CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-723

Medical Review(s)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

MEMORANDUM

DATE: August 5, 2004

TO: File, NDA 21-723

FROM: Celia Jaffe Winchell, M.D.
Medical Team Leader

RE: Supervisory Review of NDA 21-723
Lyrica (pregabalin)
Post-herpetic Neuralgia
Pfizer

1 BACKGROUND

NDA 21-723 for Lyrica (pregabalin) was submitted by Pfizer on 10/30/03. Pregabalin is a new chemical entity structurally related to L-leucine and γ-aminobutyric acid (GABA), which has been developed by Pfizer for the treatment of epilepsy, generalized anxiety disorder, and the pain associated with post-herpetic neuralgia (PHN) and the pain associated with diabetic peripheral neuropathy (DPN). The molecule is structurally similar to that of another Pfizer anticonvulsant, gabapentin (Neurontin). Applications for all four indications were submitted simultaneously, but were administratively split into four NDAs to facilitate review. The application for the treatment of diabetic neuropathy was accorded priority review status, and received an approvable action letter on 7/29/04. This review addresses the application for the treatment of PHN.

The most notable issue in the administrative history of this application is the identification of hemangiosarcomas in animal studies. This finding resulted in the imposition of a clinical hold on 1/26/01 (later modified to partial clinical hold permitting enrollment of only treatment-refractory patients on 2/08/01). At that time, the clinical trial program for many of the indications was essentially complete, but some planned trials were terminated early. Pfizer's contention was, and continues to be, that the animal findings were due to a mechanism of action which applied only to the species in which the tumors were observed, and that the findings were not relevant to humans. The pharmacology/toxicology review team gave close attention to the evaluation of these findings and the sponsor's studies to support the non-applicability of the findings in humans and did not find them persuasive in dismissing the relevance of the animal findings. Review of the data as part of the DPN application determined that the carcinogenicity risk should be described in labeling but would not preclude approval. Therefore, the clinical hold was removed on April 7, 2004, allowing future studies to occur under the IND.

At the time of IND submission for DPN and PHN, these indications were the regulatory responsibility of the Division of Analgesic, Anti-Inflammatory, and Ophthalmologic Drug Products (HFD-550), and the development programs for were well underway at the time the IND was transferred to this Division. Agency efforts to adopt a standard approach to neuropathic pain drugs, as well as emerging science on the topic, have led the Division to develop policies concerning the nature of studies to be conducted to support DPN and PHN indications. The PHN studies in this application meet the basic requirements now expected for drugs being developed for this indication.

Pregabalin received marketing authorization in the European Union in April, 2004.

This application is based on the available safety results for eleven US controlled clinical trials, sixteen non-US controlled clinical trials, one uncontrolled non-US clinical study, and pharmacokinetic data from 20 clinical trials. Efficacy data for this indication derive primarily from three controlled trials in the PHN population. The clinical studies of the effectiveness and safety of this product in PHN, as well as safety information from the DPN and PHN populations have been reviewed by Mwango Kashoki, M.D., who has also

undertaken an integrated safety review incorporating findings from the generalized anxiety disorder and epilepsy populations from the primary review of the safety team in the Division of Neuropharmacologic Drug products, primarily conducted by Gerard Boehm, M.D. The application has also been reviewed by Joan Buenconsejo, Ph.D. (biostatistics), Sue-Chi Lee, Ph.D. (clinical pharmacology and biopharmaceutics), Sharon Kelly, Ph.D., (chemistry), and a team of pharmacology/toxicology reviewers including Jerry Cott, Ph.D. and Terry Peters, Ph.D. Chemistry, clinical pharmacology, and pre-clinical issues were addressed in the context of the DPN review and no new issues specific to this indication have arisen. In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, focusing only on the PHN population, and make appropriate recommendations for action on the NDA.

2 EFFECTIVENESS

2.1 Overview

Evidence of efficacy has been submitted in the clinical studies 1008-045, 1008-127, and and 1008-196. Additional efficacy studies which did not provide evidence of efficacy included study 1008-030, which failed to show a difference between pregabalin 75 mg/day or 150 mg/day and placebo, and 1008-132, which was prematurely terminated due to the imposition of clinical hold on the IND.

All studies enrolled adult patients with pain persisting after healing of a herpes zoster rash. In studies 127 and 196, pain was to be of at least 3 months' duration without any maximum duration. Enrollment in Study 045 was limited per protocol to patients with pain lasting at least 6 months, but not more than 5 years, after rash healing, although this upper limit seems to have been ignored. Patients were without other significant illnesses. Concomitant therapies were to be stable during the study. Patients were to be excluded if they had a history of non-response to treatment with gabapentin. Patients with a creatinine clearance <30 mL/min were ineligible. Some studies stratified dosing by creatinine clearance, using 60 mL/min as the dividing point between strata. Throughout this memo, the term "low CLcr" refers to patients with creatinine clearance between 30 and 60 mL/min, while the term "normal CLcr" refers to patients with creatinine clearance of at least 60 mL/min. It is acknowledged that patients at the lower end of the "normal" stratum do fall within the range of mild renal impairment; however, this terminology is used for ease of communication of the results.

Each study employed a one-week forced titration period and a fixed dosing period (seven weeks in studies 1008-045 and 1008-127; 12 weeks in study 1008-196). Patients who could not tolerate the assigned dose were discontinued. Patients were seen at 1 – 2 week intervals and at a safety follow-up after study completion, or continued in an open-label extension.

Daily pain scores and ratings on other measures were to be recorded in a patient diary.

The tables below briefly summarize the features of the studies reviewed for efficacy and the major results.

Protocol # and Title	Design
Protocol 1008-045: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin (150 and 300 mg/d) in patients with postherpetic neuralgia	53 centers (Europe and Australia) randomized, double-blind, placebo-controlled, parallel groups N = 240 **Dose**: 150 vs 300 mg/day vs placebo (given in 3 divided doses, TID) **Duration**: 8 weeks (1-week titration, 7 weeks fixed dose phase)
Protocol 1008-127: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin in patients with postherpetic neuralgia	29 U.S. Centers, randomized, double-blind, placebo-controlled, parallel groups N = 173 **Dose**: 300 mg/day OR 600 mg/day (assigned based on ClCr) vs placebo (given in 3 divided doses, TID) **Duration**: 8 weeks (1-week titration, 7 weeks fixed dose phase)
Protocol 1008-196: A 13-week randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) in the treatment of postherpetic neuralgia	76 European and Australian Centers, randomized, double-blind, placebo-controlled, parallel groups N = 368 **Dose**: 150 mg/day vs 300 mg/day vs [300 mg OR 600 mg/day (assigned based on ClCr)] vs placebo (given in 2 divided doses, BID) **Duration**: 13 weeks (1-week titration, 12 weeks fixed dose phase)

The table below summarizes the results of these three studies, showing the statistical evaluation of the primary efficacy outcome (endpoint mean pain score, ANCOVA analysis), the change in pain score and the responder rate *based on reviewers' computation of these figures*:

Protocol	**RxGrp**	**Δ pain score**	Endpont mean pain score	Endpont mean pain score p-value, ANCOVA	**% responder**	p-value
045	PBO	-0.49	6.3		9%	
	150 (50 tid), Low CLcr	-1.88	4.9	.0003	29%	.0132
	300 (100 tid) Low CLcr	-1.13	5.7	.0587	11%	.1758
	150 (50 tid); Normal CLcr	-1.36	5.5	.0587	21%	.8342
	300 (100 tid), Normal CLcr	-2.38	4.6	.0003	35%	.0032
127	PBO	-1.18	5.25		20%	
	300 (100 tid); Low CLcr	-1.84	4.76	.005	30%	.1556
	600 (200 tid); normal CLcr	-1.89	4.24	.003	34%	.1556
196	PBO		6.19		6%	
	150 (75 bid); Low CLcr	-0.55	5.76	.35	19%	0.0216
	300 (150 bid); Low CLcr	-1.38	6.84	.058[1]	19%	0.0008
	150 (75 bid); Normal CLcr	-1.48	5.12	.008	28%	0.0200
	300 (150 bid); Normal CLcr	-1.18	5.54	.1064[1]	20%	0.0200
	600 (300 bid); Normal CLcr	-1.95	4.72	.0005	31%	0.0005

[1]comparison was significant at week 8 but not at endpoint

In the table below, results from the two analytic approaches are tabulated by dose for each of the two subpopulations (creatinine clearance strata). Studies in which results were entirely supportive are indicated by bold, italic study numbers. Studies with entirely negative results for that dose/population are indicated by normal font study numbers. Studies in which positive results (statistical significance) exists on one, but not both, of the efficacy analyses, are indicated with italic study numbers. It should be noted that the primary, protocol-specified analysis was the endpoint mean pain score, and that sample sizes were calculated based on the assumption that the two creatinine clearance strata would be analyzed together, rather than separately as they are presented below. The rate of discontinuation due to adverse events is presented to illustrate the risk/benefit balance.

	Pregabalin Dose		
Creatinine Clearance	150 mg/day	300 mg/day	600 mg/day
30-60 mL/min	***045***: Adverse dropouts 14% (vs.10% placebo) Responder rate 29%* (vs 9% placebo) Endpoint mean pain score 4.9* *196*: Adverse dropouts 19% (vs. 5% placebo) Responder rate 19%* (vs. 6% placebo) Endpoint mean pain score 5.76 (NS)	045: Adverse dropouts 27% (vs.10% placebo) Responder rate 11% (NS) (vs 9% placebo) Endpoint mean pain score 5.7 (NS) *127*: Adverse dropouts 37% (vs 5% placebo) Responder rate 30% (vs. 20% placebo) (NS) Endpoint mean pain score 4.76* *196*: Adverse dropouts 22% (vs. 5% placebo) Responder rate 19%* (vs. 6% placebo) Endpoint mean pain score 6.84 (NS)†	
>60 mL/min	045: adverse dropouts 8% (vs.10% placebo) Responder rate 21% (vs 9% placebo) (NS) Endpoint mean pain score 5.5 (NS) ***196***: Adverse dropouts 3% (vs. 5% placebo) Responder rate 28% (vs 6% placebo)* Endpoint mean pain score 5.12*	***045:*** adverse dropouts 0%(vs.10% placebo) Responder rate 35%* (vs 9% placebo) Endpoint mean pain score 4.6* *196*: Adverse dropouts 11%(vs. 5% placebo) Responder rate: 20% (vs 6% placebo)* Endpoint mean pain score 5.54 NS†	*127*: adverse dropouts 29% (vs 5% placebo) Responder rate 34% (vs. 20% placebo) (NS) Endpoint mean pain score 4.24* ***196***: adverse dropouts 22%(vs. 5% placebo) Responder rate 31%(vs 6% placebo)* Endpoint mean pain score 4.72*
****statistically significant †N.S. at study endpoint (week 13) but significant at week 8***			

2.2 Population

All studies had similar inclusion and exclusion criteria. To be eligible, subjects were required to be adults with post-herpetic neuralgia, experiencing pain at least 3 months after the healing of a herpes zoster rash (6 months for study 1008-045), with a minimum pain score of 40 mm on the Visual Analog Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) and a score of at least 4 on the daily Likert pain rating scale over the week prior to randomization. A normal chest x-ray was required for entry into study 1008-045, while other studies permitted stable abnormalities. Patients were excluded for

- Previous neurolytic or neurosurgical therapy for PHN
- Presence of other severe pain that may confound assessment or self-evaluation of pain due to PHN
- Skin conditions in the affected dermatome that could alter sensation;
- Failure to respond to previous treatment with gabapentin (Neurontin) for postherpetic neuralgia at ≥ 1200-mg/day dose
- Clinically significant hepatic, respiratory, hematological illnesses, or cardiovascular disease
- Abnormal 12-lead ECG
- WBC <2500/ mm^3, neutrophil count <1500/ mm^3, platelet count <100 $x10^3/mm^3$
- Immunocompromised state (ie, conditions known to be associated with an immunocompromised state);
- Clinically significant or unstable medical or psychological conditions that would compromise participation in the study
- Creatinine clearance ≥ 30 mL/min (estimated from serum creatinine);
- Malignancy
- History of illicit drug or alcohol abuse in the past 2 years
- Use of prohibited medications in the absence of appropriate washout periods

Design and Endpoints
The designs differed slightly in duration, as well as timing and frequency of efficacy assessments. Studies 1008-045 and 1008-127 featured four on-treatment visits at 2-3 week intervals for assessment of efficacy. Study 1008-196 featured one on-treatment visits at the end of the one-week titration, and three subsequent on-treatment visits at intervals of 3-5 weeks. All studies required subjects to complete daily diaries of pain ratings.

The following measures of patient pain and function were used:
- *Daily pain score*, as measured on an 11-point Likert-type numerical scale
- *Short Form McGill Pain Questionnaire (SF-MPQ)* which comprises
  - a standard 100 mm visual analog scale (VAS)
  - a Present Pain Intensity (PPI) scale : a 6-point categorical scale from 0 (no pain) to 5 (excruciating pain)
  - 15 pain descriptors, each rating pain on a 4-point categorical scale from 0 (no

pain) to 3 (severe pain)

- *Daily diary of sleep interference*: 11-point Likert-type numerical rating scale from 0 (pain did not interfere with sleep) to 10 (pain completely interfered; patient was unable to sleep due to pain)
- *Clinical Global Impression of Change (CGIC):* a 7-point scale from 1 (very much improved) to 7 (very much worse)
- *Patient Global Impression of Change (PGIC):* a 7-point scale from 1 (very much improved) to 7 (very much worse)
- *Other patient-reported measures including*
  - *SF-36 Health Survey Questionnaire (SF-36 QOL)*
  - *POMS*
  - *Zung Self-Rating Depression Scale*
  - *Hospital Anxiety and Depression Scale*
  - *Profile of Mood States*
  - *Medical Outcomes Study Sleep Scale*
  - *Euro QOL Health State Profile*

2.3 Outcome Measures and Analytic Approaches

For all studies, several analyses were undertaken. The sponsor identified as the outcome of primary interest a comparison across treatment groups of the *final (endpoint) weekly mean pain score,* defined as the mean of the last 7 diary entries while on study medication. The scores did not need to be recorded on consecutive days, and if fewer than 7 were recorded, the available scores were used to determine a mean. The use of "last 7 available" entries implies a last-observation-carried-forward (LOCF) imputation strategy for missing data and early terminators. The shortcomings of the LOCF approach in chronic pain studies have been discussed extensively within the Division and the Agency. It is noted that patients achieving adequate symptom control but experiencing intolerable side effects often terminate the study with "good" pain scores, which are carried forward in the LOCF analysis. However, these subjects are true treatment failures because they were unable to tolerate the dose necessary to achieve symptom control. Therefore, the LOCF analysis overestimates the benefit of the drug. Consequently, the Agency prospectively expressed a primary interest in an analysis which compared change from baseline in mean pain scores using a baseline-observation-carried-forward (BOCF) imputation strategy for missing data, and in a responder analysis which identified patients in whom pain was reduced at least 50% from baseline, using BOCF imputation. (Note that when baseline observation is carried forward for subjects who terminated prior to the final week of the study, the change from baseline is, by definition, zero, and therefore all early terminators are categorized as non-responders.) The sponsor's final study reports provide results of analyses using their own prospectively-defined outcome of interest, and their approach to BOCF and responder analyses.

In this memo, I will describe only the sponsor's primary analysis (endpoint mean scores using LOCF, and LOCF-based responder analysis), and the BOCF-based analyses conducted by Drs. Kashoki and Buenconsejo. The results of other analyses are documented in the primary reviews.

