CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-872

MEDICAL REVIEW

MEMORANDUM

DATE: July 31, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-872

SUBJECT: Action Memo for NDA 21-872, for the use of Keppra (levetiracetam) Intravenous (IV)

NDA 21-872, for the use of Keppra (levetiracetam) Intravenous (IV), was submitted by UCB, Inc., on 12/20/04. This product is intended to be used in patients being treated with Keppra tablets or oral solution who cannot take oral products for brief periods of time. The primary source of evidence supporting approval of the application was a bioavailability study that compared the kinetics of Keppra when given as a 15 minute infusion with those of the tablet; similar Cmax and AUC were seen between the two products under these conditions of use.

The division issued an Approvable (AE) letter on 1/20/06. The sponsor had proposed a change in the facility of drug manufacture, so numerous questions were asked in the AE letter pertaining to this proposed change. In addition,

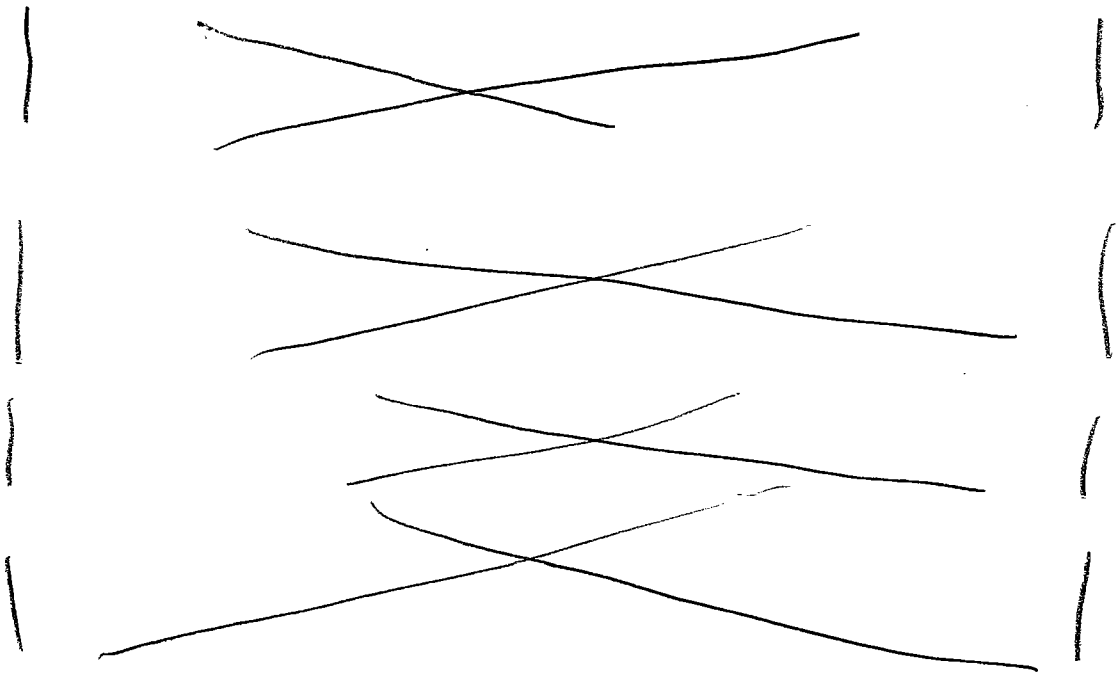
(the oral products are approved in pediatric patients down to the age of 4 years). Further, numerous requests for changes in the carton and container labeling were included in the letter.

Finally, DSI had noted what they believed to be numerous, serious deficiencies in the conduct and reporting of the critical bioavailability study (see Dr. Vishwanathan's 9/20/05 memo and Dr. O'Shaughnessy's 11/18/05 memo). My memo of 1/20/06 noted that these issues would need to be resolved before the application could be approved.

The sponsor responded to the AE letter in a submission dated 1/31/06. This response has been reviewed by Dr. Vinayak Pawar, microbiologist, Dr. David Claffey, chemist, and Tina Tezky, Division of Medication Errors and Technical Support (DMETS). These reviewers have concluded that the CMC and carton and container labeling issues raised in the AE letter have been resolved.

They have committed to performing a pediatric study in Phase 4.

With regard to the issues of study conduct and reporting identified by DSI, a regulatory briefing was held on 7/14/06 to obtain wider input on the question of whether or not these deficiencies were sufficiently severe as to warrant further Agency action (for example, were the deficiencies sufficient to cast doubt on the reliability of the data, or to take further action against the company). There was general agreement that, although the sponsor did not present certain data in as transparent a manner as would have been desirable (most critically, many at the briefing felt that the sponsor's characterization of the use of an underfilled vial of product as a "dosing error" was inappropriate, especially given that an earlier, internal company version of a report of this study accurately characterized the vial as being underfilled), the submission taken as a whole did not raise serious questions about the reliability of the data. There was further general agreement that no adverse regulatory action against the sponsor was warranted.



We have agreed with the sponsor on product labeling and carton and container labeling, and also on the specifics of their Phase 4 commitment to study pediatric patients.

For the reasons given above, then, I will issue the attached Approval letter with appended product labeling.

Russell Katz, M.D.

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/s/

Russell Katz
7/31/2006 02:49:35 PM
MEDICAL OFFICER

MEMORANDUM

DATE: January 19, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-872

SUBJECT: Action Memo for NDA 21-872 for Keppra (levetiracetam) Injection

NDA 21-872 for Keppra (levetiracetam) Injection was submitted by UCB Pharma, Inc., on 12/20/04. Keppra tablets and solution are currently approved as adjunctive treatment for partial seizures in adults and pediatric patients 4 years old and older. The injection is intended to be used in patients who cannot take oral drug for short periods of time (e.g., several days). The primary data supporting the effectiveness of Keppra Injection derives from a study comparing the kinetics of a single 1500 mg dose of the injection given over 15 minutes to a single 1500 mg dose given as the tablet. In addition, patients from this study were then randomized to receive either 4 days of (BID) dosing with the injection or placebo. The sponsor also provided safety data from more rapid infusions and higher doses (maximum dose of 4000 mg given over 15 minutes; maximum dose of 2500 mg given over 5 minutes).

The application has been reviewed by Dr. Norman Hershkowitz, medical officer, Drs. Kofi Kumi and Leslie Kenna, Office of Clinical Pharmacology and Biopharmaceutics, Dr. Edward Fisher, pharmacologist, Dr. David Claffey, chemist, Dr. Vinayak Pawar, Microbiology, Dr. Tina Tezky, Division of Medication Errors and Technical Support, Dr. C.T. Vishwanathan, Division of Scientific Investigations, and Dr. John Feeney, Neurology Team Leader.

As noted above, the sponsor has submitted Study N01077, a single dose cross-over study in adults comparing the kinetics of the injection to the tablet. AUC and Cmax met bioequivalence standards, Cmins were essentially the same, and the Tmax of the injection was about 15 minutes compared to about 45 minutes for the tablet. As Dr. Hershkowitz notes, there are no significant differences between the safety profile of the tablet and that of the injection. Because the study was performed in adults, and the tablet is approved for pediatric patients down to the age of 4 years.

The sponsor has also performed various non-clinical studies of rapid IV infusions that document a transient increase in pulmonary artery pressure in the dog. According to Dr. Fisher, there is a no-effect plasma level for this increase that is about 10 fold the exposure seen in humans. The sponsor has performed an investigation of this phenomenon in adults, and found no such increase.

As Dr. Pawar notes, the sponsor proposed, during the review cycle, to institute significant changes to the manufacturing site. As a result, they must submit substantial additional stability data and validation of the new processes to be used before the application can be approved.

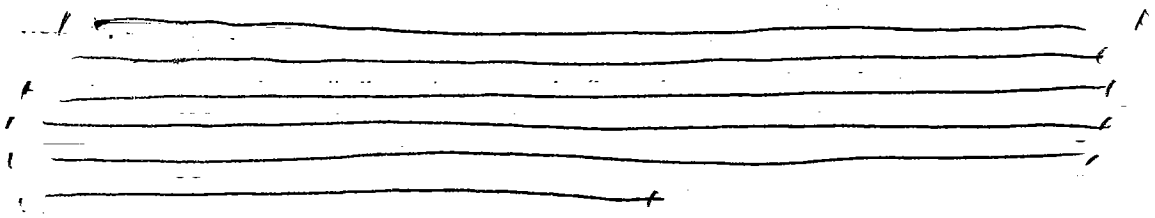
DSI has uncovered what they believe to be very significant, troubling problems in the conduct and reporting of the results of the critical kinetic study. [redacted] that the ampoule used for one patient was underfilled; [redacted] the rate of manufacturing failures was misstated). In an attempt to consider whether or not some of these problems would have affected the results of Study N01077, OCPB performed additional analyses in which the data from the patient who was documented to have been underdosed was removed, as well as simulations in which the data from random samples of X of the patients (corresponding to the manufacturing failure rate) were removed; bioequivalence standards were met in all of these analyses.

The division and DSI met with the sponsor on 9/29/05 to discuss the inspection findings. According to the sponsor, the errors were primarily due to misunderstandings and were not intentional. [redacted]

COMMENTS

The sponsor has demonstrated that a 15 minute intravenous infusion of Keppra Injection is "bioequivalent" to the same dose given orally, with a slightly decreased Tmax. There are no safety issues associated with the injection that are not already known to be associated with the oral product. Although the [redacted]

I have discussed the animal findings of increased pulmonary artery pressure with the review team. [redacted]



As noted above, the sponsor must address significant CMC questions before the application may be approved.

Finally, although the division found the sponsor's explanations for the deficiencies identified by DSI somewhat reassuring, clearly DSI still has significant residual concerns. The ultimate approvability of this application will also, therefore, depend in part on the resolution of these issues.

For the reasons given above, then, I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

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/s/

Russell Katz
1/20/2006 03:52:40 PM
MEDICAL OFFICER

MEMORANDUM

NDA 21-872 Keppra Injection

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: New Formulation for Adult and Pediatric Patients 4 Years and Older

DATE: January 18, 2006

Keppra is currently approved as oral tablets and an oral solution for the adjunctive treatment of partial seizures in adult patients and pediatric patients, ages 4-16 years of age. Of note, the pediatric claim was granted in mid-2005, during the review cycle for this NDA for Keppra Injection.

In the current NDA, the sponsor has provided data demonstrating the bioequivalence of Keppra oral tablets to Keppra IV, when the IV formulation is infused over 15 minutes. This data was collected in adult patients.

The sponsor has provided safety data from a small cohort of 54 adult healthy volunteers. Additionally, safety data was provided from 25 adult patients with epilepsy who had their oral Keppra replaced with IV Keppra for up to 4 days. Dr.Norman Hershkowitz has reviewed the safety data.

To explore the safety of the IV formulation, the sponsor administered some single doses larger than the currently recommended largest single dose of 1500mg. The sponsor chose 2000mg, 3000mg, and 4000mg, all administered over 15 minutes. The sponsor also explored the safety of administering doses of 1500mg, 2000mg, and 2500mg over 5 minutes. Dr.Hershkowitz, has not identified any new safety concerns when Keppra is administered IV. In particular, the local tolerability appeared reasonably safe.

IV Keppra, in animal studies, was associated with a rise in pulmonary artery pressure. To investigate this further, the sponsor performed cardiac ultrasounds in a subgroup of the adult volunteers administered IV Keppra. No difference between adults administered IV Keppra and IV placebo was observed in this study. Given the lack of a finding in these adults and given that IV Keppra is designed to be only a temporary substitute for oral Keppra, this does not appear to be a relevant safety concern.

After oral Keppra was approved in pediatric patients in the summer of 2005 [redacted]

levetiracetam is almost 100% bioavailable. [redacted]

[redacted]

Chemistry

The chemistry review was performed by Dr.David Claffey. The chemistry and manufacturing are acceptable.

Relatively recently, the sponsor made changes to what will be the primary manufacturing site at Cardinal Health, a contract manufacturer for the sponsor. Having done this, the sponsor is obliged to provide sterility assurance data. The exact requirements are detailed in the microbiology review of Dr.Vinayak Pawar. This data must be submitted for review prior to final approval of this application.

Division of Scientific Investigation

[redacted]

The bioequivalence study was performed at a single site with one clinical investigator and one assistant. One of the vials administered in the study was noted to be underfilled by the clinical investigator. He noted this in the record.

The clinical study report did not fully describe this event and DSI learned that an earlier draft version of the study report had described the event accurately [redacted]

DNP met with DSI and the sponsor on September 29, 2005 to fully discuss the DSI concerns. During that meeting, the sponsor clearly described a failure rate in the glass ampoule manufacturing process that was fairly high [redacted]. However, the sponsor also described multiple checks of the fill volume performed after manufacture, checks that seemed to capture the vast majority of errant ampoules.

The sponsor also described the check of the fill volume performed by the clinical investigator and his assistant at the site. It was during these final checks of fill volume that the underfilled ampoule was initially discovered.

After the meeting, I believe members of the clinical review team were in general agreement that the fill volumes of the ampoules administered in the bioequivalence study were correct (and adequately documented to be correct) with the exception of the one ampoule captured by the investigators. [Note that the results of the bioequivalence study were analyzed excluding the subject who received this ampoule and did not change.]

Several other issues raised by the DSI inspection are addressed in various reviews. After review, none impact directly on the validity of the overall results of the bioequivalence study discussed above.

Conclusions

In adults, Keppra Injection when administered as directed has been shown to be bioequivalent to the same oral dose of Keppra. No local tolerability issues have been raised during the review. Therefore, once the microbiology concerns are addressed, Keppra Injection can be approved for adults.

[redacted] I believe the sponsor should collect some experience in a small cohort of pediatric patients [redacted] for patients age 4-16 years.

As noted above, the sponsor has not provided all the needed data for microbiology.

[redacted] the DSI findings, the clinical review team does not believe the issues raised bring the fundamental findings of the bioequivalence study into question. [redacted]

Recommendations

The sponsor should be sent an Approvable Letter for Keppra Injection for temporary substitution for oral Keppra in adult patients. Final approval for this indication should be contingent upon submission of microbiology data described above.

[redacted] the sponsor should gather experience in 20-30 pediatric patients [redacted] pediatric patients.

[redacted]

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/s/

John Feeney
1/18/2006 12:07:27 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	21872
Submission Number	000
Letter Date	12/20/04
Stamp Date	12/23/04
PDUFA Goal Date	1/21/06
Reviewer Name	Norman Hershkowitz MD, PhD
Review Completion Date	1/20/05
Established Name	Levetiracetam
(Proposed) Trade Name	Keppra Injection
Therapeutic Class	Anticonvulsant
Applicant	UCB Pharma
Priority Designation	Standard
Formulation	Sterile Solution for iv Use
Dosing Regimen	BID
Indication	Partial Onset Seizures
Intended Population	Adults and Children ($\geq$ 4 years)

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approvable, pending facility and major equipment changes validation and requalification is required. If Sponsor desires pediatric labeling they should complete a small pediatric safety trial.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None recommended.

1.2.2 Required Phase 4 Commitments

No new phase 4 commitments.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

A total of 117 patients from 8 studies have been exposed to intravenous Keppra. Ofthese 3 of these studies (79 pateints) were specifically designed to examine the present iv formulation (N01077, N01165 and N01166). N01077 (n=36) examined normal healthy volunteers, that were administered doses equivalent to the highest suggested labeled infusion dose and rate (1500 mg over 15 minutes). This study included an open label crossover bioavailability comparison of tablet to iv formulation (7 day washout) as well as a blinded placebo-control four day multiple dose (bid) comparison to a saline based placebo control. The second study (N01165: n=36) was a single blind placebo saline diluent control tolerability study that examined doses and infusion rates (2,00 -4000 mg over 15 minutes and 1,000 – 2,500 mg over 5 minutes) that were greater then the proposed recommended labeled doses and rates. The third study to use the

formulation to be marketed (N01166: n=25), examined multiple doses over a 4 day period at the suggested labeled dose (1,000 -3,000 mg/day: bid). This study examined 25 seizure patients who were currently on adjunctive levetiracetam for seizure control. Patients were simply maintained on their ongoing levetiracetam dosage, but were converted to the intravenous formulation.

An additional 38 individuals (35 normal healthy and 3 post-surgical) were exposed to an older formulation of levetiracetam in 5 studies. These studies were performed in the 1980s in Europe. All except one study examined single doses in healthy individuals. The exception was study N099 that examined a daily dose of levetiracetam, for up to 3 days in post surgical patients. Doses and infusion rates for these older studies were different then those presently proposed in the label. Both higher and lower rates of infusion were examined.

1.3.2 Efficacy

No efficacy studies were required. It was assumed that bioequivalence would reflect phramacodynamic equivalence. . A comparison of an oral dose of 1500 mg of levetiracetam with an intravenous dose of the new formulation administered over a 15 minute period revealed bioequivalence (equivalency based upon AUC and Cmax comparison in study N01077). Extrapolation of the expected Cmin revealed similar values with both routes of administration Tmax between the two formulations were different with a median Tmax of 0.75 hours for a 1500 mg dose of levetiracetam administered orally and 0.25 hours for the same dose infused over a 15 min period.

1.3.3 Safety

One death was observed in an older trial that studied the potential for levetiracetam in preventing post-surgical prevention of DVTs. This patient suffered a hemhoragic stroke thought to have resulted from the unintentional penetration of the carotid artery during an operation to repair an aortic aneurysm. This adverse event did not appear to be related to levetiracetam treatment.

There were no serious events, other then that associated with the single death noted above. There where no discontinuations. The value of the absence of discontinuations must be viewed against the fact that only 40 of the 117 patients were exposed to multiple dosing.

Adverse event rates were observed in 28% to 89%of patients on levetiracetam in studies that examined the new formulation. Common adverse events included somnolence, headache, and dizziness. This is similar to those events that were observed in studies using oral routes of administration. Unlike oral formulation studies, where gait disturbance is a common adverse event, gait disturbance was not commonly reported in studies using the proposed formulation. This may have resulted from a number of factors including the fact that patients may not be challenged to ambulate in the hospital setting of the present studies. Older intravenous studies, where gait was specifically tested, reported a higher rate of gait disturbances. In general, the

types of common adverse events appear similar to that seen in prior studies using oral administration. Comparison of somnolence, headache, and dizziness appeared somewhat more commonly reported in the present studies using proposed intravenous formulation then in prior studies that examined oral administration. This data needs to be viewed with caution, as the intravenous study predominately examined a single dose in a relatively small population size. Moreover, intravenous protocol designs did not incorporate a titration phase as did the prior studies. It, however, appears that adverse events are qualitatively similar and would likely not differ greatly in rates.

Local injection site reactions were uncommon and mild in nature. Thus, of the 79 patients receiving the new intravenous formulation of levetiracetam only 2 reported injection site pruritis. These injection site symptoms where not reported in the study examining higher doses and rapid infusion rates. In an older single dose study, examining a different formulation, using higher infusion rates and concentrations, all 12 participating patients experienced burning during infusion.

Vital signs where carefully examined in the three studies using the new formulation. Thus, vital signs where examined during and up to 2 hours following the completion of infusion in study N01077 as well as N01166 and upon completion of infusion and the subsequent 24 hours in N01165. These data were analyzed by examining outlier and central tendencies. The results indicated little or no effect on systolic or diastolic blood pressure or heart rate during or following infusion completion. Of the studies examining the new formulation, 2 patients in study N01077 exhibited a drop in systolic blood pressure reported as an adverse event. Examination of the data revealed that patients where asymptomatic and drops were small (10 and 16 mmHg) but reported as an adverse event because of the low absolute baseline value (i.e. screening systolic blood pressures as low as 94 and 100). Lastly, a drop in systolic blood pressure in N01166 was reported in one patient. This drop was also minimal (13 mm Hg) but reported as an adverse event because of the low starting baseline value (i.e. drop from 101 to 88 mmHg). These drops appeared somewhat sporadic and where not seen at maximally expected Tmax (e.g. the three events occurred in the different patients 5 minutes into infusion and 15 minutes and 2 hours following infusion completion). In summary, no obvious clinically significant reductions in blood pressure were apparent in these studies.

EKGs were monitored throughout and following infusion in the three studies that examined the new formulations. The corrected QT intervals were calculated (QTcF and QTcB). No consistent alterations in corrected QT intervals was apparent. No consistent changes in PR interval and the QRS segment were observed. One patient was reported to have a first degree heart block 2 hours post injection. This patent however was noted to have a prolonged PR interval at screening and during study discharge. This, along with the lack of significant effect in the analysis of PR intervals in all studies, suggests that this was likely not related to drug.

CBC and a full chemistry panel were monitored in studies. No clinically significant abnormal laboratories were apparent in these studies.

