CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-446

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-446 21-723	Submission Date(s): 10/31/2003, 2/5/04, 2/12/04
Brand Name	Lyrica
Generic Name	Pregabalin
Reviewers	Sue-Chih Lee, Ph.D. and Srikanth Nallani, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
Pharmacometrics Consultant	He Sun, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)
Sponsor	Pfizer
Relevant IND(s)	— 53,763; —
Submission Type; Code	Original; 1P (NDA 21-446); 1S (NDA 21-723)
Formulation; Strength(s)	Capsules, 25/50/75/100/150/200/225/300 mg
Proposed Indications	Treatment of diabetic peripheral neuropathy, postherpetic neuralgia, ⊏ ⅃
Proposed Dosage Regimen	Starting dose: 75 mg — (150 mg/day) Optimal dose: 150 mg — (for most patients) Maximum dose: 300 mg —

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1. EXECUTIVE SUMMARY

1.1 RECOMMENDATIONS

From the Clinical Pharmacology and Biopharmaceutics standpoint, the application is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and Agency regarding the language in package insert and the following deficiencies are adequately addressed:

1) The issue of QTc prolongation potential of pregabalin has not been adequately addressed. [ ] For study design considerations, the sponsor may reference the Preliminary Concept Paper entitled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs."
2) The potential for CYP induction by pregabalin has not been systematically studied. The sponsor should conduct an *in vitro* study in primary cultures of human hepatocytes to address this issue.

1.2 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Pregabalin is an alpha-2-delta ($\alpha_2\delta$) ligand that has analgesic, anxiolytic, and anticonvulsant activity. The sponsor is seeking approval of pregabalin capsules for the treatment of diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN) [ ] Only DPN indication has the priority designation [ ] Currently, there is no approved drug for DPN. This review covers all clinical pharmacology and biopharmaceutics information for pregabalin as submitted by the sponsor [ ]

For both DPN and PHN indications, the sponsor is proposing BID regimens (starting at 75 mg BID with a maximum of 300 mg BID). For DPN, however, the sponsor does not have any successful trial with BID regimens. One BID trial (Study 149) failed to show statistical significance against placebo at all dose levels (75 mg BID, 150 mg BID and 300 mg BID). Another BID trial was prematurely terminated due to nonclinical toxicity findings (hemangiosarcoma in mice). Note that there are successful TID trials to support the 300 mg/day and 600 mg /day regimens (i.e., 100 mg TID and 200 mg TID). The sponsor conducted an exposure-response analysis relating daily dose to pain score over time using pooled data from 8 trials for diabetic neuropathy and postherpetic neuralgia. This exposure response relationship was used by the sponsor as one of the evidences that BID and TID dosing will result in similar efficacy. However, in Agency's evaluation of the BID dosing, the review team focused on the PK information and observed response data and did not need to rely on the exposure response modeling. Several internal discussions on this issue were held within DPEII and with the clinical division (HFD-170). Pharmacokinetics cannot explain the failure of the 300 mg BID regimen in

Study 149 as evidenced by the comparative plasma concentration-time profiles for this regimen and the 100 mg TID regimen. It appears that the highly variable, time-dependent placebo effect could have contributed to this unfavorable outcome.

There are no prospectively designed QT studies for this drug. The sponsor conducted an analysis of pooled QT data from Phase 1 studies and concluded a negative QT effect. However, the data are inadequate for a definite analysis. In addition, the concentration range studied did not cover the highest exposure expected (e.g. in renal impairment patients).

Pregabalin is a BCS Class 1 drug with a high oral bioavailability (≥90%). Under fasting conditions, peak plasma concentrations occurred within 1.5 hours. High-fat meal delayed absorption (Tmax: ↑1-2 hrs; Cmax: ↓25%) but did not change the extent of absorption (AUC). Pregabalin capsules can be administered without regard to timing of meals.

Linear pharmacokinetics was observed following administration of pregabalin capsules. Both Cmax and AUC are dose proportional within the therapeutic dose range. Multiple dose pharmacokinetics can be predicted from single dose data with steady state achieved within 24 to 48 hours. Mean accumulation ratio was 1.37 after BID dosing and ranged 1.70 to 1.96 for TID dosing.

Pregabalin is a substrate for System L amino acid transporters, which mediate transport of large neutral amino acids through the epithelial cells of blood-tissue barriers (BBB and placenta), small intestine, renal proximal tubules. Nonclinical studies indicate that pregabalin crosses blood brain barrier and placenta and is present in the milk of lactating rats. This carrier-mediated transport process may be involved in the absorption, distribution and elimination of pregabalin in humans.

Elimination of pregabalin is primarily (>90%) via renal excretion of the unchanged drug with a terminal elimination half-life of approximately 6 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects, indicating that renal tubular reabsorption is involved since pregabalin is not bound to plasma proteins. Dosage adjustment is necessary in patients with creatinine clearance (CLcr) of ≤ 60 mL/min. Hemodialysis reduced plasma pregabalin concentrations by approximately 50% in 4 hours and may be utilized in case of overdose. For renal impairment patients requiring hemodialysis, a supplemental dose of pregabalin is necessary immediately after hemodialysis

Pregabalin undergoes negligible metabolism in humans with the major metabolite (a N-methylated derivative) accounting for 0.9% of the administered dose in a mass balance study. The effect of hepatic insufficiency on pregabalin clearance has not been studied but is expected to be minimal. In animal studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer.

In a population pharmacokinetic analysis of pooled data from various Phase 1/2/3 studies, age, gender, race (Blacks and Hispanics) were not detected as factors influencing the pregabalin pharmacokinetics when the difference in creatinine clearance is accounted for.

Pharmacokinetics in pediatric patients have not been characterized. The sponsor is seeking both DPN and PHN indications in adults only. Waiver of pediatric studies for PHN has been granted. The sponsor requested a waiver of pediatric studies for DPN which is under evaluation.

The pharmacokinetics of pregabalin is not likely to be affected by other agents through metabolic interactions since pregabalin undergoes negligible metabolism in humans. *In vitro* studies indicate that pregabalin does not appear to be a P-gp substrate, and does not inhibit any of the major CYP enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4). However, the potential for CYP induction or P-gp inhibition by pregabalin has not been systematically studied by the sponsor. In addition, pregabalin is a substrate for the system L amino acid (carrier-mediated) transporter (LAT). Potential for interactions at this transporter system cannot be ruled out. As active transport process is involved in renal excretion of pregabalin, there is a possibility of drug interactions through renal pathway.

The sponsor conducted several drug-drug interaction studies in humans. Interaction studies related to seizure or anxiety drugs are being evaluated by the OCPB review team co-located with the Division of Neuropharmacological Drug Products. Results from studies investigating the interaction with oral contraceptive (Ortho-Novum), gabapentin, oxycodone, ethanol are summarized in the table below. No clinically significant pharmacokinetic interactions were observed in these studies but some studies used relatively low dose (see table below). On the pharmacodynamic level, pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone and may potentiate the effects of ethanol. A population pharmacokinetic analysis in patients with — pain did not reveal any effect on pregabalin clearance with the concomitant use of certain oral hypoglycemics (metformin and glibenclamide), diuretics (furosemide), and insulin.

As indicated earlier in this section, the sponsor conducted an exposure-response analysis relating daily dose to pain score over time using pooled data from 8 trials for diabetic neuropathy and postherpetic neuralgia. The exposure-response model underpredicts the pain relief at 300 mg/day dose. Apparently, the model has some weakness. However, the data (>80% from TID regimens) clearly indicate a dose-response relationship (for TID regimens). Since creatinine clearance (CLcr) is a critical factor influencing the exposure (AUC), it is thought that this factor should be incorporated into the model using the known relationship between CLcr and pregabalin clearance.

In clinical trials, the most prevalent adverse events were dizziness and somnolence. The sponsor conducted dose-response analyses for both adverse events using pooled data from all four indications (17 clinical trials). The sponsor did not attempt to identify factors influencing the relationship and did not use these dose-response modeling for other purposes. A dose-response relationship was observed for both adverse events. For dizziness, there was a higher incidence rate in female patients compared to male patients.

In Vivo Drug-Drug Interaction Study Results

Co-administered Drug	Effect of pregabalin on coadministered drug	Effect of coadministered drug on pregabalin	Clinical Significance
Ortho-Novum	*Ethinyl estradiol* Cmax: ↑5% (90% CI: 95.6-115%) AUC: ↑14% (90% CI: 106-122%) *Norethindrone* Cmax: no change AUC: ↑16% (90% CI: 109-124%)	Not evaluated.	Pregabalin does not change the pharmacokinetics of ethinyl estradiol and norethindrone following coadministration.
Gabapentin	Cmax: ↓4.8% (90% CI: 89.0-102%) AUC: ↓3.6% (90%CI: 91.5-102%)	Cmax: ↓17.6% (90% CI: 77.9-87.2%) AUC: ↓7.8% (90%CI: 88.6-95.9%)	In this study, both pregabalin (200 mg tid) and gabapentin (400 mg tid) doses were low. The results may not be applicable to higher doses.
Oxycodone	Cmax: ↓1.1% (90% CI: 91.9-107%) AUC: ↓5.9% (90%CI: 87.2-102%)	Cmax: ↓4.5% (90% CI: 88.7-103%) AUC: no change (90%CI: 96.8-103%)	No significant interactions found in this study. However, oxycodone dose is relatively low (single 10 mg dose).
Ethanol	Cmax: ↓8.9% (90% CI: 84.1-98.7%) AUC: ↓12.3% (90%CI: 79.9-96.3%)	Cmax: ↑21% (90% CI: 107-137%) AUC: ↑1% (90%CI: 96.6-106%)	The 90% CI for Cmax and AUC were within the 70-143% and 80-125% ranges. However, pregabalin was administered 30 minutes prior to ethanol consumption. It is difficult to extrapolate these results to other possible scenarios such as more ethanol consumption or simultaneous administration of the two agents.

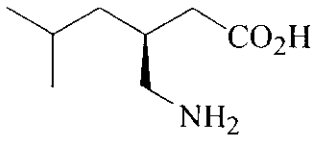
2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulations of the drug product?

The information is given below:

Structure:



Empirical formula:	$C_8H_{17}NO_2$
Molecular weight:	159.23
Chemical name:	(S)-3-(aminomethyl)-5-methylhexanoic acid
Dissociation constant (pKa):	4.2 and 10.6
Partition coefficient octanol:water (log P):	-1.90 -1.35 (pH 7.4)
Solubility:	soluble in aqueous media of various pH's

Figure 1

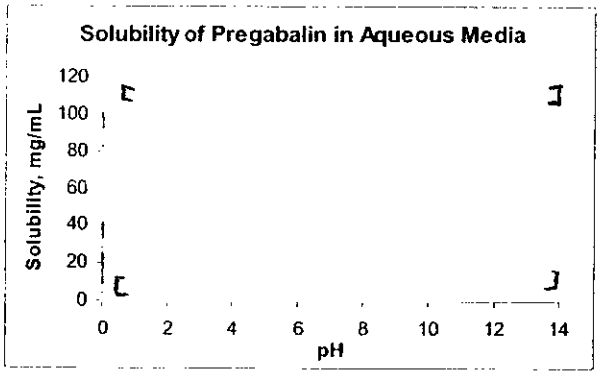


Table 1. To-Be-Marketed Formulations

Component	Wt (mg/capsule)							
	Formulation #/Capsule Strength							
	53 (A) 25 mg	62 (A) 50 mg	63 (C) 75 mg	64 (C) 100 mg	65 (C) 150 mg	66 (C) 200 mg	67 (C) 225 mg	68 (C) 300 mg
Pregabalin	25.0	50.0	75.0	100.0	150.0	200.0	225.0	300.0
Lactose Monohydrate Corn Starch Talc	(							)
Fill Weight	100.0	200.0	100.0	133.34	200.0	266.66	300.0	400.0
Capsule Size	# 4	#3	#4	#3	#2	#1	#1	#0

2.1.2 What is the proposed mechanism of action, therapeutic indication and dosage recommendations for pregabalin?

Mechanism of Action

Pregabalin is an alpha-2-delta (α2δ) ligand that has analgesic, anxiolytic, and anticonvulsant activity. Alpha-2-delta is an auxiliary protein associated with voltage-gated calcium channels. Nonclinical studies suggested that pregabalin bind to the α2δ subunit, leading to a reduction of calcium influx at nerve terminals which in turn leads to a reduction of release of several neurotransmitters, including glutamate, noradrenaline, and substance P. These activities and effects result in the analgesic, anxiolytic, and anticonvulsant activity exhibited by pregabalin. Pregabalin is inactive at γ-aminobutyric acid (GABAA and GABAB) receptors, it is not converted metabolically into GABA or a GABA antagonist, and it does not alter GABA uptake or degradation.

Proposed Indications

The sponsor is seeking the approval for the following indications:

- Diabetic peripheral neuropathy: management of neuropathic pain
- Postherpetic neuralgia: management of neuropathic pain
- [redacted]
- [redacted]

(NOTE: This review only covers studies related to neuropathic pain.[redacted]

Proposed Dosage Recommendation

The sponsor proposed the same dosing regimen for both diabetic peripheral neuropathy and postherpetic neuralgia:

[redacted]

To discontinue, withdraw the drug gradually over a minimum of 1 week.

The sponsor proposed dosage adjustment for renal impairment patients with CLcr < 60 mL/min.

Table 2. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose[a]		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥60			
30-60			
15-30			
<15			
Supplementary dosage following hemodialysis (mg)			

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the pivotal clinical trials?

The pivotal trials were double-blind, placebo-controlled trials. Earlier pivotal trials were conducted for a shorter duration (~6 weeks) and later trials were up to 13 weeks as the Agency's requirements changed. The sponsor conducted 6 trials for DPN (4 TID and 2 BID trials with one trial terminated early) and 7 trials for PHN (3 TID and 4 BID trials with 2 trials terminated early). Most trials included a titration period of 1-2 weeks to improve tolerability. In some trials, patients who were randomized to the 300/600 mg/day group received their dose according to their renal function (CLcr > 60 mL/min: 600 mg/day; 30 mL/min <CLcr≤60 mL/min: 300 mg/day).

2.2.2 What are the response endpoints and how are they measured in clinical pharmacology and clinical studies?

The response measure is pain score. Patients kept diaries of their daily pain scores using the 11-point numerical rating scale (NRS). The primary efficacy measure was the percent change in end point mean pain score (of last 7 days) from baseline. Determination of efficacy was based on comparison of the primary efficacy measure in treatment arms against placebo.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

YES.

Validated HPLC methods were used to assess pharmacokinetic parameters. However, the sponsor conducted dose-response analysis for efficacy and safety measures. Concentration (or AUC)-response analysis was not feasible because there were some uncertainties in the individual PK parameter values due to incomplete dosing records. The sponsor did try to incorporate known factors to modify the dose to more closely reflect individual exposure (AUC).

2.2.4 Are the proposed dosing regimens supported by clinical studies?

For DPN - NO.
For PHN - TO BE DETERMINED:

The following discussions relate to DPN only.

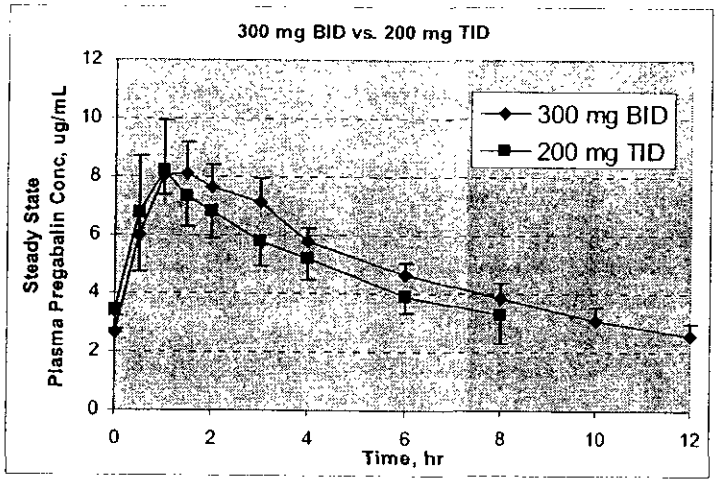
TID trials: The sponsor has two successful trials to support 100 mg TID (300 mg/day) and 200 mg TID (600 mg/day) regimens. The sponsor conducted only one trial for 50 mg TID regimen, which successfully beat the placebo arm based on the Agency's analysis. The study duration for these trials ranged from 5 to 8 weeks.

BID trials: The sponsor conducted two clinical trials for BID regimens (75 mg BID, 150 mg BID and 300 mg BID). One trial was prematurely terminated due to nonclinical toxicity findings (hemangiosarcoma in mice). The completed 12-week trial (Study 149) failed at all dose levels according to the Agency's analysis. However, the sponsor is proposing BID dosing for DPN.

Sponsor's rationale for BID dosing:

1. *PK*: The PK profiles were similar whether the same daily dose is administered as BID or TID. Figure 2 shows the steady state plasma concentration profiles for 200mg q8h and 300 mg q12h in a study of 2 parallel groups

Figure 2.



2. *PK for practical dosing interval*: In clinical practice, a drug prescribed in a TID regimen is more likely to approximate to a 6-6-12 hourly regimen, i.e. a more than eight hour time interval between evening and morning doses. As the q8h regimen diverges from an even eight hour dosing interval to an uneven regimen (e.g. shorter time intervals between doses taken during the day and a longer interval between the

evening and morning doses), the difference in the Cmax,ss and Cmin,ss for q8h and q12h administration would be further reduced.

3. *Exposure-response relationship*: Assessments in rat indicate that there is a negative hysteresis relationship between CNS concentrations and effect. As such, there is a lag in both the onset and offset of effect relative to concentration over time. The hysteresis was corroborated by dose-response modeling of data from neuropathic pain studies, which revealed a half life of drug-effect onset of approximately 16 hours. Since this half life of drug effect onset (16 hrs) is longer than the dosing interval of either a BID (12 hourly) or TID (8 hourly) regimen, the fluctuation in actual clinical response associated with peak and trough CSF/effect compartment concentrations would be less than that anticipated if only the plasma PK characteristics of pregabalin were taken into consideration (plasma elimination half life of ~6 hrs).

4. *Simulation:* Although not included in the rationale for BID dosing, in a separate section of the submission, the sponsor did report a simulation study and suggested that there were no differences in the dose-response between BID and TID regimens. The sponsor developed a dose-response model for neuropathic pain using data mostly (>80%) from TID trials. Based on this model, the sponsor conducted a simulation study to assess the predictive performance of the model against data from an independent study (#1008-196, a 13-week study with a BID regimen in PHN patients) that was not used in the model development. The observed dose-response for the BID regimens in this study is consistent with model predictions. Therefore, the sponsor concluded that there is no evidence to suggest differences in the exposure-response between BID and TID regimens for neuropathic pain.

5. *Clinical studies*: The efficacy of BID dosing of pregabalin in neuropathic pain (reviewer's note: for PHN only), [redacted] have been confirmed in clinical trials.

Reviewer's comments on the failed BID trial:

1) *PK:* Comparative steady state plasma concentration-time profiles for the 100 mg TID and 300 mg BID dosing regimens are shown in Figure 3 (Left panel: mean±SD concentrations within a dosing interval; Right panel: mean concentrations over a 24-hr time interval). The sponsor has demonstrated efficacy for the 100 mg TID regimen. Based on the concentration-time profiles, one would expect the 300 mg BID regimen to be efficacious. The BID trial (Study 149) failed to show efficacy at all dose levels, including the 300 mg BID regimen. Apparently, PK cannot explain the failure of the trial at least for the 300 mg BID regimen.

Figure 3A

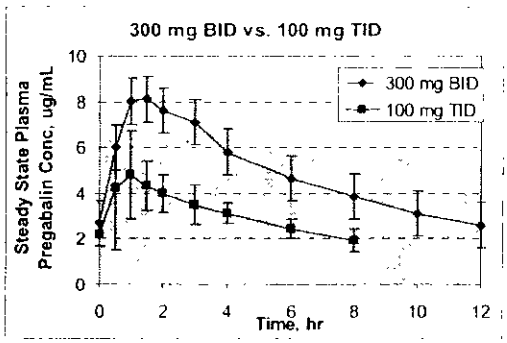
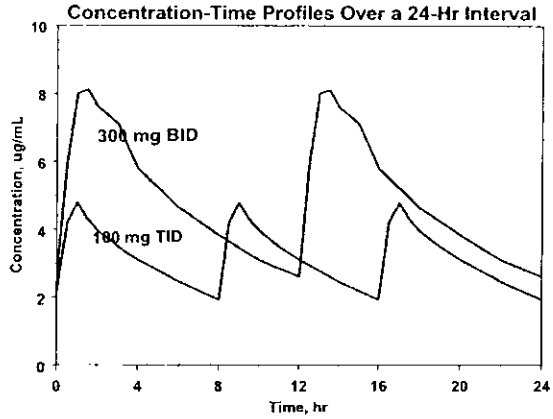


Figure 2B: Mean Steady State Plasma Pregabalin Concentration-Time Profiles Over a 24-Hr Interval



2) *Placebo effect*:

- Placebo effect was highly variable among DPN trials as illustrated in Figure 4. (NOTE: To put the variability in a proper perspective, one should compare the pain scores between placebo and active treatment arms. See Figure 5.)
- Both drug effect and placebo effect are time-dependent (Figure 5). Clinical trial data indicated that in general the onset of drug effect is fast relative to that of the placebo effect.
- Because of the above reasons, trials with longer duration and higher placebo effect may be more difficult to beat the placebo to declare efficacy. For Study 149, the placebo effect was large and did not appear to reach a plateau even at the end of the trial (12 weeks). (Note: Study 40 is a failed TID trial at 600 mg/day, which also showed a large placebo effect.)

Figure 4.

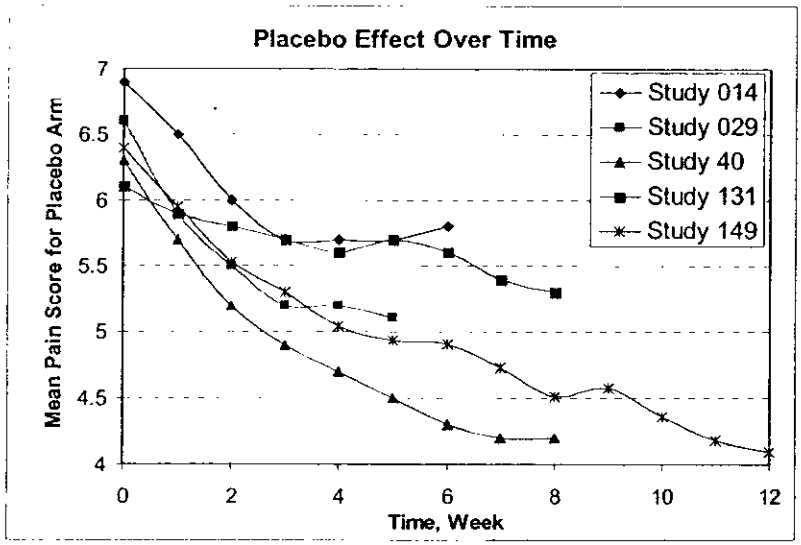
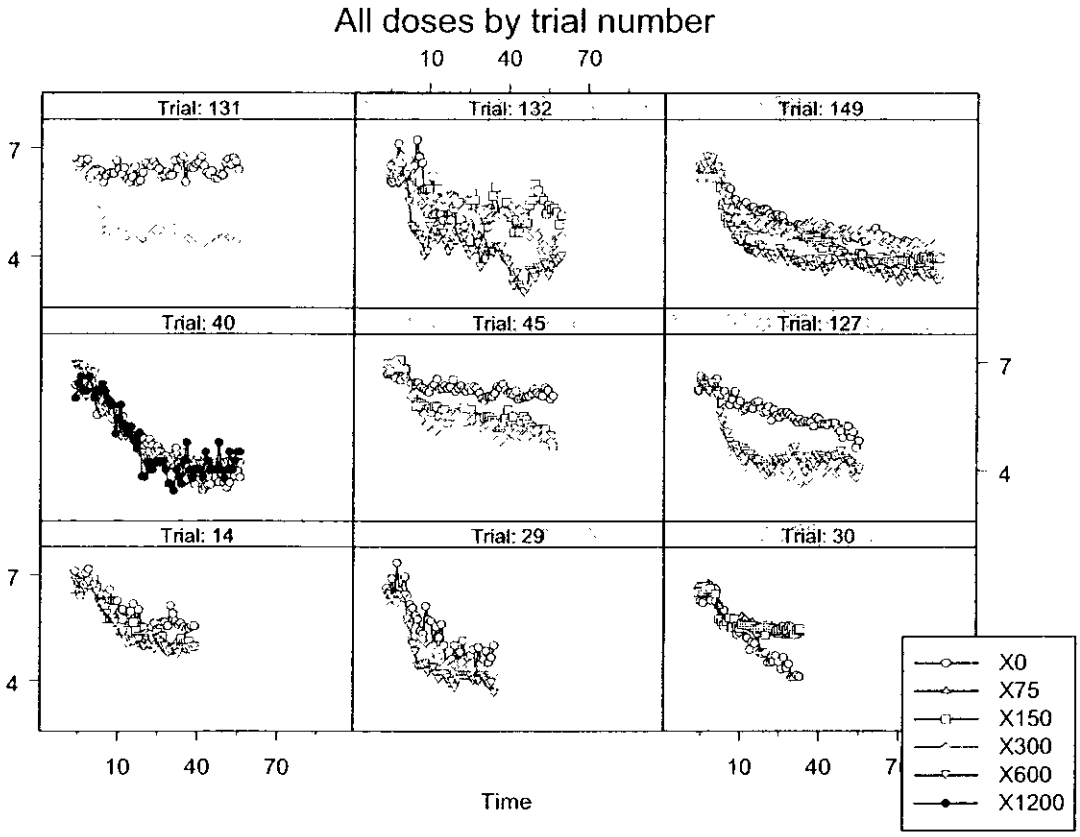


Figure 5. Time Course of Mean Pain Score at Various Doses Stratified by Study
Legend: X0: placebo; X150: 150 mg/day; X300: 300 mg/day, and so on
DPN: Studies 014, 029, 040, 131 & 149; PHN: Studies 030, 045, 127 & 132
(Provided by Dr. He Sun)



Reviewer's comments on the proposed BID dosing:

- The exposure-response relationship may be different for different diseases. Successful demonstration of efficacy for BID regimens in other diseases does not guarantee efficacy of BID regimens in DPN.
- Based on PK, one would expect 300 mg BID regimen to be efficacious. However, PK alone cannot support the BID dosing in view of the failed BID trial (Study 149).

2.2.5 What are the characteristics of the exposure-response relationships for efficacy?

The sponsor conducted an exposure-response analysis to relate daily dose to daily pain score using pooled data from 4 trials for diabetic neuropathy and 4 trials for postherpetic neuralgia. The exposure-response relationship was used by the sponsor as one of the

evidences that BID and TID dosing will result in similar efficacy. However, in our evaluation of the BID dosing, we focused on the PK information and observed response data and did not need to rely on the exposure-response modeling. A tabular summary of the observed endpoint mean pain scores and placebo-corrected changes for the pooled data is given below, which shows that there is a dose-response relationship.

Table 3. Observed Endpoint Mean Changes from Baseline

Dose (mg/day)	N	Mean ± SE	Placebo-Corrected
0	632	-1.06 ± 0.08	0
75	160	-1.39 ± 0.15	0.330
150	200	-1.46 ± 0.11	0.399
300	343	-2.26 ± 0.12	1.19
600	336	-2.60 ± 0.13	1.54

The sponsor made extensive efforts to conduct this exposure-response analysis. However, uncertainties about the model exist as pain relief at the 300 mg dose, which is an important therapeutic dose, was not well predicted (see figure below). Although disease type was included as a covariate for some parameters (such as Emax), there may be other differences that were not examined. It may be helpful to model the two indications separately.

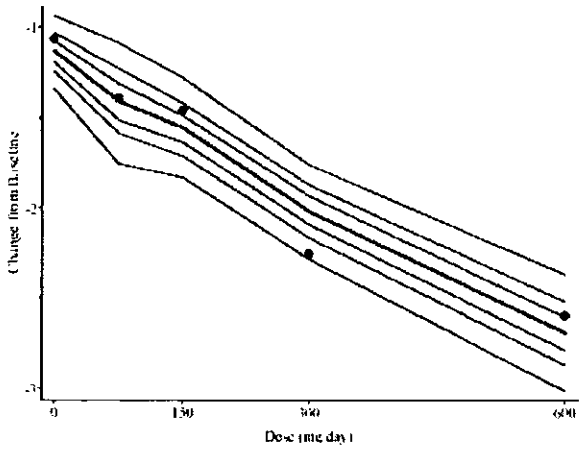


Figure 6. Observed (•) endpoints mean changes from baseline as compared with select percentiles. The select percentiles were constructed from 1000 simulated trials based on the xposure-response model and patient demographics in the clinical trials. (Median: bold line; 1st and 3rd quartiles: solid lines; 10th and 90th percentiles: dashed lines; 1st and 99th percentiles: dotted lines)

2.2.6 What are the characteristics of the exposure-response relationships for safety?

The most prevalent adverse events occurred in clinical trials were dizziness (AE1) and somnolence (AE2). Incidence (%) of treatment-emergent adverse events of AE1 and AE2 in DPN and PHN trials is presented in the table below, which indicates that there is a dose-response relationship for either adverse event.

Table 4. Incidence (%) of Treatment-Emergent Adverse Events by Dose in Neuropathic Pain Trials

Adverse Event	Pregabalin Dose			
	Placebo	150 mg/day	300 mg/day	600 mg/day
Dizziness	6.8	14.2	27.2	31.4
Somnolence	3.9	9.7	15.5	18.7

The sponsor conducted dose-response analyses for both adverse events using pooled data from all four indications (17 clinical trials). The sponsor did not attempt to identify factors influencing the relationship and did not use these dose-response modeling for other purposes.

Dizziness (AE1):

The sponsor developed separate models for (i) incidence of AE1, and (ii) severity of AE1 on condition that an event has occurred. The unconditional distribution was calculated by convolving the 2 probability distributions from the separate fits. (Severity of AE1 was graded from 0 to 3 with 0 as being no event.)

Incidence of dizziness: The probability (P) for a subject to experience AE1 during the trial increased with dose as shown in the Figure 7. At the 600 mg/day, the incidence of AE1 averaged to be approximately 30% (range: from <20% to >50%). Female patients apparently reported higher incidence of AE1. It is clear that the variability was high among various trials. The sponsor used a nonlinear (sigmoidal Emax) regression model to relate probability of AE1 to dose. The ED_{50} was estimated to be 153±8 mg/day.

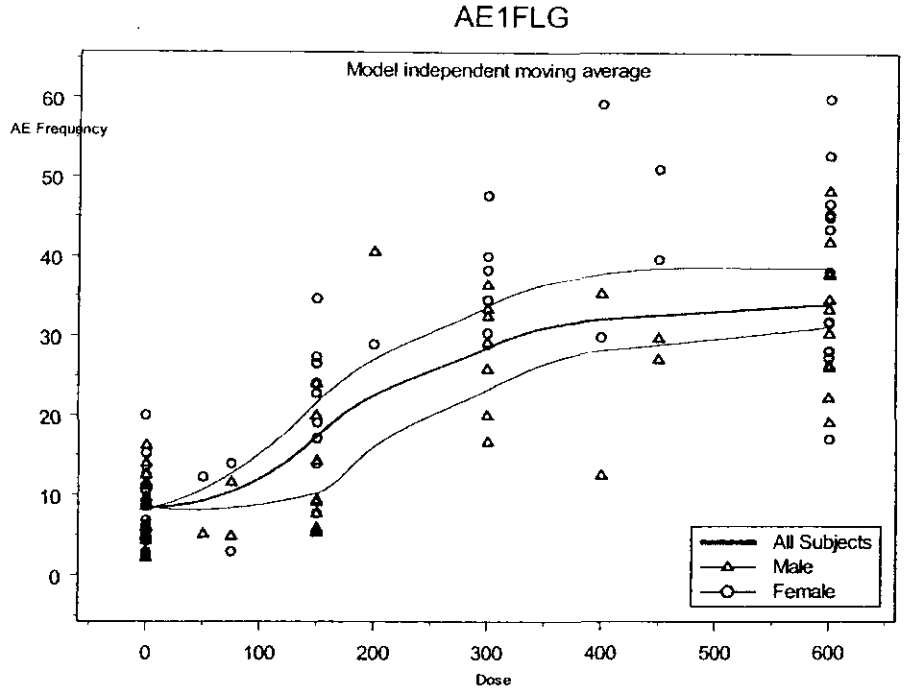
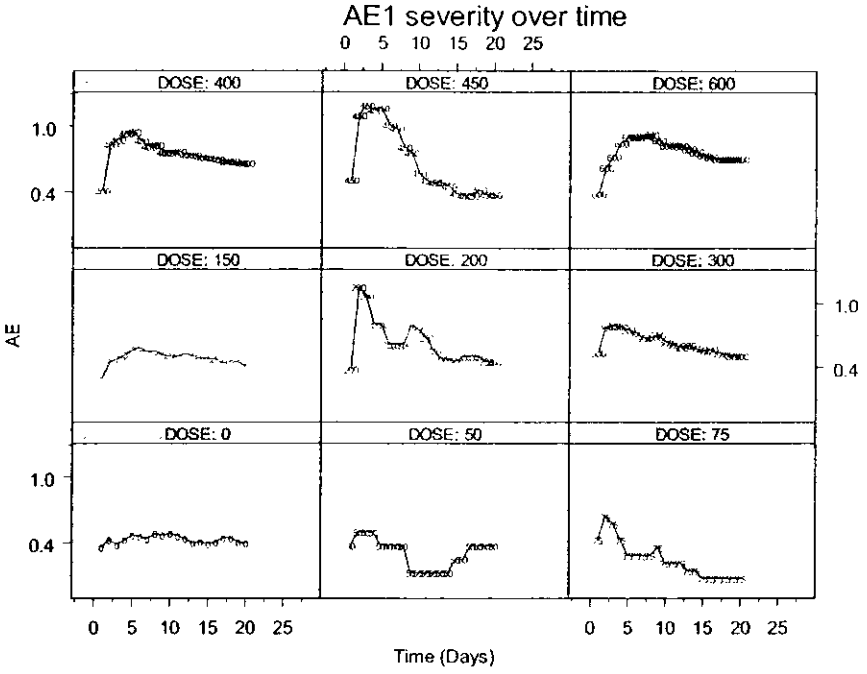


Figure 7. Incidence of Dizziness in All 17 Trials. (This is a model-independent plot by Dr. He Sun. x-axis: daily dose; y-axis: frequency (%) of AE1; Each point represents a trial stratified by gender)

Severity of Dizziness (conditional): For patients who reported AE1 at least once during the trial, the mean AE1 severity score varied with time and dose as shown in the figure below. In the sponsor's model, AE1 severity score was treated as ordered categorical outcome. The model for the dose-AE1 severity response relationship in AE1 patients is a mixed-effect logistic regression model that includes a sigmoidal Emax model with a time-dependent exposure effect on dose and a component that allows for an exponential attenuation of Emax to a plateau to describe the observed data. ED50 was estimated to be 275±32 mg/day.

Figure 8: Time Course of Mean AE1 Severity Score (for patients who did experience AE1 during the trial)



Unconditional Probability of AE1: The unconditional distribution for AE1 was calculated by convolving the probability distribution for the incidence of AE1 with the conditional probability for the severity of AE1. Figure 9 shows the time course of the probability of experiencing various degrees of severity of AE1 by dose. The prediction deviated from the observed data for the 200 mg and 450 mg doses. It is noted that these doses had fewer subjects.

