CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-724

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Pregabalin
NDA:	21-724 and 21-725
PRODUCT (Brand Name):	LYRICA
DOSAGE FORM:	Capsules
DOSAGE STRENGTHS:	25, 50, 75, 100, 150, 200, 225 and 300 mg
INDICATION:	Treatment of diabetic peripheral neuropathy, postherpetic neuralgia, and as an adjunct therapy for epilepsy
NDA TYPE:	1S
SUBMISSION DATES:	10/30/03, 2/12/04, 2/5/04, 2/25/04, 3/3/04
SPONSOR:	Pfizer
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
PHARMACOMETRICS TEAM LEADER	Joga Gobburu, Ph.D
OCPB DIVISION:	DPE I, HFD 860
OND DIVISION:	HFD 120

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APPEARS THIS WAY
ON ORIGINAL

1.0 EXECUTIVE SUMMARY

Pregabalin is an alpha-2-delta (a2d) 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), and [redacted] and as an adjunct therapy for epilepsy in patients [redacted] Only DPN indication was designated for priority review while the other three are given a standard designation. Indications of DPN (N21-446) and PHN (N21-723) are being reviewed by the Division of Anesthetic, Critical Care and Addiction Drug Products.

The overall clinical pharmacology and biopharmaceutics section of the NDA has been reviewed by Dr. Sue Chih Lee for N21-446 (pregabalin indicated for the treatment of Diabetic Peripheral Neuropathy) from the Clinical Division of Anesthetic, Critical Care and Addiction Drug Products. This review summarizes the clinical pharmacology section of pregabalin that pertains to indications of epilepsy (N21-724) [redacted] These include drug-drug interaction studies with drugs that are likely to be administered in the epilepsy [redacted] patient populations, pharmacokinetics in these patient populations and exposure-response relationship in epilepsy [redacted] patients.

Excerpts from Dr. Lee's review have been resummarized in this review for the completeness of information for the readers of this review for N21-724 [redacted]

1.1 RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPE-I) has reviewed Clinical Pharmacology sections of NDA 21-724 [redacted] The submission is acceptable from a Clinical Pharmacology and Biopharmaceutics point of view provided that the sponsor agrees with the Agency's label recommendations.

Labeling comments outlined in the Detailed Labeling Recommendation section of the review on page 44 should be conveyed to the sponsor.

The following recommendations/comments should be conveyed to the Medical Officer:

- [redacted]
- [redacted]

2 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 3

[redacted]

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

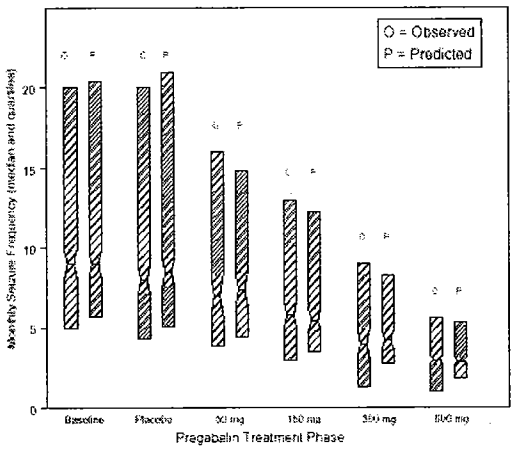
Pregabalin is an alpha-2-delta ($\alpha_2\delta$) ligand that has analgesic, anxiolytic, and anticonvulsant activity. The sponsor is seeking approval of pregabalin capsules for the treatment of diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), [redacted] and as an adjunct therapy for epilepsy in patients [redacted] Only DPN indication was designated for priority review while the other three are given a standard designation.

The dosing recommendation for epilepsy patients is a starting dose of 75 mg BID to a maximum of 300 mg BID, with dose increments at 1 week interval.

The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Exposure-Response for Effectiveness:

- Epilepsy: The pharmacodynamic endpoint to assess the exposure-response relationship in epilepsy patients was the reduction in monthly seizure frequency. The exposure-response analysis showed that 75% of the patients were responders and 25% of the patients were non-responders. There was no covariate attributed to these non-responders. In the subset of patients that are not refractory to pregabalin, a dose of approximately 186 mg daily is expected to decrease the baseline seizure rate by about 50% of maximum. In general, for a given pregabalin dose men have a slightly lower response (22%) than females. The dose-response relationship is shown in the following figure:



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Exposure-Response for Safety:
Dizziness and somnolence were the most prevalent adverse events associated with pregabalin treatment. The total number of observations of dizziness and somnolence increased with the increase in dose. Female patients apparently reported higher incidence of dizziness. The TID regimen studies in some clinical trials showed greater number of observations of both dizziness and somnolence as compared to the proposed BID regimen. This could be due to the sustained levels of pregabalin with TID dosing.

The potential for pregabalin to prolong QT interval was evaluated in Phase II/III studies. There was little difference when comparing treatments (drug vs. placebo) for any of the different indication groups in these studies. However, there was no adequately designed Phase I study with positive controls/placebo to evaluate meaningful exposure-response relationships for QT prolongation.

General Pharmacokinetics (ADME characteristics) of pregabalin:
Absorption: Pregabalin has high oral bioavailability (≥90%), with peak concentrations occuring at 1.5 (0.5-2) hours following both single and multiple dose administration and was independent of the dose.

Distribution: Pregabalin is not bound to plasma proteins. The apparent volume of distribution following oral administration is 0.5L/Kg. 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 and renal proximal tubules. Nonclinical studies indicate that pregabalin crosses blood brain barrier and placenta and is present in the milk of lactating rats.

Metabolism: 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.

Elimination: 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.

Single dose and multiple dose pharmacokinetics:
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 from 1.70 to 1.96 for TID dosing.

Dose proportionality: Following single-dose (25-300 mg) and multiple-dose (25-300 mg q8h, i.e 75-600 mg/day) administration of pregabalin, the pharmacokinetics of pregabalin is linear.

Pharmacokinetics in patients: The pharmacokinetics of pregabalin is not different in patients with epilepsy [redacted] as compared to healthy volunteers.

Special Populations:
Renal Impairment: Pregabalin CL/F increases linearly with the increase in CrCl. In the population analysis, the relationship was expressed as CL/F=0.0459xCrCL which plateaus at CrCL of 105 mL/min. Dosage adjustment is considered necessary only for patients with CLcr ≤60 mL/min.
The sponsor's proposed dosage adjustment for the renally impaired is acceptable and has been confirmed by simulations by Dr. Lee (please refer to her review of N21-446 for further details).

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)	
≥60			
30-60			
15-30			
<15			
Supplementary dosage following hemodialysis (mg)			

Hepatic Impairment: 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.

Age: *Elderly:* The sponsor has evaluated subjects up to the age of 75 years in the epilepsy studies and [redacted] No age related differences were observed in exposure-response relationships. A population analysis, after correction for CrCl showed that there were no age related differences in the pregabalin clearance.
Pediatrics: The only age group studied is the adolescents (12-17 years) in the clinical trials in patients with partial seizures. However, there were only 11 adolescents enrolled in these studies (with sparse sampling), hence, no conclusions can be drawn regarding pharmacokinetics or pharmacodynamics in adolescents. The sponsor has requested waiver or deferral for conducting studies in the other pediatric subgroups in patients with partial seizure [redacted] An agreement on waiver/deferral will be made after it is determined that pregabalin can be safely administered to adults and is under evaluation.

Gender: No significant gender related differences were observed.

Race: No significant race related differences were observed. The races evaluated in adequate numbers were White (N=2001), Black (N=109) and Hispanics (N=132). Other races with subjects less than 20 were Asians, American Indians and others.

Drug-drug Interactions:

Effect of pregabalin on pharmacokinetics of other drugs:
No effect of pregabalin on the pharmacokinetics of sodium valproate, carbamazepine, lamotrigine, phenytoin, phenobarbital, topiramate and lorazepam was found.

Effect of other drugs on pregabalin pharmacokinetics:
No effect of sodium valproate, carbamazepine, lamotrigine, phenytoin, phenobarbital, topiramate, tiagabine and lorazepam on the pharmacokinetics of pregabalin was found.

Biopharmaceutics:

BCS Class: Pregabalin is a BCS Class I drug
Bioequivalence: Proposed to-be-marketed formulations were same as the clinical trial formulations, with minor changes of capsule size and color. Waiver of bioequivalence study is granted.
Food Effect: 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.
Dissolution: The dissolution methodology is USP Apparatus [redacted] rpm with [redacted] N HCl, [redacted] ml. A Q of [redacted] in [redacted] minutes was set as the quality control specification.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D._____

Pharmacometrics Team Leader: Joga Gobburu, Ph.D._____

2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: 25, 50, 75, 100, 200, 225 and 300 mg Capsules

Indication: Pregabalin is used for the treatment of 4 different indications. Out of these diabetic peripheral neuropathy received a priority review.

- Diabetic peripheral neuropathy: management of neuropathic pain
- Postherpetic neuralgia: management of neuropathic pain
- Epilepsy: as adjunct therapy in the treatment of partial seizures with

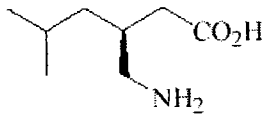
(Note: The indication of Diabetic peripheral neuropathy has an action date prior to this application. This indication along with postherpetic neuralgia is being reviewed by HFD 170. Epilepsy indications are reviewed in this Division).

Dosage and administration (Sponsor's Proposed):

Epilepsy
Adults
LYRICA is recommended as adjunctive therapy in the treatment of partial seizures in patients The recommended effective starting dose for LYRICA is 75 mg BID (150 mg/day), with or without food. The dose may be increased to 150 mg BID after 1 week, and if needed, to a maximum dose of 300 mg BID after an additional week.

Pharmacologic Class: alpha-2-delta (α2δ) ligand

Chemical Name: (S)-3-(aminomethyl)-5-methylhexanoic acid



The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23

Physical Characteristics: Soluble in aqueous media of various pHs. The pKa's are 4.2 and 10.6

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 binds 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 ($GABA_A$ and $GABA_B$) receptors, it is not converted metabolically into GABA or a GABA antagonist, and it does not alter GABA uptake or degradation.

Formulation: Quantitative formula for all the dose strengths

Component	**Wt (mg/capsule)** **Formulation #/Capsule Strength**							
	25 mg	**50 mg**	**75 mg**	**100 mg**	**150 mg**	**200 mg**	**225 mg**	**300 mg**
Pregabalin								
Lactose Monohydrate								
Corn Starch								
Talc								
Fill Weight								
Capsule Size								

2.2 GENERAL CLINICAL PHARMACOLOGY

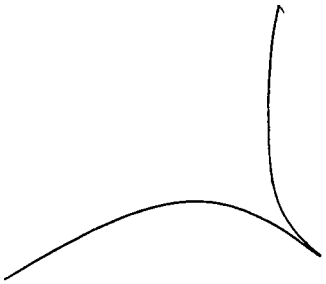
What are the clinical studies used to support dosing or claims and what are their design features?

For Adjunct-therapy in Epilepsy:

The efficacy of pregabalin in partial seizure patients was established in three Phase 3 randomized, double-blind, parallel, placebo-controlled multi-center trials of 12 weeks duration conducted as an add-on treatment of patients with refractory partial seizures. Of these 3 studies only two studies used a BID regimen (proposed regimen). The 300 mg/day dose was not replicated in any study. Patients with refractory seizures not adequately controlled by 1-3 concomitant antiepileptic agents (AEDs) could be enrolled in these studies.

Protocol	N	Duration	Population	Pregabalin Dose
1008-009	308	12 weeks	≥18 years patients with partial seizure	600 mg/day (300 mg BID) 600 mg/day (200 mg TID)
1008-011	287	12 weeks	≥18 years	150 mg/day (50 mg TID) or 600 mg/day (200 mg TID)
1008-034	447	12 weeks	≥12 years with body weight ≥ 40 kg	50 mg/day (25 mg BID), 150 mg/day (75 mg BID), 300 mg/day (150 mg BID), 600 mg/day (300 mg BID)

In studies 11 and 34, patients with CrCL ≤ 60 ml/min were excluded from the trial. Study 9 did not have exclusion criteria regarding CrCL values.



What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

For Epilepsy:
The primary criterion to establish the efficacy of pregabalin was the reduction in the frequency of all partial seizures during the double-blind period compared with the baseline period. The observed seizure rate during baseline and double-blind was standardized for a 28-day period.

$$28\text{ day rate} = \frac{\#\text{ of partial seizures in period}}{[\#\text{ of days in period} - \#\text{ of missing diary days in period}]} \times 28$$

The primary efficacy parameter was:

- Response ratio (RRatio or symmetrized percent change), a comparison of baseline seizure frequency (B) with treatment seizure frequency (T). The RRatio is calculated by dividing the difference between 28-day seizure rates during treatment and baseline by the sum of baseline and double-blind seizures:

$$\text{RRatio} = \frac{T - B}{T + B} \times 100$$

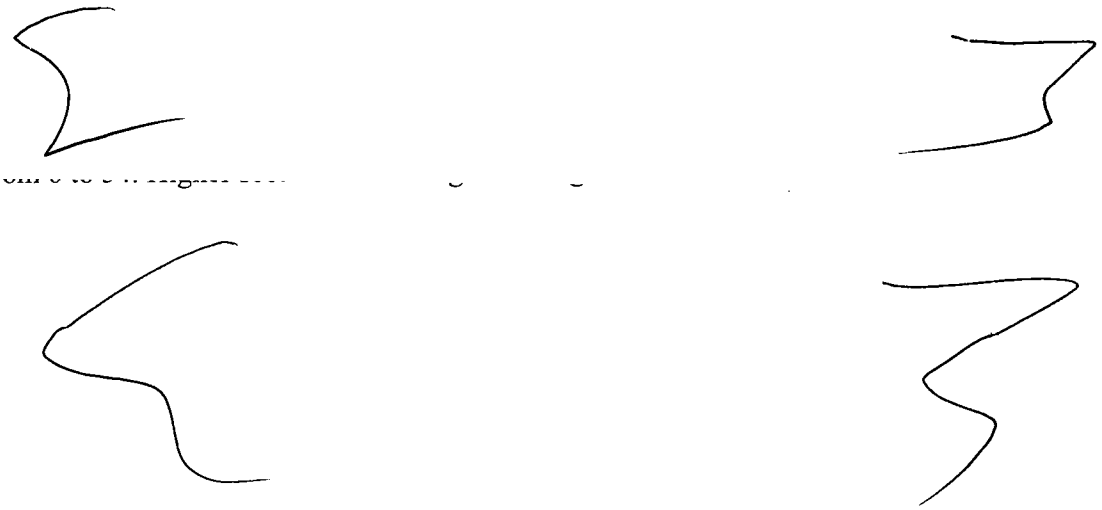
The RRatio is always between 100 and -100. Negative values for the RRatio indicated reductions in seizures. An RRatio of -33 is equivalent to a 50% reduction from baseline

in seizures.

The secondary efficacy parameters were:

- Responder rate, which was defined as the percent of patients who had at least a 50% reduction in 28-day frequency of seizures during treatment compared with baseline.

- Percent change, which was defined as percent change in 28-day seizure frequency during treatment compared with baseline.



What are the characteristics of exposure/effectiveness relationships?

For Efficacy in Epilepsy patients:

An exposure (dose) -response analysis was conducted in 1042 patients with partial seizures pooled from 3 studies (Study 009, 011 and 034). A subject-specific random-effects model was used to characterize the relationship between monthly seizure frequency and pregabalin dose in individual patients, taking into account placebo effect. Seizure frequency was normalized for 28 days so that the information consisted of 4 observations per individual, the baseline value and Months 1, 2, and 3 expressed as number of seizures per month.

A mixture model, a model that implicitly assumes that some fraction p of the population has one set of typical values of response, and that the remaining fraction 1-p has another set of typical values, was fit to the data.

The following equations describe the final model, which was a mixture model:

Population A (75%)

$$\lambda = Base_A \cdot \left(1 - \frac{FCB_A \cdot GEN \cdot dose}{ED_{50} + dose} \cdot D_1 - Placebo_A \cdot D_0\right) \cdot e^{\eta_1}$$

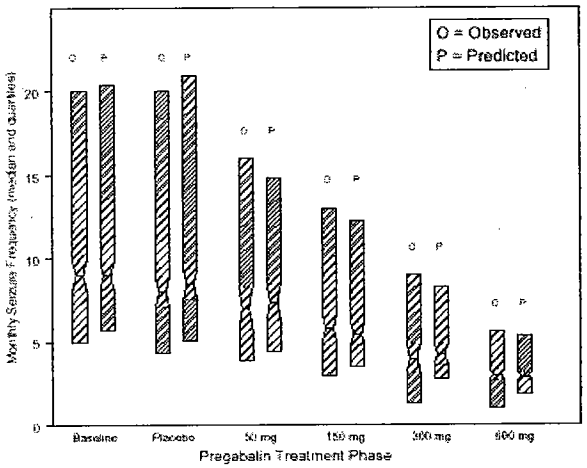
Population B (25%)

$$\lambda = Base_B \cdot \left(1 - FCB_B \cdot D_1 - Placebo_B \cdot D_0\right) \cdot e^{\eta_2}$$

Where:

$Base_A$ =	Baseline seizure frequency for Subpopulation A (per month).
$Base_B$ =	Baseline seizure frequency for Subpopulation B (per month).
FCB_A =	Maximal fractional change in baseline seizures due to drug treatment for Subpopulation A.
FCB_B =	Fractional change in baseline seizures due to drug treatment for Subpopulation B.
GEN =	Proportional difference of males relative to females in FCB_A.
ED_{50} =	Dose which provides a 50% reduction in FCB_A.
$Placebo_A$ =	Influence of placebo on baseline seizure frequency for Subpopulation A.
$Placebo_B$ =	Influence of placebo on baseline seizure frequency for Subpopulation B.
D_1 =	1 during drug treatment and 0 during placebo treatment.
D_0 =	0 during drug treatment and 1 during placebo treatment.
η_1 =	intersubject random effect for Population A.
η_2 =	intersubject random effect for Population B.

The model showed a dose response relationship as shown in the following plot for the observed and predicted seizure frequency at the various doses:



- The mixture analysis revealed that 75% of the patients were responders (Subgroup A) and 25% were non-responders (Subgroup B). These results are consistent with literature values that establish that approximately 30% of patients are refractory to drug treatment (BMJ 1996; 313: 1169-74). Therefore, pregabalin add-on treatment in refractory patients shows a dose-response relationship in 3 out of 4 patients with partial seizures.

- In the subset of patients that are not refractory to pregabalin, a dose of approximately 186 mg daily is expected to decrease the baseline seizure rate by about 50% of maximum.

- In general, for a given pregabalin dose men have a slightly lower response (22%) than females.

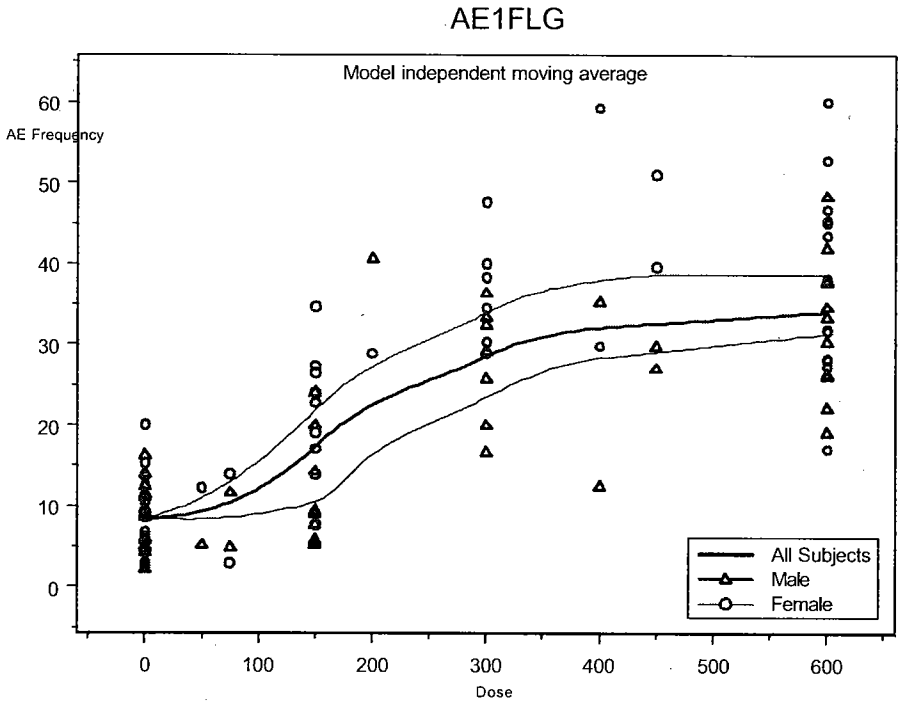
- The dose-response relationship of pregabalin on seizure frequency was independent of age and menopausal status of women.

What are the characteristics of exposure-safety relationships?

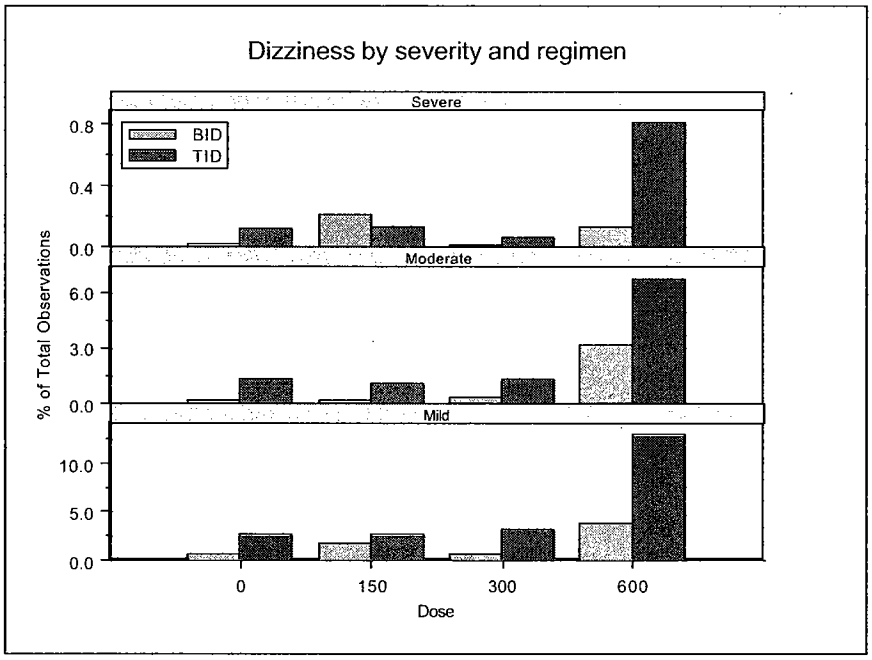
The exposure response relationships for safety have been reviewed by Drs Lee and Sun. For details please refer to the review of N21-446. Key points from Dr. Lee's review have been summarized here.

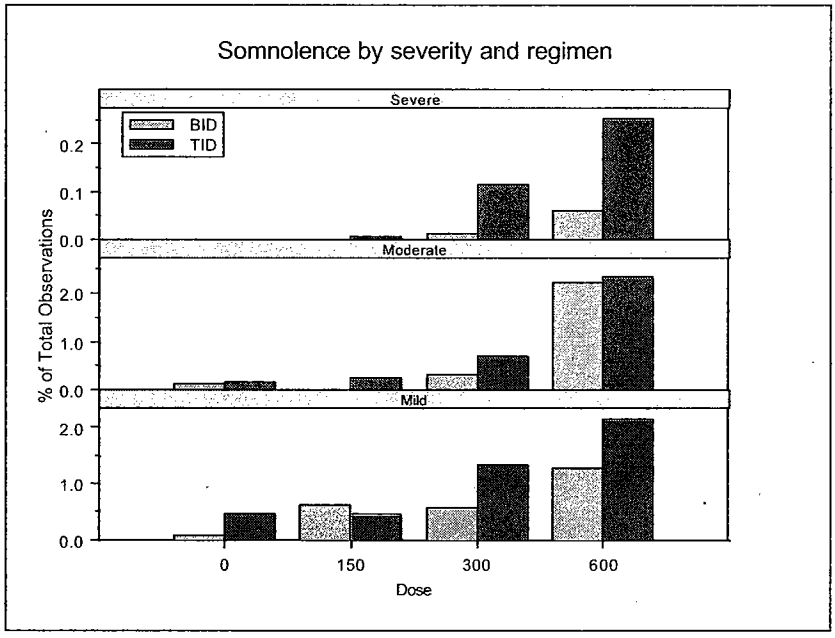
Dizziness and somnolence were the most prevalent adverse events associated with pregabalin treatment.

The probability for a subject to experience dizziness (AE1) increased with the dose. 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 dizziness. It is clear that the variability was high among various trials as shown in the following figure (created by Dr. He Sun). The ED_{50} for incidence of dizziness was estimated to be 153±8 mg/day. ED50 for severity of somnolence was estimated to be 275±32 mg/day.



The incidence and severity of dizziness and somnolence can also be depicted by the following figures. These figures were made by this reviewer in an attempt to differentiate the incidence of adverse events for the BID and TID regimens. These figures show that higher proportion of patients receiving TID regimen experience dizziness and somnolence as compared to the BID regimen. These differences were more obvious at pregabalin doses higher than 300 mg.





Does pregabalin prolong QT or QTc interval?

The potential of pregabalin to prolong QT interval in the Phase II and III studies is being evaluated by the safety review team in the Division of Neurological Drug Products. The mean maximum QTc changes from baseline for pregabalin and placebo from the Phase

II/III studies are summarized in the following Tables taken from the Medical Safety review. One ECG analysis report from the sponsor included 4757 patients of pain, epilepsy and psychiatry indications and the second analysis report included 2757 patients from GAD and new psychiatric indications. In all studies summarized here, an ECG was collected at baseline before exposure to study medication, and at least one ECG was collected during double- blind treatment. The number of ECGs collected from each patient as well as the timing of collection varied from study to study (1-3 in the double blind phase). There was little difference when comparing treatments (drug vs. placebo) for any of the different indication groups.

Unadjusted Mean Maximum Change from Baseline, QTc* Interval

Treatment (n)	QTc mean max change from baseline (ms)	Difference from placebo
Pooled Pain Studies		
Placebo (n=782)	2.8	--
Pregabalin (n=1510)	2.3	-0.5
Pooled Diabetic Neuropathic Pain Studies		
Placebo (n=291)	3.6	--
Pregabalin (n=483)	3.8	0.2
Pooled Epilepsy Studies		
Placebo (n=190)	7.9	--
Pregabalin (n=534)	4.1	-3.8
Pooled Psychiatry Studies		
Placebo (n=201)	3.1	--
Pregabalin (n=396)	-0.1	-3.2

*linear correction for heart rate

Unadjusted Mean Maximum Change from Baseline, QTc* Interval

Treatment (n)	QTc mean max change from baseline (ms)	Difference from placebo
Pooled GAD Studies		
Placebo (n=250)	3.8	--
Pregabalin (n=676)	-0.9	-4.7
Pooled New Psychiatry Studies		
Placebo (n=219)	4.1	--
Pregabalin (n=645)	0.4	-3.7
Study 082		
Placebo (n=36)*	-2.9	--
Pregabalin (n=36)*	0.8	3.7
Placebo (36) ‡	1.0	--
Pregabalin (34) ‡	-1.4	-2.4
Study 088		
Placebo (n=125)*	-1.7	--
Pregabalin (n=114)*	-3.5	-1.8
Placebo (n=122) ‡	-0.2	--
Pregabalin (n=113) ‡	-2.1	-1.9

*linear correction for heart rate
*Uses open label baseline
‡Uses double blind baseline

The effect on QT prolongation from the Phase I studies had been reviewed by Dr. Sue Chih Lee in the review of N21-446. For additional details please refer to her review of N21-446.

Some limitations of ECG analyses are:

- No nonclinical studies evaluating QTc prolongation effects of this drug.
- No prospectively designed Phase I study with positive controls and no placebo arm in 5 of the 7 Phase I studies, although the Phase II/III studies were placebo controlled.

No signals of QTc prolongation were observed from the Phase 2/3 studies (N=4394 on pregabalin and N=2094 on placebo) based on discussions with the Safety Reviewer. Given the large data base and lack of any signal from Phase 1/2/3 studies, additional QTc studies are not warranted.

Are the proposed dosage regimens for epilepsy —— indications adequately supported by the clinical trial and consistent with the dose-response relationship?

The following are the sponsor proposed dosage regimen for epilepsy and —— patients:

Patient Population	Age Group	Starting Dose	Maximum Dose	Increments
Epilepsy		75 mg BID	300 mg BID	weekly

Age Group:

For Epilepsy:

Regimen: BID vs TID

From a pharmacokinetic perspective:

Based on a half-life of 6 hours, pregabalin appears to be suitable for the TID regimen. However, the sponsor has conducted pharmacokinetic studies to show that 200 mg q8h vs. 300 mg q12h showed similar pharmacokinetic profiles.

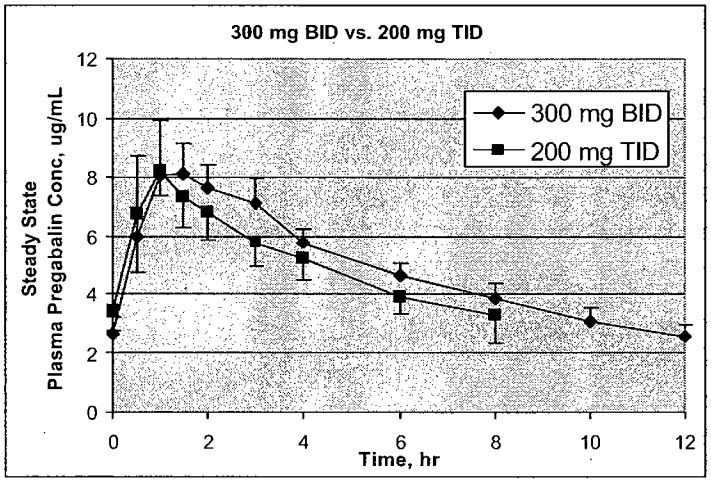
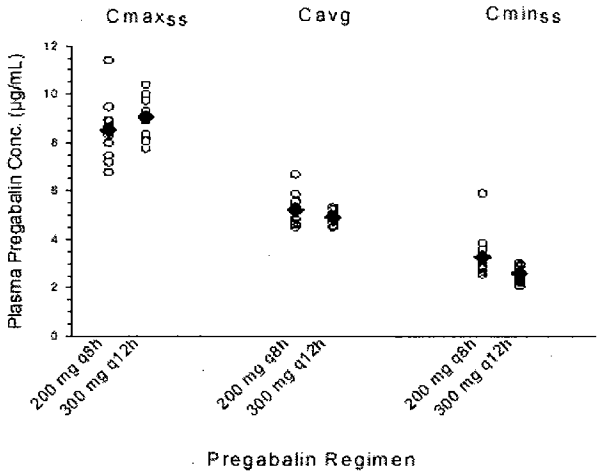


Figure: Pharmacokinetics over one dosing interval (Taken from Review of Dr. Lee)

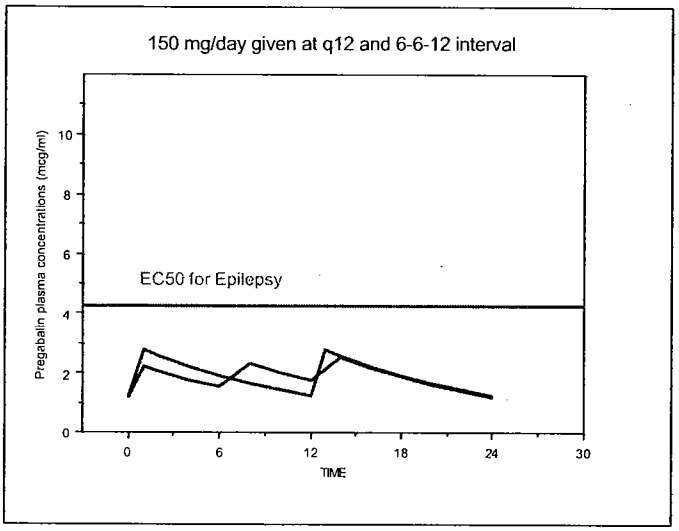
Differences in steady state plasma concentration versus time profiles for q8h and q12h dosing regimens can also be evaluated by comparing the differences in C_{maxss} and C_{minss} for these two dosing regimens. As the dosing interval is increased from q8h to q12h, the fluctuation between C_{maxss} and C_{minss} would be expected to increase, while C_{ave} would be expected to remain constant. The following figure illustrates that the differences between regimens are small when individual and mean steady-state C_{maxss}, C_{minss}, and Cave values are compared following pregabalin doses of 600mg/day administered q8h and q12h in healthy subjects.