Intravenous pre-clinical dog studies suggested a potential for a transient elevation in pulmonary arterial pressures during levetiracetam injection. Because of this continuous-wave Doppler transthorasic echocardiograms were used to evaluate pulmonary arterial pressures in patients receiving levetiracetam (n=12) or placebo (n=6) in study N01077. The systolic pulmonary artery pressure was mathematically determined by the measurement of the tricuspid regurgitation peak jet velocity. These studies did not indicate an increase in pulmonary pressures in the highest dose and rates recommended in the proposed labeling.

1.3.4 Dosing Regimen and Administration

The Sponsor notes that: "Keppra® Injection is for intravenous use only and must be diluted prior to administration. Keppra® Injection (500 mg/5mL) should be diluted in at least 100 mL of a compatible diluent (see Compatibility and Stability) and administered intravenously as a 15-minute I.V. infusion." This is replace mg-for-mg of the oral Keppra dosage.

1.3.5 Drug-Drug Interactions

This new formulation of Keppra was found compatible with the following diluents: normal saline, 5% dextrose and lactated ringers. *In vitro* mixing of the levetiracetam formulation with phenytoin resulted in a precipitate. *In vitro* mixing with lorazepam, diazepam and valproate sodium was unremarkable.

1.3.6 Pediatric Populations

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Keppra (levetiracetam) is an anticonvulsant that is labeled for the adjunctive treatment of partial onset seizures in adults and children >4 years of age. This drug is in a chemically unique class amongst the anticonvulsants. It is presently available as tablets and an oral solution. The present submission is for a new, saline based, intravenous formulation.

2.2 Currently Available Treatment for Indications

See above.

2.3 Availability of Proposed Active Ingredient in the United States

Levetiracetam is available in tablet and as an oral solution only.2.4 Important Issues With Pharmacologically Related Products
None.

2.5 Presubmission Regulatory Activity

The division has had a number of meeting with the Sponsor in which it was decided that the demonstration of bioequivalence would be adequate for labeling in an adult population. The division also requested additional safety data for rapid infusion rates.

2.6 Other Relevant Background Information

None.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology)

Since the submission of this NDA the Sponsor has informed the division of their intent to change the facility and form of production and packaging of this product. [redacted]

product will be packaged in vials. Because of the facility and major equipment changes validation and requalification is required. This must result in an approvable status.

3.2 Animal Pharmacology/Toxicology

One new issue pertinent to the present application was encountered in pre-clinical studies. Intravenous levetiracetam administration in dogs appeared to produce a transient elevation in pulmonary arterial pressure. These issues are further discussed in the section "Additional Analysis and Explorations" under the major heading of "ECG" in the ISS.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

A total of 117 patients from 8 studies have been exposed to intravenous Keppra. These studies are summarized in the two continuous tables below.

Only 3 of these studies (total n=77) were specifically designed to examine the present iv formulation and two of these were of primary importance (N01077 and N01165) in the submitted ISS as data analysis was still ongoing in one (N01166) at the time of submission. N01077 examined infusion rates, in normal healthy volunteers, that were administered doses equivalent to he highest suggested labeled infusion dose and rate (1500 mg over 15 minutes). This study included an open label crossover bioavailability comparison of tablet to iv formulation (7 day washout) as well as a blinded placebo-control four day dosing multiple dose (bid) comparison to a saline based placebo control. The second study (N01165) was a single blind placebo saline diluent control study that examined doses and infusion rates (2,00 -4000 mg over 15 minutes and 1,000 – 2,500 mg over 5 minutes) that were greater then the recommended labeled doses and rates. This study specifically requested by the division. Both were performed in normal healthy volunteers and exposed a total of 54subjects to drug.

The third study to use the formulation to be marketed (N01166), requested by the European Union, examined multiple doses over a 4 day period at the suggested labeled dose (1,000 -3,000 mg/day: bid). This study examined 25 seizure patients who were currently on levetiracetam adjunctively for seizure control. Patients were simply maintained on their ongoing levetiracetam dosage but were converted to the intravenous formulation. Some aspects of the data analysis (see below) were ongoing at the time of the original submission.

An additional 38 individuals (35 normal healthy and 3 post-surgical) were exposed to an older formulation of levetiracetam in 5 studies. These studies were performed in the 1980s in Europe. All except one study examined single dose in healthy individuals. The exception was study N099 that examined a daily dose of levetiracetam, for up to 3 days in post surgical patients. Doses and infusion rates were different then that being developed for labeling.

A summary of the study design for all studies and dosing regimen can be found in the following 3 tables.

Study No. Source	Country (Year)	Design / Dose	N	Status
Studies Using Proposed Formulation				
Healthy Subjects				
N01077	Belgium (2003)	Randomized, open-label, two-way crossover study comparing the bioavailability of levetiracetam 1500 mg as a 15-minute I.V. infusion and as oral tablets (Part A). The two single administrations were separated by a 7-day washout period. Randomized, double-blind, placebo-controlled, parallel-group study of the safety, tolerability, and pharmacokinetics of levetiracetam 1500 mg as a 15-minute I.V. infusion b.i.d. for 4 days (Part B)	18	Completed
N01165	Belgium (2004)	Randomized, single-blind, placebo (PBO)-controlled, parallel group study to assess pharmacokinetics and safety. Dose escalation study: 2000 to 4000 mg I.V. administered over 15 minutes and 1500 to 2500 mg I.V. administered over 5 minutes	LEV 36 PBO 12	Completed
Patients with Partial Onset Seizures				
N01166	Germany, U.K., France (database lock 17 Sept 2004)	A multicenter, open-label study evaluating the safety and tolerability of levetiracetam 15-minute I.V. infusion in doses ranging from 1000 to 3000 mg/day, administered b.i.d. as adjunctive treatment for 4 days	25	All data collected – data analysis ongoing
Studies of Faster-than-Recommended Infusion Times (Older Formulations)				
Healthy Subjects				
N058	Belgium (1985)	Open-label, dose escalation phase (25 mg to 1600 mg administered I.V. over 5 minutes) followed by a double-blind, cross-over phase (1600 mg *versus* placebo)	6	Completed
N069	Belgium (1986)	Three-way crossover study with a 1-week interval period. 1000 mg, either as I.V. formulation (injected over 2 minutes) or oral solution or oral capsules	12	Completed
Studies of Longer Infusion Times or an Unknown Infusion Time (Older Formulations)				
Healthy Subjects				
N204	Italy (1985)	Double-blind, placebo-controlled infusion of single doses of 1000 mg or placebo administered I.V. over 3 hours	8	Completed
N060	Italy (1985)	Single-blind, non-comparative infusion of single doses of 500 mg administered I.V. over 3 to 4 hours	9	Completed

DVT Prevention in Surgical Patients				
N099	Belgium (1989)	Open-label, randomized pilot study comparing the efficacy and safety of calcium heparin (HEP) and levetiracetam for DVT in patients undergoing major elective chest and/or abdominal surgery or orthopedic surgery of the lower limbs Levetiracetam administered orally on the day prior to surgery (250mg b.i.d.), with 250mg levetiracetam given I.V. starting on the day of surgery and continuing for up to 3 days before switching to oral levetiracetam. Post operatively, levetiracetam was to be continued for up to Day 7 or 14, depending on the nature of the surgery.	LEV 3 HEP 3	Completed
Total number of study participants (all treatments)			132	
Total number exposed to levetiracetam (all studies, completed and ongoing)			117	
Total Number exposed to levetiracetam in completed studies			92	

Study	N	Dose (mg)	Frequency	Infusion Time
Studies Using Proposed Infusion Time				
N01077	18	1500	Single dose	15 minutes
	12[a]	1500	b.i.d. × 4 days	15 minutes
N01165	6	2000	Single dose	15 minutes
	6	3000	Single dose	15 minutes
	6	4000	Single dose	15 minutes
Studies of Faster-than-Recommended Infusion Time				
N01165	6	1500	Single dose	5 minutes
	6	2000	Single dose	5 minutes
	6	2500	Single dose	5 minutes
N058	6	25 - 1600	Single dose	5 minutes
N069	12	1000	Single dose	2 minutes
Studies of Longer Infusion Times or an Unknown Infusion Time				
N204	8	1000	Single dose	3 hours
N060	9	500	Single dose	3 - 4 hours
N099	3	250	Up to 3 days	Not Reported

[a] Subset of subjects exposed in the single-dose part

Data collection in most studies consisted of simple adverse event reporting, vital sign measurement and routine clinical laboratory collection. The three more recent studies using the intended marketed formulation has examined EKGs and after infusion. One of these studies (N01077) also examined echocardiography to examine for potential pulmonary artery hypertension observed in some animal studies (see below). A table that describes the various endpoint testing is presented in the table below. Older studies are categorized by the relative rate of infusion to that in the present development program development.

Assessments	Proposed Formulation				Faster Infusion Times		Longer or Unknown Infusion Times		
	N01077		N01165	N01166 (ongoing)	N058	N069	N204	N060	N099
	Single Dose	Multiple Dose							
Adverse Events	x	x	x	x	x [a]	x [b]	x	x [c]	x [c]
Clinical Laboratory Tests	x	x	x	x [d]	x [a]	x [b]	–	–	x [c]
Vital Signs	x [e]	x [e]	x [f]	x	x [a]	x [b]	x	x [c]	x [c]
Electrocardiogram	x [e]	x [e]	x [f]	x	–	–	–	–	–
Echocardiography	–	x	–	–	–	–	–	–	–
Concomitant Meds	x	x	x	x	–	–	–	–	–
Final Post-treatment Assessment	1 - 8 days	1 - 8 days	within 7 days	1 - 7 days	24 hours	24 - 48 hours	–	–	–

[a] pre-dose and 4 and 24 hours post-dose; for vital signs and adverse events (cross-over phase): 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, and 24 hours post-dose
[b] adverse events and vital signs: pre-dose and 30 minutes and 1, 4, 6, 12, and 24 hours post-dose; laboratory tests pre-dose and at frequent intervals up to 48 hours post-dose
[c] adverse events and vital signs daily; laboratory tests at screening and Day 14
[d] including levetiracetam and concomitant AED plasma levels
[e] pre-dose and 5, 15, and 30 minutes; 1 hour; and 2 hours after study drug administration and at follow up discharge
[f] pre-dose, at the end of infusion, 15 minutes and 30 minutes after the end of the infusion, 1, 2, 12, and 24 hours post-dose, and at follow up discharge

4.5 Compliance with Good Clinical Practices

DSI has performed an evaluation of the Belgium site where study N01077 (the pivotal PK) was performed. They concluded that a number of major irregularities had occurred. [redacted] This division, as well as the OCPB, believed that these irregularities should not compromise the scientific conclusions of this study. OCPB asked for additional analysis to help confirm this conclusion (see the Clinical Pharmacology review). [redacted] The draft minutes, composed by this reviewer, for a face-to-face meeting with UCB on 9/29/05 regarding these irregularities is included in Appendix C.

4.6 Financial Disclosures

The Sponsor has submitted a financial disclosure.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

OCPB concluded, from the intravenous oral comparison of 1500 mg of levetiracetam in study N01077, that the intravenous formulation administered over a 15 minute period was

bioequivalent. Data for this analysis is presented below. Note, that patient 007 is excluded from this analysis because of a reported under-dosing, which resulted from an under-filled ampoule.

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

The OCPB reviewer noted that: "DSI reported that the QC samples included in the analytical run for samples for subjects 0001 and 0002 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 of at least [redacted] The OCPB reviewer concluded that the analysis noted above is adequate for determining bioequivalence. Notwithstanding, a repeat analysis excluding patients 0001, 0002 and 0007 still indicated bioequivalence.

[redacted]

One factor that is not considered in the calculation for bioequivalence but which differed between iv and oral drug administration of a single dose of 1500 mg of levetiracetam (part A of N01077)is Tmax. Thus, median Tmax was much lower with intravenous administration (median, 0.25 hours: range, 0.2 -3.0 hours) then with oral administration (median 0.75 hours: range, 0.2-2.0 hours).

Off note Dr Gobburu was questioned whether Cmin would be similar between iv and po formulations. He has responded in an e-mail dated 1/17/06 that they are similar. Thus he states:

> Study N135 (from the original NDA) reported a Cmin value of 5.2 (+/-1.3) ug/mL at 500 mg bid keppra oral. Study N01077 (current submission) reported a Cmin of 14.1 (+/- 3.8) ug/mL after 1500 mg bid IV, which is equivalent to 4.7 ug/mL at 500 mg bid keppra IV. Keppra exhibits linear pk over this dose

range. The mean Cmin after oral (5.2 ug/mL) and IV (4.7 ug/mL), after 500 mg bid doses, are in close agreement

6 INTEGRATED REVIEW OF EFFICACY

No efficacy studies were required. It was assumed that pharmacokinetic equivalence would be sufficient to expect similar pharmacodynamic effects.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

One death was reported amongst all the iv studies. This occurred in study N099 and involved a 79 year old female who was scheduled to have resection of her aortic aneurysm. This patient received two doses of 250 mg (bid) levetiracetam orally the day before surgery and one dose of iv levetiracetam on the morning preoperatively. The resection was performed and 12 hours later the patient suffered a "massive cerebrovascular hemorrhage with hemiplegia. She died 4 days later. The narrative reveals no mention of clotting or platelet abnormality and very clearly notes that the surgeon accidentally punctured the carotid artery. The investigator concluded that an accidental puncturing of a "highly atherosclerotic carotid had led to athromboebolism in the arteria cerbri media."

The investigate further examined this issue of post surgical hemorrhage the Sponsor searched their data base for hemorrhagic complications of surgery unassociated with thrombocytopenia and identified one case of a intraoperative hemorrhagic complication in a 34 year old female with a history of heavy menstrual bleeding on oral levetiracetam who experienced hemorrhagic complications during a laparotomy . A laparoscopic cauterization of a bleeding artery was necessary and the patient recovered.

A literature search revealed an abstract[1] that reported on 2 patients receiving oral levetiracetam who suffered a hemorrhagic complication of two patients on oral levetiracetam associated with epilepsy surgery. One patient had chronically abnormal coagulation abnormalities.

1 Eccher M, Swartz BE, Werz MA, et al. Possible relationship of levetiracetam therapy to hemorrhagic complications in epilepsy surgery (abstract). Epilepsia 2002;43 (Suppl 7): 206.

From these studies it is difficult to determine whether these complications are above the expected background and therefore it likely does not need to be considered in labeling revision. Such complications are not unexpected. This reviewer has presently requested a consult form ODS on thrombocytopenia that he will request be expanded to all hemorrhagic events.

7.1.2 Other Serious Adverse Events

There were no serious adverse events other then the case of cerebral hemorrhage noted in the section on deaths.

7.1.3 Dropouts and Other Significant Adverse Events

No adverse events lead to patient withdrawal or a lowering of infusion rate. It should, however, be noted that all but two studies involved the examination of a single dose.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events in the present studies were coded according to the MedDRA dictionary. Off note, previous studies using the oral formulation reviewed by this division used the COSTART dictionary. These are acceptable dictionaries for categorization of adverse events.

7.1.5.3 Incidence of common adverse events

In their analysis of adverse events the Sponsor has divided analysis into two groups: those using the proposed formulation and those using older formulations. This may be further subdivided by studies examining the proposed labeled rate of infusion, higher rates of infusion and lower rates of infusion.

1.1.1.1.1 Proposed formulation

Proposed labeling in adults calls for dilution of a dose of 500 to 1500 mgs of levetiracetam solution, derived from the 100mg/ml formulation, in 100 ml of saline. This is to be administered over a 15 minute period of time. Three studies using this formulation have been carried out at various dosages and rates. Those studies that examined infusion of doses over a 15 minute period of time utilized the dilution as specified in the label. Those studies that used a 5 minute infusion period administered the indicated dose without dilution (i.e. directly from the ampoule).

Study N01077 used the present formulation. Part A was of an open-label, crossover, seven day wash-out, study that simply compared 1500 mg infused over 15 minutes with an identical oral dosage administration. All treatment emergent adverse events are presented in the table below. Treatment emergent adverse events were only slightly more common in patients receiving an injection as compared to oral formulation (88.9% versus 72.2%). All but one reported adverse event were of mild severity. The single case of influenza like illness was reported as moderate. Adverse events referable to the nervous system were the most common. This class of adverse events , in descending order, was somnolence, dizziness-postural, dizziness and headache. Interestingly, dizziness and postural dizziness was more commonly reported with oral administration. Other nervous system adverse events were more common with intravenous infusion. Injection site pruritus, but no other injection site problems, was reported in two patients receiving intravenous levetiracetam.

Part A (Single Dose Administration)		
	LEV 1500 mg oral tablet	LEV 1500 mg I.V. infusion
Total subjects exposed:	(N = 18)	(N = 18)
Number of subjects with treatment emergent AEs:	13 (72.2%)	16 (88.9%)
System Organ Class AE Preferred Term (MedDRA)		
Gastrointestinal disorders	0	2 (11.1%)
Flatulence	0	1 (5.6%)
Loose stools	0	2 (11.1%)
General disorders and administration site conditions	0	4 (22.2%)
Fatigue	0	1 (5.6%)
Feeling cold	0	1 (5.6%)
Influenza like illness	0	1 (5.6%)
Injection site pruritus	0	2 (11.1%)
Infections and infestations	1 (5.6%)	0
Nasopharyngitis	1 (5.6%)	0
Musculoskeletal and connective tissue disorders	0	1 (5.6%)
Chest wall pain	0	1 (5.6%)
Nervous system disorders	12 (66.7%)	15 (83.3%)
Dizziness	3 (16.7%)	1 (5.6%)
Dizziness postural	7 (38.9%)	3 (16.7%)
Headache	1 (5.6%)	3 (16.7%)
Somnolence	5 (27.8%)	11 (61.1%)

Part B of study N01077 was a double blind comparison of 1500 mg administered intravenously bid for 4 days with placebo (saline) administered at a similar regimen. The rate of infusion was identical to that used in part A. Twice as many patients receiving intravenous dosing of levetiracetam experienced adverse events (66.7% versus 33.3%). The treatment emergent

adverse events reported are presented in the table below. Nervous system related symptoms were the most common class of adverse events with intravenous drug administration with somnolence, headache and postural dizziness occurring most commonly. All of these events were considerable more common with the drug then placebo. Decrease in blood pressure was reported in 2 patients (16.7%) receiving intravenous levetiracetam and none on placebo. These patents were asymptomatic and are discussed below in the section on vital signs. No patients in either group reported injection site adverse events.

Part B (Multiple Dose Part)		
	Placebo	LEV 1500 mg I.V. infusion
Total subjects exposed:	(N = 6)	(N = 12)
Number of subjects with treatment emergent AEs:	2 (33.3%)	8 (66.7%)
System Organ Class AE Preferred Term (MedDRA)		
Gastrointestinal disorders	0	3 (25.0%)
Dry mouth	0	1 (8.3%)
Flatulence	0	1 (8.3%)
Loose stools	0	1 (8.3%)
Nausea	0	1 (8.3%)
General disorders and administration site conditions	1 (16.7%)	1 (8.3%)
Chest pain	1 (16.7%)	0
Thirst	0	1 (8.3%)
Investigations	0	2 (16.7%)
Blood pressure decreased	0	2 (16.7%)
Nervous system disorders	1 (16.7%)	6 (50.0%)
Disturbance in attention	0	1 (8.3%)
Dizziness	1 (16.7%)	1 (8.3%)
Dizziness postural	0	3 (25.0%)
Headache	0	3 (25.0%)
Somnolence	1 (16.7%)	4 (33.3%)
Psychiatric disorders	1 (16.7%)	1 (8.3%)
Euphoric mood	1 (16.7%)	1 (8.3%)

Increased infusion rate with the present formulation was investigated in Study N01165. This was a single blind placebo controlled study that examined higher doses and higher infusion rates (1500 mg, 2000mg and 2500 mg over a 5 minute period and 2,000 mg, 3,000 mg and 4,000 mg over 15 minutes). All reported treatment emergent adverse events from this study are presented in the table below. Similar overall rates of adverse events were reported in this study as compared to the prior lower dose slower infusion study. Thus 86% of patients receiving levetiracetam reported adverse events here and 89% in the prior study. Faster rates or higher doses did not produce an obvious increase in adverse event reporting within this study, although there was a subtle trend, with regard to some common adverse events, for higher incidences at greater doses or faster infusion rates. This was most apparent with the adverse event of somnolence. This conclusion must be interpreted with caution because of the small size of the study. Similar to the prior study, the most common class of adverse events was those referable to the central nervous system,. However, events were generally reported at increased rates. Dizziness was by far the most common event (52.8%) followed by Somnolence (33.3%),

dizziness-postural (19.4%) and headache (13.9%). Fatigue was also reported in a 2 patients (11.1%). With one exception the reporting rates for these events in the placebo group was 0. Two separate cardiac events were noted, one bradycardia and the other first degree heart block: these will be discussed in the cardiac section below. All but 2 adverse events were rated as mild. The two exceptions was one case of dizziness and one of somnolence that was rated as moderate. There were no reported injection site adverse events.