2.4 Results

The results of the three supportive efficacy trials, as documented in Dr. Kashoki's and Dr. Buenconsejo's reviews, are briefly summarized below:

2.4.1 Protocol 1008-045: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin (150 and 300 mg/d) in patients with postherpetic neuralgia

This study was a randomized, double-blind, placebo-controlled, parallel group, multi-center comparison of pregabalin 150 mg/d (50 mg TID), 300 mg/d (100 mg TID), and placebo for the treatment of adult patients with PHN, conducted at 53 sites in Europe and Australia grouped into 11 study clusters. The study consisted of a one-week baseline phase and an 8-week double-blind treatment phase including a one-week baseline phase, a one-week titration period and a 7-week fixed dose period. Patients were required to complete at least 4 pain diaries and to have an average pain score of at least 4 during the baseline phase to be randomized to treatment.

A total of 306 subjects experiencing pain at least 6 months[1] following healing of a herpes zoster skin rash were enrolled in the baseline phase, and 238 subjects were subsequently randomized to pregabalin 150 mg/day vs 300 mg/day vs placebo (given in 3 divided doses) and treated for 8 weeks (1-week titration, 7 weeks fixed dose phase). Patients could participate in an optional open-label extension following study completion.

2.4.1.1 Demographics and Patient Disposition

The demographic characteristics and pain scores of the treatment groups (patients randomized) were similar at baseline.

Patient disposition is tabulated in Dr. Buenconsejo's and Dr. Kashoki's reviews. Overall, 81% of randomized subjects completed the study. Study completion was highest among the patients randomized to pregabalin 150 mg/day and lowest among patients randomized to placebo (88% vs. 75%). Discontinuations were primarily due to adverse events, with 10% of the placebo group, 11% of the pregabalin 150 mg/day group, and 16% of the pregabalin 300 mg/day group discontinuing prematurely due to AEs. Lack of efficacy was cited as a reason for discontinuation by 9% of subjects randomized to placebo, and 0-1% of patients randomized to pregabalin. "Other" reasons were cited by 1-4% of the randomized patients across groups.

Dr. Kashoki reviewed the protocol violations and did not feel they would affect the interpretation of the study results.

2.4.1.2 Efficacy Results

2.4.1.2.1 Mean Pain Scores at Endpoint

The primary efficacy outcome was the endpoint mean pain score, defined as the mean of

[1] Although the protocol specified that enrollment should be limited to those with pain lasting less than five years , it appears to have been eliminated as a criterion without formal protocol amendment

the last 7 entries of the daily pain diary while the patient was on study medication. Pfizer's analysis imputed missing data using a last observation carried forward (LOCF) strategy and employed analysis of covariance with treatment and cluster as fixed effects and with the baseline mean pain score as covariate. This analysis found improvement (i.e. decreases) in mean pain scores for all 3 treatment groups, with the greatest improvement in the pregabalin 300 mg/d group. The ANCOVA results showed that both the mean pain scores for the pregabalin 150- and 300 mg/d treatment groups were significantly different from placebo. The following tables, from Dr. Kashoki's and Dr. Buenconsejo's reviews, illustrate the results of this analysis.

Study 1008-0045 Mean pain score: Descriptive statistics – Protocol 045

Time point	Placebo			Pregabalin 150 mg/day			Pregabalin 300 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	81	6.6 (1.6)	4, 10	81	6.9 (1.7)	4, 10	76	7.0 (1.6)	4, 10
Endpoint[b]	81	6.2 (2.3)	1.3, 10	81	5.2 (2.5)	0.1, 10	76	4.9 (2.5)	0, 10
Change[c]	81	-0.5 (1.7)	-6.1, 3.1	81	-1.7 (2.0)	-8.4, 1.9	76	-2.1 (2.4)	-9, 1.9

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day1.
[b] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.
[c] Change is from Baseline to Endpoint
(Applicant's Table 11, RR 720-04356, 1008-045, P. 44)

Study 1008-045 Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance (ITT Population)

Treatment	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin - Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Placebo	81	6.33	0.22				
Pregabalin 150	81	5.14	0.22	-1.20	(-1.81, -0.58)	0.0002	0.0002
Pregabalin 300	76	4.76	0.23	-1.57	(-2.20, -0.95)	0.0001	0.0002
PGB 150 vs PGB 300	--	--	--	-0.38	(-1.00, 0.24)	0.2323	0.2323

SE Standard error; CI Confidence interval.
[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.
[b] Adjustment based on Hochberg's procedure for the 2 pairwise comparisons versus placebo.

Source: Table 12 from Applicant's report
PGB: pregabalin
Baseline = last 7 available scores before taking study mediation, up to and including Day 1
Endpoint = last 7 available scores while on study medication, up to and including day after last dose
Change = change from baseline to endpoint

The sponsor also conducted an analysis identified as a BOCF analysis, which yielded similar results to the primary analysis. The sponsor's definition of study completer, however, required only that the subject complete all visits, and not the entire treatment period. Therefore, in some cases, subjects termed "completers" had not completed the full 8 weeks of treatment. Accordingly, Drs. Kashoki and Buenconsejo determined a more appropriate method of applying the BOCF strategy (see their reviews), and calculated pain scores and responder rates (below) using their approach. The pain scores and comparisons computed using the BOCF imputation strategy are shown in the table below, adapted from Dr. Kashoki's review.

Study 1008-045 Descriptive statistics: Mean pain score by Study Week – Protocol 045

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline[1]	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Endpoint[2]	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)
Change from BL	-0.49	-1.62	-1.64

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose (as defined by the Applicant)

Study 1009-0045 Endpoint mean pain scores: Results of ANCOVA with BOCF

				Treatment comparisons (Pregabalin – Placebo)			
Treatment	N	Least Squares Means	SE	Difference	95% CI	Un-adjusted p-value	Adjusted p-value
Placebo	81	6.32	0.22				
Pregabalin 150	81	5.20	0.21	-1.12	(-1.718-0.522)	0.0003	0.0004
Pregabalin 300	76	5.21	0.22	-1.11	(-1.723-0.502)	0.0004	0.0004
SE = Standard error; CI = Confidence interval							
Endpoint = Last 7 available scores while on study medication, up to and including day after last dose							
Adjustment based on Hochberg's procedure							

(Applicant's Table E1, Appendix D.23, RR 720-04356, 1008-045, P. 1889)

2.4.1.2.2 Responder analysis

Responder analysis was also undertaken, at the Agency's request, by the sponsor. In this analysis, patients who had at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. According to the sponsor's calculations, which used the LOCF imputation strategy, the proportion of responders in the 300 mg/day group (28%) and the pregabalin 150 mg/day group (26%) were significantly different from placebo (10%, p = 0.006).

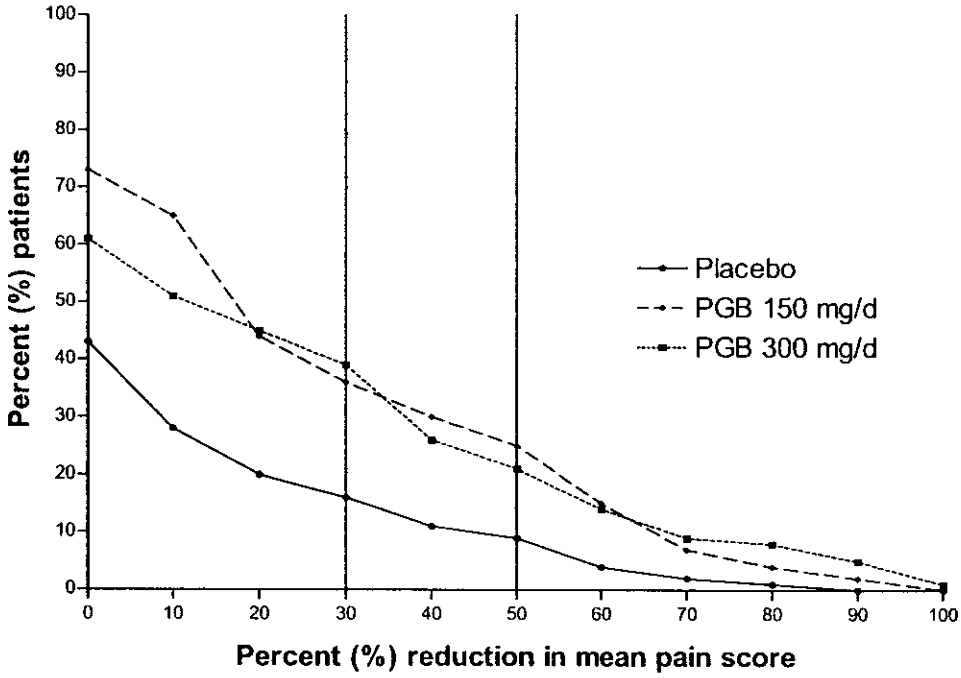
Drs. Kashoki and Buenconsejo recalculated change from baseline using the BOCF strategy and tabulated the results as shown below. The percentages shown are cumulative. Non-responders are in the shaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this data presentation, 9% of the placebo group, 25% of the pregabalin 150 mg/day group, and 21% of the 300 mg/day group meet the definition of responder (50% reduction in pain). The effect of pregabalin is further highlighted by the differences in proportions of patients experiencing even greater degrees of improvement in pain.

Study 1008-045 Percent change in endpoint mean pain score by dose – BOCF imputation

	PLACEBO		PGB150		PGB300	
	Total	%	Total	%	Total	%
Any increase	19	23%	11	14%	9	12%
None	**27**	**33%**	**11**	**14%**	**21**	**28%**
>0 % decrease	**35**	**43%**	**59**	**73%**	**46**	**61%**
≥ 10%	23	28%	53	65%	39	51%
≥20%	16	20%	36	44%	34	45%
≥ 30%	13	16%	29	36%	30	39%
≤ 40%	9	11%	24	30%	20	26%
≥50%	**7**	**9%**	**20**	**25%**	**16**	**21%**
≥ 60%	3	4%	12	15%	11	14%
≥ 70%	2	2%	6	7%	7	9%
≥ 80%	1	1%	3	4%	6	8%
≥ 90%	0	0%	2	2%	4	5%
=100%	0	0%	0	0%	1	1%

The results in the table above are also illustrated graphically in the figure below.

Study 1008-0045 Response profile at endpoint



2.4.1.2.3 Exploration by Creatinine Clearance Strata

Because of differential results in patients with moderate renal impairment (CLcr 30-60 mL/min) in other studies in this development program and the DPN development program, Dr. Buenconsejo separately tabulated patient disposition and efficacy results for

this study at my request.

Study 1008-045 Patient Disposition by Creatinine Clearance Strata

Disposition	Treatment Group				
	PLB	PGB 150-L	PGB 150-N	PGB 300-L	PGB 300-N
Randomized	81	42	39	45	31
ITT	81	42	39	45	31
Completed Study	61	36	35	30	30
Withdrawn:					
Adverse Event	8 (10%)	6 (14%)	3 (8%)	12 (27%)	0 (0%)
Lack of Compliance	2 (25%)	0	0	0	1 (3%)
Lack of Efficacy	7 (9%)	0	0	1 (2%)	0
Consent withdrawn	3 (4%)	0	1 (3%)	2 (4%)	0

Clear differences in tolerability are seen between the creatinine clearance strata. Because non-completers are assessed as unchanged in the BOCF responder analysis (% change from baseline is, by definition, zero, when the baseline observation is carried forward), it is not surprising that differences are also seen in responder rates. As shown below, only 11% of patients with CLcr <60mL/min in the 300 mg/day group met the definition of responder, compared to 35% of the patients with CLcr>60 treated with that dose. Notably, the low CLcr had a slightly better response to 150 mg/day than the normal CLcr group, reflecting the higher plasma exposure in the low CLcr group.

Study 1008-045 Percentage change in Endpoint mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

	PLACEBO		**PGB 150 LOW[1]**		**PGB 150 NORMAL[2]**		**PGB 300 LOW[1]**		**PGB 300 NORMAL[2]**	
	Total	**%**	**Total**	**%**	**Total**	**%**	**Total**	**%**	**Total**	**%**
Any increase	19	23%	3	7%	8	21%	4	9%	5	16%
None	27	33%	6	14%	5	13%	16	36%	5	16%
> 0 % decrease	35	43%	33	79%	26	67%	25	56%	21	68%
≥ 10%	23	28%	30	71%	23	59%	20	44%	19	61%
≥ 20%	16	20%	22	52%	14	36%	17	38%	17	55%
≥ 30%	13	16%	18	43%	11	28%	13	29%	17	55%
≥ 40%	9	11%	14	33%	10	26%	7	16%	13	42%
≥ 50%	**7**	**9%**	**12**	**29%**	**8**	**21%**	**5**	**11%**	**11**	**35%**
≥ 60%	3	4%	7	17%	5	13%	4	9%	7	23%
≥ 70%	2	2%	3	7%	3	8%	2	4%	5	16%
≥ 80%	1	1%	1	2%	2	5%	1	2%	5	16%
≥ 90%	0	0%	1	2%	1	3%	1	2%	3	10%
=100%	0	0%	0	0%	0	0%	1	2%	0	0%

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Statistical analysis shows that the 300 mg/day, normal CLcr group and the 150 mg/day, low CLcr group had statistically superior results compared to placebo. However, the 150 mg/day, normal CLcr group did not separate from placebo. This may be due to the sample size, as the trial was not powered for these subset analyses.

2.4.1.2.4 Secondary endpoints

Secondary endpoints analyzed included SF-MPQ (sensory, affective, VAS, PPI, and total scores); Sleep interference; global impression (patient and clinician); SF-36 QOL; and Zung self-rating depression scale. These measures supported the primary outcome analysis.

2.4.1.3 Efficacy Conclusion, Study 1008-045

This study provides evidence of efficacy for pregabalin, 100 mg t.i.d, in a dose regimen employing a 1-week titration period, in the relief of pain associated with post-herpetic neuralgia in patients with CLcr>60 mL/min. It provides evidence that 50 mg t.i.d. is effective in patients with lower creatinine clearance, and that 100 t.i.d is so poorly tolerated as to be ineffective in this group.

2.4.2 Study 1008-127: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin in patients with postherpetic neuralgia

This was a randomized, double-blind, placebo-controlled, parallel groups study conducted at 29 centers in the U.S. A total of 245 subjects with post-herpetic neuralgia pain at least 3 months post-healing of herpes zoster skin rash entered the baseline phase. After the one-week baseline, 173 subjects completed at least 4 pain diaries and had an average pain score of at least 4, and were subsequently randomized to treatment with placebo or pregabalin, given as 100 mg t.i.d to patients with creatinine clearance ≤60 mL/min and 200 mg t.i.d. to patients with creatinine clearance >60 mL/min, titrated to target dose over one week and treated at the target dose for 7 additional weeks. Patients could participate in an optional open-label extension following study completion.

2.4.2.1 Demographics and Patient Disposition

The demographic characteristics of the treatment groups (patients randomized) were similar at baseline. The pain scores were also similar at baseline for the placebo group and the pregabalin group as a whole; however, when the 300 mg/day (100 mg t.i.d) group and the 600 mg/day (200 mg t.i.d) group were considered separately, differences were noted. The these differences were taken into consideration in the statistical review (as described below).

	Placebo N = 84	Pregabalin 300 mg/d N = 30	Pregabalin 600 mg/d N = 59
Baseline mean pain score	6.43	6.60	6.13

Patient disposition is tabulated in Dr. Buenconsejo's and Dr. Kashoki's reviews. Overall, 76% of randomized subjects completed the study. Study completion was higher among placebo-treated than pregabalin-treated patients (88% vs 65%). Discontinuations were primarily due to adverse events, with 5% of the placebo group and 32% of the pregabalin group discontinuing prematurely due to AEs. Lack of efficacy was cited as a reason for discontinuation by 7% of subjects randomized to placebo, but no patients randomized to pregabalin discontinued for this reason. When separated by dose group/creatinine clearance stratum, further differences also emerged, with discontinuations due to AEs occurring in 37% of the 300 mg/day group (CLcr≤60 mL/min) and 29% of the 600 mg/day group (CLcr>60 mL/min).

Dr. Kashoki reviewed the protocol violations and did not feel they would affect the interpretation of the study results.

