042					
001/0043					
N	6	6	6	6	6
Geometric mean	484.229	429.392	56.337	4.130	60.563
Exp(Mean *f* SD) (a)	(420.161,558.066)	(374.577,492.228)	(36.539,86.860)	(3.584,4.760)	(41.213,88.998)
Arithmetic mean	488.427	432.838	61.096	4.164	64.517
SD	72.341	61.633	28.034	0.564	25.935
CV(%) (b)	14.811	14.239	45.885	13.554	40.199
Minimum	424.26	380.85	37.69	3.26	37.69
Median	470.110	404.131	54.803	4.257	61.020
Maximum	612.68	532.26	109.16	4.71	109.16

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2000 mg iv 5 min
Gender: Overall

 23JUL2004 at 11:58

Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0018				
001/0019				
001/0020				
001/0041				
001/0042				
001/0043				
N	6	6	6	6
Geometric mean	0.090	7.715	0.170	45.972
Exp(Mean ± SD) (a)	(0.079,0.102)	(6.803,8.749)	(0.071,0.409)	(39.033,54.144)
Arithmetic mean	0.090	7.766	0.236	46.479
SD	0.011	0.968	0.207	7.424
CV(%) (b)	12.613	12.468	87.655	15.972
Minimum	0.08	6.68	0.08	36.78
Median	0.089	7.838	0.125	47.701
Maximum	0.10	8.90	0.50	55.95

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2500 mg iv 5 min
Gender: Overall

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Subject	AUC [ug*h/mL]	AUC(0-t) [ug*h/mL]	C(t) [ug/mL]	CL [L/h]	Cmax [ug/mL]
001/0021					
001/0023					
001/0024					
001/0045					
001/0046					
001/0047					
N	6	6	6	6	6
Geometric mean	584.547	530.536	91.278	4.277	94.310
Exp(Mean ∓ SD) (a)	(531.213,643.236)	(479.780,586.661)	(63.540,131.125)	(3.887,4.706)	(66.392,133.967)
Arithmetic mean	586.800	532.771	97.213	4.293	99.956
SD	56.878	53.448	43.468	0.404	42.368
CV(%) (b)	9.693	10.032	44.715	9.420	42.387
Minimum	518.89	460.12	64.96	3.77	65.11
Median	565.133	529.010	83.650	4.424	87.694
Maximum	662.43	607.69	184.13	4.82	184.13

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 14.2.1:4 Descriptive Statistics on Levetiracetam Pharmacokinetic Parameters after a Single Dose of Levetiracetam iv 5 min by Gender and Overall - PP Population

Treatment: Levetiracetam 2500 mg iv 5 min
Gender: Overall

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Subject	Lambda_z [1/h]	t1/2 [h]	tmax [h]	Vz [L]
001/0021				
001/0023				
001/0024				
001/0045				
001/0046				
001/0047				
N	6	6	6	6
Geometric mean	0.099	6.982	0.105	43.079
Exp(Mean ± SD) (a)	(0.088,0.113)	(6.155,7.920)	(0.073,0.150)	(36.674,50.603)
Arithmetic mean	0.100	7.027	0.111	43.549
SD	0.013	0.843	0.043	7.056
CV(%) (b)	13.226	11.998	38.765	16.202
Minimum	0.09	5.61	0.08	35.55
Median	0.096	7.216	0.083	42.603
Maximum	0.12	7.79	0.17	53.26

NC = Not Calculated, SUS = Suspicious data, NE = Not Estimable
(a) Mean and SD are calculated on logarithmically transformed data
(b) CV (%) = 100 x SD/Arithmetic Mean

Table 12:2 Number (%) of Subjects with Treatment-Emergent Adverse Events Overall and for Each Dose of Levetiracetam IV and Placebo - ITT Population