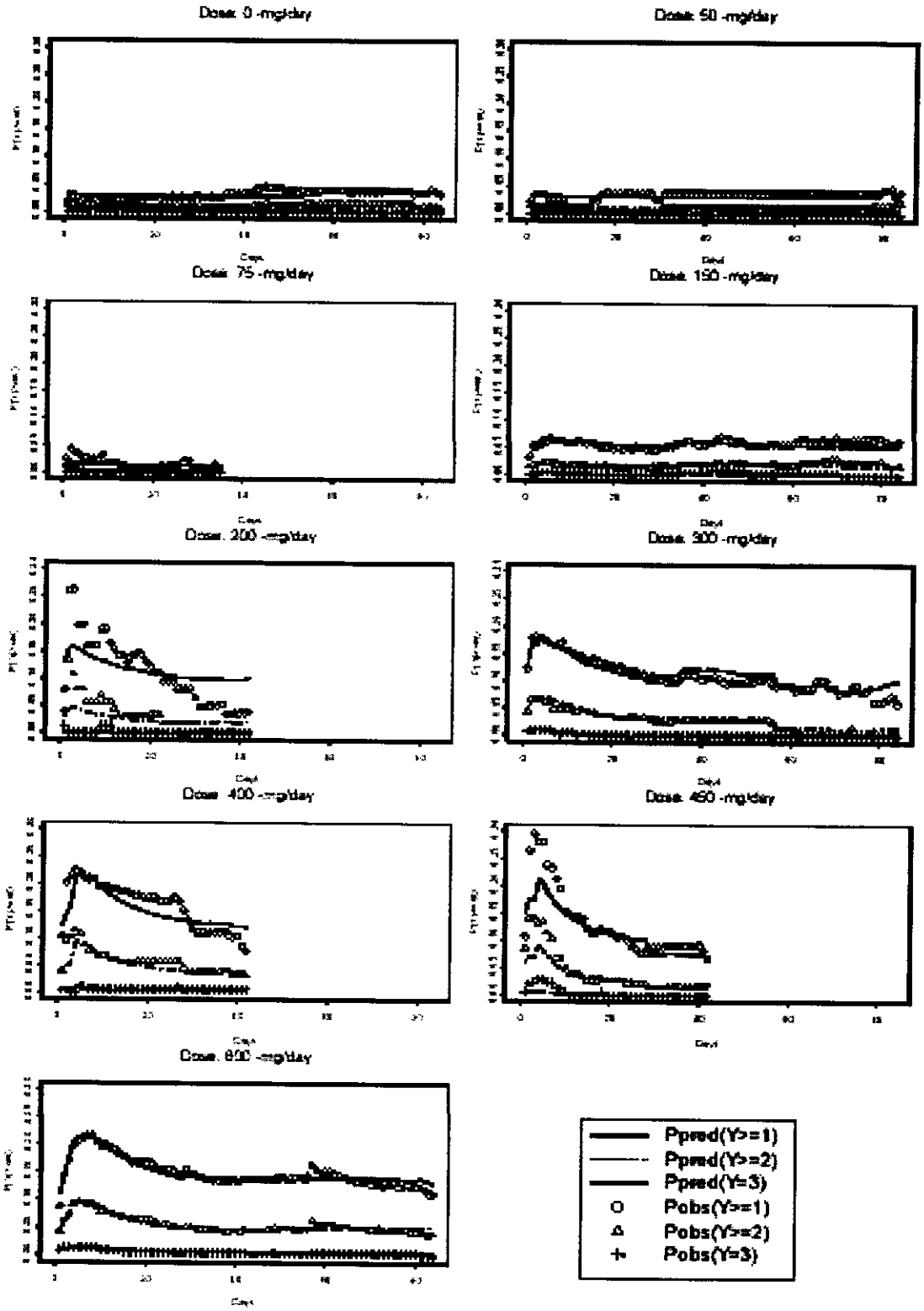


Figure 9. Probability of experiencing various degrees of severity of dizziness by dose

Model-predicted unconditional probability (%) of experiencing AE1 as a function of time after 600 mg pregabalin daily is presented in Table 5.

Table 5.

Time (days)	Any Dizziness	Dizziness of Moderate Intensity or Greater	Severe Dizziness
	Mean (95%CI)	Mean (95% CI)	Mean (95% CI)
1	10.9 (9.8-12.1)	4.38 (3.53-5.23)	0.67 (0.36-0.98)
6	21.7 (20.6-22.7)	9.86 (8.75-10.96)	1.43 (0.94-1.93)
14	18.0 (16.8-19.3)	7.08 (6.03-8.13)	0.91 (0.47-1.35)
21	15.5 (14.3-16.8)	5.57 (4.58-6.57)	0.68 (0.28-1.08)
28	13.8 (12.5-15.2)	4.67 (3.68-5.67)	0.60 (0.18-1.03)
84	13.1 (10.2-15.9)	5.10 (2.90-7.30)	0.52 (0.00-1.18)

Somnolence (AE2)

The sponsor conducted a similar exposure-response analysis for AE2. Because of differences among indications, the results do not represent neuropathic pain. The incidence rate for neuropathic pain by dose is given in the table below.

Adverse Event	Pregabalin Dose			
	Placebo	150 mg/day	300 mg/day	600 mg/day
Somnolence	3.9	9.7	15.5	18.7

2.2.3 Does pregabalin has the potential to prolong QT?

The potential of pregabalin as a QT prolonger is still under evaluation by the Review Team. According to Dr. Jerry Cott, the Pharm/Tox reviewer, there are no nonclinical studies evaluating QTc prolongation potential of this drug. Phase 1 QT data were inadequate for exposure-response analysis.

There is no prospectively designed QT study. The sponsor conducted a QT analysis using pooled data from 164 subjects in 7 Phase 1 multiple dose trials. QT measurements were made 1-2 hrs postdose. QTc interval measurements were calculated using Bazett's, Fridericia's, and linear model-based corrections. Linear regression analysis of QTc change from baseline vs. Cmax yielded a negative slope (Note: The slope may not be statistically significantly different from zero). The sponsor concluded that as Cmax increases the change from baseline QTc decreases. It should be noted that none of the studies had a positive control and there was no placebo arm to serve as a negative control for 5 out of the 7 studies. In addition, there was no plasma concentration data at the times of ECG measurements and Cmax values were used as a surrogate in the regression. Therefore, the regression analysis is not meaningful. Further, the highest exposure included in the analysis does not cover the concentration range expected for patients with renal impairment (expected Cmax: > 20 μg/mL at 300 mg BID for patients with CLcr ~ 60 mL/min). Phase 3 QT data and other cardiac events are being evaluated by the clinical Team.

2.2.4 What are the basic pharmacokinetic characteristics of pregabalin in healthy young subjects?

2.2.4.1 What are the single dose and multiple dose PK parameters in healthy young volunteers?

Following single and multiple-dose administration under fasting conditions in healthy young subjects, plasma pregabalin concentrations peaked within 1.5 hours postdose and then declined biphasically. Steady state plasma concentration-time profiles for various dosing regimens are shown in the figure below.

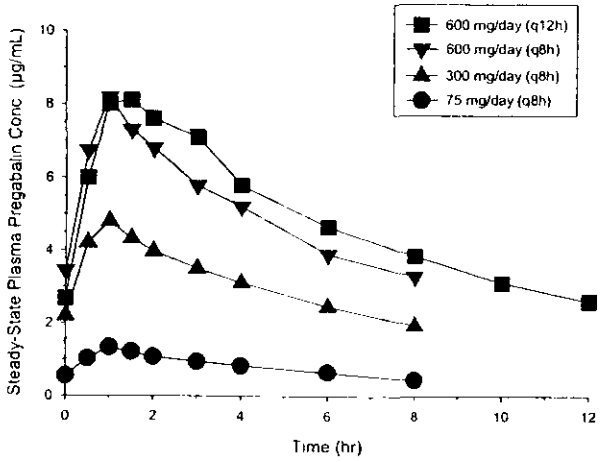


Fig. 10: Mean steady state plasma concentration-time profiles in healthy young volunteers following various dosing regimens (25 mg q8h, 100 mg q8h, 200 mg q8h and 300 mg q12h)

Mean pharmacokinetic parameters for single- and multiple-dose administration at the dose range of 25-300 mg are given in the table below:

Table 6. Mean (%CV) Pharmacokinetic Parameter Values in Healthy Young Volunteers (single dose: 25-300 mg; multiple dose administration: 25-300 mg q8h & 300 mg q12h)

Dose	Dosing Regimen	N	Cmax	tmax	AUC	λz	t½	Ae%	CLr
					Day 1				
25	SD	10	0.864	0.850	5.633	0.130	5.476	87.7	67.0
			(19.3)	(28.4)	(21.6)	(17.6)	(18.1)	(13.8)	(20.6)
100	SD	6	2.987	0.833	22.130	0.116	6.099	90.2	69.3
			(16.2)	(31.0)	(16.8)	(16.2)	(18.0)	(8.4)	(15.2)
200	SD	13	5.227	1.308	37.658	0.115	6.127	90.6	80.9
			(27.0)	(33.3)	(16.3)	(15.4)	(13.7)	(21.1)	(23.4)
300	SD	8	7.565	1.375	62.752	0.105	6.635	91.2	73.2
			(16.4)	(57.5)	(9.3)	(8.7)	(10.1)	(4.8)	(9.8)
300	SD	8	8.585	1.000	71.376	0.107	6.617	96.9	68.8
			(17.4)	(26.7)	(14.4)	(15.0)	(13.1)	(13.0)	(16.6)
					Day 22				
25	q8h	8	1.388	0.938	6.67	0.119	5.940	94.3	--
			(19.5)	(34.2)	(18.3)	(15.1)	(17.3)	(22.6)	
100	q8h	6	5.028	0.833	25.19	0.113	6.309	107.8	--
			(21.3)	(31.0)	(23.0)	(17.0)	(19.6)	(11.6)	
200	q8h	11	8.519	0.909	41.72	0.113	6.270	82.0*	--
			(14.8)	(22.2)	(12.8)	(14.5)	(13.6)	(30.6)	
300	q12h	8	9.066	1.438	59.00	0.105	6.697	91.2	--
			(10.5)	(57.1)	(6.4)	(13.0)	(16.2)	(14.6)	
300	q8h	8	13.426	1.000	67.35	0.109	6.452	99.3	--
			(14.5)	(26.7)	(15.4)	(14.6)	(13.3)	(11.9)	

*Ae%: percent of dose recovered in urine as the unchanged drug

2.2.4.2 How does the PK of the drug in healthy volunteers compare to that in patients?

The sponsor conducted a population PK analysis using data from Phase 1 trials in healthy subjects and Phase 3 trials in neuropathic pain (DPN and PHN) patients. The disease status was not found to be a significant factor.

2.2.4.3 What are the characteristics of drug absorption?

Following oral administration of pregabalin under fasting conditions, peak plasma concentrations occurred within 1.5 hours. Based on a mass balance study and urinary recovery of the unchanged drug in various studies, the absolute bioavailability is estimated to be >90%. It is thought that active transport process is involved in the absorption of pregabalin. Pregabalin is a substrate for the system L transporter. In a sponsor funded project, Jezyk et. al. (1999, Pharm. Res. 16 (4):519-526) studied transport of pregabalin in rat intestine and Caco-2 cell monolayers. While paracellular transport was predominant in Caco-2 cells, pregabalin transport was carrier-mediated in rat Ileum.

2.2.4.4 What are the characteristics of drug distribution?

In vitro studies indicate that pregabalin is not bound to plasma proteins. In a radiolabeled study, the mean erythrocyte-to-plasma radioactivity ratio was 0.77±0.08. The apparent volume of distribution was estimated to be ~0.54 L/kg. (Note: Available nonclinical data indicate that pregabalin crosses blood brain barrier in mice, rats and monkeys and crosses placenta in rats and is present in the milk of lactating rats.)

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Pregabalin is eliminated from the systemic circulation predominantly through renal excretion of the unchanged drug. In a radiolabeled mass balance study, mean (%CV) cumulative recovery of total radioactivity was 92.0± 8.7% of the dose in the urine and <0.1% in the feces. Approximately 90% of the administered dose was recovered as the unchanged pregabalin in the urine. The elimination half-life was approximately 6.3 hours. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects, indicating that renal tubular reabsorption is involved since pregabalin is not bound to plasma proteins.

2.2.4.6 What are the characteristics of drug metabolism?

Pregabalin undergoes negligible metabolism in humans. In *in vitro* studies using human liver microsomes and viable human hepatocyte suspensions, there was no indication of metabolism of pregabalin. In a radiolabeled mass balance study, approximately 90% of the administered dose was recovered in the urine as the unchanged pregabalin. The major metabolite found in the urine was the N-methylated derivative of pregabalin, which accounted for 0.9% of the administered dose. (Note: In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.)

2.2.4.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Following single-dose (25-300 mg) and multiple-dose (25-300 mg q8h) administration of pregabalin, the pharmacokinetics of pregabalin is linear.

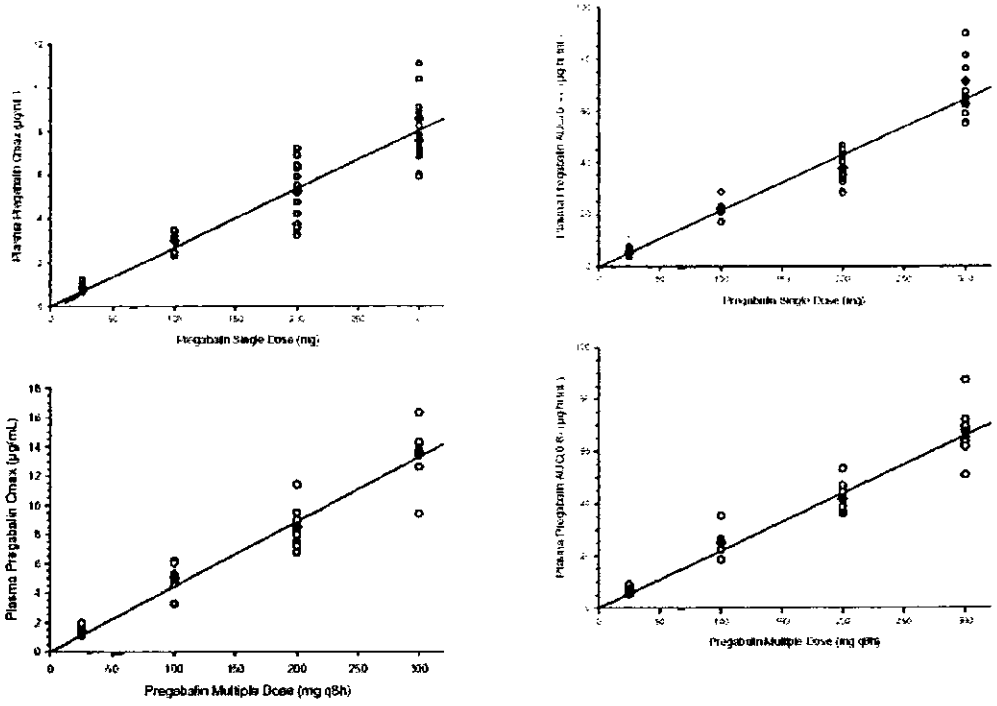


Figure 11. Pregabalin Cmax (left panel) and AUC (right panel) Values Following Single-Dose (25-300 mg; upper panel) and Multiple-Dose (25-300 mg q8h; lower panel) Administration

2.2.4.8 How do the PK parameters change with time following chronic dosing?

There is no evidence that the PK parameters change with time. Multiple dose pharmacokinetics can generally be predicted from single dose data. Steady state is reached within 24-48 hours with a mean accumulation ratio of 1.37 after BID dosing and ranging from 1.70 to 1.96 after TID dosing.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

In a population PK analysis using pooled Phase 1 and Phase 3 data, age (adults), weight, race (Blacks and Hispanics), gender and disease status (DPN and PHN) were not found to be significant factors influencing pregabalin clearance when CLcr was taken into account.

Pharmacokinetics in pediatric patients have not been characterized. The sponsor is seeking both DPN and PHN indications in adults only. Waiver of pediatric studies for PHN has been granted. The sponsor requested a waiver of pediatric studies for DPN which is under evaluation.

Pregabalin undergoes negligible metabolism in humans. The effect of hepatic insufficiency on total body clearance of pregabalin has not been studied but is expected to be minimal.

Creatinine clearance was identified as an important factor from both a renal impairment study and the PPK analysis. The relationship between pregabalin clearance and CLcr as observed in the renal impairment study is shown in the figure below (Regression line: CL/F = 5.51 + 0.547 x CLcr, R = 0.890, R^2 = 0.79). In the PPK analysis, the relationship was expressed as: CL/F = 0.0459 x CLcr which plateaus at CLcr of 105 mL/min.

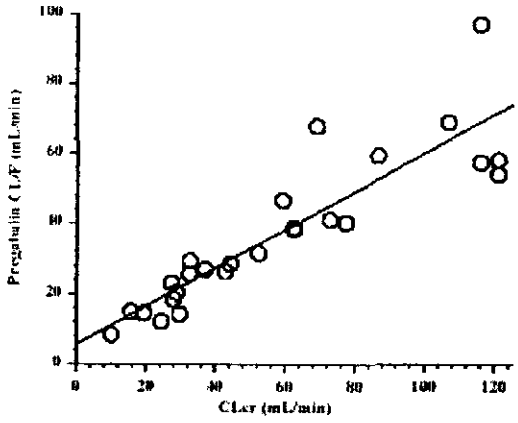


Figure 12. Pregabalin CL/F vs. CLcr

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustment, if any, are recommended for each of these subgroups?

Dosage adjustment is necessary for patients with impaired renal function due to age and/or diseases. Clinical trials have enrolled patients with CLcr > 60 mL/min without dosage adjustment. With acceptable safety data in these patients, dosage adjustment is considered necessary only for patients with CLcr ≤ 60 mL/min. The sponsor's proposed dosing regimens for patients with impaired renal function will result in similar exposure (AUC) in these patients. The concentration-time profiles at steady state were simulated for the maximal dose for each specified CLcr range. Comparative profiles (Figure 13, a-c) indicate that with the proposed dosing regimen, Cmax and Cmin for the renal impairment patients are within the range seen in the group with CLcr> 60 mL/min. Therefore, the sponsor's proposed dosing regimen is considered acceptable. A 4-hour hemodialysis reduced the palsam pregabalin concentration by 52±For clarity and safety, some modification on the label for the supplementary dose after hemodialysis is recommended.

Sponsor's Proposal for Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose[a]		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
Supplementary dosage following hemodialysis (mg)			

For clarity, supplementary dosage immediately following a 4-hr hemodialysis is specified as follows:

- Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg
- [redacted]
- Patients on the 75 mg QD regimen: take one supplemental dose of [redacted] mg or 100 mg

Fig. 13-a

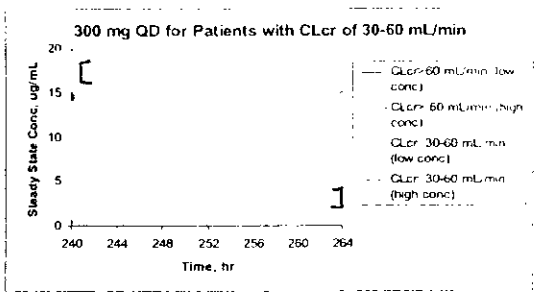


Fig. 13-b

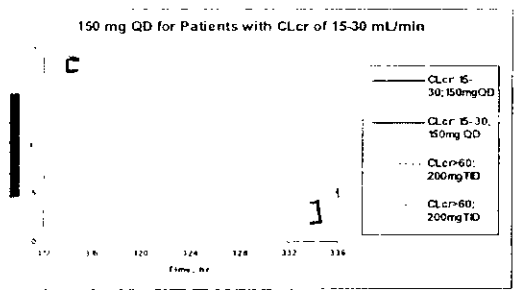
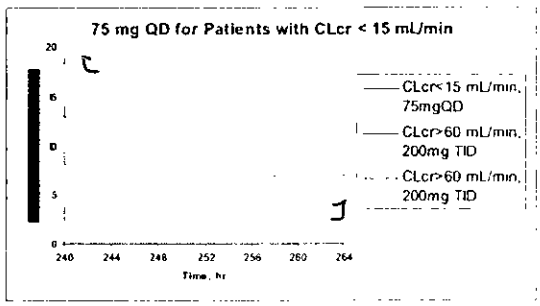


Fig. 13-c



Reference profiles for all 3 plots:
Highest (blue) and lowest (green) steady state conc in the CLcr > 60 mL/min group at 200 mg TID.

Fig. 13-a: Highest and lowest steady state conc in the qroup with CLcr of 30-60 mL/min at 300 mg QD

Fig. 13-b: Highest and lowest steady state conc in the group with CLcr of 15-30 mL/min at 150 mg QD

Fig. 13-c: Steady state conc in a subject with CLcr = ___ mL/min at 75 mg QD

2.3.3 What pregnancy and lactation use information is there in the application?

There are no data to indicate that pregabalin crosses human placenta or is secreted into human milk. However, available nonclinical data indicate that pregabalin does cross placenta in rats and is present in the milk of lactating rats.

2.4 EXTRINSIC FACTORS

2.4.1 Drug-drug Interactions

The sponsor evaluated effect of pregabalin on metabolic enzymes, *in vitro*, and performed several clinical pharmacokinetics studies to evaluate its potential for pharmacokinetic and/or pharmacodynamic drug interactions upon coadministration with various drugs.

2.4.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Available data do not suggest potential for pharmacokinetic drug-drug interactions. However, certain characteristics of pregabalin as related to drug-drug interaction potential have not been fully assessed.

2.4.1.2 Is the drug a substrate of CYP enzymes?

Pregabalin is not significantly metabolized in various hepatic tissue matrices. In an in vitro study, [14C] pregabalin (100 nM or 16 ng/mL) was not metabolized upon incubation with human liver microsomes for up to 120 minutes (Study Report #RR 764-02235). In addition, incubation of ~25 μg/mL of [14C] pregabalin for up to 180 minutes with viable (~80%) human hepatocyte suspensions did not yield any metabolite (Study Report # RR 764-03070). Mass balance study in healthy volunteers suggests that < 2% of pregabalin is metabolized. Further characterization of pregabalin metabolism, to resolve specific CYP enzyme involvement, may not be necessary.

2.4.1.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

CYP Inhibition: Pregabalin does not inhibit any of the major CYP enzymes.
In an in vitro study pregabalin (up to 1000 μM) did not significantly inhibit CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in vitro in three different batches of human liver microsomes (Study Report #RR 764-03016).

CYP Induction: Potential for CYP induction by pregabalin was not systematically studied. There is evidence from preclinical studies suggesting possible increase in CYP2B and CYP2E immunoreactive enzyme level and activity by pregabalin upon repeat high dose (1250 mg/kg) administration in rats (Poster presented at the Seventh Internal congress of Toxicology, 1995, Abstract # 35-P-1). The rat plasma concentrations achieved are very high compared to the steady state concentrations achieved following highest human dose. Although there is no evidence from any of the clinical pharmacokinetic studies performed that would suggest CYP induction, the potential for CYP induction by pregabalin was not fully evaluated.

2.4.1.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

P-gp Substate: Pregabalin does not appear to be a P-gp substrate in vitro. A published report indicates that while paracellular transport of pregabalin was predominant in Caco-2 cells, pregabalin transport was carrier-mediated in rat Ileum. Pregabalin transport in Caco-2 cells was concentration- and direction-independent and equivalent in magnitude to the paracellular transport marker, mannitol (Jezyk et.al. 1999, Pharm. Res. 16 (4):519-526).

P-gp inhibitor: P-gp inhibition by pregabalin was not studied by the sponsor.

2.4.1.5 Are there other transporter pathways that may be important?

Yes, pregabalin appears to be a substrate for the system L amino acid (carrier-mediated) transporter (Study Report # RR 761-00007). In addition, in a sponsor funded project, Jezyk et. al. (1999, Pharm. Res. 16 (4):519-526) studied transport of pregabalin in rat intestine and Caco-2 cell monolayers. While paracellular transport was predominant in Caco-2 cells, pregabalin transport was carrier-mediated in rat Ileum. It is noteworthy that pregabalin structural congener, gabapentin, is also a substrate for system L transporters.

System L consists of several basolateral membrane transporters, which mediate Na+-independent transport of large neutral amino acids through the epithelial cells of Blood-tissue barriers(BBB and placenta), small intestine, renal proximal tubules. Recently, several types of human L-type amino acid transporters (LATs) have been cloned. Uchino et. al. (2002, Mol. Pharmacol. 61(4): 729-737) demonstrated that gabapentin is a substrate for LAT1, however status of pregabalin is not known.

2.4.1.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Yes, pregabalin is intended for several indications and coadministration is foreseen with a variety of classes of drugs in the treatment and management of epilepsy, – pain disorders, diabetes etc. Pharmacokinetic drug interaction studies between pregabalin and drugs used in — pain disorders and oral contraceptives are evaluated in this review.

Drug interaction study with Oral Contraceptive (OC) Agent, Ortho-Novum®.
Pharmacokinetic drug interaction was not observed following multiple dose coadministration of pregabalin and Ortho-Novum®. Oral contraceptive regimen was administered for a total of three cycles in healthy female volunteers. The pharmacokinetics of ethinyl estradiol and norethindrone alone, determined at the end of second cycle, were similar to the PK assessments, at the end of third cycle of OC administration, made after 22 days of coadministration with pregabalin (200 mg tid).

Drug interaction study with gabapentin
Clinically relevant pharmacokinetic drug interaction may not result upon coadministration of gabapentine (400 mg tid) and pregabalin (200 tid). Gabapentin is clinically used at doses up to 3600 mg/day and pregabalin doses up to 600 mg/day in divided doses for various indications. The results of the multiple dose drug interaction study reviewed here may not be applicable to other higher dose coadministration regimens of gabapentin and pregabalin.

Drug interaction study with oxycodone
Clinically relevant pharmacokinetic drug interaction may not result upon coadministration of pregabalin (300 mg bid) and oxycodone (10 mg bid). The study also indicates that at the doses employed, pregabalin coadministration does not enhance the respiratory depression caused by oxycodone.

Drug interaction study with ethanol
Clinically relevant pharmacokinetic drug interaction may not result upon coadministration of pregabalin and ethanol. A 21% increase in pregabalin Cmax was observed following administration 30 minutes prior to ethanol consumption. However, the above tabulated pharmacokinetic parameters indicate that the 90% confidence intervals for Cmax and AUC(0-12 or 0-∞) values were within the 70% to 143% and 80% to 125% ranges, respectively, indicating absence of a pharmacokinetic interaction of between ethanol and pregabalin. However, it may be difficult to extrapolate these results to other possible scenario's such as administration of higher dose of pregabalin (600 mg)

or more ethanol consumption or more importantly simultaneous administration of the two agents.

2.4.1.7 What other co-medications are likely to be administered to the target patient population?

In patients suffering from diabetic peripheral neuropathy, pregabalin is anticipated to be coadministered with a variety of other drugs used in diabetes disease management. Some of the classes of agents DPN patients might be receiving are antidiabetic and antidiuretic drugs. Tabulated below are some of agents that were administered in the clinical studies submitted as a part of this NDA. The sponsor performed a population analysis for pregabalin disposition in these patients and concluded that there was no significant difference in pregabalin pharmacokinetics.

Table 7: Elimination Pathway of Co-Administered Drugs

Coadministered drug	1° route of elimination	2° route of elimination	Basis for dosage adjustment
Metformin	Renal (tubular secretion Cl_r > 3.5 Cl_{cr})	-	Renal impairment
Glyburide, Glibenclamide	Hepatic metabolism and Renal elimination		
Glipizide	Hepatic metabolism Renal excretion of metabolites		Caution with renal and hepatic failure
Troglitazone	Hepatic metabolism		
Glimepiride	Hepatic metabolism Renal excretion of metabolites		Renal function (Metabolite elimination decreased in renal failure)
Repaglinide	Hepatic metabolism	-	Hepatic impairment
Furosemide	Hepatic (glucuronidation) and renal elimination		Hepatic and renal dysfunction
Hydrochlorthiazide	Renal elimination		Caution with renal failure
Triamterene	Hepatic (sulfatation) metabolism and Renal excretion of parent and metabolites		Contraindicated in renal function impaired subjects
Indapamide	Hepatic metabolism and renal excretion of metabolites		Caution with renal and hepatic failure

A brief review of potential for drug-drug interactions between these agents and pregabalin is presented below.

Potential for drug metabolism-related drug interactions with pregabalin: From a drug metabolism perspective, pregabalin is not metabolized in humans and it is known not to inhibit any of the major CYP isoforms at physiologically relevant concentrations. Hence, CYP inhibition-related drug-drug interactions with pregabalin and other coadministered drugs are not anticipated.

Potential for drug-protein binding/displacement-related drug interaction with pregabalin: Pregabalin is not bound to the plasma proteins; hence drug interactions due to plasma protein displacement are not anticipated.

Potential for renal excretion-related drug interaction with pregabalin:
As indicated in the table above, several drugs coadministered with pregabalin are excreted by renal route either intact or following metabolism. In addition, urinary excretion data from the mass balance study suggests significant tubular reabsorption of

pregabalin. It is not certain if pregabalin and coadministered drugs would compete or inhibit one or more of renal excretion or reabsorption mechanisms. Effect of pregabalin specifically on the tubular reabsorption or secretion is not known.

2.4.1.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

The above studied pharmacokinetic pharmacodynamic drug interactions studies did not yield any significant information indicating an exposure-response relationship following coadministration or pregabalin with other drugs.

2.4.1.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There is no mechanistic basis suggesting pharmacodynamic drug-drug interactions following coadministration of pregabalin and other drugs mentioned above. In in vitro binding assays, pregabalin was found to have low binding potential to a variety of receptors involved in neurotransmitter activity and uptake, ion channels, kappa opioid receptor, prostaglandin receptors. The purported mechanism of action of analgesic, anxiolytic and antiseizure activity of pregabalin may be via binding to alpha2-delta protein (a calcium channel subunit). Pregabalin shares this mechanism of action with another structurally similar compound, gabapentin (Gong HC et. al. J. Membrane Biol. 184: 35-43). There may be a possibility of additive pharmacodynamic effects upon coadministration of pregabalin and gabapentin. However, the sponsor did not perform a clinical study looking at potential for pharmacodynamic effects of pregabalin and gabapentin coadministration in patients.

2.4.1.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

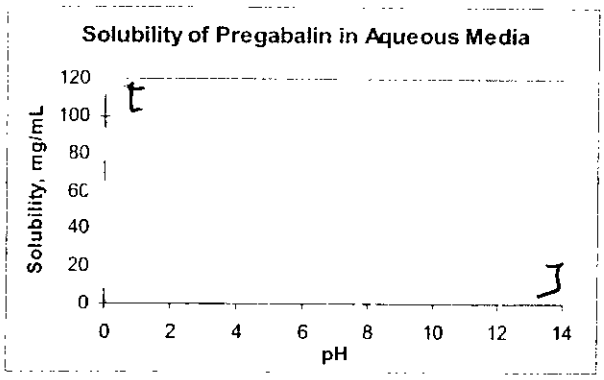
The induction potential of pregabalin has not been evaluated. The sponsor is encouraged to conduct an *in vitro* study for this purpose.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Solubility:

Pregabalin is an amino acid having 2 pKa values of approximately 4.2 and 10.6. The lowest aqueous solubility (at its iso-electric point of pH ~7.4) is — mg/mL. The highest immediate release dose strength developed for pregabalin is 300 mg. The volume of aqueous media required to dissolve 300 mg of pregabalin at the lowest solubility is — mL. Therefore, pregabalin is considered a high solubility drug.



Permeability:
The oral bioavailability of immediate release pregabalin capsules was at least 90% based on percentage of dose excreted unchanged in the urine (averaged 91.1% in one single dose study; 90% in the mass balance study). The BCS guidance suggest that compounds may be classified as highly permeable if the extent of absorption is >90%. Therefore, pregabalin is a highly permeable compound. Exploratory preclinical data using in situ rat intestinal (jejunal) perfusion model relative to reference compounds atenolol, metoprolol, and propranolol showed that effective permeability of pregabalin was comparable to that of metoprolol (32.0 × 10-6 ± 5.33 cm/s versus 30.2 × 10-6 ± 12.8 cm/s), suggesting that pregabalin is a high permeability compound. Although active transport is believed to be involved in the absorption of pregabalin, dose proportionaility within the therapeutic dose range indicated no saturation of the absorption process.

Dissolution:
Dissolution data in [redacted] (pH 1.2) [redacted] (pH 4.5) and [redacted] (pH 6.8) indicated that pregabalin capsules were rapidly dissolving with [redacted] dissolved within 30 minutes.

BCS Class:
Based on the solubility, bioavailibity/permeability and dissolution data, pregabalin capsules are considered BCS Class 1 drug.

2.5.2 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The proposed to-be-marketed formulations are the same as the clinical trial formulations except for minor changes such as capsule size and color. The sponsor conducted dissolution testing in three dissolution media for all clinical trial formulations and calculate f2 values to demonstrate that all clinical trial formulations are considered bioequivalent. Since pregabalin capsules are BCS Class 1 drug with acceptable dissolution data, waiver for a bioequivalence study is granted.

Table 8. Similarity Factors (f_2) for Dissolution Results Obtained in [ ] (pH 1.2), [ ] (pH 4.5), and [ ] (pH 6.8)

Media pH	Formulation Number (Series, Capsule Strength) and Lot Number			
	7 (Series A, 25 mg) Lot K32-AX1/I	27 (Series C, 75 mg) Lot K32-BN1/I	45 (Series A, 150 mg) Lot 80289V	13 (Series C, 300 mg) Lot K32-BA1/II
1.2	75	81	86	74
4.5	82	68	49	55
6.8	82	55	52	72

USP Apparatus II (Paddle) at 50 rpm was used for all dissolution tests.
Formulation 15 (Series B, 100-mg capsules) Lot K32-AY1/V was used as reference for calculation of the similarity factors.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal type?

High fat meal decreased the rate of pregabalin absorption (mean Cmax: ↓25%; mean Tmax: ↑1 hr) but the extent of absorption was similar between fed and fasting conditions. The 90% confidence interval was 68.0-82.3% for Cmax, and 91.4-95.2% for AUC. (Note: Similar findings were reported in another study, in which food reduced Cmax by 29% and delayed Tmax by 2.5 hrs without affecting the AUC.) In clinical trials, pregabalin capsules were administered without regard to meal time. As such, no restrictions will be indicated in the label.

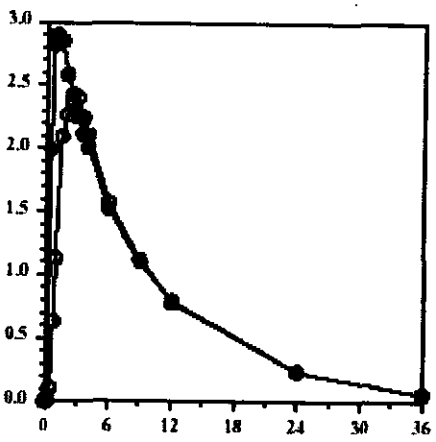


Figure 14. Mean Pregabalin Plasma Concentrations Following Administration of 150-mg Market-Image Capsules to Fasting Subjects (Closed Symbol) and With a High-Fat Meal (Open Symbol)

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The sponsor proposed the following dissolution test method and specifications:

Dissolution medium: [ ] mL
Method: Apparatus 2 (Paddle), 50 rpm
Specification: NLT [ ] (Q) of the label claim dissolved in 30 minutes

The dissolution specification is set within the definition for fast dissolving drug products. Currently available stability data meet the specification. Both the method and specification are considered acceptable.