2.4.2.2 Efficacy Results

2.4.2.2.1 Mean Pain Scores at Endpoint

The primary efficacy outcome was the endpoint mean pain score, defined as the mean of

the last 7 entries of the daily pain diary while the patient was on study medication. Pfizer's analysis pooled data from both pregabalin doses, imputed missing data using a last observation carried forward (LOCF) strategy, and employed analysis of covariance with treatment and cluster as fixed effects and with the baseline mean pain score as covariate. This analysis found improvement (i.e. decreases) in mean pain scores for both treatment groups, with greater improvement in the pregabalin group. The ANCOVA results showed that both the mean pain score for the pregabalin group was significantly different from placebo. The following tables, from Dr. Kashoki's and Dr. Buenconsejo's reviews, illustrate the results of this analysis.

Study 1008-127 Mean pain score: Descriptive statistics, LOCF

Time point	Placebo			Pregabalin		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	84	6.4 (1.5)	4, 10	89	6.3 (1.4)	3.7, 9.1
Endpoint[b]	84	5.3 (2.6)	0, 10	88	3.6 (2.3)	0, 9.6
Change[c]	84	-1.1 (2.0)	6.6, 3.9	88	-2.7 (2.1)	-7.3, 2.4

SD = Standard deviation
a Baseline = Last 7 available scores before taking study medication, up to and including Day 1.
b Endpoint = Last 7 available scores while on study medication, up to and including day after last dose
c Change is from baseline to endpoint
(Applicant's Table 11, RR 720-04457, 1008-127, P. 42)

Study 1008-127 Endpoint mean pain score: Ancova results

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
				Difference	95% CI	p-value
Placebo	84	5.29	0.24			
Pregabalin	88	3.60	0.24	-1.69	(-2.33, -1.05)	0.0001

SE = Standard error; CI = Confidence interval
Endpoint = last 7 available scores while on study mediation (if less than 7, then whatever scores are available)
(Applicant's Table 12, RR 720-04457, 1008-127, P. 43)

The sponsor also conducted an analysis identified as a BOCF analysis, which yielded similar results to the primary analysis.

The sponsor's definition of study completer, however, required only that the subject complete all visits, and not the entire treatment period. Therefore, in some cases, subjects termed "completers" had not completed the full 8 weeks of treatment. Accordingly, Drs. Kashoki and Buenconsejo determined a more appropriate method of applying the BOCF strategy (see their reviews), and calculated pain scores and responder rates (below) using their approach. In addition, the primary reviewers separated the 300 mg/day and 600 mg/day dose groups. The assignment of dose based on creatinine clearance was done on the assumption that the plasma levels (exposure) would be similar in patients with a lower creatinine clearance treated with 300 mg/day and patients with higher creatinine clearance treated with 600 mg/day. However, this assumption was also made in one of the studies reviewed in the portion of the application supporting the indication for pain associated with diabetic peripheral neuropathy, and the data did not support the assumption. In that study, the treatment response for the pooled "300 mg/600 mg" group

appeared to be driven entirely by the patients treated with 600 mg/day; those treated with 300 mg/day had a very poor response. Therefore, based on that observation, the reviewers did not feel it was appropriate to pool these two groups together in this study and ascribe the overall group success to both subgroups, if it were, in fact, driven by only one subgroup.

Assessment of baseline scores by dose group showed that the pregablin 600 mg/d group had the lowest baseline score (6.13) compared to the 300 mg/d group (6.6) and placebo group (6.43). All of the treatment groups had a decrease in endpoint mean pain score at Week 8. Descriptive statistics suggest that similar decreases in score from baseline to endpoint occurred in the 600 mg/d group (change in score = -1.89) and 300 mg/d group (change = -1.84). These decreases were larger than in the placebo group (change = -1.18). The table below is adapted from Dr. Kashoki's review.

Study 1008-127 Reviewer's analysis: Descriptive statistics, mean pain score, BOCF method

	Placebo N=84	PGB300/600 N=89	PGB 300 N=30	PGB 600 N=59
Baseline[1]	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Endpoint[3]	5.25 (2.5)	4.42 (2.4)	4.76 (2.4)	4.24 (2.4)
Change	-1.18	-1.87	-1.84	-1.89

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

ANCOVA of the weekly and endpoint mean pain scores was performed. Treatment, cluster, creatinine clearance stratum, and baseline pain score were included in the analysis. The ANCOVA showed a statistically significant difference between the 600 mg/d and placebo groups in each weekly mean pain score, starting at Week 1. A difference in pain scores between the 300 mg/d and placebo was evident only at Weeks 1 and 2. However, due to the small number of patients in this group, the results for the 300 mg/d group should be interpreted cautiously. Notably, the rate of dropout due to adverse events was higher in the 300 mg/day group than in the 600 mg/day group (37% vs 29%), suggesting that tolerability may have limited the response of the 300 mg/day group.

2.4.2.2.2 Responder analysis

In the responder analysis conducted by the sponsor, using LOCF imputation, Pfizer found that the proportion of responders in the pregabalin treatment group was 50%, compared to 20% in the placebo group, a difference that was statistically significant.

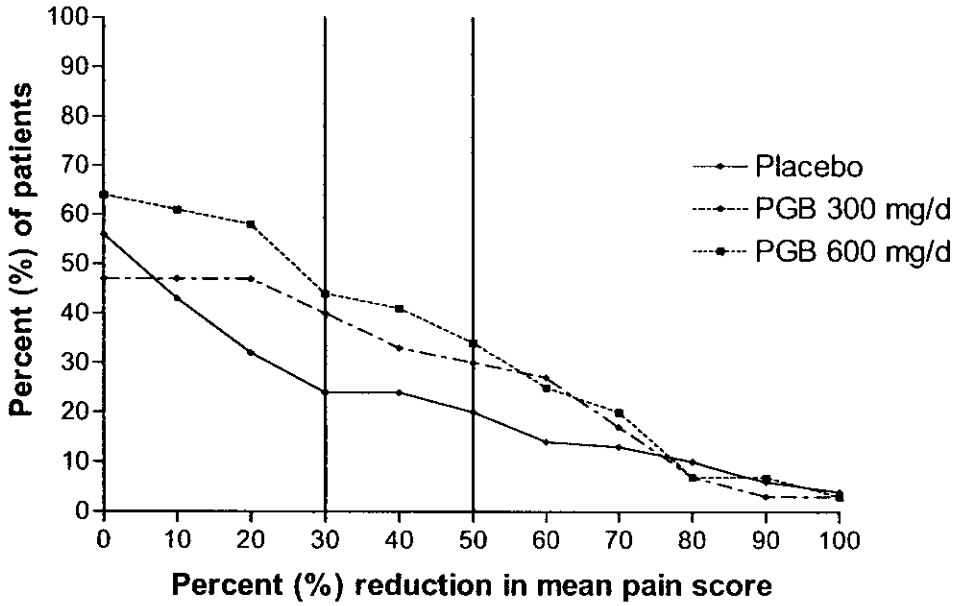
Drs. Kashoki and Buenconsejo recalculated change from baseline using the BOCF strategy and tabulated the results as shown below. The percentages shown are cumulative. Non-responders are in the shaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this data presentation, 20% of the placebo group, 30% of the pregabalin 300 mg/day group, and 34% of the 600 mg/day group meet the definition of responder (50% reduction in pain). The effect of pregabalin is further highlighted by the differences in proportions of patients

experiencing even greater degrees of improvement in pain.

Study 1008-127 Reviewer's Analysis: Percent change in endpoint mean pain score by dose

	PLACEBO		PGB300		PGB600	
Change in pain	**Total**	**%**	**Total**	**%**	**Total**	**%**
Any increase	16	19.1	3	10.0	3	5.1
None	21	25.0	13	43.3	18	30.5
> 0 % decrease	47	56.0	14	46.7	38	64.4
≥10%	36	42.9	14	46.7	36	61.0
≥ 20%	27	32.1	14	46.7	34	57.6
≥ 30%	20	23.8	12	40.0	26	44.1
≥ 40%	20	23.8	10	33.3	24	40.7
≥50%	**17**	**20.2**	**9**	**30.0**	**20**	**33.9**
≥ 60%	12	14.3	8	26.7	15	25.4
≥ 70%	11	13.1	5	16.7	12	20.3
≥ 80%	8	9.5	2	6.7	4	6.8
≥ 90%	5	6.0	1	3.3	4	6.8
=100%	3	3.6	1	3.3	2	3.4

The results in the table above are also illustrated graphically in the figure below.



It should be noted that the number of true "non-responders" (any increase or zero decrease in pain score) is actually higher in the 300 mg/day group than in the placebo group. This reflects the high number of dropouts due to adverse events in the 300 mg/day group, all of whom had CLcr<60 mL/min. Consistent with the findings of Study 1008-045, statistical significance was not reached in the comparisons of 300 mg/day to placebo, plausibly due to tolerability limitations.

2.4.2.2.3 Secondary endpoints

Secondary endpoints analyzed included SF-MPQ (sensory, affective, VAS, PPI, and total scores); Sleep interference; global impression (patient and clinician); SF-36 QOL; POMS; and MOS. These analyses supported the primary endpoint.

2.4.2.3 Efficacy Conclusion, Study 1008-127

This study provides evidence of efficacy for pregabalin, 200 mg t.i.d. (600 mg/day given as three divided doses), using a dosing regimen that employs a one week titration period, in the relief of pain associated with post-herpetic neuralgia in patients with a creatinine clearance of at least 60 mL/min.

The reviewers' analysis, which separated the 100 mg t.i.d. dose group (creatinine clearance less than 60 mL/min) from the 200 mg t.i.d dose group did not demonstrate a statistically significant effect of pregabalin 100 mg t.i.d. on endpoint mean pain score. The number of patients in the 300 mg/d group was small, and therefore there could have been insufficient power to detect a difference from placebo, particularly as the trial was not prospectively sized for this subset analysis. On evaluation of the proportion of treatment responders across treatment groups, the proportions of patients meeting the definition of responder (at least 50% reduction in pain) in the pregabalin groups were similar, but again, the statistical analysis did not show that 300 mg/day (in patients with CLcr<60 mL/min) was superior to placebo. The rate of non-response (zero pain improvement or any increase in pain) was higher in the 300 mg/day group than in the placebo group, and the rate of dropout due to adverse events was higher (37%) in this group than in the 600 mg/day group (29%). This suggests that tolerability may limit the likelihood of the more renally-impaired patients experiencing a favorable treatment outcome at a dose of 300 mg/day.

2.4.3 Study 1008-196: A 13-week randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) in the treatment of postherpetic neuralgia

This study was a randomized, double-blind, placebo-controlled, parallel group, multi-center comparison of pregabalin 150 mg/d (75 mg b.i.d.), 300 mg/d (150 mg b.i.d.), 600 mg/day (300 mg b.i.d.) and placebo for the treatment of adult patients with PHN, conducted at 76 sites in Europe and Australia. The study consisted of a one-week baseline phase and an 13-week double-blind treatment phase including a one-week titration period[2] (for the 300 mg/day and 600 mg/day groups) and a 12-week fixed dose period. Subjects were stratified on the basis of creatinine clearance, and subjects with creatinine clearance of <60 mL/min who were assigned to 600 mg/day were, instead, treated with 300 mg/day. This combined group was described by the sponsor as the "300/600 mg/day" group. Notably, subjects with a creatinine clearance <60 mL/min who were randomized to the 300 mg/day group were also treated with 300 mg/day.

Patients were required to complete at least 4 pain diaries and to have an average pain score of at least 4 during the baseline phase to be randomized to treatment.

A total of 435 subjects experiencing pain at least 6 months following healing of a herpes zoster skin rash were enrolled in the baseline phase, and 370[3] subjects were subsequently randomized to treatment with pregabalin 150 mg/d (75 mg b.i.d.), 300 mg/d (150 mg b.i.d.), 600 mg/day (300 mg b.i.d.), or placebo, and were treated for 13 weeks (1-week titration, 12 weeks fixed dose phase). Patients could participate in an optional open-label extension following study completion.

2.4.3.1 Demographics and Patient Disposition

The demographic characteristics of the treatment groups were similar at baseline. However, when the treatment groups were divided by CLcr strata, differences in baseline pain scores were noted. The table below, from Dr. Kashoki's review, illustrates the range of baseline pain scores. Dr. Buenconsejo's analysis adjusted for these differences.

Study 1008-196 Reviewer's Analysis: Summary of baseline mean pain score (ITT population)

	Placebo	Pregabalin 150 mg/d		Pregabalin 300 mg/d		Pregabalin 600 mg/d
		Low[a]	Normal[b]	Low[a]	Normal[b]	Normal[b]
N	93	26	61	59	65	64
Mean (SD)	6.85 (1.49)	6.77 (1.72)	6.30 (1.51)	6.84 (1.42)	6.60 (1.44)	6.64 (1.42)
Median	7.0	7.0	6.29	7.0	6.86	6.66
Range	1.7 – 10.0	3.14 – 10.0	2.57 – 10.0	4.14 – 9.71	3.71 – 9.14	3.86 – 10.0

[a]Low = creatinine clearance is between 30 and 60 mL/min

[2] For the 300 mg/day and 600 mg/day groups. The 150 mg/day group was treated with a fixed dose for 13 weeks.

[3] Two patients did not take study drug. The ITT population was defined as patients who took at least one dose of medication; therefore the population is 368.

[b]Normal = creatinine clearance >60 mL/min

Patient disposition is tabulated in Dr. Buenconsejo's and Dr. Kashoki's reviews. Overall, 66% of randomized subjects completed the study. Study completion was highest among the patients randomized to pregabalin 150 mg/day and lowest among patients randomized to placebo or 300 mg/day (placebo, 63%; pregabalin 150 mg/day, 70%; pregabalin 300 mg/day 63%; pregabalin "300/600 mg/day," 67%). Discontinuations were primarily due to lack of efficacy and adverse events. Five percent of the placebo group, 8% of the pregabalin 150 mg/day group, 15% of the pregabalin 300 mg/day group, and 21% of the pregabalin "300/600 mg/day" group discontinued prematurely due to AEs. Lack of efficacy was cited as a reason for discontinuation by 24% the placebo group, 18% of the pregabalin 150 mg/day group, 13% of the pregabalin 300 mg/day group, and 7% of the pregabalin "300/600 mg/day" group. "Other" reasons were cited by 3-8% of the randomized patients across groups.

When separated by creatinine clearance strata, some differences emerge in patient disposition. A clear difference in the rates of discontinuation due to adverse events is apparent in the table below, generated at my request by Dr. Buenconsejo.

Study 1008-196 Patient Disposition by Creatinine Clearance Strata

Disposition	Treatment Group						
	PLB	PGB 150-L	PGB 150-N	PGB 300-L	PGB 300-N	PGB 600	All
Randomized	94	26	61	59	65	65	370
ITT	93	26	61	59	65	64	368
Completed Study	59	15	46	35	43	44	242
Withdrawn:							
Adverse Event	5 (5%)	5 (19%)	2 (3%)	13 (22%)	7 (11%)	14 (22%)	46 (13%)
Lack of Compliance	0	0	0	0	1 (2%)	1 (2%)	2 (<1%)
Lack of Efficacy	22 (24%)	5 (19%)	11 (18%)	9 (15%)	9 (14%)	1 (2%)	57 (15%)
Withdrew Consent	7 (8%)	1 (4%)	2 (3%)	2 (3%)	5 (8%)	4 (6%)	21 (6%)

With regard to study conduct, Dr. Kashoki reviewed the protocol violations and did not feel they would affect the interpretation of the study results.