Primary System Organ Class Preferred term	Placebo	LEV IV-15 min (mg)			LEV IV-5 min (mg)			Overall
		2000	3000	4000	1500	2000	2500	
	N = 12	N = 6	N = 6	N = 6	N = 6	N = 6	N = 6	N = 48
Infections and infestations	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Herpes simplex	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Psychiatric disorders	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Irritability	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Nervous system disorders	2 (16.7)	4 (66.7)	4 (66.7)	6 (100)	5 (83.3)	3 (50.0)	6 (100)	30 (62.5)
Balance disorder	0	0	0	0	1 (16.7)	0	0	1 (2.1)
Dizziness	0	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	19 (39.6)
Dizziness postural	0	0	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	0	7 (14.6)
Dysgeusia	1 (8.3)	0	0	0	0	0	0	1 (2.1)
Headache	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (16.7)	6 (12.5)
Somnolence	0	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	12 (25.0)
Eye disorders	0	0	0	0	0	0	1 (16.7)	1 (2.1)
Vision blurred	0	0	0	0	0	0	1 (16.7)	1 (2.1)
Cardiac disorders	0	0	1 (16.7)	0	1 (16.7)	0	0	2 (4.2)
Atrioventricular block first degree	0	0	1 (16.7)	0	0	0	0	1 (2.1)
Sinus bradycardia	0	0	0	0	1 (16.7)	0	0	1 (2.1)
Gastrointestinal disorders	1 (8.3)	0	0	1 (16.7)	0	1 (16.7)	0	3 (6.3)
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (2.1)
Nausea	1 (8.3)	0	0	1 (16.7)	0	0	0	2 (4.2)
Vomiting	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Musculoskeletal and connective tissue disorders	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (4.2)
Back pain	0	0	0	0	0	1 (16.7)	0	1 (2.1)
Sensation of heaviness	0	1 (16.7)	0	0	0	0	0	1 (2.1)
General disorders and administration site conditions	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	5 (10.4)
Fatigue	0	1 (16.7)	2 (33.3)	0	0	0	1 (16.7)	4 (8.3)
Feeling drunk	0	0	1 (16.7)	0	0	0	0	1 (2.1)
Thirst	0	0	0	0	0	1 (16.7)	0	1 (2.1)

Source: Table 14.3.1.2.

Table 12:3 Number (%) of Subjects with Study-Drug Related Treatment-Emergent Adverse Events Overall and for Each Dose of Levetiracetam IV and Placebo - ITT Population

Primary System Organ Class Preferred term	Placebo N = 12	LEV IV-15 min (mg) 2000 N = 6	 3000 N = 6	 4000 N = 6	LEV IV-5 min (mg) 1500 N = 6	 2000 N = 6	 2500 N = 6	Overall N = 48
Nervous system disorders	1 (8.3)	3 (50.0)	4 (66.7)	6 (100)	5 (83.3)	3 (50.0)	6 (100)	28 (58.3)
Balance disorder	0	0	0	0	1 (16.7)	0	0	1 (2.1)
Dizziness	0	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	19 (39.6)
Dizziness postural	0	0	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	0	7 (14.6)
Dysgeusia	1 (8.3)	0	0	0	0	0	0	1 (2.1)
Headache	0	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	3 (6.3)
Somnolence	0	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	12 (25.0)
Eye disorders	0	0	0	0	0	0	1 (16.7)	1 (2.1)
Vision blurred	0	0	0	0	0	0	1 (16.7)	1 (2.1)
Gastrointestinal disorders	0	0	0	1 (16.7)	0	1 (16.7)	0	2 (4.2)
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (2.1)
Nausea	0	0	0	1 (16.7)	0	0	0	1 (2.1)
Vomiting	0	0	0	1 (16.7)	0	0	0	1 (2.1)
General disorders and administration site conditions	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	5 (10.4)
Fatigue	0	1 (16.7)	2 (33.3)	0	0	0	1 (16.7)	4 (8.3)
Feeling drunk	0	0	1 (16.7)	0	0	0	0	1 (2.1)
Thirst	0	0	0	0	0	1 (16.7)	0	1 (2.1)

Related included possible, probable and highly probable relationship to the study medication according to the Investigator.
If a preferred term was both Related and Not Related for a subject, it was counted as Related.
AEs with a missing relationship to study drug were considered as drug related.

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