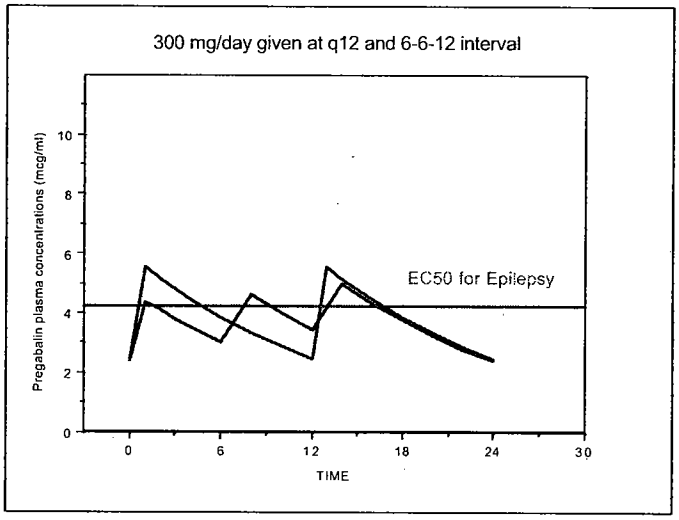


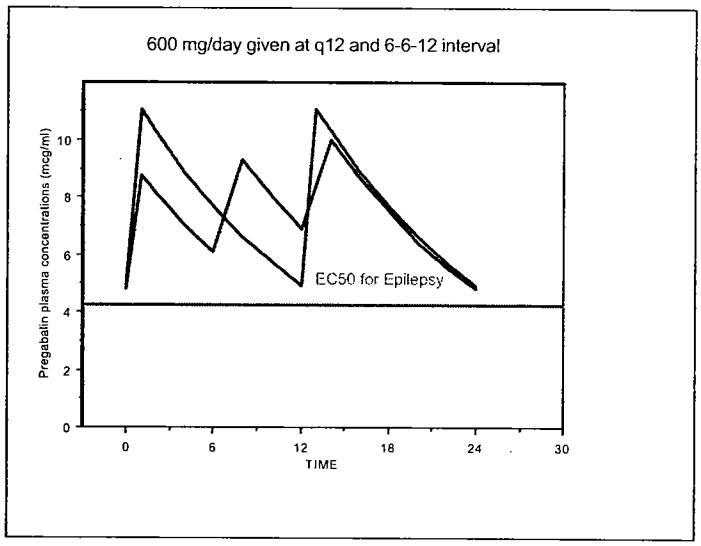
Furthermore, as the q8h regimen diverges from an even eight hour dosing interval to an uneven regimen (eg shorter time intervals between doses taken during the day and a longer interval between the evening and morning doses, a 6-6-12 dosing), the difference in the Cmaxss and Cminss for q8h and q12h administration would be further reduced.

From a pharmacodynamic perspective:

The following simulations were done with the 150, 200, 300 and 600 mg/day doses given q12h and at 6-6-12h intervals (more likely interval as compared to a Q8 interval) to see the difference in the pharmacokinetic profiles. The EC50 for the epilepsy patients is shown in the solid lines. Based on the exposure-response analysis, the EC50 is the plasma concentration of pregabalin to produce 50% of reduction in the seizure frequency.



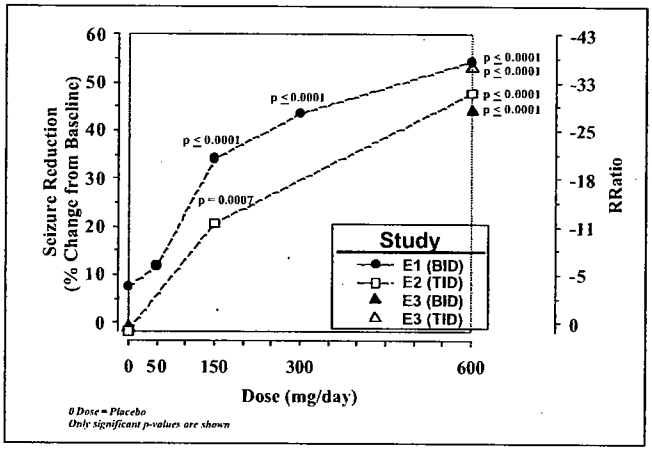




These figures show that doses 300 mg and above may perform better than the lowest recommended dose for epilepsy patients based on the EC50 values. However, titrating with a lower dose is desirable for tolerability reasons.
These also show that both BID and TID doses may be acceptable, however, for practical administration reasons BID may be the preferred choice.

For Epilepsy:

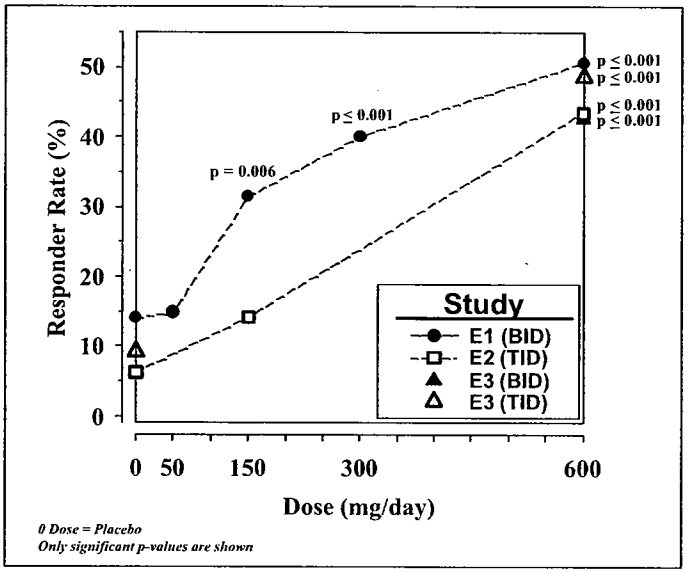
For epilepsy patients the seizure reduction and Rratio by dose and epilepsy study is given in the following Figure:



where E1=Study 034, E2=Study 011 and E3= Study 009.

Based on all these information, both BID and TID regimens were better than placebo in terms of efficacy, but the TID regimen in Study 9 (E3) performed better than the BID

regimen for the 600 mg dose for the primary endpoint, although these differences were not statistically different for the primary endpoint. The BID regimen offered lower efficacy for all secondary efficacy parameters in this study. (see Tables below, based on Sponsor's analysis). After correcting for placebo differences between studies these differences may not be of any significance.



Study 009 (E3) - Summary of RRatio analysis (ITT)				
Treatment group	**N**	**Treatment differences****		**P value*****
		Mean (SE)	**95% CI**	
PGB 600 (TID) vs placebo	111 vs 98	-36.7 (5.0)	-46.4, -27.0	0.0001*
PGB 600 (BID) vs placebo	103 vs 98	-29.0 (5.0)	-38.9, -19.0	0.0001*
PGB 600 (TID) vs (BID)	**111 vs 103**	**-7.7 (4.9)**	**-17.4, 1.9**	**0.1092**

* Statistically significant based on Hochberg's procedure (p 0.049).
** Based on treatment means for the raw RRatio
*** Hochberg procedure applied to the ranked RRatio

Summary of secondary endpoints (ITT)							
Study	**Placebo**	**Pregabalin dose and regimen**					
#		**50mg/day**	**150mg/day 300mg/day**			**600mg/day**	
		BID	**BID**	**TID**	**BID**	**BID**	**TID**
Responder rate							
009	N=98	-	-	-	-	N=103	N=111
	9%					43%*	49%*
011	N=96	-	-	N=99	-	-	N=92

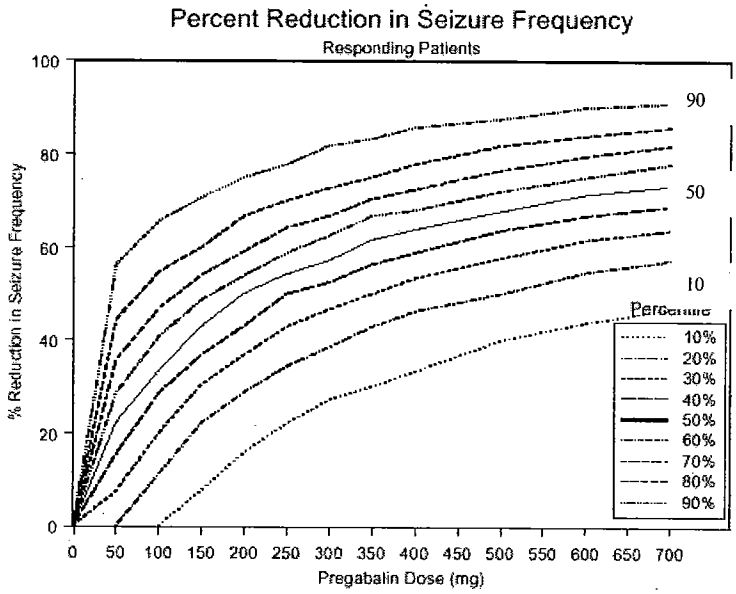
	6%			14%			44%*
034	N=100	N=88	N=86	-	N=90	N=89	-
	14%	15%	31%*		40%*	51%*	
Median percent change from baseline in seizure frequency**							
009	-1%	-	-	-	-	-36%*	-48%*
011	1%	-	-	-17%*	-	-	-43%*
034	0%	-9%	-35%*	-	-37%*	-51%*	-
Seizure free (last 28 days)**							
009	3%	-	-	-	-	3%	14%*
011	1%	-	-	7%	-	-	12%*
034	8%	5%	6%	-	11%	17%	-

*statistical significance for difference between pregabalin dose and placebo (and/or 95% CI exclude zero for Median change figures)
**subject numbers for ITT population are constant across secondary parameters in this table

For epilepsy patients BID dosing will lead to better compliance than TID dosing and clinically is the preferred choice.

The following figure shows the expected percent reduction in seizure frequency with increasing dose, which was generated using Monte Carlo simulation along with the pharmacodynamic parameters for the population that shows a dose-response.

11000 individuals were simulated (50% female) at doses from 50 to 700 mg pregabalin daily. The individuals were pared to exclude estimates with a baseline value less than 6 seizures per month to emulate the inclusion criteria for these studies. The result was 8852 individuals of which 51% were female. The percent reduction from baseline seizure frequency was calculated for each individual simulated. Percentiles were determined for percent reduction in seizure frequency at each dose and is presented in the following Figure:



From the figure, the percent of reduction in seizure frequency at a given dose in 10%, 50% and 90% of the population is shown in the following Table:

Reduction in seizure frequency given in %:

Dose	Percent of population		
	10%	50%	90%
	% Reduction in seizure frequency		
150 mg	71%	43%	7.8%
300 mg	82%	57%	27%
600 mg	90%	71%	44%

This shows that 50% of population will achieve 43% reduction in seizure frequency with 150 mg dose and 71% reduction reduction in seizure frequency with 600 mg dose.

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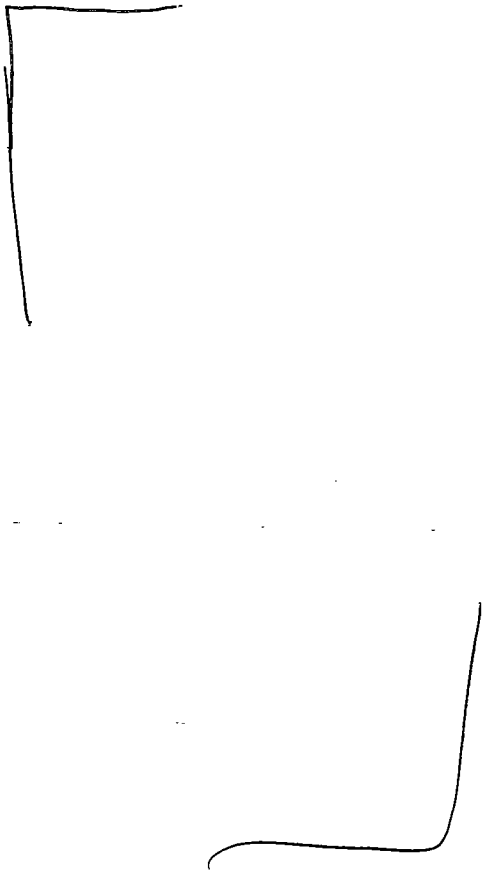
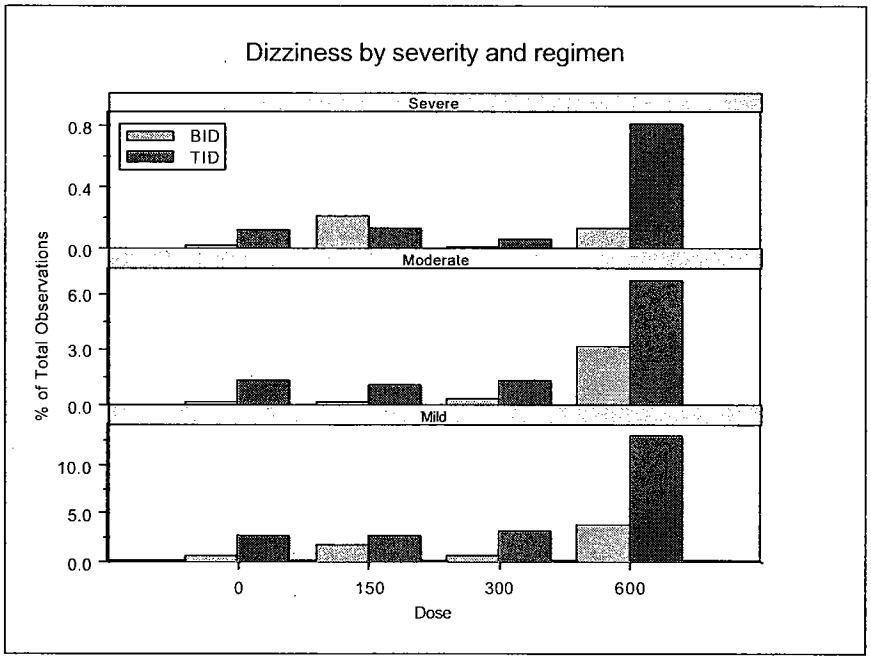
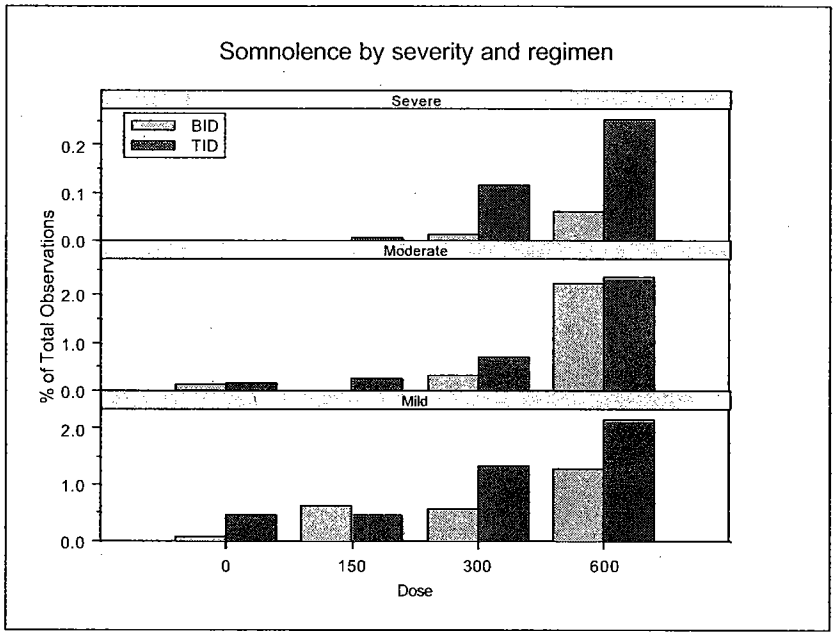


From a safety perspective:

The two main adverse events of dizziness and somnolence was evaluated in terms of various doses given BID and TID conditioned on severity of the adverse event. The following plots show that TID regimen had higher percent of observation for both dizziness and somnolence. This could be due to sustained concentration of pregabalin with TID dosing.





Titration Scheme:

For epilepsy indication the sponsor is recommending titration at weekly intervals and for

None of the clinical trials for either indication was done with this proposed tritration scheme. It is difficult to simulate the proposed titration scheme based on exposure-response analysis because for both indications it is difficult to titrate up to a desired effect.

Thus overall from a pharmacokinetic, effectiveness and safety prespective the following dosing recommendations are being made by this reviewer:

Epilepsy: There does not seem to be adequate information in adolescents, pregabalin should therefore be approved only for adults at this time.

Titration Scheme for both indications: The appropriateness of the titration scheme will be assessed by the Medical Officers based on the Clinical Trials.

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

Yes, for further details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.

What are the general ADME (absorption, distribution, metabolism and elimination) characteristics of pregabalin?

This has been reviewed by Dr. Lee. For details please refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.

The key points of the ADME characteristics of pregabalin are summarized below as taken from Dr. Lee's review:

Absorption:

- 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.
- 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.

Distribution:

- *In vitro* studies indicate that pregabalin is not bound to plasma proteins.

- The apparent volume of distribution was estimated to be ~0.54 L/kg.

Metabolism:

- Pregabalin undergoes negligible metabolism in humans.
- The major metabolite found in the urine was the N-methylated derivative of pregabalin, which accounted for —— of the administered dose.

Elimination:

- Pregabalin is eliminated from the systemic circulation predominantly through renal excretion of the unchanged drug. Based on a radiolabeled mass balance study, mean (%CV) cumulative recovery of total radioactivity was 92±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 drug.

What are the basic pharmacokinetic parameters of pregabalin after single and multiple doses?

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.
Mean pharmacokinetic parameters after single and multiple doses are given in the following Table:

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)	

Do the pharmacokinetic parameters change with time following chronic dosing?

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

- 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.

How do the pharmacokinetics of the drug in healthy volunteers compare to that in patients (—— and Epilepsy patients)?

The pharmacokinetics of pregabalin are similar in patients with epilepsy —— as compared to the healthy volunteers, as seen in the figure below. Population analysis was conducted in the combined population of all patients for which an indication is proposed, including healthy volunteers and patients with renal impairment.

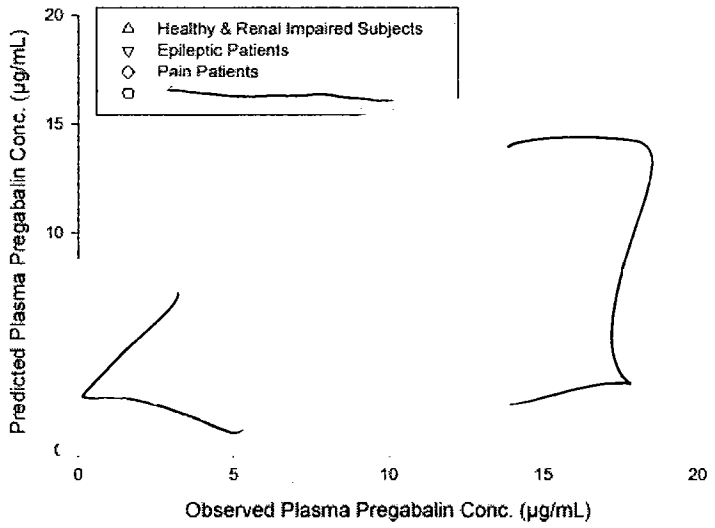


Figure: Individual Predicted Versus Observed Plasma Pregabalin Concentrations In Healthy Volunteers, Patients With Impaired Renal Function, Patients With Chronic Pain, Patients With Partial Seizures, And Patients With ——

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

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

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

2.3 INTRINSIC FACTORS

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

2.3.1 Effect of Renal Impairment:

The effect of renal impairment on the pharmacokinetics of pregabalin has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

- Pregabalin CL/F increases with the increase in CrCl. In the population analysis, the relationship was expressed as CL/F=0.0459xCrCL which plateaus at CrCL of 105 mL/min.
- Dosage adjustment is considered necessary only for patients with CLcr ≤60 mL/min. Most clinical trials have enrolled patients with CLcr > 60 mL/min without dosage adjustment.

Dr. Lee has conducted simulations to validate sponsor's proposal for dosage adjustment and the sponsor's proposal for dosage adjustments appears acceptable solely from the pharmacokinetic perspective.
The sponsor's proposal for dosage adjustment in the renally impaired subjects is given in the following Table:

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)	
≥60			
30-60			
15-30			
<15			
Supplementary dosage following hemodialysis (mg)			

Supplementary dosage immediately following a 4-hr hemodialysis is specified as follows:

The sponsor has chosen not to dose adjust in patients with CrCL ≥60 ml/min, although healthy subjects (requiring no dose adjustment) are considered to be subjects with CrCL ≥80 ml/min. The breakdown for the various degrees of renal impairment proposed by the sponsor seems acceptable as the pharmacokinetic data truly reflected the proposed breakdown. In clinical trials subjects with CrCL ≥60 ml/min were enrolled without dosage adjustments. In the Epilepsy and GAD trials the lowest CrCL of the enrolled patients was about 39 ml/min.

2.3.2 Effect of Hepatic Impairment:

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.

2.3.3 Effect of age:

Elderly:

The sponsor has evaluated subjects up to the age of 75 years in the epilepsy studies and 78 years in the GAD studies. No age related differences were observed in either exposure or exposure-response relationships. A population analysis, after correction for CrCl showed that there were no age related differences in the pregabalin clearance.

Pediatrics:

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2.3.4 Effect of Gender:

In a population analysis with pooled data from all four indications, including healthy volunteers and patients with renal impairment, the Vd/F was approximately 16% higher in males. This could be attributed to differences in percent body fat between males and females. This difference is not likely to be clinically significant and no dosage adjustments are necessary.

There were no gender related differences in CL/F after correction for CrCL.

Exposure-response analyses in epilepsy patients showed that the males had 22% lower response than the females. These differences are not likely to be clinically significant.

2.3.5 Effect of Race:

In a population analysis with pooled data from all four indications, including healthy volunteers and patients with renal impairment there were no race related differences. The races evaluated in adequate numbers were White (N=2001), Black (N=109) and Hispanics (N=132). Other races with subjects less than 20 were Asians, American Indians and others.

2.3.6 . Effect of pregnancy or lactation:

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.

2.3 EXTRINSIC FACTORS

What extrinsic factors (such as herbal products, diet, smoking and alcohol) influence exposure and or response and what is the impact of any differences in exposure on pharmacodynamics?

The effect of extrinsic factors like herbal products and smoking has not been studied. Pregabalin is not metabolized by any of the CYP enzymes. Multiple dose administration of pregabalin (300 mg BID) did not effect the rate and extent of ethanol after a single dose of ethanol. Similarly ethanol did not affect the pharmacokinetics of pregabalin. (For details please refer to the review of N21-446 by Dr. Sue Chih Lee).

Are there any in-vivo drug-drug interaction studies that indicate the exposure alone and/or exposure response relationships are different when drugs are coadministered? If yes, is there a need for dosage adjustment?

Only the concomitant antiepileptic drugs (AED) and lorazepam (for the treatment of GAD) were evaluated by this reviewer. The sponsor has conducted other drug interaction studies with oral contraceptives, gabapentin, oxycodone and ethanol, which were reviewed by Dr. Sue Chih Lee and are not repeated here. Please refer to her review of N 21-446.

There are no AEDs that showed exposure to be different when the AED and pregabalin are coadministered. Dosage adjustment is not needed in any of these cases.

Pharamcokinetic Interactions:
Influence of pregabalin on the pharmacokinetics of concomitant drugs and the influence of these drugs on the pharmacokinetics of pregabalin is summarized in the following Table:

Concomitant Medication	Pregabalin doses evaluated	Pregabalin on Co-Med PK	Co-Med on Pregabalin PK	Evaluation Method	Dosage Adjustment
Sodium Valproate	200 mg q8 for 7 days	No effect on SS trough vaproic acid plasma concentrations	No effect on pregabalin plasma concentrations	Traditional PK and POP PK	none
Carbamazepine	200 mg q8 for 7 days	No effect on SS plasma trough concentrations of carbamazepine and carbamezepine 10,11, epoxide	No effect on pregabalin plasma concentrations	Traditional PK and POP PK	none
Lamotrigine	200 mg q8 for 7 days	No effect on SS plasma trough concentrations of lamotrigine	No effect on pregabalin plasma concentrations	Traditional PK and POP PK	none
Phenytoin	200 mg q8 for 7 days	No effect on SS plasma trough concentrations of phenytoin	No effect on pregabalin plasma concentrations	Traditional PK and POP PK	none
Phenobarbital	150-600 mg/day	No effect on SS PK of phenobarbital	No effect on pregabalin plasma concentrations	POP PK only	none
Topiramate	150-600 mg/day	No effect on SS PK of Topiramate	No effect on pregabalin plasma concentrations	POP PK only	none
Tiagabine	150-600 mg/day	A 34% increase in SS plasma concentrations of tiagabine was observed in a population analysis, however, no mechanistic basis of interaction is known (pregabalin does not affect CYP P450-based	No effect on pregabalin plasma concentrations	POP PK only	none

		metabolism and tiagabine is metabolized by CYP P450 system). Therefore such an interaction seems unlikely.			
Lorazepam	300 mg q12 for 3 doses, 3rd dose given with 1 mg lorazepam or placebo	No effect on lorazepam	No effect on pregabalin plasma concentrations	Traditional PK only	none

Pharmacodynamic interactions:

Lorazepam:

- When pregabalin and lorazepam were coadministered, the deficits in performance quality on cognitive and motor tests became even more extensive and of longer duration. For some response variables and at certain times, the deficits stemming from the combination dosing treatment were not merely additive but suggestive of a synergistic interaction. These interactions were most apparent among the reaction times, speed of performing tasks, and postural stability response variables.

- Pregabalin potentiates lorazepam-related impairment of cognitive and gross motor function. These results suggest that patients should exercise caution when concurrently taking pregabalin and benzodiazepines, either alone or in combination, especially when performing tasks dependent on attention, concentration, reaction time, and postural stability.

Is there an in vitro basis to suspect drug-drug interaction?

This has been reviewedby Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

There does not seem to be an in vitro basis for drug-drug interactions.

- Mass Balance studies in healthy volunteers suggest that less than 2% of pregabalin is metabolized.
- In an in vitro study with human liver microsomes, no metabolites were formed for up to 180 minutes of incubation.
- Pregabalin is not bound to plasma proteins.

Is pregabalin a substrate, inhibitor or inducer of CYP enzymes?

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

- In an in vitro study with human liver microsomes, no metabolites were formed for up to 180 minutes of incubation.
- Pregabalin does not inhibit any of the major CYP enzymes.
- 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). In vivo studies suggest no effect on oral contraceptive. This may suggest no induction of CYP 3A.

Is pregabalin a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

- Pregabalin does not appear to be a P-gp substrate in vitro.
- P-gp inhibition by pregabalin was not studied by the sponsor.
- Pregabalin appears to be a substrate for the system L amino acid (carrier-mediated) transporter.

2.5 GENERAL BIOPHARMACEUTICS

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

This has been reviewed Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.

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

Is the proposed to-be-marketed formulation of pregabalin bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The proposed to-be-marketed formulations are the same as the clinical trial formulations

except for minor changes such as capsule size and color. Since pregabalin capsules are BCS Class 1 drug with acceptable dissolution data on the clinical trial batches, waiver for a bioequivalence study was granted. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.

What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of pregabalin in relation to meals or meal types?

This has been reviewed by Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04. The following key points are taken from her review.

- 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.
- In clinical trials, pregabalin capsules were administered without regard to meal time. As such, no restrictions related to meal will be indicated in the label.

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

This has been reviewed Dr. Lee. For details refer to the review of N21-446 by Dr. Sue Chih Lee dated 3/22/04.

The following method has been found acceptable:

Dissolution medium: ———
Method: Apparatus ———
Specification: NLT —— (Q) of the label claim dissolved in —minutes

2.6 ANALYTICAL

What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

HPLC-UV methodology was used to assess the pregabalin concentrations in the plasma and the urine, with limit of detection being ——µg/ml and — µg/ml respectively. The assay performance were acceptable for the epilepsy ——— studies. For further details please refer to Dr. Lee's review of N21-446 dated 3/22/04.

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4.0 APPENDIX

4.1 APPENDIX I

INDIVIDUAL STUDY REVIEW

Study: 74400481: ***A Multiple-Dose Drug Interaction Study of Pregabalin (CI-1008) in Patients With Epilepsy Maintained on Sodium Valproate, Protocols 1008-018-0 and 1008-126-0***

Rationale:

In patients with epilepsy, pregabalin will probably be administered with other antiepileptic agents such as sodium valproate. Since valproate is a commonly used antiepileptic drug with a high potential for interaction with other drugs, these studies were conducted to investigate its potential interaction with pregabalin. Protocols 1008-18 and 1008-126 were identical and were conducted at 2 different sites. Data from these studies were combined.

Objectives:

- To determine the effect of pregabalin on trough valproate plasma concentrations
- To determine the effect of chronic sodium valproate therapy on multiple-dose pharmacokinetics of pregabalin

A brief overview of some essential components of the study design is given below:

Study Design	Open-label, multiple-dose Data from 2 identical studies were combined.
Study Population	N=16 enrolled, 12 completed patients with epilepsy maintained on sodium valproate monotherapy (for 2 studies combined, N=7 and 5) 4 withdrew due to adverse events Age: 18-58 years (mean 37 years) Gender: 7 males and 5 females Weight: 51.9-87.9 kg (mean 73.5 kg) Race: whites
Treatment Group	Single group
Dosage and Administration	Patients maintained on individualized sodium valproate therapy for 4 weeks or more received 200-mg pregabalin doses (2 × 100-mg capsules) q8h for 7 days (Days 1-7) followed by a single AM dose on Day 8. Each trough plasma concentration of valproate prior to initiation of pregabalin therapy was to be within the therapeutic range of 50 to 100 µg/mL. Two trough valproate concentrations determinations were made approximately 1 week apart during the 14 days prior to the first dose of pregabalin. The second valproate determination was to be within 20% of the first determination. Patients were not receiving other anticonvulsant medication. Lot no CF0010198 (pregabalin) Diet: Patients were required to fast for 8 hours before each morning pregabalin dose and/or clinical laboratory assessment. Each dose was

	administered with 250 mL of water. On Day 8, patients remained fasting until after the 4-hour blood collection.
Sampling: Blood	For Pregabalin: Day 8: At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after the pregabalin dose on Day 8. Trough Concentrations: before the AM dose on Days 1, 2, 3, 4, 6, and 7 for pregabalin trough determinations. For Valproic Acid: Trough Concentrations: before the AM dose of sodium valproate on Days 1, 2, 3, 4, 6, 7, 8, 9, and 10.
Urine	none
Feces	none
Analysis	Method Pregabalin: HPLC Valproic acid: Lower Limits of Quantitation Plasma Pregabalin µg/mL Valproic Acid µg/mL Pregabalin: Linear range : µg/mL Accuracy (%Relative Error for Quality Controls) 1008-018: % 1008-126: % Precision (%CV for Quality Controls) 1008-018: % 1008-126: % Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and Analysis of a Sample: 8 Mo. Long-term Stability Under Storage Conditions: 480 Days Valproic acid: Linear range: µg/mL Accuracy (%Relative Error for Quality Controls) 1008-018: % 1008-126: % Precision (%CV for Quality Controls) 1008-018: = 1008-126: = % Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C
PK Assessment	AUC0-8, Cmax, Tmax, T1/2, Cmin, CL/F
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

Valproic Acid:

Premorning dose valproic acid plasma concentrations prior to, during, and after q8h dosing with 200 mg pregabalin are summarized in the following Table and shown in the following Figure:

Figure: Mean Premorning Dose Valproic Acid Concentrations Prior to, During, and After q8h Dosing With 2 × 100-mg Pregabalin Capsules:Protocols 1008-18 and -126

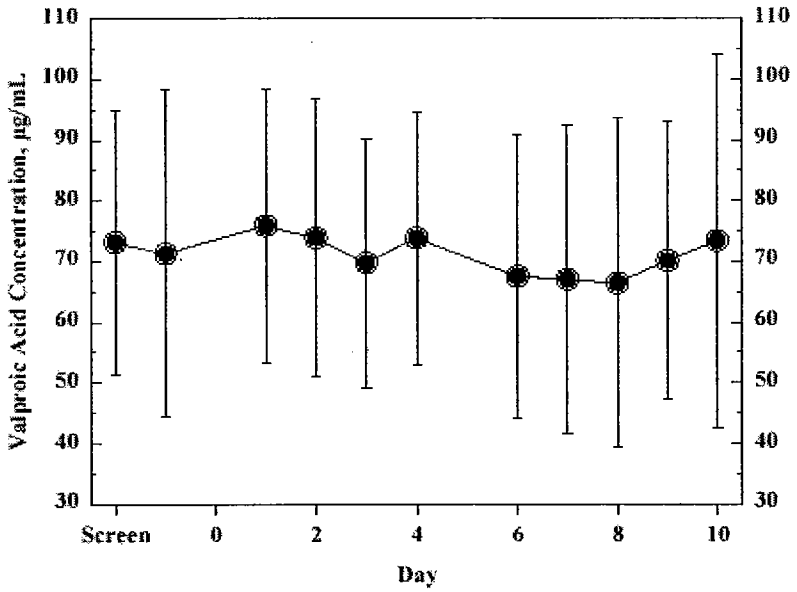


Table: Summary of premorning dose valproic acid concentrations

Least-Squares Mean Predose Concentrations, µg/mL			
Prior To Pregabalin	During Pregabalin		After Pregabalin
70.1	66.4		62.6
Comparisons Across the Collection Period:			
Reference	Test	Ratio	90% Confidence Interval
Prior to	During	94.7	83.4-108
Prior to	After	89.3	74.9-106
During	After	94.2	80.5-110

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of reference mean.
Prior to = Screening samples plus Day 1 predose.
During = Days 2, 3, 4, 6, 7, and 8.
After = Days 9 and 10.