2.4.3.2 Efficacy Results

Because patients with CLcr <60 mL/min, treated with 300 mg/day, were included in both the 300 mg/day group and the "300/600 mg/day" group, the reviewers determined that it would be more appropriate to group together all such patients into a single "300 mg/day, low CLcr" group. In addition, patients with creatinine clearance <60 mL/min in the 150 mg/day were separated from those with creatinine clearance ≥60 mL/min for analysis. Furthermore, several patients were incorrectly randomized to study drug within the "300/600 mg" group, not actually being assigned to the dose that would be appropriate as determined by their CLcr. In the reviewers' analysis these patients are analyzed according to the dose they received (e.g., patients with CLcr ≥60 mL/min in the "300/600

mg group" who were inadvertently assigned 300 mg/day were analyzed with the 300 mg/day group).

However, the sponsor's analysis uses the original groupings of patients.

2.4.3.2.1 Mean Pain Scores at Endpoint

The primary efficacy outcome was the endpoint mean pain score, defined as the mean of the last 7 entries of the daily pain diary while the patient was on study medication. Using the ANCOVA model, the endpoint mean pain score for all pregabalin treatment groups was significantly lower than the placebo group's score. The effect of the drug was also examined at the end of 8 weeks of treatment, both for comparison with the other studies submitted, and because the current Agency recommendation for trial duration in this indication is 8 weeks.

The tables below, from Dr. Kashoki's review, illustrates the week 8 and endpoint pain scores and changes from baseline, and the results of the sponsor's analysis.

Study 1008-196 Mean pain score: Descriptive statistics

	Placebo		Pregabalin					
			150 mg/d		300 mg/d		300/600 mg/d	
Time point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	93	6.9 (1.5)	87	6.4 (1.6)	98	6.7 (1.4)	90	6.7 (1.4)
Week 8	65	5.7 (2.1)	66	4.6 (2.3)	68	4.6 (2.5)	64	4.0 (2.2)
Week 8 endpoint	93	6.2 (2.2)	87	5.0 (2.3)	98	5.0 (2.5)	88	4.4 (2.4)
Endpoint	93	6.2 (2.3)	87	5.1 (2.6)	98	5.0 (2.6)	88	4.3 (2.6)
Change from baseline to Week 8 endpoint	93	-0.7 (1.8)	87	-1.5 (1.9)	98	-1.7 (2.1)	88	-2.3 (2.3)
Change from baseline to Endpoint	93	-0.6 (2.0)	87	-1.4 (2.1)	98	-1.7 (2.3)	88	-2.4 (2.5)

Baseline = last 7 available pain scores before taking study medication, up to and including Day 1. If less than 7 scores were available, then the baseline consists of all scores that were available

Week 8 endpoint = Last 7 available scores, up to and including Day 57. If less than 7 scores were available, then the endpoint consisted of all scores that were available

Endpoint = Last 7 available pain scores while on study medication, up to and including the day after the last dose. If less than 7 scores were available, then Endpoint consisted of all scores that were available

Study 1008-196 Endpoint[a] Mean Pain Scores: Results of Analysis of covariance (ITT Population)

Treatment (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Placebo	93	6.14	0.23				
PGB 150 mg	87	5.26	0.24	-0.88	(-1.53, -0.23)	0.0077	0.0077
PGB 300 mg	98	5.07	0.23	-1.07	(-1.70, -0.45)	0.0008	0.0016
PGB 300/600 mg	88	4.35	0.24	-1.79	(-2.43, -1.15)	0.0001	0.0003
Interactions treatment by:							
• Cluster (Generalizability)		p = 0.2965					
• CLcr Stratum		p = 0.3991					
• Baseline Score		p = 0.4771					

SE = Standard error; CI = Confidence interval; PGB = Pregabalin.

[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, CLcr stratum and the baseline score value as covariate).

[b] Adjustment based on Hochberg's procedure.

The sponsor also conducted an analysis identified as a BOCF analysis, which yielded similar results to the primary analysis. The sponsor's definition of study completer, however, required only that the subject complete all visits, and not the entire treatment period. Therefore, in some cases, subjects termed "completers" had not completed the full period of treatment. Accordingly, Drs. Kashoki and Buenconsejo determined a more appropriate method of applying the BOCF strategy (see their reviews), and calculated pain scores and responder rates (below) using their approach. In addition, their analyses group patients according to CLcr and dose received. The pain scores and comparisons computed using the BOCF imputation strategy are shown in the tables below, adapted from Dr. Kashoki's review.

Study 1008-196 Reviewer's analysis: Descriptive statistics, mean pain score at week 8 and endpoint, BOCF method

	Mean Pain Score					
	Placebo	PGB 150		PGB 300		PGB 600
Study Week		Low[2]	Normal[3]	Low[2]	Normal[3]	Normal[3]
Baseline[4]	6.85 (1.5)	6.77 (1.7)	6.30 (1.5)	6.84 (1.4)	6.60 (1.4)	6.64 (1.4)
Week 8 Endpoint[5]	**6.28 (2.1)**	**5.83 (2.3)**	**4.75 (2.2)**	**5.58 (2.1)**	**5.33 (2.4)**	**4.76 (2.5)**
change from BL	**-0.57**	**-0.94**	**-1.55**	**-1.26**	**-1.27**	**-1.88**
Endpoint[6]	**6.30 (2.2)**	**5.90 (2.2)**	**4.82 (2.6)**	**5.46 (2.3)**	**5.42 (2.4)**	**4.69 (2.7)**
change from BL	**-0.55**	**-0.87**	**-1.48**	**-1.38**	**-1.18**	**-1.95**

[2] Low = creatinine clearance is between 30 and 60 mL/min

[3] Normal = creatinine clearance >60 mL/min

[4] Baseline = Last 7 available scores before taking study medication, up to and including Day 1

[5] Week 8= Average of the last 7 available scores up to day 57, and baseline mean pain scores for non-completers at week 8 and onwards

[6] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers

Study 1008-196 Reviewer's analysis: ANCOVA, mean pain score at Endpoint (BOCF) –

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.19	0.22			
PGB 150							
Low[4]	26	6.77	5.76	0.41	-0.43	0.3514	0.3514
Normal[5]	61	6.30	5.12	0.27	-1.07	0.0020	0.0080
PGB 300							
Low[4]	59	6.84	5.38	0.27	-0.81	0.0194	0.0582
Normal[5]	65	6.60	5.54	0.26	-0.65	0.0532	0.1064
PGB 600	64	6.64	4.72	0.26	-1.47	<0.0001	0.0005

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the two pairwise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min

Study 1008-196: Reviewer's analysis: ANCOVA, mean pain score at Week 8 (BOCF)

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.11	0.20			
PGB 150							
Low[4]	26	6.77	5.79	0.38	-0.31	0.4461	0.4461
Normal[5]	61	6.30	5.00	0.25	-1.11	0.0006	0.0024
PGB 300							
Low[4]	59	6.84	5.22	0.26	-0.89	0.0066	0.0174
Normal[5]	65	6.60	5.29	0.24	-0.82	0.0087	0.0174
PGB 600	64	6.64	4.74	0.25	-1.37	<0.0001	0.0005

[1] Week 8= Average of available scores between day 51 to day 57, for subjects who completed that week, and baseline mean pain score for non-completers
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the six pairwise comparisons versus placebo
[3]Low = creatinine clearance is between 30 and 60 mL/min
[4]Normal = creatinine clearance >60 mL/min

All groups experienced an improvement in pain from baseline to week 8 and to endpoint. However, the comparison to placebo did not reach statistical significance for patients with a low CLcr who were in the pregabalin 150 mg/day group at either Week 8 or at endpoint. Also, the mean score for the pregabalin 300 mg/day-normal CLcr group was not significantly different from the placebo group's score at endpoint, although significance was seen at week 8. It is noted that the trial size was based on the assumption that this group would be pooled with the patients with low CLcr assigned to this arm, and loss of significance may be explained by the smaller-than-expected N.

2.4.3.2.2 Responder analysis

Responder analysis was also undertaken, at the Agency's request, by the sponsor. In this analysis, patients who had at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. According to the sponsor's calculations, which used the LOCF imputation strategy, the proportion of responders in the pregabalin 300/600 mg/day group (38%), the pregabalin 300 mg/day group (27%), and the pregabalin 150 mg/day group (27%), were significantly different from placebo (8%, p = 0.001 for each comparison).

Drs. Kashoki and Buenconsejo recalculated change from baseline using the BOCF strategy and tabulated the results at both week 8 and study endpoint as shown below. The percentages shown are cumulative. Non-responders are in the shaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this data presentation, 6% of the placebo group, 8% of the pregabalin 150 mg/day-low CLcr group, 21% of the pregabalin 150 mg/day-normal CLcr group, 17% of the pregabalin 300 mg/day-low CLcr group, 23% of the pregabalin 300 mg/day-normal CLcr group, and 30% of the pregabalin 600 mg/day meet the definition of responder (50% reduction in pain) at week 8. At study endpoint, 6% of the placebo group, 19% of the pregabalin 150 mg/day-low CLcr group, 28% of the pregabalin 150 mg/day-normal CLcr group, 19% of the pregabalin 300 mg/day-low CLcr group, 20% of the pregabalin 300 mg/day-normal CLcr group, and 31% of the pregabalin 600 mg/day meet the definition of responder

The effect of pregabalin is further highlighted by the differences in proportions of patients experiencing even greater degrees of improvement in pain.

Study 1008-196 Reviewer's analysis: Percent change in mean pain score by treatment dose, BOCF imputation, Study endpoint

	PLACEBO		PGB 150 Low[1]		PGB 150 Normal[2]		PGB 300 Low[1]		PGB 300 Normal[2]		PGB 600 Normal[2]	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	26	28%	2	8%	9	15%	2	3%	8	12%	6	9%
None	36	39%	14	54%	16	26%	27	46%	24	37%	20	31%
> 0 % decrease	36	39%	10	38%	36	59%	30	51%	33	51%	38	59%
≥10%	25	27%	8	31%	31	51%	27	46%	29	45%	35	55%
≥20%	19	20%	6	23%	30	49%	21	36%	22	34%	30	47%
≥30%	15	16%	5	19%	25	41%	14	24%	21	32%	27	42%
≥40%	8	9%	5	19%	19	31%	13	22%	18	28%	24	38%
≥ 50%	**6**	**6%**	**5**	**19%**	**17**	**28%**	**11**	**19%**	**13**	**20%**	**20**	**31%**
≥60%	6	6%	1	4%	11	18%	6	10%	11	17%	15	23%
≥70%	5	5%	1	4%	7	11%	6	10%	7	11%	12	19%
≥ 80%	4	4%	0	0%	3	5%	5	8%	1	2%	10	16%
≥ 90%	3	3%	0	0%	2	3%	2	3%	0	0%	4	6%
=100%	2	2%	0	0%	2	3%	1	2%	0	0%	3	5%

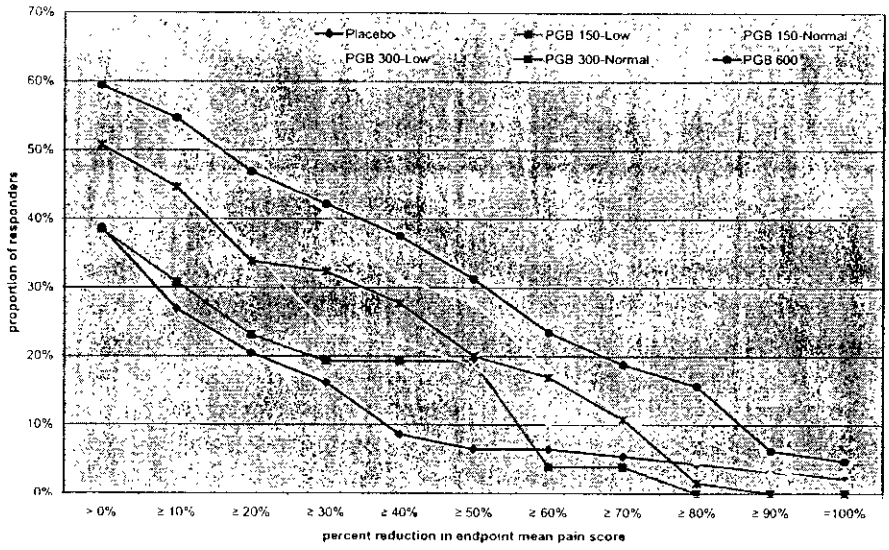
Study 1008-196 Reviewer's analysis: Percent change in mean pain score by treatment dose, BOCF imputation, Week 8

	PLACEBO		PGB 150 Low[1]		PGB 150 Normal[2]		PGB 300 Low[1]		PGB 300 Normal[2]		PGB 600 Normal[2]	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	18	19%	2	8%	5	8%	2	3%	8	12%	3	5%
None	39	42%	13	50%	17	28%	26	44%	23	35%	22	34%
> 0 % decrease	36	39%	11	42%	39	64%	31	53%	34	52%	39	61%
≥ 10%	27	29%	8	31%	36	59%	27	46%	31	48%	36	56%
≥ 20%	22	24%	8	31%	31	51%	21	36%	22	34%	33	52%
≥ 30%	18	19%	5	19%	26	43%	15	25%	21	32%	24	38%
≥ 40%	8	9%	5	19%	18	30%	13	22%	17	26%	22	34%
≥ 50%	**6**	**6%**	**2**	**8%**	**13**	**21%**	**10**	**17%**	**15**	**23%**	**19**	**30%**
≥ 60%	3	3%	2	8%	10	16%	7	12%	12	18%	14	22%
≥ 70%	3	3%	2	8%	6	10%	3	5%	7	11%	11	17%
≥ 80%	3	3%	1	4%	2	3%	1	2%	2	3%	8	13%
≥ 90%	1	1%	1	4%	0	0%	0	0%	0	0%	4	6%
=100%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%

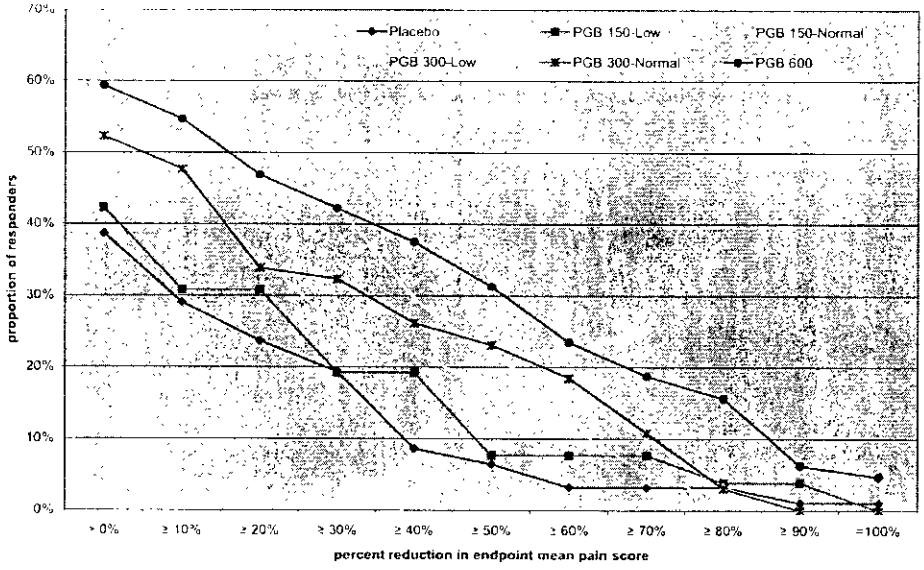
[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

The results in the tables above are also illustrated graphically in the figures below, from Dr. Buenconsejo's review.

Response Profile at Week 13 (New Treatment Group Assignment)



Response Profile at Week 8 (New Treatment Group Assignment)



Using this analytic approach, all treatment arms except the 150 mg/day-low CLcr show a superior response to placebo. This provides reassurance regarding the efficacy of 300 mg/day, which failed to reach statistical significance on the analysis of endpoint mean pain score in the normal Clcr group, possibly due to the sample size created by the

reviewers' (appropriate) regrouping of the patients into 5, rather than 3, treatment arms. However, the failure of the 150 mg/day-low CLcr group is confirmed in this analysis. The less favorable response of the low CLcr group compared to the normal CLcr group is also observed at the 300 mg/day dose based on the response profiles above. Notably, differential response between normal and low CLcr groups was also observed other studies, in this development program and in the single study in the DPN program which allowed enrollment of patients with CLcr<60 mL/min. Because pregabalin is renally cleared, exposures are expected to be higher in patients with lower CLcr; therefore the poorer responses in this group, compared to patients with relatively normal CLcr, treated with the same dose may be explained by the higher rate of dropouts due to adverse events.