Primary System Organ Class Preferred term (MedDRA)	Placebo N = 12	LEV I.V. 15 min (mg) 2000 N = 6	 3000 N = 6	 4000 N = 6	LEV I.V. 5 min (mg) 1500 N = 6	 2000 N = 6	 2500 N = 6	All LEV doses N = 36
Number of subjects with at least one TE AE:	3 (25)	5 (83.3)	5 (83.3)	6 (100)	6 (100)	3 (50.0)	6 (100)	31 (86.1)
Infections and infestations	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Herpes simplex	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Psychiatric disorders	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Irritability	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Nervous system disorders	2 (16.7)	4 (66.7)	4 (66.7)	6 (100)	5 (83.3)	3 (50.0)	6 (100)	28 (77.8)
Balance disorder	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Dizziness	0	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	19 (52.8)
Dizziness postural	0	0	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	0	7 (19.4)
Dysgeusia	1 (8.3)	0	0	0	0	0	0	0
Headache	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (16.7)	5 (13.9)
Somnolence	0	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	12 (33.3)
Eye disorders	0	0	0	0	0	0	1 (16.7)	1 (2.8)
Vision blurred	0	0	0	0	0	0	1 (16.7)	1 (2.8)
Cardiac disorders	0	0	1 (16.7)	0	1 (16.7)	0	0	2 (5.6)
Atrioventricular block first degree	0	0	1 (16.7)	0	0	0	0	1 (2.8)
Sinus bradycardia	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Gastrointestinal disorders	1 (8.3)	0	0	1 (16.7)	0	1 (16.7)	0	2 (5.6)
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (2.8)
Nausea	1 (8.3)	0	0	1 (16.7)	0	0	0	1 (2.8)
Vomiting	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Musculoskeletal and connective tissue disorders	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (5.6)
Back pain	0	0	0	0	0	1 (16.7)	0	1 (2.8)
Sensation of heaviness	0	1 (16.7)	0	0	0	0	0	1 (2.8)
General disorders and administration site conditions	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	5 (13.9)
Fatigue	0	1 (16.7)	2 (33.3)	0	0	0	1 (16.7)	4 (11.1)
Feeling drunk	0	0	1 (16.7)	0	0	0	0	1 (2.8)
Thirst	0	0	0	0	0	1 (16.7)	0	1 (2.8)

Study N01166 administered to epilepsy patients in doses at the proposed labeled infusion rates (over 15 minutes) in doses of 500 mg to 1500 mg bid over 4 days as replacement to their ongoing levetiracetam treatment. The sponsor presents preliminary adverse event reporting in the ISS. This is reproduced in the table below. Similar to studies above headache and fatigue were reported. Other commonly reported adverse events were not observed. One case of blood pressure decrease was observed. This case will be discussed in the safety update section.

Primary System Organ Class Preferred Term (MedDRA)	n (%) (N = 25)
Nervous system disorders	7 (28.0%)
Disturbance in attention	1 (4.0%)
Dizziness	1 (4.0%)
Headache	5 (20.0%)
Eye disorders	1 (4.0%)
Vision blurred	1 (4.0%)
Ear and labyrinth disorders	1 (4.0%)
Ear pain	1 (4.0%)
Renal and urinary disorders	1 (4.0%)
Dysuria	1 (4.0%)
General disorders and administration site conditions	4 (16.0%)
Asthenia	1 (4.0%)
Fatigue	3 (12.0%)
Investigations	1 (4.0%)
Blood pressure diastolic decreased	1 (4.0%)

1.1.1.1.2 Older Formulations

1.1.1.1.2.1 Faster then Proposed labeled Infusion Times

Study N058

Study N058 was a dose escalation study performed in 1985. The study was divided in to 2 parts with the first part of the study being an open-label 5 minute single dose escalation study (25 mg to 1600 mg). This was followed by a double-blind crossover placebo-control phase where each patient received a dose of 1600 mg of levetiracetam and placebo separated by a washout. Six healthy subjects (4 men and 2 women) participated in this trial. This report was translated into English from French. The study, being an old study, is very informally presented. The Sponsor reports that no adverse events were reported during the dose escalation phase until a dose of 400 mg was achieved. The adverse events at this dose are not reported. At 800 mg one patient reported "dizziness" and one patient reported "slump." It is unclear what "slump" means At 1600 mg 4 of the six patients studied reported "feeling tipsy and dizziness" and the other 2 reported euphoria. The Sponsor was called on 1/11/05 with the request to clarify what is meant by "slump." They returned the call the same day and noted that a better translation may be "in a daze."

Adverse events reported during the 1600 mg/5min versus placebo crossover phase are presented in the table below. From this table it can be appreciated that central nervous system related adverse events is clearly predominates and are nearly exclusive. Most common reported events

include adverse events related to gait and balance disturbances, dizziness, drowsiness, sleep or dry mouth. These are generally well differentiated from placebo treatment in which only one adverse event was reported. All these reported events are similar to that reported in other studies, except gait and balance disturbances appear more common. This difference may have resulted from the differences in the protocol, i.e. the protocol called for specific testing of "static equilibrium" through Romberg and "dynamic equilibrium" by the examination of straight line walking.

A more formal investigation of adverse events after dosage was performed by examining a number of adverse event parameters[2] using subject rated analog scale. This were then compared between placebo and control by a paired t test for periods of time up to 24 hours after infusion but does not appear to be corrected for multiple comparisons. A statistically significant difference was observed at multiple time points for one of the endpoints referred to as "identity" and for malaise at 24 hours post-injection and vigilance 90 minutes post injection.

Equilibrium was also formally tested by "various means including the use of the Romberg test." Because the analog scale has not been validated it is difficult to interpret. The Sponsor notes that there was a dose related increase in equilibrium and motor coordination adverse events. Two patients showed a very positive Romberg 15 to 90 minutes after administration to the extent that one patient fell on testing. These data on stability are not inconsistent with the newer studies examining the formulation being proposed in this IND; i.e. they may be consistent with dizziness. Gait problems may not have been observed in the more recent studies using the proposed labeled formulation because, as noted above, they were specifically targeted in this but not more recent studies. The increase risk here was probably not simply the result of the more rapid infusion rate. It should be noted that in placebo-controlled efficacy studies, ataxia was the third most common neurologically related event related to the use of levetiracetam. Somnolence and dizziness were the first and second most common neurological events. This reviewer believes that the lower risk observed in the recent studies for gait disturbance when compared to previous oral studies is that there was less opportunity in the hospital based studies to challenge gait function. The present study that directly examined this issue is likely a better representation of the risk of this adverse event. This reviewer believes that this supports the similarity of adverse event profile between levetiracetam administered through an intravenous and oral route.

2 The following parameters were examined "activity," "concentration," "fatigue," "identity," malaise," "nervousness," "somnolence," "tension," and "vigilance." The meaning of "identity" is not clear from the translated protocol report.

Adverse Event (Verbatim Terms)	LEV 1600 mg No. of Reports	Placebo No. of Report
Drunken gait	4	0
Difficulty in concentrating	2	0
Drunken feeling	2	0
Dry mouth	2	1
Spinning head, dizziness	2	0
Tiredness, drowsiness	2	0
Tripping feeling	2	0
Deep sleep (slept very soundly)	1	0
Euphoria	1	0
Feeling in great form	1	0
Heavy headedness	1	0
Impaired equilibrium	1	0
Inefficacy	1	0
Sluggish ideation	1	0
Blurred vision	0	1

Study N069

Study N069 was a three –way crossover study with a one week wash in 12 healthy volunteers that compared that compared 1,000 mg of levetiracetam orally as a solution, orally as tablets and intravenously with a 2 minute infusion rate. All subjects completed the study and according to the Sponsor in the ISS "no major safety issues were reported." The translation of the original report noted that "no important side effects were reported." The Sponsor notes that "2 subjects in all three sessions reported moderate drowsiness and dizziness that lasted 3 hours after drug is taken" It us not differentiated what treatment these subjects were receiving. Vigilance, as measured by a "visual analog rating scale (not further described)" was decreased between 0.5 to 4 hours after drug administration to a similar degree in all treatment groups. All of the subjects experienced a burning sensation at the iv site that lasted up to several seconds after the injection was completed (see section on local injection effects).

1.1.1.1.2.2 Slower then Proposed Infusion Rates

Study N204

Study N204 was a single dose, single blind study in 1985 that examined the effect of 1,000 mg of levetiracetam infused over a 3 hour period with placebo in eight healthy. All subjects completed the study and none reported adverse events.

Study N060

Study N060 was conducted in 1985 and was a single blind, "non-comparative" that examined the effects of 500 mg of levetiracetam administered over a 3 – 4 hour period in 9 aged (59-84 years old) individuals. All subjects completed the trial and none reported adverse events.

1.1.1.1.2.3 Studies with Unknown infusion Rates

Study N099

This study was conducted in 1989 and was an open label study designed to compare heparin to levetiracetam in prevention of deep venous thrombosis in patients undergoing "major elective chest and/or abdominal; surgery." Patients were started on either heparin or levetiracetam 1 day prior to surgery and continued after surgery for up to 7-14 days. Levetiracetam dose was 250 mg BID and was administered orally accept for the day of surgery and up to 3 days following surgery at which time it was administered intravenously. Six patients were evaluated, 3 in each treatment group. Two patients received intravenous heparin for up to 2 days post-operatively without adverse events. A third patient undergoing resection for an aortic aneurysm received one dose of levetiracetam intravenously post-operatively and subsequently developed a "massive hemiplegia (side and cause unknown)." This is discussed in the section on deaths.

7.1.5.6 Additional analyses and explorations

Local injection adverse events

Seventy-nine subjects received the present formulation of levetiracetam (100mg/ml; see Appendix A for composition). Of these subjects, 61 (36 healthy individuals and 25 epileptic patients) had their mg dose (1500 to 4,000 mg) diluted in 100 ml of 0.9% NaCl and infused over a 15 minute period. Eighteen healthy subjects received undiluted formulation in doses of 1500 and 2500 mg over 5 minutes. Of all these patients only 2 subjects, receiving 1500 mg over a 15 minute period (study N01077), experienced any type of injection site adverse event. This was reported as a transient mild pruritus at the injection site.

In study N069, where a higher undiluted concentration of solution (200 mg/ml) from an older formulation, was directly infused at a rapid rate (1,000 mg over 2 minutes) every subject experienced a burning sensation at the injection site that lasted a few seconds following the completion of the injection.

There is no documentation of local injection adverse events for any of the remaining studies.

7.1.5.5 Identifying common and drug-related adverse events

Although common adverse events were identified that appeared to be linked to drug use, these could not always be considered definitive because of the limited population size studied, a majority of studies utilizing a single dose, and the limited placebo comparison. Some adverse events that appeared to clearly be associated with intravenous drug treatment included somnolence, headache, dizziness and gait disturbance. Although the study that identified gait disturbance as common problem used a more rapid infusion rate, this reviewer feels that this identification may not be related to the rate but the fact that gait was more rigorously examined. These adverse events are very similar to those observed in oral tablet studies. The Sponsor submitted a tabulation of common adverse events (>1% of patients) for patients who participated in adjunctive double blind- blind, placebo-control trials where the adverse events were more common in drug treatment then placebo treatment groups (see table below). The data were derived from the Table 5 in the present labeling. Unlike the iv studies that coded according to the MedDRA dictionary these trials were coded according to COSTART. Events identified as common adverse events in the above intravenous trials are similarly observed as common adverse events in the oral studies. The common adverse events of somnolence, headache, and dizziness generally appeared more commonly reported in study N01077 and N01065 then that reported in placebo control trials for oral levetiracetam. For example somnolence was reported in 33 to 61% of patients in study N01077 as compared to 15% in oral studies and dizziness (combined dizziness and postural dizziness) was reported in 22 to 33% of patients in study N01077 and 9% in all oral studies. This may have resulted form the different route of administration, but this reviewer feels that it more likely results from differences in study designs. Thus, iv studies do not incorporate a titration period that was used in the oral studies. Perhaps supporting this is the fact that neither somnolence nor dizziness was reported in study N0166 where levetiracetam was administered to patients who were on oral levetiracetam. Thus, somnolence, dizziness (and vertigo), headache and gait disturbance (ataxia) were reported in oral studies. Other events (e.g. infection and depression and other neuropsychiatric events) were observed in the oral studies but not observed in the iv studies study. This is most likely because of the different designs (e.g. chronic versus single dose and short term exposure) and small "n" size observed. Some sporadic adverse events were observed in uncontrolled and controlled studies are, however, similar to those seen in controlled studies using the oral formulation. These included adverse events of loose stools, nausea/vomiting, loose stools, euphoria," "disturbance of attention," "sluggish ideation." Except for the mild local intravenous site events (pruritus) seen with injection, there is no reason to believe that effects produced by the intravenous administration of levetiracetam are different from those produced by oral administration.

COSTART Body System / Adverse Event	Oral Keppra® (N = 769) %	Placebo (N = 439) %
Body as a Whole		
Asthenia	15	9
Headache	14	13
Infection	13	8
Pain	7	6
Digestive System		
Anorexia	3	2
Nervous System		
Amnesia	2	1
Anxiety	2	1
Ataxia	3	1
Depression	4	2
Dizziness	9	4
Emotional Lability	2	0
Hostility	2	1
Nervousness	4	2
Paresthesia	2	1
Somnolence	15	8
Vertigo	3	1
Respiratory System		
Cough Increased	2	1
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1
Special Senses		
Diplopia	2	1

There were three reports of lowering of blood pressure: 2 n the placebo control (with 0 in placebo) and one in a non-placebo controlled study using the present formulation at the recommended infusion rate. A more thorough analysis of blood pressure is required in order to determine causality. This will be discussed in the section on vital signs below.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine clinical laboratories (hematology, blood chemistries[3] and urinalysis) were monitored in all three studies using the new iv formulation (N01077n N01165 and N01166). Complete data for N01077 and N01165 were available in the initial submission of this NDA. Laboratory data for No1166 was in the process of being analyzed at the time of submission and was therefore not included in its entirety. These data will be available in safety update (see safety update).

Data from European studies N058, N069 and N099 were not included in the ISS discussion because, according to the Sponsor, the small number of patients and lack of clinically significant effects. This information, however, was included in the provided study reports. Clinical laboratory testing was not performed in the European studies N204 and N060.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Of the two studies for which a through database is available at the time of filling (i.e. N01077 and N01165) study N01077 is most relevant as drug treatment lasted for a period of 4 days. The tables below presents mean laboratory data from study N01077. It compares screening values for laboratories of interest with those following a four day treatment in both placebo and levetiracetam groups. The differences between these values are also presented. The final laboratory values were generally observed within 24 hours of the last iv infusion period. Examination of the selected hematology and serum chemistry values did not reveal any clinically significant differences between the placebo and treatment groups.

3 The blood chemistry evaluation was similar to an SMA 20.

Parameter (Unit) Period	Statistic	Placebo (N = 6)	LEV 1500 I.V. (N = 12)
WBC Count ($\times 10^3/\mu L$)			
Baseline	Mean ± SD	7.10 ± 2.41	5.87 ± 1.26
Final	Mean ± SD	6.38 ± 1.23	6.42 ± 1.82
	Mean Change ± SD	-0.72 ± 1.25	0.55 ± 1.76
Neutrophil Count (%)			
Baseline	Mean ± SD	57.3 ± 11.55	54.85 ± 9.35
Final	Mean ± S.D	54.52 ± 4.71	57.08 ± 9.41
	Mean Change ± SD	-2.78 ± 10.03	2.23 ± 8.81
RBC Count ($\times 10^6/\mu L$)			
Baseline	Mean ± SD	4.84 ± 0.51	4.74 ± 0.42
Final	Mean ± SD	4.64 ± 0.56	4.81 ± 0.49
	Mean Change ± SD	-0.20 ± 0.29	0.06 ± 0.26
Hemoglobin (g/dL)			
Baseline	Mean ± SD	14.80 ± 1.14	14.18 ± 1.18
Final	Mean ± SD	13.82 ± 1.61	13.93 ± 1.47
	Mean Change ± SD	-0.98 ± 0.81	-0.25 ± 0.62
Hematocrit (%)			
Baseline	Mean ± SD	43.83 ± 4.24	42.50 ± 3.22
Final	Mean ± SD	42.0 ± 5.18	42.72 ± 4.27
	Mean Change ± SD	-1.83 ± 3.01	0.22 ± 2.17
Platelet Count ($\times 10^3/\mu L$)			
Baseline	Mean ± SD	295.8 ± 66.4	279.1 ± 54.6
Final	Mean ± SD	275.7 ± 87.3	295.5 ± 86.2
	Mean Change ± SD	-20.2 ± 53.5	16.4 ± 56.1

Parameter (Unit) Period	Statistic	Placebo (N = 6)	LEV 1500 I.V. (N = 12)
AST (U/L)			
Baseline	Mean ± SD	22.8 ± 5.3	24.1 ± 5.3
Final	Mean ± SD	22.0 ± 8.2	19.0 ± 4.2
	Mean Change ± SD	-0.8 ± 5.9	-5.1 ± 4.9
ALT (U/L)			
Baseline	Mean ± SD	29.3 ± 6.6	33.1 ± 10.0
Final	Mean ± SD	32.8 ± 12.3	32.4 ± 14.3
	Mean Change ± SD	3.5 ± 10.4	-0.7 ± 9.3
Bilirubin (mg/dL)			
Baseline	Mean ± SD	0.833 ± 0.308	0.758 ± 0.211
Final	Mean ± SD	0.617 ± 0.232	0.658 ± 0.278
	Mean Change ± SD	-0.217 ± 0.354	-0.10 ± 0.217
Urea (mg/dL)			
Baseline	Mean ± SD	23.2 ± 5.6	28.7 ± 8.2
Final	Mean ± SD	28.7 ± 6.6	31.8 ± 6.0
	Mean Change ± SD	5.5 ± 6.4	3.2 ± 7.6
Creatinine (mg/dL)			
Baseline	Mean ± S.D.	0.84 ± 0.15	0.91 ± 0.18
Final	Mean ± S.D.	0.83 ± 0.14	0.91 ± 0.18
	Mean Change ± SD	-0.01 ± 0.04	0.00 ± 0.06
Sodium (mEq/L)			
Baseline	Mean ± SD	142.0 ± 1.8	142.0 ± 1.8
Final	Mean ± SD	141.7 ± 2.4	143.0 ± 2.3
	Mean Change ± SD	-0.3 ± 3.5	1.0 ± 3.0
Potassium (mEq/L)			
Baseline	Mean ± SD	4.40 ± 0.23	4.25 ± 0.24
Final	Mean ± SD	4.28 ± 0.18	4.28 ± 0.18
	Mean Change ± SD	-0.12 ± 0.26	0.02 ± 0.26

The Sponsor does not present central analysis in the ISS for study N01165. In this study clinical laboratories were performed prior to drug administration at the screening visit and within 7 days of the single dose treatment at the discharge visit. This reviewer examined original tabulated data

in the study reports which where means were calculated for patients grouped by dose/infusion-rate. A total of 6 groups were examined with 6 patients in each group (3 male and 3 female). Tabulated data included that of CBC and blood chemistry (equivalent of SMA 20). No clinically meaningful change in mean values for any group between time points was observed.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

According to the Sponsor "clinically important alterations in clinical laboratory tests did not occur" in study N01077 after 4 days of treatment with levetiracetam. This reviewer examined the tabulated outlier data and concurs. This occurred in patient 0006 who had a WBC count of 6.2 at screening and 2.5 just prior to entering phase B and after a two single doses of 1500 mg of levetiracetam (over 1 1/2 week period) during the A phase of this study. This patient went on to receive placebo for 4 days and follow up 5 days later revealed a WBC of 5.8. This rapid recovery (2.5 to 5.8 in 5 days) likely indicates a spurious value.

Tables are not presented in the ISS for laboratory outliers for study N01165. Such tables (serum chemistry, CBC and urinalysis) were found in the study report and examined by this reviewer No meaningful clinically significant laboratory changes were identified following iv treatment with levetiracetam.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

No patients in any of the studies were reported to withdraw because of abnormal laboratory values.

Although data from study N01166 has not be completely analyzed at the time of submission the Sponsor notes a platelet count of 64,000 in one patient (N001/005) at final discharge. Additional later platelet counts revealed values of 188,000 and 244,000 at 5 and 10 days post treatment, respectively. This rapid resolution suggests the low value represented a spurious result. Of note, this reviver has requested a consult from ODS because of a number of cases of thrombocytopenia identified in the post marketing database.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital sign monitoring, consisting of supine blood pressure (check if supine), heart rate and respiratory rate, is reported by the Sponsor in the two most recent studies (N01077 and N01165).