Valproic acid concentrations were not substantially different across the 10-day sampling period. Concentrations during 200 mg q8h pregabalin dosing were similar to those prior to pregabalin dosing. Similarly, valproic acid plasma concentrations after the last pregabalin dose were similar to those prior to and during pregabalin dosing. Although the 90% CI for valproic acid concentrations after the last pregabalin dose when compared to that prior to dose was not within the limits. Differences in mean concentrations were <11%. Therefore, pregabalin did not significantly alter steady-state trough valproic acid concentrations.

Pregabalin:

This study in patients maintained on valproate therapy did not allow for a true comparison of pregabalin pharmacokinetic profiles in the same patients without valproate. However, profiles in patients receiving valproate were similar to those in healthy subjects receiving pregabalin alone in a previous study. Based on this comparison, valproate appeared to have no effect on pregabalin pharmacokinetics.

Table: Summary of Pregabalin Pharmacokinetic Parameter Values Following q8h Administration of 200 mg Pregabalin During Individualized Valproate Therapy (Protocols 1008-18 and -126) and Without Valproate Administration From a Historical Study

Parameter	Mean (%CV) Pregabalin Parameter Values		Ratio
	With Sodium Valproate (current study)	Without Sodium Valproate (historical data)	
n	12	11	
Cmax, µg/mL	9.80 (32.8)	8.52 (14.8)	115
tmax, hour	1.08 (67.7)	0.909 (22.2)	119
AUC(0-8), µg·hr/mL	48.1 (33.8)	41.7 (12.8)	115
t½, hour	6.21 (26.6)	6.27 (13.6)	99.0
Cmin, µg/mL	3.90 (31.6)	--	--

Adverse Events:
44 adverse events, 43 treatment related.
The most common events included:
somnolence reported in 8 subjects (50.0%),
asthenia occurring in 5 subjects (31.3%),
convulsion and vertigo reported in 3 subjects (18.8%),
and dizziness and headache reported in 2 subjects (12.5%).

Withdrawals due to adverse events:

Subject 001, a 31-year-old white man with a 16-year history of partial epilepsy (seizure frequency 3-4/year; last seizure 4 months previously), developed left-sided repetitive muscular contractions on Study Day 2 following 4 doses of pregabalin 200 mg. The episode quickly resolved following administration of diazepam 10 mg IV. The subject previously reported an episode of moderate somnolence on Day 1 and had a high level of anxiety. The patient was also receiving sodium valproate 1.5 g. A sodium valproate determination was slightly above the therapeutic range (107 µg/mL; normal therapeutic range = 50-100 µg/mL).

Subject 5, a 28-year-old white woman with an 18-year history of idiopathic generalized and partial epilepsy (last generalized seizure 4 years previously; seizure frequency 3-4 partial seizures/year; last partial seizure 3 months previously), developed a seizure on Study Day 1, 6 hours following the first 200-mg dose of pregabalin. The seizure resolved spontaneously within 20 minutes without intervention. The subject experienced a disturbance of sleep the night before dosing and reported an episode of mild somnolence approximately 2.5 hours postdose on Study Day 1. The patient was receiving sodium valproate 2 g and a hormonal contraceptive.

Subject 8, a 24-year-old white man with a 5-year history of idiopathic generalized epilepsy (seizure frequency 4/year; last seizure 4 months previously), developed a seizure on Study Day 1, approximately 6 hours following the second 200-mg dose of pregabalin. The seizure resolved spontaneously within 45 minutes without intervention. No subsequent pregabalin doses were administered. The subject was receiving sodium valproate 1 g. The seizure resolved spontaneously within 45 minutes without intervention.

Subject 108, a 27-year-old white woman with a 12-year history of idiopathic generalized epilepsy (seizure frequency 3-4/year; last seizure 4 months previously), developed a seizure on Study Day 2, approximately 6.5 hours following the third 200-mg dose of pregabalin. The seizure resolved spontaneously within 10 minutes without intervention. The subject also experienced headache, vertigo, and somnolence approximately 2 hours following the first pregabalin dose on Study Day 1 and lasting 12.5 hours. The subject was receiving sodium valproate 1 g and a hormonal contraceptive. A blood determination for sodium valproate at the time of the event was slightly under the therapeutic range (45 µg/mL, normal therapeutic range = 50-100 µg/mL).

Electrocardiogram:

There were no clinically relevant changes in QTc.

Regimen	Mean QTc Change[a,b,c] Day 8	Cmax[d]	tmax[e]	n
200 mg q8h	(-) 4.5 msec	9.80 µg/mL	1.08 hr	12[f]

[a] Mean QTc change from baseline (screening) following 7 days of multiple dosing (ECG's performed approximately 1-2 hours post dose)
[b] Individual subject QTc interval change from baseline ranged from -40 to +70 (Days 2 and 8) msec during multiple dosing
[c] No individual subject QTc interval exceeded 449 (Days 2 and 8) msec at any time point during multiple dosing
[d] Mean maximal plasma pregabalin concentration following 7 days of multiple dosing
[e] Mean time of maximal plasma pregabalin concentration following 7 days of multiple dosing
[f] Subjects 1, 5, 8, and 108 are excluded from this table as they withdrew prior to Day 8.

None of the events appeared to be the result of a pharmacokinetic interaction between pregabalin and sodium valproate. The temporal relationship of seizures to initiation of pregabalin therapy in these patients suggests the possibility that pregabalin may have exacerbated their underlying seizure disorder.

Conclusions:

- Pregabalin has no effect on steady-state valproic acid trough plasma concentrations.
- Valproate therapy has no apparent effect on pregabalin pharmacokinetics.

Study: 1008-019: ***A Multiple-Dose Drug Interaction Study of Pregabalin (CI-1008) in Patients with Epilepsy Maintained on Carbamazepine***

Rationale:

In patients with epilepsy, pregabalin may be administered with other antiepileptic agents such as carbamazepine. Since carbamazepine is a commonly used antiepileptic drug with a high potential for interaction with other drugs, this study was conducted to investigate its potential interaction with pregabalin.

Objectives:

- To determine the effect of pregabalin on trough carbamazepine and carbamazepine epoxide plasma concentrations
- To determine the effect of chronic sodium carbamazepine therapy on multiple-dose pharmacokinetics of pregabalin

A brief overview of some essential components of the study design is given below:

Study Design	Open-label, multiple-dose
Study Population	N=14 enrolled, 12 completed patients with epilepsy maintained on sodium carbamazepine monotherapy 2 withdrew due to adverse events Age: 22-62 years (mean 43 years) Gender: 8 males and 6 females Weight: 52.3-123 kg (mean 79.2 kg) Race: whites
Treatment Group	Single group
Dosage and Administration	Patients maintained on individualized carbamazepine therapy for 4 weeks or more received 200-mg pregabalin doses (2 × 100-mg capsules) q8h for 7 days (Days 1-7) followed by a single AM dose on Day 8. Each trough plasma concentration of carbamazepine prior to initiation of pregabalin therapy was to be within the therapeutic range of 3 to 8 µg/mL. Two trough carbamazepine and its epoxide concentrations determinations were made approximately 1 week apart during the 14 days prior to the first dose of pregabalin. The second carbamazepine determination was to be within 20% of the first determination. Patients were not receiving other anticonvulsant medication. Lot no CF0010198 (pregabalin) Diet: Patients were required to fast for 8 hours before each morning pregabalin dose and/or clinical laboratory assessment. Each dose was administered with 250 mL of water. On Day 8, patients remained fasting until after the 4-hour blood collection.
Sampling: Blood	For Pregabalin:

	Day 8: At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after the pregabalin dose on Day 8. Trough Concentrations: before the AM dose on Days 1, 2, 3, 4, 6, and 7 for pregabalin trough determinations. For Carbamazepine: Trough Concentrations: before the AM dose of carbazepine on Days 1, 2, 3, 4, 6, 7, 8, 9, and 10.
Urine	none
Feces	none
Analysis	Method Pregabalin: HPLC-[redacted] Carbamazepine: HPLC [redacted] Lower Limits of Quantitation Plasma Pregabalin 0.05 µg/mL Carbamazepine 0.1µg/mL Carbamazepine 10, 11-epoxide 0.01 µg/mL Pregabalin: Linear range : [redacted] µg/mL Accuracy (%Relative Error for Quality Controls, [redacted] µg/mL) [redacted] Precision (%CV for Quality Controls) [redacted] Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and Analysis of a Sample: 11 Mo. Long-term Stability Under Storage Conditions: 480 Days Carbamazepine and carbamazepine 10, 11-epoxide: Linear range: Carbamazepine [redacted] µg/mL Carbamazepine 10, 11-epoxide [redacted] µg/mL Accuracy (%Relative Error for Quality Controls, [redacted] µg/mL for carbamazepine, [redacted] µg/mL for epoxide) Carbamazepine: [redacted] 10,11-Epoxide: [redacted] Precision (%CV for Quality Controls) Carbamazepine: [redacted]% 10,11-Epoxide: [redacted]% Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and analysis: 13 months
PK Assessment	AUC0-8, Cmax, Tmax, T1/2, Cmin, CL/F
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

Carbamazepine and Carbamazepine Epoxide

Premorning dose carbamazepine and carbamazepine epoxide plasma concentrations prior to, during, and after q8h dosing with 200 mg pregabalin are depicted in the following Figure and are summarized in the following Table.

Figure: Mean Premorning Dose Carbamazepine (Filled Circles) and Carbamazepine Epoxide (Open Circles) Concentrations Prior to (Screen), During, and After q8h Dosing With 2 × 100-mg Pregabalin Capsules

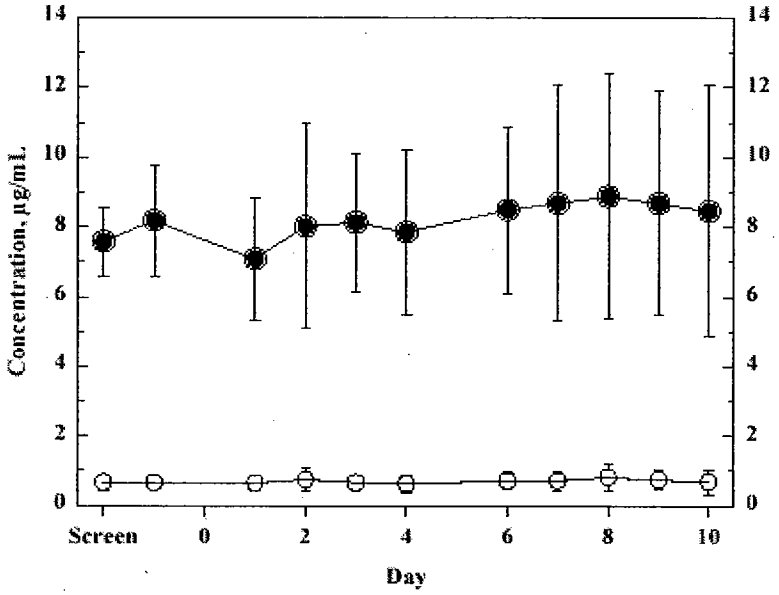


Table: Summary of Premorning Dose Carbamazepine and Carbamazepine Epoxide Plasma Concentrations

Carbamazepine	Least-Squares Mean Predose Concentrations (µg/mL):			
	Prior To Pregabalin		During Pregabalin	After Pregabalin
	7.82		8.06	7.99
	Comparisons Across the Collection Period:			
	Reference	Test	Ratio	90% Confidence Interval
	Prior to	During	103	96.8% to 110%
	Prior to	After	102	94.6% to 111%
	During	After	99.2	92.8% to 106%
Carbamazepine 10,11-Epoxide	Least-Squares Mean Predose Concentrations (µg/mL):			
	Prior To Pregabalin		During Pregabalin	After Pregabalin
	0.643		0.683	0.655
	Comparisons Across the Collection Period:			
	Reference	Test	Ratio	90% Confidence Interval
	Prior to	During	106	97.9% to 115%
	Prior to	After	102	92.0% to 113%
	During	After	95.9	87.8% to 105%

Ratio = Ratio of mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of mean values, expressed as a percentage of reference mean.

Carbamazepine as well as carbamazepine epoxide concentrations were not significantly different across the 10-day sampling period. Concentrations during 200-mg q8h pregabalin dosing were similar to those prior to pregabalin dosing. Similarly, carbamazepine as well as carbamazepine epoxide plasma concentrations after the last pregabalin dose were similar to those prior to and during pregabalin dosing. Differences in mean concentrations were less than 6% and the 90% confidence intervals were within the 80% to 125% range. Based on these results, pregabalin did not alter the extent of carbamazepine absorption or the metabolism of carbamazepine to carbamazepine epoxide.

Pregabalin

This study in patients maintained on carbamazepine therapy did not allow for a true comparison of pregabalin pharmacokinetic profiles in the same patients without carbamazepine. However, profiles in patients receiving carbamazepine were similar to those in healthy subjects receiving pregabalin alone in a previous study. Based on this comparison, carbamazepine appeared to have no effect on pregabalin pharmacokinetics. The pharmacokinetic parameters of pregabalin are summarized in the following Table:

Table: Summary of Pregabalin Pharmacokinetic Parameter Values Following q8h Administration of 200 mg Pregabalin During Individualized Carbamazepine Therapy (Protocol 1008-19) and Without Carbamazepine Administration From a Historical Study

Parameter	Mean (%CV) Pregabalin Parameter Values		Ratio
	With Carbamazepine (Current Study)	Without Carbamazepine (Historical Data)	
n	12	11	
Cmax, µg/mL	8.20 (50.7)	8.52 (14.8)	96.2
tmax, hr	1.45 (32.9)	0.909 (22.2)	1.60
AUC(0-8), µg·hr/mL	38.3 (29.0)	41.7 (12.8)	91.9
t½, hr	7.22 (45.0)	6.27 (13.6)	115
Cmin, µg/mL	3.21 (24.7)	--	--

Adverse Events:

71 adverse events, 70 were treatment emergent
Most common ones being:
Dizziness: 11 subjects (78.6%)
Nystagmus: 8 subjects (28.6%)
Asthenia, dry mouth, incoordination, and somnolence reported in 4 subjects (28.6%); and
Confusion, convulsion, and headache reported in 2 subjects (14.3%)

There were 4 serious adverse events, of these 2 subjects were withdrawn. One event of myocardial infarction was reported in subject 11.

Withdrawals due to adverse events:

Two subjects withdrew from this study due to serious adverse events.

Subject 6 was withdrawn from the study by the Investigator on Day 2, prior to her morning pregabalin dose following a third generalized seizure. The subject was treated with IV diazepam and subsequently made a full recovery. An EEG was conducted the day after her seizure activity and was found to be abnormal consistent with a focal-onset seizure disorder.

Subject 8 was withdrawn prior to her second dose of pregabalin on Day 1 because of facial twitching (which was felt to represent simple partial seizure activity) for which she was treated with rectal diazepam. Immediately following these events the subject experienced a right-sided complex partial seizure followed by a generalized tonic-clonic seizure. The subject remained post ictal for several hours but subsequently made a full recovery.

Electrocardiogram:

There were no clinically relevant changes in QTc intervals as a result of treatment with pregabalin in this study.

Regimen	Mean QTc Change[a,b,c] Day 8	Cmax[d]	tmax[e]	n
200 mg q8h	(-) 1.6 msec	8.20 µg/mL	1.42 hr	12[f]

[a] Mean QTc change from baseline following 7 days of multiple dosing (ECGs performed approximately 1 to 2 hr postdose)
[b] No individual subject QTc interval change from baseline exceeded +36 (Days 2 and 8) msec at any time point during multiple dosing.
[c] No individual subject QTc interval exceeded 454 (Days 2 and 8) msec at any time point during multiple dosing.
[d] Mean maximal plasma pregabalin concentration following 7 days of multiple dosing
[e] Mean time of maximal plasma pregabalin concentration following 7 days of multiple dosing
[f] Subjects 6 and 8 were excluded as they withdrew prior to Day 8.

Conclusions:

- Based on similar steady state carbamazepine and carbamazepine epoxide trough plasma concentrations in patients maintained on carbamazepine therapy prior to, during, and after 200 mg pregabalin q8h, pregabalin does not alter the extent of carbamazepine absorption or the metabolism of carbamazepine to carbamazepine epoxide.
- Carbamazepine therapy has no apparent effect on pregabalin steady-state pharmacokinetics.

Study: 10080-020: A Multiple-Dose Drug Interaction Study of Pregabalin (CI-1008) in Patients With Epilepsy Maintained on Lamotrigine

Rationale:

In patients with epilepsy, pregabalin may be administered with other antiepileptic agents such as lamotrigine. Since lamotrigine is a commonly used antiepileptic drug with a high potential for interaction with other drugs, this study was conducted to investigate its potential interaction with pregabalin.

Objectives:

- To determine the effect of pregabalin on trough lamotrigine plasma concentrations;
- To determine the effect of chronic lamotrigine therapy on multiple-dose pharmacokinetics of pregabalin

A brief overview of some essential components of the study design is given below:

Study Design	Open-label, multiple-dose
Study Population	N=12 enrolled, 12 completed patients with epilepsy maintained on lamotrigine monotherapy Age: 22-61 years (mean 41 years) Gender: 7 males and 5 females Weight: 56.5-114 kg (mean 79.1 kg) Race: 11 White, 1 Black
Treatment Group	Single group
Dosage and Administration	Patients maintained on individualized lamotrigine therapy received 200-mg pregabalin doses (2 × 100-mg capsules) q8h for 7 days (Days 1-7) followed by a single AM dose on Day 8. Lot no CF0010198 (pregabalin) Diet: Patients were required to fast for 8 hours before each morning pregabalin dose and/or clinical laboratory assessment. Each dose was administered with 250 mL of water. On Day 8, patients remained fasting until after the 4-hour blood collection.
Sampling: Blood	For Pregabalin: Day 8: At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after the pregabalin dose on Day 8. Trough Concentrations: before the AM dose on Days 1, 2, 3, 4, 6, and 7 for pregabalin trough determinations. For Lamotrigine: Trough Concentrations: before the AM dose of lamotrigine on Days 1, 2, 3, 4, 6, 7, 8, 9, and 10.
Urine	none

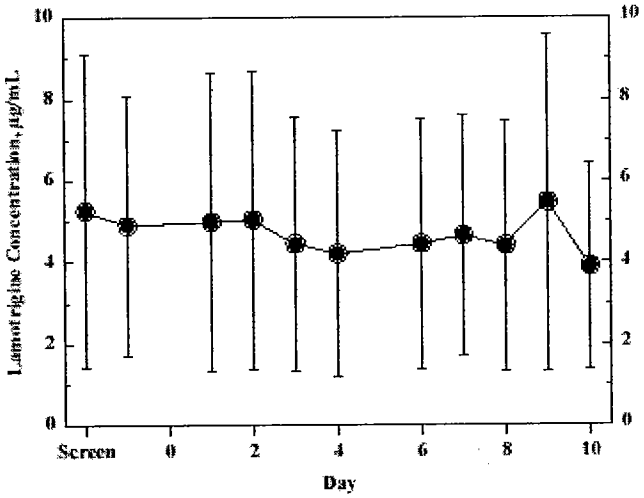
Feces	none
Analysis	Method Pregabalin: HPLC-[redacted] Lamotrigine: LC/MS/MS Lower Limits of Quantitation Plasma Pregabalin [redacted] µg/mL Lamotrigine [redacted] ng/mL Pregabalin: Linear range : [redacted] µg/mL Accuracy (%Relative Error for Quality Controls) : [redacted] % Precision (%CV for Quality Controls) = [redacted]% Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and Analysis of a Sample: 140 days. Long-term Stability Under Storage Conditions: 480 Days Lamotrigine: Linear range: [redacted] ng/mL Accuracy (%Relative Error for Quality Controls):- [redacted] % Precision (%CV for Quality Controls) = [redacted]% Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -22°C
PK Assessment	AUC0-8, Cmax, Tmax, T1/2, Cmin, CL/F
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

Lamotrigine

Premorning dose lamotrigine plasma concentrations prior to, during, and after q8h dosing with 200 mg pregabalin are depicted in the following Figure.

Figure: Mean Premorning Dose Lamotrigine Concentrations Prior to (Screen), During, and After q8h Dosing With 2 × 100-mg Pregabalin Capsules



The least square mean concentrations and the 90% confidence intervals are shown in the following Table:

Table:Summary of Premorning Dose Lamotrigine Plasma Concentrations

Least-Squares Mean Predose Concentrations (µg/mL):			
Prior To Pregabalin	During Pregabalin	After Pregabalin	
3.95	3.59	3.69	
Comparisons Across the Collection Period:			
Reference	Test	Ratio	90% Confidence Interval
Prior to	During	90.9	85.0 to 97.3
Prior to	After	93.2	85.5 to 102
During	After	102	94.9 to 111

Ratio = Ratio of mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of mean values, expressed as a percentage of reference mean.

Lamotrigine concentrations were not significantly different across the 10-day sampling period. Concentrations during 200-mg q8h pregabalin dosing were similar to those prior to pregabalin dosing. Similarly, lamotrigine plasma concentrations after the last pregabalin dose were similar to those prior to and during pregabalin dosing. Differences in mean concentrations were <10% and the 90% confidence intervals were within the 80% to 125% range. Therefore, pregabalin did not alter the extent of lamotrigne absorption.

Pregabalin

Pregabalin pharmacokinetic parameter values are summarized in the following Table:

Table: Summary of Pregabalin Pharmacokinetic Parameter Values Following q8h Administration of 200 mg Pregabalin During Individualized Lamotrigine Therapy and Without Lamotrigine Administration From a Historical Study

Parameter	Mean (%CV) Pregabalin Parameter Values		Ratio
	With Lamotrigine (Current Study)	Without Lamotrigine (Historical Data)	
n	12	11	
Cmax, µg/mL	8.99 (18.5)	8.52 (14.8)	106
tmax, hour	1.10 (23.3)	0.909 (22.2)	121
AUC(0-8), µg·hr/mL	46.9 (18.9)	41.7 (12.8)	112
t½, hour	7.81 (19.5)	6.27 (13.6)	125
Cmin, µg/mL	3.55 (19.5)	--	--

This study in patients maintained on lamotrigine therapy did not allow for a true comparison of pregabalin pharmacokinetic profiles in the same patients without lamotrigine. However, profiles in patients receiving lamotrigine were similar to those in healthy subjects receiving pregabalin alone in a previous study. Based on this comparison, lamotrigine appeared to have no effect on pregabalin pharmacokinetics.

Adverse Events:

Twelve subjects reported a total of 57 adverse events during this study; of those 56 were treatment emergent. The most common events included
dizziness and dry mouth reported in 7 subjects (58.3%),
asthenia and somnolence reported in 4 subjects (33.3%),
nausea reported in 3 subjects (25%),
and headache and incoordination reported in 2 subjects (16.7%).

There were no withdrawals from the study.

There were 2 serious adverse events reported in Subjects 4 and 11, both of which occurred after completion of pregabalin dosing. Subject 4 was hospitalized for postictal confusion on Day 10, after completing 7 days treatment with 200-mg q8h. Subject 11 experienced a tonic clonic seizure approximately 17 hours after receiving the last 200-mg dose of pregabalin. These were probably related to study medication.

Vital signs: No clinically relevant changes were observed.
ECGs: No clinically significant changes were observed.

Conclusions:

- Pregabalin has no effect on steady-state lamotrigine trough plasma concentrations.

- Lamotrigine therapy has no apparent effect on pregabalin pharmacokinetics.

Study: 10080-140: ***A Multiple-Dose Drug Interaction Study of Pregabalin (CI-1008) in Patients With Epilepsy Maintained on Phenytoin monotherapy***

Rationale:

Pregabalin will probably be administered to patients with epilepsy receiving other antiepileptic agents such as phenytoin. Since phenytoin is a commonly used antiepileptic drug with a high potential for interaction with other drugs, this study will investigate its potential interaction with pregabalin. However, interaction of pregabalin with phenytoin is not anticipated in humans, because pregabalin does not bind with plasma proteins, is not appreciably metabolized (>90% of dose renally excreted as unchanged drug), and does not inhibit hepatic metabolizing enzymes.

Objectives:

- To determine the effect of pregabalin on trough phenytoin plasma concentrations.
- To determine the effect of chronic phenytoin therapy on multiple-dose pharmacokinetics of pregabalin.

A brief overview of some essential components of the study design is given below:

Study Design	Open-label, multiple-dose
Study Population	N=11 enrolled, 10 completed patients with epilepsy maintained on phenytoin monotherapy Age: 18-65 years (mean 43 years) Gender: 10males and 1 females Weight: 66.8-135.9 kg (mean 90.8 kg) Race: 8 white, 3 Black
Treatment Group	Single group
Dosage and Administration	Potential patients will be screened 2 weeks before study initiation (Days -14 to -3). On 2 occasions during screening, blood samples will be withdrawn approximately 1 week apart before the 5 to 7 PM dose of phenytoin to determine trough plasma phenytoin concentrations. Patients maintained on individualized phenytoin therapy for 4 weeks received 200-mg pregabalin doses (2 × 100-mg capsules) q8h±1h for 7 days (Days 1-7) followed by a single AM dose on Day 8. Lot no CF0010198 (pregabalin) Diet: Patients were required to fast for 8 hours before each clinical laboratory assessment. Each pregabalin dose was administered with food (meal or snack) and 250 mL of water. For each self-administered generic phenytoin dose, patients who took doses with food before beginning the

	study were instructed to continue to take doses with food from Screening through Closeout. Conversely, patients who did not take generic phenytoin doses with food before beginning the study were instructed to continue not taking generic phenytoin doses with food (fasting 2 hours before and 2 hours after dosing) from Screening through Closeout. Dilantin® could be taken without regard to meals.
Sampling: Blood	For Pregabalin: Day 8: At 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, and 48 hours after the pregabalin dose on Day 8. Trough Concentrations: before the AM dose on Days 1, 2, 3, 4, 6, 7 and 8 for pregabalin trough determinations and to determine when and whether steady-state was achieved. For Phenytoin: Trough Concentrations: Predose PM plasma phenytoin concentrations from Days -14 to -8, -7 to -3, and Day 1 will be compared by inspection to predose PM phenytoin concentrations from Days 2, 3, 4, 6, 7, 8, 9, and 10 to determine whether pregabalin coadministration had any effect on phenytoin pharmacokinetics.
Urine	none
Feces	none
Analysis	Method Pregabalin: HPLC-[redacted] Phenytoin: LC/MS/MS Lower Limits of Quantitation Plasma Pregabalin [redacted] µg/mL Phenytoin [redacted] µg /mL Pregabalin: Linear range : [redacted] µg/mL Accuracy (%Relative Error for Quality Controls) :- [redacted] % Precision (%CV for Quality Controls) = [redacted] Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and Analysis of a Sample: 96 days. Long-term Stability Under Storage Conditions: 480 Days Phenytoin: Linear range: [redacted] µg /mL Accuracy (%Relative Error for Quality Controls): [redacted] % Precision (%CV for Quality Controls) = [redacted] Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -22°C Longest Interval Between Collection and Analysis of a Sample: 96 days. Long-term Stability Under Storage Conditions: 383 Days
PK Assessment	AUC0-8, Cmax, Tmax, T1/2, Cmin, CL/F

Safety Assessment	General adverse events, vital signs, ECG
PD Assessment	None

Pharmacokinetic Results:

Effect of Pregabalin on Total Phenytoin Trough Concentrations

AM predose total phenytoin plasma concentrations prior to, during, and after q8h dosing with 200 mg pregabalin are depicted in the following Figure and summarized in Table below.

Figure: Mean AM Predose Total Phenytoin Concentrations Prior to (Screen), During, and After q8h Dosing With 2 × 100-mg Pregabalin Capsules:

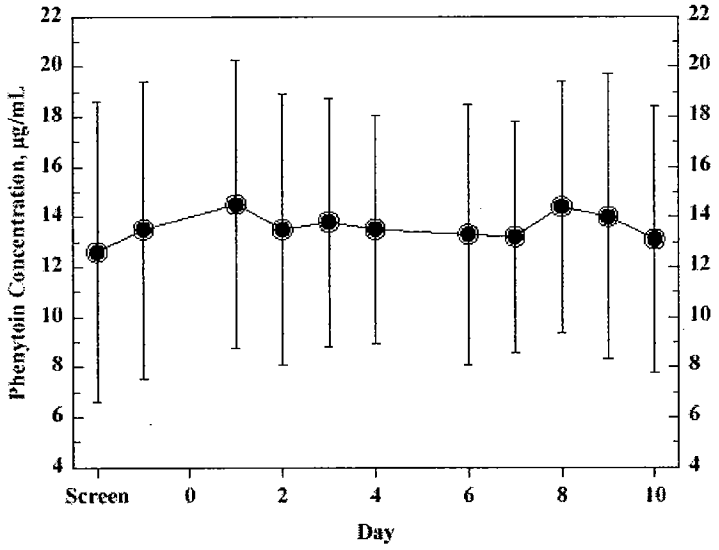


Table: Summary of AM Predose Total Phenytoin Concentrations

Least-Squares Mean Predose Concentrations (µg/mL)			
Prior To Pregabalin	During Pregabalin	After Pregabalin	
12.5	12.5	12.8	
Comparisons Across the Collection Period			
Reference	Test	Ratio	90% Confidence Interval
Prior to	During	100	94.1 to 106
Prior to	After	102	95.7 to 107
During	After	102	96.4 to 108

Ratio = Ratio of treatment mean values, expressed as a percentage (100% × test/reference).
90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of reference mean.
Prior to = Screening samples plus Day 1 predose.
During = Days 2, 3, 4, 6, 7, and 8.
After = Days 9 and 10.

Phenytoin concentrations were not significantly different across the sampling period. Concentrations observed during 200-mg q8h pregabalin dosing were similar to those prior to pregabalin dosing. Similarly, phenytoin plasma concentrations after the last pregabalin dose were similar to those observed prior to and during pregabalin dosing. Differences in mean concentrations were =2%. Therefore, pregabalin did not significantly alter steady-state trough phenytoin concentrations.

Pregabalin:

Pregabalin pharmacokinetic parameter values are summarized in the following Table:

Table: Summary of Pregabalin Pharmacokinetic Parameter Values Following q8h Administration of 200 mg Pregabalin During Individualized Phenytoin Therapy and Without Phenytoin Administration From a Historical Study

Parameter	Mean (%CV) Pregabalin Parameter Values		Ratio
	With Phenytoin (current study)	Without Phenytoin (historical data)[1]	
n	10	11	
Cmax, µg/mL	5.81 (14.0)	8.52 (14.8)	68.2
tmax, hour	2.65 (37.8)	0.909 (22.2)	292
AUC(0-8), µg·hr/mL	35.8 (18.6)	41.7 (12.8)	85.9
$t_{1/2}$, hour	6.79 (17.0)	6.27 (13.6)	108
Cmin, µg/mL	3.44 (23.6)	--	--

This study in patients maintained on phenytoin therapy did not allow for a true comparison of pregabalin pharmacokinetic profiles in the same patients without phenytoin. Based on tmax and Cmax values, the rate of pregabalin absorption (given in the fed state) in patients receiving phenytoin appeared to be slower than that in healthy subjects receiving pregabalin alone (fasted state) in a previous study. In this study subjects were asked to take their pregabalin doses with food (meal or snack). This was done intentionally so that adverse events with the coadministration of pregabalin and phenytoin could be reduced because of higher Cmax obtained under fasting conditions. Similarly according to the sponsor phenytoin exposure (AUC) may also be reduced by food intake if dosage form of the drug is generic, i.e. not Dilantin®. For each self-administered generic phenytoin dose, patients who took doses with food before beginning the study were instructed to continue to take doses with food from Screening through Closeout. Conversely, patients who did not take generic phenytoin doses with food before beginning the study were instructed to continue not taking generic phenytoin doses with food (fasting 2 hours before and 2 hours after dosing) from Screening through Closeout. Dilantin® could be taken without regard to meals. The timing of meal in relation to dosing for each subject was not provided, therefore the reviewer could not evaluate the number of subjects on generic phenytoin under fasted or fed conditions. In any case pregabalin was administered under fed conditions (meal or snack)

The change in tmax (1.7 hours) and Cmax (32% reduction) values observed in this study is consistent with what was observed in the pregabalin food effect studies (tmax was delayed 1-2.5 hours and Cmax was reduced 25-31%). Mean pregabalin AUC(0-8) value with phenytoin was approximately 14% lower relative to that without phenytoin. The

change in AUC(0-8) value (14% decrease) for this study was not considered clinically relevant and the change was similar to that observed in the two food effect studies. Based on these comparisons, the administration of pregabalin with food rather than phenytoin coadministration most likely contributed to the changes observed in pregabalin pharmacokinetics.