The sponsor's analysis concludes that all treatment arms were successful. The reviewers' analyses differ from the sponsor's in two important ways. First, the BOCF imputation strategy was chosen. The pattern of dropouts (primarily for adverse events in the active treatment groups vs. primarily for lack of efficacy in placebo group) confirms the appropriateness of this choice in avoiding bias. An LOCF imputation strategy could inappropriately assign favorable pain scores to patients who were on an intolerable dose of medication and subsequently discontinued. The second key difference was that the reviewers grouped the patients based on creatinine clearance strata and dose received. The emergence of clear tolerability differences confirms the appropriateness of this analytic approach. The illogical division of patients with CLcr <60, treated with 300 mg/day, into two different treatment arms was also corrected in the reviewer's analysis. It is understandable that the sponsor would want to ensure that patients with low CLcr would not be exposed to the 600 mg/day dose; however, the proper approach to this problem would have been to stipulate that these patients could only be randomized to placebo, 150 mg/day, or 300 mg/day. Only patients with CLcr>60 would be eligible to be randomized to the highest dose. The reviewers' analyses are clearly more appropriate, but because they were unplanned, the sample size was not selected with these analyses in mind. I believe the responder analysis, which supports the efficacy of pregabalin in all treatment arms but the 150 mg/day-low CLcr group, illustrates clearly the clinical benefit of the product.

2.4.3.3 Secondary endpoints

Secondary endpoints analyzed included SF-MPQ (sensory, affective, VAS, PPI, and total scores); Sleep interference; MOS sleep scale scores; global impression (patient and clinician); SF-36 QOL; and EQ-5D utility and VAS scores. These measures, in general, supported the primary outcome analysis.

2.4.3.4 Efficacy Conclusion, Study 1008-196

This study provides evidence of efficacy of pregabalin 75 mg b.i.d. (150 mg/day), 150 mg b.i.d. (300 mg/day), and 300 mg b.i.d. (600 mg/day) in patients with CLcr of at least 60 mL/min. In addition, the study provides evidence of efficacy for pregabalin 150 mg b.i.d. (300 mg/day) in patients with CLcr of less than 60 mL/min.

2.5 Overall Efficacy Conclusion

The data provide evidence that pregabalin, at doses of 300-600 mg/day, is effective in the treatment of post-herpetic neuralgia in patients with a creatinine clearance of at least 60 mL/min. Tolerability limits response at the higher dose, therefore, for these patients, the recommended dose should be 300 mg/day. Only patients with an unsatisfactory response at 300 mg/day, who can tolerate a dose increase, should be titrated upward to 600 mg/day.

Results were inconsistent in the subset of patients with lower creatinine clearance, with one positive and one negative study of 150 mg/day, one positive study at 300 mg/day, and two studies in which tolerability limited the effectiveness of 300 mg/day. Therefore, pregabalin should be titrated to tolerability and effect in these patients, beginning with a target dose of 150 mg/day and titrating upward for patients with unsatisfactory response who can tolerate dose increases.

3 SAFETY

The PHN population is typically elderly, and, as expected, the age of the PHN subjects was higher than the subjects in the other development programs. However, the findings of the overall safety review are expected to be applicable to the PHN population with respect to rare AEs, SAEs, and general effects on vital signs or laboratory parameters. For common AEs, a separate tabulation in the PHN population was undertaken to highlight the particular experiences of this group.

In a safety database of sufficient size and using suitable safety monitoring procedures, pregabalin was associated with nervous system abnormalities (dizziness, somnolence, ataxia, abnormal gait, incoordination, and mental status changes including confusion, "thinking abnormal," amnesia, and "speech disorder") edema, blurred/abnormal vision, dry mouth, and constipation in patients with post-herpetic neuralgia. Approximately 12% of PHN subjects discontinued due to adverse events, in a dose-dependent fashion, with as many as 29% of subjects with CLcr ≥60 mL/min discontinuing due to AEs in the 600 mg/day groups and as many as 37% of subjects with CLcr<60 mL/min in the 300 mg/day groups. Adverse events reported most commonly in association with premature discontinuation were dizziness, somnolence, confusion, and ataxia.

No specific SAE was clearly linked to pregabalin treatment.

An effect of pregabalin on platelets (reduction in platelet count) is also noted but not linked to any specific clinical consequences. Pregabalin is also associated with moderate increases in creatine kinase (CK). No clinical consequences of elevated CK in the PHN population were noted.

Other safety concerns of note include ophthalmologic effects which require further study for complete characterization, and animal findings of carcinogenicity and dermatopathy for which no clinical correlations have been identified.

3.1 Exposure

The overall exposure to pregabalin was adequate to characterize the safety profile and met ICH requirements. The overall safety database for all pregabalin development programs includes 9278 individuals who were exposed to pregabalin and are included in the integrated safety database/safety update, including 2701 exposed for at least one year. In the PHN program, a total of 924 patients received at least one dose of pregabalin in controlled trials (including those reported in the safety update), and an additional 259 participated in uncontrolled trials. The PHN population was 98% Caucasian, 53% female/47% male, and primarily elderly, with a median age of 73 years and 89% of patients at least 65 years old.

Chronic use for this indication is not anticipated; however, there is more than sufficient exposure to meet ICH requirements for a chronically-administered drug in the integrated safety database for all indications.

3.2 Deaths

No deaths reported appear to be clearly associated with pregabalin. One death in the PHN population (reported in the Safety Update) occurred as a result of head injury sustained in a fall. It cannot be determined whether adverse events associated with pregabalin (e.g. somnolence, dizziness, ataxia) may have contributed to this fall.

A higher mortality rate was seen in the PHN population compared to other trial populations, which is not unexpected due to the advanced age of the PHN subjects.

3.3 Discontinuations

Dr. Kashoki examined available CRFs to assess the appropriateness of the sponsor's characterization of reason for early termination. Based on her review, events described under "other" were recategorized as appropriate.

In the overall database, 27% of placebo subjects in controlled trials for all indications in the development program discontinued prematurely, while 32% of pregabalin-treated subjects discontinued prematurely. Lack of efficacy was the most commonly-reported reason among placebo-treated subjects (12% of subjects), while adverse event was the most commonly-reported reason among pregabalin-treated subjects (13% of subjects). In the uncontrolled trials across all indications, approximately 73% of subjects prematurely terminated participation. By far, the most common category of reason for discontinuation in this group was "other," comprising approximately 40% of the participants and accounting for over half of the early terminations. Lack of efficacy was cited by 17% of participants and adverse events by 14%.

In the PHN population, adverse events were cited as the reason for early termination in approximately 12% (vs. 13% of subjects in the overall population). Similar to the overall database, in the PHN population, dizziness, somnolence, confusion, and ataxia emerged as the most common adverse event-related reasons for discontinuation.

Discontinuations due to adverse events were consistently higher in patients with a CLcr<60 mL/min compared to those with CLcr≥60 mL/min, with 23% (47/202) of the low CLcr patients, pooled across doses in the three pivotal studies, discontinuing due to AEs. By comparison, 10% of the patients with CLcr≥60 mL/min discontinued due to AEs. In uncontrolled trials in PHN, 19% of subjects (treated with various doses) dropped out prematurely due to adverse events.

The tables below illustrates the dose-dependency of dropout due to adverse events in the controlled studies, and the left-shift in the dropout rates seen in the more renally impaired subgroup. It also clearly demonstrates that 600 mg/day is associated with a dramatically higher dropout rate than lower doses. Conversely, the efficacy is not dramatically better. This suggests that the optimal risk/benefit ratio for patients with CLcr>60mL/min is at the 300 mg/day dose, and that further titration should be reserved for patients with poor response at 300 mg/day who can tolerate dose increases.

Disposition = Withdrawn Due to Adverse Events, CLcr <60 mL/min

	Placebo	PGB 150	PGB 300	
1008-045	8/81 (10%)	6/42 (14%)	12/45 (27%)	
1008-127	4/84 (5%)		11/30 (37%)	
1008-196	5/95 (5%)	5/26 (19%)	13/59 (22%)	
ALL	17/260 (7%)	11/68 (16%)	36/134 (27%)	

Disposition = Withdrawn Due to Adverse Events, CLcr ≥60 mL/min

	Placebo	PGB 150	PGB 300	PGB 600
1008-045	8/81 (10%)	3/39 (8%)	0/31 (0%)	
1008-127	4/84 (5%)			17/59 (29%)
1008-196	5/95 (5%)	2/61 (3%)	7/65 (11%)	14/64 (22%)
ALL	17/260 (7%)	5/100 (5%)	7/96 (7%)	31/123 (25%)

3.4 Serious Adverse Events

In the overall database, no specific serious adverse event emerged as clearly related to pregabalin treatment. However, two cases of edema were lacking alternative explanation and are consistent with the observation that pregabalin was associated with edema in the overall adverse event database. In the PHN population, the relative risk of SAE was 1.32 (3.3% of pregabalin-treated patients vs. 2.5% of placebo-treated patients in controlled trials). No specific SAE term was reported in more than 1% of PHN patients. Notable events lacking alternative explanation in this population included one patient who developed a visual field defect after 153 days of exposure to pregabalin, and a patient who developed macular degeneration after approximately 296 days of drug exposure. One of the unexplained cases of edema was in the PHN population, involving a patient who developed peripheral and facial edema after approximately 2 weeks of pregabalin therapy. Other cases lacking explanation included one case of lung fibrosis, one case of pancreatitis, and one anaphylactoid reaction (see Dr. Kashoki's review).

3.5 Other Significant Adverse Events

As noted above, pregabalin was carcinogenic in mouse studies, producing angiomas and angiosarcomas. Dr. Kashoki examined the overall database for any neoplasms suggestive of a similar process in humans, although such findings were considered unlikely given the relatively brief exposures. No case of neoplasm suggested drug-relatedness.

Additionally, due to the reports of peripheral edema and vision abnormalities in early clinical studies, Dr. Kashoki queried the integrated safety database for AEs related to the eye, and metabolic/nutritional AEs and reviewed the CRFs and narratives of all subjects with reports of (a) edema, face edema, peripheral edema, and generalized edema; (b) vision abnormal, diplopia, amblyopia, retinal edema, retinal disorder, eye disorder, and visual field defect.

3.5.1 Ophthalmologic Events

In the controlled trial database across indications, 704 patients reported one of the following eye-related AEs: abnormal vision, amblyopia (verbatim term "blurry vision"), diplopia, or visual field defect. The frequency of these AEs by treatment group is shown in the table below ("amblyopia" has been replaced with the term "blurred vision"):

					Total pregabalin daily dose (mg/d)							
Preferred term	**Placebo N=2308**		**All PGB N=5508**		**150 N=1164**		**300 N=1224**		**450 N=501**		**600 N =1802**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Abnormal vision	12	0.50	101	1.83	16	1.37	20	1.63	4	0.80	51	2.83
Blurred vision	51	2.14	361	6.55	54	4.64	68	5.56	36	7.19	164	9.10
Diplopia	12	0.50	113	2.05	17	1.46	24	1.96	7	1.40	60	3.33
Visual field defect	18	0.76	53	0.96	14	1.20	12	0.98	4	0.80	19	1.05

All PGB includes other doses of pregabalin (50, 75, 200, and 400 mg/d)

Within the adverse event database, an effect of pregabalin is apparent for various visual complaints; it is less evident for the less common "visual field defect."

Within the PHN database specifically, the most commonly-reported visual AE was blurry vision (sponsor's preferred term: "amblyopia"), occurring in 5% of pregabalin-treated and 2% of placebo-treated patients, in a dose-dependent fashion. Visual field defects were reported in two patients treated with placebo (0.5%) and two treated with 600 mg/day (1.3%).

Specific visual field testing and visual acuity testing was also included in some clinical trials. These data were reviewed by Dr. Wiley Chambers, HFD-550 (see Dr. Chambers' review for detail). Dr. Chambers noted a number of methodological flaws in the collection of data, preventing definitive conclusions. As designed and executed, the testing program was judged by Dr. Chambers to be insensitive to minor changes and unlikely to detect a difference across treatments. Nevertheless, he noted an effect of pregabalin on both visual field loss and on impairment in visual acuity.

3.5.2 Peripheral Edema

Peripheral edema, noted as a drug-related adverse event in the all-indications safety database, was seen at a higher rate in the PHN population than in other populations. Terms including edema, face edema, and peripheral edema were all more common in pregabalin-treated than in placebo-treated patients. In the overall database, peripheral edema was reported in 6% of pregabalin-treated vs. 2% of placebo-treated patients. The table below shows the incidence of edema-related events in the PHN population.

Term	Placebo N = 398		75 mg/d N = 84		150 mg/d N = 302		300 mg/d N = 312		600 mg/d N = 154		All PGB N = 852	
	N	%	N	%	N	%	N	%	N	%	N	%
Face edema	3	1%	0	0	5	2%	3	1%	5	3%	13	2%
Peripheral edema	14	4%	0	0	27	9%	48	15%	25	16%	100	12%
Edema	4	1%	0	0	3	1%	7	2%	9	6%	19	2%

In the DPN population, an interaction between thiazolidinedione hypoglycemic medications was explored, because these medications are ligands for peroxisome proliferator activated receptors (PPARs) and are known themselves to be associated with peripheral edema. Concern over the contribution of this effect to the occurrence of heart failure in diabetic patients has led to cautionary language in labels for these drugs. The interaction between PPARS and pregabalin was predicted to be of great importance to the DPN population; however, even in populations without DPN these medications may be used. Furthermore, a significant number of participants in the PHN studies used alpha-tocopherol (Vitamin E), which is similar in structure to the thiazolidines.

Analysis showed that, in addition to a clear dose-dependent effect of pregabalin on peripheral edema, a interaction was seen when PPAR medications were added. The table below illustrates the incidence of edema and related AEs in patients using antidiabetic PPAR medications. The data is shown in the DPN population because the majority of patients using PPARs were in that population.

Heart Failure, Edema, and Weight Gain Controlled DPN Studies (Protocols 014, 029, 040, 131, 149, 173)

	Number of Patients (%)					
Adverse Event	**Placebo**	**75 mg/day PGB**	**150 mg/day PGB**	**300 mg/day PGB**	**600 mg/day PGB**	**All PGB**
DPN Non-PPAR Preferred Term	N=399	N=62	N=195	N=279	N=323	N=859
Congestive heart failure	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Edema	0 (0.0)	0 (0.0)	4 (2.1)	13 (4.7)	7 (2.2)	24 (2.8)
Peripheral edema	9 (2.3)	2 (3.2)	10 (5.1)	24 (8.6)	33 (10.2)	69 (8.0)
Weight gain	2 (0.5)	0 (0.0)	8 (4.1)	9 (3.2)	18 (5.6)	35 (4.1)
DPN PPAR Preferred Term	N=60	N=15	N=17	N=42	N=46	N=120
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)	1 (2.2)	3 (2.5)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral edema	2 (3.3)	1 (6.7)	3 (17.6)	6 (14.3)	13 (28.3)	23 (19.2)
Weight gain	0 (0.0)	0 (0.0)	1 (5.9)	3 (7.1)	5 (10.9)	9 (7.5)
Percent of DPN Patients reporting PPAR Use	13.1%	19.5%	8.0%	13.1%	12.5%	12.3%

DPN: diabetic peripheral neuropathy
(Prepared by Sponsor at Dr. Kashoki's request)

A similar tabulation shows a less clear-cut interrelationship between edema and Vitamin E. The table below, prepared by Pfizer at Dr. Kashoki's request, illustrates the occurrence of edema and possible edema-related AEs in the PHN population, by dose and use of Vitamin E. A possible supra-additive effect is seen at the highest dose of pregabalin, but is less clearly evident in the pooled pregabalin group.