Schedule for vital sign monitoring in both studies is presented as follows:

- N01077: Supine (along with orthostatic changes) blood pressure was monitored at screening. Supine pressures were also monitored before each dose of medication and 5, 15 and 30 minutes during as well as 1 and 2 hours after infusion was initiated or oral administration was taken. Supine pressure was also obtained at follow-up.
- N01165: Supine (along with orthostatic changes) blood pressure was monitored at screening. Supine pressures were also monitored before each dose and at the end of infusion, 15 and 30 minutes after infusion was completed and 1,2 12, and 24 hours after infusion completion. Supine pressure was also obtained at follow-up.

7.1.8.3.1 Analyses focused on measures of central tendencies

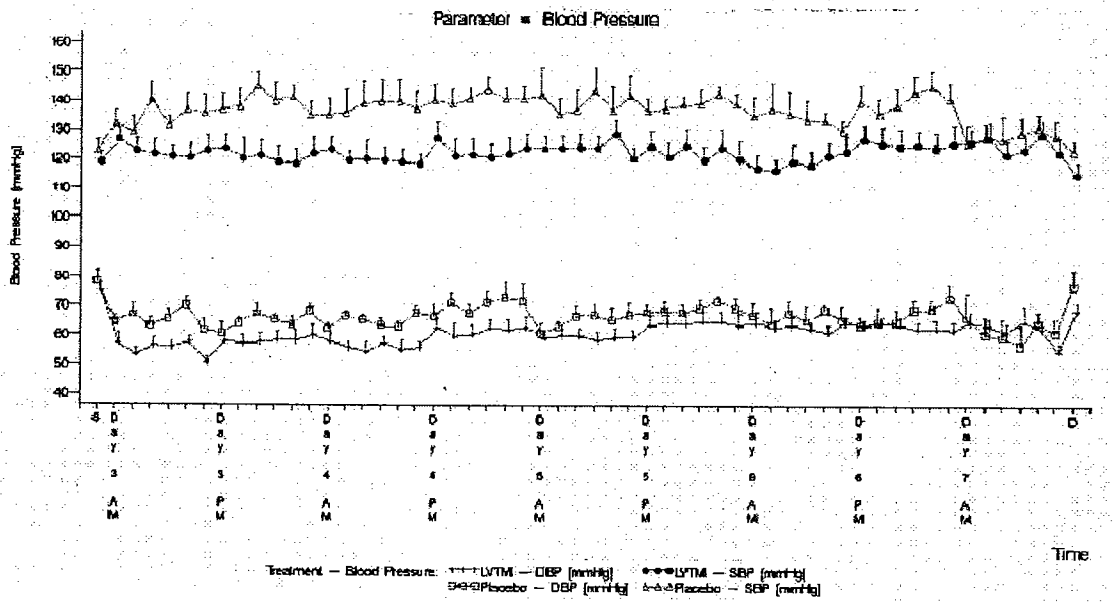
Study N01077:

The Sponsor provided an analysis of central tendency in the form of systolic and diastolic blood pressure and heart rate at screening, pre-dose and various post dose measures. These data for Part A (single dose) of the study for both iv and oral administration is presented in the table below. There are little obvious changes in diastolic blood pressure when post-dose is compared to the pre-dose baseline for both iv and oral dose. Small changes in systolic pressures were observed with intravenous and oral administration. Small mean reductions were observed 5 minutes after infusion but not after oral administration, however, similar changes were observed 1 to 2 hours after infusion was started (infusion lasted only 15 minutes). These mean changes are minimal and likely not related to drug. All changes in heart rate were minimal and unlikely to be clinically significant. Respiratory rate changes (not shown) were unremarkable.

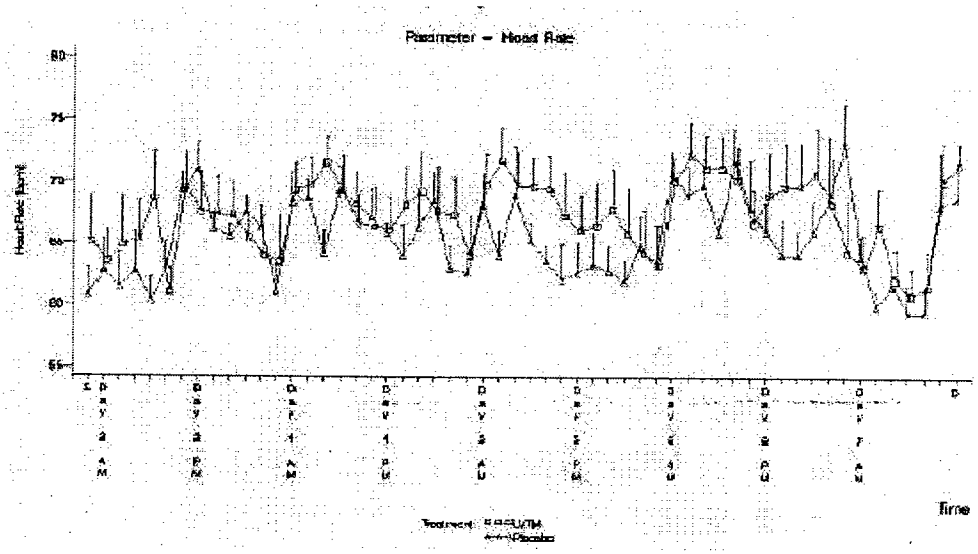
	Oral			Intravenous		
Time after infusion started (infusion as completed at post 15 min)	Systolic Mean (+SD)	Diastolic Mean (+SD)	Heart Rate Mean (+SD)	Systolic Mean (+SD)	Diastolic Mean (+SD)	Heart Rate Mean (+SD)
Screening	120.3 (11.0)	76.4 (7.0)	63.7 (10.6)	120.3 (11.0)	76.4 (7.0)	63.9 (10.6)
Pre-dose	131.5 (13.9)	64.2 (10.0)	61.9 (7.7)	131.3 (17.2)	62.4 (12.5)	64.7 (10.8)
Post 5 min	134.2 (17.1)	66.9 (8.3)	61.1 (8.2)	128.4 (16.9)	63.4 (10.0)	62.7 (9.6)
Post 15 min	130.6 (15.7)	66.0 (10.5)	60.2 (7.3)	130.4 (14.5)	62.1 (10.6)	63.6 (10.6)
Post 30 min	133.8 (14.7)	67.0 (9.7)	60.1 (7.3)	130.2 (15.20	62.9 (12.6)	61.4 (9.8)
Post 1 hour	127.2 (21.1)	62.2 (9.5)	60.6 (11.3)	125.3 (15.2)	61.2 (8.7)	64.3 (12.5)
Post 2 hour	129.5 (16.2)	60.2 (9.7)	58.5 (8.9)	124.7 (14.3)	62.8 (10.3)	61.3 (12.1)

The Sponsor presents a graph of systolic and diastolic pressures for part B of study N01077 (4 days of multiple doses of 1500 mg iv bid versus placebo). This is reproduced below. Note open symbols (square and triangle) represents placebo with other symbols representing drug. The first

point in this figure represents supine screening pressures. Subsequent points represent pre-dose and 5min, -15 min, 30 min, 1 hour and 2 hour post-infusion initiation values (infusion lasted only 15 minutes). Somewhat large swings in pressure were noted in pressures from screening to first pre-dose measures: e.g. placebo group this constituted a change from 78.2 to 64.5 and for drug 75.5 to 57.0. These changes are not related to the drug as no drug is given under both conditions. While no large swings are noted in the blood pressure measures, examination of the graph, and tabulations from which it was derived, suggested a possible small lowering of systolic and diastolic blood pressure following the initiation of drug infusion; i.e. there may be some indication of a periodicity in blood pressure changes synchronized to time of administration. This periodicity was examined closer in an analysis below.



A similar graphic representation for heart rate in phase B of this study is presented below (squares representing levetiracetam and circles representing placebo). As is apparent there was no definitive trend (periodicity) in blood pressure changes synchronized to the time of dosing.



To better examine a potential small drug induced change the Sponsor was requested to calculate the central tendency of vital signs for each time point before and after infusion during this 4 day (bid) multiple dosing phase: for example, all doses 5 minutes after the infusion was initiated was averaged together. This can be considered a signal averaging analysis. This data for drug and placebo treatments was submitted on 12/22/05 and are presented in the table below. Screening baseline pressures are presented. Changes are presented in terms of difference from the screening baseline. There was a very small tendency for a small 1-2 mmHg lowering of blood pressure for pressures (systolic and diastolic) in patients receiving levetiracetam as compared to placebo during and after drug administration when compared to pre-dose values (pre-dose – dose during or after drug administration). Comparison to screening baseline values would appear greater; however, the first pre-dose measure (see above figures) before drug administration, before, was substantially lower then screening values. The reason for this is unknown but is likely related to the fact that blood pressures obtained during screening was probably performed under different circumstances then pressures obtained during pre dose and post dose evaluations. This emphasizes the point that this analysis is useful principally in identifying small changes that may occur during the infusion period. These changes were minimal and not likely clinically relevant. No consistent heart rate changes are apparent.

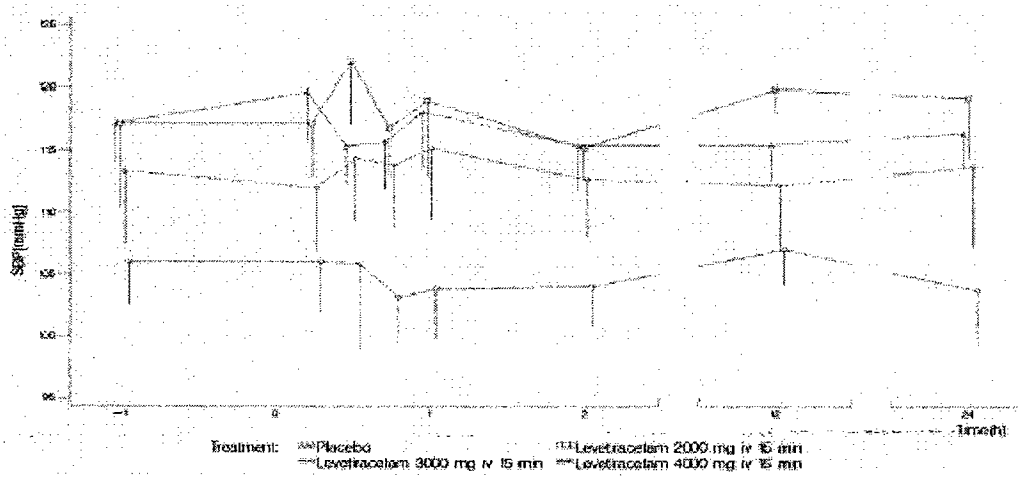
	Baseline (Screening)	Change from Baseline Post Dose [a]					
		Pre-dose	5 min	15 min	30 min	1 h	2 h
SBP Supine (mmHg)							
Placebo (N=6 subjects)							
Mean ± SD	123.0 ± 7.7	13.0 ± 16.0	11.9 ± 15.1	15.0 ± 15.1	15.2 ± 16.8	15.6 ± 14.0	13.5 ± 14.6
Median	123.0	12	11	15	11.5	16	12
Minimum	115	-13	-12	-22	-11	-22	-11
Maximum	133	64	54	48	57	56	49
Levetiracetam (N=12 subjects)							
Mean ± SD	118.9 ± 12.5	5.5 ± 9.6	3.1 ± 10.1	3.2 ± 10.7	2.3 ± 9.6	4.0 ± 11.1	3.2 ± 10.8
Median	116.0	4	1.5	2.0	1.5	4.0	2.5
Minimum	100	-16	-16	-34	-19	-24	-22
Maximum	139	32	41	28	22	33	35
DBP Supine (mmHg)							
Placebo (N=6 subjects)							
Mean ± SD	78.2 ± 8.4	-13.7 ± 10.7	-12.8 ± 8.9	-12.7 ± 7.9	-12.3 ± 9.9	-10.5 ± 8.5	-11.0 ± 10.9
Median	74.5	-14	-12	-13	-13.5	-12	-10
Minimum	70	-47	-34	-32	-48	-34	-38
Maximum	93	28	2	2	13	10	16
Levetiracetam (N=12 subjects)							
Mean ± SD	75.5 ± 6.3	-14.3 ± 9.3	-15.4 ± 9.0	-15.2 ± 8.9	-14.6 ± 8.6	-15.1 ± 9.1	-16.1 ± 9.0
Median	75.0	-14.5	-15.5	-15.	-16.5	-16	-16.5
Minimum	64	-32	-38	-39	-37	-32	-43
Maximum	85	9	5	13	26	9	5
Heart Rate Supine (mmHg)							
Placebo (N=6 subjects)							
Mean ± SD	60.8 ± 5.5	5.8± 6.7	3.7 ± 6.7	4.2 ± 7.3	4.1 ± 7.2	4.6 ± 8.5	5.3 ± 9.3
Median	60.0	6	4	3	5	4	6
Minimum	56	-8	-7	-9	-14	-13	-13
Maximum	71	19	22	22	18	33	31
Levetiracetam (N=12 subjects)							
Mean ± SD	65.2 ± 12.4	2.0 ± 12.5	3.4 ± 12.9	3.1 ± 13.4	2.6 ± 13.7	0.7 ± 13.8	1.0 ± 13.7
Median	64.5	3.0	3.5	5.0	4.0	2.0	3.0
Minimum	46	-34	-34	-36	-39	-40	-41
Maximum	93	31	40	26	44	39	32

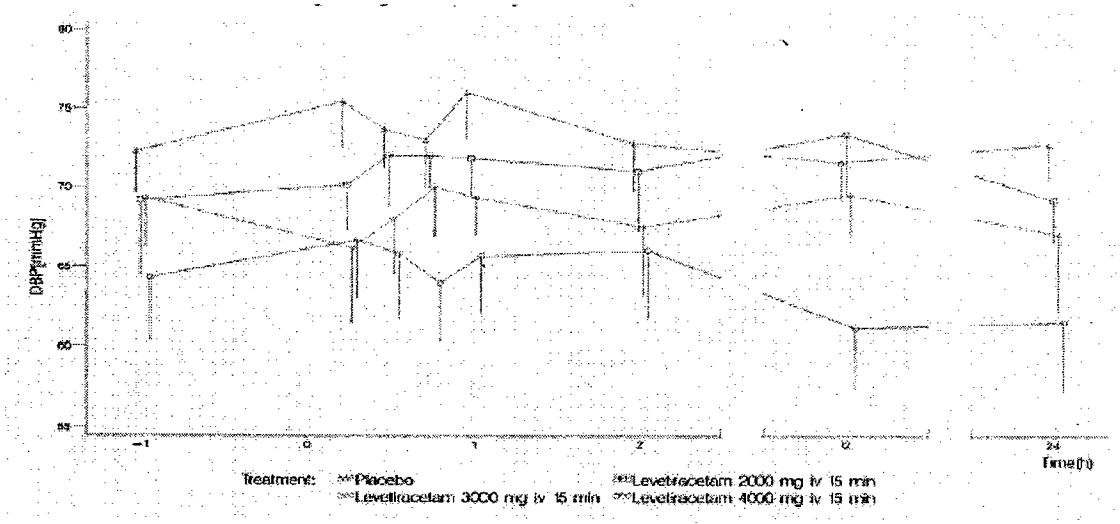
Source: CSR N01077 Table 14.3.6.1 (baseline) and new Table (change from baseline)
[a] For each time-point (except baseline), statistics are computed on all observations during multiple dosing (9 doses; n = 54 observations in placebo and n = 108 observations in levetiracetam).

Study N01165

Data for mean (± SEM) systolic blood pressures during a 15 minute infusion of placebo (triangles), 2,000 mg (squares), 3,000 mg (diamonds) and 4,000 mg (circles) is presented in the two following figures. The first figure presents data for systolic and the second for diastolic pressure changes. It should be noted that values above the abscissa point "-1" represents pre-dose measurements. The "0" value on the abscissa represents the time immediately upon infusion completion The second plotted value along the abscissa is the measurement taken 15 minutes after infusion completion Subsequent measures represent those taken after infusion over a 24 hour period. Only small erratic mean blood pressure changes are apparent. These are likely not significant. Thus, although the largest mean drop in blood pressure (approximately 4

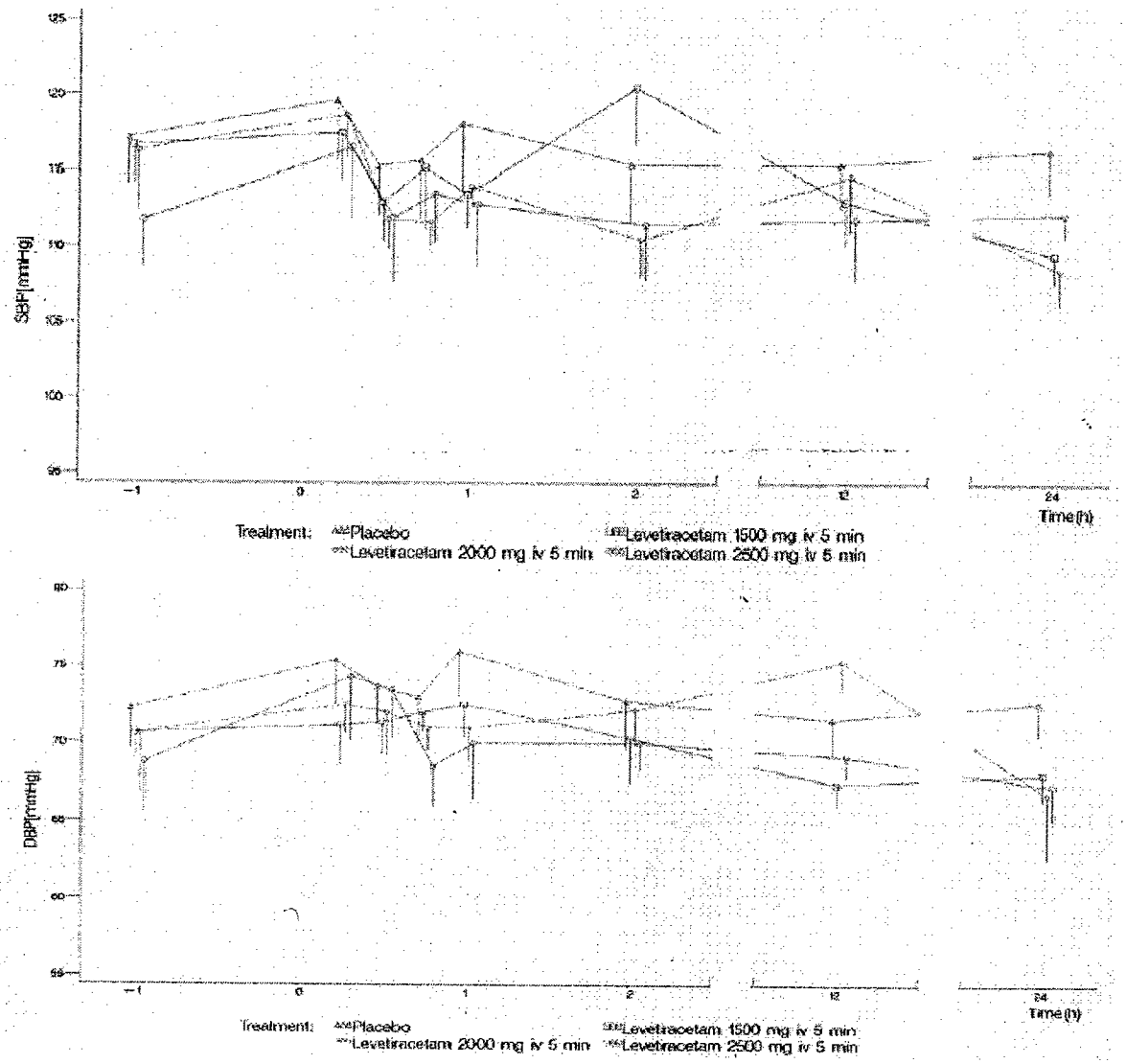
mmHg) occurs in diastolic pressure immediately after infusion of 3,000 mg and continues for about 1 hour afterward, no reduction is apparent for the similar time points at a higher dose (4,000 mg). Examination of the magnitude of effects and the standard errors does not reveal any obvious changes that are likely to be statistically significant.