Adverse Events:

Eleven of 11 patients reported 55 adverse events during this study, all of which were considered treatment emergent. Of the 55 treatment emergent signs and symptoms (TESS), 48 were considered to be mild in intensity, 5 were considered moderate, and 2 were considered severe. Fifty-four of the 55 adverse events were considered to be associated with pregabalin treatment.

Nervous system adverse events were reported by 11 (100%) patients; somnolence (9 patients), dizziness (7 patients), and ataxia and nystagmus (3 patients each) were the most commonly reported.

Digestive system adverse events were reported by 4 (36.4%) patients; nausea (3 patients) and vomiting (2 patients) were the most commonly reported.

Special senses adverse events (amblyopia) were reported by 2 (18.2%) patients.

No clinically significant drug-related changes in blood pressure and heart rate were observed throughout the study. There were no clinically relevant changes in QTc intervals as a result of treatment with pregabalin in this study.

There were no withdrawals due to adverse events.

Conclusions:

- Pregabalin administration has no effect on steady-state phenytoin trough plasma Concentrations under fed conditions.
- Phenytoin therapy has no apparent effect on pregabalin pharmacokinetics. The changes seen were probably due to the effect of food on pregabalin pharmacokinetics. The reduction in Cmax (32%) and increase in Tmax (1.7 hours) was consistent with the food effect of pregabalin.
- Since, the intake of food in this trial was intentional to avoid adverse events of sufficient severity so as to impair physical and/or mental function when pregabalin is given in fasted conditions, the label should ideally specify that when coadministering phenytoin with pregabalin, pregabalin should be given with food (meal or snack). However, the clinical studies were done without regard to food. The population analysis conducted showed the phenytoin had no effect on pregabalin CL, therefore, it is adequate to state this in the label and have no restrictions on food intake for concomitant administration of phenytoin with pregabalin.

Study: 10080-076: ***Evaluation of the Potential Pharmacodynamic Interaction Between Pregabalin and Lorazepam Administered Orally to Healthy Volunteers***

Rationale:

Lorazepam is an intermediate acting benzodiazepine used in the treatment of anxiety and as medication prior to surgery. Benzodiazepines are considered CNS depressants, are known to produce dose-dependent impairments to a wide range of cognitive functions, and can impair respiration. Concurrent use of small or moderate amounts of benzodiazepines and therapeutic doses of anticonvulsants may increase drowsiness and reduce alertness. This may make the performance of everyday tasks more difficult and potentially hazardous. This study evaluated the potential pharmacodynamic interaction between lorazepam and pregabalin utilizing pharmacokinetics, psychometric measures, and respiratory parameters in healthy volunteers.

Objectives:

- To measure and compare psychometric and respiratory responses obtained before and after multiple oral doses of placebo or 300 mg pregabalin, given in combination with 1 mg oral lorazepam or placebo
- To evaluate the potential relationship between plasma drug concentrations and pharmacodynamic responses obtained during psychometric and respiratory evaluation (if appropriate)

A brief overview of some essential components of the study design is given below:

Study Design	partial double-blind, randomized, placebo controlled, 4-way crossover study
Study Population	N=12 healthy volunteers Age: 26-47 years (mean 35.3 years) Gender: 8 males and 4 females Weight: 50.5-86.4 kg (mean 66.4 kg) Race: White
Treatment Group	Single group
Dosage and Administration	Treatment 1: 300-mg pregabalin q12h for 3 doses -the third dose is given with 1-mg lorazepam tablet. Treatment 2: 300-mg pregabalin q12h for 3 doses -the third dose is given with placebo capsule. Treatment 3: Pregabalin placebo capsules q12h for 3 doses -the third dose is given with 1-mg lorazepam tablet. Treatment 4: Pregabalin placebo capsules q12h for 3 doses -the third dose is given with a placebo capsule. All doses were administered with 250 mL of water. Subjects were to swallow the capsules and tablets intact.

	Lot no CF0200498 (pregabalin) Diet: Subjects were required to fast (water permitted ad-lib) for 8 hours before each AM dose and/or clinical laboratory assessment and for 4 hours after the single AM dose given on Days 2, 9, 16, and 23. Alcohol was not allowed 48 hours before Day 1 and for the duration of the study. Smoking and caffeine containing beverages were not permitted from 48 hours before until last assessment 24 hours after administration of each dose.
Sampling: Blood	For Pregabalin and lorazepam: At 1, 2.5, 4, 6,9, 12, and 24 hours following the dose on Days 2, 9, 16, and 23.
Urine	none
Feces	none
Analysis	Method Pregabalin: HPLC-[redacted]) Lorazepam: LC/MS/MS Lower Limits of Quantitation Plasma Pregabalin [redacted] µg/mL Lamotrigine [redacted] ng/mL Pregabalin: Linear range : [redacted] µg/mL Accuracy (%Relative Error for Quality Controls) :- [redacted] % Precision (%CV for Quality Controls) = [redacted]% Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C Longest Interval Between Collection and Analysis of a Sample: 172 days. Long-term Stability Under Storage Conditions: 480 Days Lorazepam: Linear range: [redacted] ng/mL Accuracy (%Relative Error for Quality Controls):- [redacted]% Precision (%CV for Quality Controls) = [redacted]% Longest Interval Between Collection and Analysis of a Sample: 97 days. Long Term Stability: 92 days Condition of Samples on Receipt: Frozen, dry ice present Storage Conditions: -20°C
PK Assessment	AUC0-8, Cmax, Tmax, T1/2, Cmin, CL/F
Safety Assessment	General adverse events
PD Assessment	Psychometric testing: Cognitive and gross motor function were assessed using a selection of tasks from the Cognitive Drug Research (CDR) computerized assessment system: Word Recognition, Word Recall, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, VisualTracking,

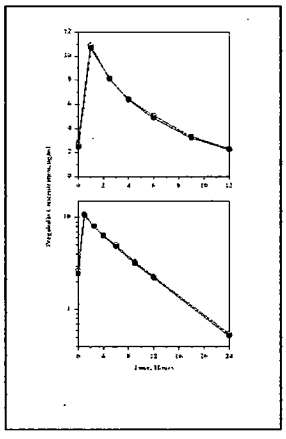
	Numeric Working Memory, Picture Recognition, Critical Flicker Fusion (CFF), computerized Bond-Lader Visual Analogue Scales, and Body Sway. Following training on the cognitive test procedures 4 times during Screening, the CDR assessments were completed at 1 hour before the first dose of each treatment, and at 1, 2.5, 4, 6, 9, 12, and 24 hours after the last dose of each treatment on Days 2, 9, 16, and 23. Tidal volume and respiratory rates: After sitting quietly for 5 minutes, spirometric measurements of tidal volume and respiratory rates were performed at Screening, predose on Days 1, 8, 15, and 22, predoseand at 1, 2.5, 4, 6, and 24 hours postdose on Days 2, 9, 16, and 23. The predose measurements on Days 1, 8, 15, and 22 were used as the baselines for the measurements on Days 2, 9, 16, and 23, respectively. For both tidal volume and respiratory rate, the change from baseline was determined at each time point.

Pharmacokinetics:

Pregabalin

Mean plasma pregabalin concentration-time profiles for each treatment (with and without lorazepam) are depicted in the following figure and the pharmacokinetic parameters with the ratios and CIs in the adjacent Table:

Figure: Mean Pregabalin Plasma Concentration-Time Profiles Following the Third Pregabalin Capsule Dose Administered Alone (Filled Symbols) and With 1-mg Lorazepam Tablets

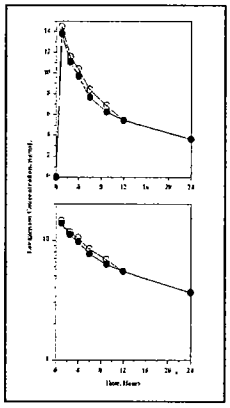


Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Pregabalin Alone (Reference)	With Lorazepam (Test)		
n	12	12		
Cmax, µg/mL	10.8	11.0	102	93.9 to 110
tmax, hr	1.00	1.25	125	Not Applicable
AUC(0-12), µg hr/mL	63.3	62.2	98.2	95.8 to 101
Cmin, µg/mL	2.41	2.29	95.2	90.5 to 100
t½, hr	5.59	5.52	98.8	Not Applicable

Lorazepam

Mean plasma lorazepam concentration-time profiles for each treatment (with and without pregabalin) are depicted in the following figure and the pharmacokinetic parameters with the ratios and CIs in the adjacent Table:

Figure: Mean Lorazepam Plasma Concentration-Time Profiles Following Administration of 1-mg Lorazepam Tablets alone (Filled Symbols) and With the Third 300-mg Pregabalin Capsule Dose (Open Symbols):



Parameter	Least-Squares Mean Values		Ratio	90% Confidence Interval
	Lorazepam Alone (Reference)	With Pregabalin (Test)		
N	12	12		
Cmax, ng/mL	13.8	14.6	106	91.8 to 122
tmax, hr	1.54	1.38	89.2	Not Applicable
AUC(0-tldc), ng hr/mL	133	149	112	99.7 to 125
AUC(0-∞), ng hr/mL	215	232	108	102 to 114
t½, hr	16.2	17.1	105	Not Applicable

Pharmacodynamic Evaluation:

Psychometric Evaluation

The following terms are used to evaluate performance outcome in the Numeric Working Memory, Delayed Word Recall, Immediate Word Recall, Digit Vigilance, Word Recognition, and Picture Recognition tasks:

Accuracy — Percent correct word recall or choice reaction
Speed —Time in milliseconds (msec) to recall words or to react to stimuli
Sensitivity —signal detection theory based index used for the working memory and recognition tasks to provide an overall measure of quality of recognition. Scores range from 0 (chance performance) to 1 (perfect recognition performance).

Pregabalin Administered Alone

In this study, pregabalin administered alone produced decrements in performance on the following tasks:

- Simple Reaction Time was prolonged by 16 to 34 msec at several time points between 2.5 and 24 hours following pregabalin administration.
- Choice Reaction Time was prolonged by 30 to 63 msec at several time points between 2.5 and 24 hours following pregabalin administration.
- Statistically significant decrements in performance were observed for these response variables at various times after pregabalin administration:
  - -Numeric Working Memory —Sensitivity
  - - Delayed Word Recall —Accuracy and Sensitivity

- Tracking
- Body Sway
- Self-Rated Alertness

In summary, pregabalin administered alone produced consistent decrements in performance of reaction times, Body Sway and Alertness, starting at 2.5 hours postdose. The remaining decrements in performance appear to be sporadic and transient.

Lorazepam Administered Alone

Lorazepam administered alone generally produced more extensive decrements in task performance than when pregabalin was administered alone. Exceptions include Simple Reaction Time, which was prolonged by 19 and 26 msec at 2.5 and 24 hours postdose, respectively, and Choice Reaction Time, prolonged by 34 and 39 msec at 1 and 2.5 hours postdose, respectively. In contrast to pregabalin, lorazepam significantly diminished Choice Reaction Time — Accuracy at Hours 1, 4, 6, 9, and 12. Statistically significant decrements in performance were observed for these response variables at various times postdose:

- Digit Vigilance — Accuracy
- Digit Vigilance — Speed
- Numeric Working Memory —Sensitivity
- Numeric Working Memory —Speed
- Delayed Word Recall —Sensitivity and Accuracy
- Immediate Word Recall —Accuracy
- Word Recognition —Speed
- Picture Recognition —Sensitivity
- Picture Recognition —Speed
- Tracking
- Body Sway

Pregabalin and Lorazepam Coadministration

When pregabalin and lorazepam were coadministered, the deficits were more extensive than those seen with pregabalin or lorazepam alone. For some response variables at certain times postdose, the combination of both compounds on task performance was not only worse than either pregabalin or lorazepam administered alone: the effect of the combination was more than additive. These findings suggest that for some response variables, there is a synergistic interaction between the effects of pregabalin and lorazepam.

- Simple Reaction Time was significantly prolonged at 1, 2.5, 4, 6, and 24 hours postdose. At 1 hour postdose, the combination of pregabalin and lorazepam significantly worsened reaction time compared to either lorazepam or pregabalin alone (42 msec for the combination, 17 msec for pregabalin, and 11 msec for lorazepam). The magnitude of the response (greater than the sum of the effects)

suggests a synergistic interaction.

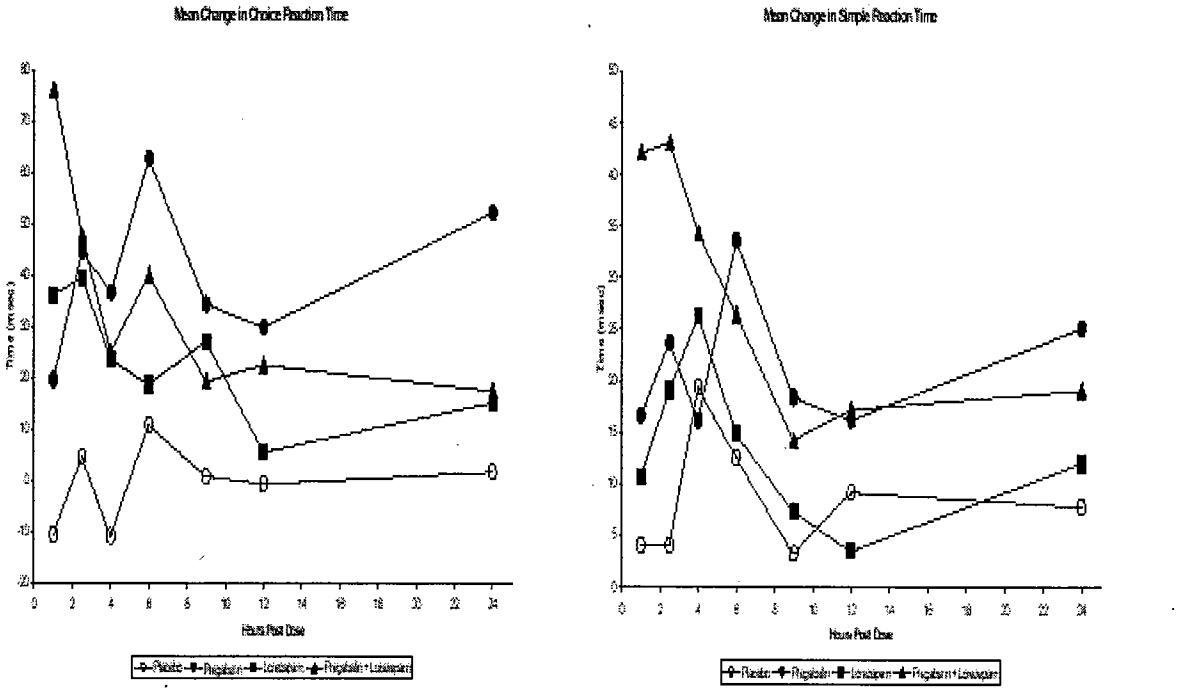
- Choice Reaction Time was significantly prolonged at 1, 2.5, and 6 hours postdose. At 1 hour postdose, the combination of pregabalin and lorazepam significantly worsened reaction time compared to either lorazepam or pregabalin administered alone (76 msec for the combination, 20 msec for pregabalin, and 34 msec for lorazepam). Again, this suggests a synergistic interaction.

- Choice Reaction Time — Accuracy: statistically significant deficits in reaction time accuracy occurred at 1, 2.5, 4, and 6 hours postdose. At 2.5 hours, the pregabalin with lorazepam combination significantly worsened reaction time compared to either lorazepam or pregabalin administered alone (-7.5 % change reaction time accuracy for pregabalin and lorazepam combined, -1.5% change in accuracy with pregabalin, and a - 1.7% change in accuracy with lorazepam).

- Body Sway (measured in units of 1/3° of angle arc) 1 to 6 hours: The combination of pregabalin and lorazepam produced significantly greater body sway than with pregabalin alone at 1, 2.5, and 6 hours postdose; significantly worse than lorazepam at 2.5 hours postdose. The magnitude of the effects of pregabalin and lorazepam combined suggests a synergistic interaction at 2.5 hours postdose (38.9 for the combination, 12.1 for pregabalin, and 13.1 for lorazepam); and at 6 hours postdose (25.8 for the combination, 3.4 for pregabalin, and 11.2 for lorazepam).

The following Figures illustrates the pattern of effects produced by the interaction of pregabalin and lorazepam on cognitive and motor functioning. The strongest effect (slowing) of the pregabalin + lorazepam interaction on Choice Reaction Time occurred at 1 hour postdose. The strongest effect on Simple Reaction time occurred between 1 and 4 hours postdose. A similar pattern was seen for each of the variables (Simple and Choice Reaction Time speed, Choice Reaction Time accuracy, and Body Sway) showing a decrement in performance resulting from the combination dose of pregabalin and lorazepam.

Figure: Mean Change From Baseline in Choice and Simple Reaction Times for Each Dosing Group for Each TimePoint Postdose



Statistically significant decrements in performance were also observed with the combination of pregabalin and lorazepam for the following response variables at various time points postdose when compared to pregabalin and/or lorazepam alone:

- Digit Vigilance: Accuracy
- Digit Vigilance: Speed
- Numeric Working Memory: Speed
- Immediate Word Recall: Accuracy
- Delayed Word Recall: Sensitivity and Accuracy
- Word Recognition: Speed
- Picture Recognition: Speed

The magnitude of the effects on these parameters were generally no more than additive, with the exception of speed of Word and Picture Recognition, which appeared to be synergistic and are presented in the following Tables.

Table: Word Recognition —Speed: Least-Squares Mean of the Change From Baseline Score (Msec)

Hours Postdose	CI-1008 + Lorazepam	CI-1008 + Placebo	Placebo + Lorazepam	Placebo + Placebo
1	156*	31	101*	25
2.5	87*	0	66*	36
4	91*	6	17	31
6	58*	-44	-6	18
9	72*	5	-12	-7
12	49	-13	-66*	-5
24	-17	-2	-10	4

*Indicates change from baseline was significant at $p < 0.05$.

Table: Picture Recognition —Speed: Least-Squares Mean of the Change From Baseline Score (Msec)

Hours Postdose	CI-1008 + Lorazepam	CI-1008 + Placebo	Placebo + Lorazepam	Placebo + Placebo
1	201*	26	154*	-3
2.5	143*	27	66*	-20
4	127*	30	42	-4
6	76*	-4	38	-19
9	78*	17	0	1
12	59*	7	2	1
24	36	9	1	4

*Indicates change from baseline was significant at $p<0.05$.

Respiratory Evaluations

The largest mean change from baseline in tidal volume occurred when CI-1008 is administered by itself, at 6 hours postdose. This extreme change can be attributed to Subject 7; this subject on this treatment had the largest baseline tidal volume (2790 mL) and the largest decrease from baseline (-1500 mL). All other mean changes in tidal volume and respiratory rate, while on active treatments, are similar in magnitude to those mean changes observed while on placebo. These descriptive statistics, and the results obtained from the analyses, suggest that no respiratory suppression occurs when pregabalin and lorazepam are administered, either alone or in combination, at the doses studied.

Table: Mean (%RSD) Change From Baseline in Tidal Volume (mL)

Hours Postdose	CI-1008 + Lorazepam[a]	CI-1008 + Placebo[a]	Placebo + Lorazepam[b]	Placebo + Placebo[a]
Baseline Values	**1379 (41.5%)**	**1333 (46.8%)**	**1333 (48.2%) (N = 12)**	**1379 (35.0%)**
0	20.0 (2441%)	-40.8 (-699%)	23.6 (1910%)	-86.7 (-640%)
1	-101.7 (-717%)	-47.5 (-991%)	-33.6 (-1901%)	149.2 (457%)
2.5	105.8 (783%)	24.2 (1523%)	118.2 (708%)	-73.3 (-658%)
4	75.0 (642%)	-135.8 (-204%)	-135.5 (-293%)	115.0 (456%)
6	-121.7 (-508%)	-210.0 (-279%)	61.0 (775%) (N = 10)	118.3 (484%)
24	172.5 (384%)	-84.2 (-490%)	123.6 (417%)	118.3 (503%)

Baseline statistics are boldfaced.
[a] N = 12.
[b] N = 11, except where noted.

Table: Mean (%RSD) Change From Baseline in Respiratory rate (min^{-1})

Hours Postdose	CI-1008 + Lorazepam[a]	CI-1008 + Placebo[a]	Placebo + Lorazepam[b]	Placebo + Placebo[a]
Baseline	**15.7 (18.7%)**	**16.1 (14.6%)**	**16.3 (23.1%) (N = 12)**	**13.9 (18.0%)**
0	0.750 (365%)	0.417 (789%)	0.818 (450%)	2.167 (94%)
1	0.583 (471%)	-0.667(-471%)	-0.364 (-1009%)	1.250 (160%)
2.5	0.000 (NA)	-0.583 (-493%)	-0.909 (-493%)	0.917 (177%)
4	-0.167 (-1466%)	0.000 (NA)	-0.091 (-4494%)	-0.083 (-4999%)
6	0.500 (422%)	1.750 (181%)	1.091 (356%)	2.833 (109%)
24	0.000 (NA)	-0.167 (-1275%)	0.182 (1870%)	2.750 (92%)

Baseline statistics are boldfaced.
[a] N = 12.
[b] N = 11, except where noted.

Adverse Events:

During treatment with pregabalin alone and in combination with lorazepam, subjects most commonly experienced adverse events related to the nervous system (58.3% in both treatments) and the special senses (25.0% and 16.7%).

The most frequently reported adverse events (2 subjects) during treatment with pregabalin alone were:
dizziness (3 subjects),
nervousness (2 subjects), and
amblyopia (2 subjects).

During concomitant treatment with lorazepam, the incidence of adverse events did not increase over the rate observed with pregabalin alone. The most frequently reported events during treatment with pregabalin and lorazepam were:
dizziness (4 subjects),
somnolence, nervousness, and amblyopia (3 subjects each), and
in-coordination (2 subjects).

During treatment with lorazepam alone, the most frequently reported events were: somnolence and depression (1 subject each).

The most frequently reported events during placebo treatment were somnolence and pharyngitis (2 subjects each).

No clinically important changes in vital signs were noted.

Conclusions:

- There was no PK interaction of pregabalin on lorazepam or lorazepam on pregabalin.
- At the doses studied, pregabalin and lorazepam administered alone or in combination did not result in respiratory suppression.
- Pregabalin administered alone produced consistent decrements in performance on the

following cognitive and motor function tests: Simple and Choice Reaction Times, Body Sway and Alertness. The decrease in performance began at 2.5 hours postdose.

- Lorazepam 1 mg showed a pattern of deficits consistent with previous work with the compound. Disruptions were seen to Choice Reaction Time, Numeric Working Memory Speed, Word Recognition Sensitivity, Picture Recognition Speed and Postural Stability.
- When pregabalin and lorazepam were coadministered, the deficits in performance quality on cognitive and motor tests became even more extensive and of longer duration. For some response variables and at certain times, the deficits stemming from the combination dosing treatment were not merely additive but suggestive of a synergistic interaction. These interactions were most apparent among the reaction times, speed of performing tasks, and postural stability response variables.
- Overall, pregabalin potentiates lorazepam-related impairment of cognitive and gross motor function. These results suggest that patients should exercise caution when concurrently taking pregabalin and benzodiazepines, either alone or in combination, especially when performing tasks dependent on attention, concentration, reaction time, and postural stability.

Study 3729: Population Pharmacokinetics of Marketed Anti-Epileptic (AEDs) Drugs Coadministered With Pregabalin in Patients With Partial Seizures

Objective:

To determine the effect of pregabalin add-on therapy on the pharmacokinetics of marketed antiepileptic agents during Phase 3 trials in patients with partial seizures

Data from 3 clinical efficacy studies in patients with partial seizures were used in the population pharmacokinetic analyses.

Table 1. Study Design Summary

Protocol	Design	Duration	Population	Pregabalin Dose	Formulation	No. of AED Serum Samples Collected/Patient
1008-009	Double-blind, parallel, placebo-controlled, randomized	8-week baseline and 12 week double-blind treatment	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	600 (300 mg BID and 200 mg TID) mg/day	25- and 100-mg pregabalin capsules and matching placebo	7
1008-011	Double-blind, parallel, placebo-controlled, randomized	8-week baseline and 12 week double-blind treatment	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	150 (50 mg TID) or 600 (200 mg TID) mg/day	25- and 100-mg pregabalin capsules and matching placebo	7
1008-034	Double-blind, parallel, placebo-controlled, randomized	8-week baseline and 12-week double-blind treatment	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	50 (25 mg BID), 150 (75 mg BID), 300 (150 mg BID), and 600 (300 mg BID) mg/day	25- and 100-mg pregabalin capsules and matching placebo	2

AED Dataset Requirements:

Forty patients, maintained on a given AED and receiving either placebo or pregabalin, was selected as the minimum number of subjects required in order for that AED to be included in this analysis. Seven AEDs met this requirement: carbamazepine, lamotrigine, phenobarbital, phenytoin, tiagabine, topiramate, and valproate.

In all 3 studies, blood samples for the quantitation of AEDs were collected randomly with respect to time postdose. One dataset was created for each AED being investigated by nonlinear mixed effects modeling (NONMEM). Each dataset included study number, subject identification, demographics, AED daily dose, time of last AED dose, AED

plasma concentration, time of sample collection (hours postdose), study phase (baseline/double blind), study day associated with each AED sample collection, study month associated with each AED sample collection, pregabalin daily dose, and pregabalin dosing regimen. Study month was calculated from the study day assuming a 28-day month. For example, Study Days -28 to -1 (last 28 days in baseline prior to initiation of the double-blind phase) comprised Study Month -1 and Study Days 1 to 28 (first 28 days in the double-blind phase) comprised Study Month 1.

Plasma AED Sample Inclusion/Exclusion Criteria:

The following inclusion/exclusion criteria were used to determine which plasma samples were used in the pharmacokinetic analysis:

- Plasma samples from patients receiving placebo or pregabalin and collected during the baseline and double-blind treatment phases of the study were included;
- Plasma samples with AED concentrations below the limit of quantitation or with missing concentrations were excluded;
- Plasma samples having incomplete or inaccurate (eg, resulting in a negative value for the calculated hours postdose) sample collection/last dose information were excluded;
- Plasma samples obtained within 4, 28, 5, 16, 2, 5, and 4 days of a dose adjustment for carbamazepine, phenytoin, lamotrigine, phenobarbital, tiagabine, topiramate, and valproate, respectively, were excluded. The time interval between dose adjustment and sample collection was based on each AED's elimination t½ and the estimated time required for the patient to reach steady state.

Pharmacokinetic Model:

Plasma concentrations versus time data were modeled using a population analysis approach (NONMEM Version V) to estimate oral clearance of the seven AEDs and the effect of pregabalin coadministration on the oral clearance values.

Inspection of the individual concentration-time data for the different AEDs suggested that the time postdose for the sample collection was not needed for these analyses. This observation was consistent with the relatively long elimination t½ value for most of the AEDs, which suggests minimal fluctuation of the AED concentration within a dosing interval. This observation was confirmed when time postdose was added to the reference model [$\exp(-kel_{AED} \cdot time_{postdose})$] and resulted in no significant reduction in the minimum objective function.

The reference model employed was a simple relationship between daily AED dose ($DailyDose_{AED}$) and steady-state AED concentration (ConcAED) where the proportionality factor was the oral clearance of the AED (CL/F_{AED}).

$$Conc_{AED} = \frac{DailyDose_{AED}}{CL/F_{AED}}$$

Intersubject variability on the pharmacokinetic parameter, CL/F_{AED}, was modeled using

an exponential term as follows:

$$CL/F_{AED} = ?.e^{?}$$

where ? was the typical or central value of the pharmacokinetic parameter in this patient population, and ? was a random variable having a normal probability distribution with mean 0 and variance $?^2$. The 90% confidence intervals (CI) of the estimates of the pharmacokinetic parameters were calculated as ? ± 1.67·SE, where SE was the standard error obtained in NONMEM.

The estimate of intersubject variability (η) was provided as percent coefficient of

variation (%CV); %CV was calculated as $\sqrt{?^2} \bullet 100$

The 95% CI for intersubject variability was calculated as $\sqrt{?^2 \pm 2 \bullet SE} \bullet 100$

Residual variability was modeled as a combined additive/proportional error model as follows:

$Y = F + F \cdot e1 + e2$

Where,
Y was the observed AED concentration
F was the predicted AED concentration based on the pharmacokinetic model in a particular individual;
e 1 was the proportional error component of the residual variability
e 2 was the additive error component of the residual variability

To obtain estimates of weighted residuals, the error model was coded in NONMEM as:

$$Y = F + W \bullet \varepsilon 1; where W = \sqrt{(F^2 + \theta_{err}^2)}$$

where W was the weight and ? err was a proportionality constant between the coefficient of variation of the proportional error term and the standard deviation of the additive term.

The pharmacokinetic final model used to evaluate the effect of pregabalin on the CL/F of the seven different AEDs was expressed in the following equation. The categorical covariates TRT and FLGP were modelled as indicated below for the effect of treatment phase and pregabalin or placebo coadministration on typical values of CL/F:

$CL/F_{AED} = ?_{baseline} \cdot (FLGP \cdot [(1-TRT) + ?_{placebo} \cdot TRT] + (1-FLGP) \cdot [(1-TRT) + ?_{pregabalin} \cdot TRT]$

where TRT was an indicator variable;

TRT = 0 if the AED concentration was obtained during baseline phase (prior to pregabalin or placebo coadministration) and
TRT=1 during double-blind treatment phase (pregabalin or placebo coadministration).

FLGP was also an indicator variable;
FLGP = 0 if pregabalin was coadministered during the treatment phase and
FLGP =1 if placebo was coadministered during the treatment phase.

Thus, CL/F_{AED} represented the typical value of an AED CL/F during baseline (baseline) when TRT = 0 and FLGP = 0 or 1.

Likewise, CL/F_{AED} represented the typical value of AED CL/F during placebo add-on therapy when TRT = 1 and FLGP = 1 and during pregabalin add-on therapy when TRT = 1 and FLGP = 0.

The parameters, $?_{placebo}$ and $?_{pregabalin}$, corresponded to the fractional change in baseline CL/F_{AED} values resulting from placebo and pregabalin add-on therapy, respectively.

The effect of pregabalin on the pharmacokinetics of other AEDs was assessed by investigating placebo and pregabalin add-on therapy as covariates in the above Equation The change in the minimum objective function (MOF) was determined by comparing the MOF value of the final model to that obtained with the reference model below:

$$CL/F_{AED} = ?_{baseline} \cdot [(1-TRT) + ?_{db} \cdot TRT]$$

In the reference model, CL/F_{AED} represented the typical value of an AED CL/F during baseline (baseline) when TRT = 0 and during the double-blind phase (db) when TRT = 1.

The potential interaction of pregabalin with other AEDs was determined by the population estimate of $?_{pregabalin}$ representing the percent change in each AED CL/F with pregabalin add-on therapy along with its 90% confidence limits. A percent change of >20% and a confidence limit outside 80% to 125% was considered a signal for a potential drug interaction.