13:05 29JUL2004

Summary of Adverse Events of Heart Failure, Edema, or Weight Gain
Controlled Postherpetic Neuralgia Studies (Studies 1008-030,-045,-127,-132,-196)

Pregabalin Summary of Clinical Safety: Neuropathic Pain, Adjunctive Therapy for Partial Seizures, and Generalized Anxiety Disorder

TESS
Number of Patients (%)

Adverse Event	Placebo	75 mg/day PGB	150 mg/day PGB	300 mg/day PGB	600 mg/day PGB	All PGB
PHN Non-Tocopherol						
Preferred Term	N=369	N=65	N=281	N=289	N=135	N=770
Congestive heart failure	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Heart failure	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Edema	5 (1.4)	0 (0.0)	3 (1.1)	7 (2.4)	8 (5.9)	18 (2.3)
Face edema	3 (0.8)	0 (0.0)	5 (1.8)	3 (1.0)	4 (3.0)	12 (1.6)
Peripheral edema	13 (3.6)	0 (0.0)	23 (8.2)	45 (15.6)	20 (14.8)	88 (11.4)
Generalized edema	1 (0.3)	0 (0.0)	4 (1.4)	1 (0.3)	2 (1.5)	7 (0.9)
Weight gain	1 (0.3)	1 (1.5)	5 (1.8)	16 (5.5)	8 (5.9)	30 (3.9)
PHN Tocopherol						
Preferred Term	N=38	N=19	N=21	N=23	N=19	N=82
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.2)
Face edema	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (5.3)	2 (2.4)
Peripheral edema	1 (2.6)	0 (0.0)	1 (4.8)	4 (17.4)	5 (26.3)	10 (12.2)
Generalized edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight gain	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	2 (10.5)	3 (3.7)
Percent of PHN Patients reporting Tocopherol Use	9.5%	22.6%	7.0%	7.4%	12.3%	9.6%

3.6 Common Adverse Events

Dr. Kashoki examined the rates of common adverse events in the placebo-controlled clinical trials for PHN. The studies varied slightly in duration but were similar in design and population and appropriate for pooling.

A full table of adverse events is included in Dr. Kashoki's review. Overall, adverse events of the nervous system were most frequently reported. Specifically, dizziness (26%) and somnolence (16%) were the most common, with relative risks of 2.7 and 3.1 respectively. Other nervous system AEs included motor effects (ataxia, abnormal gait, incoordination), change in mental status (confusion, abnormal thinking, amnesia) and speech abnormalities ("speech disorder").

The third most frequently reported non-serious AE was peripheral edema (12% in the pregabalin group vs. 4% in the placebo group). Face edema and "edema" in general were also more common in the pregabalin group than in the placebo group. Similarly, weight gain occurred more frequently in pregabalin-treated patients (4%) compared to placebo patients (0.3%). Also, infection, blurred vision (coded as "amblyopia"), diplopia, and accidental injury were more frequent among the pregabalin group than in the placebo group. Finally, there were gastrointestinal effects of dry mouth and constipation. The PHN population emerged as more vulnerable than the population overall to edema (discussed below), as well as "abnormal vision" (5% of 600 mg/day group vs 0.25% of placebo group, compared to 3% of 600 mg/day group vs 0.5% of placebo group in overall population), and "abnormal gait" (8% in 600 mg/day group vs 0.5% in placebo group, compared to 3% in 600 mg/day group vs 0.1% in placebo group). The most common terms, such as dizziness, somnolence, and dry mouth, were no more common among the PHN patients than in the overall safety database.

3.7 Laboratory data

The most notable differences between treatment groups from analysis of laboratory data was an increase in creatinine kinase and a decrease in platelets among pregabalin treated patients compared to placebo patients. No specific clinical consequences were observed and these issues are to be included in labeling.

3.8 Vital Signs

There were no differences between placebo and pregabalin groups with respect to mean changes from baseline or in the proportion of subjects experiencing potentially clinically significant changes from baseline in vital signs. There was no difference between groups in the proportion of patients for whom a vital sign abnormality was reported as an adverse event (e.g., hyper/hypotension, brady/tachycardia).

3.9 Weight

Among all controlled studies and across indications, an evaluation of change in weight from baseline to any time showed that 12.6% of patients treated with pregabalin had an increase in weight, compared to 2.4% of placebo patients. Furthermore, among patients with a normal body mass index (BMI) at baseline, 2.2% of placebo patients versus 4.6% of pregabalin patients experienced an increase in BMI. Among DPN patients in controlled trials, 1.8% of placebo patients versus 7.5% of pregabalin patients had an increase in weight from baseline to any time in the study. The increase in weight did not appear to be dose proportional: 11.4% of patients in the 300 mg/d group compared to 5.6% in the 600 mg/d group had a weight increase. Analyses of shifts in BMI from "normal" at baseline to "high" at any time in the trial found that 1.1% of placebo patients had an increase, compared to 2.4% of pregabalin patients.

Considering change from baseline to last observation, the overall incidence of ≥7% weight gain was higher among pregabalin-treated patients (7.7%) than placebo-treated patients (1.7%), with the highest incidence in patients treated with pregabalin 600 mg/day (11.6%). The 12-week controlled epilepsy studies had the highest overall incidence of weight gain (18.0%). Pfizer tabulated the distribution of weight changes in controlled trials and illustrated that, for the majority of subjects, the amount of weight gain was 10% of baseline weight or less. However, this amount of weight gain is, itself, clinically relevant for both patient satisfaction and overall health.

Among PHN patients in controlled trials, 1.8% of placebo patients versus 6.8%% of pregabalin patients had an increase in weight of ≥ 7% from baseline to study termination. Analyses of shifts in BMI from "normal" at baseline to "high" at any time in the trial found that 2.6% of placebo patients had an increase, compared to 5.0% of pregabalin patients.

The cumulative distribution of weight gain in controlled PHN trials is shown in the table below. A dose dependent effect of pregabalin on weight gain is apparent.

		Pregabalin Dose, mg/day (BID and/or TID)				
	Placebo	75	150	300	600	Any Dose
Percent Change	**N=398**	**N=84**	**N=302**	**N=312**	**N=154**	**N=852**
N at Risk*	387	78	298	303	149	828
Increase						
>=7	7 (1.8)	3 (3.8)	11 (3.7)	28 (9.2)	14 (9.4)	56 (6.8)
>=10	3 (0.8)	1 (1.3)	4 (1.3)	6 (2.0)	6 (4.0)	17 (2.1)
>=15	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.7)	3 (0.4)
>=20	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=25	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*N at risk = the number of patients with both baseline and termination/LOCF weights recorded

Applicant's Appendix ALL.136, P. 7367

There were no apparent risk factors for weight gain, other than treatment with pregabalin. Co-occurrence of edema did not fully account for the observed weight gain.

3.10 ECGs

Overall, pregabalin treatment had no clinically significant findings for ECG parameters. Pregabalin had no consistent effect on QTs, QRS, or ventricular rate. Premature ventricular contractions (PVCs) did not occur more commonly in pregabalin-treated than placebo-treated patients in the combined pain trials, epilepsy trials, short -term GAD trials, or relapse-prevention trials. In the DPN sub-population, PVCs occurred more commonly in pregabalin-treated patients, but there was no clear dose relationship of pregabalin with PVCs.

Across all studies pregabalin was associated with a statistically significant but clinically insignificant mean increase in PR interval (3-6 msec) at doses ≥300 mg/day. The incidence of cardiovascular adverse events was similar among pregabalin-treated and placebo-treated patients. Generally, pregabalin treatment was not associated with significant cardiac-associated sequelae.

3.11 Drug Abuse, Withdrawal, and Overdose experience

The Controlled Substances Staff (CSS, HFD-009) evaluated the available non-clinical and clinical data pertinent to the abuse liability of pregabalin and its propensity to cause dependence. Their conclusions are documented in a separate review. Briefly, however, CSS concluded that the abuse liability of pregabalin is similar to that of diazepam, and that control under Schedule IV of the Controlled Substances Act (CSA) should be recommended to the Drug Enforcement Administration. An eight-factor analysis of abuse potential has been prepared by the CSS for forwarding through DHHS to DEA. If this recommendation is forwarded, the drug cannot be marketed until has completed consideration and implementation of any scheduling action. Pfizer has disputed CSS's evaluation of the data and will be meeting with the Acting Deputy Center Director to argue that the recommendation for scheduling should not be sent to the Department.

4 CONCLUSION AND RECOMMENDATIONS

This application provides substantial evidence that pregabalin, at daily doses of 300-600 mg/day, is effective for the treatment of post-herpetic neuralgia in patients with creatinine clearance of at least 60 mL/min. However, the safety data demonstrate a clear and dramatic increase in premature treatment discontinuation due to adverse events at the 600 mg/day dose. Furthermore, the dose-dependent adverse events, including dizziness, ataxia, and visual impairment are particularly concerning in the elderly population typical of PHN patients. The elderly are more vulnerable to serious sequelae of falls, and these effects of pregabalin are likely to predispose patients to falling. A dose-dependent incidence of accidental injury confirms this impression. Therefore, although the efficacy data suggest that the 600 mg/day dose may be associated with a higher response rate, this dose should only be used in patients who have not had a satisfactory response at lower doses.

The application provides inconsistent and inconclusive evidence about the use of pregabalin for post-herpetic neuralgia in patients with creatinine clearance between 30 and 60 mL/min. In one study, 150 mg/day (50 mg t.i.d.) proved effective in this population, but in another study, this dose was ineffective. A higher dose, 300 mg (150 mg b.i.d.) was effective in a second study, but ineffective in two other studies due to high rates of dropout due to adverse events. Therefore, while one might typically accept one positive study at 300 mg/day and one positive study at a lower dose as substantial evidence in support of 300 mg/day, the poor tolerability of the 300 mg/day dose makes it difficult to conclude that it can be effective in clinical use. In this population, it seems prudent to recommend initial titration to 150 mg/day, followed by upward titration as tolerated for those patients who do not have a satisfactory response. However, as in the general population with more normal creatinine clearance, aggressive titration may be unwise, as the risk of dizziness, ataxia, somnolence, visual disturbance and gait abnormality, with the attendant possibility of accidental injury, is a particular concern in this elderly population.

The safety data show that the nervous system abnormalities (dizziness, somnolence, ataxia, abormal gait, confusion/mental status changes) were the most common AES. Specifically, dizziness (26%%) and somnolence (16%) were the most frequent. Also notable were peripheral edema (12%) blurred vision and dry mouth, constipation, and dyspepsia. Approximately a quarter of subjects randomized to the maximum dose (600 mg/day in patients with CLcr>60 mL/min and 300 mg/day in subjects with lower CLcr) discontinued due to adverse events, most commonly for dizziness and somnolence. No specific SAE was clearly linked to pregabalin treatment. Weight gain, only partially explained by edema, is also observed. An effect of pregabalin on platelets (reduction in platelet count) and creatine kinase (increase) is also noted.

The ophthalmologic effects have not been fully characterized, but even with supra-threshhold testing, pregabalin appears to be associated with both signs and symptoms of visual impairment, including the development of visual field defect, loss of visual acuity on formal testing, and complaints of blurred vision. Agreement has not been reached with Pfizer concerning the presentation of the findings in labeling.

The preclinical data illustrate the risks of concern, including carcinogenicity, and dermatopathy. Although it was not possible to establish a clinical correlation with the animal findings, none would be expected in a safety database encompassing exposures of largely brief duration. Review of the potential human carcinogenicity of this product has been undertaken by the safety team in the Division of Neuropharmacologic Drug Products, who have expressed concern that Pfizer has not correctly established the expected background rate of cancers in the population to facilitate comparison.

Dr. Kashoki has recommended against approval of this application, citing concerns about the risks of visual impairment, dizziness, somnolence, and ataxia, all of which can contribute to falls in this vulnerable population of elderly patients. Knowing the substantial morbidity and mortality associated with falls and fractures in this population, her point is valid. However, I believe that the risk/benefit ratio of this product appears acceptable in this population, provided that cautious dosing and titration are employed. However, unresolved issued concerning the scheduling of the product and the communication of ophthalmologic risk remain. I recommend approvable action pending resolution of these issues.

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/s/

Celia Winchell
8/6/04 10:33:34 AM
MEDICAL OFFICER

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Medical Officer Review

Date of Submission: October 31, 2003

Type of Submission: New Drug Application

Product: Pregabalin (LYRICA™)

Sponsor: Pfizer

Review Date: August 30, 2004

Medical Officer: Mwango A. Kashoki, M.D., M.P.H

Project Manager: Lisa Malandro

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The Executive Summary of the Primary Clinical Review

Recommendations

Recommendations on Approvability
Pfizer provided evidence of efficacy of pregabalin (300- and 600-mg/d, administered in two or three divided doses) as treatment of postherpetic neuralgia. Efficacy is apparent only in patients with a creatinine clearance (CLcr) > 60 mL/min. Patients with a lower CLcr are unable to tolerate the effects of pregabalin and subsequently discontinue treatment, thereby limiting efficacy. Pregabalin causes CNS-related adverse effects including dizziness, somnolence, ataxia, and visual impairment. The risk of these and other non-CNS adverse effects increases with ascending doses. These effects could predispose patients to falling and other injuries, which is of serious concern given that patients with postherpetic neuralgia are older, and therefore more susceptible to grave consequences of injuries. The data from controlled studies in postherpetic neuralgia which show that more pregabalin-treated patients experienced accidental injury than placebo patients support this argument.

The vision-related effects of pregabalin are of concern, especially for the postherpetic neuralgia population. Patients with postherpetic neuralgia tend to be older and are therefore already at considerable risk of certain eye disorders and vision loss. Addition of the apparent visual effects of pregabalin could add considerably to these patients' morbidity. . At present, Pfizer has not adequately characterized the effects of pregabalin on vision.

Comparison of the frequency of treatment responders (i.e. patients with ≥ 50% decrease in pain from baseline) and the frequency of adverse events shows that patients who have a favorable treatment outcome are at equal or greater risk of experiencing one or more of the common adverse effects of pregabalin. Furthermore, although increased efficacy is observed at higher doses, so are greater adverse events.

In summary, the data show that pregabalin is efficacious in only a subset of patients with postherpetic neuralgia, with greater efficacy seen at the higher dose (600 mg/d). However, the likelihood of adverse effects is greater at this dose, thereby limiting the amount of drug that can be administered. Also, the CNS effects of the drug place the elderly population with postherpetic neuralgia at considerable risk for fall and other injuries, thereby possibly increasing their morbidity and mortality. Hence, the risk-to-benefit ratio of this drug is not sizeable. Given these concerns, as well as the availability of other FDA-approved therapies for postherpetic neuralgia, I do not recommend approval of this product for this treatment population.

Summary of Clinical Findings

Pregabalin is structurally related to both the inhibitory neurotransmitter, gamma aminobutyric acid (GABA) and to the endogenous amino acid, L-leucine. Pregabalin is not active at $GABA_A$, $GABA_B$, or benzodiazepine receptors and it does not alter GABA degradation nor acutely change GABA uptake in brain tissue. Pregabalin and L-leucine bind with high affinity to an auxiliary protein associated with voltage-gated calcium channels (α_2-δ protein), and it is this binding that is related to pregabalin's pharmacological activity. The exact mechanism by which pregabalin exerts its analgesic and anticonvulsant effects is as yet unknown.

Pregabalin has been approved for marketing in Europe.