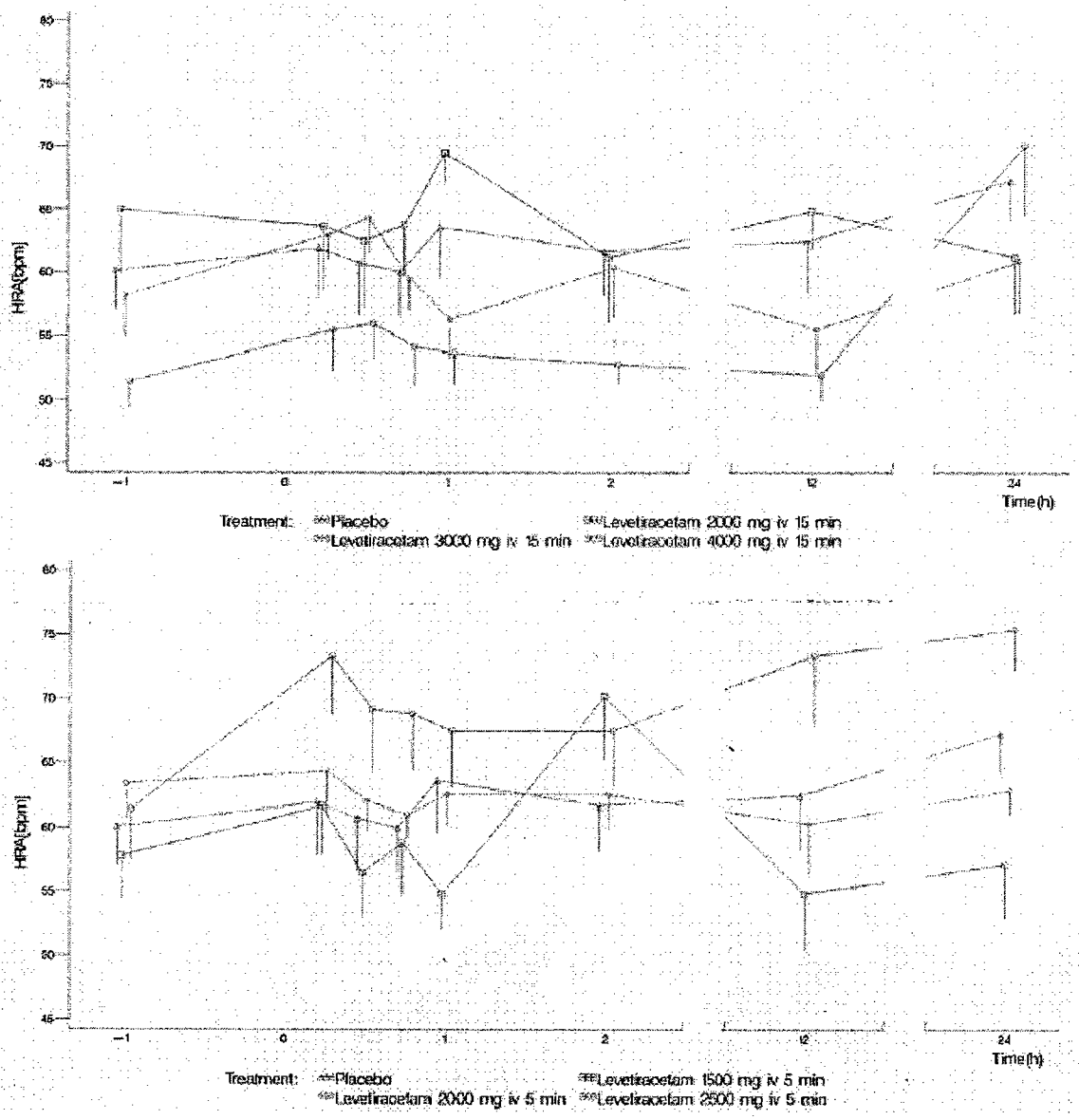


Data for mean (± SEM) systolic blood pressures during a 5 minute infusion of placebo (triangles), 1,500 mg (squares), 2,000 mg (diamonds) and 2,500 mg (circles) is presented in the two following figures. The first presents data for systolic and the second on diastolic pressure changes. The point above the abscissa has the same meaning as in the above graphs. .No meaningful changes in blood pressure can be appreciated. The most obvious pattern that can be

observed in these figures is a small (<5 mmHg) reduction in systolic blood pressure within the first hour after infusion. This however was not seen immediately after infusion and was seen in placebo as well as all levetiracetam groups. No significant changes in blood pressure can therefore be observed in these data for the rapid infusion rates.



The following two figures present an analysis of mean heart rate for the two rate of infusion (15 and 5 minutes). The graphs are in the same format as those for blood pressure that were presented above. With one exception, no obvious changes were observed. This exception occurred in the 15 min infusion of 4,000 mg at the post 24 hour time point when there was a mean rise of 15 BPM. It is very unlikely that this represents a real effect at this late time. No such effects were observed in any other group.



This reviewer would conclude that there are no obvious clinically significant alterations in blood pressure and heart rates revealed by the examination of the central tendency.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

A formal outlier analysis was not provided by the Sponsor for studies N01165 and N0177. The Sponsor, however, notes notable vital sign changes for both studies:

- Study N01077: In the multiple-dose portion of this study, 2 subjects (No. 001/0013 and 001/0014) had low systolic blood pressure measurements (= 100 mmHg). The lowest on-treatment blood pressure value for patient 001/0013, recorded in the supine position, was 85/48 mmHg, measured 2 hours following the Day 5 evening dose; this subject had repeated measurements made at screening as a result of similarly low recordings (lowest 94/33 mmHg). For 001/0014, the lowest screening recording (in a supine position) was 100/67 mmHg. The lowest on treatment measurements occurred 5 minutes following the evening dose on Day 3 (84/41 mmHg) and Day 4 (90/29 mmHg and 84/38 mmHg, retest value). Both were reported as adverse events. The patients were otherwise asymptomatic. The Sponsor argues that as these values were present at pre- and post-dose time points they are not clearly attributable to treatment. The Sponsor notes that there were no other individual clinically significant changes, including no observations of orthostatic hypotension in these patients. This reviewer generally agrees but, requested more thorough outlier analysis for all patients (see below).

- Study N01165: Subject No. 001/0016 (1500 mg/5 minutes) showed heart rate values below 50 bpm at pre-dose and at several on-treatment time points. Asymptomatic sinus bradycardia (35 bpm) was reported as an adverse event at 12 hours post-dose but was not judged as related to the study treatment by the Investigator. Blood pressure measurements were within the normal range throughout (ECG data for this patient are further described in the section on ECGs. This reviewer feels that such an isolated bradycardia, temporally distant, from the infusion is likely not caused by drug infusion. Subject No. 001/0036 (4000 mg/15 min) presented a slight decrease of the systolic blood pressure 15 minutes after the end of infusion but with low systolic blood pressure value at screening. Examination of the data sets revealed that this represented a drop in systolic blood pressure from 101 at pre-dose measurement to 88 at 15 minutes after infusion was completed. Systolic pressure at the end of infusion was 106 and 94 30 minutes after infusion. Moreover, the diastolic pressure was unchanged 15 minutes after infusion was unchanged. The heart rate was only minimally increased by 7 BPM at this time. These changes are likely not significant. This reviewer requested an outlier analysis that is presented below.

This reviewer requested an analysis of outlier data in a phone call with the Sponsor (12/13/05). These data were submitted on 12/22/05 and are discussed below.

The table below presents outlier systolic and diastolic blood pressure data for part A of study N10077 (single 1500 mg dose crossover comparison between oral and intravenous levetiracetam. The change from baseline is based upon a comparison of pre-drug screening values. This reviewer believes that comparison to the "pre-dose" values would have been better, but this problem may be offsite by comparing incidences occurring after infusion was initiated with those

of pre-dose, which is included in this table. As can be observed there does not appear to be any obvious increases pressures: i.e. distribution of outlier increases in systolic and diastolic are similar between pre- and post-dose period for oral and intravenous formulations . Outlier decrease in systolic blood pressure was a bit more common following levetiracetam then during the pre-dose period, but there were few instances that blood pressure was decreased by >20 mm Hg and such decreases exclusively occurred in the tablet formulation. Reductions in diastolic pressures were much more common then systolic decreases but were similar between pre- and post-dose measures and therefore not strongly related to drug. These reductions were generally similar with oral and intravenous formulations. These data suggest no significant drug related alterations in blood pressure in general and specifically with intravenous treatment.

	Change from Baseline Post Dose					
SBP Supine (mmHg)	**Pre-dose n (%)**	**5 min n (%)**	**15 min n (%)**	**30 min n (%)**	**1 h n (%)**	**2 h n (%)**
Tablet (N=18)						
Decrease: ≤ -30	0	0	0	0	0	0
Decrease: -29 to -20	0	0	0	0	1 (6%)	1 (6%)
Decrease: -19 to -10	0	0	3 (17%)	0	2 (11%)	1 (6%)
Normal (-9 to 9)	8 (44%)	7 (39%)	5 (28%)	8 (44%)	5 (28%)	7 (39%)
Increase: 10-19	7 (39%)	7 (39%)	7 (39%)	7 (39%)	6 (33%)	7 (39%)
Increase: 20-29	2 (11%)	2 (11%)	0	1 (6%)	3 (17%)	0
Increase: ≥ 30	1 (6%)	2 (11%)	3 (17%)	2 (11%)	1 (6%)	2 (11%)
Intravenous (N=18)						
Decrease: ≤ -30	0	0	0	0	0	0
Decrease: -29 to -20	0	0	0	0	0	0
Decrease: -19 to -10	1 (6%)	2 (11%)	0	0	1 (6%)	1 (6%)
Normal (-9 to 9)	5 (28%)	7 (39%)	10 (56%)	9 (50%)	11 (61%)	14 (78%)
Increase: 10-19	8 (44%)	7 (39%)	6 (33%)	6 (33%)	4 (22%)	1 (6%)
Increase: 20-29	3 (17%)	1 (6%)	1 (6%)	2 (11%)	1 (6%)	2 (11%)
Increase: ≥ 30	1 (6%)	1 (6%)	1 (6%)	1 (6%)	1 (6%)	0
DBP Supine (mmHg)						
Tablet (N=18)						
Decrease: ≤ -30	1 (6%)	1 (6%)	2 (11%)	0	0	2 (11%)
Decrease: -29 to -20	4 (22%)	2 (11%)	1 (6%)	3 (17%)	6 (33%)	3 (17%)
Decrease: -19 to -10	6 (33%)	5 (28%)	6 (33%)	6 (33%)	7 (39%)	6 (33%)
Normal (-9 to 9)	7 (39%)	10 (56%)	9 (50%)	9 (50%)	4 (22%)	7 (39%)
Increase: 10-19	0	0	0	0	1 (	0
Increase: 20-29	0	0	0	0	6%) 0	0
Increase: ≥ 30	0	0	0	0	0	0
Intravenous (N=18)						
Decrease: ≤ -30	1 (6%)	0	0	1 (6%)	0	0
Decrease: -29 to -20	8 (44%)	6 (33%)	5 (28%)	5 (28%)	4 (22%)	6 (33%)
Decrease: -19 to -10	3 (17%)	6 (33%)	8 (44%)	5 (28%)	11 (61%)	7 (39%)
Normal (-9 to 9)	6 (33%)	6 (33%)	5 (28%)	7 (39%)	3 (17%)	5 (28%)
Increase: 10-19	0	0	0	0	0	0
Increase: 20-29	0	0	0	0	0	0
Increase: ≥ 30	0	0	0	0	0	0

Note: Percentages computed by time-point.

Outlier data for phase B (4 day multiple dosing) is presented in the table below. The table is similar to that above except comparisons are between intravenous levetiracetam and intravenous

placebo administration. There is no preponderance of increase or decrease outliers with levetiracetam then with placebo. If anything there were fewer of outliers in both directions with drug. With regard to diastolic pressures, there was a slight preponderance of outliers with blood pressure reductions between 20 and 29 mmHg in the levetiracetam group, but these were not observed to occur during intravenous administration (5 and 15 minutes) and similar rates were observed at pre-dose measure. This indicates that reduction may not be clinically significant.

	Change from Baseline Post Dose					
SBP Supine (mmHg)	**Pre-dose n (%)**	**5 min n (%)**	**15 min n (%)**	**30 min n (%)**	**1 h n (%)**	**2 h n (%)**
Placebo (N=6) (a)						
Decrease: ≤ -30	0	0	0	0	0	0
Decrease: -29 to -20	0	0	1 (2%)	0	1 (2%)	0
Decrease: -19 to -10	2 (4%)	5 (9%)	2 (4%)	1 (2%)	0	1 (2%)
Normal (-9 to 9)	21 (39%)	16 (30%)	13 (25%)	21 (39%)	16 (30%)	22 (42%)
Increase: 10-19	19 (35%)	20 (38%)	21 (40%)	14 (26%)	22 (41%)	14 (26%)
Increase: 20-29	6 (11%)	5 (9%)	8 (15%)	10 (19%)	8 (15%)	8 (15%)
Increase: ≥ 30	6 (11%)	7 (13%)	8 (. 15%)	8 (15%)	7 (13%)	8 (15%)
Levetiracetam (N=12) [a]						
Decrease: ≤ -30	0	0	1 (1%)	0	0	0
Decrease: -29 to -20	0	0	0	0	2 (2%)	2 (2%)
Decrease: -19 to -10	4 (4%)	8 (7%)	9 (8%)	12 (11%)	12 (11%)	6 (6%)
Normal (-9 to 9)	73 (68%)	76 (70%)	66 (62%)	68 (63%)	58 (54%)	77 (71%)
Increase: 10-19	24 (22%)	16 (15%)	24 (22%)	25 (23%)	26 (24%)	13 (12%)
Increase: 20-29	5 (5%)	7 (6%)	7 (7%)	3 (3%)	9 (8%)	8 (7%)
Increase: ≥ 30	2 (2%)	1 (1%)	0	0	1 (1%)	2 (2%)
DBP Supine (mmHg)						
Placebo (N=6) (a)						
Decrease: ≤ -30	2 (4%)	2 (4%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Decrease: -29 to -20	11 (20%)	9 (17%)	8 (15%)	7 (13%)	6 (11%)	11 (21%)
Decrease: -19 to -10	26 (48%)	24 (45%)	27 (51%)	30 (56%)	23 (43%)	16 (30%)
Normal (-9 to 9)	14 (26%)	18 (34%)	17 (32%)	15 (28%)	23 (43%)	23 (43%)
Increase: 10-19	0	0	0	1 (2%)	1 (2%)	1 (2%)
Increase: 20-29	1 (2%)	0	0	0	0	0
Increase: ≥ 30	0	0	0	0	0	0
Levetiracetam (N=12) [a]						
Decrease: ≤ -30	4 (4%)	6 (6%)	6 (6%)	1 (1%)	5 (5%)	5 (5%)
Decrease: -29 to -20	27 (25%)	30 (28%)	27 (25%)	28 (26%)	29 (27%)	39 (36%)
Decrease: -19 to -10	45 (42%)	46 (43%)	52 (49%)	55 (51%)	45 (42%)	38 (35%)
Normal (-9 to 9)	32 (30%)	26 (24%)	21 (20%)	23 (21%)	29 (27%)	26 (24%)
Increase: 10-19	0	0	1 (1%)	0	0	0
Increase: 20-29	0	0	0	1 (1%)	0	0
Increase: ≥ 30	0	0	0	0	0	0

[a] For each time-point, frequencies are computed on all observations during multiple dosing (9 doses; n = max. 54 observations in placebo and n = max. 108 observations in levetiracetam).
Note: Percentages computed by time-point.

Heart rate outlier data is presented for phase A (first table) and phase B (second table) of study N1077. No obvious differences in the distribution of outliers are observed between tablet and intravenous administration phase A. There was a small tendency for a wider spread of outliers in phase B in the levetiracetam group compared to placebo. That is, a greater number of outliers with both increases and decreases were observed. The significance of this spread is unknown,

but as it was observed throughout the study (i.e. pre-dose and after infusion is completed) it is likely not related to the infusion.

	Change from Baseline Post Dose					
Heart Rate Supine (bpm)	**Pre-dose n (%)**	**5 min n (%)**	**15 min n (%)**	**30 min n (%)**	**1 h n (%)**	**2 h n (%)**
Tablet (N=18)						
Decrease: ≤ -30	0	0	0	0	1 (6%)	1 (6%)
Decrease: -29 to -15	1 (6%)	2 (11%)	2 (11%)	2 (11%)	1 (6%)	2 (11%)
Normal (-14 to 14)	16 (89%)	16 (89%)	16 (89%)	16 (89%)	15 (83%)	15 (83%)
Increase: 15-29	1 (6%)	0	0	0	0	0
Increase: ≥ 30	0	0	0	0	1 (6%)	0
Intravenous (N=18)						
Decrease: ≤ -30	0	0	1 (6%)	1 (6%)	1 (6%)	1 (6%)
Decrease: -29 to -15	1 (6%)	2 (11%)	0	1 (6%)	1 (6%)	1 (6%)
Normal (-14 to 14)	15 (83%)	15 (83%)	16 (89%)	16 (89%)	13 (72%)	14 (78%)
Increase: 15-29	2 (11%)	1 (6%)	1 (6%)	0	3 (17%)	2 (11%)
Increase: ≥ 30	0	0	0	0	0	0

Note: Percentages computed by time-point.

	Change from Baseline Post Dose					
Heart Rate Supine (bpm)	**Pre-dose n (%)**	**5 min n (%)**	**15 min n (%)**	**30 min n (%)**	**1 h n (%)**	**2 h n (%)**
Placebo (N=6) [a]						
Decrease: ≤ -30	0	0	0	0	0	0
Decrease: -29 to -15	0	0	0	0	0	0
Normal (-14 to 14)	48 (89%)	49 (92%)	46 (87%)	50 (93%)	48 (89%)	45 (85%)
Increase: 15-29	6 (11%)	4 (8%)	7 (13%)	4 (7%)	5 (9%)	7 (13%)
Increase: ≥ 30	0	0	0	0	1 (2%)	1 (2%)
Levetiracetam (N =12) [a]						
Decrease: ≤ -30	2 (2%)	3 (3%)	3 (3%)	3 (3%)	3 (3%)	5 (5%)
Decrease: -29 to -15	6 (6%)	5 (5%)	7 (7%)	5 (5%)	10 (9%)	5 (5%)
Normal (-14 to 14)	86 (80%)	83 (77%)	77 (72%)	84 (79%)	81 (75%)	82 (76%)
Increase: 15-29	13 (12%)	15 (14%)	20 (19%)	14 (13%)	13 (12%)	15 (14%)
Increase: ≥ 30	1 (1%)	2 (2%)	0	2 (2%)	1 (1%)	1 (1%)

[a] For each time-point, frequencies are computed on all observations during multiple dosing (9 doses; n = max. 54 observations in placebo and n = max. 108 observations in levetiracetam).
Note: Percentages computed by time-point.

Requested outlier data from the Sponsor's submission (12/22/05) for study N01165 are presented in the tables below. All infusion rates and doses are combined in this table. No systolic or diastolic blood pressure decreases >20 mmHg were observed in any group. In general, table below shows no obvious significant difference between placebo and drug treatments with regards to reductions or increases in systolic or diastolic blood pressure immediately after the completion of infusion and during the subsequent 24 hours.

	Change from Pre-dose at following Time-point						
SBP Supine (mmHg)	**end of infusion n (%)**	**15 min after end of infusion n (%)**	**30 min after end of infusion n (%)**	**1 h n (%)**	**2 h n (%)**	**12 h n (%)**	**24 h n (%)**
Placebo (N=12)							
Decrease: ≤ -30	0	0	0	1 (8%)	0	0	0
Decrease: -29 to -20	0	1 (8%)	1 (8%)	0	0	0	0
Decrease: -19 to -10	0	0	1 (8%)	0	1 (8%)	3 (25%)	3 (25%)
Normal (-9 to 9)	11 (92%)	11 (92%)	9 (75%)	10 (83%)	11 (92%)	8 (67%)	7 (58%)
Increase: 10-19	1 (8%)	0	1 (8%)	1 (8%)	0	1 (8%)	2 (17%)
Increase: 20-29	0	0	0	0	0	0	0
Increase: ≥ 30	0	0	0	0	0	0	0
Levetiracetam Intravenous (N=36) all doses and duration of infusion							
Decrease: ≤ -30	0	0	0	0	0	0	0
Decrease: -29 to -20	0	0	0	0	0	0	0
Decrease: -19 to -10	2 (6%)	5 (14%)	3 (9%)	3 (9%)	6 (17%)	2 (6%)	6 (18%)
Normal (-9 to 9)	29 (83%)	27 (77%)	30 (86%)	28 (80%)	25 (71%)	30 (86%)	27 (79%)
Increase: 10-19	4 (11%)	2 (6%)	2 (6%)	3 (9%)	4 (11%)	2 (6%)	1 (3%)
Increase: 20-29	0	1 (3%)	0	1 (3%)	0	1 (3%)	0
Increase: ≥ 30	0	0	0	0	0	0	0
DBP Supine (mmHg)							
Placebo (N=12)							
Decrease: ≤ -30	0	0	0	0	0	0	0
Decrease: -29 to -20	0	0	0	0	0	0	0
Decrease: -19 to -10	0	0	1 (8%)	1 (8%)	1 (8%)	0	0
Normal (-9 to 9)	11 (92%)	12 (100%)	10 (83%)	9 (75%)	10 (83%)	12 (100%)	12 (100%)
Increase: 10-19	1 (8%)	0	1 (8%)	1 (8%)	1 (8%)	0	0
Increase: 20-29	0	0	0	1 (8%)	0	0	0
Increase: ≥ 30	0	0	0	0	0	0	0
Levetiracetam Intravenous (N=36) all doses and duration of infusion							
Decrease: ≤ -30	0	0	0	0	0	0	0
Decrease: -29 to -20	0	0	0	0	0	0	0
Decrease: -19 to -10	1 (3%)	1 (3%)	0	0	1 (3%)	1 (3%)	4 (12%)
Normal (-9 to 9)	30 (86%)	32 (91%)	31 (89%)	33 (94%)	31 (89%)	30 (86%)	28 (82%)
Increase: 10-19	3 (9%)	0	4 (11%)	2 (6%)	3 (9%)	2 (6%)	2 (6%)
Increase: 20-29	1 (3%)	2 (6%)	0	0	0	2 (6%)	0
Increase: ≥ 30	0	0	0	0	0	0	0

Note: Percentages computed by time-point.