2.6 ANALYTICAL

Validated HPLC methods were used for assay of pregabalin in blood and plasma samples. Assay method for plasma samples was validated down to — μg/mL for earlier studies and — μg/mL for later studies most likely due to the concentration range needed for the studies. Plasma samples containing pregabalin and internal standard (PD 403609) were

The reaction was terminated with

The — phase was

in mobile phase. Separation was achieved using an aqueous acetonitrile mobile phase. Absorbance was monitored at — nm. Quantification of pregabalin concentrations was based on peak-height ratio.

Table 9. Assay Validation Results for Plasma Samples

Precision (%CV)	— % — at LLOQ
Accuracy	— % — at LLOQ
Linearity	— μg/mL (—
Sensitivity	LLOQ: — μg/mL
Specificity	No interference from 6 human plasma samples
Stability Stock solution	4°C for — days : — (pregabalin); — (internal standard)
Plasma samples	
	RT for hrs: % RT for hrs: % -20°C for — days: % Freeze & thaw %

The assay method for urine samples was similar to that for plasma samples, involving derivatization of pregabalin with TNBSA.

Table 10. Assay Validation Results for Urine Samples

Precision (%CV)	% at LLOQ
Accuracy	% at LLOQ
Linearity	μg/mL (—
Sensitivity	LLOQ: μg/mL
Specificity	No interference from 8 human urine samples
Stability Stock solution	4°C for — days — (pregabalin);

Plasma samples	— (internal standard) RT for] hrs: (RT for] hrs: (-20°C for \ days: / Freeze & thaw — /

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4 APPENDICES

4.1 INDIVIDUAL STUDY REVIEWS

FORMULATION

Component	Wt (mg/capsule)							
	Formulation #/Capsule Strength							
	53 (A) 25 mg	62 (A) 50 mg	63 (C) 75 mg	64 (C) 100 mg	65 (C) 150 mg	66 (C) 200 mg	67 (C) 225 mg	68 (C) 300 mg
Pregabalin	25.0	50.0	75.0	100.0	150.0	200.0	225.0	300.0
Lactose Monohydrate Corn Starch Talc	}							}
Fill Weight	100.0	200.0	100.0	133.34	200.0	266.66	300.0	400.0
Capsule Size	# 4	#3	#4	#3	#2	#1	#1	#0

PROTEIN BINDING

Report#: RR 764-02316

Method: *In vitro;* ultrafiltration; 37°C
Pregabalin concentrations: 0.1, 0.5, 1, 2, 5, 10 and 20 • g/mL
Assay: HPLC; LLOQ: — · g/mL (ultrafiltrate)
Results: No binding to human plasma proteins at all concentrations tested.

MASS BALANCE

Protocol 1008-5: A Study of the Mass Balance and Metabolism of [^{14}C]CI-1008 (Pregabalin) in Healthy Volunteers

Studied Period: 07/14/97 to 07/21/97 Clinical Phase: I

OBJECTIVE:
To determine the mass balance and metabolic profile of [^{14}C]CI-1008 after oral administration to healthy volunteers

METHODOLOGY:
Study design: Open-label, single-dose study in healthy volunteers under fasting conditions.

Subjects: Six subjects entered and completed this study;
Six males & 0 female; age: 27.7 (20-44) yrs; wt: 69.1 (61.0-78.2) kg

Treatment: single oral 100-mg (107.9 • Ci) dose of [^{14}C]CI-1008 in 10 mL water.
Subjects were required to fast for 8 hrs before the dose and to remain fasting for 4 hrs following the dose.

Sampling Scheme:
Blood samples: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 8, 12, 16, 24, 36, 48, and 60 hrs post-dose.
Urine samples: pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, and 72-96 hrs postdose
Fecal samples: predose and 0-24, 24-48, 48-72, and 72-96 hours

Assay methods:
Pregabalin in plasma: HPLC-UV — nm)
Validation report: RR 764-02905; Stability reference: RR 764-03219
LLOQ: — g/mL ULOQ: — g/mL

Pregabalin in urine: HPLC-UV — nm)
Validation report: RR 764-02906
LLOQ: — g/mL ULOQ: — g/mL

Radioactivity: liquid scintillation spectrometry (LSC)
Reports: DB 63438 and NB 61260

Metabolite Identification: LC/MS
Potential metabolites were screened by performing selective MS/MS parent scans. Structure identification was performed by tandem mass spectrometry.

Partition into Erythrocyte:
Erythrocyte radioactivity was determined indirectly from whole blood and plasma radioactivity. The partition coefficient (Kp) between erythrocyte and plasma was then calculated by C_{RBC}/Cp.

Results

Mean Plasma Pregabalin and Radioactivity (Whole Blood and Plasma) Concentration-Time Profiles Following Administration of a Single Oral 100-mg (107.9 mCi) [^{14}C]CI-1008 Dose are shown below.

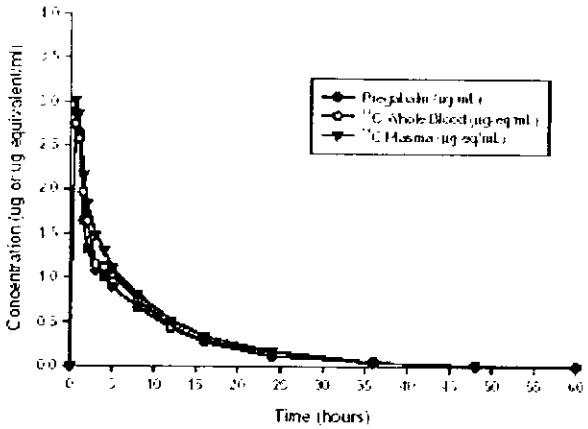


Figure 1. Mean Plasma Pregabalin and Radioactivity (Whole Blood and Plasma) Concentration-Time Profiles Following a Single Oral Radiolabeled dose of 100-mg

Mean (%RSD) pregabalin and total 14C radioactivity pharmacokinetic parameter values are summarized in the following table.

Parameter	Arithmetic Mean (%RSD) Parameter Values		
	Plasma Pregabalin (N = 6)	Plasma Total Radioactivity (N = 6)	Whole Blood Total Radioactivity (N = 6)
Cmax[a]	3.11 (45)	3.23 (25)	2.90 (26)
tmax (hr)	0.67 (39)	0.75 (37)	0.75 (37)
AUC(0-tldc)[b]	15.9 (33)	20.0 (26)	17.8 (23)
AUC(0-)[b]	16.1 (33)	20.1 (26)	17.9 (24)
CL/F (L/hr)	6.71 (27)	5.27 (25)	5.87 (24)
λz (hr^{-1})	0.09 (23)	0.12 (29)	0.11 (25)
t½ (hr)	7.59 (20)	6.42 (20)	6.66 (28)

- Plasma samples: HPLC radioactivity profiles of selected plasma samples showed primarily unchanged pregabalin.
- Recovery: Mean (%CV) cumulative recovery of total radioactivity was 92.0% (8.7) of the dose in the urine and <0.1% in the feces.
- Radioactivity in the urine: Urine profiling collected over 48 hours postdose indicated the presenceof 3 radiolabeled components labeled C1 through C3, comprising 0.4, 89.9, and 0.9% of dose. These components accounted for approximately 100% of the urinary radioactivity (91% of dose) in the 0-48 hr collection period.
- The major component (C2) was identified by mass spectrometry and co-chromatography as unchanged pregabalin while the minor component (C3) showed chromatographic characteristics consistent with the N-methylated derivative of pregabalin (RR 764-02815).
- Mean (±SE) erythrocyte-to-plasma radioactivity ratio: 0.77±0.08

Comment:

- Individual values of %dose excreted in the urine as unchanged drug were: [illegible] (Mean±SD: 92.0±8.7%)
- Absolute bioavailability of pregabalin is greater than 90%.

Conclusions

- CI-1008 (pregabalin) undergoes negligible metabolism in healthy volunteers following a single 100-mg (107.9 mCi) solution dose of [^{14}C]CI-1008 with approximately 92% recovery of dose in urine and feces.
- Urine is the primary route of elimination for CI-1008-derived radioactivity (92% of dose) with unchanged parent identified as the major radioactive component.
- The N-methylated derivative of CI-1008 was tentatively identified as a minor urinary metabolite.

SINGLE-DOSE PK

PROTOCOL 1008-001: An oral, rising single-dose tolerance and pharmacokinetic study of CI-1008 solution and capsule doses in healthy volunteers

Studied Period: 02/24/96 to 06/29/96

OBJECTIVE(S):
To determine the safety and tolerance of rising, single oral CI-1008 solution and capsule doses in healthy volunteers, and to assess the single-dose pharmacokinetic characteristics of CI-1008

METHODOLOGY:
This was a randomized, double-blind, rising single-dose, tolerance study comparing the effects of orally administered CI-1008 solution or capsules with those of placebo. Dose escalation was based on the absence of significant adverse effects (including ataxia) at lower doses and individual-subject plasma Cmax values ≤9.7 μg/mL (the no-adverse-effect plasma drug concentration in monkey; the most sensitive species in multidose toxicology studies).

Subjects: Twenty-nine healthy subjects entered and completed the study.

Subject Characteristic	Total Population N = 29
Gender, N (%)	
Men	14 (48.3)
Women	15 (51.7)
Race, N (%)	
White	24 (82.8)
Black	1 (3.4)
Hispanic	4 (13.8)
Age, yr	
Mean	40.1
Range	29.0, 49.0
Screening Weight, kg	
Mean	77.4
Range	60.2, 91.1

Test Product:

CI Number	Strengths and Dosage Forms	Lot	Formulation
1008	5 mg per vial for dissolution (1 mg/mL)	CF 0341295	WL 144723A-5PK1
1008	5-mg capsule, Size 4	CF 0060495	WL 144723A-1
1008	25-mg capsule, Size 4	CF 0070495	WL 144723A-2
1008	100-mg capsule, Size 1	CF 0080495	WL 144723A-3
1008	300-mg capsule, Size 0	CF 0090495	WL 144723A-4

Dosing Schedule:

Groups	Day 1	Day 8
Group 1	**Week 1**	**Week 2**
3 subjects	1 mg	placebo
3 subjects	placebo	2 mg
Group 2	**Week 4**	**Week 5**
3 subjects	5 mg	placebo
3 subjects	placebo	10 mg
Group 3	**Week 7**	**Week 8**
3 subjects	25 mg	placebo
3 subjects	placebo	50 mg
Group 4	**Week 10**	**Week 11**
3 subjects	75 mg	placebo
3 subjects	placebo	125 mg
Group 5	**Week 13**	**Week 14**
3 subjects	200 mg	placebo
3 subjects	placebo	300 mg
Group 6	**Week 16**	**Week 17**
3 subjects	450 mg	placebo
3 subjects	placebo	600 mg

*Actual dose administered: 1-300 mg (capsules); 1-2 mg (solution); under fasting conditions
**Group 6 did not receive study drug because designated maximal plasma concentration limits were reached at the 300-mg (Group 5) dose level.
***Due to recruitment difficulties, 5 subjects instead of 6 subjects were enrolled to Group 1.

Sampling Scheme:
Blood samples: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours postdose.
Urine samples: pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, and 48-60 hours postdose

Assay
Plasma CI-1008 concentrations were determined using a validated HPLC-UV method ([redacted] and [redacted] Limit of quantitation was [redacted] µg/mL for a 1-mL sample.

Results

Typical plasma concentration-time profile following oral administration of pregabalin is presented below:

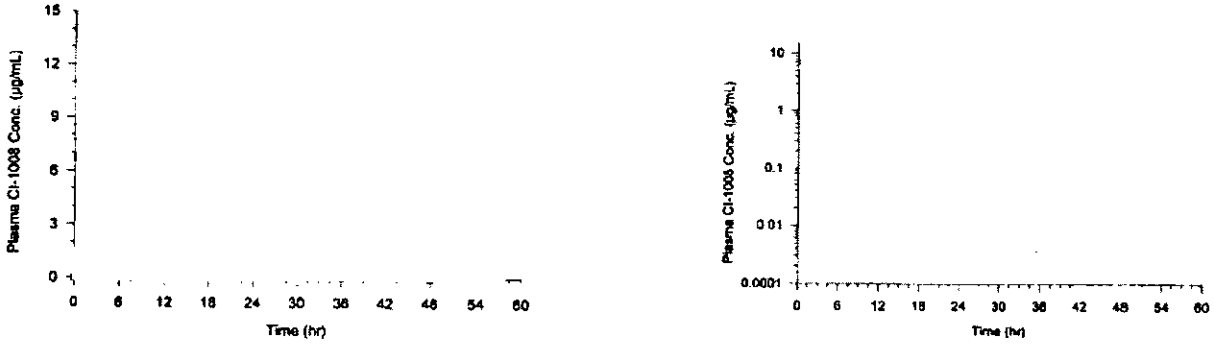


Figure: Plasma pregabalin concentration-time profiles following administration of a 300-mg dose. (Left panel: linear scale; Right panel: semilog scale)

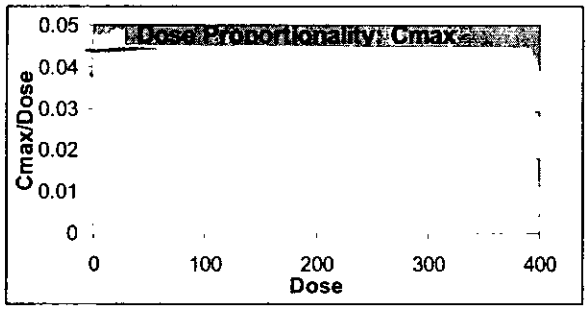
Mean PK parameters are given in the following table.

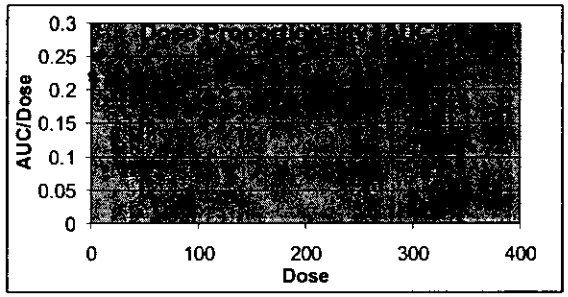
Table: Mean (%RSD) CI-1008 Pharmacokinetic Parameters in Healthy Subjects Following Single Oral Doses of 1, 2, 5, 10, 25, 50, 75, 125, 200, or 300 mg CI-1008

Dose	Formulation	Cmax (µg/mL)	tmax (hr)	t½ (hr)	AUC(0-∞) (µg*hr/mL)	Ae(%)
1	Solution	0.0383	0.7	5.7	0.223	92.4
		(10.1)	(43.3)	(13.9)	(13.5)	(7.3)
2	Solution	0.0848*	0.8*	4.6*	0.428*	88.8*
		NC	NC	NC	NC	(NC)
5	Capsule	0.156	0.9	6.8	1.24	88.9
		(12.9)	(20.7)	(17.0)	(11.8)	(2.3)
10	Capsule	0.459	0.8	6.0	2.54	86.8
		(14.7)	(34.6)	(9.4)	(13.8)	(11.2)
25	Capsule	0.918	1.0	5.6	5.83	85.8
		(21.5)	(0.0)	(16.6)	(12.7)	(10.7)
50	Capsule	1.61	1.2	5.8	12.2	89.5
		(25.7)	(23.3)	(16.0)	(11.9)	(2.7)
75	Capsule	2.18	1.3	6.6	15.6	94.3
		(8.9)	(43.3)	(11.7)	(15.5)	(6.2)
125	Capsule	3.59	1.0	5.8	24.6	89.7
		(8.0)	(0.0)	(26.7)	(19.1)	(0.6)
200	Capsule	5.96	1.2	5.2	46.0	91.8
		(11.7)	(24.7)	(13.5)	(17.6)	(6.2)
300	Capsule	9.46	0.8	5.6	66.3	89.9
		(11.0)	(34.6)	(17.1)	(6.8)	(3.9)

*Ae(%) = Percentage of CI-1008 dose excreted in urine as unchanged drug.

- Following oral administration of single 1- to 300-mg doses, individual tmax ranged from 0.5 to 2.0 hrs.
- Mean AUC(0-∞) values were approximately dose proportional following 1 to 300 mg dose of CI-1008 and mean Cmax values were approximately dose proportional in the dose range of 50-300 mg.
- Mean elimination t½ values ranged from 4.6 to 6.8 hours.
- The sponsor indicated that percentage of dose excreted unchanged in urine was independent of dose and averaged 89.8%. Based on the excretion data, mean oral bioavailability was ≥89.8% for the studied doses. However, the urine data are not provided except for the mean (±SD) percent of pregabalin dose excreted as unchanged drug.
- Single oral CI-1008 doses ranging from 1 to 300 mg are generally well-tolerated by healthy subjects.





Multiple-Dose Study (1)

Protocol 1008-002: An Oral, Rising, Single- and Multiple-Dose, Tolerance and Pharmacokinetic Study of Pregabalin (CI-1008) Capsules in Healthy Volunteers

Studied Period (years): 09/04/96 to 12/08/97

Objective(s):
To determine the safety and tolerance of rising, multiple oral doses of pregabalin capsules in healthy subjects, and to assess the multiple-dose pharmacokinetic characteristics of pregabalin

Study Design:
This study was a randomized, double-blind, placebo-controlled, parallel group, staggered-start, rising single- and multiple-dose tolerance study in healthy subjects. Dose escalation was to be based on the absence of significant adverse events (including ataxia) at lower doses and mean plasma pregabalin Cmax and AUC(0-8) values of ≤9.7 mg/mL and ≤59 mg·hr/mL, the no adverse effect plasma Cmax and one-third the AUC(0-24) exposure in initial monkey and rat toxicology studies, respectively. For pregabalin administration q12h, the mean plasma Cmax limit was ≤9.7 mg/mL, and the mean plasma AUC(0-12) limit was ≤89 mg·hr/mL. The protocol was later amended to increase the plasma pregabalin Cmax and AUC(0-8) limit values to ≤10.8 mg/mL and ≤63 mg·hr/mL, respectively, prior to administering 300 mg q8h in the final dose group, based on subchronic toxicology studies.

Subjects:
Fifty-seven healthy subjects (33 men and 24 women; age: 19-50 yrs (mean: 35.7 yrs); wt: 60.5-93.5 kg (mean: 74.5 kg)) entered the study and 53 completed the study. One subject was withdrawn from the study due to adverse events. The number of subjects in each group is presented below. Each subject received single dose on Days 1 and 22, and multiple doses q8h on Days 8-21 except for Group 6. Subjects were required to fast overnight and for 4 hours following morning dose on Days 1 and 22.

Group 1: 5 subjects (4 active, 1 placebo); 25-mg doses
Group 2: 8 subjects (6 active, 2 placebo); 25-mg doses
Group 3: 8 subjects (6 active, 2 placebo); 100-mg doses
Group 4: 6 subjects (5 active, 1 placebo); 200-mg doses
Group 5: 10 subjects (8 active,2 placebo); 200-mg doses
Group 6: 10 subjects (8 active, 2 placebo); 300-mg doses q12h
Group 7: 10 subjects (8 active, 2 placebo); 300-mg doses

Test Product:
· Pregabalin, 25-mg capsule, Size 4 (Lot CF 0070495, Formulation WL 144,723A-2)
· Pregabalin, 100-mg capsule, Size 1 (Lot CF 0080495, Formulation WL 144,723A-3)
· Pregabalin, 300-mg capsule, Size 0 (Lot CF 0090495, Formulation WL 144,723A-4)

Sampling Scheme: on Days 1 & 22
Blood samples: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hrs postdose.
Urine samples: pre-dose, 0-4, 4-8, 8-12, 12-24, 24-48, and 48-60 hours postdose

Assay
Plasma CI-1008 concentrations were determined using a validated HPLC-UV method (— and — Limit of quantitation was — ·g/mL for a 1-mL sample.

Urine samples were analyzed for pregabalin using a validated HPLC method. Limit of quantitation was — µg/mL for a 0.5-mL sample.

Results

Mean plasma pregabalin concentration-time profiles for both single- and multiple-dose administration are shown in Figure 1 and Figure 2. Mean pregabalin PK parameter values are reported in Table .

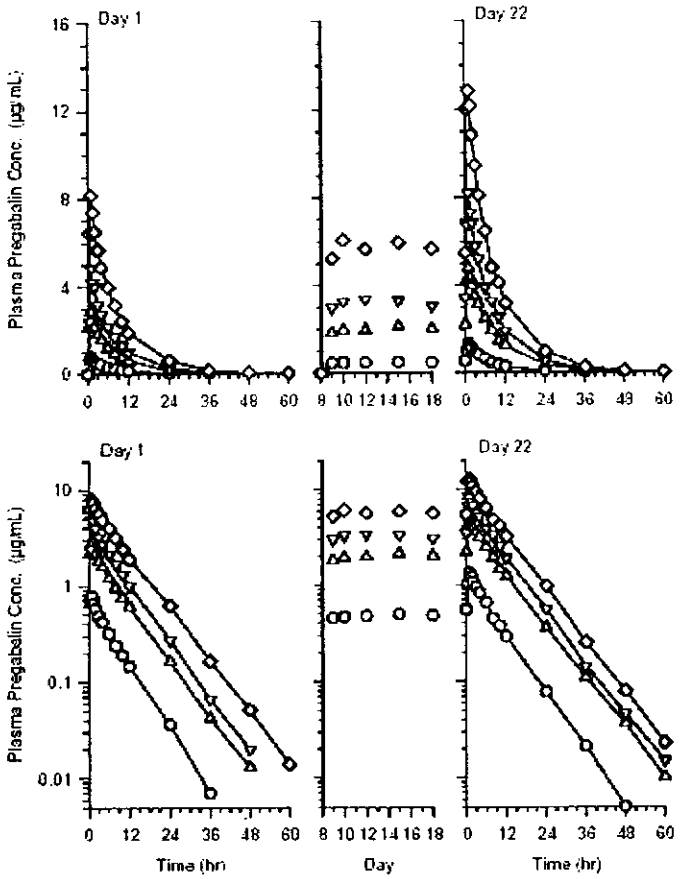


Figure 1. Mean Plasma Pregabalin Concentration-Time Profiles Following Administration of a Single 25 (o), 100 (Δ), 200 (▽), and 300 mg (◊) Pregabalin Dose on Days 1 and 22 and Morning Trough Plasma Pregabalin Concentrations on Days 8 Through 18 Following 25, 100, 200, and 300 mg of Pregabalin Every 8 Hours on Days 8 Through 21 to Healthy Volunteers (Study 1008-002-0)

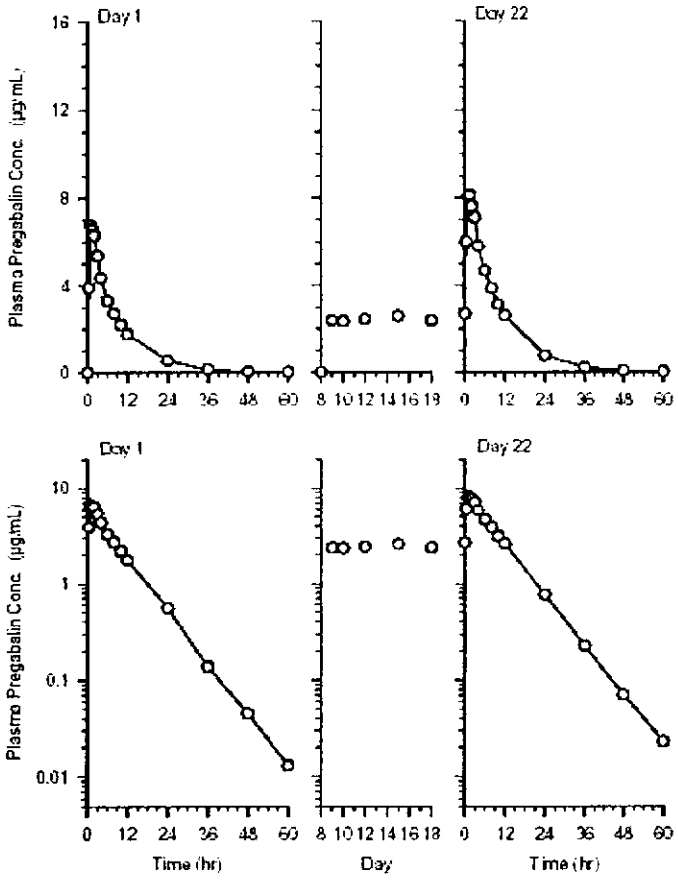


Figure 2. Mean Plasma Pregabalin Concentration-Time Profiles Following Administration of a Single 300 mg Pregabalin Dose on Days 1 and 22 and Morning Trough Plasma Pregabalin Concentrations on Days 8 Through 18 Following 300 mg of Pregabalin Every 12 Hours on Days 8 Through 21 to Healthy Volunteers (Study 1008-002-0)

Table: Summary of Mean (%RSD) Pregabalin PK Parameter Values

Dose	Dosing Regimen	N	Cmax	tmax	AUC	λz	t½	Ae%	CLr
					Day 1				
25	SD	10	0.864	0.850	5.633	0.130	5.476	87.7	67.0
			(19.3)	(28.4)	(21.6)	(17.6)	(18.1)	(13.8)	(20.6)
100	SD	6	2.987	0.833	22.130	0.116	6.099	90.2	69.3
			(16.2)	(31.0)	(16.8)	(16.2)	(18.0)	(8.4)	(15.2)
200	SD	13	5.227	1.308	37.658	0.115	6.127	90.6	80.9
			(27.0)	(33.3)	(16.3)	(15.4)	(13.7)	(21.1)	(23.4)
300	SD	8	7.565	1.375	62.752	0.105	6.635	91.2	73.2
			(16.4)	(57.5)	(9.3)	(8.7)	(10.1)	(4.8)	(9.8)
300	SD	8	8.585	1.000	71.376	0.107	6.617	96.9	68.8
			(17.4)	(26.7)	(14.4)	(15.0)	(13.1)	(13.0)	(16.6)
					Day 22				
25	q8h	8	1.388	0.938	6.67	0.119	5.940	94.3	--
			(19.5)	(34.2)	(18.3)	(15.1)	(17.3)	(22.6)	
100	q8h	6	5.028	0.833	25.19	0.113	6.309	107.8	--
			(21.3)	(31.0)	(23.0)	(17.0)	(19.6)	(11.6)	
200	q8h	11	8.519	0.909	41.72	0.113	6.270	82.0[a]	--
			(14.8)	(22.2)	(12.8)	(14.5)	(13.6)	(30.6)	
300	q12h	8	9.066	1.438	59.00	0.105	6.697	91.2	--
			(10.5)	(57.1)	(6.4)	(13.0)	(16.2)	(14.6)	
300	q8h	8	13.426	1.000	67.35	0.109	6.452	99.3	--
			(14.5)	(26.7)	(15.4)	(14.6)	(13.3)	(11.9)	

*Unit for parameters: Cmax (μg/mL); AUC (μg.h/mL); CLr (mL/min)

Dose Proportionality: Both mean Cmax and AUC are dose proportional within the dose range of 25-300 mg.

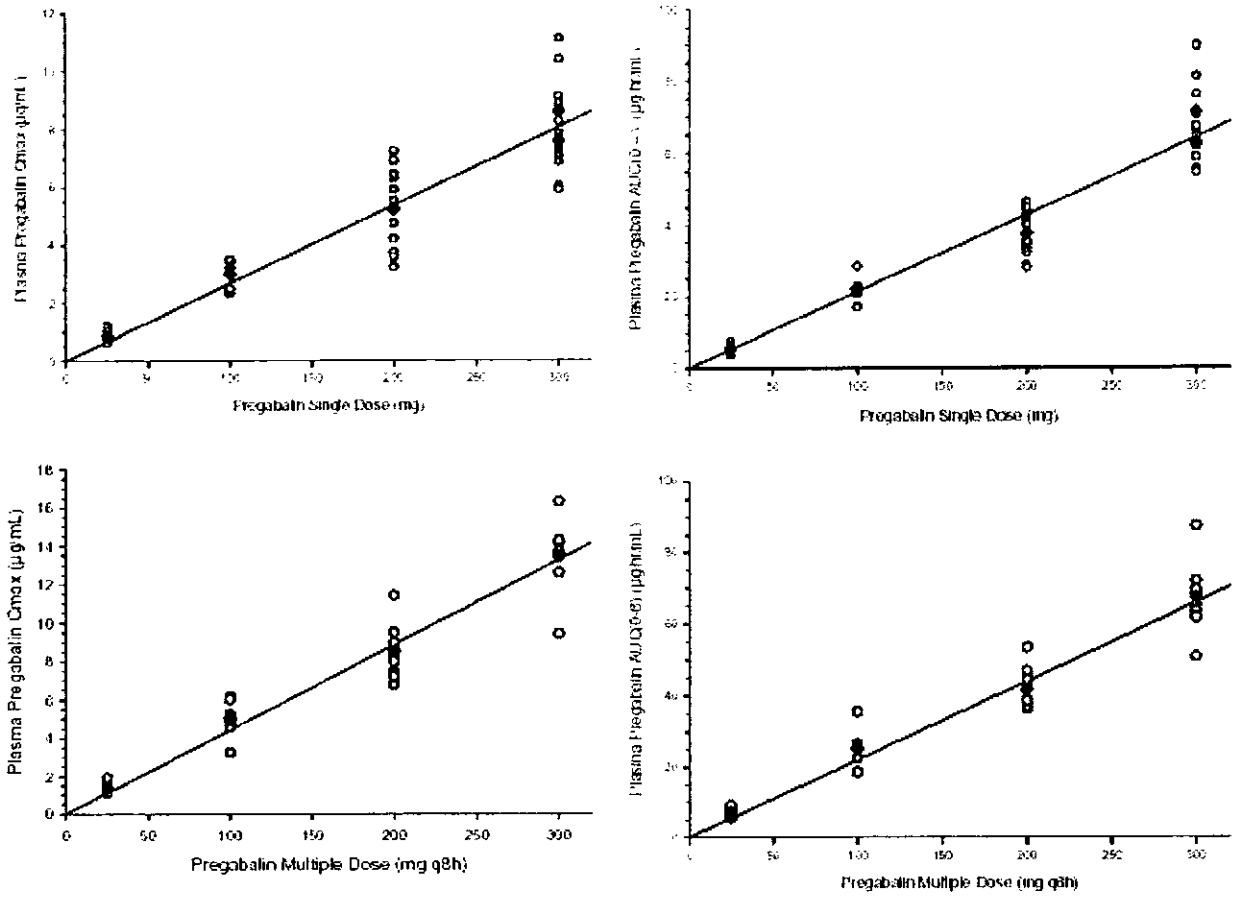


Figure. Pregabalin Cmax (left panel) and AUC (right panel) Values Following Single-Dose (upper panel) and Multiple-Dose (lower panel) Administration of Pregabalin to Healthy Volunteers (Study 1008-002-0)

Findings:

- Tmax: Following single- and multiple-dose administration of pregabalin, mean tmax values ranged from 0.8 to 1.4 hr.
- Dose proportionality: After single-dose administration of pregabalin (25-300 mg), mean Cmax and AUC(0-∞) values increased approximately dose proportionally (Cmax: 0.864-8.59 µg/mL; AUC: 5.63-71.4 µg·hr/mL). Likewise, mean Cmax and AUC(0-8) values (dose: 25-300 mg q8h) following multiple-dose administration were approximately dose proportional and ranged from 1.39 to 13.4 mg/mL and 6.67 to 67.4 mg·hr/mL, respectively. (Vd/F was estimated to be 36-48L across doses).
- Half-life: Elimination half-life values were similar after single- and multiple-dose administrations and averaged 5.5 to 6.7 hours.
- Accumulation: Observed average accumulation ratio ranged from 1.70 to 1.96 following q8h administration (1.37 following q12h), which was generally consistent with pregabalin elimination half-life.
- Steady state: Steady state was achieved within 24 to 48 hours after initiation of repeated drug administration.

- Urinary excretion: Percent of dose excreted as unchanged drug in urine averaged 87.7-96.9% following single-dose administration and 82.0-108% following multiple-dose administration.
- Renal clearance: Mean pregabalin renal clearance following single-dose administration ranged from 67.0 to 80.9 mL/min and was independent of dose. This indicates renal tubular reabsorption is involved since pregabalin is not bound to plasma proteins.
- Adverse events: Adverse events generally increased in frequency at pregabalin dose of 600 mg/day. The most frequent adverse events were dizziness (23 subjects), headache (14 subjects), stupor (12 subjects), somnolence (9 subjects), liver function tests abnormal (7 subjects), and rhinitis and amblyopia (6 subjects each).

MULTIPLE-DOSE STUDY (2)

Protocol 1008-023: An Oral, Multiple-Dose Tolerance and Pharmacokinetic Study of Pregabalin Capsules in Healthy Volunteers

Studied Period (years): 02/18/98 to 04/15/98

Objective:
To determine safety and tolerance of pregabalin capsules administered as 300-mg doses q8h for 4 weeks and to assess single- and multiple-dose pharmacokinetic characteristics of pregabalin in healthy volunteers.

Study Design

This was a randomized, double-blind, placebo-controlled, multiple-dose, tolerance and pharmacokinetic study in healthy subjects.

Subjects: Sixteen subjects (14 men and 2 women; mean age: 31.0 yrs; mean wt: 75.5 kg) entered and 15 completed the study. Twelve of the 16 subjects received multiple doses of CI-1008, and 1 received a single dose before withdrawing from the study; 3 subjects received placebo.

Test Product: CI-1008, 300-mg capsule, Size 0 (Lot CF 0090495; Formulation WL 144,723A-4)
Duration of Treatment: 300 mg q8h on Days 1 through 28; single dose on Day 29

Blood Sampling:
Day1: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 hours following the AM dose.
Days 2, 3, 4, 7, 11, 14, 18, 22, and 26: pre-AM dose
Day 29: pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, and 48 hours

Results

Pharmacokinetic parameter values following multiple-dose administration of 300-mg pregabalin every 8 hours for 4 weeks in this study were similar to those observed following the same dose regimen administered for 2 weeks in a previous study (Protocol 1008-002).

(Safety: According to the sponsor's report, pregabalin 300 mg administered q8h for 4 weeks is generally well tolerated by healthy subjects. Safety profile appears to be consistent with previous multiple-dose clinical pharmacology studies. There were no withdrawals due to adverse events.)

Mean Pregabalin Pharmacokinetic Parameter Values (Protocol 1008-023)

Dosing Regimen	N	Cmax	tmax	AUC	λz	t½	CL/F	Vd/F
Single Dose (Day 1)	12	8.99	1.00	64.1	0.118	6.01	80.4	41.4
		(18.5)	(21.3)	(19.8)	(15.9)	(15.5)	(16.7)	(19.4)
Multiple Dose (Day 29)	12	13.2	1.08	67.4	0.107	6.55	75.6	42.8
		(16.8)	(43.3)	(14.5)	(11.8)	(11.2)	(14.4)	(17.4)

FOOD EFFECT

Protocol 1008-128-0: A Single-Dose Study to Assess the Effect of Food on the Pharmacokinetics of CI-1008 Market-Image Capsules in Healthy Volunteers

Studied Period (years): 10/04/99 to 10/15/99 Clinical Phase: I

OBJECTIVE:
To determine the effect of a high-fat meal on the pharmacokinetics of 150-mg market-image pregabalin capsules (Formulation A) in healthy volunteers

METHODOLOGY:
This was an open-label, single-dose, randomized, 2-way crossover study in healthy volunteers.