Results:

Dataset and Demographics:

Table 2. AED Dosing Information, AED Concentrations, and Time of Collection (Mean ± SD; Range)

AED	N conc[a]	Dose (mg)	Concentration (µg/mL)	Time Postdose (hr)
Carbamazepine	2565	1188 ± 420 (200-2600)	9.40 ± 2.71 (0.80-19.2)	5.4±6.9 (0-146)
Lamotrigine	1010	510 ± 253 (25-1500)	7.09 ± 4.77 (0.20-32.0)	5.7±8.7 (0-171)
Phenobarbital	245	115 ± 46.4 (60-330)	22.4 ± 9.88 (2.1-61.8)	8.9±6.0 (0-39)
Phenytoin	1272	385 ± 115 (50-800)	16.2 ± 7.35 (0.80-50.4)	6.8±8.9 (0-184)
Tiagabine	332	33 ± 17.9 (4-96)	93.5 ± 81.5 (8.50-536)	5.4±6.7 (0-103)

Topiramate	704	464 ± 273 (50-1600)	8.34 ± 6.01 (1.0-43.7)	6.5±6.9 (0-75)
Valproate	908	1994 ± 2044 (500-30000)	80.1 ± 31.9 (3.0-212)	5.3±6.6 (0-131)

a Number of samples drawn during baseline and double-blind treatment phases

AED	N[b]	Age (yr)	Weight (kg)	Height (cm)	CLcr (mL/min)
Carbamazepine	540	37.4 ± 11.2	77.3 ±20.0	168.0 ± 11.1[c]	111.8 ± 31.8[c]
Lamotrigine	198	37.9 ± 11.7	77.1 ± 18.5[d]	167.5 ± 10.5[e]	106.1 ± 31.1[d]
Phenobarbital	47	39.5 ± 10.8	74.3 ± 17.7	166.0 ± 11.3	105.3 ± 31.2
Phenytoin	267	40.6 ± 12.0	76.4 ± 18.0	169.2 ± 10.9[e]	107.7 ± 28.8
Tiagabine	69	38.2 ± 11.9	79.8 ± 22.3	169.4 ± 11.5	112.0 ± 36.0
Topiramate	142	37.7 ± 11.7	75.5 ± 20.6[d]	168.1 ± 9.37[d]	102.8 ± 29.4[d]
Valproate	189	36.1 ± 12.1	77.7 ± 19.4[d]	169.9 ± 11.5[e]	115.9 ± 32.8[d]

a Value of the variable at the time of screening
b Number of patients receiving AEDs
c N = N-2.
d N = N-1.
e N = N-3.

	AED							
Variables	CBZ	LMG	PB	PHY	TGB	TPM	VA	
Gender								
Male	266 (49)	96 (48)	19 (40)	151 (57)	35 (51)	73 (51)	106	(56)
Female	274 (51)	102 (52)	28 (60)	116 (43)	34 (49)	69 (49)	83	(44)
Race								
White	467(86)	170 (86)	34(72)	229(86)	59(86)	125(88)	153(81)	
Black	24(4)	13(7)	6(13)	16(6)	7(10)	5(4)	15(8)	
Hispanic	27(5)	8(4)	5(11)	15(6)	2(3)	7(5)	11(6)	
Asian or	11(2)	3(2)	1(2)	2(1)	1(1)	1(1)	4(2)	
Pacific								
Islander								
American	1(0)	2(1)	0(0)	1(0)	0(0)	1(1)	0(0)	
Indian or								
Alaskan								
Native								
Other	10(2)	2(1)	1(2)	4(1)	0(0)	3(2)	6(3)	

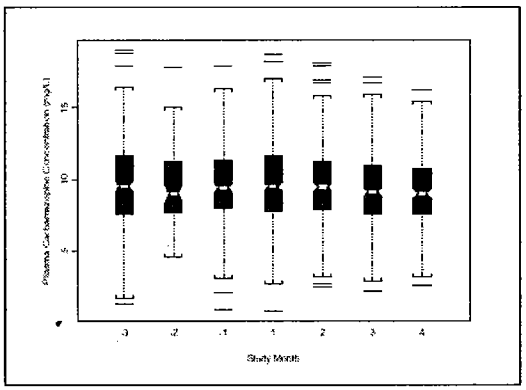
CBZ =Carbamazepine.
LMG =Lamotrigine.
PB =Phenobarbital.
PHY =Phenytoin.
TGB =Tiagabine.
TPM =Topiramate.
VA =Valproate.

Analyses:

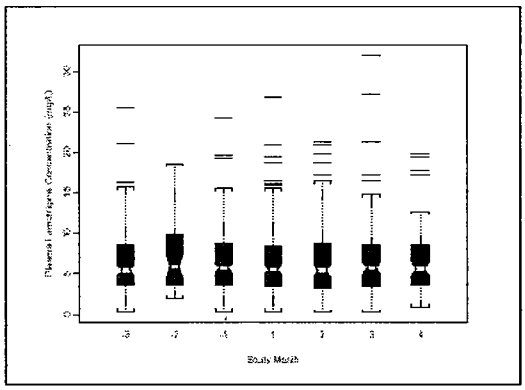
The following figures illustrate the distribution of AED steady-state concentrations by study month for patients maintained on each of the 7 AEDs and who received pregabalin during the double-blind phase of the study.

Negative study months indicate the baseline phase and positive study months indicate the double-blind phase of the study, where placebo or pregabalin was added on to the maintenance therapy. The median value is represented by the notch in the box and the upper and lower portions of the box signifies the spread of the middle 50% of the data.

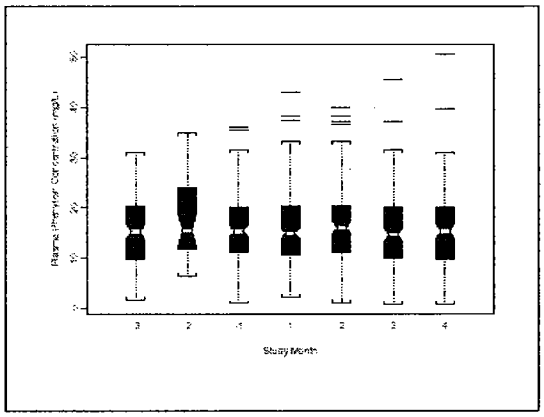
Carbamazepine



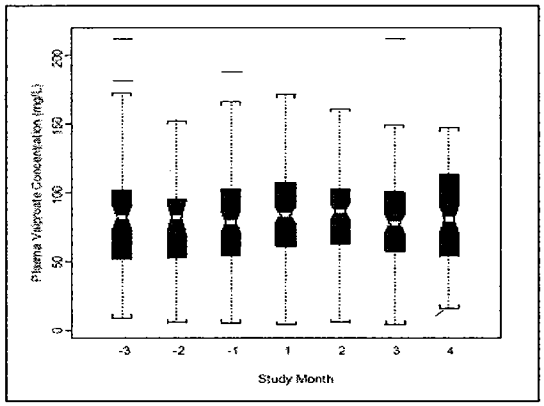
Lamotrigine



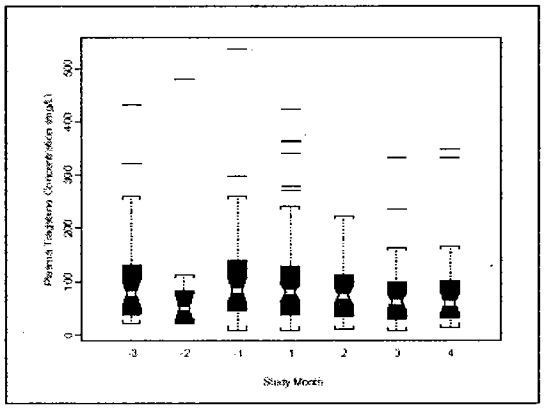
Phenytoin



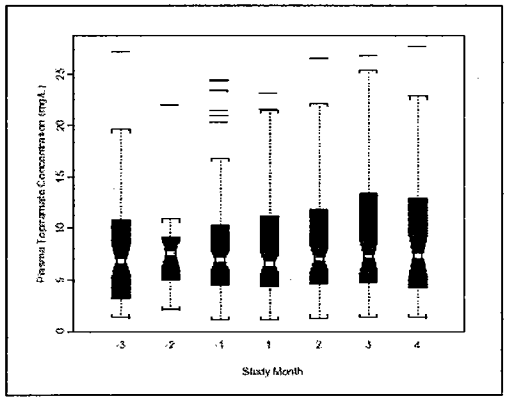
Valproate



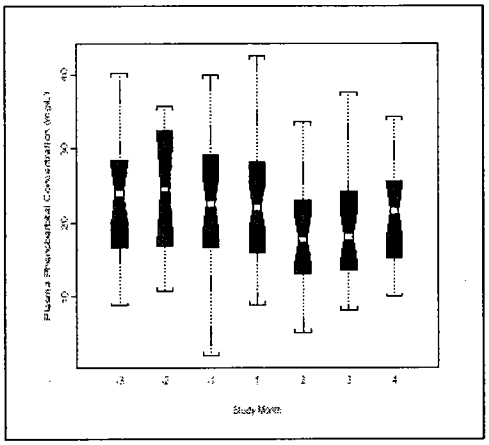
Tiagabine



Topiramate



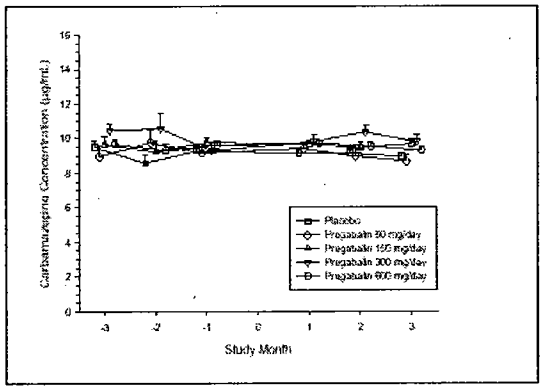
Phenobarbital



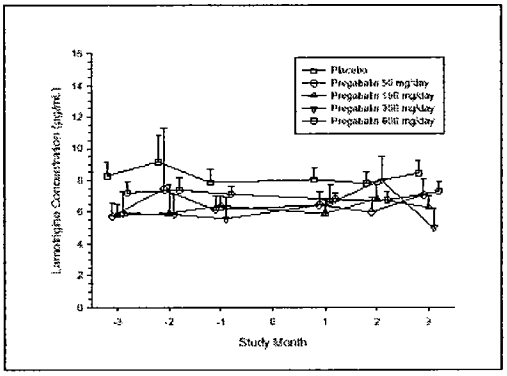
These figures suggest that the steady-state concentrations of the 7 AEDs were not affected by pregabalin coadministration.

This conclusion is consistent across different doses of pregabalin as shown in the figures below.

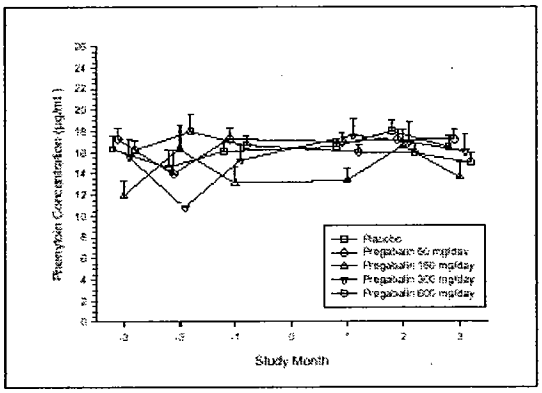
Carbamazepine



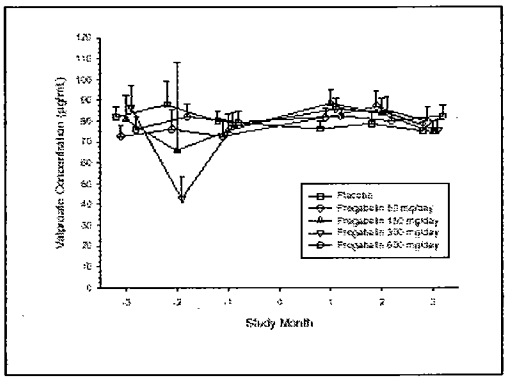
Lamotrigine



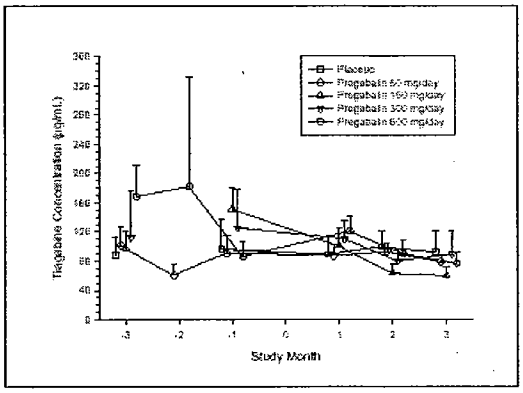
Phenytoin



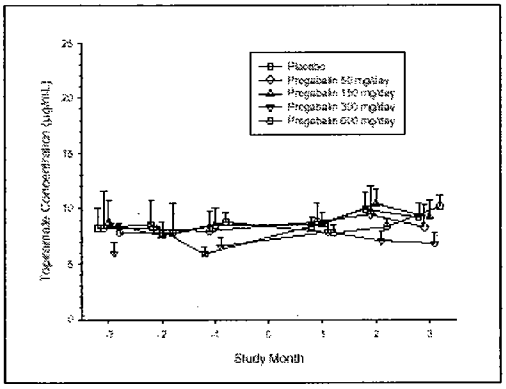
Valproate



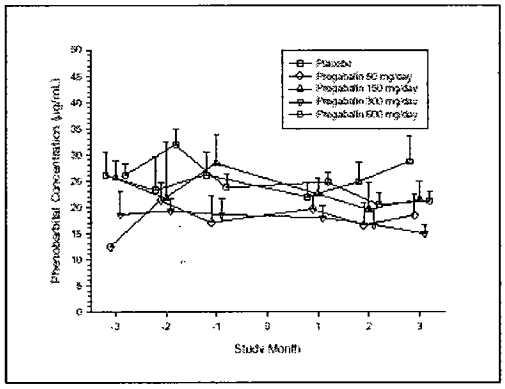
Tiagabine



Topiramate

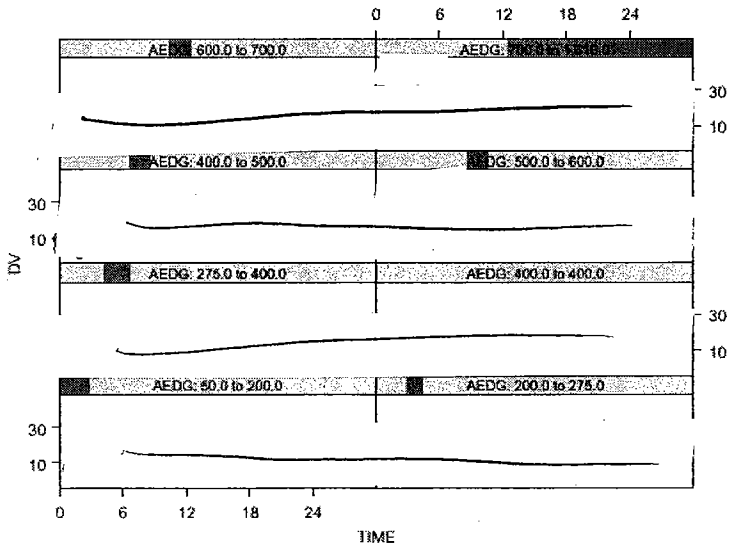


Phenobarbital



Similar figures were ploted to show that the AED dose did not make a difference on the AED plasma concentration-time profile in the presence of pregabalin. A representative figure for topiramate is given below:

Figure: Topiramate Concentration (DV, µg/mL) –Time (hr) Relationship by Daily Dose (AEDG mg/day) in Patients Receiving Topiramate



The influence of pregabalin and placebo add-on therapies was assessed as covariates and the percent change in each AED CL/F along with the 90% confidence limits were calculated as a measure of the possible drug-drug interaction. The first-order estimation method of NONMEM was used. The following Table summarizes the results of the population pharmacokinetic analyses conducted by the sponsor.

AED	ΔMOF[a]	Pregabalin Treatment				Placebo Treatment	
		N[b]	Ratio[c]	90% CI[d]	N[b]	Ratio[c]	90% CI[d]
Carbamazepine	-4.66	400	99.2	97.6—100.7	140	102.3	99.8—104.7
Lamotrigine	-1.54	146	102.0	99.2—104.9	52	98.9	94.5—103.3
Phenobarbital	-3.40	32	107.4	103.7—111.1	15	101.2	97.1—105.2
Phenytoin	-5.84	190	100.7	97.1 —104.3	77	94.6	89.7—99.6
Tiagabine	-0.61	58	134.9	112.1—157.7	11	120.3	63.3—177.3
Topiramate	-8.89	101	98.3	91.9—104.6	41	84.8	70.5—99.2
Valproate	-0.10	140	99.6	96.1—103.1	49	100.7	92.9—108.5

a Change in minimum objective function values, -2 times the log of the likelihood, between the reference and full model with 1 degree of freedom
b Number of subjects receiving specified treatment
c Ratio of AED CL/F with pregabalin relative to that without pregabalin (expressed as a percent)
d 90% confidence interval estimate for the ratio expressed as a percent

For carbamazepine, lamotrigine, phenytoin, valproate, topiramate and phenobarbital the percent change in the population estimate of the AED CL/F values with pregabalin add-on therapy was within -2% to + 7%. The 90% CIs for these same AEDs were all within 80% to 125%. The results for pregabalin add-on therapy were similar to those observed for the placebo add-on therapy, suggesting that pregabalin add-on therapy had no significant effect on the steady-state pharmacokinetics of these AEDs.

These results are consistent with pharmacokinetic studies conducted previously which showed that pregabalin had no effect on the pharmacokinetics of carbamazepine, lamotrigine, valproate, and phenytoin. No traditional studies were conducted with phenobarbital and topiramate amongst these 6 AEDS. In vitro metabolism work showed that pregabalin did not inhibit cytochrome P450 enzymes.

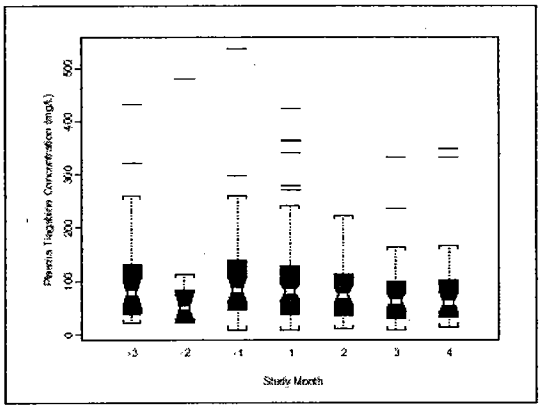
Interpretation of the tiagabine data was less straightforward as increases in tiagabine CL/F from baseline were observed for both the pregabalin and placebo treatment groups. The mean tiagabine CL/F for the pregabalin treatment group was approximately 12% higher (134.9% versus 120.3%) than that observed for the placebo treatment group. However, the change in tiagabine CL/F associated with either treatment group was not statistically significant, based on the change in MOF (-0.61). Furthermore, the 90% CI for the change in CL/F were much wider than for all other AEDs, indicating there was more uncertainty associated with the effect of pregabalin on tiagabine. Inspection of the box plot for tiagabine did not reveal a substantial difference or trend in the tiagabine concentrations between the baseline and pregabalin add-on treatment phases. Based on the results of this study, no definitive conclusions could be reached concerning the effects of pregabalin on tiagabine pharmacokinetics.

Asymptotic standard errors are known to be biased under certain circumstances. To alleviate this understanding, the reviewer also calculated the 90% confidence interval by bootstrapping method. For the pregabalin treatment phase the 90% CI was [redacted] % (sponsor's 112-157.7) and for the placebo treatment the 90% CI was [redacted] % (sponsor's 63-177.3). This suggests the 90% CI calculated is not much different from that calculated by bootstrapping and we agree with the sponsor's analysis on drug interaction with concomitant AEDs.

Based on *in vitro* data, tiagabine is likely to be metabolized primarily by the 3A isoform subfamily of hepatic cytochrome P450 (CYP 3A), although contributions to the metabolism of tiagabine from CYP 1A2, CYP 2D6 or CYP 2C19 have not been excluded.

However, since in vitro studies suggested that pregabalin did not affect cytochrome P450-based metabolism and is neither an inhibitor of the P450 isoenzymes. Systematic induction studies with pregabalin have not been conducted but preclinical data suggested possible increase in CYP2B and CYP2E activity. Given this information pregabalin is not expected to alter the steady-state pharmacokinetics of tiagabine.

Moreover, the tiagabine plasma concentrations shown below as baseline phase (tiagabine alone) versus double blind phase (tiagabine+pregabalin) did not show any trends of increased concentrations with the two drugs were administered together.



Given these data, tiagabine is not likely to have any significant drug interaction with pregabalin.

Conclusions:

- Pregabalin has no clinically significant effect on the steady-state pharmacokinetics of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, or valproate and there does not seem to be a mechanistic expectation for a drug interaction because pregabalin does not bind with plasma proteins, is not appreciably metabolized (>90%

of dose renally excreted as unchanged drug), and does not inhibit hepatic metabolizing enzymes.

- No definitive conclusion can be reached from this analysis about the effect of pregabalin on tiagabine steady-state pharmacokinetics, however a drug interaction with tiagabine and pregabalin does not seem to be likely. In the label the sponsor is silent about the effect of pregabalin on tiagabine pharmacokinetics, but has included no effect of tiagabine on pregabalin pharmacokinetics. Based on the above discussion pregabalin is unlikely to have any effect of tiagabine concentrations.

NOMMEM CONTROL STREAM FOR STUDY 3729:
(Similar control streams for each AED)

```
$PROB POP-PK ANALYSIS OF CBZ: NMIN2.TXT SEPARATES DB FROM BASELINE
; Modeling Data from Studies 9, 11, &34
; Fitting AED CL to Daily dose / Css (assumes SS) (CL/F)
; Additive & Proportional error terms for residual variability
; CL/F covariates: TRT
$INPUT OBS STUD SITE=DROP SUB=DROP ID AGE GDER RACE HT=DROP WT SCR=DROP
CLCR PGDG SDMD TIME AEDG DV TRT SDAY=DROP SMTH TMLD=DROP
; OBS : Data Line Number
; STUD: Study Protocol Number
; SITE: Protocol Site Number
; SUB : Protocol Subject Number
; ID : Nonmem ID Number
; AGE : Age of Subject in Years
; GDER: Gender 0=Females, 1=Males
; Race: Race 1=whites, 2=blacks, 3=Hispanic, 4=asian, 5=Native AM, 6=others
; HT : Height in cm
; WT : Weight in kg
; SCR : Serum creatinine conc in mcg/dl
; CLCR: Creatinine clearance in ml/min
; PGDG: Pregabalin daily dose group
; SDMD: Dosing regimen, 0= no pregabalin, 1= single dose, 2= q8h, 3=bid, 4=tid
; Time: Time postdose in hours
; AEDG: AED Dose Group, Dose in mg/day
; DV : Dependent Variable, observed AED conc, mcg/ml
; TRT : Treatment phase 0=baseline, 1=double-blind phase (pregabalin/placebo admin)
; SDAY: Study day that the other AED blood sample was drawn
; SMTH: Study month that the other AED blood sample was drawn
; TMLD: Time of day of last AED dose (hr)
$DATA CBZDATA IGNORE=#
$PRED
; PK MODEL
; SEPARATES DB PHASE (TRT=1) FROM BASELINE PHASE (TRT=0)
TVCL=THETA(1)*((1-TRT)+THETA(2)*TRT)
CL=TVCL*EXP(ETA(1))
F=AEDG/CL
Y = F*(EXP(ERR(1))) + ERR(2)
IPRED=Y
$THETA (0.0, 100., 1000) ; AED CL BASELINE
$THETA (0.0, 1.0, 10.) ; AED CL DB
$OMEGA 0.5 ; CL
$SIGMA 0.03 ; Proportional
$SIGMA 0.1 ; Additive
$EST NOABORT SIGDIGITS=3 MAXEVAL=9000 PRINT=30 POSTHOC
$COV
$TABLE ID STUD AGE GDER RACE WT CLCR PGDG SDMD AEDG TRT CL ETA1
NOPRINT ONEHEADER FIRSTONLY NOAPPEND FILE=dmpktab2
$TABLE ID STUD TRT PGDG SDMD AEDG CL
NOPRINT ONEHEADER NOAPPEND FILE=cltab2



; PK MODEL
; SEPARATES DB PHASE (TRT=1) FROM BASELINE PHASE (TRT=0)
; SEPARATES PLACEBO TREATMENT (FLGP=1) FROM PREGABALIN TREATMENT (FLGP=0)
FLGP=0
IF (SDMD.EQ.0) FLGP=1
TVCL=THETA(1)*(FLGP*((1-TRT)+THETA(2)*TRT) + (1-FLGP)*((1-TRT)+THETA(3)*TRT))
CL=TVCL*EXP(ETA(1))
F=AEDG/CL
Y = F*(EXP(ERR(1))) + ERR(2)
IPRED=Y
```

Study 3298: Population Pharmacokinetics of Pregabalin in Healthy Volunteers and Patients With Partial Seizures

Objective:

To describe the pharmacokinetics of pregabalin following single and multiple doses in healthy volunteers and subjects with renal impairment, and following multiple doses in patients with partial seizures using a population approach, and to identify the factors that impact pregabalin pharmacokinetics in this population.

DataSet:

One full dataset was created for the analysis that combined the data from the studies involving healthy volunteers and patients with partial seizures. The dataset included subject identification, demographics, dosing information, pregabalin concentration, time of sample collection, fed/fasted state at time of the last dose prior to blood sample collection, and concomitant AED administration for the patients with partial seizures in the add-on studies.

The full dataset was comprised of 2868 pregabalin concentrations which were collected following single- and multiple-dose administration in 123 healthy volunteers (includes subjects from the renal study) and 1515 pregabalin concentrations which were collected following multiple-dose administration in 627 patients.

The studies included in the population pharmacokinetic analysis were 5 pharmacokinetic studies (1008-001, -002, -003, -023, and -049) utilizing intense serial sampling in healthy volunteers and subjects with impaired renal function, and 4 clinical safety and efficacy trials (1008-007, -009, -011, and -034) utilizing sparse sampling in patients with partial seizures.

The population characteristics of continuous variables included in the dataset were:

Study	N	Age (yr)	Weight (kg)	Height (cm)	CLcr (mL/min)
1008-001	29	40.1 ± 5.6	77.4 ± 7.2	173 ± 8.2	104.3 ± 18.6
1008-002	45	35.4 ± 9.3	75.5 ± 9.0	174.0 ± 8.9	107.7 ± 20.9
1008-003	11	54.2 ± 10.3	72.2 ± 10.8	168 ± 6.8	100.0 ± 29.3
1008-007	37	36.9 ± 10.4	80.6 ± 21.2	170 ± 10.4	113.0 ± 34.1
1008-009	170	39.7 ± 11.6	79.0 ± 19.3	168 ± 11.4[c]	111.5 ± 33.0
1008-011	108	35.9 ± 10.7	75.2 ± 16.5	168 ±10.9	148.6 ± 40.7
1008-023	12	31.8 ± 8.1	75.0 ± 7.1	178 ± 7.8	120.0 ± 17.3
1008-034	311	38.7 ± 11.7	78.8 ± 21.5	168 ± 10.5[d]	109.8 ± 30.6
1008-049	26	56.4 ± 11.9	80.8 ± 14.1	168 ± 8.7	57.0 ± 34.7
All Studies (Range)	749	39.0 ± 11.8 (13-75)	78.1 ± 18.8 (37.7-180)	169[b] ± 10.6 (130-206)	113.8 ± 36.4 (10-281)

[a] Value of the variable at the time of screening.
[b] N = 744.
[c] N = (N-2).
[d] N = (N-3).

The population characteristics of the categorical variables are given in the Table below:

Variables	Study Number (1008-)					
	001, 002, 003, 023, 049	007	009	011	034	All Studies
Gender						
Male	70 (57)	20 (54)	89 (52)	51 (47)	142 (46)	372 (50)
Female	53 (43)	17 (46)	81 (48)	57 (53)	169 (54)	377 (50)
Ethnic Origin						
White	93 (76)	29 (78)	147 (86)	100 (93)	261 (84)	630 (84)
Black	4 (3)	2 (5)	7 (4)	3 (3)	23 (7)	39 (5)
Hispanic	23 (19)	6 (17)	13 (8)	1 (1)	19 (6)	62 (8)
Asian or Pacific Islander	0 (0)	0 (0)	1 (1)	2 (2)	5 (2)	8 (1)
American Indian or Alaskan Native	1 (1)	0 (0)	1 (1)	0 (0)	1 (0)	3 (0)
Other	2 (2)	0 (0)	1 (1)	2 (2)	2 (1)	7 (1)
Anticonvulsant Concomitant Medications						
Carbamazepine			97 (57)	67 (62)	160 (51)	324 (55)
Lamotrigine			53 (31)	37 (34)	66 (21)	156 (26)
Phenobarbital			8 (5)	13 (12)	19 (6)	40 (7)
Phenytoin			60 (35)	16 (15)	100 (32)	176 (30)
Tiagabine			14 (8)	5 (5)	51 (16)	70 (12)
Topiramate			35 (21)	20 (19)	56 (18)	111 (19)
Valproic Acid			27 (16)	29 (27)	64 (21)	120 (20)

The following tables lists all studies with their respective dose, dosing regimen, and pharmacokinetic sampling time information.

Protocol	Design	Duration	Population	Sampling	Pregabalin Dose	Formulation[a]
1008-001	Randomized, double-blind, 2-way crossover, rising single-dose, tolerance, and pharmacokinetic study	Single dose	Healthy volunteers	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours	1- to 600-mg single doses[b]	Pregabalin 5-, 25-, 100-, and 300-mg capsules. Pregabalin 5 mg per vial for dissolution (1 mg/mL)
1008-002	Randomized, double-blind, placebo-controlled, parallel-group, staggered-start, rising single- and multiple-dose tolerance and pharmacokinetic study	Single (Study Day 1) and multiple dose (14 days of dosing, Study Days 8-22)	Healthy volunteers	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours following single dose and last multiple dose. Morning predose samples were collected on Days 8, 9, 10, 12, 15, and 18 following multiple-doses	25, 100, 200, or 300 mg as single doses and 75 (25 mg q8h), 300 (100 mg q8h), 600 (200 mg q8h or 300 mg q12h), and 900 (300 mg q8h) mg/day	Pregabalin 25-, 100-, and 300-mg capsules
1008-003	Open-label, single-dose, randomized, 3-way crossover study in healthy volunteers	Single dose	Healthy volunteers	Predose, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 60 hours postdose	100-mg single doses	Pregabalin 100-mg capsules

[a] A solution of pregabalin was shown to be bioequivalent to pregabalin 100-mg capsules used in clinical trials. The various strengths of the pregabalin capsules used in clinical trials were considered bioequivalent based on a biowaiver[13] which documented that the pregabalin capsule formulations used in the clinical trials were rapidly dissolving, and that pregabalin was a high solubility, high permeability drug.

[b] Single 600- mg dose was not administered as maximum pregabalin exposure was attained with the single 300-mg dose

Protocol	Design	Duration	Population	Sampling	Pregabalin Dose	Formulation[a]
1008-007	Inpatient, randomized double-blind, parallel-group and low-dose active controlled multicenter study	8 days	Patients with seizures diagnosed as a CP, with or without secondary generalization	Sparse samples (7)[b]	600 mg/day (200 mg q8h)	Pregabalin 25- and 100-mg capsules
1008-009	Randomized, double-blind, parallel-group, placebo-controlled, multicenter study	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	Sparse samples (7)[b]	600 mg/day (300 mg BID or 200 mg TID)	Pregabalin 25- and 100-mg capsules
1008-011	Randomized, double-blind, parallel-group, placebo-controlled, multicenter study	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	Sparse samples (7)[b]	150 (50 mg TID) or 600 (200 mg TID) mg/day	Pregabalin 25- and 100-mg capsules

[a] A solution of pregabalin was shown to be bioequivalent to pregabalin 100-mg capsules used in clinical trials. The various strengths of the pregabalin capsules used in clinical trials were considered bioequivalent based on a biowaiver[11] which documented that the pregabalin capsule formulations used in the clinical trials were rapidly dissolving, and that pregabalin was a high solubility, high permeability drug.

[b] Number of samples specified in the protocol

Protocol	Design	Duration	Population	Sampling	Pregabalin Dose	Formulation[a]
1008-023	Randomized, double-blind, placebo-controlled, multiple-dose, tolerance and pharmacokinetic study	Multiple-dose on Days 1 through 28 and a single dose on Day 29	Healthy volunteers	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours following first dose on Day 1 and Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 16, 24, 36, and 48 hours following dose on Day 29. Morning predose samples on Days 2, 3, 4 7, 11, 14, 18, 22, and 26	900 mg/day (300 mg q8h) on Days 1 through 28 and 300-mg dose on Day 29	Pregabalin 300-mg capsule
1008-034	Randomized, double-blind, parallel-group, placebo-controlled, multicenter study	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic)	Sparse samples (2)[b]	50 (25 mg BID), 150 (75 mg BID), 300 (150 mg BID), and 600 (300 mg BID) mg/day	Pregabalin 25- and 100-mg capsules
1008-049	Open-label, parallel-group, single-dose study	Single dose	Subjects with various degrees of renal function	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours	50-mg single doses	Pregabalin 25-mg capsules

Sampling:

In all 4 partial seizure studies, blood samples for the quantitation of pregabalin were collected randomly with respect to time postdose. The information collected relative to the blood sample included date and time of blood draw, date and time of last pregabalin dose prior to blood draw, and date and time of last meal prior to pharmacokinetic blood sample (time of last meal was not collected in Study 1008-007).

These data were used to calculate hours postdose, the time elapsed between last dose and blood sample collection, and to determine the time elapsed between last dose and last meal (fed/fasted status of the patient).