Brief Overview of Clinical Program
Product name: Pregabalin
Route of administration: Oral
Indication: Management of pain associated with postherpetic neuralgia

The application contained 3 efficacy trials which contributed to the finding of efficacy. These 3 trials were of variable duration (8-13 weeks) and also varied with respect to titration of study drug: one study did not incorporate a titration period, while the other two studies had dose titration of 1 week. The three efficacy trials included 258 placebo-treated subjects and 512 subjects treated with pregabalin. Overall exposure (both controlled and open-label PHN trials) to the proposed marketed doses was212 patients for at least 6 months, and 48 patients for at least 1 year. While long-term exposure for the PHN population is low, exposure based on the total population (i.e. all treated populations) is adequate to characterize the safety profile and met ICH requirements. Safety data were obtained from 53 phase 2/3 trials in multiple indications (epilepsy, osteoarthritis, fibromyalgia, chronic – pain, generalized anxiety disorder, acute mania, social anxiety disorder, postherpetic neuralgia, and pain due to diabetic peripheral neuropathy). In total, there were 8,666 patients in the original safety database.

Efficacy
In three clinical trials of pregabalin in patients with postherpetic neuralgia, the mean pain score at study endpoint for subjects randomized to pregabalin 300-, and 600 mg/d was significantly lower than the score for patients randomized to placebo. Also, subjects randomized to 300- and 600 mg/d were more likely than placebo-treated subjects to report a decrease in pain of at least 50%. Two trials showed efficacy of a TID dosing regimen, and one trial showed efficacy of BID dosing.

Efficacy of pregabalin 150 mg/d was also evaluated in two separate trials. There was a considerable difference between pregabalin and placebo groups with respect to the proportions of patients who reported at least a halving of their pain from baseline. However, superiority to placebo with respect to the primary outcome, mean pain score at study endpoint, was shown only in a single trial, and among patients with a creatinine clearance greater than 60 mL/min.

The three trials that showed efficacy were:

- **Protocol 1008-045:** An 8-week, double, bind, placebo controlled, parallel group study of pregabalin (150 and 300 mg/d) in patients with postherpetic neuralgia
- **Protocol 1008-127:** An 8-week, double, bind, placebo controlled, parallel group study of pregabalin in patients with postherpetic neuralgia
- **Protocol 1008-196:** A 13-week, randomized, double-blind, multi-center, placebo-controlled study of pregabalin twice a day (BID) in the treatment of postherpetic neuralgia.

The primary endpoint was the final weekly mean pain score. The primary analysis was to compare the primary endpoint. The size of the treatment effect was based on previous findings

of efficacy and clinical relevance of that size difference in trials of gabapentin in patients with postherpetic neuralgia. There were multiple secondary analyses, including a comparison of the responder rate between treatment groups.

The FDA's statistical reviewer calculated the change in mean pain scores and responder rates for the three trials and obtained the following efficacy results for the above three trials:

Appears This Way
On Original

Protocol	RxGrp	Δ pain score	Endpoint mean pain score	Endpoint mean pain score p-value, ANCOVA	% responder	p-value
045	PBO	-0.49	6.3		9%	
	150 (50 tid), Low CLcr	-1.88	4.9	.0003	29%	.0132
	300 (100 tid) Low CLcr	-1.13	5.7	.0587	11%	.1758
	150 (50 tid); Normal CLcr	-1.36	5.5	.0587	21%	.8342
	300 (100 tid), Normal CLcr	-2.38	4.6	.0003	35%	.0032
127	PBO	-1.18	5.25		20%	
	300 (100 tid); Low CLcr	-1.84	4.76	.005	30%	.1556
	600 (200 tid); normal CLcr	-1.89	4.24	.003	34%	.1556
196	PBO		6.19		6%	
	150 (75 bid); Low CLcr	-0.55	5.76	.35	19%	0.0216
	300 (150 bid); Low CLcr	-1.38	6.84	.058[1]	19%	0.0008
	150 (75 bid); Normal CLcr	-1.48	5.12	.008	28%	0.0200
	300 (150 bid); Normal CLcr	-1.18	5.54	.1064[1]	20%	0.0200
	600 (300 bid); Normal CLcr	-1.95	4.72	.0005	31%	0.0005

Safety
Treatment with pregabalin is associated primarily with CNS adverse effects. Dizziness and somnolence occurred most frequently, and were the most common effects that led to discontinuation of treatment. Other CNS effects are blurring of vision, changes in, mental status (confusion, abnormal thinking, and euphoria), ataxia/incoordination, and vertigo. Non-CNS effects include edema, weight gain, dry mouth, and constipation. Accidental injury also occurred more frequently among pregabalin-treated patients in PHN controlled trials. The available data do not suggest an association between pregabalin and a specific SAE in this treatment population. Pregabalin is also associated with decreases in platelet count and increases in creatinine kinase, however there were no clear clinical correlates (e.g. thrombocytopenia, acute renal failure) to these effects.

Development of edema in patients with postherpetic neuralgia is also of concern, given that these patients tend to be older and therefore more likely to have cardiac-related disease. The edema could lead to worsened heart function. Another worrisome potential effect is the development of severe edema in patients who are also taking a thiazolinedione for diabetes. These patients could develop or experience worsening heart failure.

Since pregabalin is cleared by the kidneys, and because older patients such as those with postherpetic neuralgia experience a decline in renal function over time, these patients will be progressively exposed to higher systemic levels of pregabalin, and will be more likely to experience adverse effects.

The non-clinical studies show that pregabalin is carcinogenic, teratogenic, and causes dermatopathic changes. There was no clinical correlation with the findings of hemangiomas and hemangiosarcomas in mice, however this is to be expected, given the relatively brief period over which subjects were observed. There were 3 human reports of vascular tumors, only 1 of which was considered 'serious,' however the details of these events are pending at the time of this review.

Dosing, Regimen, and Administration
The data support either twice or three times daily dosing with pregabalin. Pregabalin can be administered with or without food. Dose modification for hepatically impaired patients is not necessary since the drug is not metabolized. There is a need for dose adjustment in renal impairment, as well as for supplemental dosing following hemodialysis

Drug-Drug Interactions
In clinical pharmacology studies, pregabalin did not appear to alter the pharmacokinetics of several antiepileptic drugs, oxycodone, gabapentin, and the oral contraceptive Ortho-Novum. Population PK analyses showed that commonly used antihypoglycemic agents did not alter the pharmacology of pregabalin. In trials using low doses of oxycodone, lorazepam, and ethanol, pregabalin (300 mg) was shown to augment the CNS effects of these drugs. It can therefore be anticipated that higher doses of either pregabalin or the other drugs would result in even greater CNS effects.

Special Populations
Overall, minorities were poorly represented in the clinical trials database. Otherwise, there was adequate representation of women, pediatric patients, and patients over age 65. There do not appear to be gender or age differences in the efficacy of pregabalin as treatment of pain due to DPN. The safety data do not suggest that any particular demographic group is particularly vulnerable to the adverse effects of pregabalin.

Use in pregnancy or in lactating women has not been evaluated. There was also evidence of maternal toxicity with higher pregabalin doses, and pregabalin has been detected in the milk of lactating rats. Additionally, non-clinical data showed decreased fetal body weight, abnormalities in ossification, decreased post-natal survival, and delay in developmental landmarks. All of these findings therefore suggest that pregabalin not be used during pregnancy or lactation, until further data showing safety are available.

Clinical Review

1 INTRODUCTION AND BACKGROUND

1.1 General information

- Established Drug Name: Pregabalin capsules
- Proposed Trade Name: LYRICA
- Applicant's Proposed Indication(s): For the treatment of postherpetic neuralgia
- Dose: 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules
- Regimens:
  - 50mg, 100mg, or 200 mg p.o. T.I.D.

    or
  - 75mg, 150mg, or 300 mg p.o. B.I.D.
- Age groups: Adults; Studies in children waived

1.2 State of Armamentarium for Indication

There are three FDA-approved pharmacological therapies for postherpetic neuralgia. Two therapies are for topical application – lidocaine patch (Lidoderm) and capsaicin ointment (Zostrix). Gabapentin (Neurontin), is the only approved oral agent for postherpetic neuralgia.

1.3 Important Milestones in Product Development

Pregabalin is a synthetic molecule, originally identified by Pfizer Inc. The initial IND was submitted to the Division of Neurpharmacological Drug Products (DNDP) on December 8, 1995 for the treatment of epilepsy. [redacted] The IND for the treatment of neuropathic [redacted] (I 53, 763) was submitted on July 24, 1997, to the Division of Anti-Inflammatory, Analgesic and Ophthalmologic drug Products (DAAODP). The IND was then transferred to this Division in July 2000.

In initial discussions with DAAODP, the Applicant proposed to evaluate the efficacy of pregabalin for 'neuropathic' and 'chronic' pain indications. Single studies in diabetic neuropathy [redacted] were proposed, with a t.i.d. dosing regimen. Following further discussion with the Agency, Pfizer modified its development program, seeking separate indications for treatment of pain due to diabetic neuropathy, and postherpetic neuralgia.

Pfizer initially submitted 3 trials of t.i.d. dosing of pregabalin in patients with postherpetic neuralgia. At the pre-NDA meeting in 2002, the company stated that it would include in the NDA data from additional studies in which pregabalin was given twice daily (b.i.d).

Several milestones in the neuropathic pain development program, as they pertain to the indication for postherpetic neuralgia, are noted in the table below:

07/24/97	IND 53, 763 opened	
12/18/97	Pre-IND meeting with DAAODP	Proposal for the broad indication, "treatment of neuropathic pain" if one study is conducted in diabetic neuropathic pain and in postherpetic neuralgia. Additional proposal for [ ]. Agreement in principle by DAAODP. DAAODP recommended a middle dose between 150- and 600 mg to help identify a minimally effective dose, and studies of up to 12 weeks to support efficacy.
06/17/99	EOP 2 meeting with DAAODP	Preference for replication in both a neuropathic [ ] pain model to show efficacy for [ ] indication. For diabetic neuropathy, need evidence that benefit is not due to nerve damage. Preference for 12 weeks at steady state to show efficacy, however 5 weeks is acceptable for NDA filing. Sponsor should submit a proposal for a waiver of studies of pregabalin in pediatric pain population.
12/20/99	EOP 2 meeting with DAAODP	Two positive diabetic neuropathy and one postherpetic neuralgia study constitute replicated evidence of efficacy for "peripheral neuropathic pain" and not [ ]" indication.
06/07/00	Pre-NDA meeting With DAAODP	Data regarding hemangiosarcomas in animal studies could impact approvability of the NDA.
07/2000	IND transfer to DACCADP	
08/03/00	Meeting	Discussion of Pfizer's plan to analyze visual field data. Ophthalmologic data were collected based on reports of visual field defects during clinical trials.
12/12/00	Executive CAC meeting	Increased incidence of hemangiosarcomas in mice is indicative of a true tumorigenic response to pregabalin. E-CAC disagreed with Pfizer that hemangiosarcomas are specific to the mouse strain that was studied. Another 2-year bioassay in a different mouse strain, and reanalysis of the rat data, were suggested.
01/26/01	Clinical hold	Sponsor informed that based on the E-CAC conclusions and with little safety margin between mouse exposure and intended human exposure levels, the risk-benefit ratio does not justify continued clinical development. A **complete hold** was proposed for neuropathic pain and anxiety disorders, and all ongoing studies, including the 12- and 13-week trials of BID dosing in postherpetic neuralgia, were discontinued. A **partial hold** was effected for epilepsy trials. Carcinogenicity of pregabalin is an approvability issue.
02/08/01	Revision of the clinical hold	All neuropathic pain trials were placed on **partial clinical hold**, where only patients meeting refractory criteria may be treated with pregabalin: (for studies ≤ 12 wks) failure of both a TCA and gabapentin; (for studies > 12 wks) failure of a TCA, gabapentin, and a 3rd line agent (e.g. analgesic, opioid, anticonvulsant). Agreement by the Agency that an 8-week pivotal trial in neuropathic pain is fileable.
10/30/03	NDA submission	

1.4 Other Relevant Information

In June 2004, pregabalin was approved for marketing in Europe.

1.5 Important Issues with Pharmacologically Related Agents

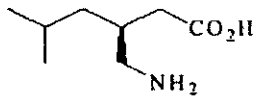
Pregabalin is structurally similar to gabapentin, which is approved for the treatment of partial seizures and postherpetic neuralgia. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid), but the mechanisms by which gabapentin exerts its analgesic and anticonvulsant effects are unknown. Gabapentin does not modify GABA binding, is not metabolically converted to GABA or a GABA agonist, and is not an inhibitor of GABA uptake or degradation. In rat studies, gabapentin was associated with an increased risk of pancreatic acinar cell adenomas, however the relevance of this finding to humans is unclear. In clinical trials, treatment with gabapentin was associated with higher incidences of dizziness, somnolence, blurry vision, and peripheral edema than treatment with placebo.

2 SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

Much of the material is taken from my previous NDA review of pregabalin as, and the Agency's proposed product label for the indication, "treatment of neuropathic pain associated with diabetic peripheral neuropathy."

2.1 Chemistry, manufacturing, and controls

LYRICA (pregabalin) Capsules are supplied as imprinted hard-shell capsules containing 25, 50, 75, and 100 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. Pregabalin is described as (S)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin is a white to off-white, crystalline solid with a pK_{a1} of 4.2 and a pK_{a2} of 10.6. It is freely soluble in water and both basic and acidic aqueous solutions. The log of the partition coefficient (n-octanol/0.05M phosphate buffer) at pH 7.4 is – 1.35.

Pregabalin stored for up to 3 years showed good stability over the wide range of packaging alternatives and conditions evaluated.

2.2 Preclinical efficacy

Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) indicate that selective binding to the alpha$_2$-delta subunit is required for pregabalin's antinociceptive effect in animal models. *In vitro*, pregabalin reduces the release of several neurotransmitters in hyper-excited neurons, presumably by modulation of calcium channel function.

Given systemically, pregabalin prevents pain-related behaviors in animal models involving hyperalgesia (exaggerated responses to painful stimuli) or allodynia (pain-related responses to stimuli that are normally innocuous). In addition, pregabalin prevents pain-related responses in several animal models of neuropathic pain, including a peripheral nerve ligation model, a nerve section model, a diabetes model, and a vincristine chemotherapy model.

2.3 Preclinical safety

2.3.1 Safety pharmacology

Only minimal changes were observed in hepatic microsomal enzyme activities taken from rats given pregabalin for 7 days. Pregabalin administration did not significantly alter blood pressure and/or heart rate at relatively high doses in rats, dogs, or monkeys. Pregabalin has no effect on pulmonary function in dogs. The effects of pregabalin on gastric motility are contradictory in

different rat models, but there is evidence in rats that high doses reduce the rate of emptying the stomach and the lower gastrointestinal tract.

2.3.2 General toxicology

Studies of up to 1 year were performed in rats. Ataxia, hypoactivity, weight gain, urinary bladder changes, and sporadic mortality associated with pyelonephritis and cystitis were observed. Tail dermatopathy was observed at doses of ≥ 250 mg/kg, and was characterized by hyperkeratosis, acanthosis, fibrosis, and necrosis. Hematological changes associated with the 1-year rat studies consisted of increases of up to 16% of red blood cell parameters, and decreases of up to 36% in platelet counts. A single 4-week study that incorporated a 4-week withdrawal phase resulted in reversal of the adverse hematological changes. The etiology of the hematological changes is unknown, but does not appear to occur in mice or monkeys. Epididymal hypospermia was also associated with pregabalin treatment.

Monkeys were treated in studies of up to 69 weeks duration. The animals experienced nasal discharge, diarrhea, and hypoactivity. Deaths occurred within 3 days of treatment with 1000- or 2000 mg/kg. There were no effects on body weight, RBC, bone marrow parameters, sperm count, sperm motility, or sperm morphology after 69 weeks of dosing with pregabalin 500 mg/kg. Tail dermatopathy was observed at ≥ 25 mg/kg.