Subjects: Fourteen subjects enrolled in and completed this study
12 males & 2 females; age: 46.2 (31-65) years; weight: 85.3 (66.2-108.3) kg

Test product: 150-mg pregabalin market-image capsule (WL 144723A-45, Lot CV1600899)
Dissolution: 81% at 10 min, 97% at 20 min, 96% at 30 min (set #1 of 6)
83% at 10 min, 95% at 20 min, 97% at 30 min (set #2 of 6)

Treatments: #1 (Ref.): One capsule taken after a 10-hour overnight fast
#2 (Test): One capsule taken immediately following completion of a high-fat breakfast administered orally following a 10-hour overnight fast.
Subjects remained fasting for 4 hours after the dose/breakfast.

High-fat breakfast: 2 eggs scrambled in butter, 2 pieces of bacon, 4 oz of hash-brown potatoes, 2 pieces of white toast spread with 2 teaspoons of butter, and 8 oz of whole milk.

Sampling Scheme: Blood samples
Pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 9, 12, 24, 36 & 48 hrs postdose.

Assay method: Plasma CI-1008 concentrations were determined using a validated HPLC-UV method (—). Limit of quantitation was — g/mL.

Results:

Mean plasma pregabalin concentration-time profiles under fasting and fed conditions are presented in Figure 1.

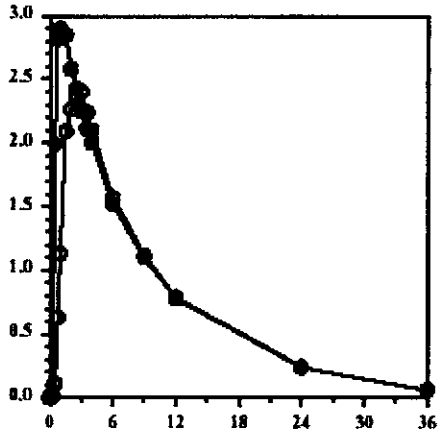


Figure 1. Mean Pregabalin Plasma Concentrations Following Administration of 150-mg Market-Image Capsules to Fasting Subjects (Closed Symbol) and With a High-Fat Meal (Open Symbol)

Mean pregabalin pharmacokinetic parameter values are presented in the table below along with ratios and confidence intervals for Cmax and AUC.

Table 1. Summary of Pregabalin Pharmacokinetic Parameter Values Following Administration of 150-mg Market-Image Capsules to Fasting Subjects (Reference) and with a High-Fat Meal (Test)

	Mean Values			
Parameter	Fasting (Reference)	High-Fat Meal (Test)	Ratio	90% Confidence Interval
n	14	14		
Cmax, µg/mL	3.47	2.60	74.8	68.0%—82.2%
tmax, hr	1.25	2.29	183	Not Applicable
AUC(0-tlqc), µg hr/mL	26.2	24.3	92.6	90.4%—94.9%
AUC(0-∞), µg hr/mL	27.3	25.5	93.3	91.4%—95.2%
t½, hr	6.70	6.72	100	Not Applicable

Plots of Cmax and AUC values are presented in Figure 2. Individual subjects and mean values are represented by numbers and diamonds, respectively. No sequence or period effects were observed following ANOVA evaluations of pharmacokinetic parameter values.

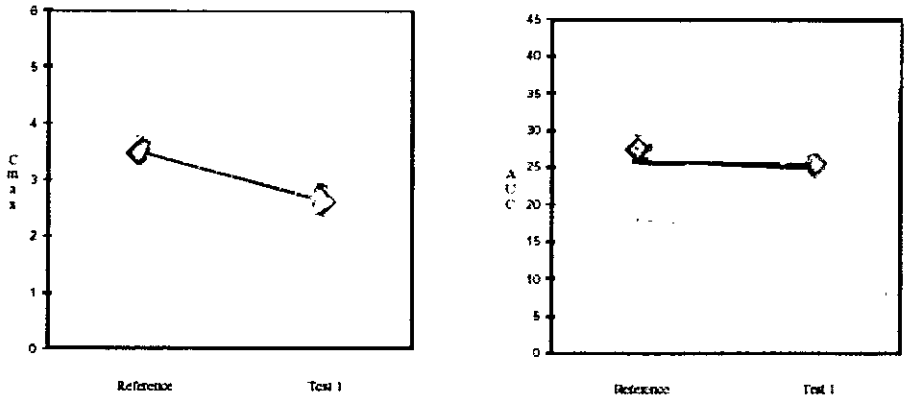


Figure 2. Individual Pregabalin Cmax (µg/mL, Left Panel) and AUC(0-∞) (µg hr/mL, Right Panel) Values Following Administration of 150-mg Market-Image Capsules to Fasting Subjects (Reference) and With a High-Fat Meal (Test 1)

Findings:

- Following administration of 150-mg market-image capsules with a high-fat meal, the rate of pregabalin absorption was reduced but the extent of absorption was similar compared to that observed for fasting subjects.
- The mean Cmax value with the meal was approximately 25% lower and the mean Tmax value was approximately 1 hour later, relative to those in fasting subjects. The 90% confidence interval (68.0-82.3%) for Cmax values was below the 70-143% range proposed to establish absence of a food effect on Cmax.
- The mean AUC(0-∞) value with food was approximately 7% lower, relative to that in fasting subjects. The 90% CI (91.4-95.2%) was within the 80-125% range establishing absence of a food effect.
- Pregabalin elimination t½ values were similar for each treatment, averaging ~6.7 hours.

Note: In a previous food-effect study (Protocol 1008-003-0), a 100-mg pregabalin capsule dose administered with a standard breakfast delayed mean tmax by 2.5 hours and reduced mean Cmax by 29% as compared with a 100-mg pregabalin capsule dose administered while fasting; however, mean AUC(0-∞) and T1/2 values were similar in the fed and fasted state.

RENAL IMPAIRMENT STUDY

Protocol 1008-049: An Oral, Single-Dose Pharmacokinetic Study of Pregabalin (CI-1008) in Subjects With Various Degrees of Renal Function

OBJECTIVES:
1. To determine the single-dose pharmacokinetics of pregabalin in subjects with various degrees of renal function
2. To determine the relationship between pregabalin clearance and estimated creatinine clearance (CLcr)

METHODOLOGY: Open-label, parallel-group, single-dose study
Dose: 50 mg

Subjects:
20 subjects with impaired renal function and 6 healthy subjects

	n	Sex	Mean (Range) Age in years	Mean (Range) Weight in kg
Group 1	6	4 Male, 2 Female	53 (46-64)	79.5 (70.5-91.6)
Group 2	7	3 Male, 4 Female	57 (44-74)	83.0 (61.6-105.0)
Group 3	5	5 Male	64 (38-75)	89.2 (61.6-105.9)
Group 4	8	3 Male, 5 Female	53 (40-73)	74.7 (44.5-92.7)
All Subjects	26	15 Male, 11 Female	57 (38-75)	80.8 (44.5-105.9)

Group	CLcr, mL/min
1	> 80
2	51-80
3	30-50
4	< 30 (but not on dialysis)

Treatment:
Two 25-mg pregabalin capsules (WL 144,723A-7A2, Lot CV 0120199) administered orally following an 8-hour overnight fast.

Sample Collection:
Plasma samples: collected serially for 72 hrs after the dose in Groups 1, 2, and 3, and for 168 hrs after the dose in Group 4, and assayed for pregabalin concentration by a validated HPLC method (LLOQ: — µg/mL, ULOQ: — µg/mL).
Urine samples: collected serially for 72 hours after the dose in Groups 1, 2, and 3, and for 168 hours after the dose in Group 4, and assayed for pregabalin concentration by a validated HPLC method (LLOQ: — µg/mL; ULOQ: — µg/mL).

Results

The PK parameters following single dose of pregabalin 50 mg are presented in the table below.

Table 1: Pregabalin PK Parameter Values Following Single Oral Dose of Pregabalin 50 mg to Healthy Subjects and Renal Impairment patients

CLcr mL/min	Subject	Group	Cmax µg/mL	tmax hr	AUC(0-tlqc) µg·hr/mL	AUC(0-∞) µg·hr/mL	%AUC Extrap	λz 1/hr	t½ hr	CL/F mL/min	Vd/F L	Ae%	CLr mL/min
10.0	19	4		1.0	90.9	101	9.75	0.0142	48.7	8.3	34.9	52.0	4.3
15.6	20	4		1.0	54.2	56.5	4.11	0.0296	23.5	14.8	29.9	79.2	11.7
19.3	26	4		4.0	55.9	57.9	3.55	0.0273	25.4	14.4	31.6	82.2	11.8
24.5	5	4		1.0	66.3	69.8	5.03	0.0321	21.6	11.9	22.3	41.9	5.0
27.4	11	4		0.5	33.3	36.2	7.96	0.0518	13.4	23.0	26.7	61.0	14.1
27.9	9	4		1.0	41.6	45.6	8.79	0.0252	27.5	18.3	43.5	46.3	8.5
28.8	16	4		2.0	36.2	41.3	12.4	0.0197	35.1	20.2	61.5	29.8	6.0
29.7	17	4		4.0	55.5	59.1	6.18	0.0246	28.2	14.1	34.4	53.4	7.5
32.5	15	3		1.0	28.4	32.7	13.3	0.0417	16.6	25.5	36.7	35.9	9.2
32.7	3	3		1.0	26.0	28.5	8.82	0.0323	21.4	29.2	54.3	46.3	13.6
37.1	2	3		1.5	29.3	31.0	5.54	0.0410	16.9	26.9	39.3	42.5	11.4
42.9	13	3		1.0	28.9	31.8	9.32	0.0330	21.0	26.2	47.6	49.8	13.1
44.3	12	3		2.0	24.9	29.3	15.2	0.0394	17.6	28.4	43.3	60.6	17.2
52.4	14	2		1.5	24.3	26.5	8.29	0.0511	13.6	31.5	36.9	35.9	11.3
59.1	4	2		1.0	16.7	17.9	7.01	0.0728	9.52	46.6	38.4	68.3	31.8
62.3	10	2		0.5	18.4	21.7	15.3	0.0536	12.9	38.4	43.0	70.2	27.0
62.4	6	2		1.0	20.0	21.5	7.36	0.0718	9.66	38.8	32.4	35.2	13.6
68.9	8	2		1.5	10.7	12.3	13.0	0.0880	7.87	67.8	46.2	57.3	38.8
72.6	7	2		1.0	19.6	20.3	3.57	0.0882	7.86	41.1	27.9	44.3	18.2
77.2	1	2		1.0	19.3	20.7	6.98	0.0564	12.3	40.3	42.8	50.3	20.3
86.4	21	1		1.0	13.3	14.0	4.72	0.0840	8.25	59.5	42.5	94.7	56.4
107	25	1		1.0	11.4	12.1	5.84	0.0751	9.23	68.9	55.0	88.2	60.8
116	24	1		1.0	7.66	8.57	10.6	0.144	4.82	97.2	40.5	94.1	91.5
116	22	1		1.0	13.3	14.5	8.18	0.0659	10.5	57.5	52.3	92.8	53.4
121	23	1		1.0	13.1	14.3	8.97	0.153	4.52	58.3	22.9	101.1	58.9
121	18	1		1.0	13.8	15.4	10.1	0.0565	12.3	54.1	57.5	101.2	54.7

Findings:

- Following single oral dose of pregabalin 50 mg, Tmax ranged from 0.5 to 4 hours. Cmax, AUC(0-∞), and T½ values increased with decreasing renal function (Figures 1 & 2).
- There is a trend of decreasing Vd/F values with decreasing renal function.
- Decreases in CL/F and CLr values correlated with decreasing CLcr values (Figure 3).
- Based on a small intercept in the relationship between CL/F and CLcr values, nonrenal clearance was only a minor route of pregabalin elimination. (Regression line: CL/F = 5.51 + 0.547 x CLcr; R = 0.890, R^2 = 0.79).
- Relationships between subject CLcr values and pregabalin clearances are illustrated in the following figure:

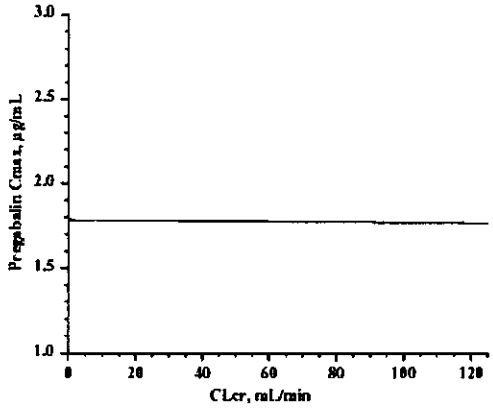


Figure 1. Cmax vs. CLcr

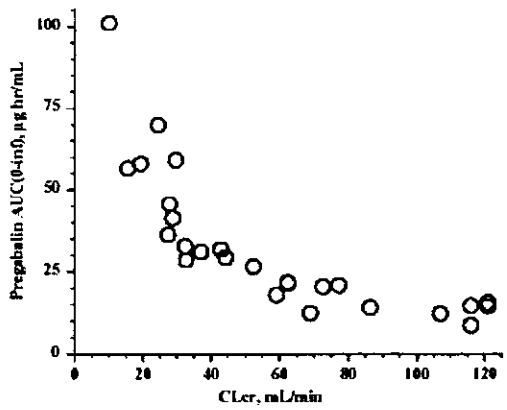


Fig. 2: AUC vs. CLcr

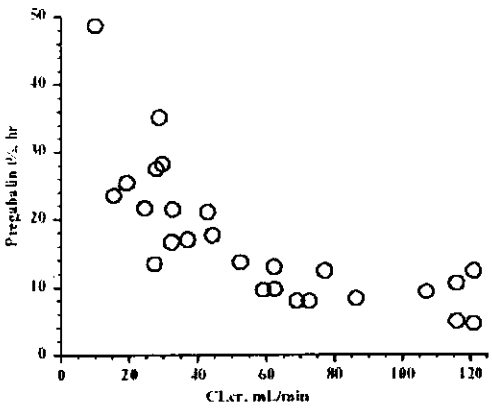


Fig. 3. T1/2 vs. CLcr

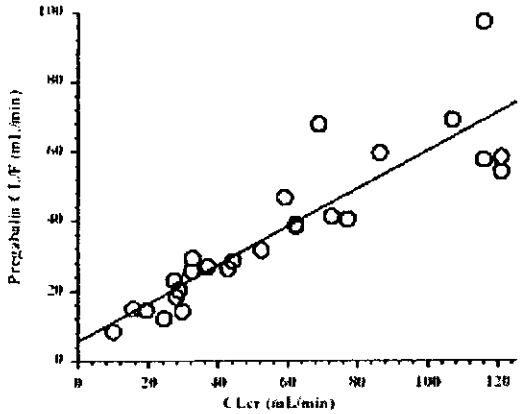
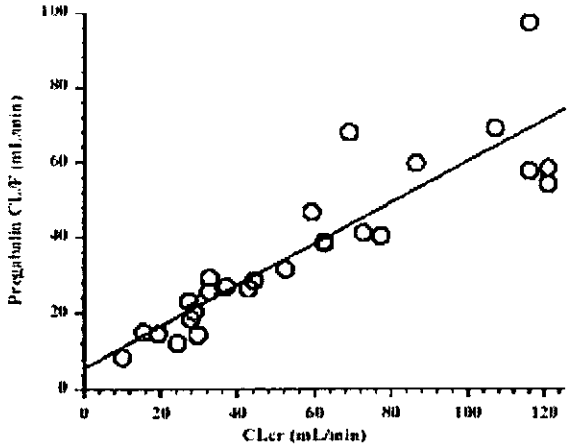


Fig. 4. Pregabalin CL/F vs. CLcr



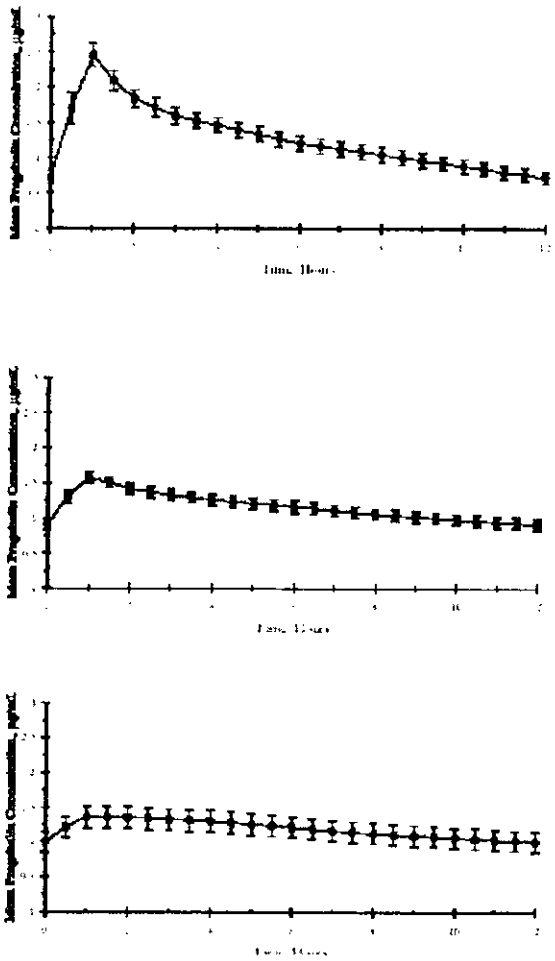


Fig. Predicted Steady-State Mean (Standard Error Bars) Pregabalin Plasma Concentrations During BID Dosing.

Top: 50-mg BID dosing to subjects with normal renal function (CLcr >60 mL/min).
Middle: 25-mg BID dosing to subjects with CLcr between 30 and 60 mL/min.
Bottom: 12.5-mg BID dosing to subjects with CLcr <30 mL/min.

Sponsor'sDosing Recommendations for Patients with Various Degrees of Renal Function:
Renal impairment patients with CLcr values of 30-60 mL/min had pregabalin CL/F values half of that in subjects with normal renal function (CLcr: 60-100 mL/min). Therefore, the sponsor recommended that patients having a CLcr value of <60 mL/min have their daily pregabalin dose reduced by one-half, relative to that in patients with normal renal function. Further, based on the above relationship, the daily dose in patients having a CLcr value <30 mL/min should be one-quarter of that in patients having normal renal function.

Sponsor's proposed label:

Table. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose[a]		Dose Regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥60			
30-60			
15-30			
<15			
Supplementary dosage following hemodialysis (mg)			

Conclusions:
Changes in pregabalin pharmacokinetic parameters correlate with decreases in renal function. Therefore, it is recommended that patients be dosed with pregabalin based on CLcr. Patients having a CLcr value between 30 and 60 mL/min should have their daily dose reduced by one-half, and the daily dose in patients having a CLcr <30 mL/min should be one-quarter of that in subjects having normal renal function.

RENAL IMPAIRMENT STUDY (2)

Protocol 1008-121: An Oral, Single-Dose Pharmacokinetic Study of Pregabalin (CI-1008) in Patients on Chronic Hemodialysis

Objectives

- To determine the single-dose pharmacokinetics of pregabalin in patients on chronic hemodialysis
- To gain information on the safety of pregabalin in patients with end-stage renal disease.

Study Design

- Open-label, single-dose study
- Twelve subjects with end-stage renal disease receiving chronic hemodialysis treatments 3 times each week (8 males and 4 females; age: 48.8 (30-66) yrs; weight: 93.7 (73.2-115.5) kg)
- Dosage form: 2 x 25-mg pregabalin capsules (WL 144,723A-7A2, Lot CV 0120199)
- 100
- Treatment: Single dose of pregabalin 50 mg administered orally following an 8-hour overnight fast and 24 hours before the beginning of the first scheduled 4-hour hemodialysis treatment.

PK Sampling

Blood samples:

- Day 1: pre-dose and at 2, 4, 6, and 8 hours post-dose
- Days 2, 4 & 7: immediately before beginning hemodialysis and at 5 and 6 hrs after beginning hemodialysis; Additionally, 5 mL of blood were withdrawn from the lines entering and exiting the dialyzer at 1, 2, 3, and 4 hours after beginning hemodialysis
- Days 3, 5, and 8: at 24 hrs after the beginning of each previous day's hemodialysis procedure

Urine samples: 0-48 hrs for non-anuric patients

Assay

Plasma and dialysate samples were assayed for pregabalin concentrations by a HPLC method validated from — µg/mL to — µg/mL. Urine samples were assayed for pregabalin concentrations by a HPLC method with a LLOQ of —• g/mL.

Results

Mean plasma concentration time-profile is shown in Figure 1 (0-168 h).

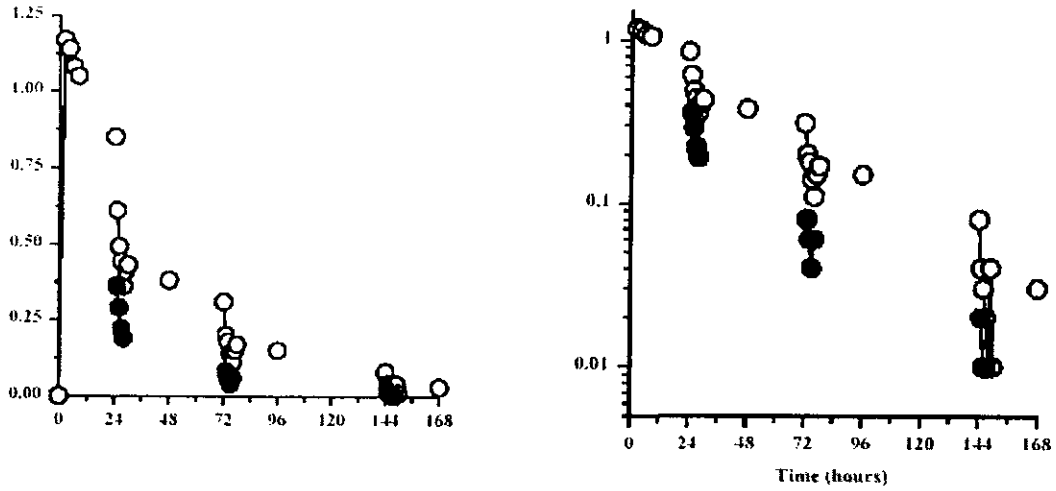


Figure 1. Mean Pregabalin Plasma Concentrations Following Administration of a Single 50-mg Oral Dose to Subjects With Renal Failure Requiring Hemodialysis (4-hr hemodialysis was conducted on Days 2, 4, and 7; Filled symbols represent mean plasma concentrations in samples exiting the dialyzer)

Mean PK parameter values are listed in Table 1:

Table 1

Parameter	Mean (%RSD)	
CLcr, mL/min	13.6	(26)
Cmax, µg/mL	1.24	(23)
tmax, hr	3.18	(62)
AUC(0-∞), µg hr/mL	94.6	(52)
t½, hr	54.7	(55)
t½HD, hr	3.00	
CL/F without hemodialysis, mL/min	118	(68)
Ae%	2.23	(99)
CLr, mL/min	0.453	(133)
CLd, mL/min	192	
f	58.1	

t½HD: Mean t½ during hemodialysis on Days 2, 4, and 7.
Ae: Amount of drug eliminated unchanged in urine in 48 hr
CLd: Mean dialysis clearance on Days 2, 4, and 7.
f : Mean percent of amount in body eliminated by each 4-hr dialysis

- The mean pregabalin T1/2 of 54.7 hours in subjects with impaired renal function requiring hemodialysis was substantially longer than those observed in a previous study (T1/2: 9 hrs for subjects with CLcr >60 mL/min; 28 hrs for subjects with CLcr of 15-30 mL/min).
- The mean T1/2 during hemodialysis was approximately 3 hours, reflecting a high pregabalin dialysis clearance.

Sponsor's Dosing Recommendation for Patients on Dialysis

To provide dosing recommendation for patients with CLcr values <15 and 15 to 30 mL/min, the sponsor primarily aims to achieve similar average steady-state plasma pregabalin concentrations as that observed in patients with CLcr> 60 mL/min receiving 300 mg/day.

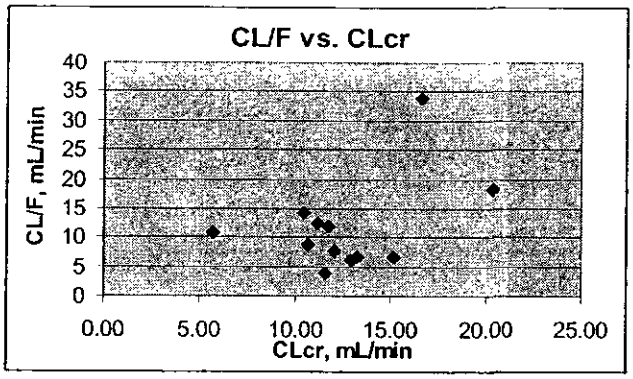
Non-Dialysis Days: Since pregabalin is almost exclusively eliminated by renal excretion, the daily dose of pregabalin is reduced one-half for each 50% decrease in renal function. This means the daily dose of pregabalin is halved for each step in CLcr reduction from >60 mL/min to 30 to 60, 15 to 30, and <15 mL/min. Thus, patients having CLcr values between 15 to 30 mL/min should have their daily dose reduced 4-fold to a daily dose of 75 mg/day. Likewise, patients having CLcr values of <15 mL/min should have their daily dose reduced 8-fold to a dose of 25 to 50 mg/day.

Dialysis Days: For a patients taking a he sponsor proposed a supplemental dose of 50 mg after dialysis. The rationale is as follows: Since pregabalin is well absorbed ($F \cong 1$), the average amount of pregabalin in the body at steady-state is Cavg·Vd/F (3 mg/L · 34 L) or approximately 100 mg. In this study, a 4-hour hemodialysis treatment reduced the amount of pregabalin in the body by approximately 50%. Thus, a replacement dose of 50 mg (0.5 · 100 mg) would be necessary to replace the amount removed by the dialysis treatment.

Sponsor's Conclusion: On nondialysis days, the pregabalin daily dose in patients with severe renal failure requiring dialysis should be based on their renal function. Pregabalin is highly cleared by dialysis. Therefore, following dialysis, patients should receive an additional 50-mg dose of pregabalin to maintain a steady-state pregabalin plasma concentration time profile similar to that in patients with normal renal function receiving 300 mg/day.

Reviewer's Comment:

1. Because of the sampling scheme, the Tmax value is only a crude estimate.
2. A plot of apparent pregabalin clearance (CL/F) vs. creatinine clearance indicates that two subjects with CLcr>15 mL/min had a CL/F > 15 mL/min. Excluding these two subjects resulted in a mean CLcr of 11.4 mL/min (CV: 21.4%), and a mean CL/F of 8.97 mL/min (CV: 36.2%).



JAPANESE SUBJECTS (1)

Protocol 1008-1J: An Open, Placebo-Controlled, Single-Dose Safety and Pharmacokinetics Study of Oral CI-1008 in Healthy Japanese Elder Male Subjects

(Note: The title is confusing. The report indicated that it's a single-blind study in young healthy male subjects)

Objective:

- To investigate safety and pharmacokinetics after a single oral dose of pregabalin
- To investigate food effect

Study Design

Randomized, single blind, placebo controlled, single oral dose trial

Subjects: 40 healthy Japanese male volunteers (age: 23.2±2.5 yrs; wt: 63.6±8.2 kg)
8 subjects (6 on active and 2 on placebo) per dose group

Test Product: 25 or 100 mg capsules

Drug Administration: Five dose levels (50, 100, 200, 250 and 300 mg)
Fasting condition; sequential design
Food effect: 100-mg dose, cross-over

Step	Dose	Number of subjects		Subject Number	Administration method
		CI-1008	Placebo		
1	50mg(25mg capsule × 2)	6	2	1~8	Oral administration with 200mL of water under fasting conditions in the morning.
2 I	100mg(100mg capsule × 1)	3×2	1×2	11~18	Oral administration with 200mL of water under fasting conditions or 30 minutes after breakfast
2 II	100mg(100mg capsule × 1)	3×2	1×2	11~18	
3	200mg(100mg capsule × 2)	6	2	21~28	Oral administration with 200mL of water under fasting conditions in the morning.
4	250mg(100mg capsule × 2 +25mg capsule × 2)	6	2	31~38	
5	300mg(100mg capsule × 3)	6	2	41~48	

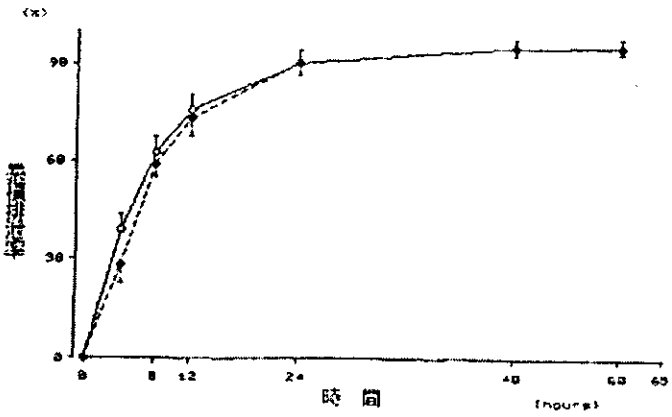
Result

Mean (±SD) PK parameter values following single oral administration of 50-300 mg dose are presented in the table below.

Parameter	Dose					
	50 mg	100 mg (fast)	100 mg (fed)	200 mg	250 mg	300 mg
Tmax, h	0.67±0.26	0.75±0.27	3.33±0.52	1.00±0.32	1.17±0.52	1.08±0.38
Cmax, • g/mL	2.03±0.40	3.56±0.67	1.86±0.25	6.35±0.73	7.18±1.43	8.25±1.36
AUC, • g.h/mL	10.68±1.07	20.38±1.31	17.90±1.12	43.24±2.94	49.16±6.05	61.66±6.25
T1/2, h	6.0	5.7	5.5	5.9	5.6	5.8
CL/F, L/h	4.72±0.44	4.93±0.35	5.61±0.35	4.64±0.32	5.15±0.61	4.91±0.52
Vd/F, L	40.6±4.9	40.3±6.4	-	39.7±2.7	41.0±3.8	40.9±4.3
Vdss/F, L	36.6±5.4	38.7±6.3	-	37.8±1.7	40.1±4.3	39.5±5.2

Urinary excretion of pregabalin: Urinary excretion of pregabalin up to 60 hrs postdose were 84% (50-mg dose), 95% (100-mg), 92% (200-mg), 96% (250-mg) and 98% (300-mg) and more than 80% was excreted within 24 hours.

Food effect: Mean Cmax reduced ~ 50%, Tmax extended for ~ 2 hrs and mean AUC reduced 12.6%



Conclusion:

- Dose proportional for Cmax (??) and AUC from 50 mg to 300 mg.
- Linear Pharmackinetics
- Food effect;

Comment:

Compared to Study 002, Cmax values in Japanese subjects in this study were 19%↑, 22%↑ and 9%↑ and AUC were 8%↓, 15%↑ and 2%↓, for the 100-mg, 200-mg and 300-mg doses, respectively. Within Study 002, the AUC and Cmax for the two 300-mg dose groups differed by 14% in Cmax and AUC. Bear in mind that this is a cross-study comparison, it would appear that the Japanese subjects tended to have higher Cmax but comparable AUC.

JAPANESE SUBJECTS (2)

Protocol 1008-2J: An Open, Placebo-Controlled, Single-Dose Safety and Pharmacokinetics Study of Oral CI-1008 in Healthy Japanese Elder Male Subjects

Objective:
To investigate safety and pharmacokinetics after a single oral dose of pregabalin in healthy Japanese elderly male subjects

Study Design
Randomized, single blind, placebo controlled, single oral dose trial

Subjects:	8 healthy Japanese elderly males (6 on active and 2 on placebo) age: 71.8±4.3 yrs; wt: 60.1±8.0 kg; CLcr: 75.2±16.3 mL/min
Test Product:	100 mg capsules
Drug Administration:	Dose: 100 mg; Fasting condition

Results

Mean PK parameter values are listed in the table below. Compared to the previous study in healthy young Japanese male subjects, mean Cmax was comparable (3.23±0.55 μg/mL vs 3.56±0.67 μg/mL; 9% lower for the elderly) but AUC was 30% higher for the elderly (26.6±4.3 μg.h/mL vs. 20.4±1.3 μg.h/mL).

Parameters	(Unit)	CI-1008 (N=6)		
		Mean	±	SD
C_{max}	(ng/mL)	3235	±	548
t_{max}	(hr)	1.4	±	0.5
t_{last}	(hr)	36	±	8
C_{last}	(ng/mL)	61.2	±	22.4
AUC_{last}	(ng•hr/mL)	26233	±	4378
$AUC_{0-\infty}$	(ng•hr/mL)	26600	±	4268
LambdaZ	(/hr)	0.11129	±	0.01462
$t_{1/2}$	(hr)	6.317	±	0.818
AUC_{0-INF}	(ng•hr/mL)	26771	±	4263
MRT_{last}	(hr)	8.542	±	1.417
MRT_{0-INF}	(hr)	9.272	±	1.310
CL/F	(mL/hr)	3822	±	654
VZ/F	(L)	34.5	±	4.7

Study # 1008-075
Title: Pharmacokinetic drug interaction study evaluating pharmacokinetics of Oral Contraceptives upon coadministration with pregabalin.

This study (Protocol # 1008-075, report # RR 744-00484) was designed to evaluate the effect of multiple-dose administration of pregabalin on the pharmacokinetics of ethinyl estradiol and norethindrone acetate following administration of Ortho-Novum (ethinyl estradiol 1 mg and Northindrone 35 µg). Ortho-Novum® (Lot 28G059) was administered once daily for a total of three cycles (cycle = 21 days OC + 7 days OC free) in healthy female volunteers (n = 16). Pharmacokinetics of ethinyl estradiol and norethindrone alone were determined following the last dose of the second cycle of OC administration (Day 49 from the start of first OC treatment). Pregabalin (2 x 100 mg capsules tid, Lot CF0150398, Formulation WL 144723A-15) was administered starting on day 57 for 22 days along with OC (once daily). Pharmacokinetics of ethinyl estradiol and norethindrone were determined following the last dose of OC and pregabalin on Day 77. The following tables indicate the schedule of events during the study.

Study Day		-21 to -1	1 to 20	21	22 to 28	29 to 44	45	46	47	48	49												50		51	52 to 56
Hour											0	0.5	1	1.5	2	3	4	6	8	10	12	16	24	36	48	
Orientation		X																								
History		X																								
Physical Examination		X									X[b]															
Clinical Laboratory	1) Hematology	X																							X	
	2) Chemistry	X																							X	
	3) Urinalysis	X[a]																							X	
	4) Pregnancy Test	X																							X	
Vital Signs		X		X[c]							X[c]															
Electrocardiogram		X																								
Ethinyl Estradiol/Norethindrone Sample											X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Progesterone Sample							X[c]		X[c]		X[c]														X	
Sex Hormone Binding Globulin											X[c]															
Pregabalin Blood Collection																										
Drug Administration	Ortho-Novum		X	X		X	X	X	X	X	X															
	Pregabalin																									

[a] Included urine drug screen
[b] Anytime on Day 49
[c] AM predose

Validated methods were used for plasma samples analyses for the determination of pregabalin (HPLC/ UV Validation report # RR 764-03219), ethinyl estradiol and norethindrone (GC/MS Valdiation report # C J
Pharmacokinetic parameters for ethinyl estradiol and norethindrone for each treatment and subject were performed by noncompartmental analysis of concentration time data (WinNonlin Pro, Version 2.1). Mean pharmacokinetic parameters and 90% confidence interval (CI) for the ratio (test/reference) of back-transformed (natural log data) treatment least-squares mean values were calculated.