Outlier heart rate data for study N01165 is presented in the table below. As apparent no obvious significant difference is apparent between placebo and levetiracetam treated groups.

	Change from Pre-dose at following Time-point						
Heart Rate Supine (bpm)	**end of infusion n (%)**	**15 min after end of infusion n (%)**	**30 min after end of infusion n (%)**	**1 h n (%)**	**2 h n (%)**	**12 h n (%)**	**24 h n (%)**
Placebo (N=12)							
Decrease: ≤ -30	0	0	0	0	0	0	0
Decrease: -29 to -15	0	0	0	0	0	0	0
Normal (-14 to 14)	12 (100%)	12 (100%)	12 (100%)	11 (92%)	12 (100%)	11 (92%)	9 (75%)
Increase: 15-29	0	0	0	1 (8%)	0	1 (8%)	3 (25%)
Increase: ≥ 30	0	0	0	0	0	0	0
Levetiracetam Intravenous (N=36) all doses and duration of infusion							
Decrease: ≤ -30	0	0	0	0	0	0	0
Decrease: -29 to -15	0	0	0	0	0	0	0
Normal (-14 to 14)	33 (94%)	34 (97%)	35 (100%)	34 (97%)	33 (94%)	34 (97%)	29 (85%)
Increase: 15-29	2 (6%)	1 (3%)	0	1 (3%)	1 (3%)	1 (3%)	4 (12%)
Increase: ≥ 30	0	0	0	0	1 (3%)	0	1 (3%)

Note: Percentages computed by time-point.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

The Sponsor presents data, previously submitted and presumably reviewed in the original NDA that indicated that oral levetiracetam is without a significant effect on blood pressure or heart rate. Data is also presented that indicates levetiracetam does not produce orthostatic changes in blood pressure.

7.1.9 Electrocardiograms (ECGs)

Twelve lead EKGs were performed and data presented, for the two principal studies (N01077 N01165). Measurements were made with the subject in a supine position after a 5-minute rest. Ventricular rate and PR, QRS, QT, and QTc (Bazett's correction) analysis was performed.

With regard to QTc evaluation, these studies need to be interpreted with caution as they were not designed according to recommended guidelines (e.g. positive controls, inadequately powered, multiple baseline data points were only obtained for only study N01065, etc). These data can only serve as a rough guide to determine a possibility of an obvious effect.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Study N01077: EKG evaluations were performed with each dose in phase A and B at the following time points: pre-dose and at 5, 15, 30, 60, and 120 minutes after infusion was initiated (infusion duration was 15 minutes). Single EKG record were analyzed for each data point

In Study N01165: EKG evaluations were performed pre-dose, at the end of infusion, and 15 minutes and 30 minutes after the end of infusion, 1 hour, 2 hours, 12 hours, and 24 hours post-dose or more frequently if necessary. Single EKGs were analyzed for each data point except for the pre-dose measurement where 3 EKGs were averaged fro the QTc evaluation.

It is noteworthy that the Sponsor was requested to provide a formal QT study according to the ICH guidelines as part of a prior phase 4 commitment. This study is presently under development.

7.1.9.3.1 Analyses focused on measures of central tendency

1.1.1.1.2.3.1 QT interval Analysis

Study N01077:

The Sponsor presented Bazett's correction for QT interval (QTcB) for part A (single dose) of this study in the table below. As apparent there were no mean increases in the duration corrected QT interval for levetiracetam when it was administered by an oral or intravenous route when compared to baseline screening values.

QTc (msec)	Baseline (Screening)	Change from Baseline Post Dose				
		5 min	15 min	30 min	1 h	2 h
Tablet (N=18)						
Mean ± SD	407.5 ± 17.4	-0.5 ± 18.1	0.1 ± 20.2	-5.2 ± 19.2	-0.7 ± 21.7	-6.2 ± 17.1
Median	409.0	5.5	2.5	-1.0	3.5	-3.0
Minimum	368	-34	-41	-47	-48	-57
Maximum	445	23	37	17	35	16
Intravenous (N=18)						
Mean ± SD	407.5 ± 17.4	1.2 ± 16.64	-1.1 ± 16.8	-2.7 ± 12.6	-0.9 ± 14.3	-1.9 ± 17.7
Median	409.0	4.5	-1.5	-1.0	-3.5	-0.5
Minimum	368	-30	-32	-25	-21	-49
Maximum	445	25	30	21	25	36

Although not included in the ISS the Sponsor was requested, in a series of telecoms (12/13/05 to 12/19/05), to provide a Fridericia's correction of the QT interval (QTcF). Data for phase A of N01077 were included as a response to these communications (12/21/05) and provided in the

table below. No clinically significant mean change in the QTcF is apparent from this table; i.e. the longest mean prolongation was 1.1 msec with either form of administration. Note the Sponsor provided a comparison based upon the screening baseline. This reviewer feels that the pre-dose baseline would be a more accurate measure for a baseline comparison as it was performed the same day. Information provided by the Sponsor (see Appendix B) allowed this reviewer to obtain an estimation of the mean change based upon the pre-dose baseline value. In this case there was a 3.2 to 5.1 msec shortening of the QTcF interval with a 4.7 msec shorting occurring upon infusion completion (i.e. 15 minute time point). These data do not suggest significant prolongation with the intravenous formulation.

QTcF (msec)	Baseline (Screening)	Change from Baseline Post Dose				
		5 min	15 min	30 min	1 h	2 h
Tablet (N=18)						
Mean ± SD	406.3 ± 17.7	0.1 ± 15.3	0.5 ± 15.8	-1.8 ± 16.4	2.8 ± 18.6	-0.8 ± 14.7
Median	405.4	0.7	1.1	-1.4	-0.3	-2.4
Minimum	370	-31	-35	-33	-42	-47
Maximum	451	19	22	25	39	16
Intravenous (N=18)						
Mean ± SD	406.3 ± 17.7	-0.6 ± 15.2	0.9 ± 16.7	-0.2 ± 13.8	1.3 ± 13.1	1.1 ± 17.4
Median	405.4	-2.5	3.0	-2.8	1.4	6.1
Minimum	370	-29	-33	-28	-27	-40
Maximum	451	22	29	21	27	22

The Bazett's corrected QTc for phase B of this study is presented in the table below. Here again there was no time point where a mean of greater then 5 msec was observed. However, QTcB changes of drug group relative to placebo (placebo-drug) at the time points 5 and 30 minutes post infusion (5 min after 15 min infusion was initiated and 15 minutes after its completion) revealed a prolongation greater then 5 msec extension. This QT extension needs to be interpreted with caution as other time points, where drug exposure is likely to be greater (e.g. 15 minutes) did not show an effect of similar magnitude. To this reviewer these data cannot be interpreted as suggesting a QT prolongation. This is a small study (6 placebo and 12 drug) that does not follow normally accepted guidelines for QT study analysis. With such a study only consistent large effects would be interpretable. This reviewer does not believe that these data suggest a significant drug induced prolongation of the QT interval.

QTc (msec)	Baseline (Screening)	Change from Baseline Following the Final Dose				
		5 min	15 min	30 min	1 h	2 h
Placebo (N = 6)						
Mean ± SD	412.5 ± 14.0	-9.7 ± 20.3	-9.7 ± 12.8	-14.2 ± 15.8	-4.7 ± 18.3	-4.0 ± 21.2
Median	413	-3.5	-9.0	-12.0	-1.0	-3.0
Minimum	394	-42	-26	-41	-31	-27
Maximum	428	14	4	6	21	27
Levetiracetam 1500 mg (N = 12)						
Mean ± SD	405.0 ± 18.9	-1.4 ± 10.9 [a]	-6.4 ± 14.1	-5.9 ± 10.9	-1.3 ± 12.6	-2.8 ± 19.5
Median	406.0	1.0	-6.0	-6	-3.5	-3.5
Minimum	368	-20	-34	-21	-19	-32
Maximum	445	14	22	20	21	29

The analysis of the QTcF provided on 12/21/05 is presented in the table below. These data are similar to that of the QTcB with no absolute prolongations but with some values of prolongations relative to placebo being greater then 5 msec. The same cautions in interpretation of this data are indicated as noted above.

QTcF (msec)	**Baseline (Screening)**	**Change from Baseline Following the Final Dose**				
		5 min	**15 min**	**30 min**	**1 h**	**2 h**
Placebo (N = 6)						
Mean ± SD	411.9 ± 12.4	-9.5 ± 16.4	-10.5 ± 12.6	-14.4 ± 15.9	-4.6 ± 17.0	-13.9 ± 13.5
Median	409.9	-7.4	-5.5	-13.9	-3.7	-11.5
Minimum	397	-38	-30	-42	-35	-35
Maximum	431	11	3	1	18	-2
Levetiracetam 1500 mg (N = 12)						
Mean ± SD	403.5 ± 19.7	-3.6 ± 11.1[a]	-7.0 ± 15.6	-5.2 ± 11.2	-1.6 ± 12.6	-9.7 ± 14.9
Median	401.4	-0.2	-7.1	-5.6	-2.1	-7.2
Minimum	370	-26	-39	-27	-22	-36
Maximum	451	10	14	14	21	16

Source: CSR N01077 Table 14.3.6.3 (baseline) and Table 14.3.6.4 (change from baseline): at last dosing day.
[a] N = 11

Study N01165

The Sponsor notes that "no relevant modifications were observed in the ECG parameters." The Sponsor was asked to provide more specific tabulated data on alterations in QTcF alterations which are presented in the table below. The analysis derives a single mean for all patients studied in the increased dose and increased infusion rate groups. No absolute increased mean QTcF values were greater then 5 msec. When compared to change from placebo (placebo-drug) two values exhibited a greater then 5 msec prolongation; values at post 2 hour and post 24 hours. This reviewer feels that this borderline effect does not indicate a QTcF prolongation. It seems more likely related to the small size of the placebo group and a subsequent sampling error.

	n	Mean (±SD) Baseline QTcF (msec)	Mean (± SD) Change from Pre-Dose Control (msec)						
			End of infusion	15 min post-infusion end	30 min post-infusion end	1 h post-infusion end	2 h post-infusion end	12 h post-infusion end	24 h post-infusion end
Placebo	12	387.3 (13.5)	2.6 (6.8)	-0.4 (8.2)	-1.5 (7.1)	-2.2 (8.4)	-8.6 (10.1)	1.3 (10.6)	-7.7 (8.6)
Levetiracetam	36	392.4 (12.9)	0.7 (9.0)	-0.3 (6.4)	2.2 (8.0)	-1.1 (10.0)	-0.2 (8.7)	1.9 (8.7)	-2.6 (7.6)

1.1.1.1.2.3.2 Other interval and segment analysis

An analysis of central tendency for PR interval, QRS segment as well as ventricular rates in studies N01077 and N01165 was not provided in the ISS. This was requested by this reviewer and was subsequently provided in the 12/22/05 submission. These can be found in Appendix B of this review. No obvious trends associated with intravenous administration are apparent.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The Sponsor did not perform a formal outlier analysis for EKG parameters, but presented information on a number of EKGs that may have been clinically remarkable. These cases are presented in this section. This reviewer requested a formal outlier analysis of the QTcF. This analysis is presented in the section on "marked outliers."

Study N01077

The Sponsor did not perform a formal outlier examination for QTc but notes with regard to the QTcB that: "Three of 18 subjects had single isolated recordings >450 msec (Subjects 001/0006, 001/0010, and 001/0011); the longest of the values was 461 msec." These changes do not seem remarkable in nature.

Stuy01165:

The Sponsor notes that EKG abnormalities in two patients were determined to be "clinically significant." These are described as follows:

- Subject No. 001/0016 (41.4-year old male, 1500 mg/5 minutes) exhibited heart rates below 50 bpm at screening (49 bpm) and during the study (range 42 to 40 from the end of the infusion to 24 hours post-dose). Twelve hours post-dose, a heart rate of 35 bpm was reported as clinically significant sinus bradycardia; the subject was asymptomatic. Blood pressure measurements were within the normal range throughout. Moreover, this subject had prolongation of the QRS interval at 24 hours post-dose (128 msec), but the QRS interval was already prolonged at screening (=109 msec). With these abnormalities existing prior to drug it is difficult to attribute them to treatment.
- Subject No. 001/0032 (38.4-year old female, 3000 mg/15 minutes) exhibited first degree atrioventricular block reported as an adverse event during the treatment period. She had a slight prolongation of PR interval at baseline (screening 200 msec with heart rate 61 bpm;

pre-dose 205 msec with heart rate 57 bpm), with a maximum prolongation of PR interval to 239 msec (heart rate 56 bpm) at 1 hour post-dose. The PR interval prolongation was also present at discharge (220 msec with heart rate 62 bpm). The subject was asymptomatic. This single isolated heart block, which tends to be a benign rhythm disturbance, cannot be attributed to drug. Supporting this is that no consistent lengthening of the PR interval is apparent in the central tendency analysis included in Appendix B for this study

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

As noted above, in communications with the Sponsor, this reviewer requested an outlier analysis of QTcF intervals for study N01077 and N01165. None were provided in the original ISS. These were subsequently included in the submission sent by the Sponsor on 12/22/05.

Data for part A of study N01077 are presented in the table below. Change is presented in relation to screening values and not pre-dose value. These data do not indicate any significant changes from screening baseline >30 for intravenous formulation and only one for the tablet ((30-60 msec) following administration. These changes do not suggest a prolongation in the QTc interval.

	Change from Baseline Post Dose					
QTcF (ms)	Pre-dose n (%)	5 min n (%)	15 min n (%)	30 min n (%)	1 h n (%)	2 h n (%)
Tablet (N=18)						
Normal (< 30 ms)	17 (94 %)	18 (100%)	18 (100%)	18 (100%)	17 (94 %)	18 (100%)
30-60 ms	1 (6%)	0	0	0	1 (6%)	0
> 60 ms	0	0	0	0	0	0
Intravenous (N=18)						
Normal (< 30 ms)	18 (100%)	18 (100%)	18 (100%)	18 (100%)	18 (100%)	18 (100%)
30-60 ms	0	0	0	0	0	0
> 60 ms	0	0	0	0	0	0

Outlier QTcF data for phase B of study N01077(4day multiple bid dosing) are presented in the table below. Changes are calculated from baseline screening values. Only 2 of 108 observations in the drug group exhibited a QTcF prolongation of 30-60 msec. Both observations were made at 15 minutes post-dose; i.e. at infusion completion. Two observations, 1 at pre-dose and 1 at 5 minutes following the initiation of infusion, out of 54 total observations where observed in the placebo group. Thus, there is little difference in incidences of such events between placebo and drug groups suggesting a lack of significant prolongation of the QTc by intravenous levetiracetam.

QTcF (ms)	Change from Baseline Post Dose					
	Pre-dose n (%)	5 min n (%)	15 min n (%)	30 min n (%)	1 h n (%)	2 h n (%)
Placebo (N=6 subjects; n = 54 obs. Max by time-point)						
Normal (< 30 ms)	53 (98%)	53 (98%)	52 (100%)	54 (100%)	53 (100%)	52 (100%)
30-60 ms	1 (2%)	1 (2%)	0	0	0	0
> 60 ms	0	0	0	0	0	0
Levetiracetam Intravenous (N=12 subjects; n = 108 obs. Max by time-point)						
Normal (< 30 ms)	108 (100%)	106 (100%)	105 (98%)	108 (100%)	108 (100%)	104 (100%)
30-60 ms	0	0	2 (2%)	0	0	0
> 60 ms	0	0	0	0	0	0

Outlier QTcF data for study N01165 (high dose/rapid infusion rate study) are presented in the table below. QTcF prolongation is calculated based upon pre-dose control. All data from various rates and doses are combined and grouped as per the time after infusion. There where no QTcF prolongations in the placebo group that where >30 msec. Only 2 values where noted to be prolonged by 30-60 msec in the levetiracetam treatment groups. These occurred well after infusion was completed (1 and 2 hours post infusion). No prolongations of >60 msec were noted. These data do not suggest a significant prolongation of the QT interval by intravenous levetiracetam treatment.

QTcF (ms)	Change from Pre-dose at following Time-point						
	end of infusion n (%)	15 min after end of infusion n (%)	30 min after end of infusion n (%)	1 h n (%)	2 h n (%)	12 h n (%)	24 h n (%)
Placebo (N=12)							
Normal (< 30 ms)	12 (100 %)	12 (100 %)	12 (100 %)	12 (100 %)	12 (100 %)	12 (100 %)	12 (100 %)
30-60 ms	0	0	0	0	0	0	0
> 60 ms	0	0	0	0	0	0	0
Levetiracetam Intravenous (N=36) all doses and duration of infusion							
Normal (< 30 ms)	36 (100%)	36 (100%)	36 (100%)	35 (97%)	35 (97%)	36 (100%)	36 (100%)
30-60 ms	0	0	0	1 (3%)	1 (3%)	0	0
> 60 ms	0	0	0	0	0	0	0

7.1.9.4 Additional analyses and explorations

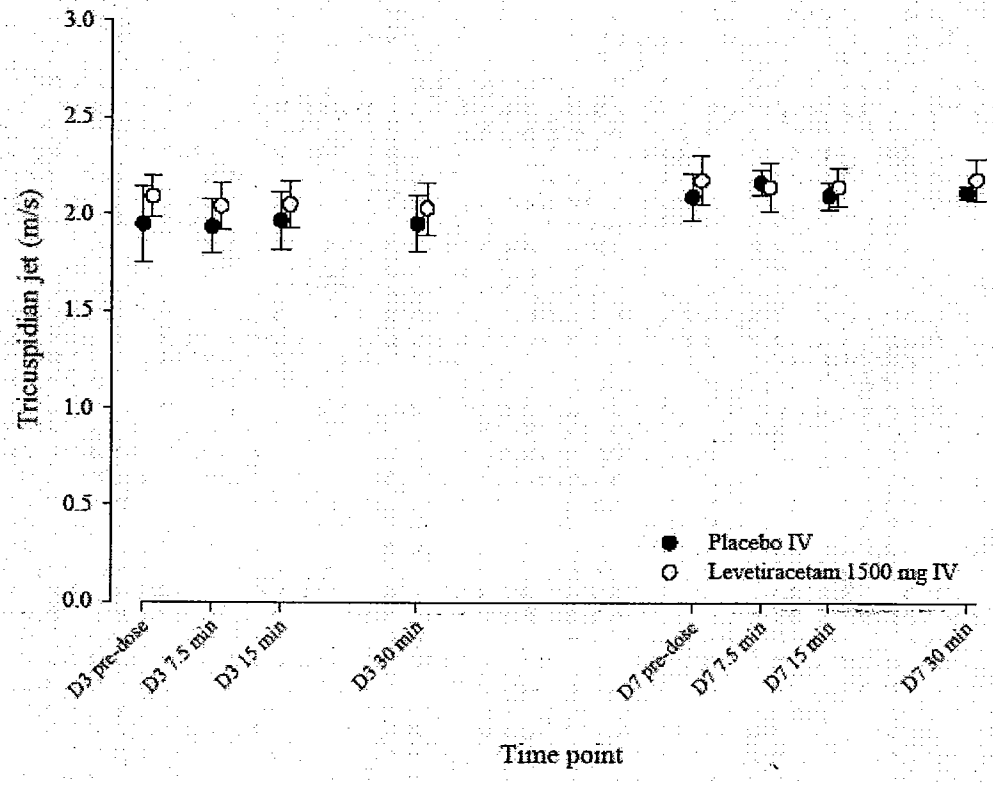
Pre-clinical dog studies suggested that rapid iv infusion (5 minute infusions) or high iv doses of levetiracetam have the potential of producing transient increases in heart rate and pulmonary arterial pressures. Some of the studies indicated that nausea and vomiting, seen in conscious dogs, associated with these regimens may contribute to this effect. Another component of this effect may have resulted from infusion volume. Nonetheless, one study in anesthetized dogs indicated that a rapid 5 minute infusion of doses levetiracetam, as a 2.5 ml/kg volume, in doses that produced post-45 minute drug levels of 57.8 ug/ml, 208 ug/ml, and 634 ug/ml resulted in 4, 14 and 35 times increase, respectively, in pulmonary artery pressure. These values are in relation to a reduction seen in vehicle control trials. When viewed in terms of same animal vehicle controls (i.e. animal was administered a vehicle control prior to the drug administered) the greatest increase was approximately 4 times (not 34 times). These changes occurred within 5

minutes of infusion and returned to baseline 15 minutes after infusion. It is noteworthy that a single, 15 minute infusion of a dose of 1500 mg produced a Cmax of 50.5 ug/ml in study N01077.