Dosing Regimen Representation in database:

For BID regimens: Every 12 hour dosing interval was used
For Q8 regimens: Every 8 hour interval was used
For TID regimen: A dosing interval of 6, 6 and 12 hours was used. From previous analysis this regimen showed a better fit. And also uneven dosing interval better reflected the actual pregabalin administration practiced by the patients.

Because of the uneven dosing interval used for TID administration, the blood samples drawn for pregabalin plasma concentrations needed to be assigned to the first, second, or third dose of the day.
For modeling purposes, any dose recorded as being taken between
— 2 AM and 11 AM was considered the first dose of the day (morning dose).
— 11 AM and 5 PM was considered the second dose of the day (afternoon dose).
— 5 PM and 2 AM was considered the third dose of the day (evening dose).

The plasma pregabalin concentration and time postdose for each blood sample collected was then associated with the morning, afternoon, or evening dose from which it followed.

Covariates included in the dataset:

The covariates included were age, weight, serum creatinine, status of patients whether maintained on 1 or more AEDs, fed/fasted state of each subject.

Meal status was:
—0 if the blood sample was considered drawn during the fasted state.
—1 if the dose preceding the blood sample was administered within 1 hour of a meal.
—2 if the dose preceding the blood sample was given 1 to 2 hours before a meal.
—3 where the fed/fasted status was not collected, recorded as unknown

Model Building:

Randomly the full dataset was separated into a model building set (75% of the subjects) and a model validation set (~25% of the subjects). From the model building dataset, a

basic pharmacokinetic model (model with no covariates added) was identified, with estimates of intersubject and residual variability. Covariates that may be important determinants of the pharmacokinetics were identified using plots of posthoc pharmacokinetic parameter estimates versus covariates. Covariates were tested one at time to obtain the full model. The covariate was left in the model if a statistically significant ($p < 0.01$) decrease in the NONMEM objective function (>6.6 units) was observed. The final model was validated using the validation set. The final model parameters were obtained from the full dataset.

Initial Model:

The initial model was selected from a 1-compartment pharmacokinetic model with first-order absorption and a Tlag term and elimination and intersubject variability on drug oral clearance (CL/F), volume of distribution (Vd/F), and absorption rate constant (Ka) or the same model with a. Intersubject variability on the pharmacokinetic parameter, CL/F, was modeled using an exponential term as follows:

$$CL/F = ?.e^{?}$$

where ? was the typical or central value of the pharmacokinetic parameter in this patient population, and ? was a random variable having a normal probability distribution with mean 0 and variance $?^2$. The 90% confidence intervals (CI) of the estimates of the pharmacokinetic parameters were calculated as $? \pm 1.67 \cdot SE$, where SE was the standard error obtained in NONMEM.

The estimate of intersubject variability (η) was provided as percent coefficient of variation (%CV); %CV was calculated as $\sqrt{?^2} \bullet 100$

The 95% CI for intersubject variability was calculated as $\sqrt{?^2 \pm 2 \bullet SE} \bullet 100$

Residual variability was modeled as a combined additive/proportional error model as follows:

$$Y = F + F \cdot e1 + e2$$

Where,
Y was the observed AED concentration
F was the predicted AED concentration based on the pharmacokinetic model in a particular individual;
e 1 was the proportional error component of the residual variability
e 2 was the additive error component of the residual variability

To obtain estimates of weighted residuals, the error model was coded in NONMEM as:

$$Y = F + W \bullet \varepsilon_1; where W = \sqrt{(F^2 + \theta_{err}^2)}$$

where W was the weight and ? err was a proportionality constant between the coefficient of variation of the proportional error term and the standard deviation of the additive term.

Continuous covariates were added to the model as described below for the effect of creatinine clearance on the typical value of oral clearance (CL/F):

$$CL/F = \theta_1 + \theta_{CLcr} \cdot CLcr$$

where θ_1 is the estimate of the oral clearance not dependent on creatinine clearance, ie, when CLcr is equal to 0, and $\theta_{CLcr} \cdot CLcr$ is the renal portion of the oral clearance with θ_{CLcr} being the coefficient of the relationship between renal clearance and creatinine clearance.

Categorical covariates were modeled as indicated below for the effect of gender on typical value of volume (Vd/F):

$$Vd/F = \theta_2 \cdot (GDR + \theta_{GDR} \cdot (1-GDR))$$

where GDR is an indicator variable equal to 1 in males and equal to 0 in females. Thus, θ_2 represents the typical value of Vd/F in male patients and θ_{GDR} represents the fractional change in females relative to males.

When all significant covariates were included in NONMEM, this "full" model was further tested by eliminating each parameter one at a time to evaluate the change in the objective function and determine if a model with fewer parameters could be used to describe the data. The p value for statistical significance was adjusted for multiple comparisons ($p < 0.001$). The final model included only those parameters that produced an increase in the objective function of >10.8 for 1 degree of freedom when each parameter was excluded one at a time.

Final Model:

The specific model developed for pregabalin is described mathematically by the following 4 equations:

$$CL/F = \theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \cdot \theta_{CLcrBP}) \cdot (1-CFLG)$$

where θ_{CLcrBP} is defined as the creatinine clearance breakpoint value. If creatinine clearance (CLcr) $\leq \theta_{CLcrBP}$, pregabalin clearance will be proportional to creatinine clearance (θ_{CLcr}) and the indicator variable, CFLG, is equal to 1. Otherwise, if CLcr > θ_{CLcrBP}, pregabalin clearance will be independent of creatinine clearance and the indicator variable, CFLG, is equal to 0.

$$Vd/F = \theta_{WT} \cdot ((WT/80.5)^{\theta_{pwr}}) \cdot (GDER + \theta_{GDER} \cdot (1-GDER))$$

where WT is subject weight in kg, 80.5 is the mean weight (kg) of all subjects in the dataset and GDER is an indicator variable equal to 1 for males and 0 for females. θ_{WT} is the proportionality constant between Vd/F and subject WT to the power of θ_{pwr}. θ_{GDER} is the fraction of the Vd/F value for females.

$$Ka = (EKEL \cdot \theta_{fast}) \cdot (1 + \theta_{fed} \cdot (1 - FFA))$$
$$Tlag = \theta_{Tlag}$$

where FFA is an indicator variable equal to 1 when pregabalin was administered in the fasted state and equal to 0 for fed and unknown meal states. Pregabalin elimination rate constant, EKEL, is (CL/F)/(Vd/F) such that θ_{fast} is the proportionality constant between Ka and EKEL. θ_{fed} is the fractional change in Ka for subjects receiving pregabalin in the fed state.

Plasma concentrations versus time data were modeled using a population analysis approach using the first-order estimation method (NONMEM Version V, University of California at San Francisco, California).

Effect of Concomitant Anticonvulsant (AEDs) Therapy on Pregabalin Pharmacokinetics:

The final pregabalin model was used to test the effect of concomitant AED administration on pregabalin CL/F. Forty was selected as the minimum number of subjects maintained on an AED in order for that AED to be tested in the model. Seven different AEDs met the criteria of having at least 40 subjects maintained on that AED. The AEDs tested were carbamazepine, phenytoin, lamotrigine, valproate, topiramate, tiagabine, and phenobarbital. Pregabalin CL/F values for subjects maintained on a marketed AED were compared to those obtained for all other subjects who were not receiving the marketed AED.

Pregabalin Pharmacokinetics in Adolescent Patients:

Pregabalin pharmacokinetics in adolescent patients with partial seizures (ages 12 through 18 years) were evaluated by comparing pregabalin CL/F in this population to that observed in adults. Only 11 patients from Study-034 were within the adolescent age range.

Results:

Plasma concentration-time data (n = 4381 concentrations) from 749 subjects were combined and included in this final analysis. Pregabalin concentrations ranged from 0.005 to 18.2 µg/mL. The time of sample collection varied from 0.02 to 168 hours postdose.

The final model provided a good fit of the data for both the healthy volunteers

and patients with partial seizures as evidenced in (1) the population predicted versus observed concentrations (2) individual predicted concentrations versus observed concentrations and (3) individual weighted residuals versus individual observed concentrations.

As expected, larger variability was observed for patients with epilepsy compared to healthy volunteers.

Figure: Population Predicted Versus Observed Pregabalin Concentrations in Healthy Volunteers (Left Figure) and in Patients With Partial Seizures (Right Figure)

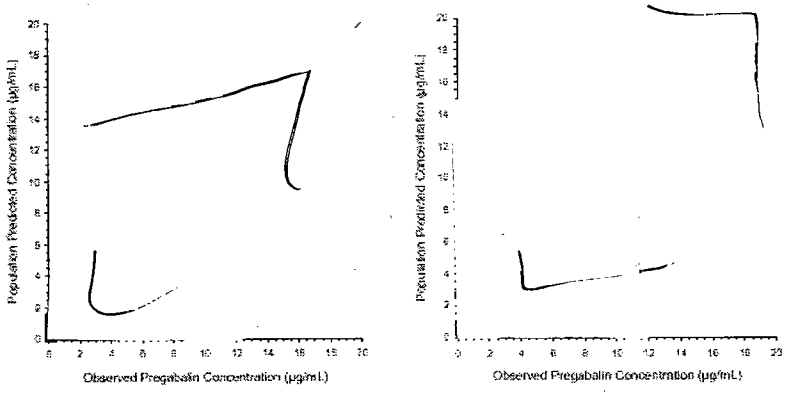
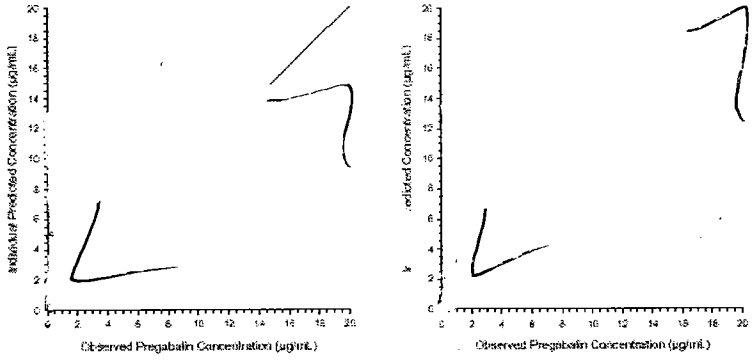


Figure: Individual Predicted Versus Observed Pregabalin Concentrations in Healthy Volunteers (Left Figure) and Patients With Partial Seizures (Right Figure)



Intersubject variability on all pharmacokinetic parameters was described with an exponential error. Final pharmacokinetic parameter estimates are summarized in the following Table.

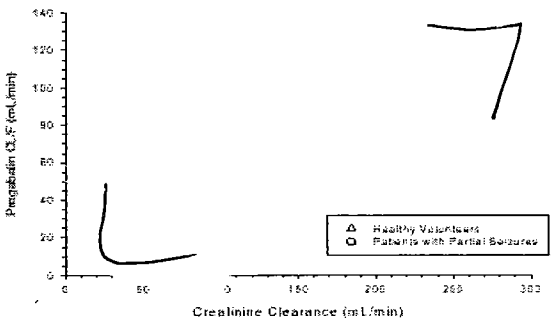
Parameter	θ	(95% CI)	%CV	(95% CI)
CL/F = θCLcr·CLcr·CFLG+(θCLcr·θCLcrBP)·(1-CFLG) (L/hr)			19.1	(15.3-22.2)
θCLcr (L·min/mL·hr)	0.0466	(0.0434-0.0498)		--
θCLcrBP (mL/min)	105	(98.3-111.7)		--
Vd/F = θWT·((WT/80.5)$^{\theta pwr}$)·(GDER+θGDER·(1-GDER)) (L)			12.4	(10.2-14.3)
θWT (L)	43.8	(38.9-48.7)		--
θpwr	0.573	(0.678-0.918)		--
θGDER	0.798	(0.678-0.918)		--
Ka = (EKEL·θfast)·(1+θfed·(1-FFA)) (1/hr)			182.	(103.9-235.8)
θfast	76.5	(46.5-106.5)		--
θfed	-0.866	(-0.888-0.844)		--
Tlag (hr)	0.170	(0.163-0.177)	1.51	(0.00-2.58)

CI = Confidence interval.
CV = Coefficient of variation.
CL/F = Oral clearance (L/hr).
CFLG = Indicator variable for creatinine clearance.
Vd/F = Apparent distribution volume (L).
Ka = Absorption rate constant (1/hr).
EKEL = Elimination rate constant (1/hr).
Tlag = Lag time (hr).

The following figure shows that Pregabalin CL/F increased proportionally to CLcr from zero up to a CLcr breakpoint value of 105 mL/min. Above a CLcr value of 105 mL/min, pregabalin CL/F was independent of CLcr. A decrease in CLcr relative to normal CLcr values would require a proportional decrease in pregabalin daily dose to maintain comparable drug exposure.

Reviewer's Note: The reason for pregabalin CL/F being independent of CLcr at values >105 mL/min is believed to be a result of how CLcr was calculated rather than a result of how pregabalin is eliminated. The equation of Cockcroft and Gault was used to estimate each subject's CLcr. The CLcr estimates are directly proportional to body weight when all other variables are constant. Numerous subjects in the Phase 2/3 studies were overweight with body weights approaching 180 kg. The overweight subjects had derived CLcr values which were over-estimates of their actual renal function.

Figure: Individual CL/F Values Versus Creatinine Clearance Values in Healthy Volunteers and Patients With Partial Seizures



The relationship between CLcr and pregabalin CL/F had a y-intercept of 0 and CL/F was directly related to CLcr up to a population. The lack of a positive y-intercept in the final model is consistent with pregabalin pharmacokinetics where the drug is predominately eliminated by renal excretion (>90% of the administered dose) with minimal metabolism (<2% of the dose has been recovered in the urine as metabolites). The relationship between pregabalin CL/F and CLcr was unaffected by gender, race, hormonal status, age, or pregabalin dosing regimen. There was no difference in CL/F between healthy volunteers and patients with partial seizures.

The population estimate of volume of distribution (Vd/F) was dependent on body weight. After accounting for differences in weight, male Vd/F was approximately 20% higher than females. This could be attributed to the difference in percent body fat between males and females. This difference is not likely to be clinically significant.

The administration of pregabalin with food decreased the rate of drug absorption relative to administration of pregabalin in the fasted state. The rate of drug absorption was faster in fasted state than the rate of pregabalin elimination. A lag time prior to absorption of about 10 minutes (0.17 hour) was also observed. These observations are consistent with a study in healthy volunteers that showed that the rate but not the extent of pregabalin absorption was reduced when given with a meal.

Intersubject variability, reported as the percent coefficient of variation (%CV), was about 19% for CL/F, 12% for Vd/F, 182% for Ka, and 1.5% for Tlag. Residual variability is summarized in the following Table . In healthy volunteers, residual variability was characterized by both an additive and a proportional error component with a coefficient of variation for the proportional component of about 14.8%. In patients with partial seizures, 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 24.5%. The greater residual variability in the patients with partial seizures is most likely due to differences in study conditions (supervised dosing versus outpatient conditions, greater inherent variability with the sparse sampling strategy employed in the clinical efficacy/safety studies versus that introduced by the intense

sampling strategy under relatively controlled conditions) between healthy volunteers (including subjects from the renal study) and patients with partial seizures.

Population	Proportional		Additive (μg/mL)	
	%CV	(95% CI)	SD	(95% CI)
Healthy Volunteers	14.8	(9.75-18.5)	0.019	(0.00-0.062)
Patients With Partial Seizures	24.5	(20.2-28.2)	0.455	(0.168-0.621)

Effect of concomitant AEDs on pregabalin clearance:

The possible effect of concomitant AED therapy on pregabalin CL/F was investigated using the final pharmacostatistical model. Actual AED concentrations were measured in the clinical studies. A covariate for concomitant AED therapy was added to the final equation to determine the effect of each AED on pregabalin CL/F.

The following equation was used where AED is an indicator variable, where

AED = 0 if a patient was not receiving a given AED,

AED = 1 if a patient was receiving a given AED,

θ_{AED} is the fraction of the reference pregabalin CL/F for patients maintained on a given AED.

$$CL/F = (\theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \theta_{CLcrBP}) \cdot (1-CFLG)) \cdot (1-AED+AED \cdot \theta_{AED})$$

The following Table summarizes the NONMEM analyses of the possible effect of concomitant AED therapy on pregabalin CL/F. ΔMOF is the change in the minimum objective function value resulting from incorporating a given AED therapy as a covariate in the pregabalin CL/F model.

For the 7 AEDs studied, concomitant AED administration resulted in a mean pregabalin CL/F, expressed as a percentage of the reference value, ranging from 93.5% to 107%. The 90% CI for all AEDs was well within the usual 80% to 125% interval needed to establish lack of a significant interaction.

AED	No. of Subjects	ΔMOF[a]	Ratio[b]	90% CI[c]
Carbamazepine	324	-0.20	100.8	96.0-105.6
Lamotrigine	156	-8.10	93.5	88.4-98.5
Phenobarbital	40	-2.18	93.6	84.9-102.3
Phenytoin	176	-3.19	95.8	88.5-103.2
Tiagabine	70	-3.20	107.1	97.2-117.1
Topiramate	111	-0.02	99.6	93.3-106.0
Valproate	120	-2.16	96.1	88.1-104.1

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 CL/F values, expressed as a percentage (100% × test: pregabalin CL/F in patients receiving AED/reference: pregabalin CL/F in patients not receiving the AED)

c 90% confidence interval estimate for the ratio (test/reference) of treatment mean values,expressed as a percentage of the reference mean

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Conclusions:

- The sponsor's model is acceptable.
- Pregabalin pharmacokinetics were characterized using a 1-compartment model with first order absorption and elimination and a lag time prior to absorption.
- Apparent distribution volume was dependent on gender and body weight.
- After correcting for CLcr, the post hoc estimates of pregabalin CL/F values were similar among healthy volunteers (including subjects from the renal study) and patients with partial seizures.
- No differences in the relationship between pregabalin CL/F and CLcr were observed in healthy volunteers and patients with partial seizures.
- Pregabalin CL/F was not affected by the use of anticonvulsant drugs known to induce or inhibit drug metabolism, such as carbamazepine, phenytoin, lamotrigine, valproate, topiramate, tiagabine, and phenobarbital. The results of 4 of these AEDs were consistent with clinical pharmacology studies, using intense sampling, which demonstrated a lack of interaction with phenytoin, carbamazepine, lamotrigine, and valproate.
- No conclusions can be drawn regarding differences in pregabalin CL/F
- The only factor having a clinically significant impact on steady-state plasma pregabalin concentrations is renal function. Patients with impaired renal function should have their dosing regimen adjusted in proportion to the decline in their CLcr.