Summary of Ethinyl Estradiol Pharmacokinetic Parameter Values Following Administration of 1/35 Ortho-Novum Tablets Alone (Reference) and During Steady-State 200-mg q8h Dosing with Pregabalin (Test): Protocol 1008-075

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Ortho-Novum Tablets Alone (Reference)	Ortho-Novum Tablets with Pregabalin (Test)		
n	16	15		
Cmax, ng/mL	0.152	0.159	105	95.6 to 115
AUC(0-24), µg hr/mL	1.30	1.48	114	106 to 122
Cmin, ng/mL	0.0258	0.0317	123	111 to 136

Summary of Norethindrone Pharmacokinetic Parameter Values Following Administration of 1/35 Ortho-Novum Tablets Alone (Reference) and During Steady-State 200 mg q8h Dosing with Pregabalin (Test): Protocol 1008-75

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Ortho-Novum Tablets Alone (Reference)	Ortho-Novum Tablets with Pregabalin (Test)		
n	16	15		
Cmax, ng/mL	21	21	100	92 to 109
AUC(0-24), µg hr/mL	151	175	116	109 to 124
Cmin, ng/mL	2.64	3.40	129	118 to 142

As indicated in the above tables, the Cmax and AUC(0-24) ethinyl estradiol and norethindrone in the Test and Reference treatments appears to be similar (calculated 90% CI of parameter estimates are with in 80 -125% range). Hence, a pharmacokinetic drug interaction is not anticipated following coadministration multiple dosing regimen of pregabalin and Ortho-Novum®. The study design and conclusions are acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

Study # 1008-144

Title: Pharmacokinetic drug interaction study evaluating pharmacokinetics of gabapentin and pregabalin upon multiple-dose coadministration.

A multiple-dose drug interaction study (Protocol # 1008-144, Report # 744-00616) was performed to determine the pharmacokinetics of pregabalin and gabapentin following administration either alone or in combination in healthy volunteers (n = 18) in a single-blind, randomized, 3-way crossover design. The treatment groups are indicated in the table as follows:

Treatments Evaluated in Protocol 1008-144

Treatment	Day	Dosing Regimen	Duration
1. Pregabalin Alone (Formulation WL 144,723 X-15, Lot C 10060299)	1	1 × 100-mg pregabalin capsules q8h	3 Doses
	2	2 × 100-mg pregabalin capsules q8h	3 Doses
	3	2 × 100-mg pregabalin capsules	Single AM dose
2. Gabapentin Alone (Formulation WL 87,842-19 XL, Lot C 10070399)	1	1 × 400-mg gabapentin capsule q8h	3 Doses
	2	1 × 400-mg gabapentin capsule q8h	3 Doses
	3	1 × 400-mg gabapentin capsule	Single AM dose
3. Pregabalin and Gabapentin together	1	1 × 100-mg pregabalin capsule q8h + 1 × 400-mg gabapentin capsule q8h	3 Doses
	2	2 × 100-mg pregabalin capsules q8h + 1 × 400-mg gabapentin capsule q8h	3 Doses
	3	2 × 100-mg pregabalin capsules + 1 × 400-mg gabapentin capsule	Single AM dose

Blood samples before starting each treatment regimen on Days 1, 8, and 15; and before and at 0.33, 0.67, 1, 1.5, 2, 3, 3.5, 4, 6, 8, 12, 16, 24, and 36 hours after the dose on Days 3, 10, and 17. Validated methods (LC/MS/MS, Validation Report # RR 764-03581) were employed for the analyses of pregabalin and gabapentin in plasma samples. Pharmacokinetic parameters for pregabalin and gabapentin for each treatment and subject were performed by noncompartmental analysis of concentration time data (WinNonlin Pro, Version 2.1). Mean pharmacokinetic parameters and 90% confidence interval (CI) for the ratio (test/reference) of back-transformed (natural log data) treatment least-squares mean values were calculated.

Summary of Gabapentin Steady-State Pharmacokinetic Parameter Values Following Administration of 400 mg Gabapentin q8h Alone (Reference) and With 200 mg Pregabalin q8h (Test): Protocol 1008-144

Parameter	Mean Gabapentin Parameter Values		Ratio	90% Confidence Interval
	Gabapentin Alone (Reference)	Gabapentin With Pregabalin (Test)		
n	18	18		
Cmax, µg/mL	5.71	5.44	95.2	89.0 to 102
tmax, hr	2.45	2.22	90.6	Not applicable
AUC(0-8), µg·hr/mL	34.6	33.3	96.4	91.5 to 102
Cmin, µg/mL	3.10	2.96	95.7	83.7 to 109
t½, hr	7.04	7.15	102	97.4 to 106

Summary of Pregabalin Steady-State PK Parameter Values Following Administration of 200 mg Pregabalin q8h Alone (Reference) and With 400 mg Gabapentin q8h (Test):

Parameter	Mean Pregabalin Parameter Values		Ratio	90% Confidence Interval
	Pregabalin Alone (Reference)	Pregabalin With Gabapentin (Test)		
n	18	18		
Cmax, µg/mL	8.45	6.97	82.4	77.9 to 87.2
tmax, hr	0.959	1.02	107	Not applicable
AUC(0-8), µg·hr/mL	40.0	36.9	92.2	88.6 to 95.9
Cmin, µg/mL	3.25	3.07	94.2	88.9 to 99.9
t½, hr	6.77	6.86	101	99.5 to 103

Although the Cmax and AUC(0-8) of gabapentin were not altered upon coadministration with pregabalin. However, the Cmax of pregabalin was ~ 18% lower (90% lower CI of parameter estimate was below 80 – 125% range), without significant change in AUC(0-8) upon coadministration with gabapentin. The clinical implications of these observations may not be significant for the dosing regimen studied; however extrapolation of these results should not be made to higher dosing regimens of gabapentin and pregabalin. The study design and conclusions are acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

The sponsor submitted a single-dose drug interaction study (Protocol # 1008-077, Report # RR 744-00505) performed to determine the pharmacokinetics of pregabalin (100 mg capsule) and gabapentin (300 mg capsule) administered either alone or in combination in healthy volunteers. However, this study report was not reviewed as the study design was not optimal, i.e., lower than clinically anticipated dosing regimen was employed. In addition, the utility of this study is minimal in light of the observations from multiple dose drug interaction study.

Study # 1008-78
Title: Pharmacokinetic and Pharmacokinetic drug interaction between pregabalin and oxycodone following oral administration of multiple doses in healthy volunteers.

The sponsor performed a randomized, partial double-blind, placebo-controlled, multiple-dose, 4-way crossover pharmacokinetic study in 12 healthy volunteers receiving three doses of pregabalin (300 mg) and/or three doses of oxycodone (10 mg) and/or three doses of placebo. Treatments were administered on Days 2, 9, 16 and 23 with a washout period of 6 days. The specific information on dosage forms and dosing schedule is as follows:

Dosage Forms (Protocol 1008-078-0)

Study Medication	Strengths and Dosage Forms	Lot No.	Formulation No.
CI-1008	300-mg pregabalin capsule	CF-0200498	WL 144,723A-13
Placebo	Matching placebo capsule	CX-0860997	WL 14,964-24P
Oxycodone	10-mg oxycodone tablets	10001221	NA

Dosing Schedule (Study 1008-078-0)

	Period			
Sequence	1	2	3	4
A	Treatment 1	Treatment 2	Treatment 3	Treatment 4
B	Treatment 2	Treatment 3	Treatment 4	Treatment 1
C	Treatment 3	Treatment 4	Treatment 1	Treatment 2
D	Treatment 4	Treatment 1	Treatment 2	Treatment 3

Treatment 1: 300 mg pregabalin q12h for 3 doses—the third dose is given with a 10-mg oxycodone tablet
Treatment 2: 300 mg pregabalin q12h for 3 doses—the third dose is given with a placebo capsule
Treatment 3: Placebo q12h for 3 doses—the third dose is given with a 10-mg oxycodone tablet
Treatment 4: Placebo q12h for 3 doses—the third dose is given with a placebo capsule

The pharmacokinetic (blood sampling scheme) and pharmacodynamic observations (psychometric testing, Spirometry, Respiratory measurements) were sampled and recorded as per the schedule below. Validated analytical methods were employed for analysis of plasma for pregabalin (HPLC/UV, Validation Report # RR 764-03219) and oxycodone (GC/MS, Validation report — determination.

Schedule of Observations and Procedures

Study Day		-14 to -8	-7 to -1	1[a]	2[b]							3[c]	29 to 35
Hour					0	1	2.5	4	6	9	12	24	
Orientation		X											
History		X											
Physical Examination		X	X[e]									X	X
Clinical Laboratory	1) Haematology	X	X[e]										X
	2) Chemistry	X	X[e]										X
	3) Urinalysis	X[d]	X[d,e]										X
	4) Pregnancy Test	X	X[e]										X
	5) Breathalyzer Measurements		X[e]										
Vital Signs and Respiratory Measurements		X[i]		X[i]	X[h]	X[h]	X[h]	X[h]	X[h]			X[h]	X[j]
Electrocardiogram and Spirometry		X											
Psychometric Testing			X[f]		X	X	X	X	X	X	X	X	
Pregabalin Blood Collection					X	X	X	X	X	X	X	X	
Oxycodone Blood Collection					X	X	X	X	X	X	X	X	
Drug Administration	Pregabalin or Placebo			X[g]	X								
	Oxycodone or Placebo				X[k]								

[a] Repeated on Days 8, 15, and 22 [b] Repeated on Days 9, 16, and 23 [c] Repeated on Days 10, 17, and 24
[d] Included urine drug screen [e] Days 1, 7, 14, and 21 only
[f] Psychometric testing, 4 times for training purposes, with the last session on Day -1
[g] Pregabalin capsules (300 mg) or placebo capsules (matching) administered q12h
[h] Included respiratory measurements prior to psychometric testing
[i] Included respiratory measurements [j] Vital sign measurement only [k] Oxycodone tablet (10 mg) or placebo capsule

Pharmacokinetic parameters for pregabalin and oxycodone were calculated by noncompartmental analyses of the plasma concentration-time data (WinNonlin Pro Version 2.1). Mean pharmacokinetic parameters and 90% confidence interval (CI) for the ratio (test/reference) of back-transformed (natural log data) treatment least-squares mean values were calculated. Lack of pharmacokinetic interaction would be concluded if the 90% confidence intervals for natural log-transformed Cmax and AUC values were within the 70% to 143% and 80% to 125% ranges, respectively.

Summary of Pregabalin Pharmacokinetic Parameter Values Following the Third 300-mg Pregabalin Capsule Dose Administered Alone (Reference) and With Oxycodone (Test): Protocol 1008-78

	Least-Squares Mean Values			
Parameter	Pregabalin Alone (Reference)	Pregabalin With Oxycodone (Test)	Ratio	90% Confidence Interval
N	12	12		
Cmax, µg/mL	9.24	8.82	95.5	88.7 to 103
tmax, hr	1.38	1.38	100	Not Applicable
AUC(0-12), µg hr/mL	59.4	59.4	100	96.8 to 103
Cmin, µg/mL	2.59	2.61	101	94.6 to 107
CL/F, mL/min	85.1	84.6	99.4	Not Applicable
$t_{1/2}$, hr	6.25	6.41	102	Not Applicable

As indicated in the above tables, the Cmax and AUC of oxycodone and pregabalin following administration of the Test and Reference treatments appear to be similar (calculated 90% CI of parameter estimates are with in 80 -- 125% range). Hence, a pharmacokinetic drug interaction is not anticipated following coadministration of multiple doses of pregabalin (300 mg) and oxycodone (10 mg). The pharmacokinetic study design and conclusions are acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

Study # 1008-079

Title: Pharmacokinetic and pharmacokinetic drug interaction between pregabalin and ethanol following coadministration in healthy volunteers.

The sponsor performed a randomized, double-blind, placebo-controlled, 4-way crossover study in 12 healthy volunteers receiving 3 doses of pregabalin (300 mg capsule, Lot CF-0200498 formulation WL 144,723A-13) and/or ethanol (0.7 g/kg in orange juice, Lot 114698 or 117624) and/or placebo. Pregabalin or placebo was administered 30 minutes prior to ethanol or placebo-equivalent ethanol (0.4%). The schedule of pharmacokinetic and pharmacodynamic observations and procedures is shown in the table below.

Schedule of Observations and Procedures

Study Day		-14 to -8	-7 to -1	1[a]	2[b]							3[c]	29 to 35
Hour					0	0.5	1	2.5	4	6	9	12	24	
Orientation		X												
History		X												
Physical Examination		X		X									X	X
Clinical Laboratory	1) Haematology	X		X										X
	2) Chemistry	X		X										X
	3) Urinalysis	X[d]		X										X
	4) Pregnancy Test	X	X[e]											X
	5) Breathalyzer Measurements		X[e]											
Vital Signs and Respiratory Measurements		X[f]		X[f]	X[g]		X[h]	X[h]	X[h]	X[h]			X[h]	X[f]
Screening Electrocardiogram and Spirometry		X												
Psychometric Testing			X[i]		X		X	X	X	X	X	X	X	
Pregabalin Blood Collection					X		X	X	X	X	X	X	X	
Ethanol Blood Collection					X		X	X	X	X	X	X	X	
Drug Administration	Pregabalin or Placebo			X[j]	X									
	Ethanol or Placebo					X								

[a] Repeated on Days 8, 15, and 22 [b] Repeated on Days 9, 16, and 23 [c] Repeated on Days 10, 17, and 24 [d] Included urine drug screen
[e] Days -1, 7, 14, and 21 only [f] Psychometric testing, 4 times for training purposes, with the last session on Day-1
[g] Pregabalin capsules (300 mg) or placebo capsules (matching) administered q12h [h] Included respiratory measurements prior to psychometric testing
[i] Included respiratory measurements [j] Vital sign measurement only

Pharmacokinetic parameters for pregabalin and ethanol were estimated using standard noncompartmental methods (WinNonlin Pro 2.1). Results from analysis of variance (ANOVA) of natural log-transformed Cmax and AUC values were used to calculate 90% confidence intervals for the ratio of treatment means. Lack of pharmacokinetic interaction was concluded by the sponsor if the 90% confidence intervals for natural log-transformed Cmax and AUC values were within the 70% to 143% and 80% to 125% ranges, respectively.

Summary of Pregabalin Pharmacokinetic Parameter Values Following the Third 300-mg Pregabalin Capsule Dose Administered Alone (Reference) and With Ethanol (Test): Study 1008-79-0

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Pregabalin Alone (Reference)	With Ethanol (Test)		
n	11	13		
Cmax, µg/mL	8.22	9.96	121	107 to 137
tmax, hr	1.14	1.00	88.1	Not Applicable
AUC(0-12), µg hr/mL	53.9	54.5	101	96.6 to 106
Cmin, µg/mL	2.23	2.11	94.5	89.4 to 99.9
CL/F, mL/min	93.9	93.9	99.3	Not Applicable
t½, hr	5.95	5.86	98.5	Not Applicable

Summary of Ethanol Pharmacokinetic Parameter Values Following Administration of Ethanol Alone (Reference) and With the Third 300-mg Pregabalin Capsule Dose (Test): Study 1008-79-0

Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Ethanol Alone (Reference)	With Pregabalin (Test)		
n	12	12		
Cmax, mg/mL	1.04	0.947	91.1	84.1 to 98.7
tmax, hr	1.05	1.36	129	Not Applicable
AUC(0-tlqc), mg hr/mL	3.96	3.47	87.7	79.9 to 96.3
AUC(0-∞), mg hr/mL	4.15	3.76	90.4	84.6 to 96.6
t½, hr	0.870	1.03	118	Not Applicable

AUC(0-tlqc) = Area under the concentration-time profile from time zero to the time for the last quantifiable concentration (lqc).

A 21% increase in pregabalin Cmax was observed following administration 30 minutes prior to ethanol consumption. However, the above tabulated pharmacokinetic parameters indicate that the 90% confidence intervals for Cmax and AUC(0-12 or 0-□) values were within the 70% to 143% and 80% to 125% ranges, respectively, indicating absence of a pharmacokinetic interaction of between ethanol and pregabalin. It may be difficult to extrapolate these results to other possible scenario's such as administration of higher dose of pregabalin (600 mg) or more ethanol consumption or more importantly simultaneous administration of the two agents.

PPK Analysis

RR 764-03296: Population Pharmacokinetics of Pregabalin in Healthy Volunteers, Renally Impaired Patients, and Patients With — Pain

Objective

To describe the pharmacokinetics of pregabalin following single and multiple doses in healthy volunteers and subjects with various degrees of renal impairment, as well as multiple doses in patients with — pain using a validated population model, and to identify concomitant medications that impact pregabalin pharmacokinetics in this population.

Methods

Data:

Data from 9 studies in adult patients with — pain, 4 studies in healthy volunteers, and 1 study in subjects with renal impairment were pooled for the population analysis.

- Healthy volunteer studies: Studies 1008-001, -002, -003, and -023.
- Renal impairment study: Study 1008-49
- — pain studies: Studies 1008-014 (DPN), -029 (DPN), -030 (PHN), -031 — -032 — -045 (PHN), -104 — -105 — and -127 (PHN).

In the efficacy trials, pharmacokinetic blood samples were collected randomly with respect to last dose. Date and time were collected for the blood sample collection, last dose prior to the blood sample collection, and last meal prior to the blood sample collection. The dates and times were used to determine time intervals between the pharmacokinetic blood sample and last dose and between last dose administered and last meal.

The dataset was prepared which contained drug dosing information, plasma pregabalin concentration-time data, covariate information, and patient demographic information. It included a total of 4072 plasma pregabalin concentrationtime data from a total of 1099 subjects; 2868 concentration-time data were from 97 healthy volunteers and 26 renally impaired subjects, and 1204 concentration-time data were from 976 patients with — pain. Of the entire population, 515 were males and 584 were females. 993 (90%) of the subjects were Caucasian, 43 (4%) were Black, and 55 (5%) were Hispanic. Mean ± SD (range) age, weight, height, and creatinine clearance were 57.9 ± 14.4 years (19- 100), 86.7 ± 19.9 kg (44.5- 160.9), 170 ± 10.1 cm (142- 196), and 91.9 ± 31.6 mL/ min (10- 243), respectively.

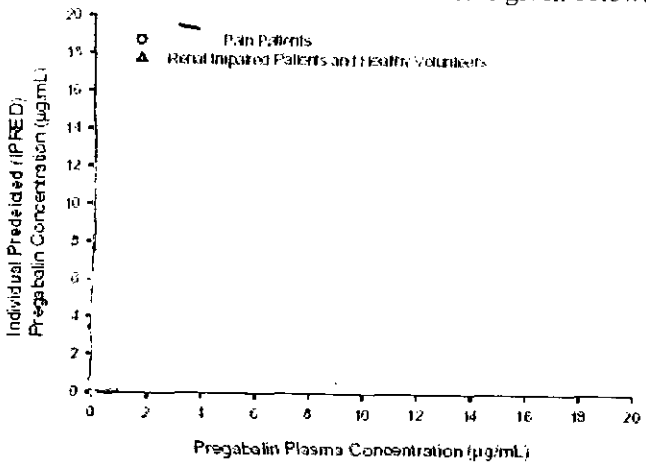
Analysis:

Plasma concentration-time data were modeled using a population analysis approach in NONMEM to estimate pregabalin population pharmacokinetic parameters (mean and intersubject variability). A one-compartment pregabalin pharmacokinetic model with first order absorption and a lag time was used and the effect of concomitant medications (oral antidiabetics, insulins, and diuretics) on pregabalin clearance was tested. Intersubject variability on the pharmacokinetic parameters (CL/F, V/F, and Ka) was modeled using an exponential error model and the residual error was modeled using a combination (additive+proportional) model. The final model included only those covariates that produced a change in the objective function of >10.8 for 1 degree of freedom ($p<0.001$).

The fed/fasted status of each patient was determined and incorporated into the NONMEM model using the following criteria: A blood sample was considered drawn during the fed state if the dose preceding the blood sample was administered within 1 hour of a meal. Otherwise, the blood sample was considered drawn during the fasted state and analyzed as such.

RESULTS

The diagnostic plot of IPRED vs. OBS for the final model is given below:



Pharmacokinetic Model in All Subjects:

The population pharmacokinetic parameters in healthy subjects, renally impaired subjects, and patients with — pain are summarized in the following table. The table includes estimates of oral clearance (CL/F) related to creatinine clearance (CLcr) and its breakpoint value (CLcrBP), volume of distribution (Vd/F) related to body weight (WT) and gender (GDER), as well as estimates of first order absorption (KA) related to fasted (fast) or fed (fed) state and lag time (TLAG). The indicator variable for creatinine clearance (CFLG) is a flag set to 1 when CLcr was $\leq\theta_{CLcrBP}$ and set to 0 for CLcr values $>\theta_{CLcrBP}$. Intersubject variability was reported as the percent coefficient of variability (%CV).

Table: Population Pharmacokinetic Parameter Estimates (θ) of the Final Model in All Subjects

Parameter	θ	(95% CI)	%CV
$CL/F = \theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \cdot \theta_{CLcrBP}) \cdot (1-CFLG)$			23.0
θ_{CLcr}	0.0459	(0.045-0.047)	--
θ_{CLcrBP}	105	(103-106)	--
$Vd/F = (\theta_{Wt} \cdot (WT/80.4)^{\theta_{pwr}}) \cdot (1+GDER \cdot \theta_{gd.r})$			11.9
θ_{Wt}	43.1	(41.8-44.5)	
θ_{pwr}	0.691	(0.540-0.839)	
$\theta_{gd.r}$	0.806	(0.774-0.838)	--
$KA = (EKEL \cdot \theta_{fast}) \cdot (1+\theta_{fed} \cdot (FED))$			187
θ_{fast}	73.6	(67.5-79.7)	--
θ_{fed}	-0.688	(-0.888-0.848)	--
TLAG (hr)	0.158	(0.150-0.166)	--

CI = Confidence Interval.
CV = Coefficient of Variation.
CL/F = Oral Clearance.
CFLG = Indicator Variable for Creatinine Clearance.
Vd/F = Apparent Distribution Volume.
KA = Absorption Rate.
EKEL = Elimination Rate Constant.
TLAG = Lag Time.

Note:
1. There is an error in the equation for Vd/F.
2. θ_{fed} should be -0.868 (not -0.688).

Effect on CL/F:
Pregabalin CL/F increased proportionally to CLcr from zero up to a value of approximately 105 mL/min. Above a CLcr value of 105 mL/min, pregabalin's CL/F was independent of CrCl.

Effects on Vd/ F:
The population estimate of Vd/ F was proportional to body weight centered on mean weight of the subjects (80.4 kg) with weight to the power of 0.691 (θpwr). After accounting for differences in weight, male Vd/ F was approximately 19% higher than females.

Effects on KA:
The administration of pregabalin in a fed state decreased the rate of drug absorption relative to administration of pregabalin given fasted. A lag time prior to absorption of about 10 minutes was also observed.

Intersubject and residual Variability:
Intersubject variability was about 23% for CL/ F, 11.9% for Vd/ F, and 187% for KA. In healthy subjects, residual variability was characterized by both an additive and a proportional error component with a coefficient of variation for the proportional component of about 14.6%. In patients with — pain residual variability was also characterized by both an additive and a proportional error component with a coefficient of variation for the proportional component of about 37.2%. The greater residual variability in — pain patients is most likely due to differences in sampling conditions between healthy volunteers or renally impaired patients versus — pain patients. Standard deviation for the additive error term was 0.02 and 1.87 µg/ mL for healthy volunteers and — pain patients, respectively.

Effect of Concomitant Medications on Pregabalin Oral Clearance:
Three commonly prescribed drug classes used in pregabalin neuropathic pain clinical trials were analyzed to determine their effect on pregabalin CL/ F (see table below). Insulins does not appear to affect the pregabalin clearance. Diuretics decreased pregabalin oral clearance by approximately 7%. Oral antidiabetic agents increased pregabalin clearance by approximately 10%. The 90% CI for each of these concomitant medication classes was within 80% to 125%. None of these differences are expected to be clinically significant and do not warrant dosage adjustment.

Table: Effect of Concomitant Medications on Pregabalin Plasma Clearance (CL/ F)

Parameter	No of Subjects	ΔMOF[a]	Ratio[b]	90% CI[c]
Oral Antidiabetics	248	-19.22	110	105-115
Diuretics	163	-9.69	93	80-105
Insulin	123	-0.36	102	96-108

[a]Change in minimum objective function values, -2 times the log of the likelihood, between the reference and full model. A change of >-10.8 in ΔMOF is significant at the p <0.001 level.
[b]Ratio of mean CL/F values, expressed as a percentage (100% × test: pregabalin CL/F in patients receiving concomitant med/reference vs. pregabalin CL/F in patients not receiving the concomitant med).
[c]90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percent of the reference mean.

Sponsor's Conclusions

- Pregabalin oral clearance (CL/F) is related to creatinine clearance (CLcr) and this relationship is similar between healthy volunteers and patients with — pain.

- Dosage adjustment is recommended based on the degree of renal impairment.
- Pregabalin dosage adjustment is not required for concomitant administration of insulins, diuretics, or oral antidiabetics.

Reviewer's Comments

1 The exact time of collection of the pharmacokinetic blood sample was not prescribed in the protocol. To facilitate the modeling of the pharmacokinetic data, an 8 AM-2 PM-8 PM dosing regimen was assumed for all patients in the analysis, resulting in a 6-hour time interval between doses taken during the day and a 12-hour interval between the evening and morning dose. Any dose recorded as being taken between 2 AM and 11 AM was considered the first dose of the day (morning dose) and was treated as if it was an 8 AM dose. Any dose taken between 11 AM and 5 PM was considered the second dose of the day (afternoon dose) and was treated as if it was a 2 PM dose. Any dose taken between 5 PM and 2 AM was considered the third dose of the day (evening dose) and was treated as if it was an 8 PM dose. Although the dosing time before blood sampling was recorded, there is uncertainty in dosing time for the dose immediately before that. This point was discussed with Dr. He Sun, Pharmacometrics Expert of DPE II. Considering that the error in dosing time as random, the population mean parameter estimate would still be reliable but not the individual Bayesian estimates in absolute terms.

2. Concomitant diuretics were pooled as one category of drugs in the analysis. The same was done with antidiabetics. Pooling of data averaged out the effect over all diuretics used by patients included in the analysis and does not represent that of individual diuretic medication. The same argument applies to antidiabetics. Upon request, the sponsor submitted a list of drugs used by these patients and indicate the number of patients for each drug and provided plots of parameter values. Because of some uncertainties related to dosing time (see comment #1) and dosing conditions, the population analysis results cannot be applied to all the concomitant diuretic or hypoglycemic drugs included in the analysis. The results are considered acceptable for drugs with sufficient sample size (metformin, glibenclamide and furosemide).

3. A 2-compartment model would fit the profiles better. However, a one-compartment model is deemed sufficient for the CL/F estimate.

4. The 90% CI for drug interaction parameter estimates was calculated as $\theta \pm 1.67$ SE. This interval only reflects the uncertainty in mean parameter estimate and does not represent the interval based on intersubject variability.

TITLE:
Pregabalin Exposure-Response Analysis in Patients With Diabetic Neuropathy or Postherpetic Neuralgia

Objective:
To describe the exposure-response relationship of pregabalin following multiple doses in patients with diabetic peripheral neuropathy (DPN) or postherpetic neuralgia (PHN) using a population approach, and to identify the factors that impact pregabalin exposure-response in these patients.

Data:

Patients data from five clinical trials (1008-014, -029, -040, -131, and -149) in patients with DPN and four trials (1008-030, -045, -127, and -132) in patients with PHN were used for the analysis. All these nine studies were double-blind, placebo-controlled trials.

Study 1008-014:	6-week, TID, 150 and 600 mg/day
Study 1008-029:	5-week, TID, 75, 300, and 600 mg/day
Study 1008-040:	8-week, TID, 600 mg/day pregabalin and 75 mg/day amitriptyline
Study 1008-131:	8-week, TID, 300 mg/day
Study 1008-149[(1)]:	12-week, BID, 150, 300, or 300/600 mg/day stratified by CLcr
Study 1008-030:	5-week, TID, 75 and 150 mg/day
Study 1008-045:	8-week, TID, 150 and 300 mg/day
Study 1008-127:	8-week, TID, 300 and 600 mg/day stratified by patient CLcr
Study 1008-132[(2)]:	12-week, BID, 150, 300, or 300/600 mg/day stratified by CLcr

Note: [1]Validation dataset
[2]Study terminated early due to a partial clinical hold. For this study, all available data at the time of study termination were included in the analysis.

Study	N	Age (yr)	CLcr (mL/min)	Weight (kg)	Average Baseline Pain Score	Disease Onset (Days Prior To Study Start)
1008-014	243	57.1 ± 9.6	103.8 ± 31.9	95.3 ± 19.6	6.71 ± 1.51	3587 ± 3200
1008-029	336	60.0 ± 10.5	97.8 ± 30.2	98.1 ± 19.7	6.41 ± 1.45	3629 ± 3054
1008-040	165	61.4 ± 10.5	90.0 ± 30.9	86.5 ± 17.6	6.58 ± 1.64	4783 ± 3283
1008-131	144	59.6 ± 11.4	121.1 ± 47.3	96.3 ± 20.1	6.34 ± 1.60	3641 ± 3794
DN Studies[b] (Median, Range)	888	59.4 ± 10.5 (60.0, 21-85)	101.8 ± 35.4 (94.8, 32-314)	94.9 ± 19.8 (92.9, 44.5-187)	6.51 ± 1.53 (6.43, 2.86-10)	3834 ± 3292 (2832, 17-22889)
1008-030[c]	252	71.7 ± 9.2	63.9 ± 24.6	75.9 ± 17.1	6.57 ± 1.57	981 ± 1053
1008-045	238	72.2 ± 10.2	59.6 ± 21.1	70.7 ± 13.5	6.85 ± 1.63	1307 ± 1320
1008-127	171	71.4 ± 10.9	76.8 ± 27.6	77.4 ± 15.2	6.34 ± 1.48	1043 ± 1088
1008-132[d]	215	71.4 ± 11.6	67.8 ± 26.0	79.3 ± 17.9	6.50 ± 1.54	1040 ± 1153
PHN Studies (Median, Range)	876	71.7 ± 10.4 (74.0, 21-100)	66.2 ± 25.4 (61.1, 19-202)	75.6 ± 16.4 (74.0, 29.1-141)	6.58 ± 1.57 (6.57, 3.43-10)	1097 ± 1167 (704, 38-8159)
Index Dataset (Median, Range)	1764	65.5 ± 12.1 (67.0, 21-100)	84.1 ± 35.6 (78.4, 19-314)	85.3 ± 20.6 (83.0, 29.1-187)	6.55 ± 1.55 (6.43, 2.86-10)	2475 ± 2829 (1448, 17-22889)
1008-149	538	59.4 ± 11.6	110.9 ± 40.7	88.6 ± 18.3	6.46 ± 1.45	4729 ± 3177
All Studies (Median, Range)	2302	64.1 ± 12.3 (65.0, 21-100)	90.4 ± 38.5 (83.8, 19-314)	86.1 ± 20.1 (84.1, 29.1-194)	6.53 ± 1.53 (6.43, 2.86-10)	3001 ± 3066 (1899, 17-22889)

CLcr = Creatinine clearance.

[a] Based on Visit 1 data

[b] Excluding Study 1008-149 which was not included in the index dataset

[c] Demographics include 2 patients (ID 122007and ID 133005) who were not included in the analysis.

[d] Demographics include 1 patient (ID 141002) who was not included in the analysis.

Dataset:

Index dataset: The dataset was comprised of all studies except Study 1008-149. There were 1761 patients providing 68247 pain score observations (25,722 observations from 632 patients in the placebo group; 4,996 observations from 160 patients in the 75-mg/day group; 11254 observations from 290 patients in the 150-mg/day group; 13429 observations from 343 patients in the 300-mg/day group; and 12846 observations from 336 patients in the 600-mg/day group).

Validation dataset: The sponsor indicated that Study 1008-149 was not completed in time for model development and was used for an independent evaluation of the model. The dataset consisted of 32,438 pain score observations from 538 patients. There were 7898 observations from 125 patients in the placebo group; 8339 observations from 132 patients in the 150-mg/day group; 9099 observations from 162 patients in the 300-mg/day group; and 7102 observations from 119 patients in the 600-mg/day group.

The overall mean ± SD (range) age, weight, CLcr, daily baseline pain score, and time since disease onset were 64.1 ± 12.3 years (21-100 years), 86.1 ± 20.1 kg (29-194 kg), 90.4 ± 38.5 mL/min (19-314 mL/min), 6.53 ± 1.53 (2.86-10), and 3001 ± 3066 days (17-22889 days), respectively. There were a total of 1257 males and 1045 females, with 939 females being postmenopausal and 106 premenopausal. There were a total of 2149 whites (93%), 59 blacks (3%), 58 Hispanics (3%) and 36 of other ethnic origin (1%).

Pain score: Individual daily pain scores, recorded during the baseline, titration, and fixed-dose phases of the study using an 11-point Likert scale (0 = No Pain to 10 = Worst Possible Pain), were used for the analyses.

Model:

Model fitting was performed using a population analysis approach (NONMEM Version V). A subject-specific random-effects model was used to characterize the relationship between daily pain score and pregabalin exposure in individual patients, taking into account placebo and baseline effect. The daily pain scores were modeled as an ordered categorical variable. Covariate effects for age, gender, body weight, race, CLcr, average baseline pain score, disease (PHN vs DN), disease duration, and regimen (TID vs BID) were investigated to determine the impact of these factors on the exposure-response relationship. The general form of the population pharmacodynamic (PD) model is given by the following expression:

$$\text{logit}\left[P(PS_{ij} \le m)\right] = \sum_{k=0}^{m} \beta_k + \theta_{base}(\overline{PS}_{i0} - 6.5) + f_p(t_j, X_i) + f_d(D_{ij}, t_j, X_i) + \eta_i$$

where logit(p) = log(p)-log(1-p), $P(PS_{ij} \le m)$ denotes the probability that the daily pain score, PS_{ij}, for patient i at time t_j is less than or equal to some score m, $\overline{PS}_{i0}$ denotes the average baseline PS for patient i, f_p denotes the placebo-time effect, f_d denotes the drug effect where D_{ij} denotes the pregabalin dose, X_i denotes a vector of patient covariates that may influence the placebo-time and/or drug effects, and η_i denotes an interindividual random effect with zero mean and variance. θ_{base} is a regression parameter that adjusts the population mean baseline logit probabilities (β_k) for the individual's observed average baseline pain score.

Placebo effect: A placebo-time step function model was used in the exploratory stage which revealed that an asymptotic exponential model describe well the placebo-time effect (fp).

$$f_p(t_j) = P_{max}\left(1 - e^{-k_{plc} \cdot t_j}\right)$$

where P_{max} is the asymptotic maximum placebo effect, and k_{plc} is a constant that governs the rate at which the placebo effect reaches this maximum. Plots of the conditional mean pain scores for the placebo group for each study reveals substantial differences among studies. Consequently, the model was expanded to include study-dependent estimates of P_{max}.