Because of this effect the Sponsor used serial continuous-wave Doppler transthoracic echocardiograms to evaluate pulmonary arterial pressures in patients in part B (multiple-dose) of study N01077 on day 3 (first drug dose) and day 7 (last drug dose) before and various times after drug administration. This type of study is considered the "gold standard in noninvasivelly establishing the diagnosis of pulmonary[4]." The systolic pulmonary artery pressure may be determined mathematically by the measurement of the tricuspid regurgitation peak jet velocity and calculation through a simplified Bernoulli equation[5]. This analysis was performed before drug and 7.5, 15 and 30 minutes after the 15 minute infusion initiation. The Sponsor examined maximum velocity of tricuspid regurgitation jets, time to peak flow and cardiac output in 6 patients receiving placebo and 12 patients receiving 15 mg of levetiracetam over a 15 minute infusion period. Below is a graph presented by the Sponsor of maximal tricuspid regurgitation jet velocity during the study. According to the equation[6] the pulmonary arterial pressure is proportional to four times the square of the value graphed in this figure. It is noteworthy that there is no evidence from the mean values in the patents who received drug for any increase in the maximal tricuspid regurgitation jet velocity. If anything there is a reduction in the jet velocity with levetiracetam during and up to 15 minutes when compared to pre-dug control after infusion. This is not so obviously seen with placebo. The effect is likely not significant, but it is reassuring that no increase is apparent. No significant changes were observed in the other measured parameters (i.e. time to peak flow and cardiac output).

It is important to note that measured time points in these clinical studies appear to be correctly selected: i.e. the increased pressures were observed 5 to 15 minutes following infusion after administration in dogs.

4 Chemia, D et al, Eur Respir. J., 20: 1314-1331, 2002.
5 Equation: PAP= $4V^2$ RAP, where PAP is the pulmonary arterial pressure, V is the peak mitral regurgitation velocity and RAP is the right atrial pressure which is assumed to be a constant (Chemia, D et al, Eur Respir. J., 20: 1314-1331, 2002).
6 Equation: PAP= $4V^2$ RAP, where PAP is the pulmonary arterial pressure, V is the peak mitral regurgitation velocity and RAP is the right atrial pressure which is assumed to be a constant (Chemia, D et al, Eur Respir. J., 20: 1314-1331, 2002).



Although animal studies that identified the increases in pulmonary arterial pressures examined intravenous doses, no oral animal studies examined this same endpoint. There is therefore no evidence that that oral animal administration would not produce the same phenomena. Because of this, the reviewer performed a search in AERS DataMart with the search term of Pulmonary Hypertension. No cases where identified.

These data would indicate that pulmonary hypertension is not likely related to treatment with intravenous, and probably oral, Keppra at the presently recommended doses and infusion rates.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The Sponsor notes that there has been no post marketing experience with the oral formulation of levetiracetam indicating drug dependence or abuse potential. The drug is not presently scheduled. Previous animal studies have indicated no abuse potential. Of note, one involved an intravenous self administration paradigm in monkeys. This study found no reinforcing effect in doses of 4 to 16 mg/kg.

7.1.16 Overdose Experience

The highest oral daily dose exposed in the previous oral clinical development program was 6,000 mg/day. High doses in these clinical trials were associated with drowsiness. Post marketing, oral overdose has been associated with a number of adverse events including somnolence, agitation, and aggression, depressed level of consciousness, respiratory depression and coma. There is no overdose experience with the present iv formulation.

7.1.17 Postmarketing Experience

There is no post marketing experience associated with an intravenous formulation except that noted in published reports described in the section on literature.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1.2 Demographics

Demographics for studies examining intravenous Keppra is presented in the table below. Note that the studies using the intended marketed formulation examined patients between ages of approximately 19 to 65 years old. Gender , in these studies, was equally divided between male and female. Exclusively Caucasian individuals were examined. Ages varied greatly in the older studies. Predominately males were studied in these older studies.

Study	N	Gender (M/F)	Age Mean [Range] (years)	Body Weight Mean [Range] (kg)	Race (n)
Studies Using Proposed Formulation					
Healthy Subjects					
N01077	18	9/9	35.0 [19.3 - 52.9]	73.3 [50 - 94]	Caucasian (18)
N01165	48 [a]	24/24	37.8 [21.2 - 55.1]	69.8 [47 - 101]	Caucasian (48)
Patients with Partial Onset Seizures					
N01166[b] (ongoing)	25	12/13	40.8 [20.2 - 65.2]	74.6 [52 - 100]	Caucasian (25)
Studies of Faster-than-Recommended Infusion Times (Older Formulations)					
Healthy Subjects					
N058	6	4/2	35 [27 - 47]	71 [51 - 93]	NR
N069	12	12/0	26 [21 - 28]	71 [60 - 85]	NR
Studies of Longer Infusion Times or an Unknown Infusion Time (Older Formulations)					
Healthy Subjects					
N204	8	8/0	23 [21 - 25]	NR	NR
N060	9	5/4	73.3 [59 - 84]	NR	NR
Patients Undergoing Major Elective Chest and/or Abdominal Surgery or Orthopedic Leg Surgery					
N099	6 [c]	2/4	64.8 [47 - 80]	80.8 [62 - 104]	NR

NR=not reported
[a] Includes 12 patients in the placebo group
[b] The clinical portion of the study is completed but data analysis are ongoing
[c] Includes 3 patients in the heparin group

Except for one exception all patients completed the studies. The exception is one patient who died post operatively of a cerebrovascular accident in a study that examined postoperative drug administration to patients undergoing major surgery (see deaths).

7.2.1.3 Extent of exposure (dose/duration)

A total 117 subjects were exposed to levetiracetam. Eighty-nine of these were healthy, non-epileptic, subjects, 3 were non-epileptic post-surgical patients and 25 were patients with epilepsy. The dose and regimen for these patients is presented in the table below.

Off the studies performed with the intended formulation, 18 received the drug (in study N01077) at the highest labeled dose at the intended labeled rate at a single dose: 12 of these received drugs in a multiple bid regimen over 4 days. Eighteen additional subjects received single doses higher (2,000 to 4,000 mg) then that labeled over a period of time (15 min)equivalent to that recommended in the proposed labeling (study N01165). This results in a faster mg-rate of infusion. An additional 18 patients received the maximally recommended labeled dose and

higher (1500 -2500 mg) over a shorter period of time (5min) then recommended in the proposed labeling (study N01165).

Older study exposures with old formulations were principally single dose exposures at doses equivalent or less then the labeled dose at rates substantially faster (2-5 minutes) or slower (3 -4 hours) then is being proposed for this new formulation. .

Study	N	Dose (mg)	Frequency	Infusion Time
Studies Using Proposed Infusion Time				
N01077	18	1500	Single dose	15 minutes
	12[a]	1500	b.i.d. × 4 days	15 minutes
N01165	6	2000	Single dose	15 minutes
	6	3000	Single dose	15 minutes
	6	4000	Single dose	15 minutes
Studies of Faster-than-Recommended Infusion Time				
N01165	6	1500	Single dose	5 minutes
	6	2000	Single dose	5 minutes
	6	2500	Single dose	5 minutes
N058	6	25 - 1600	Single dose	5 minutes
N069	12	1000	Single dose	2 minutes
Studies of Longer Infusion Times or an Unknown Infusion Time				
N204	8	1000	Single dose	3 hours
N060	9	500	Single dose	3 - 4 hours
N099	3	250	Up to 3 days	Not Reported

[a] Subset of subjects exposed in the single-dose part

A study completed at the time of the original NDA submission in seizure patients simply replaced ongoing bid oral dose with that of iv Keppra for a period of 4 days. At the time of submission of this NDA the dose exposure data was not available (but see safety update).

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The studies submitted in the previous NDA and NDA supplements that have served as the justification for the present labeling of this drug serves as contributory data to this application.

7.2.2.2 Postmarketing experience

There are no postmarketing reports for the presently developed formulation. There is some postmarketing information of alternative intravenous formulations of levetiracetam in the research literature. These are described below.

7.2.2.3 Literature

The Sponsor performed searches in a number of databases including BIOSIS, Capulus, Drugu, EmBase, JICST-Eplu, LifeSci, Medline and SciSearch database. Levetiracetam was cross referenced to intravenous. From this search strategy three abstracts, by the same group, were identified . These describe open label studies for the treatment of 27 patients with intravenous levetiracetam for migraine and cluster headaches. As these are in abstract form it is unknown if this represents 27 unique patients. Levetiracetam solution (200mg/ml and 400 mg/ml) were compounded from Keppra tablets with a series of sterile microspore-pore filtrations and used for injection. Rates (400-600 mg/5 min) and doses (up to 5600 mg) of injections were substantially faster and higher then that being proposed in the present NDA Out of these 27 patients there were minimal adverse events reported. Thus, one case of transient nausea and 2 cases of transient drowsiness were observed. As abstracts , the results of these reports need to be interpreted with caution. These reports are briefly described as follows:

- In this study[7] it appears that 16 patients were administered 400-600 mg of levetiracetam iv every 5 minutes until a desired effect was observed. The doses achieved ranged from 400 to 11,200 (over 56 minutes). The author notes no side effects were observed.
- The second report[8] examined 6 patients with a similar iv dose regimen to that noted above; i.e. 400-600 mg/5 min, until the desired effect was achieved with a range of final doses of 1400 to 5600. Only one case of "transient nausea" lasting 15 minutes was noted in one patient.
- This third report examined 5 male patients receiving 400-800 mg every 5 minutes intravenously until an optimal effect was achieved. . A mean dose of 7520 mg over a 45-60 minute period of time. Two patients experienced transient drowsiness.

7.2.3 Adequacy of Overall Clinical Experience

7 European Journal Of Neurology, 2002, 9(Suppl.2): 154, Abs. P2177 6th Efns Congress, Vienna ,Oct, 2002
8 American Headache Society, 44th Annual Scientific Meeting, Seattle, Washington (2002).

The reader is referred to the section on "sources of clinical data" for a summary of studies used to support the safety of the present route and formulation. While the number of adult patients exposed to the intravenous formulation is small it was generally thought that if intravenous formulation demonstrated bioequivalence the vast experience with the oral formulation of the drug would serve as adequate and important contributory data to safety. The one exception to this is the fact that Tmax of the intravenous formulation was 1/3 of that of the oral formulation. Nonetheless, the safety profile of the drug administered by the intravenous route appeared quite similar to that for the drug administered orally. The studies of examining increased infusion rates, while small in number, supports the impression of the general safety of the present formulation as well as demonstrates a margin of safety if the drug is used outside labeling recommended rates.

7.2.8 Assessment of Quality and Completeness of Data

The data was generally complete with certain exceptions noted above when this reviewer requested, and received, additional analysis.

7.2.9 Additional Submissions, Including Safety Update

In April 19 , 2005 UCB submitted a safety update. This update consisted of final safety reporting on study N01166 that, while unblinded at the time the supplement was originally submitted, data had not been completely analyzed. The safety update now reports the final analyses of this data. This study replaced po levetiracetam administration with iv administration (500-1500 mg over 15 minutes) in epileptic patients who were receiving the medication for seizure control for a period of 4 days. Twenty-five patients (13 females and 12 males) participated in this study.

The median dose received in this study was 1350 mg bid and the range was 500 to 1500 bid with most of the patients on 1500 mg bid (n=19). Common adverse events have been discussed in previous sections of this review. Upon final analysis no serious or severe adverse events or premature discontinuations were observed in this study.

Mean changes in blood pressure (measured supine) before and 5, 15, 30 and 60 minutes after infusion was started were monitored. Mean change in blood pressure at various time points from pre-dose baseline following morning dosages are presented in the two tables below. The first table presents data on systolic pressure changes and the second on diastolic pressure changes. As is apparent, no clinically significant pressure changes are obvious. No significant effects were observed in changes in heart rate as well.

Study Day Statistic	Baseline (Pre-Treatment) N = 25	Change from Baseline from Start of Infusion (minutes)			
		5	15	30	60
Day 1 (Morning) N = 25					
Mean ± SD	117 ± 16	-2.7 ± 9.5	-2.7 ± 8.1	-1.2 ± 10.0	-0.1 ± 10.8
Median	120	-4.0	0.0	0.0	0.0
Minimum	80	-21.0	-27.0	-25.0	-17.0
Maximum	150	20.0	10.0	20.0	20.0
Day 2 (Morning) N = 25					
Mean ± SD	117 ± 17	-1.4 ± 9.1	-2.5 ± 10.7	-0.9 ± 12.9	-0.8 ± 13.2
Median	115	0.0	-1.0	0.0	0.0
Minimum	70	-25.0	-25.0	-25.0	-30.0
Maximum	150	20.0	25.0	35.0	30.0
Day 3 (Morning) N = 25					
Mean ± SD	114 ± 15	-2.1 ± 7.4	1.0 ± 9.3	0.6 ± 10.4	0.1 ± 10.0
Median	119	0.0	0.0	0.0	0.0
Minimum	90	-19.0	-24.0	-21.0	-30.0
Maximum	150	10.0	20.0	20.0	20.0
Day 4 (Morning) N = 25					
Mean ± SD	111 ± 17	1.4 ± 8.4	2.1 ± 8.5	4.0 ± 8.1	2.3 ± 9.8
Median	114	0.0	0.0	5.0	0.0
Minimum	80	-17.0	-19.0	-13.0	-25.0
Maximum	140	20.0	20.0	20.0	30.0

Study Day Statistic	Baseline (Pre-Treatment) N = 25	Change from Baseline from Start of Infusion (Minutes)			
		5	15	30	60
Day 1 (Morning) N = 25					
Mean ± SD	69 ± 12	-1.8 ± 4.6	-0.9 ± 6.7	-0.32 ± 5.7	-1.2 ± 6.0
Median	70	0.0	0.0	0.0	0.0
Minimum	46	-13.0	-10.0	-10.0	-13.0
Maximum	100	5.0	20.0	10.0	10.0
Day 2 (Morning) N = 25					
Mean ± SD	70 ± 12	-1.2 ± 8.2	-0.4 ± 9.4	-0.9 ± 7.9	-1.0 ± 8.7
Median	70	-2.0	0.0	0.0	-1.0
Minimum	40	-10.0	-15.0	-15.0	-11.0
Maximum	90	20.0	20.0	20.0	20.0
Day 3 (Morning) N = 25					
Mean ± SD	69 ± 13	-0.9 ± 6.3	-0.3 ± 8.1	2.2 ± 10.1	0.5 ± 8.3
Median	70	0.0	0.0	0.0	0.0
Minimum	40	-13.0	-15.0	-10.0	-20.0
Maximum	95	10.0	20.0	38.0	10.0
Day 4 (Morning) N = 25					
Mean ± SD	68 ± 14	0.7 ± 7.0	1.0 ± 6.4	2.5 ± 6.8	1.4 ± 6.1
Median	70	0.0	0.0	0.0	0.0
Minimum	42	-10.0	-10.0	-10.0	-10.0
Maximum	95	20.0	12.0	20.0	21.0

One patient had an alteration in vital signs reported as an adverse event. Thus, one patient (#005/0030), a 57 year old woman, was reported to have "mild" hypotension that was possibly related to treatment. This patient was receiving a dose of 1,000 mg bid. Screening blood pressures was low 100/60. Low pressures were also observed at each pre-dose measurement (90-117/40-53). This patient's lowest blood pressure (95/32) during infusion occurred in the morning of day-1 at 5 and 15 minutes following the initiation of the infusion. The lowest post

infusion blood pressure (86/39) occurred 30 minutes after infusion on day 1. The patient was asymptomatic. These changes are likely not significant as the patient was asymptomatic and pressures were slightly lower then pre-dose values.

The safety update included an analysis of EKG data acquired in this study. An EKG was obtained at a screening, prior to any intravenous infusion. Subsequent EKGs were obtained on day 1 and 4 of morning infusions. In this case two EKG were obtained, one prior to infusion and one immediately upon the completion of the 15 minute infusion period. PR, QRS and QT (F and B) were evaluated. The Sponsor notes that no clinically relevant changes were observed in any of the intervals that were evaluated. Examination of the study report by this reviewer did not indicate a significant change in heart rate, PR interval and QRS segment. The difference in means (±SD)of QTcF and QTcB between pre-drug period and infusion completion is presented in the table below. No consistent or significant effects on the various corrected QT are apparent. That is, while one measurement revealed increases of about 5 msec, other measured changes revealed decreases or smaller increases.

		Pre-infusion	Infusion completion
QTcB	Day 1	386.07 (33.26)	390.17 (33.95)
	Day 4	388.71 (37.68)	385.26 (32.20)
QTcF	Day 1	379.23 (33.28)	384.79 (35.53)
	Day 4	381.92 (39.26)	380.27 (37.75)

Routine serum chemistry, CBC and urinalysis were performed at screening (baseline) and following the last dose of medication (days 4) as well as on follow-up. The tabulated central tendency for baseline and day 4 are presented in the two tables below. With regard to the CBC data (first table) , there was a slight tendency for the reduction in indices but the magnitude of this effect was rather small and likely not of any significance. No obvious significant changes can be appreciated in the data on serum chemistries (second table).

Parameter (Unit) Period	Statistic	N	Value
WBC Count ($\times 10^3/\mu L$)			
Baseline	Mean ± SD	24	6.48 ± 1.85
Day 4 (morning)	Mean ± SD	25	6.15 ± 1.76
	Mean Change ± SD	24	-0.35 ± 1.54
Neutrophil Count ($\times 10^3/\mu L$)			
Baseline	Mean ± SD	24	3.89 ± 1.55
Day 4 (morning)	Mean ± SD	25	3.62 ± 1.44
	Mean Change ± SD	24	-0.28 ± 1.61
RBC Count ($\times 10^6/\mu L$)			
Baseline	Mean ± SD	24	4.51 ± 0.47
Day 4 (morning)	Mean ± SD	25	4.36 ± 0.57
	Mean Change ± SD	24	-0.08 ± 0.25
Hemoglobin (g/dL)			
Baseline	Mean ± SD	24	14.1 ± 1.5
Day 4 (morning)	Mean ± SD	25	13.7 ± 1.6
	Mean Change ± SD	24	-1.6 ± 2.6
Hematocrit (%)			
Baseline	Mean ± SD	24	41.7 ± 4.2
Day 4 (morning)	Mean ± SD	25	40.2 ± 4.9
	Mean Change ± SD	24	-1.7 ± 2.8
Platelet Count ($\times 10^3/\mu L$)			
Baseline	Mean ± SD	24	259.7 ± 53.9
Day 4 (morning)	Mean ± SD	25	256.2 ± 52.2
	Mean Change ± SD	24	-5.1 ± 19.6

Parameter (Unit) Period	Statistic	N	Value
AST (U/L)			
Baseline	Mean ± SD	25	21.8 ± 9.5
Day 4 (morning)	Mean ± SD	25	20.0 ± 6.5
	Mean Change ± SD	25	-1.8 ± 7.6
ALT (U/L)			
Baseline	Mean ± SD	25	26.0 ± 17.1
Day 4 (morning)	Mean ± SD	25	24.2 ± 14.3
	Mean Change ± SD	25	-1.8 ± 10.2
Bilirubin (µmol/L)			
Baseline	Mean ± SD	25	5.2 ± 2.4
Day 4 (morning)	Mean ± SD	25	4.2 ± 1.7
	Mean Change ± SD	25	-1.0 ± 1.9
Urea (mmol/L)			
Baseline	Mean ± SD	25	4.61 ± 1.17
Day 4 (morning)	Mean ± SD	25	4.71 ± 1.31
	Mean Change ± SD	25	0.1 ± 0.9
Creatinine (µmol/L)			
Baseline	Mean ± SD	25	70.6 ± 14.4
Day 4 (morning)	Mean ± SD	25	68.4 ± 13.7
	Mean Change ± SD	25	-2.2 ± 8.5
Creatinine Clearance (mL/min)			
Baseline	Mean ± SD	25	121.8 ± 30.7
Day 4 (morning)	Mean ± SD	25	125.9 ± 35.9
	Mean Change ± SD	25	4.1 ± 19.9
Sodium (mmol/L)			
Baseline	Mean ± SD	25	138.3 ± 4.7
Day 4 (morning)	Mean ± SD	25	139.2 ± 4.4
	Mean Change ± SD	25	0.9 ± 1.9
Potassium (mmol/L)			
Baseline	Mean ± SD	25	4.2 ± 0.3
Day 4 (morning)	Mean ± SD	25	4.2 ± 0.3
	Mean Change ± SD	25	0.0 ± 0.3

The Sponsor notes that upon examination of shifts in laboratory measurements 8 patients with a normal RBC, hemoglobin and/or hematocrit at baseline fell from normal to "slightly below normal." The Sponsor notes that "none where considered clinically significant." One patient had a neutrophil count at 1.9 that subsequently dropped to 1.4. This was thought not be clinically significant. This reviver concurs.