NOMMEM CONTROL STREAM FOR STUDY 3298:

```
$PROB 1008: epilepsypk\data runs\final\nmin0
; Same model as bldstep7\nmin1.txt (final model from poppk analysis)
; Modeling Data from healthy volunteers (1,-2,-3,&-23) & renal (049)
; and epilepsy (007, 008, 009, 010, 011, 012, 034, 035)
; One compartment model with first order absorption (CL/F, V/F, and Ka)
; Additive + prop error term for residual variability
; prop and add term diff for hvs and pts
; include tlag
; CL/F covariates: no Yint, CLvsCLcr c brkpt, then indep
; V/F covariates: Sex, Weight
; Ka covariates: (multiple of ke) fasted vs all others
; tlag covariates: none
$INPUT OBS ID TFLG=DROP STDB=DROP STOL=DROP STTY=DROP DBOL=DROP
STUD=DROP SITE=DROP SUB AGE GDER RACE HT TWT PTST SCR=DROP
TCCR ALB=DROP BUN=DROP HORM=DROP TIME AMT=DOSE SS II DV EVID
ADDL=DROP FF CDOS=DROP DG DNUM=DROP SDMD DPD=DROP CBZ=DROP LMG=DROP
PB=DROP PHY=DROP TGB=DROP TPM=DROP VA=DROP AD=DROP INSU=DROP
DIUR=DROP
; OBS : Data Line Number
; ID : Nonmem ID Number
; TFLG: Indicator variable, 0=validation or 1=model building dataset
; STDB: Double blind study number (if appropriate)
; STOL: Open label study number (if appropriate)
; STTY: For Phase 2/3 data, plasma data from 0=double-blind or 1=open label
; DBOL: FLAG, subject data in double-blind and open label studies 0=no 1=yes
; STUD: Study Protocol Number
; SITE: Protocol Site Number
; SUB : Protocol Subject Number
; AGE : Age of Subject in Years
; GDER: Gender 0=Females, 1=Males
; Race: Race 1=whites, 2=blacks, 3=Hispanic, 4=asian, 5=Native AM, 6=others
; THT : Height in cm
; TWT : Weight in kg
; PTST: Patient Status 1=healthy, 2=epilepsy, 3=pain, 4=anxiety, 5=other
; SCR : Serum creatinine (mg/dl)
; TCCR: Creatinine clearance in ml/min
; ALB : Albumin concentration
; BUN : Blood urea nitrogen
; HORM: Hormonal status, .=male, 1=premenopausal, 2=postmenopausal, 3=premenarchal
; TIME: Time postdose in hours
; AMT : Dose event: amount in mg
; SS : Steady-state data item: 0=not at ss, 1=reset ss dose, 2=ss dose
; II : Interdose Interval (hr)
; DV : Dependent Variable, observed plasma CI-1008 conc, mcg/ml
; EVID: Event Identification Number (0=conc, 1=dose, 4=reset dose)
; ADDL: Temporary variable called ADDL (not used)
; FF : Food Affect: Drug admin in 0=fasted state, 1=within 1 hr,
; 2= within 2 hr postdose, 3=unknown
; CDOS: Daily dose (mg/day)
; DG : Dose Group, Dose prior to pregabalin blood sample (mg)
; DNUM: Plasma sampled drawn after the 1st, 2nd, or 3rd dose of the day
; SDMD: Dosing regimen, 1= single dose, 2= q8h, 3=bid, 4=tid
; DPD : Doses per day
; CBZ : Flag for carbamazepine concomitant administration
; LMG : Flag for lamotrogine concomitant administration
; PB : Flag for phenobarbital concomitant administration
; PHY : Flag for phenytoin concomitant administration
; TGB : Flag for tiagabine concomitant administration
; TPM : Flag for topiramate concomitant administration
; VA : Flag for valproic acid concomitant administration
; AD : Flag for oral antidiabetics concomitant administration
; INSU: Flag for insulins concomitant administration
; DIUR: Flag for diuretics concomitant administration
$DATA datahvepidb IGNORE=#
$SUBROUTINES ADVAN2 TRANS2 SS2 INFN=infn.prn5
$PK
; ALLOWS FOR MISSING DEMOGRAPHIC INFORMATION
IF (NEWIND.LT.2) THEN
```

```
WT=TWT
CLCR=TCCR
ELSE
IF (TWT.NE.0) WT=TWT
IF (TCCR.NE.0) CLCR=TCCR
ENDIF
; SETS PTS =1 FOR HEALTHYS AND PTS=0 FOR PATIENTS
PTS=0
IF (PTST.EQ.1) PTS = 1
; FOOD EFFECT FFA=1 for fasted
IF (FF.EQ.0) THEN
FFA=1
ELSE
FFA=0
ENDIF
; Sets breakpoint on CLcr
CFLG=0
IF (CLCR.LE.THETA(5)) CFLG=1
TVCL=THETA(1)*CLCR*CFLG+(THETA(1)*THETA(5))*(1-CFLG)
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)*(GDER+THETA(7)*(1-GDER))*((WT/80.5)**THETA(8))
V =TVV*EXP(ETA(2))
EKEL = CL/V
TVKA = EKEL*(THETA(3))*(1+THETA(6)*(1-FFA))
KA = TVKA*EXP(ETA(3))
TVTL=THETA(4)
ALAG1=TVTL*EXP(ETA(4))
TLAG=ALAG1
S2=V
$ERROR
Y1 = F*(EXP(ERR(1))*PTS+(1-PTS)*EXP(ERR(2)))
Y = Y1 + (ERR(3)*PTS+(1-PTS)*ERR(4))
IPRED=Y
$THETA (0.0, 0.05, 300) ; 1 Pop CL/F ftn CLCR
$THETA (0.0, 40.0, 200) ; 2 Pop V/F FOR MALES
$THETA (0.6, 55, 600.) ; 3 POP KA FOR FASTED STATE
$THETA (0.01, 0.10, 0.5) ; 4 POP TLAG
$THETA (40.0, 100, 500) ; 5 POP Breakpoint for CLCR VS CL/F
$THETA (-1, -.5, 10) ; 6 FR OF FASTED KA FOR FED & UNK
$THETA (-1, 1.1, 10) ; 7 FR OF MALE V FOR FEMALES
$THETA (-1, 0.9, 10) ; 8 WEIGHT ON V
$OMEGA 0.05 ; CL
$OMEGA 0.05 ; V
$OMEGA 1.8 ; Ka
$OMEGA 2.4 ; TLAG
$SIGMA 0.02 ; Healthys
$SIGMA 0.07 ; Patients
$SIGMA 0.01 ; Healthys additive
$SIGMA 0.80 ; Patients additive
$EST NOABORT SIGDIGITS=3 MAXEVAL=9000 PRINT=30 POSTHOC
$COV
$TABLE ID TIME IPRED
NOPRINT ONEHEADER FILE=sdtab89
$TABLE ID V CL KA TLAG
NOPRINT ONEHEADER FILE=patab89
$TABLE ID AGE WT CLCR
NOPRINT ONEHEADER FILE=cotab89
$TABLE ID GDER RACE FF DG SDMD PTST
NOPRINT ONEHEADER FILE=catab89
$TABLE ID AGE GDER RACE WT CLCR FF SDMD DG V CL KA TLAG
NOPRINT ONEHEADER FIRSTONLY NOAPPEND FILE=dmpktab89
$TABLE OBS ID EVID TIME IPRED PTST DG SDMD
NOPRINT ONEHEADER FILE=plots89

1NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) DOUBLE PRECISION NONMEM VERSION V LEVEL
1.1
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER
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Study 0013: Population Pharmacokinetics of Pregabalin in Healthy Volunteers, Patients With Impaired Renal Function, Patients With Chronic Pain, Patients With Partial Seizures, and Patients With Generalized Anxiety Disorder

Objectives:

To describe the pharmacokinetics of pregabalin following single and multiple doses in healthy volunteers and patients with impaired renal function, as well as multiple doses in patients with chronic pain, patients with partial seizures, and patients with generalized anxiety disorder using a validated population model.

This study included the entire dataset in all populations. Hence, supercedes other population analyses.

Dataset:

The data set for this analysis was constructed by combining patients with Generalized Anxiety Disorder (GAD) to the previously used dataset for other population analyses (Study 3298 and 3771). Therefore, this study uses the largest amount of data covering all patient population as well as healthy subjects and subjects with renal impairment.

The full dataset consisted of 6137 pregabalin concentrations obtained from 2276 subjects. The full dataset contained 2868 samples which were collected serially following single- and multiple-dose administration in 123 healthy volunteers (includes the subjects from the renal study), 1204 pregabalin concentrations which were collected as sparse sampling from 976 patients in the chronic pain efficacy/safety studies, 1515 pregabalin concentrations which were collected as sparse sampling from 627 patients in the epilepsy efficacy/safety studies, and 550 pregabalin concentrations which were collected as sparse sampling from 550 patients in the generalized anxiety disorder efficacy/safety studies.

Studies from the chronic pain analyses are not outlined here.

The following tables lists all studies with their respective dose, dosing regimen, and pharmacokinetic sampling time information from the GAD Studies, for other studies please refer to summary report of Study 3298.

Protocol	Design	Duration	Population	Sampling	Dose
-025	Double-blind, parallel, placebo-controlled, active-comparator, randomized	4 weeks	Patients with generalized anxiety disorder	Visit 6 (Week 4)	0, 150, or 600 mg/day TID
-026	Double-blind, parallel, placebo-controlled, active-comparator, randomized	4 weeks	Patients with generalized anxiety disorder	Visit 6 (Week 4)	0, 150, or 600 mg/day TID
-083	Double-blind, parallel,	4 weeks	Patients with generalized	Visit 6 (Week 4)	0, 300, 450, or 600 mg/day TID

	placebo-controlled, active-comparator, randomized		anxiety disorder		
-085	Double-blind, parallel, placebo-controlled, randomized	6 weeks	Patients with generalized anxiety disorder	Visit 7 (Week 6)	0 or 450 mg/day TID or 200 or 400 mg/day BID
-087	Double-blind, parallel, placebo-controlled, active-comparator, randomized	6 weeks	Patients with generalized anxiety disorder	Visit 7 (Week 6)	0, 400, or 600 mg/day BID

Population characteristics are summarized in the following Table:

Variables	Healthy Volunteers 001, 002, 003, 023, 049	Patients With Pain 014, 029, 030, 031, 032, 045, 104, 105, 127	Patients With Partial Seizures 007, 009, 011, 034	Patients With Generalized Anxiety Disorder	All Studies
Gender					
Male	70 (57)	445 (46)	302 (48)	232 (42)	1049 (46)
Female	53 (43)	531 (54)	325 (52)	318 (58)	1227 (54)
Ethnic Origin					
White	93 (76)	900 (92)	538 (86)	470 (85)	2001 (88)
Black	4 (3)	39 (4)	35 (6)	31 (6)	109 (5)
Hispanic	23 (19)	32 (3)	39 (6)	38 (7)	132 (6)
Asian or Pacific Islander	0 (0)	3 (0)	8 (1)	9 (2)	20 (1)
American Indian or Alaskan Native	1 (1)	0 (0)	2 (0)	2 (0)	5 (0)
Other	2 (2)	2 (0)	5 (1)	0 (0)	9 (0)

Observed Dosing Interval for BID and TID Regimens

Data from 159 patients on the TID dosing regimen averaged 6 hours between the morning and afternoon doses, 7 hours between the afternoon and evening doses, and 11 hours between the evening and the morning doses. This indicates that an unequal dosing interval was used by the patients on the TID regimen and supports the use of a 6-6-12 hour dosing interval that was used in the population pharmacokinetic analyses for TID administration.

Observed Concomitant Medication:

An inspection of the concomitant medication records indicated that 40 subjects reported taking aspirin, acetaminophen, and ibuprofen. The dosing records for the majority of the individuals taking these 3 concomitant medications indicated that they were taking the drugs on a PRN or 'as needed' basis. An analysis for potential drug-drug interaction with these agents and pregabalin was not conducted as it was not possible to confirm the coadministration of these medications at the time when the pregabalin pharmacokinetic

sample was drawn.

Other concomitant medications have been evaluated under report 3298.

Final Model:

The final model was similar to that validated in earlier population studies with the pregabalin dataset (Study 3298 and 3771). The specific model developed for pregabalin is described mathematically by the following 4 equations:

$$CL/F = \theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \cdot \theta_{CLcrBP}) \cdot (1-CFLG)$$

where θ_{CLcrBP} is defined as the creatinine clearance breakpoint value. If creatinine clearance (CLcr) $\leq \theta_{CLcrBP}$, pregabalin clearance will be proportional to creatinine clearance (θ_{CLcr}) and the indicator variable, CFLG, is equal to 1. Otherwise, if CLcr > θ_{CLcrBP}, pregabalin clearance will be independent of creatinine clearance and the indicator variable, CFLG, is equal to 0.

$$Vd/F = \theta_{WT} \cdot ((WT/80.5)^{\theta pwr}) \cdot (GDER + \theta_{GDER} \cdot (1-GDER))$$

where WT is subject weight in kg, 80.5 is the mean weight (kg) of all subjects in the dataset and GDER is an indicator variable equal to 1 for males and 0 for females. θWT is the proportionality constant between Vd/F and subject WT to the power of θpwr. θGDER is the fraction of the Vd/F value for females.

$$Ka = (EKEL \cdot \theta_{fast}) \cdot (1 + \theta_{fed} \cdot (FED))$$

$$Tlag = \theta_{Tlag}$$

where FED is an indicator variable equal to 0 when pregabalin was administered in the fasted state and equal to 1 for fed and unknown meal states. Pregabalin elimination rate constant, EKEL, is (CL/F)/(Vd/F) such that θ_{fast} is the proportionality constant between Ka and EKEL. θ_{fed} is the fractional change in Ka for subjects receiving pregabalin in the fed state.

Plasma concentrations versus time data were modeled using a population analysis approach using the first-order estimation method (NONMEM Version V, University of California at San Francisco, California).

Covariate Testing in the Final Model:

The final pregabalin pharmacostatistical model (using the first-order estimation method) was used to test the effect of the categorical covariates age (65 years vs <65 years), race, gender, dosing regimen (BID vs TID), and generalized anxiety disorder indication on pregabalin CL/F. The following equation illustrates the covariate testing of gender on pregabalin CL/F:

$CL/F = \theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \cdot \theta_{CLcrBP}) \cdot (1-CFLG) \cdot ([1-FLAG] + FLAG \cdot \theta_{Female})$

where the expression within the first set of parentheses is from the final pharmacokinetic model. FLAG is an indicator variable equal to 0 for males and 1 for females and ? Female is the fractional change in pregabalin CL/F for females. All subjects from the healthy volunteer, patients with impaired renal function, patients with chronic pain, patients with partial seizures, and patients with generalized anxiety disorder studies were included in these analyses.

The strategy used for testing the effect of concomitant medications is described below:

- Test the effect of a covariate one at a time on pregabalin CL/F, by testing them as a proportion of CL/F, and assess if it is a significant change in the CL/F of pregabalin;
- Determine statistical significance by any decrease of >10.8 in the objective function(which indicates that a proposed model with 1 additional parameter is better than the reduced reference model [p <0.001]; and
- Calculate the 90% CI of the ratio of pregabalin clearance to pregabalin clearance associated with the covariate from the standard error of the estimate.

Results:

Details on the pregabalin concentrations, dosing information, and time of sample collection are summarized in the following Table.

Study 1008	N conc	Dose (mg)		Concentration (µg/mL)		Time Postdose (hour)	
-001	338	82.0 ± 98.0	(1-300)	1.2 ± 1.9	(0.005-10.5)	9.6 ± 12.1	(0.5-60.0)
-002	1409	183.3 ± 108.1	(25-300)	2.8 ± 2.9	(0.005-16.3)	12.4 ± 15.3	(0.5-60.0)
-003	401	100 ± 0.0	(100-100)	1.3 ± 1.2	(0.006-4.6)	10.9 ± 16.3	(0.17-60.0)
-007	174	197.2 ± 11.6	(150-200)	3.9 ± 2.1	(1.340-12.5)	6.8 ± 2.7	(0.02-22.9)
-009	496	249.4 ± 54.6	(200-500)	6.3 ± 2.9	(0.383-18.2)	4.8 ± 3.8	(0.00-18.8)
-011	281	121.8 ± 74.7	(50-200)	3.0 ± 2.5	(0.293-14.2)	4.2 ± 3.6	(0.00-21.3)
-014	338	125.0 ± 75.3	(50-200)	3.2 ± 2.8	(0.141-17.6)	4.7 ± 4.1	(0.00-21.0)
-021	84	110.5 ± 74.3	(33-200)	2.9 ± 2.5	(0.101-10.5)	3.6 ± 3.5	(0.00-22.2)
-023	393	300 ± 0.0	(300-300)	5.9 ± 3.2	(0.059-17.1)	8.4 ± 9.8	(0.00-48.0)
-025	52	113.9 ± 74.8	(25-200)	3.7 ± 4.1	(0.065-23.0)	4.2 ± 4.0	(0.25-22.3)
-026	77	126.0 ± 75.5	(50-200)	3.4 ± 2.9	(0.137-14.3)	3.8 ± 3.6	(0.00-16.7)
-029	139	105.0 ± 71.7	(25-200)	2.9 ± 2.5	(0.297-11.2)	4.4 ± 3.8	(0.08-20.0)
-030	92	36.3 ± 12.6	(17-50)	1.4 ± 0.8	(0.127-3.5)	4.1 ± 2.4	(0.42-16.8)
-031	85	148.2 ± 50.3	(100-200)	5.0 ± 3.1	(0.820-17.4)	4.1 ± 2.6	(1.00-15.5)
-032	67	109.9 ± 73.4	(50-200)	2.8 ± 2.3	(0.179-8.6)	4.3 ± 2.4	(0.17-13.7)
-034	562	132.2 ± 101.2	(25-300)	2.5 ± 2.4	(0.055-12.5)	5.1 ± 3.4	(0.00-21.5)
-045	84	74.7 ± 25.2	(50-100)	3.1 ± 1.8	(0.108-9.1)	4.1 ± 3.8	(0.00-23.0)
-049	327	50 ± 0.0	(50-50)	0.8 ± 0.5	(0.053-2.7)	17.9 ± 28.1	(0.50-168)
-083	135	149.3 ± 41.0	(100-200)	4.0 ± 2.4	(0.075-13.6)	4.0 ± 3.3	(0.00-14.1)
-085	99	155.1 ± 39.4	(100-200)	3.4 ± 1.8	(0.125-8.0)	4.5 ± 3.7	(0.18-21.3)
-087	103	248.5 ± 50.2	(200-300)	4.5 ± 2.8	(0.114-15.2)	6.4 ± 4.6	(0.25-21.5)
-104	114	150.9 ± 41.9	(100-200)	4.1 ± 2.4	(0.151-12.1)	4.2 ± 2.8	(0.42-20.4)
-105	181	101.0 ± 40.1	(33-150)	3.1 ± 2.0	(0.084-12.4)	4.2 ± 2.6	(0.17-16.3)
-127	102	163.5 ± 48.5	(100-200)	7.4 ± 3.3	(0.000-18.6)	3.2 ± 2.4	(0.00-17.8)

Goodness of Fit:

The model provided a good fit to the data as evidenced in the following plots of the dependent variable versus the model predicted and individual predicted results

Figure: Population Predicted Versus Observed Plasma Pregabalin Concentrations In Healthy Volunteers, Patients With Impaired Renal Function, Patients With Chronic Pain, Patients With Partial Seizures, And Patients With Generalized Anxiety Disorder

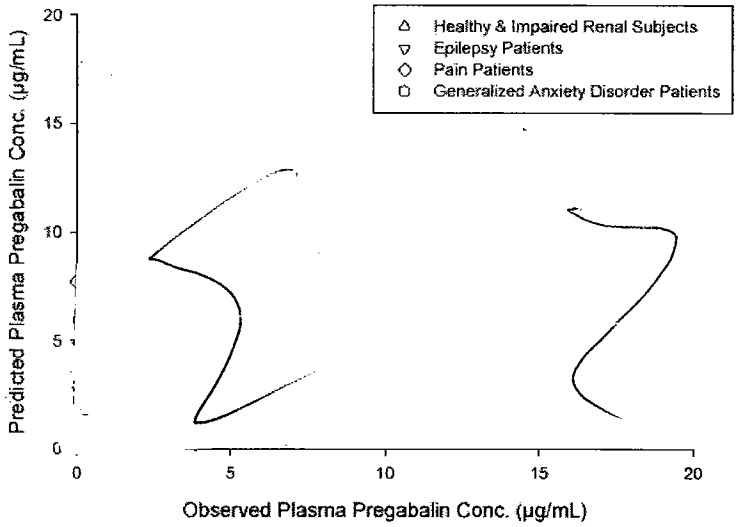
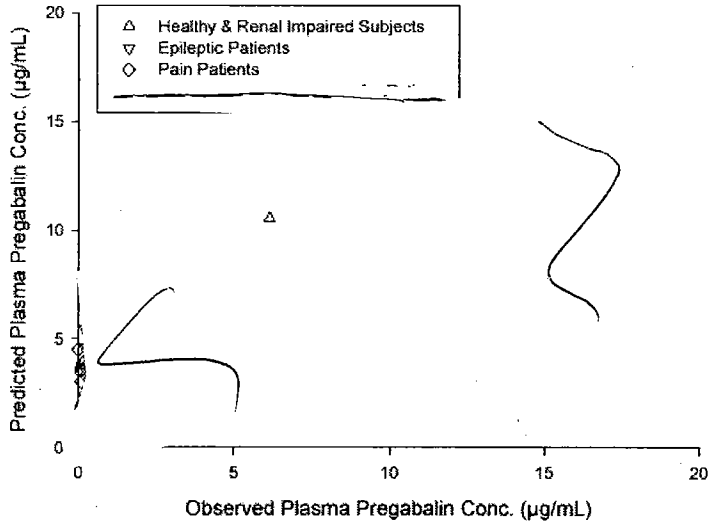


Figure: Individual Predicted Versus Observed Plasma Pregabalin Concentrations In Healthy Volunteers, Patients With Impaired Renal Function, Patients With Chronic Pain, Patients With Partial Seizures, And Patients With Generalized Anxiety Disorder



The population pharmacokinetic parameter estimates of the final model in all subjects is given in the following Table:

Parameter	θ	(95% CI)	%CV
$CL/F = \theta_{CLcr} \cdot CLcr \cdot CFLG + (\theta_{CLcr} \cdot \theta_{CLcrBP})\ (1-CFLG)$			27.6
θ_{CLcr}	0.0471	(0.0450-0.0492)	--
θ_{CLcrBP}	104.1	(98.5-109.6)	--
$Vd/F = (\theta wt*(WT/80.4)^{\theta pwr})*(1+GDER*\theta_{gder})$			17.3
θ_{wt}	43.8	(33.7-54.0)	
θ_{pwr}	0.568	(0.198-0.939)	
θ_{gder}	0.838	(0.719-0.957)	--
$KA = (EKEL \cdot \theta_{fast}) \cdot (1+\theta_{fed} \cdot (FED))$			176
θ_{fast}	77.5	(38.1-116.9)	--
θ_{fed}	-0.869	(-0.894 - -0.844)	--
TLAG (hr)	0.170	(0.159-0.182)	1.66

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.

Oral clearance (CL/F) increased proportionally to CLcr from zero up to a CLcr breakpoint value (CrCLBP) of approximately 104 mL/min. Above a CLcr value of 104 mL/min, pregabalin's CL/F was independent of CLcr. The pregabalin clearance estimates obtained in this study which included patients with generalized anxiety disorder were nearly identical to those obtained in the previous analysis which did not include the data from the generalized anxiety disorder studies. The slope relating CLcr to pregabalin clearance was 0.0471 in this analysis versus 0.0464 in the previously performed analysis. The breakpoint was estimated to be 104 mL/min in this analysis versus 107 mL/min for the analysis that did not include the generalized anxiety disorder studies. These results provide further evidence that clearance of pregabalin is independent of patient type and is solely dependent on renal function.

The population estimate of Vd/F was proportional to body weight centered on a subject weight of 80.4 kg with weight to the power of 0.568 (θ_{pwr}). After accounting for differences in weight, male Vd/F was approximately 16% higher than females. This could be attributed to the difference in percent body fat between males and females. This difference is not likely to be clinically significant.

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. These observations are consistent with a study in healthy volunteers that showed that the rate but not the extent of pregabalin absorption was reduced when given with a meal.

Intersubject variability, reported as the percent coefficient of variation (%CV), was about 28% for CL/F, 17% for Vd/F, 176% for KA, and 1.7% for TLAG. Residual variability is summarized in the following Table.

Population	Proportional		Additive (µg/mL)	
	%CV	(95% CI)	SD	(95% CI)
Healthy Volunteers and Patients With Impaired Renal Function	15.1	(0.00-21.8)	0.018	(0.00-0.077)
Patients With Chronic Pain, Patients With Partial Seizures, and Patients With Generalized Anxiety Disorder	24.3	(21.2-27.0)	0.403	(0.093-0.563)

The greater residual variability in the patients from the Phase 3 trials is most likely due to differences in study conditions (supervised dosing versus outpatient conditions) between healthy volunteers (including subjects from the renal impairment study) and patients in Phase 3 clinical trials.

Influence of Covariates on Pregabalin Clearance:

The final pharmacostatistical model was used to determine if the following covariates had an effect on pregabalin CL/F:

- patient status
- gender
- race
- age
- hormonal status and
- dosing regimen (BID vs TID)

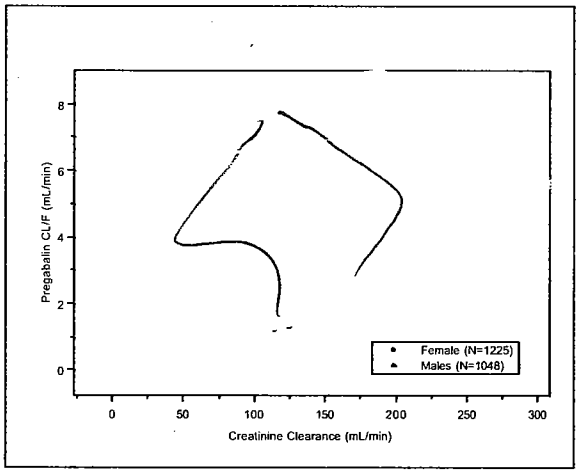
The influence of these categorical covariates was assessed as the percent change in pregabalin CL/F. The associated 90% confidence limits were also calculated as a measure of its possible influence on pregabalin CL/F, as given in the following Table. The first-order estimation method of NONMEM was used.

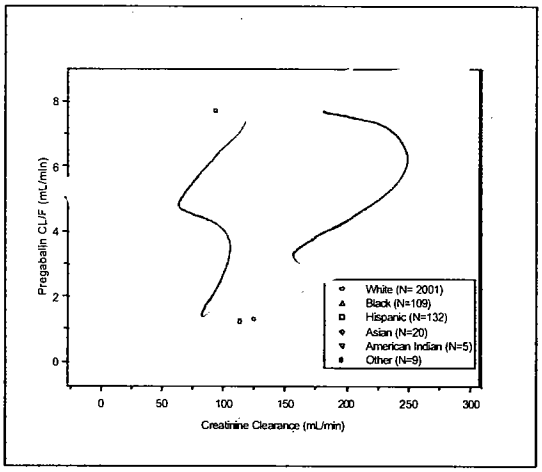
Covariate Tested	ΔMOF[a]	Ratio[b]	90% CI[c]
	Patient Status[d]		
Healthy Volunteers	-61.83	113.4	87.9 - 138.9
Patients With Partial Seizures	-0.72	101.3	92.0 - 110.6
Patients With Chronic Pain	-1.91	98.0	88.1 - 108.0
Patients With Generalized Anxiety Disorder	-56.46	88.2	75.9 - 100.6
	Gender[d]		
Females	-75.93	112.1	89.0 - 135.2
	Race[d]		
Whites	-53.96	90.4	77.6 - 103.2
Blacks	-13.77	111.6	97.8 - 125.4
Hispanics	-41.16	110.7	101.3 - 120.1
	Age[d]		
Age >65 Yr	-1.28	102.1	97.0 - 107.2

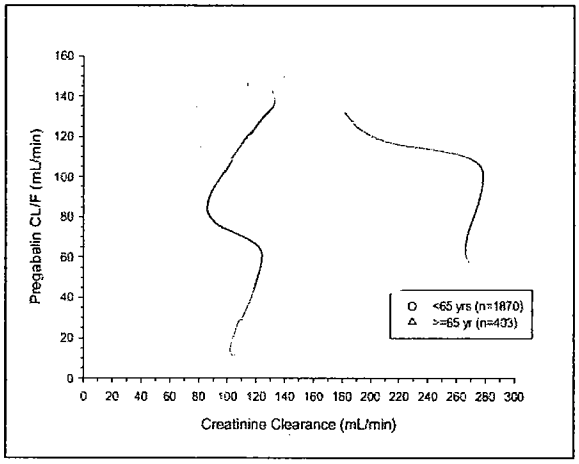
	Hormonal Status[d]		
Premenopausal	-19.98	94.3	89.5 - 99.1
Postmenopausal	-22.46	93.3	89.1 - 97.6
	Dosing Regimen[d] (BID & TID)		
BID	-47.14	93.8	82.9 - 104.6
TID	-29.91	93.0	80.2 - 105.8

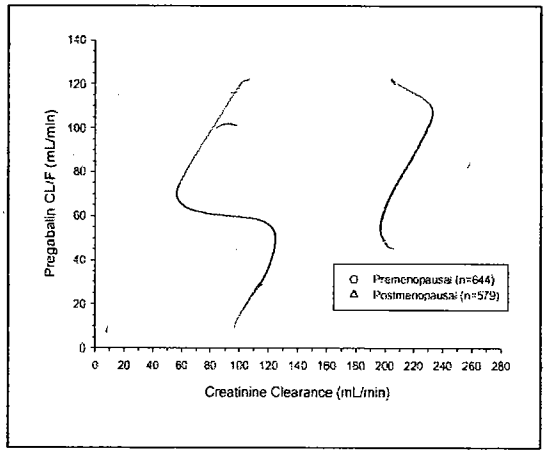
CI = Confidence interval.
[a] Change in minimum objective function values, -2 times the log of the likelihood, between the reference and full model with 1 degree of freedom.
[b] Ratio of Pregabalin CL/F for subjects associated with that covariate relative to all others (expressed as a percent).
[c] 90% CI estimate for the ratio expressed as a percent (±1.67·SE).
[d] Covariate tested relative to remaining subjects in the analysis.

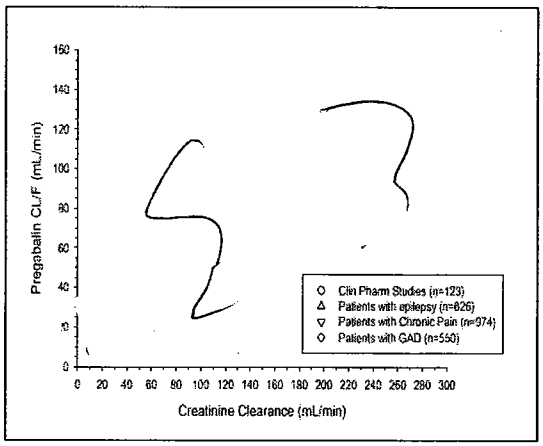
For all categorical covariates tested, the percent change in the population estimate of the pregabalin CL/F values was within -12% to +13%. The 90% CIs for most of the covariates were within 80% to 125%. Only the healthy volunteer, patients with generalized anxiety disorder, female subject and white groups fell slightly outside the 80% to 125% range. These differences in pregabalin CL/F are not expected to be clinically important. The following figures demonstrate that the covariates did not change the relationship between CrCL and CL.

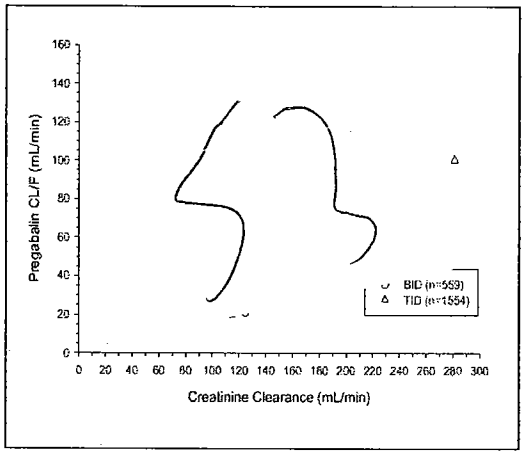












Conclusions:

- Pregabalin clearance (CL/F) is related to CLcr and this relationship is similar between healthy volunteers, patients with impaired renal function, patients with partial seizures, patients with chronic pain, and patients with generalized anxiety disorder.
- The relationship between pregabalin CL/F and CLcr is unaffected by gender, race, age, hormonal status, and dosing regimen.
- After accounting for differences in weight, male Vd/F was approximately 16% higher than females. This could be attributed to the difference in percent body fat between males and females. This difference is not likely to be clinically significant.

APPEARS THIS WAY
ON ORIGINAL

NONMEM CONTROL STREAM FOR STUDY 0013:

```
; Same final model as used in the overall pop pk analysis 764-03771
; Full model from bldstep3\nmin0.txt
; Using Full dataset of healthys, epileptic, pain, and GAD patients
; Modeling Data from pain Studies pain (14,29,30,31,32,45,104,105,127)
; epilepsy (007, 009, 011, 034)
; GAD (021, 025, 026, 083, 085, 087)
; & healthy volunteers (1,-2,-3,&-23) & renal (049)
; One compartment model with first order absorption (CL/F, V/F, and Ka)
; Additive + prop error term for residual variability
; prop and add term diff for hvs and pts
; include tlag
; CL/F covariates: no Yint, CLvsCLcr c brkpt, then indep,
; V/F covariates: Weight, Sex
; Ka covariates: none (multiple of ke) fasted vs all others
; tlag covariates: none
$INPUT OBS ID TFLG=DROP STDB=DROP STOL=DROP STTY=DROP DBOL=DROP
STUD=DROP SITE=DROP SUB AGE GDER RACE HT=DROP TWT PTST SCR=DROP
TCCR ALB=DROP BUN=DROP HORM=DROP TIME AMT=DOSE SS II DV EVID
ADDL=DROP FF CDOS=DROP DG DNUM SDMD DPD=DROP
ASA=DROP AMOX=DROP CIMT=DROP FAMO=DROP IBUP=DROP
LORA=DROP NAPX=DROP ACET=DROP ZOLP=DROP
; Following dropped input statement to match dataset
; CBZ=DROP LMG=DROP
; PB=DROP PHY=DROP TGB=DROP TPM=DROP VA=DROP AD=DROP INSU=DROP
; DIUR=DROP
; OBS : Data Line Number
; ID : Nonmem ID Number
; TFLG: Indicator variable, 0=validation or 1=model building dataset
; STDB: Double blind study number (if appropriate)
; STOL: Open label study number (if appropriate)
; STTY: For Phase 2/3 data, plasma data from 0=double-blind or 1=open label
; DBOL: FLAG, subject data in double-blind and open label studies 0=no 1=yes
; STUD: Study Protocol Number
; SITE: Protocol Site Number
; SUB : Protocol Subject Number
; AGE : Age of Subject in Years
; GDER: Gender 0=Females, 1=Males
; Race: Race 1=whites, 2=blacks, 3=Hispanic, 4=asian, 5=Native AM, 6=others
; THT : Height in cm
; TWT : Weight in kg
; PTST: Patient Status 1=healthy, 2=epilepsy, 3=pain, 4=anxiety, 5=other
; SCR : Serum creatinine (mg/dl)
; TCCR: Creatinine clearance in ml/min
; ALB : Albumin concentration
; BUN : Blood urea nitrogen
; HORM: Hormonal status, .=male, 1=premenopausal, 2=postmenopausal, 3=premenarchal
; TIME: Time postdose in hours
; AMT : Dose event: amount in mg
; SS : Steady-state data item: 0=not at ss, 1=reset ss dose, 2=ss dose
; II : Interdose Interval (hr)
; DV : Dependent Variable, observed plasma CI-1008 conc, mcg/ml
; EVID: Event Identification Number (0=conc, 1=dose, 4=reset dose)
; ADDL: Temporary variable called ADDL (not used)
; FF : Food Affect: Drug admin in 0=fasted state, 1=within 1 hr,
; 2= within 2 hr postdose, 3=unknown
; CDOS: Daily dose (mg/day)
; DG : Dose Group, Dose prior to pregabalin blood sample (mg)
; DNUM: Plasma sampled drawn after the 1st, 2nd, or 3rd dose of the day
; SDMD: Dosing regimen, 1= single dose, 2= q8h, 3=bid, 4=tid
; DPD : Doses per day
; Dropped comeds between dropped
; CBZ : Flag for carbamazepine concomitant administration
; LMG : Flag for lamotrogine concomitant administration
; PB : Flag for phenobarbital concomitant administration
; PHY : Flag for phenytoin concomitant administration
; TGB : Flag for tiagabine concomitant administration
; TPM : Flag for topiramate concomitant administration
; VA : Flag for valproic acid concomitant administration
```

```
; AD : Flag for oral antidiabetics concomitant administration
; INSU: Flag for insulins concomitant administration
; DIUR: Flag for diuretics concomitant administration
; Dropped
; ASA : Flag for aspirin concomitant administration
; AMOX: Flag for amoxicillin concomitant administration
; CIMT: Flag for cimetidine concomitant administration
; FAMO: Flag for famotidine concomitant administration
; IBUP: Flag for ibuprofen concomitant administration
; LORA: Flag for loratadine concomitant administration
; NAPX: Flag for naproxen concomitant administration
; ACET: Flag for acetaminophen (paracetamol) concomitant administration
; ZOLP: Flag for zolpidem concomitant administration
$DATA datafullgad IGNORE=#
$SUBROUTINES ADVAN2 TRANS2 SS2 INFN=infn.prn5
$PK
; ALLOWS FOR MISSING DEMOGRAPHIC INFORMATION
IF (NEWIND.LT.2) THEN
WT=TWT
CLCR=TCCR
ELSE
IF (TWT.NE.0) WT=TWT
IF (TCCR.NE.0) CLCR=TCCR
ENDIF
; SETS PTS =1 FOR HEALTHYS AND PTS=0 FOR PATIENTS
PTS=0
IF (PTST.EQ.1) PTS = 1
; FOOD EFFECT FFA=1 for fasted
FFA=0
IF (FF.EQ.0) FFA=1
; Sets breakpoint on CLcr
CFLG=0
IF (CLCR.LE.THETA(5)) CFLG=1
TVCL=THETA(1)*CLCR*CFLG+(THETA(1)*THETA(5))*(1-CFLG)
CL=TVCL*EXP(ETA(1))
TVV=THETA(2)*((WT/79.5)**THETA(7))*(GDER+THETA(8)*(1-GDER))
V =TVV*EXP(ETA(2))
EKEL = CL/V
TVKA = EKEL*(THETA(3))*(1+THETA(6)*(1-FFA))
KA = TVKA*EXP(ETA(3))
TVTL=THETA(4)
ALAG1=TVTL*EXP(ETA(4))
TLAG=ALAG1
S2=V
$ERROR
Y1 = F*(EXP(ERR(1))*PTS+(1-PTS)*EXP(ERR(2)))
Y = Y1 + (ERR(3)*PTS+(1-PTS)*ERR(4))
IPRED=Y
$THETA (0.0, 0.04, 300) ; 1 Pop CL/F ftn CLCR
$THETA (0.0, 40, 200) ; 2 Pop V/F FOR MALES
$THETA (0.6, 75, 600.) ; 3 POP KA FOR FASTED STATE
$THETA (0.01, 0.15, 0.5) ; 4 POP TLAG
$THETA (40.0, 100, 500) ; 5 POP Breakpoint for CLCR VS CL/F
$THETA (-1, -.9, 10) ; 6 FR OF FASTED KA FOR ALL OTHERS
$THETA (-1, 0.7, 10) ; 7 WEIGHT ON V
$THETA (-1, 0.9, 10) ; 8 FR OF MALE V FOR FEMALES
$OMEGA 0.05 ; CL
$OMEGA 0.03 ; V
$OMEGA 2.5 ; Ka
$OMEGA 0.8 ; TLAG
$SIGMA 0.02 ; Healthys
$SIGMA 0.02 ; Patients
$SIGMA 0.01 ; Healthys additive
$SIGMA 0.20 ; Patients additive
$EST NOABORT SIGDIGITS=3 MAXEVAL=9000 PRINT=30 POSTHOC
$COV
$TABLE ID TIME IPRED
NOPRINT ONEHEADER FILE=sdtab98
$TABLE ID V CL KA TLAG
NOPRINT ONEHEADER FILE=patab98
$TABLE ID AGE WT CLCR
```