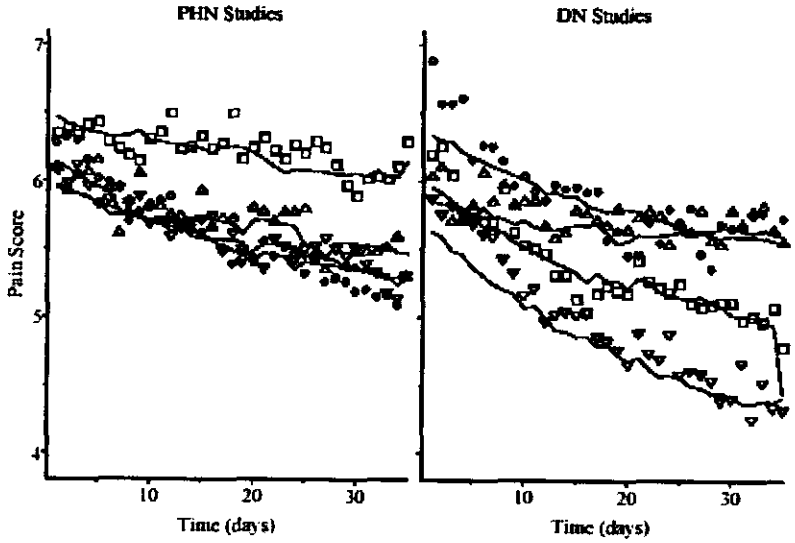


Figure: Plots of Observed and Predicted Conditional Mean Pain Scores for Placebo-Treated Patients in PHN Studies: 030 (○), 045 (□), 127 (▽), 132 (△) and DN Studies: 014 (○), 029 (□), 040 (▽), 131 (△)

Drug effect: Several parametric forms with or without the time-dependent exposure for the drug model, *fd*, were investigated, including: a linear dose-response model, an Emax model, and a sigmoid-Emax model. In addition, an asymptotic exponential model on exposure was investigated to assess time of onset of the drug effect. The Emax model was selected to relate the daily dose of pregabalin to pain score.

$$f_d(D_{ij}, t_j) = \frac{Emax\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right]^{\gamma}}{ED_{50}^{\gamma}+\left[D_{ij}\left(1-e^{-k_{eq}t_j}\right)\right]^{\gamma}}$$

The goodness of fit of the final base model was evaluated using graphical assessment of the conditional probabilities and mean daily pain scores. The frequency-based estimates of the conditional cumulative probabilities were obtained by averaging the number of observed pain scores $\leq m$ at time tj; ie,

$$P\left(PS_j \leq m \middle| T \geq t_j\right) = \frac{n\left(PS_{ij} \leq m\right)}{n\left(T_i \geq t_j\right)}$$

where n() denotes the frequency count operator, Ti denotes the time of dropout for patient i, and $Ti \geq tj$ denotes time points prior to dropout when pain scores were observed. To obtain comparable model-based conditional cumulative probabilities, the predicted individual probabilities are averaged over the patients with observed pain scores; ie,

$$P\left(PS_j \leq m \middle| T \geq t_j\right) = \frac{1}{n_j}\sum_{i=1}^{n_j} P\left(PS_{ij} \leq m \cap T_i \geq t_j\right)$$

where nj denotes the number of observed values at time tj, ie, $nj = n(Ti \geq tj)$. The observed and model-based conditional mean pain scores were also computed to assess the model fit. The observed conditional mean pain scores were obtained by simple averaging of the observed pain scores across patients at time tj. The corresponding model-based estimates were calculated using the relation.

$$E(PS_j \mid T \geq t_j) = \sum_{m=0}^{10} m \cdot \left[P(PS_j \leq m \mid T \geq t_j) - P(PS_j \leq m-1 \mid T \geq t_j) \right]$$

Histograms of the empirical Bayes predictions of the interindividual random effects were also inspected to verify that the statistical assumptions were met (ie, unimodal and symmetrically distributed about zero).

Covariate model: Covariates investigated for both the placebo and drug effect components (P_{max} and E_{max}) were gender, age, body weight, race (whites/others vs blacks vs Hispanics), average baseline pain score, and disease onset. Disease (PHN vs DN) and regimen (TID vs BID) were included for Emax but not for P_{max} since these effects were confounded with the study-dependent placebo parameters. The covariate parameters were included in the model in multiplicative form. In addition, CLcr was investigated as a covariate on drug exposure in the Emax model. Wald's approximation method (WAM) was used to rank all submodels containing covariates and NONMEM was used to fit the top 15 ranked submodels to select the final model.

Simulation: To assess the consistency of the final model with the results from Study 1008-149, 1000 hypothetical validation datasets conditioned on the observed covariates and dropouts in Study 1008-149 were simulated based on the final model. Parameter uncertainty was taken into account in the simulations. Plots of the observed endpoints means were compared to the distribution of the 1000 simulated estimates for each ITT dose by covariate strata.

Results

Parameter estimates:
The parameter estimates for the base model, base model with study-dependent placebo effects, full model and the final model are shown in the tables below:

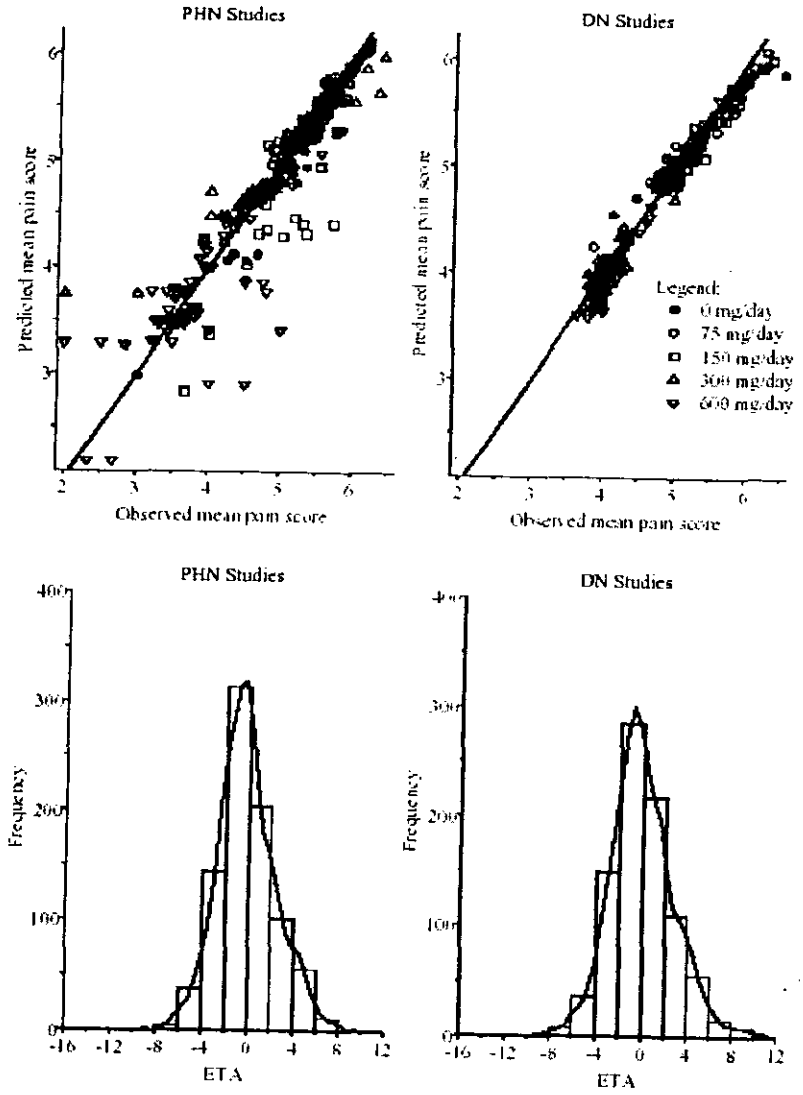
Table. Parameter Estimates ± SE

Parameter	Base	Base w/ Study-Dep Placebo	Full	Final
MOF	211,138.483	210,740.293	210,005.426	210,011.849
ω^2	7.96 ± 0.28	7.88 ± 0.28	7.57 ± 0.27	7.59 ± 0.27
Baseline				
β_0	-8.98 ± 0.09	-9.10 ± 0.10	-9.16 ± 0.09	-9.16 ± 0.09
β_1	1.84 ± 0.03	1.85 ± 0.03	1.85 ± 0.03	1.85 ± 0.03
β_2	1.53 ± 0.02	1.54 ± 0.02	1.53 ± 0.02	1.53 ± 0.02
β_3	1.47 ± 0.02	1.47 ± 0.02	1.47 ± 0.02	1.47 ± 0.02
β_4	1.43 ± 0.01	1.44 ± 0.01	1.44 ± 0.01	1.44 ± 0.01
β_5	1.50 ± 0.01	1.51 ± 0.01	1.52 ± 0.01	1.52 ± 0.01
β_6	1.57 ± 0.02	1.58 ± 0.02	1.59 ± 0.02	1.59 ± 0.02
β_7	1.81 ± 0.02	1.81 ± 0.02	1.83 ± 0.02	1.83 ± 0.02
β_8	2.37 ± 0.03	2.38 ± 0.03	2.42 ± 0.03	2.42 ± 0.03
β_9	2.30 ± 0.04	2.30 ± 0.04	2.35 ± 0.04	2.35 ± 0.04
θ_{base}	-1.46 ± 0.04	-1.46 ± 0.04	-1.83 ± 0.05	-1.82 ± 0.05
Placebo				
Pmax	1.39 ± 0.04	N/A	N/A	N/A
Pmax (Study 30)	N/A	0.895 ± 0.091	0.941 ± 0.107	0.931 ± 0.103
Pmax (Study 45)	N/A	0.870 ± 0.071	0.984 ± 0.087	0.955 ± 0.080
Pmax (Study 127)	N/A	1.39 ± 0.09	1.69 ± 0.11	1.64 ± 0.10
Pmax (Study 132)	N/A	1.69 ± 0.10	2.21 ± 0.14	2.09 ± 0.12
Pmax (Study 14)	N/A	1.65 ± 0.09	1.26 ± 0.08	1.29 ± 0.08
Pmax (Study 29)	N/A	2.17 ± 0.09	1.91 ± 0.10	2.01 ± 0.09
Pmax (Study 40)	N/A	2.47 ± 0.09	2.30 ± 0.12	2.39 ± 0.10
Pmax (Study 131)	N/A	0.608 ± 0.089	0.471 ± 0.070	0.504 ± 0.072
k_{pl} (Days^{-1})	0.0500 ± 0.0039	0.0514 ±0.0036	0.0548 ± 0.0034	0.0543 ± 0.0034
$t_{1/2}$ (Days)	13.9	13.5	12.6	12.8
Drug				
Emax	5.87 ± 0.53	4.05 ± 0.25	3.47 ± 0.32	3.49 ± 0.31
ED_{50} (mg/day)	778 ± 137	403 ± 62	419 ± 64	441 ± 64
k_{eq} (Days^{-1})	0.993 ± 0.157	1.02 ± 0.17	1.01 ± 0.16	1.02 ± 0.16
$t_{1/2}$ (Days)	0.698	0.680	0.686	0.680

Parameter	Base	Base w/ Study-Dep Placebo	Full	Final
Gender Effect				
Pmax	0	0	-0.259 ± 0.031	-0.240 ± 0.028
Emax	0	0	0.0150 ± 0.0575	0
Age Effect				
Pmax	0	0	-1.13 ± 0.09	-1.07 ± 0.08
Emax	0	0	1.97 ± 0.25	1.80 ± 0.22
Weight Effect				
Pmax	0	0	0.121 ± 0.088	0
Emax	0	0	-0.0740 ± 0.132	0
Blk. Race Effect				
Pmax	0	0	0.974 ± 0.132	1.01 ± 0.13
Emax	0	0	-1	-1
Hisp. Race Effect				
Pmax	0	0	0.592 ± 0.149	0.564 ± 0.145
Emax	0	0	-1	-1
CLcr Effect				
Exposure	0	0	0.199 ± 0.203	0
Baseline Effect				
Pmax	0	0	0.783 ± 0.097	0.770 ± 0.096
Emax	0	0	1.64 ± 0.15	1.62 ± 0.15
Disease Effect				
Emax	0	0	0.920 ± 0.164	0.901 ± 0.155
Onset Effect				
Pmax	0	0	0.0338 ± 0.0217	0
Emax	0	0	-0.217 ± 0.026	-0.203 ± 0.025
Regimen Effect				
Emax	0	0	-0.114 ± 0.103	0

The final model diagnostic plots are presented below:

Final Model Diagnostic Plots



For the final model, the pregabalin effect increased over the dose range of 75 to 600 mg/day with a half-life of drug-effect onset of 16.3 hours. The onset of the placebo effect was considerably slower than the pregabalin effect, with a half-life of 12.8 days. As a result, overall treatment effect (placebo and drug) steady state was achieved within 9 to 12 weeks. On the logit-probability scale, the maximum drug effect is predicted to be greater than the maximum placebo effect (Emax >Pmax) for all studies. The ED50 was approximately 450 mg/day.

Average baseline pain score had a substantial effect on the endpoint mean change from baseline pain scores. Patients with an average baseline pain score ≥6.43 (median of the

index dataset) had an endpoint mean change ≥1 point lower than patients with an average baseline pain score <6.43 for the 300- and 600-mg/day doses. Covariate effects for gender, age, body weight, CLcr, disease, disease duration and regimen were not clinically significant. A dose-response could not be established in the black and Hispanic populations due to the small sample sizes available for these populations.

Study 1008-149 endpoint mean changes were generally consistent with the final model predictions except for the 300mg/day dose. The endpoint mean change for females at the 300-mg/day dose is inconsistent with the observed and predicted endpoint mean changes at the other doses and in other trials.

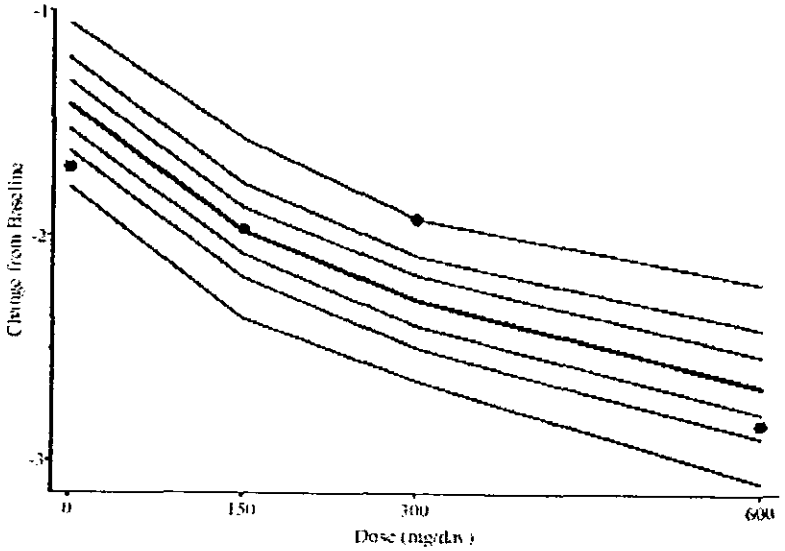


Figure . Observed (•) Endpoint Mean Changes From Baseline Pain Scores (Study 1008-149) and Comparisons With Select Percentiles (Median = Bold line, 1st and 3rd Quartiles = Solid Lines, 10th and 90th Percentiles = Dashed Lines, 1st and 99th Percentiles = Dotted Lines) of the Simulated Endpoint Means From 1000 Simulated Trials

Table . Observed Endpoint Mean Changes Stratified by Gender

Dose (mg/day)	Gender	N	Mean ± SE	Placebo-Corrected
0	Females	285	-1.17 ± 0.12	0
	Males	347	-0.971 ± 0.103	0
75	Females	77	-1.67 ± 0.25	-0.501
	Males	83	-1.13 ± 0.18	-0.160
150	Females	127	-1.63 ± 0.16	-0.455
	Males	163	-1.33 ± 0.15	-0.360
300	Females	175	-2.56 ± 0.18	-1.39
	Males	168	-1.94 ± 0.16	-0.971
600	Females	147	-2.78 ± 0.19	-1.61
	Males	189	-2.46 ± 0.17	-1.49

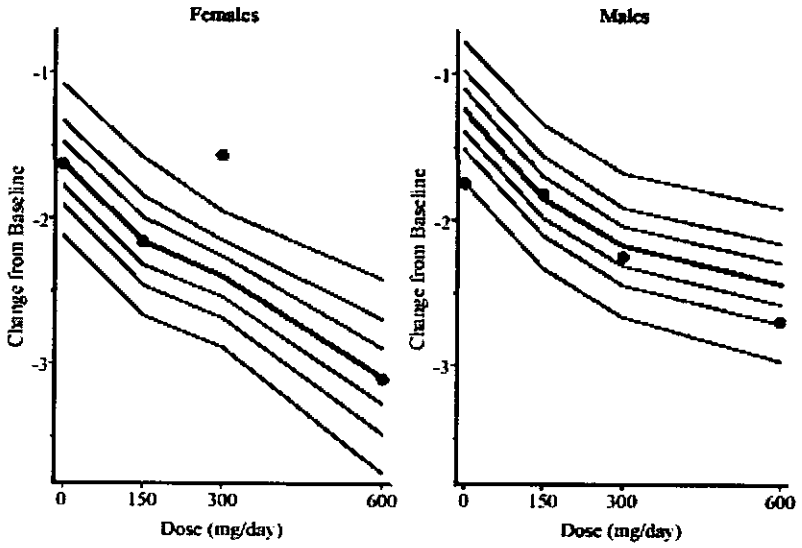


Figure . Observed (•) Endpoint Mean Changes From Baseline Pain Scores Stratified By Gender (Study 1008-149) and Comparisons With Select Percentiles (Median = Bold Line, 1st and 3rd Quartiles = Solid Lines, 10th and 90th Percentiles = Dashed Lines, 1st and 99th Percentiles = Dotted Lines) of the Simulated Endpoint Means From 1000 Simulated Trials

Sponsor's Conclusions

- An Emax model was used to describe the relationship between daily dose of pregabalin and pain score. Decrease in daily pain score is correlated with increasing pregabalin daily dose. The ED50 is approximately 400 mg/day. Increased benefit from increasing dose to 600 mg/day is observed.
- The onset of drug effect had an equilibration half-life of 0.68 days (16.3 hrs). The onset of the placebo effect is considerably slower with a half-life of approximately 13 days. Overall treatment effect (placebo and drug) steady-state is achieved within 9 to 12 weeks.
- Study-dependent placebo effects are included in the model to account for substantial study-to-study variation in the daily pain scores in the placebo groups.
- Average baseline has a marked influence on the maximum drug and placebo effect resulting in a steeper dose-response in patients with a higher average baseline pain score. Patients with an average baseline pain score ≥6.43 had endpoint mean changes ≥1 point lower than patients with a baseline pain score <6.43 for the 300- and 600-mg/day doses.

Patients with a baseline pain score ≥6.43 also had an approximate half-point lower endpoint mean change in comparison to the overall patient population at the 600-mg/day dose.

- Due to the small sample size, a dose-response could not be established in the black and Hispanic populations.
- Placebo and/or drug effects are observed for gender, age, disease (PHN vs DN) and disease onset resulting in some differences (quarter- to half-point change or less) in the endpoint mean changes.
- Covariate effects for body weight, CLcr, and regimen (TID vs BID) are not statistically significant, and are excluded from the final model.
- In several covariate strata, there is a tendency for the final model to overpredict the endpoint mean change from baseline (underpredict the reduction from baseline) for the 300-mg/day dose.
- The Study 1008-149 endpoint mean changes are generally consistent with the final model predictions providing an independent evaluation of the model since Study 1008-149 was not included in the index dataset used to build the model.
- A reduction in the endpoint mean change from baseline for the 300-mg/day pregabalin dose in females is observed. This result appears to be an anomaly since the endpoint mean changes at the other doses are well within the variation predicted by the model.

Reviewer's Comments:

1. The sponsor lumped data for the two indications (DN & PHN) to determine the exposure-response relationship for pain. Differences in Emax was determined. The possible differences in EC50 anf Hill's factor should have also been investigated. It may be more appropriate to conduct separate analyses for the two indications since the drug effect can differ in other aspects besides EC50.
2. The sponsor indicated that covariate effects for body weight, CLcr, and regimen (TID vs BID) are not statistically significant, and are excluded from the final model. However, CLcr is a known factor affecting exposure and should be modeled based on the prior knowledge on the relationship between CLcr and pregabalin exposure, which includes a cutoff value for CLcr.
3. The sponsor indicated that the results of the endpoint mean change from baseline for the 300-mg/day pregabalin dose in females in study 149 appears to be an anomaly because the endpoint mean changes at the other doses are well within the variation predicted by the model. It should be noted that the model building dataset consisted of mostly (>80%) data from TID dosing while the validation dataset (Study 149) was obtained from a BID study. It is not known whether the dose response relationship for TID dosing is different from that for the BID dosing resulting in the observed inconsistency.
4. Since patients in the 300/600 mg/day arm received 300 mg/day dose only when their CLcr is low (30 mL/min<CLcr≤60 mL/min), these patients should be included in the 600 mg dose group in the plots. Alternatively, the modified dose taking into account the individual CLcr may be used in the plots to reflect more closely the true exposure for each individual. In all graphical display of dose response relationship presented by the sponsor, the actual dose was used in the plots, which would confound the results for the 300 mg treatment arm.
5. The final model overpredicts the endpoint mean change from baseline (underpredict the reduction from baseline) for the 300-mg/day dose which could not be explained by the way the plot was handled (see Comment #4) since the overprediction was observed for subjects with high CLcr. Apparently, some modification of the model is needed.

RR-MEMO 754-00019:
A Simulation Study to Assess the Performance of the Pregabalin Pain Exposure-Response Model to Predict Weekly Pain Scores for CI-1008-196

Objectives:
An exposure-pain score response model for pregabalin was previously developed using data from mostly TID trials (RR 754-00011). A simulation study was conducted based on this model to assess the predictive performance of the model against data from an independent study (#1008-196, a 13-week study with a BID regimen in PHN patients) that was not used in the development of the model. This was done to address 2 key questions:

1. Does the treatment effect diminish over time?
2. Does the model adequately predict the dose-response for BID regimens?

Method:

A total of 300 hypothetical datasets of daily pain scores were simulated based on the model conditioning on the design, observed covariates, and dropouts in Study 1008-196. Parameter uncertainty was taken into account in the simulations by simulating a different set of population estimates for each of the 300 hypothetical trials from a multivariate normal distribution using the population mean estimates and the covariance matrix of the estimates obtained from the model fit.

The model includes study-dependent maximum placebo effect parameters to account for the substantial study-to-study variation in the placebo response. Thus, for the simulations, the only parameter directly estimated from the data in Study 1008-196 was the maximum placebo effect (Pmax; 1.07 ± 0.05.). The other parameters, including the baseline logit-probabilities of pain severity, the placebo rate constant governing the rate of onset of the apparent placebo effect, covariate effects influencing Pmax, the equilibration rate constant governing the rate of onset of the drug effect, the maximum drug effect (Emax), the dose to achieve 50% of the maximum drug effect (ED50), covariate effects influencing Emax, and the interindividual variance component, were all fixed to their previously reported estimates (RR 754-00011).

Weekly mean pain scores were calculated within a patient from the daily pain scores for the observed data and for each of the 300 hypothetical trials' simulated data. These weekly mean pain scores were then averaged across patients within each treatment group to obtain population means. To assess the impact of dropout, the population means were computed by 2 different methods: 1) for each individual, the mean of the last 7 observations were carried forward (LOCF) to impute the missing observations after dropout; and 2) the means were computed for only those patients who completed all 13 weeks of treatment (completers). Key order statistics (percentiles) of the weekly population mean pain scores for each treatment group from the 300 simulated trials were calculated and compared to the weekly population mean pain scores obtained from the observed data from Study 1008-196.

Results

Plots of the weekly mean pain scores by treatment group for the completers' population (patients completing all 13 weeks of treatment) are shown in Figure 2. The observed weekly mean scores for the completers' appear to be consistent with the simulated means predicted by the model. Note the wider distribution of the simulated means for the completers' (Figure 2) relative to the distribution of the simulated LOCF means (Figure 1). The wider distribution is most likely due to the considerably smaller number of patients completing all 13

weeks of treatment. No upward trends (towards baseline) in the weekly mean pain scores were observed to suggest that the drug and/or apparent placebo effects diminished over the 13-week study duration.

Sponsor's Conclusion

The pregabalin pain exposure-response model predictions are in good agreement with the observed weekly mean pain scores for Study 1008-196 considering that only 1 out of 28 parameters (ie, Pmax) in the model were estimated directly from Study 1008-196 data. Based on the consistency of the simulated results from the model with the Study 1008-196 observed results, the following conclusions are drawn:

1. There is no evidence to suggest that the treatment effect diminishes over time. Moreover, inference from the model suggests that the onset of the drug effect is rapid and that the treatment effect steady state is primarily governed by the slower onset of the apparent placebo effect.
2. The observed dose-response for the BID regimens in this study is consistent with model predictions which was developed using data mostly from TID trials. Therefore, there is no evidence to suggest differences in the exposure-response between BID and TID regimens.

Reviewer's Comments:

- The modeling by itself can serve as a supporting evidence but not as the primary evidence that BID and TID regimens result in the same exposure-response relationship using the mean pain score as the response measure.
- Predictability for one indication may not translate into predictability for another indication.

Figure. Observed (•) Weekly Mean Pain Scores with LOCF Imputation and comparisons with Select Percentiles (Median = Bold Line, 1st and 3rd Quartiles = Solid Line, 10th and 90th Percentiles = Dashed Line, 1st and 99th Percentiles = Dotted Line) of the Simulated Weekly Means From 300 Simulated Trials

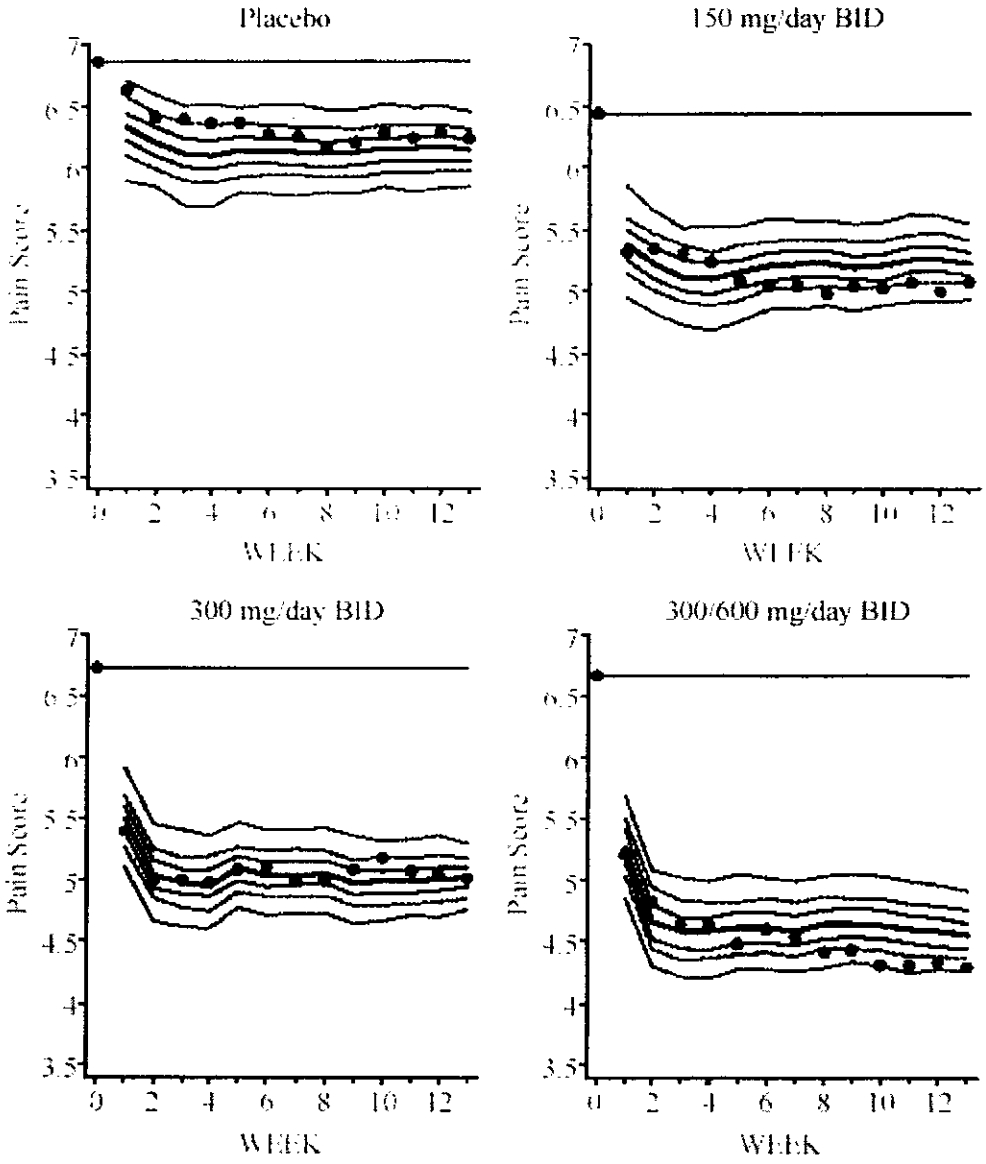
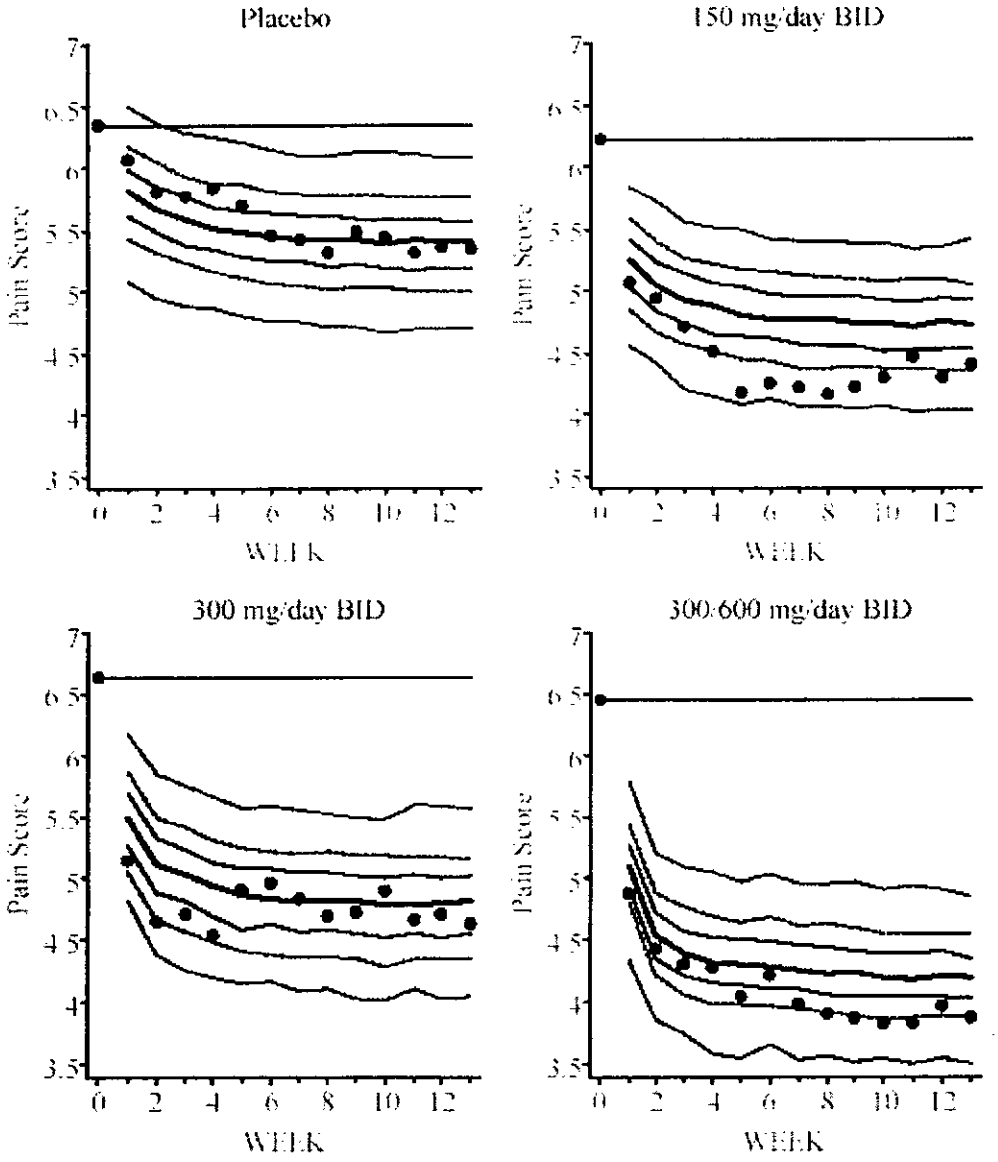


Figure. Observed (•) Weekly Mean Pain Scores For Completers and Comparisons With Select Percentiles (Median = Bold Line, 1st and 3rd Quartiles = Solid Line, 10th and 90th Percentiles = Dashed Line, 1st and 99th Percentiles = Dotted Line) of the Simulated Weekly Means From 300 Simulated Trials



Exposure-Response for Adverse Events
RR 754-00012: Pregabalin Exposure-Adverse Event Analysis in Patients With Neuropathic Pain, Generalized Anxiety Disorder, or Partial Seizures

In clinical studies conducted with pregabalin in patients with neuropathic pain, generalized anxiety disorder (GAD), or partial seizures, the 2 most prevalent adverse events reported by patients have been dizziness and somnolence. This report describes the methods and results of exposure-adverse event analyses performed for these 17 studies involving patients with neuropathic pain, GAD, or partial seizures.

Objective
To describe the pregabalin exposure-adverse event (dizziness and somnolence) relationship following multiple pregabalin doses in patients with neuropathic pain, GAD, or partial seizures.

Methods
The exposure-adverse event analyses were conducted using patient data from 17 studies. All studies were randomized, double-blind, multiple dose (TID or BID regimens), placebo-controlled, parallel-group multicenter studies. Study details are summarized in Table 1, Table 2, and Table 3 for neuropathic pain, GAD, and partial seizure studies, respectively.

Data:
Patient data from 8 neuropathic pain studies (diabetic neuropathy and postherpetic neuralgia) (1008-014, -029, -030, -040, -045, -127, -131, and -132), 3 studies in patients with partial seizures (1008-009, -011, and -034), and 6 studies in patients with generalized anxiety disorder (1008-021, -025, -026, -083, -085, and -087) were used for the analyses. A dataset was created that included subject identification, daily adverse event scores (recorded as the most severe intensity for that day) for the 2 most prevalent adverse events (dizziness and somnolence), measures of pregabalin exposure, and demographic and physiologic parameters. Individual adverse event (AE) scores recorded during the titration and double-blind phases of the study using a 4-point ordered categorical scale (0 = no adverse event, 1 = mild adverse event, 2 = moderate adverse event, 3 = severe adverse event), were used for both analyses.

The dataset prepared for the studies consisted of 194,087 observations collected in 4459 subjects. Of these, 63,059 observations were from the placebo group; 6698 were from the 50 mg/day group; 5200 were from the 75 mg/day group; 31,335 were from the 150 mg/day group; 2773 were from the 200 mg/day group; 22,652 were from the 300 mg/day group; 6829 were from the 400 mg/day group; 5386 were from the 450 mg/day group; and 50,155 were from the 600 mg/day group. For dizziness, 177,229 (91.3%) of the total observations indicated no adverse event; 11,241 (5.8%) were mild; 5016 (2.6%) were moderate; and 601 (0.3%) were severe. For somnolence, 176,494 (90.9%) of the total observations indicated no adverse event; 11,173 (5.8%) were mild; 5869 were moderate (3.0%); and 551 (0.3%) were severe. Mean ± SD (range) age, weight, height, and creatinine clearance were 49.4 ± 17.7 years (12-100), 80.7 ± 20.1 kg (29-187), 169.0 ± 10.5 cm (99-206), and 100.1 ± 36.1 mL/min (22-355), respectively. There were a total of 2153 males and 2306 females. The majority of subjects were white (88%), with 5% each black and Hispanic.