No changes in laboratories were reported as adverse events.

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

7.4 General Methodology

7.4.2.3 Explorations for drug-demographic interactions

Age

Observations, based upon previous oral studies, indicate that half life is lengthened in the elderly, but dose adjustment is only necessary if renal impairment exists. The Sponsor notes that there was no obvious increase in adverse events seen in older patients in the earlier studies. It is unclear if the Sponsor is referring to earlier iv or oral studies. If the Sponsor is referring to iv studies they may be refereeing to study N060, with a mean age of 73.3, and study N099 with a mean age is 64.8. This comparison, however, is not justified as this exposure in the elderly is low (a total of 15 patients in both studies). Formulations and rate of infusion are not analogous to the present developmental plan. The dose of exposure was also lower. Safety conclusions should therefore only be based upon the previous experience with the oral formulations. The present labeling note:

> "No overall differences in safety were observed between these subjects and younger subjects. There were insufficient numbers of elderly subjects in controlled trials of epilepsy to adequately assess the effectiveness of Keppra® in these patients."

This should remain unchanged.

Gender

The Sponsor notes that previous studies examining the oral formulation indicate no pharmacokinetic differences that cannot be explained by differences in weight are based upon gender. The difference based upon weight, according to the Sponsor, has not proven to have a clinical impact on the adverse event profile in studies using oral levetiracetam. A similar relationship was found in the present study. This AUCs and Cmax were slightly greater, but women on average were lighter. The adverse event profile, stratified by gender, for studies N01077 and N01165 is presented in the table below. There was a slight increase in occurrence in adverse events in females with somnolence and headache showing a particular increased incidence in females. These data, however, need to be interpreted with caution considering the limited number of patients sampled the differences and the absence of a parallel placebo comparison.

Adverse Event (Preferred Term)	Females (N=27)	Males (N=27)
Blood pressure decreased	2 (7.4%)	0
Dizziness	12 (44.4%)	9 (33.3%)
Dizziness postural	6 (22.2%)	7 (25.9%)
Fatigue	3 (11.1%)	2 (7.4%)
Headache	7 (25.9%)	3 (11.1%)
Injection site pruritus	2 (7.4%)	0
Loose stools	2 (7.4%)	1 (3.7%)
Somnolence	14 (51.8%)	9 (33.3%)
Thirst	2 (7.4%)	0

The present labeling should remain unchanged which states, "The overall adverse experience profile of Keppra® was similar between females and males." There should be a caveat that this is largely based upon studies examining the oral formulation and there is limited iv experience for an adequate comparison for the intravenous formulation.

Race

The present studies were performed in almost exclusively Caucasian individuals. Because of this no definitive conclusions can be made. The present labeling notes that there is insufficient information regarding racial differences. This still applies.

7.4.2.4 Explorations for drug-disease interactions

Little new information was developed on the potential for drug disease interactions for the intravenous dosing form. The Sponsor, however, notes that based upon oral experience that, other then dose adjustment in cases of renal compromise, there are no contraindications for use in the presence of other diseases.

7.4.2.5 Explorations for drug-drug interactions

No new data is presented on drug-drug interactions. Levetiracetam has previously been demonstrated to produce minimal drug-drug interactions when administered orally. The Sponsor argues that there is no reason that this would not apply to the drug when administered intravenously.

The compatibility of levetiracetam in various diluents (normal saline, 5% dextrose and lactated ringers) and potential in vitro interaction of other intravenous drugs in these diluents with levetiracetam was examined. Levetiracetam (500mg and 4,000 mg) was added to 100 ml bags of saline and 5% dextrose and 500 ml bags of lactated ringers alone or with diazepam 20 mg, valproate sodium 1200 mg, lorazepam 4 mg and phenytoin sodium 1,000 mg. The following was analyzed at 0 and 24 hours after mixing: levetiracetam and LO57 (major levetiracetam, metabolite), pH, osmolality and appearance. The Sponsor notes that because phenytoin precipitated in normal saline and 5% dextrose it was not studied This study indicted stability of levetiracetam in the media studied. Valproate caused an increase in pH of the solutions of approximately 1.0 in normal saline and 5% dextrose: smaller increases were observed in lactated ringers. Diazepam produced the greatest change in osmolality. The appearance of solutions was found to "comply" over the 24 hour period.

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.4 Pediatrics

When this NDA was in the planning stage Keppra was not labeled for the pediatric population. Since then Keppra has received approval for children ages 4 to <16. /

There is no safety information for the pediatric population presented in the present NDA. Indeed patients under 19 years old have not been exposed to any formulation of intravenous levetiracetam. /

reason this reviewer would recommend a limited safety study (perhaps n=25) for patients 4 to <16. / Although

not necessary, such a study can be performed on pediatric patients [redacted]

Depacon is an example of another anticonvulsant that was developed for intravenous use in a pediatric population [redacted] Depacon is indicated for adults and a children >10 years old. [redacted] The label presently states "No unique safety concerns were identified in the 35 patients, age 2 to 17 years, who received DEPACON in clinical trials." [redacted] This reviewer feels that this supports his recommendation to perform a limited pediatric safety study.

9 OVERALL ASSESSMENT

9.1 Conclusions

The Sponsor has demonstrated that the present new intravenous formulation exhibits bioequivalence (AUC and Tmax comparisons) to presently marketed oral tablet formulation. Extrapolated Cmin was also similar. Although no efficacy data is presented the demonstration of bioequivalence would indicate that this formulation should produce a similar therapeutic effect. Except for a low incidence of mild local injection site effects there were no adverse events that distinguished the intravenous formulation qualitatively from the presently available oral formulation. These local effects were expressed as a mild pruritus at the injection site. The common adverse events of somnolence, headache, and dizziness appeared more commonly reported in the present studies using the intravenous formulation then in prior studies that examined oral administration. This data needs to be viewed with caution as the investigated population size was small and the present intravenous design did not incorporate a titration phase as did the prior studies. No obvious change in vital signs and EKG are apparent during or after intravenous infusion in the present study. Intravenous pre-clinical dog studies suggested a potential for a transient elevation in pulmonary arterial pressures during levetiracetam injection. Because of this a patients continuous-wave Doppler transthoracic echocardiograms were used to evaluate pulmonary arterial pressures in patients receiving levetiracetam or placebo. These studies did not indicate any increase in pulmonary pressures in the highest dose and rates recommended in the proposed labeling. In conclusion, except for a mild local injection site effect, the adverse event profile for the present formulation does not appear different from that of the oral formulation.

Although there are no PK or safety issues, because of the facility and major equipment changes validation and requalification is required this submission must be made approvable.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None recommended.

9.3.2 Required Phase 4 Commitments

No new requests. Off note

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Please see labeling in the approvable letter.

10 APPENDICES

Appendix A: Composition of the proposed marketed levetiracetam (100 mg/ml) formulation.

Ingredient	Unit Quantity (amount/mL)	Function	Reference to Quality Standards
Levetiracetam (ucb L059)	0.100 g	Active ingredient	UCB Reference Standard
Sodium Acetate Trihydrate	[redacted]	Buffering agent	USP
Sodium Chloride	[redacted]	[redacted]	USP
Glacial Acetic Acid as a [redacted] Solution	As needed for pH adjustment	pH adjustment	USP
Water for Injection	QS	Drug vehicle	USP
[redacted]			NF

Appendix B: Change in EKG parameters from studies N01077 and N01165

Table 6:13 Descriptive Statistics for ECG Parameters by Treatment Over Time: Baseline (Screening) and Change from Baseline Following Single I.V. or Oral Dose of Levetiracetam 1500 mg (Study N01077 – Part A)

	Baseline (Screening)	Change from Baseline Post Dose					
PR (ms)		**Pre-dose**	**5 min**	**15 min**	**30 min**	**1 h**	**2 h**
Tablet (N=18)							
Mean ± SD	141.1± 20.5	9.6 ± 12.8	3.4 ± 15.7	6.2 ± 14.5	10.2 ± 15.4	7.2 ± 12.0	9.0 ± 15.0
Median	136.5	9	3.0	9.0	9.0	10	8.5
Minimum	114	-13	-28	-27	-15	-23	-16
Maximum	192	35	40	28	50	27	56
Intravenous (N=18)							
Mean ± SD	141.1± 20.5	5.8 ± 8.6	8.7 ± 10.4	9.4 ± 8.9	10.7 ± 12.8	9.8 ± 10.0	6.4 ± 12.2
Median	136.5	6	8.0	12.0	9.5	10	6.0
Minimum	114	-11	-14	-13	-14	-12	-20
Maximum	192	25	32	23	34	29	30
QRS (ms)							
Tablet (N=18)							
Mean ± SD	95.7± 11.1	-0.3 ± 6.3	-1.8 ± 3.7	-0.7 ± 2.7	-0.9 ± 5.2	-0.6 ± 5.6	-0.2 ± 6.7
Median	95.5	-0.5	-2.0	-1	0	0	-1
Minimum	80	-18	-10	-6	-16	-8	-14
Maximum	119	9	5	4	6	16	20
Intravenous (N=18)							
Mean ± SD	95.7± 11.1	-1.2 ± 6.4	0.0 ± 6.4	-2.5 ± 5.7	-2.2 ± 4.7	-0.7 ± 7.9	-2.4 ± 4.6
Median	95.5	-1.5	-0.5	-3	-2	0.5	-2
Minimum	80	-14	-16	-12	-12	-18	-12
Maximum	119	15	14	13	7	16	5
Ventricular Rate (bpm)							
Tablet (N=18)							
Mean ± SD	60.6± 7.8	-0.4 ± 10	-1.1 ± 8.3	-0.8 ± 8.7	-3.2 ± 7.9	-3.4 ± 8.0	-4.6 ± 6.9
Median	58	-3.0	-2.5	-1.5	-3.5	-4.5	-5.5
Minimum	46	-15	-20	-18	-22	-22	-17
Maximum	76	20	13	24	11	16	5
Intravenous (N=18)							
Mean ± SD	60.6± 7.8	0.3 ± 10.3	2.4 ± 9.9	0.4 ± 8.3	-1.5 ± 8.7	-1.6 ± 9.7	-1.8 ± 10.3
Median	58	-0.5	2	0.5	-1	-2	-4
Minimum	46	-18	-16	-12	-15	-20	-14
Maximum	76	20	24	22	20	21	20
QTcF Fridericia (ms)							
Tablet (N=18)							
Mean ± SD	406.3± 17.7	-4.1 ± 16.1	0.1 ± 15.3	0.5 ± 15.8	-1.8 ± 16.4	2.8 ± 18.6	-0.8 ± 14.7
Median	405.4	-4.8	0.7	1.1	-1.4	-0.3	-2.4
Minimum	370	-38	-31	-35	-33	-42	-47
Maximum	451	33	19	22	25	39	16
Intravenous (N=18)							
Mean ± SD	406.3± 17.7	-3.8 ± 17.4	-0.6 ± 15.2	0.9 ± 16.7	-0.2 ± 13.8	1.3 ± 13.1	1.1 ± 17.4
Median	405.4	-2.2	-2.5	3.0	-2.8	1.4	6.1
Minimum	370	-34	-29	-33	-28	-27	-40
Maximum	451	30	22	29	21	27	22

Table 6:14 Descriptive Statistics for ECG Parameters by Treatment Over Time: Baseline (Screening) and Change from Baseline Following Multiple I.V. Doses of Levetiracetam 1500 mg or Placebo (Study N01077 – Part B)

	Baseline (Screening)	Change from Baseline Post Dose					
PR (ms)		**Pre-dose**	**5 min**	**15 min**	**30 min**	**1 h**	**2 h**
Placebo (N=6 subjects) [a]							
Mean ± SD	144.2± 24.4	12.3 ± 18.7	12.8 ± 16.5	10.9 ± 15.9	12.0 ± 17.9	13.6 ± 17.5	15.4 ± 19.2
Median	136.5	7	7	8	8	9	10
Minimum	124	-21	-18	-22	-14	-32	-18
Maximum	192	64	52	54	60	59	58
Levetiracetam (N=12 subjects) [a]							
Mean ± SD	139.6± 19.3	3.6 ± 12.2	3.3 ± 11.9	5.2 ± 12.0	4.7 ± 11.2	4.6 ± 12.2	4.5 ± 12.1
Median	135	5	4	7	6	6	5
Minimum	114	-35	-31	-30	-25	-28	-37
Maximum	178	27	26	47	32	37	26
QRS (ms)							
Placebo (N=6 subjects) [a]							
Mean ± SD	93.8± 9.9	1.0 ± 4.9	0.6 ± 4.9	0.3 ± 4.6	0.1 ± 4.6	0.2 ± 4.2	-0.3 ± 4.2
Median	94	0	0	0	0	0	-1
Minimum	80	-7	-7	-8	-7	-9	-8
Maximum	105	15	15	13	12	12	10
Levetiracetam (N=12 subjects) [a]							
Mean ± SD	96.7± 11.9	0.0 ± 6.9	1.1 ± 6.7	0.3 ± 6.9	0.1 ± 7.1	0.2 ± 7.2	0.1 ± 6.5
Median	96	-1	1	0	0	1	0
Minimum	83	-19	-17	-18	-17	-22	-20
Maximum	119	21	24	21	22	24	23
Ventricular Rate (bpm)							
Placebo (N=6 subjects) [a]							
Mean ± SD	59.5± 7.7	5.2 ± 8.0	4.5 ± 7.4	4.3 ± 8.3	3.6 ± 8.6	2.8 ± 8.1	4.4 ± 9.2
Median	56.5	6	5	6	6	4	7
Minimum	55	-13	-14	-14	-16	-16	-15
Maximum	75	23	18	21	20	18	31
Levetiracetam (N=12 subjects) [a]							
Mean ± SD	61.2± 8.2	5.1 ± 8.2	4.6 ± 8.0	4.6 ± 7.6	3.4 ± 7.9	3.1 ± 8.1	3.2 ± 8.2
Median	61	4	5	4	4	3	3
Minimum	46	-12	-13	-15	-13	-14	-13
Maximum	76	30	26	23	25	22	25
QTcF Fridericia (ms)							
Placebo (N=6 subjects) [a]							
Mean ± SD	411.9± 12.4	-11.1 ± 14.5	-7.9 ± 15.5	-8.7 ± 14.0	-10.3 ± 14.7	-9.4 ± 15.5	-13.1 ± 14.8
Median	409.9	-9	-4	-4	-7	-6	-11
Minimum	397	-44	-45	-48	-55	-44	-47
Maximum	431	31	46	20	14	19	16
Levetiracetam (N=12 subjects) [a]							
Mean ± SD	403.5± 19.7	-6.9 ± 13.4	-5.4 ± 12.3	-5.6 ± 14.2	-6.7 ± 12.3	-5.4 ± 13.2	-7.7 ± 12.2
Median	401.4	-6	-6	-6	-6	-6	-7
Minimum	370	-47	-36	-39	-43	-42	-39
Maximum	451	30	20	37	24	23	20

[a] For each time-point (except baseline), statistics are computed on all observations during multiple dosing (9 doses; n = 54 observations in placebo and n = 108 observations in levetiracetam).

Table 6:15 Descriptive Statistics for ECG Parameters by Treatment Over Time: Baseline (Screening) and Change from Pre-dose Following Single I.V. Dose of Levetiracetam 1500 mg or Placebo (Study N01165)

	Baseline (Screening)	Change from pre-dose at Post Dose Time-point [a]						
PR (ms)		**End infusion**	**15 min after end infusion**	**30 min after end infusion**	**1 h**	**2 h**	**12 h**	**24 h**
Placebo (N=12)								
Mean ± SD	137.7± 16.5	2.1 ± 8.6	0 ± 7.0	2.3 ± 6.6	-1.6 ± 8.2	0.1 ± 9.0	-4.2 ± 11.3	-4.3 ± 6.6
Median	138	1	-1	0	1	-1	-2	-6
Minimum	116	-14	-12	-9	-17	-19	-30	-15
Maximum	172	16	16	18	10	17	8	5
Levetiracetam (N=36)								
Mean ± SD	140.2± 22.8	-1.2 ± 11.7	-0.9 ± 9.2	0 ± 9.8	0.9 ± 13.9	-2.1 ± 11.4	-7.3 ± 14.6	-6.8 ± 11.3
Median	136	0	1	1	0	-2	-6	-5
Minimum	97	-36	-28	-32	-29	-29	-48	-35
Maximum	200	21	21	21	40	25	33	24
QRS (ms)								
Placebo (N=12)								
Mean ± SD	92.7± 9.4	0.3 ± 5.2	-1.4 ± 4.4	-2.0 ± 2.7	-1.3 ± 3.6	-2.0 ± 2.6	-1.4 ± 4.0	-1.2 ± 4.7
Median	93	-1	0	-2	-1	-2	-2	-2
Minimum	77	-8	-14	-6	-7	-6	-7	-10
Maximum	110	13	2	2	4	2	6	7
Levetiracetam (N=36)								
Mean ± SD	93.0± 9.7	0.0 ± 4.0	-0.9 ± 4.4	-0.5 ± 4.5	0.0 ± 3.7	-1.3 ± 4.2	-0.6 ± 3.4	-0.8 ± 5.1
Median	91	0	-1	-1	0	-1	-1	-1
Minimum	78	-9	-13	-11	-6	-14	-10	-12
Maximum	118	8	10	8	12	10	6	17
Ventricular Rate (bpm)								
Placebo (N=12)								
Mean ± SD	58.5± 4.5	1.4 ± 2.0	-0.3 ± 6.0	-0.1 ± 3.2	2.3 ± 7.3	-2.6 ± 4.9	-0.1 ± 5.9	1.3 ± 5.5
Median	58	2	-1	0	1	-3	2	1
Minimum	51	-2	-10	-6	-8	-12	-13	-10
Maximum	67	4	13	6	18	6	6	11
Levetiracetam (N=36)								
Mean ± SD	60.2± 8.5	1.4 ± 5.6	-1.3 ± 5.0	0.0 ± 5.3	-1.5 ± 5.1	-1.2 ± 5.9	-2.1 ± 6.3	0.7 ± 5.8
Median	60	1	-1	0	-2	-1	-1	2
Minimum	46	-14	-17	-16	-16	-19	-20	-17
Maximum	77	12	7	9	9	12	9	13
QTcF Fridericia (ms)								
Placebo (N=12)								
Mean ± SD	387.3± 13.5	2.6 ± 6.8	-0.4 ± 8.2	-1.5 ± 7.1	-2.2 ± 8.4	-8.6 ± 10.1	1.3 ± 10.6	-7.7 ± 8.6
Median	387	4	1	0	-2	-6	-1	-7
Minimum	361	-7	-19	-18	-16	-30	-16	-23
Maximum	411	13	10	7	14	5	19	3
Levetiracetam (N=36)								
Mean ± SD	392.4± 12.9	0.7 ± 9.0	-0.3 ± 6.4	2.2 ± 8.0	-1.1 ± 10.0	-0.2 ± 8.7	1.9 ± 8.7	-2.6 ± 7.6
Median	392	0	1	0	-3	1	1	-2
Minimum	367	-18	-11	-11	-19	-18	-12	-17
Maximum	427	21	13	29	36	32	21	11

[a] all subjects with different i.v. levetiracetam doses and durations are used.

3 Page(s) Withheld

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10.2 Line-by-Line Labeling Review

See approvable letter.

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