```
NOPRINT ONEHEADER FILE=cotab98
$TABLE ID GDER RACE FF DG SDMD PTST
NOPRINT ONEHEADER FILE=catab98
$TABLE ID AGE GDER RACE WT CLCR FF SDMD DG V CL KA TLAG
NOPRINT ONEHEADER FIRSTONLY NOAPPEND FILE=dmpktab98
$TABLE OBS ID EVID TIME IPRED PTST DG SDMD
       NOPRINT ONEHEADER FILE=plots98
```

Study 3767: Exposure-Response Analysis of Pregabalin Add-On Treatment of Patients With Refractory Partial Seizures

Objectives:

To describe the exposure-response (seizure frequency) relationship of pregabalin add-on treatment following multiple dosing in patients with refractory partial seizures using a population approach, and to identify the factors that influence this relationship

Study Design:

The following studies were used in this exposure response analysis:

Protocol	Design	Duration	Population	Pregabalin Dose
1008-009	Double-blind, parallel, placebo-controlled, randomized Subjects 18 and older	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic). 240 patients anticipated.	600 mg/day (300 mg BID) 600 mg/day (200 mg TID)
1008-011	Double-blind, parallel, placebo-controlled, randomized Subjects 18 and older	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic). 240 patients anticipated.	150 mg/day (50 mg TID) or 600 mg/day (200 mg TID)
1008-034	Double-blind, parallel, placebo-controlled, randomized Subjects 12 and older With body weight ≥ 40 kg	12 weeks	Patients with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic). 400 patients anticipated.	50 mg/day (25 mg BID), 150 mg/day (75 mg BID), 300 mg/day (150 mg BID), 600 mg/day (300 mg BID)

Dataset:

A total of 1042 patients with medically uncontrolled partial seizures from Studies 1008-009, 1008-011, and 1008-034 were included in the PK/PD analysis of seizure frequency. In the full dataset, 3886 observations were collected in 1052 subjects. Study 1008-009 had 312 patients, Study 1008-011 had 287 patients, and Study 1008-034 had 447 patients. Nine subjects were excluded for analysis from the original 1052 because the seizure diary was absent. One patient was excluded as an outlier because from the day he was randomized to treatment (600 mg pregabalin daily) he experienced almost continuous seizures and was withdrawn from the study on Day 12 (1129 seizures).

The data included the 8-week baseline phase and the 12-week double-blind phase. Seizure frequency was normalized for 28 days so that the information consisted of 4 observations per individual, the baseline value and Months 1, 2, and 3 expressed as number of seizures per month.

The population characteristics are summarized in the following Table:

Population Characteristics: Continuous Variables[a] (Mean ± SD)

Study	N	Age (yr)	Weight (kg)	Height (cm)	CrCL (mL/min)
1008-009	308	39.2 ± 11.8	76.5 ± 19.2	168 ± 12.2	106.4 ± 30.8
1008-011	287	37.0 ± 11.4	73.1 ± 16.5	169 ±10.4	118.7 ± 33.6
1008-034	447	38.4 ± 11.9	78.5 ± 20.6	168 ± 10.5	109.1 ± 31.0
All Studies	1042	38.2 ± 11.8	76.4 ± 19.2	168.1± 11.0	110.9 ± 32.1
(Range)	2	(12-82)	(41-180)	(99-206)	(39-284)

a Value of the variable at the time of screening.

Characteristics of the Population: Categorical Variables [N (%)]

Variables	009		011		034		All	
Gender								
Male (1)	156	(51)	145	(51)	216	(48)	517	(50)
Female (0)	152	(49)	142	(49)	231	(52)	525	(50)
Ethnic Origin								
White	263	(85)	2669	(93)	380	(85)	909	(87)
Black	12	(4)	5	(2)	31	(7)	48	(5)
Hispanic	23	(7)	5	(2)	25	(6)	53	(5)
Asian or Pacific Islander	4	(1)	4	(1)	7	(2)	15	(1)
American Indian or Alaskan Native	1	(0)	0	(0)	1	(0)	2	(0)
Other	5	(2)	7	(2)	3	(1)	15	(1)

a Value of the variable at the time of the first dose administered.

Sponsor's Exposure-Response Model:

A subject-specific random-effects model was used to characterize the relationship between monthly seizure frequency and pregabalin dose in individual patients, taking into account placebo effect. Maximum likelihood estimates were obtained with use of the Laplacian estimation method implemented in the Nonlinear Mixed Effects Modeling (NONMEM, Version V 1.1) program.

The number of seizures is a discrete variable that can take only non-negative integer values (ie, the response is a count and cannot be a fraction). The response is therefore modeled as a Poisson process with mean . The probability that the number of seizures per month (Y) equals x is given by the equation.

$$P(Y = x) = e^{-\lambda}\frac{\lambda^x}{x!}$$

The mean number of seizures per month (λ) was modeled as a function of drug exposure, placebo effect, and subject specific random effects. Drug and placebo treatments were modeled using the following general structure;

$$\lambda = Base \cdot (1 + f_d + f_p) \cdot e^{\eta}$$

where Base is the estimated number of seizures per month reported in the baseline period before treatment, and f_d and f_p are functions describing the drug effect and placebo effect respectively, and η is the subject specific random effect.

A mixture model, a model that implicitly assumes that some fraction p of the population has one set of typical values of response, and that the remaining fraction 1-p has another set of typical values, was fit to the data. Both sets of typical values and the mixing fraction p was estimated by NONMEM. NONMEM assigns a value of 1 or 2 according to whether it computes outputs for Population A or B, respectively, as defined by the user. The same records were called twice for the same individual and NONMEM computes different outputs according to the variables assigned to the 2 subpopulations. This process is carried out for each individual record repeatedly as parameter values vary. The fitting algorithm assigns subjects to the 2 categories so that the final fit is optimal according to a likelihood function.

Criteria for model building:

The goodness of fit and hypotheses testing of different models was evaluated using the following criteria: Change in the objective function, and visual inspection of predicted versus observed plots. Any decrease of >6.6 in the objective function during model building indicated that a proposed model with 1 additional parameter is better than the reduced reference model ($p < 0.01$). The associated change in objective function for the addition of 2 parameters that can be entered uniquely, was 9.2. The full model thus obtained was tested by removing (or adding back if appropriate) parameters one at a time. The final model included only those parameters that produce an increase in the objective function >10.8 for 1 degree of freedom when they are excluded or an equivalent decrease when they are included ($p < 0.001$). The associated change in objective function for the addition or subtraction of 2 parameters that can be entered uniquely, was 13.8. The p value is adjusted to account for the multiple comparisons.

Mixture Model Evaluation:

Because the same data must be used to both classify refractory versus nonrefractory patients as well as to assess the degree of response within each subset, simulation studies were undertaken by the sponsor to assess the performance of this methodology. The intent of these simulations was to provide some assurance the mixture analysis performed could reliably distinguish the presence of a mixture while not spuriously finding mixtures

in a homogeneous population. The probability of concluding a mixture when it is not present and the probability of concluding a mixture when one is present was estimated. In the first case in only 1 out 100 sample populations was a mixture erroneously concluded. In the second case 6 out of 100 were erroneously concluded to be a non mixture when one was present. The predictive performance of the mixture model was very good. The conclusion was that the mixture analysis performed could reliably distinguish the presence of a mixture while not spuriously finding mixtures in a homogeneous population.

Basic Model:

The initial model was constructed presuming that seizure frequency was constant during baseline as well as randomized treatment phases. The only parameter estimated was λ , the mean number of seizures per month over the duration of the study. Intersubject variability in λ was modeled exponentially.

The various factors explored in the subsequent model were:

Effect of pregabalin on seizure frequency:	Describes an asymptotic decrease in seizure frequency , suggesting an Emax model provided a better fit to the data. (ΔMOF= -565). A linear exposure response model was attempted by the sponsor, but could not be concluded successfully. The Emax parameter was expressed as a fraction of the baseline and is referred to as the maximal fractional change in baseline (FCB).
Effect of placebo on seizure frequency:	Drug treatment was modeled as an Emax model and placebo treatment as a constant. (ΔMOF= -52).
Effect of population mixture:	The data suggested that there may be 2 subpopulations of patients whorespond to pregabalin differently. A mixture model assumed that for each individual there were 2 candidate submodels. A group (A) that showed a dose response relationship after pregabalin and a group (B) that that did not show improvement with drug treatment since the fractional change from baseline was not different (ΔMOF = -2307).
Effect of differential placebo:	This describes two different placebo responses for the two populations A and B (ΔMOF = -526).

Effect of average steady state (SS) plasma concentrations as a measure of exposure:
Describes SS concentrations as a measure of exposure instead of dose. (ΔMOF = -63).

Effect of gender:	Describes the influence of gender on the fractional reduction in seizure frequency (ΔMOF = -34).
Effect of dissociating pregabalin and placebo treatments:	There is no association of drug treatment with placebo treatment (ΔMOF = -71).
Effect of dose as measure of exposure:	Described dose as a measure of exposure instead of SS concentrations with gender in the model (ΔMOF = +4), therefore dose is adequate as a measure of exposure in the model.
Effect of differential baseline:	Considered the possibility that the baseline seizure frequency may have differed between the 2 subpopulations . Patients that did not respond to drug treatment and who had an increase in seizure frequency with placebo treatment (Population B) appeared to have on average a significantly higher baseline seizure frequency (15.4/month) than Population A (10.9/month). (ΔMOF = -14)
Effect of Dose Independent Treatment Effect on a Subpopulation:	Considered the possibility that in Population B there are patients that show an insignificant response irrespective of dose. (ΔMOF = -1); thus the simpler model was preferred.
Effect of maximal fractional reduction in seizure frequency in a subpopulation:	Fixed maximal fractional reduction (FCB) to 100% in population A (ΔMOF = 0), therefore fixing FCB is adequate.
Effect of hormonal status in women:	This examined the influence of menopausal status in women on FCB in patients that respond to drug treatment (Population A). Inclusion of an indicator variable for menopausal status resulted in a small improvement in the fit that was statistically significant (ΔMOF = -8). The change in FCB was not appreciably different from that for females in general and the 95% confidence interval included 1. Because this difference was marginal both in terms of fit and parameter estimate hormonal status was not included in subsequent models.
Effect of Age on Response to Pregabalin:	The influence of age on the potency (2) of pregabalin in patients who respond to drug

treatment (ΔMOF = -2), therefore not included in subsequent models.

Full Model:

From the model building process one model (given below) was picked and above described covariates and parameters were eliminated and reintroduced to select the final model. The criteria was a change in objective function of 10.8 in either direction.

$$Population\ A = \theta_3$$

$$\theta_1 \cdot \left(1 - \frac{\theta_2 \cdot G \cdot D}{\theta_2 + D} \cdot D_1 - \theta_6 \cdot D_0\right) \cdot e^{\eta_1}$$

$$Population\ B = 1 - \theta_3$$

$$\theta_0 \cdot (1 - \theta_4 \cdot D_1 - \theta_5 \cdot D_0) \cdot e^{\eta_2}$$

The covariates reintroduced one at a time were:

- The maximal fractional reduction in response fixed to 1 (ΔMOF = 0), therefore retained in final model
- Both sub populations demonstrate a dose-response (ΔMOF = 0), therefore retained in the full model
- There is only one population with placebo response (ΔMOF = +620), suggesting at least two populations with placebo response, therefore retain two different placebo responses in final model
- Baseline does not differ in two populations (ΔMOF = +12), suggesting baseline does differ, so retain different baselines in final model
- Average SS plasma concentration is a better measure of exposure than dose (ΔMOF = -6), therefore not included in final model and the full model was retained
- Placebo effect is additive in drug treatment, (ΔMOF = +204), suggesting placebo and treatment effect are best if estimated separately.
- Gender removed (ΔMOF = +94), therefore gender retained in final model

Final Model:

The following equations describe the final model, which was a mixture model:

$$\underline{Population\ A \quad (75\%)}$$

$$\lambda = Base_A \cdot \left(1 - \frac{FCB_A \cdot GEN \cdot dose}{ED_{50} + dose} \cdot D_1 - Placebo_A \cdot D_0\right) \cdot e^{\eta_1}$$

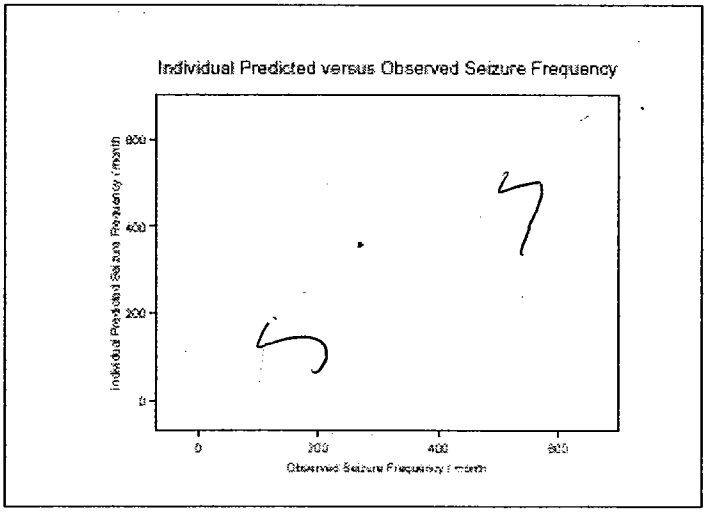
$$\underline{Population\ B \quad (25\%)}$$

$$\lambda = Base_B \cdot \left(1 - FCB_B \cdot D_1 - Placebo_B \cdot D_0\right) \cdot e^{\eta_2}$$

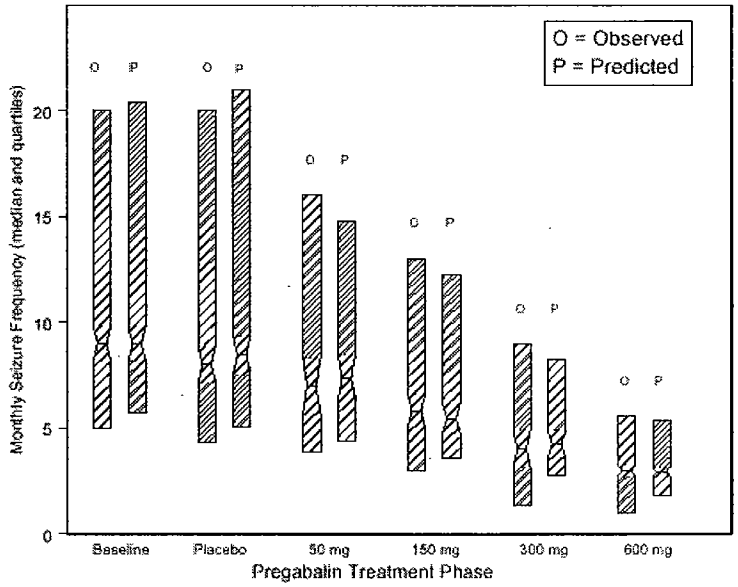
Where:

$Base_A$ =	Baseline seizure frequency for Subpopulation A (per month).
$Base_B$ =	Baseline seizure frequency for Subpopulation B (per month).
FCB_A =	Maximal fractional change in baseline seizures due to drug treatment for Subpopulation A.
FCB_B =	Fractional change in baseline seizures due to drug treatment for Subpopulation B.
GEN =	Proportional difference of males relative to females in FCB_A.
ED_{50} =	Dose which provides a 50% reduction in FCB_A.
$Placebo_A$ =	Influence of placebo on baseline seizure frequency for Subpopulation A.
$Placebo_B$ =	Influence of placebo on baseline seizure frequency for Subpopulation B.
D_1 =	1 during drug treatment and 0 during placebo treatment.
D_0 =	0 during drug treatment and 1 during placebo treatment.
η_1 =	intersubject random effect for Population A.
η_2 =	intersubject random effect for Population B.
$Var(\eta 1)$ =	$Var(\eta 2) = \Omega$

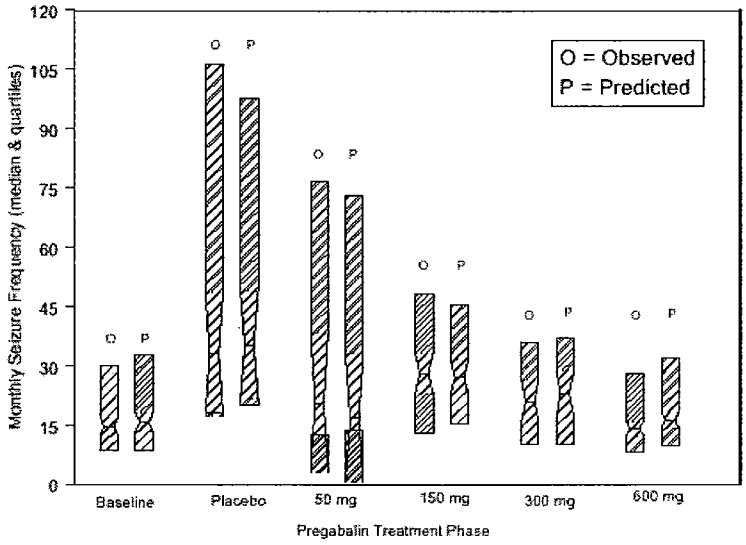
The following plot shows the individual predicted versus observed seizure frequency:



Best Available Copy



Responders



Non-Responders

Figure: Boxplot of Seizure Frequency Versus Dose for the responders and non-responders

The estimated population parameters for the dose response analysis is given in the following Table:

Model	Estimate (95% CI)	√Ω (95% CI)
Population A (75%)		
^{Base}A (seizures per month)	11.1 (10.2, 12.0)	1.0 (0.95, 1.05)
^{FCB}A (female)	1	
GEN (male relative to female)	0.78 (0.68, 0.88)	
$^{ED}50$ (mg)	186 (91.4, 280.6)	
$^{Placebo}A$	0.11 (0.03, 0.18)	
Population B (25%)		
^{Base}B (seizures per month)	15.1 (12.3, 17.9)	
^{FCB}B	-0.26 (–0.66, 0.15)	
$^{Placebo}B$	-1.44 (-2.22, -0.66)	

Reviewer's Comment:

The sponsor did not include CLCR in the final model, although the dataset had patients with CLCR >39.5 ml/min. Dosing was not corrected for CLCR during the clinical trials. Although the sponsor did use average steady state plasma concentration as a measure of exposure as compared to dose which is the same as using an AUC model. Css was individualized with CrCL based on the following equation:

Css= Dose/(24*0.047*CrCL)

This model was not superior to the model using Dose, suggesting the sponsor's model is acceptable.

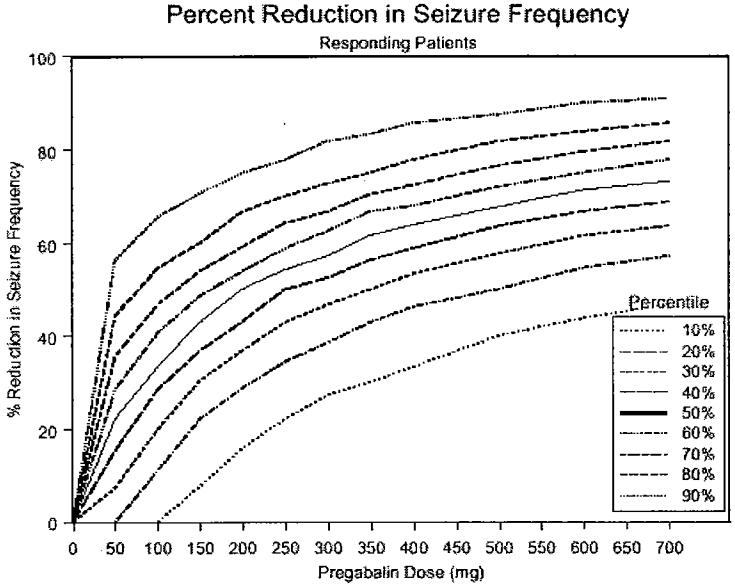
Conclusions:

- The mixture analysis revealed that 75% of the patients were responders (Subgroup A) and 25% were non-responders (Subgroup B). These results are consistent with literature values that establish that approximately 30% of patients are refractory to drug treatment (BMJ 1996; 313: 1169-74). Therefore, pregabalin add-on treatment in refractory patients shows a dose-response relationship in 3 out of 4 patients with partial seizures.

- In the subset of patients that are not refractory to pregabalin, a dose of approximately 186 mg daily is expected to decrease the baseline seizure rate by about 50% of maximum.

The following figure shows the expected percent reduction in seizure frequency with increasing dose, which was generated using Monte Carlo simulation along with the pharmacodynmaic parameters for Population A.

11000 individuals were simulated (50% female) at doses from 50 to 700 mg pregabalin daily. The individuals were pared to exclude estimates with a baseline value less than 6 seizures per month to emulate the inclusion criteria for these studies. The result was 8852 individuals of which 51% were female. The percent reduction from baseline seizure frequency was calculated for each individual simulated. Percentiles were determined for percent reduction in seizure frequency at each dose and is presented in the following Figure:



From the figure, the percent of reduction in seizure frequency at a given dose in 10%, 50% and 90% of the population is shown in the following Table:

Reduction in seizure frequency given in %:

Dose	Percent of population		
	10%	50%	90%
	% Reduction in seizure frequency		
150 mg	71%	43%	7.8%
300 mg	82%	57%	27%
600 mg	90%	71%	44%

This shows that 50% of population will achieve 43% reduction in seizure frequency with 150 mg dose and 71% reduction reduction in seizure frequency with 600 mg dose.

- In general, for a given pregabalin dose men have a slightly lower response (22%) than females.

- The dose-response relationship of pregabalin on seizure frequency was independent of age and menopausal status of women.

NONMEM CONTROL STREAM FOR STUDY 3767 (SPONSOR'S)

```
$PROB POP. COUNT DATA: SEIZURE EPISODES
;using total seizure counts, one eta
$INPUT DROP PROT ID DOSE REG TRT TIME SZNU SZDA SZRT=DV RR DROP RSP AGE SEX
$INPUT RACE HT WT SCR CRT EVID=DROP MDV=DROP

$DATA gabatime3.txt IGNORE=#
;
;FRAC= 1 month calculated as 28 days
$PRED
EST = MIXEST
FLG = 0
IF(TIME.GT.0.5)FLG=1
GEN=1
IF(SEX.EQ.1)GEN=THETA(8)
IF(DOSE.GT.0)THEN
D1=1
D0=0
ELSE
D1=0
D0=1
ENDIF
BASE1 = THETA(1)*EXP(ETA(1)) ;typical baseline count
EC50 = THETA(2)
EMAX1 = THETA(3)*GEN
EMAX2 = THETA(4)
PLAC1 = THETA(6)*FLG
PLAC2 = THETA(7)*FLG
BASE2 = THETA(9)*EXP(ETA(1)) ;typical baseline count
;typical value of count over period
IF (MIXNUM.EQ.1) THEN
A = PLAC1*D0 + DOSE*EMAX1/(EC50+DOSE).* FLG *D1
CNTW= BASE1 *(1-A) ;mean count over a MONTH
ELSE
A = PLAC2*D0 + EMAX2 * FLG *D1 ;fractional reduction
CNTW= BASE2 *(1-A) ;mean count over a MONTH
;due to drug
ENDIF
FRAC=1 ;period of counts=one MONTH
CNT=FRAC*CNTW ;indiv specific count over obs per.
;Y=(EXP(-CNT)*CNT**DV)/DV!
;DV! needed to keep the numerics
; in computational bounds
;Y=EXP(-CNT+DV*LOG(CNT)-LOG(DV!))
;Stirlings formula for log DV factorial
IF (DV.GT.0) THEN
LDVFAC=(DV+.5)*LOG(DV)-DV+.5*LOG(6.283185)
ELSE
LDVFAC=0
ENDIF
B=LOG(CNT)
Y=-2*(-CNT+DV*B-LDVFAC)
$THETA
(12) ;1 base
(180) ;2 ed50
(1 FIXED) ;3 emax1
(-0.3) ;4 emax2
(0,0.7,1) ;5 mix fraction
(0.1) ;6 placebo responder
(-1) ;7 placebo nonresponder
(0.8) ;8 gender effect (female)
(16) ;9 baseline for nonresponders
$MIX
NSPOP=2
P(1)=THETA(5)
P(2)=1-THETA(5)
$OMEGA 2
```

```
$ESTIMATION PRINT=1 MAXEVAL=9999 NOABORT METH=COND LAPLACE -2LL
$COV
;$SCAT CNT VS DV UNIT
;$SCAT ID VS RES
;$SCAT E VS DOSE ORD0
```

NONMEM CONTROL STREAM FOR STUDY 3767 (REVIEWER'S)

```
$PROB POP. COUNT DATA: SEIZURE EPISODES
;using total seizure counts, one eta
$INPUT HASH OBS=DROP PROT ID DOSE REG TRT TIME SZNU SZDA SZRT=DV RR PER=DROP
    RSP AGE SEX RACE HT WT SCR CLCR EVID=DROP MDV=DROP

$DATA ..\s3767.csv IGNORE=#
;
:FRAC= 1 month calculated as 28 days

$PRED
EST = MIXEST
FLG = 0
IF(TIME.GT.0.5)FLG=1
GEN=1
IF(SEX.EQ.1)GEN=THETA(8)
IF(DOSE.GT.0)THEN
  D1=1
  D0=0
ELSE
  D1=0
  D0=1
ENDIF
BASE1 = THETA(1)*EXP(ETA(1))                ;typical baseline count
EC50  = THETA(2) ;*(CLCR/106)**THETA(10)    ; correcting for CLCR
EMAX1 = THETA(3)*GEN
EMAX2 = THETA(4)
PLAC1 = THETA(6)*FLG
PLAC2 = THETA(7)*FLG
BASE2 = THETA(9)*EXP(ETA(1))                ;typical baseline count
;typical value of count over period
BS1   = BASE1                ;typical baseline count
EMX1  = EMAX1
EMX2  = EMAX2
PLC1  = PLAC1
PLC2  = PLAC2
BS2   = BASE2

GT105 = 0
IF(CLCR.GT.105) GT105=1

CL= 0.0459*CLCR*(1-GT105)+0.0459*105*GT105
AUC= DOSE/CL

IF (MIXNUM.EQ.1) THEN
    A = PLAC1*D0 +  AUC*EMAX1/(EC50+AUC) * FLG *D1
    CNTW= BASE1 *(1-A)                      ;mean count over a MONTH
 ELSE
    A = PLAC2*D0 +  EMAX2 * FLG *D1         ;fractional reduction
    CNTW= BASE2 *(1-A)                      ;mean count over a MONTH
                                ;due to drug
 ENDIF

FRAC=1                                  ;period of counts=one MONTH

CNT=FRAC*CNTW           ;indiv specific count over obs per.
IPRED=CNT
;Y=(EXP(-CNT)*CNT**DV)/DV!
;DV! needed to keep the numerics
;       in computational bounds
:Y=EXP(-CNT+DV*LOG(CNT)-LOG(DV!))
;Stirlings formula for log DV factorial

IF (DV.GT.0) THEN
  LDVFAC=(DV+.5)*LOG(DV)-DV+.5*LOG(6.283185)
ELSE
  LDVFAC=0
ENDIF
B=LOG(CNT)
Y=-2*(-CNT+DV*B-LDVFAC)
```

```
$THETA
$THETA
   (0,12)          ;1 base
   (0,180)         ;2 ed50
   (1 FIXED)       ;3 emax1
   (-0.3)          ;4 emax2
   (0,0.7,1)       ;5 mix fraction
   (0.1)           ;6 placebo responder
   (-2,-1.44,0)        ;7 placebo nonresponder
   (0,0.78,1)          ;8 gender effect (female)
   (0,15.1,20)         ;9 baseline for nonresponders
  ; (0,2.62,5)        ;10 corrected for diff CLCR
$MIX
   NSPOP=2
   P(1)=THETA(5)
   P(2)=1-THETA(5)
$OMEGA 1
$ESTIMATION PRINT=1 MAXEVAL=9999 NOABORT METH=COND LAPLACE -2LL
$COV
;$SCAT CNT VS DV UNIT
;$SCAT ID VS RES
;$SCAT E VS DOSE  ORD0
$TABLE ID TRT REG EST DOSE TIME CNT
    NOPRINT ONEHEADER FILE=p113aclcrmod.fit
$TABLE ID DOSE PROT ETA1 ONEHEADER NOPRINT NOAPPEND FIRSTONLY FILE=p113.tab
$TABLE ID TIME DOSE IPRED EST BS1 BS2 EMX1 EMX2 PLC1 PLC2 AUC CLCR ETA1
    NOPRINT NOAPPEND ONEHEADER FILE=mytab2
```

15 Page(s) Withheld

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

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

*Withheld Track Number: Clin Pharm/Bio-*6

4.2 APPENDIX II

PROPOSED PACKAGE INSERT

52 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2

4.3 APPENDIX III

OCPB FILING REVIEW

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N21-446, N21-723 N21-724, [redacted]	Brand Name	LYRICA
OCPB Division (I, II, III)	I	Generic Name	Pregabalin
Medical Division	120	Drug Class	Binding to Alpha-2 delta protein of Ca channels
OCPB Reviewer	Veneeta Tandon	Indication(s)	• Neuropathic pain • Posttherpetic neuralgia • [redacted] • Epilepsy
OCPB Team Leader	Ramana Uppoor	Dosage Form	Capsules, 25, 50, 75, 100, 150, 200, 225 and 300 mg
		Dosing Regimen	Neuropathic pain: starting dose 75 mg BID (150 mg/day), range 150-600 mg/day. Dose increase at an interval of 3-7 days Epilepsy: starting dose 75 mg BID (150 mg/day), range 150-600 mg/day. Dose increase at an interval of 7 days.
Date of Submission	10/30/03	Route of Administration	Oral
Estimated Due Date of OCPB Review	7/15/04	Sponsor	Pfizer
PDUFA Due Date	8/30/04	Priority Classification	1S for [redacted] and Epilepsy, 1P for Neuropathic pain
III. Division Due Date			

Background:

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (a 2-d protein) of voltage-gated calcium channels in the central nervous system, potently displacing
[^{3}H]-gabapentin. Binding to the a 2-d site is required for analgesic, anticonvulsant and anxiolytic activity in animal models. The NDA will be a coordinated review with HFD 170. The indication for neuropathic pain has received a priority review and will be reviewed by Dr. Sue Chih Lee. She will review the general PK. PK-PD related t[redacted] and Epilepsy indications will be reviewed by this reviewer.

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.				
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		
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	x	2		
Patients-				
single dose:				
multiple dose:	x			From Phase III studies
Dose proportionality -				
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x			
In-vivo effects of primary drug:	X	11	5 by this reviewer	• Valproic Acid- (Epilepsy patients)-2 Studies • Carbamazepine (Epilepsy patients) • Lamotrigine (Epilepsy patients) • Phenytoin (Epilepsy patients) • Lorazepam (healthy) • Gabapentin (healthy)-2 studies • Others-oral contraceptive, oxycodone, ethanol
In-vitro:	x			
Subpopulation studies -				
ethnicity:	x			Population analysis
gender:	x			Population analysis
pediatrics:				Pediatric waiver deferral for epilepsy
geriatrics:	x	1		Population analysis as well as study in elderly Japanese
renal impairment:	x	2		Varying degree of renal impairment and hemodialysis study
hepatic impairment:				
AIDS patients				
PD:				
Phase 2:	x			
Phase 3:	x			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	4	2 by this reviewer	Neuropathic pain [redacted] and Epilepsy PK and Safety
Population Analyses -				
Data rich:				
Data sparse:	x	3	3 by this reviewer	Effect of age, gender, race, menopause, food, BID and TID regimens, renal function, AED coadministration from 6 population analyses of various disease states
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				

traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		
Dissolution:	x			
(IVIVC):				
Bio-waiver request based on BCS	X			
BCS class	x			Class I
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				Deferred
Literature References				
Total Number of Studies		22+6 POP PK+4 PK-PD+ in vitro studies	5 DDIs and 3 POP PK and 2 PK-PD	

Filability and QBR comments

IV.	"X" if yes	Comments
V. 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?
VI. Comments sent to firm ? **VII.**	**X**	Comments to be sent to firm (or attachment included). FDA letter date if applicable. • Population PK Report 3295 is not provided and is indicated that it would be available upon request. Please provide this report. • Some NONMEM files in the "FDAdatafiles" folder under the "Programs" folder were unavailable due to compatibility reasons with our electronic system. For future submissions, please "ALWAYS USE EXTENSIONS" with the files otherwise they are unavailable to us. Files with extensions other than 'txt' and 'xpt' are not compatible with our system and hence unavailable to us. For this submission as well as future submissions please use the following format and extension: ■ Control streams: filename_ctl.txt ■ Output Listings: filename_out.txt ■ Data : filename.xpt In some cases the files could be retrieved, however for study 00010 and 00013 the following files under the "Programs' folder were missing. Please provide the following files Study 0010: ___ r1: output file for basic model ___r10: output file for basic model ___ Summary.txt: output files for two runs Study 0013: ___infn.prn5 ___nmoutbasic.txt ___nmoutfinal.txt ___datafullgad Is datafullgad file the same as s0013.xpt file under the 'POPPK' folder? If it the same it need not be resent. To avoid further confusion in data analysis we would appreciate if all the contents of the folder labeled 0010 and 0013 under the "Program" folder are resubmitted. Either way the above mentioned naming convention should be followed. Forexample the 'infn.prn5' file should be submitted as infn_ctl.txt. If you need any clarification, please do not hesitate to contact us.
QBR questions (key issues to be considered)		• **Are the proposed dosing recommendations appropriate based on PK-PD for efficacy and safety for the [redacted] and Epilepsy patient population?** • **Is dosing adjustment needed in the epileptic population due to concomitant administration of antiepileptic drugs (7 drugs evaluated)** • **Has QTc effect been adequately evaluated?**
Other comments or information not included above		

Primary reviewer Signature and Date	**Veneeta Tandon, Ph.D**
Secondary reviewer Signature and Date	**Ramana Uppoor, Ph.D**

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

/s/

Veneeta Tandon
7/1/04 03:46:06 PM
BIOPHARMACEUTICS

Jogarao Gobburu
7/1/04 03:55:52 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/2/04 05:59:38 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	N21-446, N21-723 N21-724, [redacted]	**Brand Name**	LYRICA
OCPB Division (I, II, III)	I	**Generic Name**	Pregabalin
Medical Division	120	**Drug Class**	Binding to Alpha-2 delta protein of Ca channels
OCPB Reviewer	Veneeta Tandon	**Indication(s)**	• Neuropathic pain • Posttherpetic neuralgia [redacted] • Epilepsy
OCPB Team Leader	Ramana Uppoor	**Dosage Form**	Capsules, 25, 50, 75, 100, 150, 200, 225 and 300 mg
		Dosing Regimen	Neuropathic pain: starting dose 75 mg BID (150 mg/day), range 150-600 mg/day. Dose increase at an interval of 3-7 days [redacted] Epilepsy: starting dose 75 mg BID (150 mg/day), range 150-600 mg/day. Dose increase at an interval of 7 days.
Date of Submission	10/30/03	**Route of Administration**	Oral
Estimated Due Date of OCPB Review	7/15/04	**Sponsor**	Pfizer
PDUFA Due Date	8/30/04	**Priority Classification**	1S for [redacted] and Epilepsy, 1P for Neuropathic pain
Division Due Date			

Background:

Pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). It interacts with an auxiliary subunit (α 2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Binding to the α 2-δ site is required for analgesic, anticonvulsant and anxiolytic activity in animal models. The NDA will be a coordinated review with HFD 170. The indication for neuropathic pain has received a priority review and will be reviewed by Dr. Sue Chih Lee. She will review the general PK. PK-PD related to [redacted] and Epilepsy indications will be reviewed by this reviewer.

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		
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	x	2		
Patients-				
single dose:				
multiple dose:	x			From Phase III studies
Dose proportionality -				
fasting / non-fasting single dose:	x			
fasting / non-fasting multiple dose:	x			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x			
In-vivo effects of primary drug:	X	11		• Valproic Acid- (Epilepsy patients)-2 Studies • Carbamazepine (Epilepsy patients) • Lamotrigine (Epilepsy patients) • Phenytoin (Epilepsy patients) • Lorazepam (healthy) • Gabapentin (healthy)-2 studies • Others-oral contraceptive, oxycodone, ethanol
In-vitro:	x			
Subpopulation studies -				
ethnicity:	x			Population analysis
gender:	x			Population analysis
pediatrics:				Pediatric waiver deferral for epilepsy
geriatrics:	x	1		Population analysis as well as study in elderly Japanese
renal impairment:	x	2		Varying degree of renal impairment and hemodialysis study
hepatic impairment:				
AIDS patients				
PD:				
Phase 2:	x			
Phase 3:	x			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	4		Neuropathic pain and Epilepsy PK and Safety
Population Analyses -				
Data rich:				

Data sparse:	x	3		Effect of age, gender, race, menopause, food, BID and TID regimens, renal function, AED coadministration from 6 population analyses of various disease states
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2		
Dissolution:	x			
(IVIVC):				
Bio-waiver request based on BCS	X			
BCS class	x			Class I
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				Deferred
Literature References				
Total Number of Studies		22+6 POP PK+4 PK-PD+ in vitro studies		

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 to be sent to firm (or attachment included). FDA letter date if applicable. • Population PK Report 3295 is not provided and is indicated that it would be available upon request. Please provide this report. • Some NONMEM files in the "FDAdatafiles" folder under the "Programs" folder were unavailable due to compatibility reasons with our electronic system. For future submissions, please "ALWAYS USE EXTENSIONS" with the files otherwise they are unavailable to us. Files with extensions other than 'txt' and 'xpt' are not compatible with our system and hence unavailable to us. For this submission as well as future submissions please use the following format and extension: ■ Control streams: filename_ctl.txt ■ Output Listings: filename_out.txt ■ Data : filename.xpt In some cases the files could be retrieved, however for study 00010 and 00013 the following files under the "Programs' folder were missing. Please provide the following files Study 0010: ___ r1: output file for basic model ___r10: output file for basic model ___ Summary.txt: output files for two runs Study 0013: ___infn.prn5 ___nmoutbasic.txt ___nmoutfinal.txt ___datafullgad Is datafullgad file the same as s0013.xpt file under the 'POPPK' folder? If it the same it need not be resent. To avoid further confusion in data analysis we would appreciate if all the contents of the folder labeled 0010 and 0013 under the "Program" folder are resubmitted. Either way the above mentioned naming convention should be followed. For example the 'infn.prn5' file should be submitted as infn_ctl.txt. If you need any clarification, please do not hesitate to contact us.
QBR questions (key issues to be considered)	• **Are the proposed dosing recommendations appropriate based on PK-PD for efficacy and safety for the and Epilepsy patient population?** • **Is dosing adjustment needed in the epileptic population due to concomitant administration of antiepileptic drugs (7 drugs evaluated)** • **Has QTc effect been adequately evaluated?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Veneeta Tandon, Ph.D**	
Secondary reviewer Signature and Date	**Ramana Uppoor, Ph.D**	

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/s/

Veneeta Tandon
12/17/03 01:38:07 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
12/17/03 01:41:52 PM
BIOPHARMACEUTICS