Table: Population Characteristics: Continuous Variables (Mean ± SD)

Study	N	Age (yr)	CLcr (mL/min)	Height (cm)	Weight (kg)
1008-009	312	39.1 ± 11.9	106.5 ± 30.7	167 ± 12.1	76.5 ± 19.2
1008-011	286	37.0 ± 11.5	141.2 ± 41.2	169 ± 10.4	73.1 ± 16.5
1008-014	246	57.0 ± 9.7	103.4 ± 31.9	173 ± 10.1	95.0 ± 19.7
1008-021	208	36.4 ± 11.5	100.6 ± 23.9	170 ± 10.6	76.5 ± 17.4
1008-025	212	38.1 ± 11.7	102.0 ± 28.6	172 ± 9.5	79.7 ± 19.9
1008-026	203	37.4 ± 10.9	103.7 ± 30.7	172 ± 9.8	81.2 ± 21.1
1008-029	337	59.9 ± 10.5	98.1 ± 30.7	173 ± 10.0	98.3 ± 20.0
1008-030	255	71.5 ± 9.3	64.3 ± 24.7	168 ± 10.1	75.9 ± 17.0
1008-034	453	38.4 ± 11.9	109.0 ± 31.0	168 ± 10.5	78.5 ± 20.6
1008-040	167	61.3 ± 10.5	90.3 ± 30.8	170 ± 9.8	86.4 ± 17.7
1008-045	238	72.2 ± 10.2	70.2 ± 24.9	165 ± 9.7	70.7 ± 13.5
1008-083	361	39.1 ± 11.7	100.2 ± 28.5	169 ± 10.2	78.7 ± 19.6
1008-085	339	38.5 ± 12.0	103.8 ± 27.8	170 ± 9.9	79.3 ± 18.4
1008-087	307	43.5 ± 12.2	118.2 ± 33.5	169 ± 9.6	74.7 ± 16.6
1008-127	173	71.5 ± 10.9	76.5 ± 27.6	167 ± 10.3	77.2 ± 15.2
1008-131	146	59.7 ± 11.4	121.2 ± 47.3	172 ± 9.8	96.7 ± 20.2
1008-132	216	71.4 ± 11.6	68.1 ± 26.1	167 ± 11.9	79.7 ± 18.5
ALL EPI Studies	1051	38.2 ± 11.8	117.0 ± 37.0	168 ± 11.0	76.4 ± 19.3
ALL DN Studies	896	59.4 ± 10.5	101.9 ± 35.5	172 ± 10.0	94.9 ± 20.0
ALL PHN Studies	882	71.7 ± 10.4	69.2 ± 26.0	167 ± 10.5	75.7 ± 16.5
ALL GAD Studies	1630	39.1 ± 11.9	105.1 ± 29.8	170 ± 10.0	78.2 ± 18.9
All Studies	4459	49.4 ± 17.7	100.1 ± 36.1	169 ± 10.5	80.7 ± 20.1
(Range)		(12-100)	(22-355)	(99-206)	(29-187)

Table. Population Characteristics: Categorical Variables [N (%)]

Variables	1008-009	1008-011	1008-014	1008-021	1008-025	1008-026	1008-029	1008-030	1008-034	1008-040	1008-045
Gender											
Female	156 (50)	141 (49)	97 (39)	121 (58)	116 (55)	103 (51)	135 (40)	126 (49)	235 (52)	76 (46)	131 (55)
Male	156 (50)	145 (51)	149 (61)	87 (42)	96 (45)	100 (49)	202 (60)	129 (51)	218 (48)	91 (54)	107 (45)
Ethnic Origin											
White	266 (85)	265 (93)	206 (84)	173 (83)	196 (92)	147 (72)	318 (94)	246 (96)	385 (85)	155 (93)	236 (99)
Black	13 (4)	5 (2)	19 (8)	14 (7)	9 (4)	30 (15)	12 (4)	3 (1)	31 (7)	1 (<1)	2 (<1)
Hispanic	23 (7)	5 (2)	18 (7)	12 (6)	2 (<1)	17 (8)	6 (2)	4 (2)	26 (6)	0 (0)	0 (0)
Asian or Pacific Islander	4 (1)	4 (1)	1 (<1)	7 (3)	4 (2)	7 (3)	0 (0)	2 (<1)	7 (2)	3 (2)	0 (0)
American Indian or Alaskan Native	1 (<1)	0 (0)	1 (<1)	1 (<1)	0 (0)	2 (<1)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)
Other	5 (2)	7 (2)	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	8 (5)	0 (0)

Variables	1008-083	1008-085	1008-087	1008-127	1008-131	1008-132	All EPI	All DN	All PHN	All GAD	All
Gender											
Female	228 (63)	196 (58)	187 (61)	92 (53)	64 (44)	102 (47)	532 (51)	372 (42)	451 (51)	951 (58)	2306 (52)
Male	133 (37)	143 (42)	120 (39)	81 (47)	82 (56)	114 (53)	519 (49)	524 (58)	431 (49)	679 (42)	2153 (48)
Ethnic Origin											
White	272 (75)	278 (82)	303 (99)	164 (95)	128 (88)	204 (94)	916 (87)	807 (90)	850 (96)	1369 (84)	3942 (88)
Black	34 (9)	19 (6)	0 (0)	0 (0)	9 (6)	4 (2)	49 (5)	41 (5)	9 (1)	106 (7)	205 (5)
Hispanic	49 (14)	27 (8)	0 (0)	7 (4)	8 (5)	6 (3)	54 (5)	32 (4)	17 (2)	107 (7)	210 (5)
Asian or Pacific Islander	2 (<1)	9 (3)	4 (1)	2 (1)	0 (0)	1 (<1)	15 (1)	4 (<1)	5 (<1)	33 (2)	57 (1)
American Indian or Alaskan Native	0 (0)	2 (<1)	0 (0)	0 (0)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	1 (<1)	5 (<1)	11 (<1)
Other	4 (1)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	15 (1)	9 (1)	0 (0)	10 (<1)	34 (<1)

Table . Adverse Events by Dose: Dizziness [N (%)]

Variables	None		Mild		Moderate		Severe	
Daily Dose (mg/day)	N	%	N	%	N	%	N	%
Placebo	61231	97.1	1217	1.9	555	0.9	56	0.1
50	6469	96.6	167	2.5	62	0.9	0	0.0
75	5114	98.3	79	1.5	7	0.1	0	0.0
150	29559	94.3	1236	3.9	428	1.4	112	0.4
200	2448	88.3	237	8.5	84	3.0	4	0.1
300	19825	87.5	2079	9.2	708	3.1	40	0.2
400	5735	84.0	707	10.4	344	5.0	43	0.6
450	4609	85.6	514	9.5	230	4.3	33	0.6
600	42239	84.2	5005	10.0	2598	5.2	313	0.6
Total	177229		11241		5016		601	

Model:
A subject-specific random-effects model was used to characterize the relationship between adverse event score and pregabalin exposure in individual patients. The adverse event scores were modeled as ordered categorical variables with a proportional odds model to determine the probability of adverse events on any given day. The probability that the AE score for an individual (Y) is equal to or greater than score m (m = 1, 2, 3) is given by the following model:

$$g\left[P(Y_{ij} \geq m \mid \eta_i)\right] = \sum_{k=1}^{m} \beta_k + f_d + \eta_i$$

where β_k (k = 1, 2, 3) specifies the baseline set of probabilities of the various degrees of adverse event, f_d is a function describing treatment effect, η_i is a random individual effect determining the individual sensitivity assumed to be normally distributed with variance ω^2 and a mean of zero, and g(x) denotes the logit function of the probability used to transform the probability scale from (0, 1) to the real numbers ($-\infty$, ∞).

The initial modeling approach was biased because the assumption that η is normally distributed around zero was violated. The solution was to fit separate models for incidence of AE and severity of AE conditional that an AE has occurred. The unconditional distribution was calculated by convolving the 2 probability distributions from the separate fits.

Incidence Model: The probability of an AE was modeled using a nonlinear logistic regression model given by the expression: $g\left[P(AE_i = 1)\right] = \beta + f_d$
where AE_i denotes an indicator variable for patient i taking the value of 1 if the patient has an AE at some time point during the study (ie, $Y_{ij} > 0$ for some time t_j) and 0 otherwise. The parameter β denotes the baseline logit-probability for the incidence of AEs. The function f_d denotes the function describing the exposure-response relationship and can take the forms described for the general model fitting. This model does not contain an interindividual random effect because the definition of AE_i is patient-specific and not time-specific. Since there are no repeated measures there is no need to model within-patient correlation using a mixed effects model. For this reason, the incidence model does not deal with time-varying covariates and hence, employs the intent-to-treat (ITT) dose rather than the time-varying actual dose.

Conditional Severity Model: The conditional severity model to describe the dose-AE severity response relationship in AE patients is the mixed effects logistic regression model given by the expression:

$$g\left[P\left(Y_{ij} \geq m \mid AE_i = 1, \eta_i\right)\right] = \sum_{k=1}^{m} \beta_k + f_d + \eta_i$$

where $P(Y_{ij} \geq m|AE_i=1,\eta_i)$ denotes the cumulative probability that the AE severity score is $\geq m$ (m= 1, 2, or 3) for patient i at time t_j given the patient has an AE at some time point during the study (ie, $AE_i = 1$). The models for the exposure-response relationship f_d are similarly defined as for the original severity model.

$$g\left[P\left(Y_{ij} \geq m \mid AE_i = 1, \eta_i\right)\right] = \sum_{k=1}^{m} \beta_k + f_d + \eta_i$$

Unconditional Severity Probability Predictions: The population averaged joint probability for the incidence and severity of AEs is obtained by factorization:

$$P\left(Y_j = m, AE = l\right) = P\left(Y_j = m \mid AE_i = l\right) P\left(AE = l\right)$$

where $m \in \{0,1,2,3\}$ and $l \in \{0,1\}$. By definition, $P(Y_j = 0|AE = 0) = 1$ and $P(Y_j = m|AE = 0) = 0$ for m = 1, 2, or 3 since for all non-AE patients (ie, AE = 0) all severity scores are zero (ie, $Y_{ij} = 0$ for all t_j).

Results

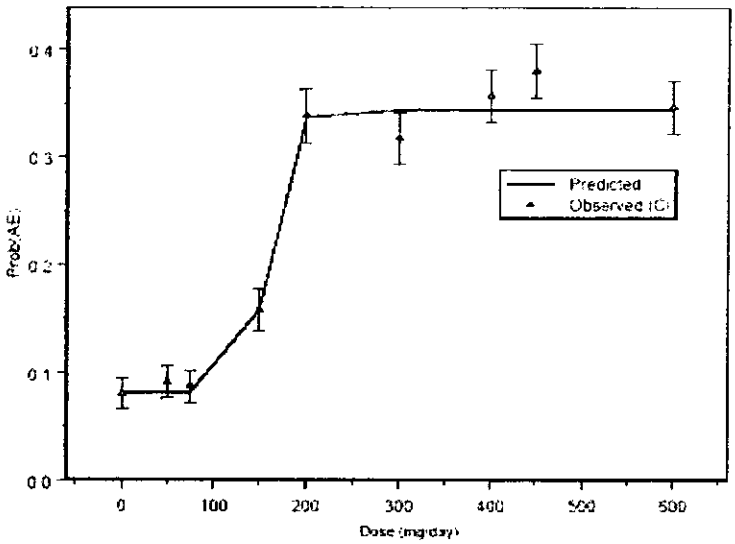
The conditional severity for dizziness and somnolence were well-described by a sigmoid Emax model that took into account a time-dependent exposure effect as well as a time-dependent attenuation of dizziness and somnolence.

a. Model for dizziness

Model for Incidence of dizziness: A sigmoidal Emax model best describes the dose-AE response relationship.

Table: Parameter Estimates

Parameter	Estimate (se)	
β	-2.42	(0.09)
Emax	1.77	(0.1)
ED50 (mg)	153	(8.06)
γ	15.4	(37.6)



Model for Conditional Severity of Dizziness:

The model that best described the data included a sigmoid Emax model with a time-dependent exposure effect on dose and a component that allows for an exponential attenuation of the AE severity with a plateau.

The time-dependent exposure effect is given by the expression:

$$E_x(D_i^*) = E_x(D_i)\left[1 - e^{-k_{e0}\cdot t_i}\right]$$

where k_{e0} is the constant that governs the rate at which the pregabalin effect reaches its maximum.

The attenuation of effect is given by the expression:

$$E\max_i = E\max\left(e^{-k_{tol}\cdot t_i} + T_p\right)$$

where k_{tol} is the constant that governs the rate at which the AE decreases to a tolerance plateau, Tp.

Model parameter estimates of the final model are presented in the table below.

Table. Parameter Estimates For Conditional Severity of Dizziness Model

Parameter	Estimate (se)	
β_1	-2.56	(0.176)
β_2	-2.88	(0.026)
β_3	-4.57	(0.076)
Emax	5.51	(0.52)
ED50 (mg)	275.0	(31.7)
γ	1.48	(0.15)
Ke0 ($Days^{-1}$)	1.18	(0.107)
Ktol ($Days^{-1}$)	0.0889	(0.0054)
Tp	0.619	(0.0497)
ω^2	8.61	(0.447)

Observed and predicted conditional probability plots are presented in the figure below.

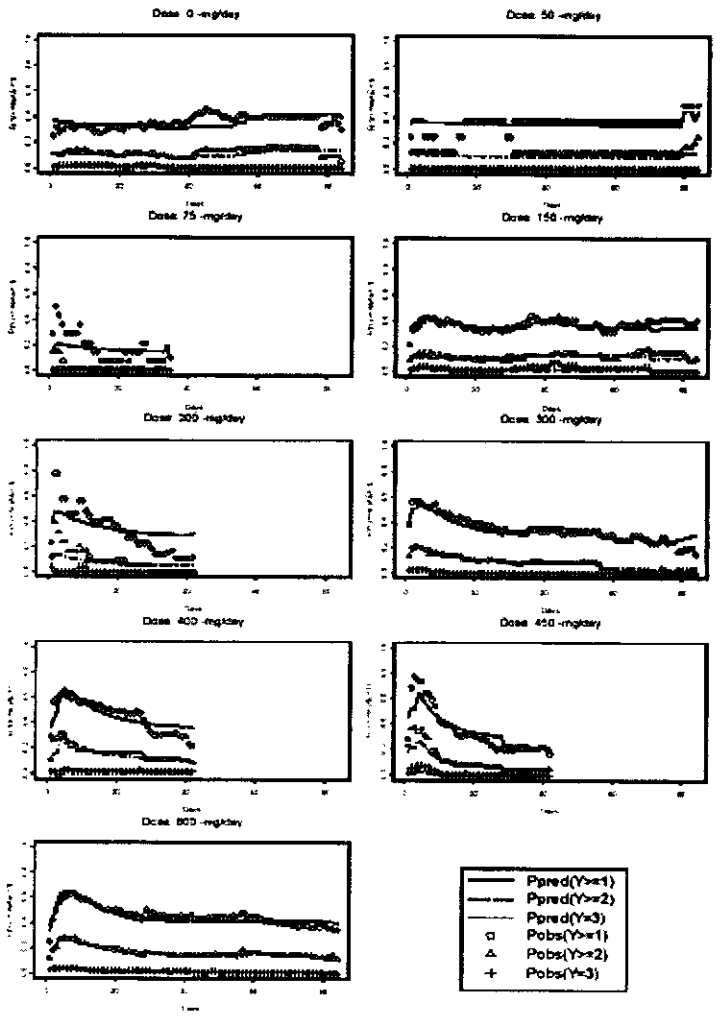


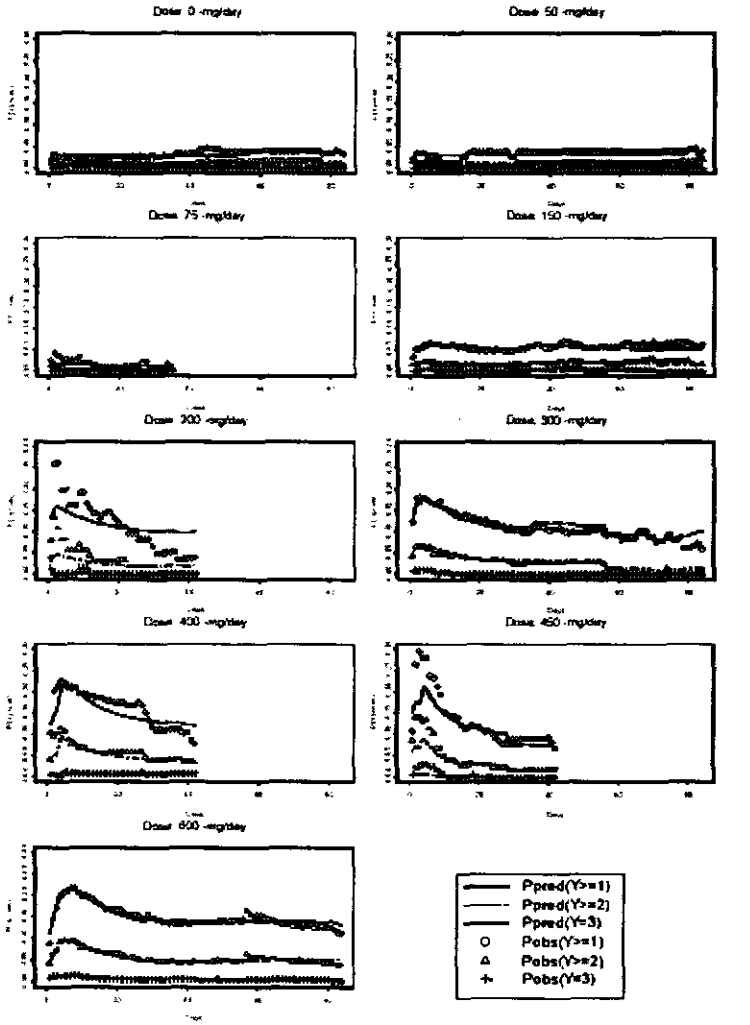
Table: Model-predicted unconditional probabilities of experiencing dizziness at each dose level averaged over the treatment period

Daily Dose (mg/day)	Any Dizziness		Dizziness of Moderate Intensity or Greater		Severe Dizziness	
	Mean (95%CI)		Mean (95% CI)		Mean (95% CI)	
Placebo	3.00	(2.9-3.08)	0.91	(0.86-0.96)	0.08	(0.06-0.09)
50	3.05	(2.8-3.3)	0 87	(0.77-0.97)	0.014	(0.012-0.016)
75	1.46	(1.31-1.61)	0.18	(0.14-0.21)	0.002	(0.0016-0.0025)
150	5.72	(5.56-5 87)	2.01	(1.90-2.11)	0.23	(0.20-0.26)
200	11.66	(10.99-12.33)	2.55	(2.28-2.82)	0.04	(0.035-0.047)
300	12.60	(12.34-12.86)	3.85	(3.68-4.01)	0.29	(0.25-0.34)
400	15.24	(14.80-15.67)	5 18	(4.84-5.53)	0.72	(0.57-0.87)
450	12.59	(12.11-13.06)	3.97	(3.65-4 30)	0.23	(0.18-0.27)
600	15.83	(15.65-16.01)	6.00	(5.86-6.14)	0.74	(0.68-0.79)

Table. Model-Predicted Unconditional Probability (%) of Experiencing Dizziness as a Function of Time After 600 mg Pregabalin Daily.

Time (days)	Any Dizziness	Dizziness of Moderate Intensity or Greater	Severe Dizziness
	Mean (95%CI)	Mean (95% CI)	Mean (95% CI)
1	10.9 (9.8-12.1)	4.38 (3.53-5.23)	0.67 (0.36-0.98)
6	21.7 (20.6-22.7)	9.86 (8.75-10.96)	1.43 (0.94-1.93)
14	18.0 (16.8-19.3)	7.08 (6.03-8.13)	0.91 (0.47-1.35)
21	15.5 (14.3-16.8)	5.57 (4.58-6.57)	0.68 (0.28-1.08)
28	13.8 (12.5-15.2)	4.67 (3.68-5.67)	0.60 (0.18-1.03)
84	13.1 (10.2-15.9)	5.10 (2.90-7.30)	0.52 (0.00-1.18)

The following is a plot of observed and predicted unconditional urobabilities of severity of dizziness:

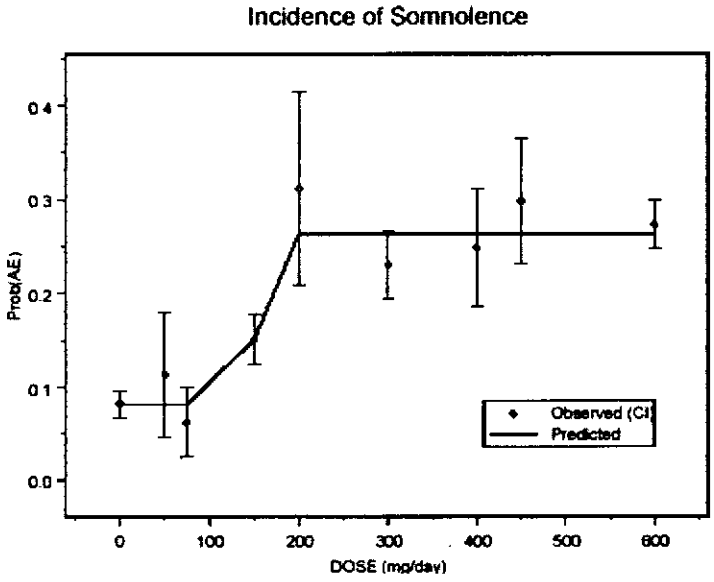


b. Model for somnolence

Incidence of somnolence: A sigmoid Emax model best describes the dose-AE response relationship.

Table: Parameter Estimates

Parameter	Estimate (se)	
β	-2.42	(0.088)
Emax	1.39	(0.099)
ED50 (mg)	150	(0.74)
γ	68.5	(36.0)



Model for Conditional Severity of Somnolence:
The model that best described the data included a sigmoid Emax model with a time-dependent exposure effect on dose and a component that allows for an exponential attenuation of the AE severity with a plateau.

The time-dependent exposure effect is given by the expression:

$$f_d(D_n^*) = f_d\left(D_n \cdot \left(1 - e^{-ke0 \cdot t}\right)\right)$$

where ke0 is the constant that governs the rate at which the pregabalin effect reaches its maximum.

The attenuation of effect is given by the expression:

$$E\max_t = E\max \cdot \left(e^{-k_{tol} \cdot t} + T_p\right)$$

where k_{tol} is the constant that governs the rate at which the AE decreases to a plateau, Tp.

Model parameter estimates of the final model are presented in the table below.

Table. Parameter Estimates For Conditional Severity of Somnolence Model

Parameter	Estimate (se)	
β_1	-1.70	(0.196)
β_2	-3.18	(0.029)
β_3	-5.20	(0.082)
Emax	4.97	(0.698)
ED50 (mg)	317.0	(53.9)
γ	1.24	(0.134)
Ke0 ($days^{-1}$)	0.595	(0.076)
Ktol ($days^{-1}$)	0.101	(0.0098)
Tp	1.09	(0.101)
ω^2	10.2	(0.592)

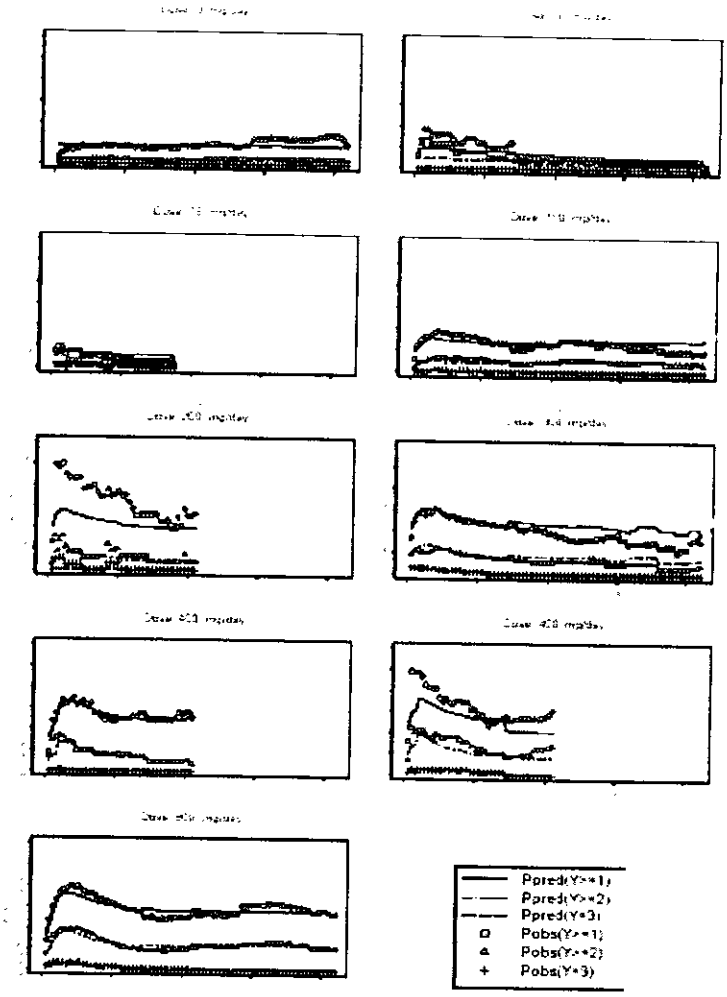
Model-predicted unconditional probabilities of experiencing somnolence at each dose level averaged over the treatment period are given in the table below.

Daily Dose (mg/day)	Any Somnolence		Somnolence of Moderate Intensity or Greater		Severe Somnolence	
	Mean (95%CI)		Mean (95% CI)		Mean (95% CI)	
Placebo	4.25	(4.17-4.32)	1.13	(1.08-1.18)	0.08	(0.06-0.09)
50	3.56	(3.32-3.79)	1.69	(1.47-1.92)	0.09	(0.07-0.10)
75	3.00	(2.76-3.24)	0.36	(0.31-0.40)	0.002	(0.0019-0.0025)
150	6.90	(6.77-7.04)	2.32	(2.21-2.43)	0.09	(0.079-0.093)
200	11.06	(10.56-11.55)	2.90	(2.58-3.22)	0.047	(0.038-0.056)
300	12.66	(12.42-12.90)	4.88	(4.67-5.09)	0.62	(0.53-0.71)
400	13.16	(12.79-13.53)	3.76	(3.49-4.04)	0.11	(0.09-0.13)
450	14.10	(13.68-14.52)	6.07	(5.68-6.46)	0.72	(0.56-0.87)
600	14.93	(14.78-15.07)	6.42	(6.27-6.56)	0.56	(0.52-0.61)

Model-predicted unconditional probabilities of experiencing somnolence together with observed frequencies over time are presented in the table and figure below.

Time (days)	Any Somnolence		Somnolence of Moderate Intensity or Greater		Severe Somnolence	
	Mean (95%CI)		Mean (95% CI)		Mean (95% CI)	
1	8.29	(7.32-9.27)	3.09	(2.40-3.77)	0.44	(0.20-0.69)
6	18.0	(17.3-18.8)	9.03	(8.04-10.02)	1.22	(0.79-1.66)
14	16.4	(15.5-17.3)	7.33	(6.31-8.36)	0.76	(0.41-1.12)
21	15.0	(14.0-16.0)	6.07	(5.06-7.08)	0.59	(0.26-0.92)
28	14.2	(13.1-15.3)	5.32	(4.31-6.33)	0.38	(0.08-0.69)
84	13.9	(11.7-16.2)	5.72	(3.57-7.86)	0.21	(0.09-0.33)

Figure: Observed and Predicted Probabilities of Unconditional Severity of Somnolence



Sponsor's conclusion:
The half-life of onset of dizziness was 0.63 days and of somnolence was 1.2 days. The half-life for attenuation of dizziness was 7.8 days and for somnolence 6.9 days. These values reflect a decrease in dizziness and somnolence that would reach a new steady state in about 3 to 4 weeks.

For both dizziness and somnolence, there is an increase in incidence and severity of AE over the first few days of initiating pregabalin dosing (probably due to accumulation of pregabalin to steady-state) which tends to decline over the next 3 to 4 weeks. To assess the impact of dropouts on this apparent attenuation of AEs, all the patients were included in a data set in which the last observation carried forward (LOCF) was included for dropouts. The trend observed in the frequency-based probabilities is similar to the previous plots for all patients and completers without LOCF. It would appear that the attenuation of adverse event is not likely to be due to patient drop out and is probably associated with tolerance development.

Figure. Observed Frequency of Dizziness (LOCF used for drop-outs)

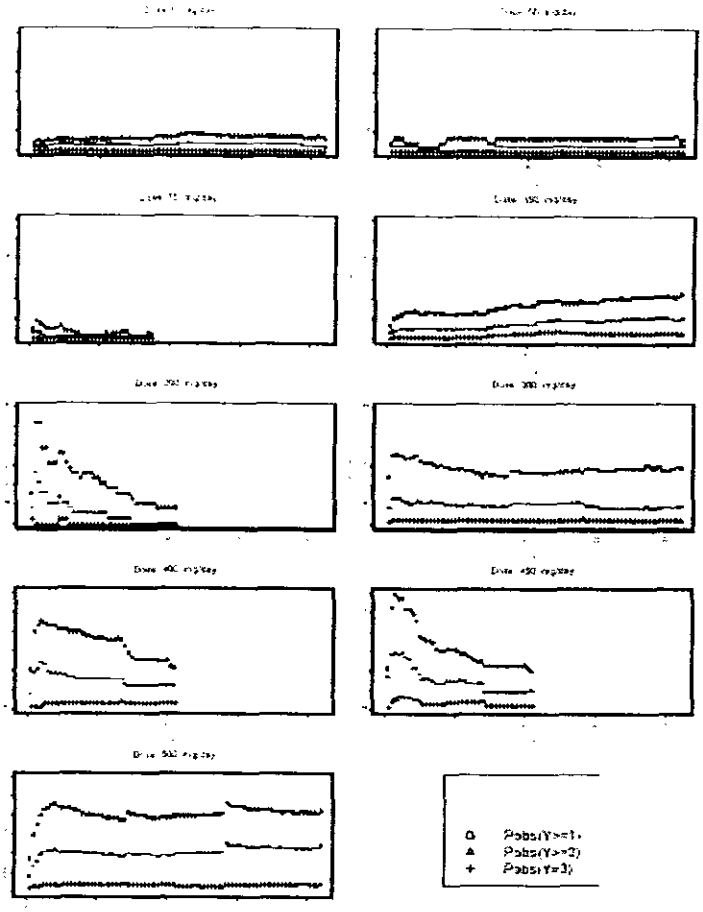
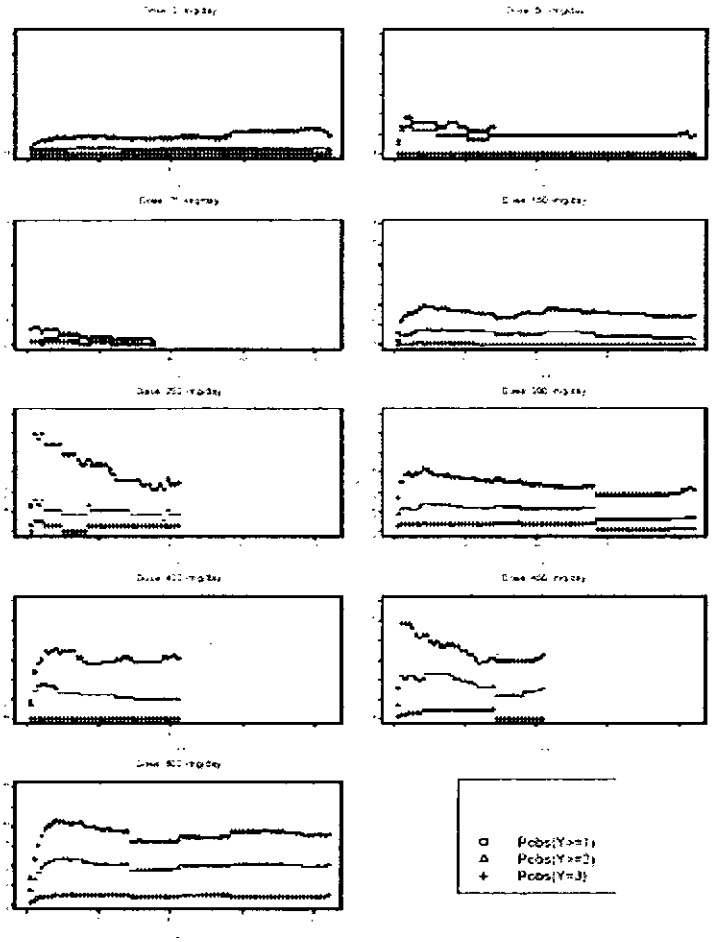


Figure. Observed Frequency of Somnolence (LOCF used for drop-outs)



Mean individual model-predicted results for dizziness are presented below.

Table: Mean Individual Model-Predicted Unconditional Probability (%) of Experiencing Dizziness on Any Day by Pregabalin Daily Dose

Daily Dose (mg/day)	Any Dizziness		Dizziness of Moderate Intensity or Greater		Severe Dizziness	
	Mean	(95%CI)	Mean	(95% CI)	Mean	(95% CI)
Placebo	3.00	(2.9-3.08)	0.91	(0.86-0.96)	0.08	(0.06-0.09)
50	3.05	(2.8-3.3)	0.87	(0.77-0.97)	0.014	(0.012-0.016)
75	1.46	(1.31-1.61)	0.18	(0.14-0.21)	0.002	(0.0016-0.0025)
150	5.72	(5.56-5.87)	2.01	(1.90-2.11)	0.23	(0.20-0.26)
200	11.66	(10.99-12.33)	2.55	(2.28-2.82)	0.04	(0.035-0.047)
300	12.60	(12.34-12.86)	3.85	(3.68-4.01)	0.29	(0.25-0.34)
400	15.24	(14.80-15.67)	5.18	(4.84-5.53)	0.72	(0.57-0.87)
450	12.59	(12.11-13.06)	3.97	(3.65-4.30)	0.23	(0.18-0.27)
600	15.83	(15.65-16.01)	6.00	(5.86-6.14)	0.74	(0.68-0.79)

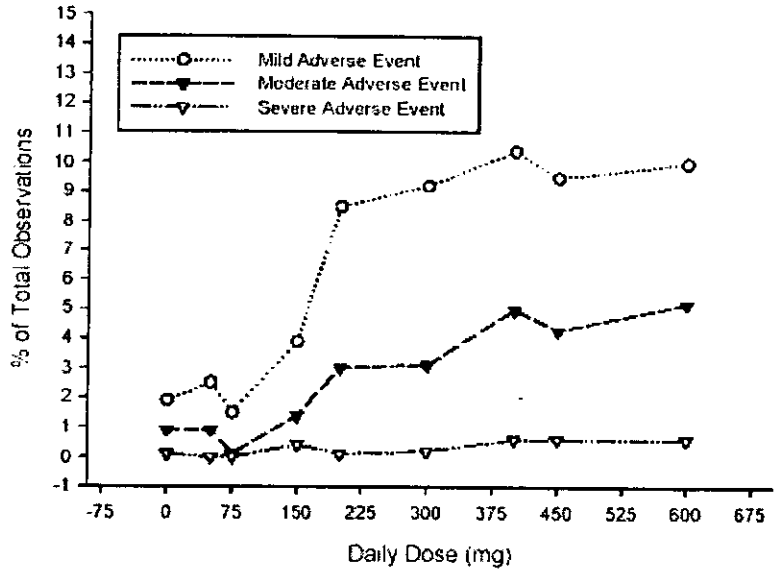


Figure 1. Percentage of Total Observations of Dizziness Reported by Adverse Event Intensity at Each Dose (AE1 = Dizziness Data)

Mean individual model-predicted results for somnolence are presented below.

Mean Individual Model-Predicted Unconditional Probability (Expressed as a Percentage) of Experiencing Somnolence on Any Day by Pregabalin Daily Dose

Daily Dose (mg/day)	Any Somnolence		Somnolence of Moderate Intensity or Greater		Severe Somnolence	
	Mean	(95%CI)	Mean	(95% CI)	Mean	(95% CI)
Placebo	4.25	(4.17-4.32)	1.13	(1.08-1.18)	0.08	(0.06-0.09)
50	3.56	(3.32-3.79)	1.69	(1.47-1.92)	0.09	(0.07-0.10)
75	3.00	(2.76-3.24)	0.36	(0.31-0.40)	0.002	(0.0019-0.0025)
150	6.90	(6.77-7.04)	2.32	(2.21-2.43)	0.09	(0.079-0.093)
200	11.06	(10.56-11.55)	2.90	(2.58-3.22)	0.047	(0.038-0.056)

300	12.66	(12.42-12.90)	4.88	(4.67-5.09)	0.62	(0.53-0.71)
400	13.16	(12.79-13.53)	3.76	(3.49-4.04)	0.11	(0.09-0.13)
450	14.10	(13.68-14.52)	6.07	(5.68-6.46)	0.72	(0.56-0.87)
600	14.93	(14.78-15.07)	6.42	(6.27-6.56)	0.56	(0.52-0.61)

The results suggested that the probabilities of experiencing dizziness and somnolence during pregabalin treatment increase with pregabalin daily dose. The predicted mean incidence of dizziness or somnolence was at least 2-fold higher at doses >200 mg/day compared to daily doses <150 mg/day. Overall, the risk of moderate or severe dizziness or somnolence at any time following pregabalin was low (<7% on average). The risk of moderate or severe dizziness or somnolence increases from <5% on Day 1, peaks at <10% on Day 6, and declines to values of <6% by the end of 4 weeks.

Sponsor's conclusions:
• The probability of experiencing dizziness or somnolence during any day increases with pregabalin daily dose.
• The increase is most evident at daily doses of 200 mg/day and greater.
• The risk of dizziness or somnolence decreases within 3 to 4 weeks after initiation of pregabalin treatment in patients that continue with treatment.
• Overall, the risk of moderate or severe dizziness or somnolence following pregabalin administration is small (<7%). At the highest dose (600 mg/day) the risk of moderate to severe dizziness or somnolence following pregabalin administration increases from Day 1 (<5%) to peak on Day 6 (<10%), declining over the next 3 to 4 weeks to plateau at <6% for both dizziness and somnolence.

Comments:
1. BID and TID trials are lumped in the analysis. The results should be put in proper perspective.
2. All 4 indications were lumped in the analysis. The incidence rate for somnolence appears quite different for different disease populations. The results do not represent the neuropathic pain population
3. CLcr should be used to modify the exposure in the analysis based on previous PK information.
4. There was only one trial with the 200 mg/day dose. The sponsor's plot showed standard deviation for this dose group. It is unclear how this was done.
5. Observed and predicted probability of unconditional severity are off for the 200 mg/day and 450 mg/day doses for both adverse events. This may be due to the small number of subjects.
6. There is dose response relationship for the adverse events. However, the quantitative relationship obtained from this analysis may not reflect the true picture because of the above reasons.

Safety: QT Prolongation

Phase 1 Trials: 7 multiple dose trials

Effects of pregabalin on electrocardiographic QTc interval were evaluated in 2- and 4-week multiple-dose tolerance studies (Studies 002 and 023, respectively), drug interaction studies with carbamazepine (Study 019), lamotrigine (Study 020), sodium valproate (Studies 018 and -126), phenytoin (Study 140), and gabapentin (Study 144). A total of 164 subjects were evaluated. QTc interval measurements were calculated using Bazett's, Fridericia's, and linear model*-based corrections.

*Linear model: QTc = QT+m.(1000 msec-RR), where m is the slope obtained from regressing the QTs on the RRs, using only placebo or off-drug data.

Table: Mean Change in QTc Measurements Associated With Pregabalin PK Parameters

Study No. 1008-	Regimen	Coadministered Study Medication	Mean Change in PR Interval (msec)	Mean QTc Change/ Bazett (msec)	Mean QTc Change/ Fridericia (msec)	Mean QTc Change/ Linear Model (msec)	$Cmax_{ss}$[a] (µg/mL)	tmax (hr)[b]	N[c]
002	Placebo	–	3.9	(-) 9.2[d]	(-) 7.7[d]	(-) 7.3[d]	--	--	12
	25 mg q8h	–	3.6	(-) 2.1[d]	(-) 0.4[d]	(-) 0.1[d]	1.39	0.94	10
	100 mg q8h	–	3.3	(-) 9.6[d]	(-) 9.4[d]	(-) 8.4[d]	5.01	0.83	6
	200 mg q8h	–	6.3	(-) 4.9[d]	(-) 4.0[d]	(-) 3.5[d]	8.52	0.91	13
	300 mg q12h	–	0.7	(-) 9.7[d]	(-) 8.8[d]	(-) 8.9[d]	9.06	1.44	8
	300 mg q8h	–	1.6	(-) 2.6[d]	(-) 8.3[d]	(-) 9.8[d]	13.43	1.0	8
023	Placebo	–	9.3	3.4[e]	5.1[e]	5.6[e]	--	–	3
	300 mg q8h	–	8.1	1.1[e]	(-) 2.9[e]	(-) 3.9[e]	13.2	1.0	13
019	200 mg q8h	Carbamazepine	1.0	(-) 7.2[f]	(-) 0.1[f]	3.3[f]	8.20	1.42	14
020	200 mg q8h	Lamotrigine	(-) 0.3	2.5[f]	2.9[f]	3.9[f]	8.99	1.10	12
018, -126	200 mg q8h	Sodium valproate	(-) 5.4	(-) 7.2[f]	(-) 6.1[f]	(-) 6.1[f]	9.80	1.08	16
140	200 mg q8h	Phenytoin	(-) 0.4	2.1[f]	(-) 6.7[f]	(-) 10.2[f]	5.81	2.65	10
144	200 mg q8h	Gabapentin	4.1	(-) 8.6[g]	(-) 9.1[g]	(-) 9.7[g]	7.80	0.99	20
	200 mg q8h	–	2.7	(-) 9.4[g]	(-) 9.7[g]	(-) 10.3[g]	8.53	0.96	19[h]

[a] Mean maximal plasma CI-1008 concentration following 7 to 28 days of multiple dosing

[b] Mean time of maximal plasma CI-1008 concentration following 7 to 28 days of multiple dosing

[c] Number of subjects contributing QTc data

[d] Mean QTc change from baseline ECG following 14 days of multiple dosing (ECGs performed approximately 1 hour postdose)

[e] Mean QTc change from baseline ECG following 28 days of multiple dosing (ECGs performed approximately 1 hour postdose)

[f] Mean QTc change from baseline ECG following 7 days of multiple dosing (ECGs performed approximately 1-2 hours postdose)

[g] Mean QTc change from baseline ECG following 2 days of multiple dosing (ECGs performed approximately 1.5 hours after the last dose)

[h] Some subjects in the combined treatment group had multiple ECG recordings, all of which were used in the analyses. One subject discontinued from the study and did not receive pregabalin monotherapy.

Sponsor's Findings:

- None of the subjects had a corrected QT interval during the study that was greater than the upper limit of normal (ULN) for males (≤450 msec) or for females (≤470 msec). (A summary table for the Fredericia's corrected data is given below.)
- For the change from baseline in the electrocardiographic PR interval, the estimated slope of the plasma Cmax effect is +0.349 msec, corresponding to a predicted 6 msec increase in the PR interval at a plasma Cmax of 18 µg/mL.
- The results from the regression of the electrocardiographic QTc intervals on pregabalin plasma Cmax indicate that as Cmax increases, the QTc interval and change from baseline QTc decrease. The magnitude of these effects is small, especially in comparison to the within and between subject variability.

Baseline Fridericia's-corrected QT Interval (msec)

Regimen	Female-QTc N	Mean (msec)	SD	Min	Max	Male-Qtc N	Mean (msec)	SD	Min	Max	Overall Regimen N	Mean (msec)	SD	Min	Max
Placebo/off-drug	109	392.2	12.9	359	425	148	376.0	18.1	339	437	257	382.9	17.9	339	437
25-mg q8h	43	391.1	18.8	359	426	5	362.2	6.4	351	367	48	388.1	20.0	351	426
100-mg q8h	10	384.4	8.5	363	393	20	368.3	16.6	342	396	30	373.7	16.2	342	396
200-mg q8h	57	388.3	17.3	349	437	139	377.4	18.9	326	439	196	380.6	19.0	326	439
300-mg q8h	17	379.5	9.2	364	393	109	374.5	18.4	335	428	126	375.2	17.5	335	428
300-mg q12h	0	*	*	*	*	40	378.9	15.7	358	418	40	378.9	15.7	358	418

Overall Female N	Mean (msec)	SD	Min	Max	Overall Male N	Mean (msec)	SD	Min	Max	"Grand" Overall N	Mean (msec)	SD	Min	Max
236	389.8	15.2	349	437	461	375.9	18.2	326	439	697	380.6	18.4	326	439

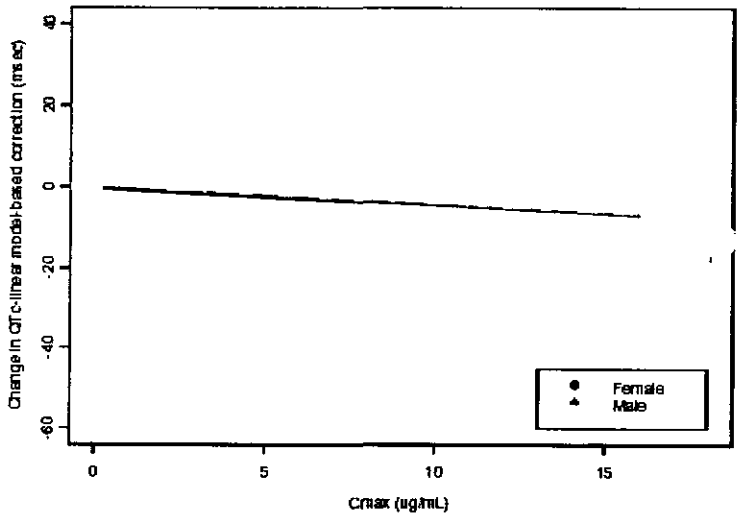


Figure. Change From Baseline (msec) in QTc Measurements (Corrected using a Linear Model) in Subjects Receiving Pregabalin Versus Pregabalin Plasma Cmax

Reviewer's Comments:

The above plot may not represent the true relationship between pregabalin concentration and ΔQTc because of the following reasons:

- Only one ECG recording (at 1 to 2 hrs postdose) per subject was taken from the volunteers in most of these Phase 1 trials. The regression slope does not represent the mean slope of these subjects.
- The concentrations (Cmax) in the plot represent the blood samples taken at the individual Tmax whereas the ECG recordings (taken at 1-2 hr postdose) do not represent the observations at the individual Tmax.
- There may be a time delay in the drug effect on QT, i.e., the maximum ΔQTc may not occur at Tmax.

It should also be noted that there is no active control for QT changes in these Phase 1 trials and most trials (5 out of 7) did not have a placebo control.

RELATIVE BIOAVAILABILITY

Protocol 1008-3: A Single-Dose Food Effect and Relative Bioavailability Study of CI-1008 Capsule and Solution Doses in Healthy Volunteers

Studied Period: 11/15/96 to 12/12/96

Objective:
To determine the effect of food on the bioavailability of CI-1008 (pregabalin) capsules, and determine the oral bioavailability of a CI-1008 capsule relative to that of a CI-1008 solution under fasting conditions

Study Design

Open-label, single-dose, randomized, 3-way crossover study in healthy volunteers

Subjects: 12 (1 male and 11 females; age: 38-65 yrs; wt: 55.5-91.5 kg) subjects enrolled and 11 completed the study.

Treatments:

1: One 100-mg pregabalin capsule administered after an 8-hour overnight fast
2: One 100-mg pregabalin capsule dissolved in 4 oz of water and administered after an 8-hour overnight fast
3: One 100-mg pregabalin capsule administered 15 minutes after a standard breakfast*

*Subjects receiving Treatment 3 were dosed 15 min after beginning a standard breakfast. The breakfast was consumed in 25 minutes and consisted of cereal, 2 eggs scrambled without fat, 2 slices of white toast spread with 2 teaspoons of margarine, and 8 oz of low-fat (2%) milk.

Study Product: One 100-mg pregabalin capsule (WL 144,723A-3, Lot CF 0080495)

Duration of Treatment: Single oral doses on Days 1, 11, and 21

Blood Sample Collection: Plasma samples collected serially for 60 hours after each treatment were assayed for pregabalin concentration by a HPLC method.

Results

Mean plasma concentration-time profiles for the three treatments are presented in the figure below and mean pharmacokinetic parameter values, ratios, and 90% confidence intervals are summarized in the following table.

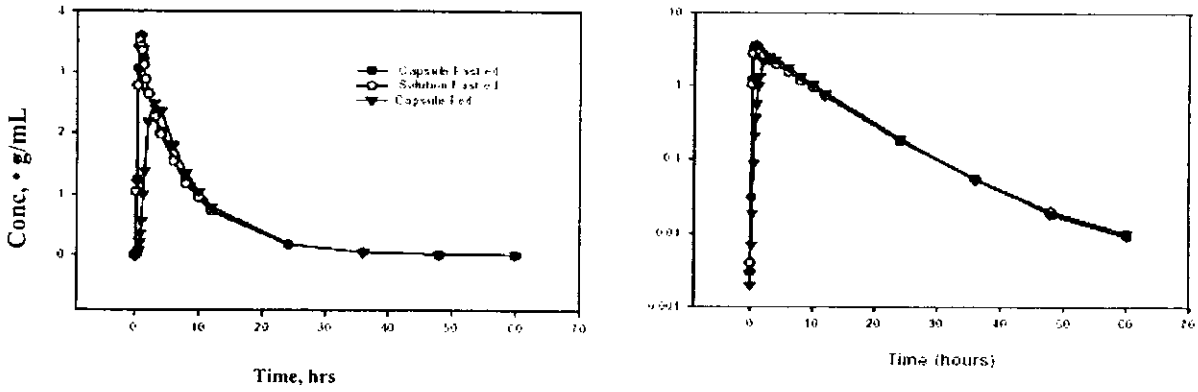


Figure 1. Mean Plasma Pregabalin Concentrations-Time Profiles Following Single-Dose Oral Administration of One 100-mg Capsule Fasted, 100-mg Solution Fasted, and One 100-mg Capsule With a Standard Breakfast

Table: Summary of Pregabalin Pharmacokinetic Parameter Values Following Single-Dose Oral Administration of One 100-mg Capsule Fasted, 100-mg Solution Fasted, and One 100-mg Capsule With a Standard Breakfast

Parameter	Treatment Mean Parameter Values		Ratio	90% Confidence Interval
	Capsule With Food (Test) N = 11	Capsule Fasting (Reference) N = 11		
Cmax, µg/mL	2.59	3.78	68.6	64.0 to 73.6
tmax, hr	3.17	0.615	515	Not applicable
AUC(0-tldc), µg·hr/mL	25.3	26.6	94.8	91.8 to 97.9
AUC(0-∞), µg·hr/mL	25.4	26.7	94.9	92.0 to 98.0
t½ (hr)	6.61	6.92	95.5	Not applicable
	Capsule Fasting (Test) N = 11	Solution Fasting (Reference) N = 11		
Cmax, µg/mL	3.78	3.71	102	94.9 to 109
tmax, hr	0.615	0.577	106	Not applicable
AUC(0-tldc), µg·hr/mL	26.6	26.9	99.0	95.9 to 102
AUC(0-∞), µg·hr/mL	26.7	27.0	99.0	95.9 to 102
t½ (hr)	6.92	7.31	95.4	Not applicable

Plots of individual Cmax and AUC values are presented in Figure 2.

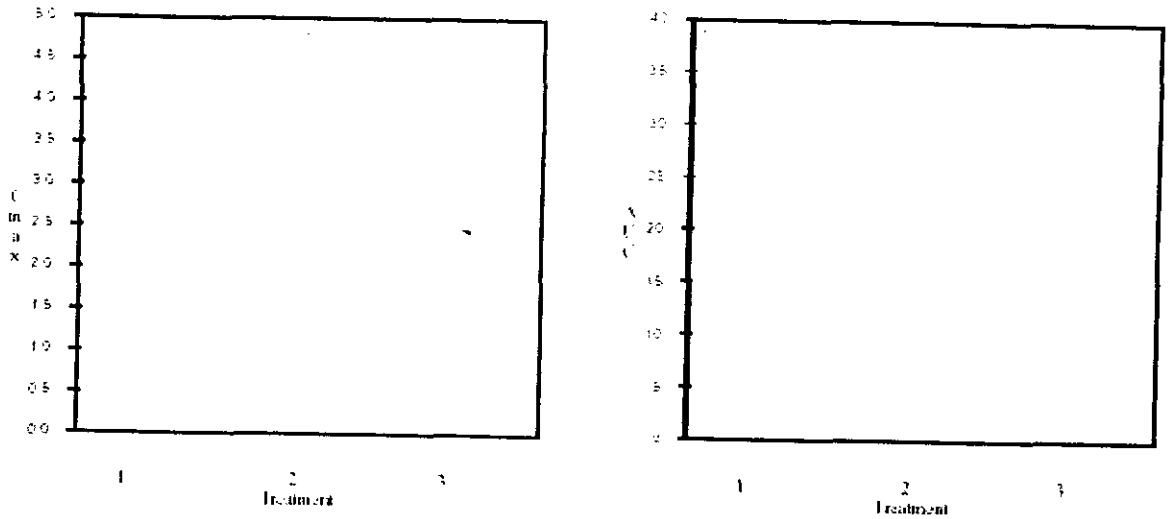


Figure 2. Differences by Treatment in Individual and Mean Pregabalin Cmax (mg/mL; Left Panel) and AUC(0-¥) (mg·hr/mL; Right Panel) Values Following Single-Dose Oral Administration of One 100-mg Pregabalin Capsule Fasted (Treatment 1), 100 mg of Pregabalin Solution (Treatment 2), and One 100-mg Pregabalin Capsule With a Standard Breakfast (Treatment 3),

Conclusion:

- Pregabalin 100-mg capsules are bioequivalent to a solution dose.
- When administered with food (a standard breakfast), rate of pregabalin absorption is affected as indicated by a delayed tmax (+2.6 hour) and a reduced Cmax (-31.4%). The extent of pregabalin absorption is not affected appreciably with a mean reduction of AUC(0-∞) values of 4.1%. The 90% CI for the ratio of AUC is 92.0-98.0%, which is within the bioequivalence criteria.

WAIVER OF BIOEQUIVALENCE STUDIES

RR 764-03669: Request a Waiver From Performing In Vivo Bioavailability/Bioequivalence Studies on Pregabalin Clinical Trial Formulations for PreNDA Meeting

Objective:
To obtain a waiver from performing in vivo bioavailability and bioequivalence studies comparing pregabalin clinical trial formulations to the pregabalin 100-mg capsule formulation which was investigated in bioavailability protocol Study 1008-003.

Rationale:
Pregabalin is highly soluble and highly permeable according to the Biopharmaceutical Classification System. Therefore, the bioequivalence of 2 formulations can be established if the *in vitro* dissolution testing indicates the formulations are fasting dissolving.

Supporting Data

Solubility of pregabalin:
Pregabalin is an amino acid having 2 pKa values of approximately 4.2 and 10.6. The lowest aqueous solubility of a zwitterion is at its iso-electric point which is near the midpoint of the 2 pKa values, or for pregabalin, a pH of ~7.4. Pregabalin solubility in distilled water is — mg/mL, which is similar to its lowest solubility observed at pH 7.4. The highest immediate release dose strength developed for pregabalin is 300 mg. The volume of aqueous media required to dissolve 300 mg of pregabalin at various pH values is listed in Table 1. The largest volume would be required at pH 7.4 (Table 1) and this volume is 1/27 of the 250 mL criteria listed in the BCS draft guidance. These results indicate that pregabalin is highly soluble, thus aqueous solubility should not be a limiting factor in drug absorption.

Table 1 Pregabalin Aqueous Solubility as a Function of Media pH

Media pH	Media	Solubility (mg/mL)	Volume Required to Dissolve 300 mg of Pregabalin [Based on Drug Solubility (mL)]

Pregabalin stability in aqueous solutions:
Stability of pregabalin solutions at 37°C was investigated at pH [redacted] All solutions were stable for — at 37°C since the percentage recovery of pregabalin was at least —. No indication of degradation was observed in the HPLC chromatograms. These results indicate that pregabalin solutions (pH — are stable for at least — at 37°C.

Pregabalin permeability properties:

Clinical Data: The oral bioavailability of immediate release pregabalin capsules based on percentage of dose excreted unchanged in the urine was determined from the human single- and multiple-dose safety and tolerance study (Protocol 1008-002). The percentage of dose recovered in urine as unchanged pregabalin averaged 91.1% following single-oral doses of 25 to 300 mg. A mass balance and metabolism study was also performed in humans. Following a single oral 100-mg dose of ^{14}C-pregabalin, mean cumulative urinary recovery of the radioactivity was 92% of the dose. Of this, 98% (90% of the total dose) was unchanged

pregabalin. The BCS guidance suggest that compounds may be classified as highly permeable if the extent of absorption is >90%. Therefore, pregabalin is a highly permeable compound with an oral bioavailability of 90% or more.

Exploratory Preclinical Data: Pregabalin permeability was studied in the in situ rat intestinal (jejunal) perfusion model relative to reference compounds atenolol, metoprolol, and propranolol. Permeability measurements from this rat model have been shown to be highly correlated with human estimates of permeability and fraction of dose absorbed. Atenolol, metoprolol, and propranolol have oral bioavailability in humans of approximately 50%, 90%, and 100%, respectively. Effective permeability of pregabalin was comparable to that of metoprolol, (32.0 × 10-6 ± 5.33 cm/s versus 30.2 × 10-6 ± 12.8 cm/s) a highly permeable compound. Thus, these results also suggest that pregabalin is a high permeability compound.

Comparison Of Clinical Trial And Market-Image Formulations Of Pregabalin

Composition of Pregabalin Formulations: The various pregabalin capsule formulations can be sorted into 3 distinct groups based on the percent of drug in the capsules (Series A, B, and C). All formulations within a series are content proportional. Table 2 lists pregabalin capsule formulations by series. The range of capsule strengths vary among series with capsule strengths of 25, 50, 75, 100, and 150 mg produced from Series A, 100 mg produced from Series B, and 75, 100, 150, 200, and 300 mg produced from Series C.

Table 2 Composition of Pregabalin Formulations for Series A, B, and C

Capsule	Formulation Series		
Characteristics	A	B	C
Pregabalin Lactose Monohydrate Corn Starch Talc			
Capsule Size	4, 3, 2, 1, and 0	1	4, 3, 2, 1, and 0
Total Fill Weight	100, 200, 300, 400, & 600 mg	— mg	100, — 200, — & 400 mg

Pregabalin Clinical Trial Formulations: Table 3 lists formulations by capsule strength and composition series used in Phase 1, 2, and 3 clinical trials through January 7, 2000. Formulations with identical capsule strengths but differing synthetic routes, capsule size, and/or capsule color have been produced in formulation Series A, B, and C. The dissolution data (Table 3) indicate that at least — of the labeled strength is dissolved within 30 minutes.

Table 3. Dissolution Data for Various Pregabalin Formulations

Formulation No.	Lot No.	Strength (mg)	Composition Series	Fill Weight (mg)	Cap Size	Color	Percent Dissolved[a] 10 min	20 min	30 min	40 min
2	CF-0070495	25	A	100	4	gray				
7[b]	804N8V	25	A	100	4	gray				
16[c]	CF-0140398	25	A	100	0	gray				
30[d]	CV-1160699	25	A	100	4	blue				
23	805N8V	50	A	200	3	gray				
36[e]	CF-0210599	50	A	200	0	gray				
24	836N8V	100	A	400	1	gray				
32[f]	CV-1210699	100	A	400	1	blue				
45	CV-1600899	150	A	600	0	gray				
3	CF-0080495	100	B		1	gray				
8[g]	CF-0251197	100	B		1	gray				
8	CF-0120398	100	B		1	gray				
15[h]	CF-0060299	100	B		0	gray				
28	CF-0190499	150	C	200	0	gray				
29	CF-0200599	200	C		0	gray				
4	CF-0090495	300	C	400	0	gray				
13[i]	CF-0200498	300	C	400	0	gray				

[a] The current procedure for assessing pregabalin in vitro dissolution characteristics involves testing the capsules in [redacted] using USP Apparatus II (Paddle) at 37°C at 50 rpm. This media was deemed acceptable by the FDA on 03/2-4/2000.

[b] Identical to Formulation 2 except for a change in pregabalin synthetic route

[c] Identical to Formulation 7 except for capsule size

[d] Identical to Formulation 7 except for capsule color

[e] Identical to Formulation 23 except for capsule size

[f] Identical to Formulation 24 except for capsule color

[g] Identical to Formulation 3 except for a change in pregabalin synthetic route

[h] Identical to Formulation 8 except for capsule size

[i] Identical to Formulation 4 except for a change in pregabalin synthetic route

In Vivo Performance of Pregabalin Capsule Formulations: Clinical studies have demonstrated that absorption is not dose-dependent across a wide dose range (Study 001) and that solution and capsule formulations are bioequivalent (Study 003). Formulations used in these studies are:

Study 001: Formulation 2 (Series A, 25 mg) Lot CF-0070495,
Formulation 3 (Series B, 100 mg) Lot CF-0080495
Formulation 4 (Series C, 300 mg) Lot CF-0090495
Study 003: Formulation 3 (Series B, 100 mg) Lot CF-0080495 capsules
100-mg pregabalin solution
*Formulation 3 was also used in pivotal Phase 3 trials.

In Vitro Performance of Pregabalin Formulations

FDA draft BCS guidance indicates that for highly soluble, highly permeable, and highly dissolving compounds bioequivalence may be established in vitro by demonstrating that dissolution profiles of formulations are similar (based on the f2 test) or that ≥85% of the drug is dissolved in 15 minutes. Dissolution profiles are to be compared under acidic conditions, at pH 4.5 and 6.8.

Preliminary work was performed to determine the dissolution characteristics of
In general, dissolution rates in the pH 4.5 and 6.8 media were slightly slower than that observed in the pH 1.2 media. These differences were mainly seen at the 10- and 15-minute sampling intervals; however, at ³20-minute sampling intervals, the percentage dissolved was similar in all 3 media. In the pH 4.5 and 6.8 media, capsule disintegration was slightly slower with a few individual capsules not disintegrating until after the 10-minute sampling time.

Formulation 13 (Series C, 300 mg) dissolved faster than the reference clinical trial Formulation 15 (Series B, 100 mg). A previous study indicated that dissolution rates faster than that of the reference clinical trial formulation did not impact in vivo

performance, as a solution was bioequivalent to the Series B, 100-mg capsule formulation. Further, mean pharmacokinetic data and dissolution profiles were virtually identical (Table D3 and Figure D1). Thus, dissolution profiles faster than the reference formulation are indistinguishable from the reference formulation in vivo. Because bioequivalence was demonstrated between the clinical reference formulation and Formulations 27 (Series C, 75 mg) and 45 (Series A, 150 mg), Formulations 27 and 45 are also expected to be bioequivalent to formulations dissolving equal to or faster than the reference clinical formulation.

Table 5 Mean Dissolution Results in — Media (pH 1.2) (n = 12)

Strength (mg/cap)	Lot No	Formulation Series	% Label Claim Dissolved after 10 min	15 min	20 min	30 min
25	K32-AX1-I	A				
75	K32-BN1-I	C				
100	K32-AY1-V	B				
150	80289V	A				
300	K32-BA1-II	C				

USP Apparatus II (Paddle) at 50 rpm was used for all dissolution tests

Table 6 Mean Dissolution Results in — (pH 4.5) (n = 12)

Strength (mg/cap)	Lot No	Formulation Series	% Label Claim Dissolved after 10 min	15 min	20 min	30 min
25	K32-AX1-I	A				
75	K32-BN1-I	C				
100	K32-AY1-V	B				
150	80289V	A				
300	K32-BA1-II	C				

USP Apparatus II (Paddle) at 50 rpm was used for all dissolution tests

Table 7 Mean Dissolution Results in — (pH 6.8) (n = 12)

Strength (mg/cap)	Lot No (Formulation)	Formulation Series	% Label Claim Dissolved after 10 min	15 min	20 min	30 min
25	K32-AX1-I	A				
75	K32-BN1-I	C				
100	K32-AY1-V	B				
150	80289V	A				
300	K32-BA1-II	C				

USP Apparatus II (Paddle) at 50 rpm was used for all dissolution tests

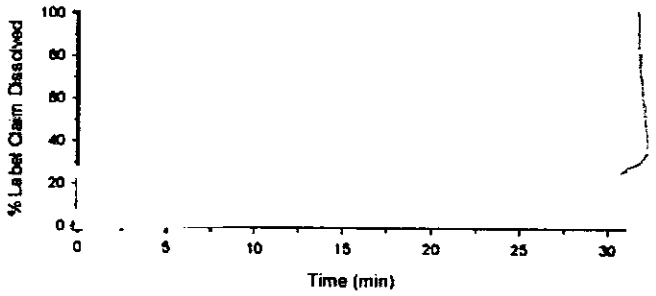


Figure 1. Mean Dissolution Profiles of Pregabalin Capsule Formulations in — (pH 1.2), USP Apparatus II, 50 rpm (n = 12)

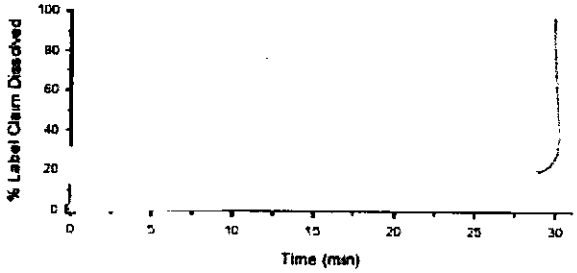


Figure 2. Mean Dissolution Profiles of Pregabalin Capsule Formulations in — — (pH 4.5), USP Apparatus II, 50 rpm (n = 12)

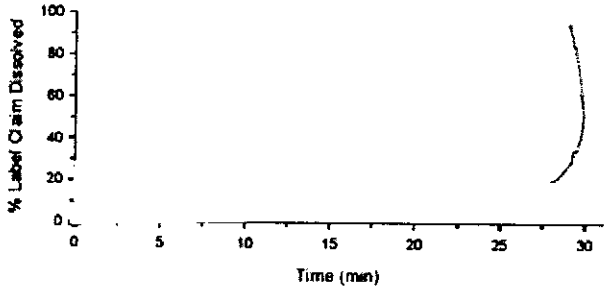


Figure 3. Mean Dissolution Profiles of Pregabalin Capsule Formulations in — (pH 6.8), USP Apparatus II, 50 rpm (n = 12)

All formulations achieved >85% dissolution in 30 minutes in each of the 3 dissolution media. Thus all formulations are considered rapidly dissolving. Furthermore, all formulations achieved — dissolved in 15 minutes at pH 1.2. Since all formulations meet bioequivalence criteria (>85% in 15 minutes) for acidic media, the similarity factor (f2) test comparing dissolution profiles between formulations is unnecessary for acidic media. All other dissolution test results met the >85% dissolved in 15-minute criteria except as follows: Formulation 7 (Series A, 25-mg capsules) in pH 4.5-media — Formulation 45 (Series A, 150-mg capsules) in pH 4.5- — and pH 6.8-media — and Formulation 27 (Series C, 75-mg capsules) in pH 4.5-media —

Table 8 lists the similarity factors (f2) for the preceding formulations relative to Formulation 15 (Series B, 100-mg capsules) in the different dissolution media. Formulation 15 is identical to

Formulation 3 (the formulation shown to be bioequivalent to a pregabalin solution) except for capsule size and synthetic route. Formulations 15 and 3 have similar dissolution profiles (Table 3).

With the exception of Formulation 45 at pH 4.5, all f2 values met bioequivalence criteria (>50). The f2 criterion for Formulation 45 was just outside the bioequivalence criteria. Further, most of the differences in dissolution profiles occurred at the initial time point (10 min & 15 min) and were due to slight differences in capsule disintegration. By 20 minutes, the formulation was dissolved. These differences are not expected to impact in vivo performance and Formulation 45 is considered bioequivalent to the reference formulation. In general, other comparisons between and across formulations support the bioequivalence of clinical formulations (Appendix D). Thus, all clinical trial formulations are considered bioequivalent to the reference formulation (Formulation 15, 100 mg, Series B).
Reviewer's comment: Acceptable.

Table 8. Similarity Factors (f_2) for Dissolution Results Obtained in (pH 1.2), (pH 4.5), and (pH 6.8)

Media pH	Formulation Number (Series, Capsule Strength) and Lot Number			
	7 (Series A, 25 mg) Lot K32-AX1/I	27 (Series C, 75 mg) Lot K32-BN1/I	45 (Series A, 150 mg) Lot 80289V	13 (Series C, 300 mg) Lot K32-BA1/II
1.2				
4.5				
6.8				

USP Apparatus II (Paddle) at 50 rpm was used for all dissolution tests.
Formulation 15 (Series B, 100-mg capsules) Lot K32-AY1/V was used as reference for calculation of the similarity factors.

DISSOLUTION

Dissolution medium: 37°C
Method: Apparatus 2 (Paddle), 50 rpm
Specification: NLT (Q) of the label claim dissolved in 30 minutes

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

4.2 OCPB FILING/REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-446; 21-723	Brand Name	Lyrica
OCPB Division (I, II, III)	II	Generic Name	Pregabalin
Medical Division	Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170)	Drug Class	α2δ ligand
OCPB Reviewers	Sue-Chih Lee Srikanth Nallani	Indication(s)	treatment of diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN)
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Capsules
Date of Submission	10/31/2003	Proposed Dosing Regimen	
Estimated Due Date of OCPB Review	March 19, 2004	Route of Administration	Oral
Medical Division Due Date	March 19, 2004	Sponsor	Pfizer
PDUFA Due Date	April 30, 2004	Priority Classification	NDA 21-446: 1P NDA 21-723 1S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x	2	2	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1	1	
multiple dose:	X	2	2	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	

fasting / non-fasting multiple dose:	x	1	1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	3	3	
In-vivo effects of primary drug:	x	10	5	
In-vitro				
Subpopulation studies -				
ethnicity:	X	1	1	
gender:				
pediatrics:				
geriatrics:	X	1	1	
renal impairment:	X	2	2	
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	5	3	
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	x	4	1	**Mixed**
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS	X	1	1	
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		36	29	

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• **Are the proposed dosing regimens supported by clinical studies?** • **What dosage regimen adjustment, if any, are recommended for subgroups?**	
Other comments or information not included above	✓	
Primary reviewer Signature and Date		

Secondary reviewer Signature and Date	

CC: NDA 21-446, HFD-870 (Electronic Entry or Lee), HFD-170 (Malandro), HFD-870 (Doddapaneni, Hunt, Malinowski), CDR (B. Murphy)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sue Chih Lee
3/19/04 03:03:24 PM
BIOPHARMACEUTICS

Srikanth Nallani
3/22/04 12:18:12 PM
BIOPHARMACEUTICS

He Sun
3/22/04 02:11:23 PM
PHARMACOLOGIST

Please sign off

Suresh Doddapaneni
3/22/04 03:52:50 PM
BIOPHARMACEUTICS