Intravenous toxicity studies in rats and monkeys were conducted to support potential parenteral administration of pregabalin. Clinical signs, similar to those seen in oral studies such as ataxia, hypoactivity, urine staining in rats, and nasal discharge in monkeys, were observed. Platelet count decreased in rats at ≥ 40 mg/kg by bolus IV injection and at ≥ 15 mg/kg/hr by continuous IV infusion. Degeneration of the urinary bladder muscularis occurred in rats given 75 mg/kg/hr by continuous IV infusion for 2 weeks, with associated steady state concentration (Css) of ≥ 396 mcg/mL. Degenerative vascular lesions in the skin, localized to the extremities and oral mucous membrane, subcutaneous edema, and lesions in the nasoturbinates were observed in monkeys given continuous IV infusion at ≥ 2 mg/kg/hr for 2 weeks. Corresponding Css was ≥ 20.5 mcg/mL in males and ≥ 14.3 mcg/mL in females at ≥ 2 mg/kg/hr. Pregabalin did not induce vascular irritation in rabbits at 12 mg/min and was compatible in vitro with human blood up to 10 mg/mL.

Pfizer reports that pregabalin is inactive at radioligand and transmitter uptake sites associated with known drugs of abuse, and it does not share pharmacological activity with benzodiazepines, barbiturates or glutamate antagonists in electrophysiological tests. Antagonists of opiates or benzodiazepines do not reverse the pharmacological actions of pregabalin. Pfizer also believed that animals trained to discriminate benzodiazepines, barbiturates or opiates from saline do not recognize pregabalin. Also, the company was of the opinion that pregabalin does not serve as a substrate for conditioned place preference in rats, is not self-administered like benzodiazepines or barbiturates in monkeys, and that discontinuation signs of pregabalin in rats are less pronounced than those of pentobarbital. Ultimately, Pfizer concluded that pregabalin has a low potential for drug abuse or physical dependence.

The Controlled Substance Staff (CSS) also reviewed the data and concluded that both the animal and human data suggest that pregabalin had a reinforcing effect in animals, and resulted in euphoria as well as a similar subjective effect to benzodizepam in humans. Furthermore, there was evidence a withdrawal syndrome in humans, thus indicating the presence of physical dependence. Consequently, CSS concluded that pregabalin has abuse potential and recommends that the drug be a controlled substance (Schedule IV).

2.3.3 Genetic toxicology

Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

2.3.4 Carcinogenicity

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposures (AUC) in the more sensitive mouse strain (B6C3F1) were approximately 150, 700, and 3800 μg·h/mL. These exposures are approximately 2, 9, and 50 times the human AUC of 75 μg·h/mL at the maximum recommended dose of 300 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidenceof carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 22 and 38 times, respectively, human exposure at the maximum recommended dose.

2.3.5 Reproductive toxicology

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 5 times human exposure at the recommended dose of 300 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology was observed in male rats exposed to pregabalin (500 to 1250 mg/kg) during general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 12 times human exposure at the recommended dose.

In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced aplasma exposure approximately 16 times that in

humans receiving the recommended dose. A no-effect dose for female reproductive toxicity in rats was not established.

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Much of the material is taken from my previous NDA review of pregabalin as, and the Agency's proposed product label for the indication, "treatment of neuropathic pain associated with diabetic peripheral neuropathy."

3.1 Pharmacokinetics

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occurred within 1.5 hours. Pregabalin oral bioavailability is ≥90% and is independent of dose. Following single- (25 to 300 mg) and multiple- dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increased linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data. Mean (% CV) PK parameter values following single- and multiple-dose administrations to healthy young subjects are presented in Table 3.1 below.

The rate of pregabalin absorption is decreased when given with food resulting in a decrease in Cmax by approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food.

Table 3.1.a.: Mean (% CV) PK Parameters[1] in Healthy Young Subjects

Dose	Regimen	N	Cmax (μg/mL)	Tmax (hr)	AUC (μg·h/mL)
50 mg	Single Dose	3	1.61 (25.7)	1.2	12.2[2] (11.9)
100 mg	Single Dose	6	2.99 (16.2)	0.83	22.1[2] (16.8)
100 mg	TID	6	5.03 (21.3)	0.83	25.2[3] (23.0)

[1]Under fasting conditions; [2]$AUC_{0-\infty}$; [3]$AUC_{0-\tau}$

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of

pregabalin found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pfizer did not conduct a formal study in patients with hepatic impairment because pregabalin does not undergo significant metabolism and over 90% of an oral dose is excreted unchanged in the urine. Therefore, hepatic impairment was not expected to alter the pharmacokinetics of pregabalin. In patients with severe hepatic impairment which may be associated with renal impairment, dose adjustments should be made according to their renal function.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 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. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr)

Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Dosage adjustment in patients with renal impairment should be based on CLcr. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients undergoing hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment.

Pregabalin oral clearance also tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of pregabalin were not significantly affected by gender or race (Caucasians, Blacks, and Hispanics).

Drug-drug interactions
Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, the pharmacokinetic parameters of pregabalin are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro studies showed that pregabalin is unlikely to inhibit the metabolism of other drugs.

Both specific studies and population analyses were conduced to evaluate the possible drug-drug interactions between pregabalin and the following commonly administered drugs:

- Antiepileptic drugs (AEDs): valproic acid, carbamazepine, lamotrigine, phenytoin
- Oral contraceptives: Ortho-Novum
- Gabapentin
- Ethanol

- Oxycodone
- Lorazepam (*see AED comment, above)*

Pfizer reports that pregabalin did not significantly alter the pharmacokinetics of the AEDs, oral contraceptive, or gabapentin. Population analyses showed that both placebo and pregabalin patients experienced increases in tiagabine CL/F. However, *in vitro* studies showed that pregabalin does not affect CYP 450 enzymes, which metabolize tiagabine. Therefore, pregabalin was not expected to affect the pharmacokinetics of tiagabine. Population analyses also showed that tiagabine, oral contraceptives, gabapentin, certain oral hypoglycemics (metformin, glibenclamide, glipizide, troglitazone), certain diuretics (furosemide and hydrochlorothiazide), and insulin do not alter the pharmacokinetics of pregabalin. There was no evidence of pharmacokinetic interactions between pregabalin and lorazepam, ethanol, or oxycodone.

3.2 Pharmacodynamics

Although other agents are not expected to affect the the pharmacokinetics of pregabalin, and pregabalin is are unlikely to inhibit other drugs' metabolism, the potential exists for drug-drug interactions through other mechanisms such as transporter-mediated processes as well as pharmacodynamic interactions.

In drug interaction studies, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. However, in these studies, the doses of lorazepam, oxycodone, and ethanol used were relatively low. Therefore, if higher doses of pregabalin and/or these drugs were administered, it is possible that pregabalin may exacerbate the effects of oxycodone, ethanol and lorazepam on cognitive and gross motor functioning.

3.3 Dosing interval

Pregabalin was originally developed with a recommendation for thrice daily dosing (TID dosing). To enhance patient compliance, a simplified dosing regimen was desired, and BID dosing was investigated. In addition to clinical trials with BID dosing, Pfizer reviewed plasma concentration data and concluded that these data support of equivalency of effect, whether the drug is administered in a TID or BID regimen. Pfizer is therefore proposing that the drug be taken on a twice daily dosing regimen.

The Division has requested that Pfizer conduct additional pharmacokinetic modeling to determine whether the efficacy of the TID regimen can be predicted from the BID regimen, and vice versa. The results of this analysis were still pending at the time of this review.

4 DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1 Sources of Clinical Data

All of the data in the NDA are from the development programs of Pfizer, Inc. Data were grouped as follows:

- *Controlled studies (n = 30)* – These are the double-blind, placebo-controlled, clinical trials related to claims of efficacy. Within this group are the efficacy studies for each proposed indication (see Section 4.2 for an overview of the efficacy trials for postherpetic neuralgia).
- *Uncontrolled studies (n = 23)* – These are the open-label extension trials that contribute to the safety database.
- *Clinical pharmacology studies (n = 28)*
- *Other studies* – These are studies that contributed neither to the efficacy nor the safety databases. They include phase 2/3 trials conducted in Japan, and acute dental pain studies.

A more complete description of these trials can be found in Sections 5.1 and Section 7.

4.2 Overview of Clinical Trials

The Applicant identified 3 trials (1008-045, -127, and -196) as contributing to evidence of efficacy of pregabalin as treatment for postherpetic neuralgia (PHN). These studies were reviewed individually for evaluation of study design and conduct, as well as assessment of the validity of the Applicant's efficacy conclusions. Pfizer considered trial 1008-030 to be a failed study, and it was consequently not reanalyzed. A fifth trial, 1008-131, was prematurely terminated due to the Agency's imposition of a partial clinical hold. The data from this trial were therefore not considered in the analysis of efficacy, but were included in the analysis of drug safety (See Section 7).

Description of the conduct of the NDA review

The Applicant's efficacy conclusions were cross-checked via analysis of primary data sets to reproduce the findings in some of the NDA tables. As indicated, revised efficacy endpoints or more appropriate statistical methods were utilized.

Data from 53 phase 2/3 controlled and uncontrolled trials were submitted to establish the safety of pregabalin. The data were reviewed to identify serious and common adverse effects of the drug in each treatment population, and in the total exposed population. Additionally, all deaths were identified, and narratives/CRFs examined for evidence of causality.

4.3 Postmarketing Experience

Although pregabalin was approved for marketing in Europe in June 2004, it had not yet been marketed in any country at the time of this review.

4.4 Literature Review

Pfizer did not submit any published literature in support of pregabalin's efficacy or safety as treatment for postherpetic neuralgia.

5 CLINICAL REVIEW METHODS

5.1 Overview of Materials Consulted in the Review

This review is based on the electronic data submission for this NDA which can be found on the internal network drive: \\Cdsesub1\N21446\N_000\2003-10-30.

A written summary of Pfizer's findings of clinical safety and efficacy of pregabalin as treatment for postherpetic neuralgia (PHN) is located at:
\\Cdsesub1\n21446\N_000\2003-10-30\summary\clinical

The electronic data sets for the three PHN efficacy studies (1008-045, -127, and –196) are under: \\Cdsesub1\N21446\N_000\2003-10-30\crt\datasets.

The electronic data set for the Summary of Clinical Safety is located at:
\\Cdsesub1\n21446\N_000\2003-10-30\crt\datasets\scs\clin

5.2 Overview of Methods Used to Evaluate Data Quality and Integrity

The Division of Scientific Investigations (DSI) was asked to audit one site from each of two efficacy trials that were conducted in Europe (Protocols 045 and 196), and two sites that from an efficacy trial conducted in the US (Protocol 127). Sites that had the largest enrollment and/or the greatest treatment-by-center interaction were identified for audit.

5.3 Were Trials Conducted in Accordance with Accepted Ethical Standards

All trials were carried out according to the EC Guidelines on Good Clinical Practice (GCP).

5.4 Evaluation of Financial Disclosure

Pfizer provided financial information from investigators who participated in 21 trials including all placebo-controlled trials for the indications being sought. With the exception of Study 1008-196 (PHN), all studies were initiated prior to the merger between Warner-Lambert with Pfizer. The collection and reporting of the financial disclosure information for these 20 studies was handled according to the Warner-Lambert SOPs. Study 1008-196 was initiated after the merger, therefore the Pfizer SOPs were applied. Nevertheless, Pfizer certifies to the absence of financial arrangements regarding compensation based on the outcome of the studies mentioned above or proprietary interest in pregabalin.

Pfizer reports that it performed due diligence when attempting to obtain information from study investigators, but was unable to obtain information from 187 investigators. A total of 9 (out of 945) investigators involved in PHN trials did not provide financial disclosure information. Of all the investigators who provided complete or incomplete disclosure forms (Form 3454), and who were involved in PHN trials, there were 6 investigators who reported significant financial interest:

Protocol [ ]
[ ] (PI, site — reported financial interest for receipt of $20,000 "for salary of research nurse." (This amount is below the threshold of $25,000). — patients, — were randomized into the study.

Protocols [ ]
[ ] (sub-investigator, site — reported financial interest because he holds 1,150 shares of Pfizer. Site — randomized — patients, —

[ ] (sub-investigator, site — reported financial interest because he received payments > $25,000 for consulting with Pfizer. Site — randomized —patients, — into the study.

[ ] (sub-investigator, site —, reported financial interest because he owns a "Listerine Royalty Initial Investment $54,000" and receives monthly Royalty. Site — randomized patients, — into the study.

[ ] (sub-investigator, site — reported financial interest because he holds 800 shares of Pfizer. No patients were randomized at this center.

[ ] : (sub-investigator, site — reported financial interest because he owns 1800 shares of Pfizer. — patients, — were randomized into the study.

Summary:
The financial disclosure information from Pfizer appears adequate, based on the available information. None of the investigators involved in PHN studies reported financial interest and also enrolled a considerable number of patients that could potentially influence that study outcome.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Brief Statement of Conclusions

In three clinical trials of pregabalin in patients with postherpetic neuralgia, the mean pain score at study endpoint for subjects randomized to pregabalin 300-, and 600 mg/d was significantly lower than the score for patients randomized to placebo. Also, subjects randomized to 300- and 600 mg/d were more likely than placebo-treated subjects to report a decrease in pain of at least 50%. Two trials showed efficacy of a TID dosing regimen, and one trial showed efficacy of BID dosing.

Efficacy of pregabalin 150 mg/d was also evaluated in two separate trials. There was a considerable difference between pregabalin and placebo groups with respect to the proportions of patients who reported at least a halving of their pain from baseline. However, superiority to placebo with respect to the primary outcome, mean pain score at study endpoint, was shown only for patients with a creatinine clearance greater than 60 mL/min.

Efficacy of pregabalin appeared to be limited by creatinine clearance. Patients with a low creatinine clearance were more likely to discontinue treatment due to associated adverse effects of the drug i.e. these patients were less able to tolerate the drug pregabalin. This was true regardless of the size of the pregabalin dose (75-, 150- or 300 mg/d). More patients with a normal creatinine clearance continued with treatment and had a greater likelihood of experience significant improvement in pain, particularly at the higher doses (300- and 600 mg/d).

A favorable treatment response appeared to be independent of dosing regimen (BID or TID dosing).

6.2 General Approach to Review of the Efficacy of the Drug

Three efficacy studies were provided for review with full study reports and primary data sets. Two were studies conducted in Europe and Australia (1008-045 and 1008-196), and the third was a trial conduced in the US (1008-127). The final reports for all of these studies conformed to the FDA guidelines on format and content. Attention was given to understanding how data were collected for analysis, with particular emphasis on understanding how assessments of pain were captured and analyzed.

The application also contained data and a brief study report for one US study, 1008-132, which was prematurely terminated following the Agency's imposition of a partial clinical hold for neuropathic pain trials. Due to the paucity of data, this study was not considered as contributory to the evaluation of efficacy of the drug.

The table below summarizes the studies included in the PHN efficacy database:

Prot	Design	No. of subjects (ITT)	Treatment Duration	PGG Dose
030 USA	Pro., MC, R, DB, PC trial of 2 doses of pregabalin given as a TID regimen	PGB: 167 Placebo: 88	Titration: 0 wks Fixed dose: 5 wks	75 mg/day 150 mg/day
045 Intl	Pro., MC, R, DB, PC trial of 2 doses of pregabalin given as a TID regimen	PGB: 157 Placebo: 81	Titration: 1 wk Fixed dose: 7 wks	150 mg/day 300 mg/day
127 US	Pro., MC, R, DB, PC trial of pregabalin (300 or 600 mg/d) given as a TID regimen. PGB dose dependent on CLcr	PGB: 89 Placebo: 84	Titration: 1 wks Fixed dose: 7 wks	300 mg/day 600 mg/day
132 US	Pro., MC, R, DB, PC trial of pregabalin given as a BID regimen. Only patients with CLcr > 60 mL/min were treated with the highest PGB dose	PGB: 164 Placebo: 52	Titration: 1 wk Fixed dose: 11 wks	150 mg/day 300 mg/day 600 mg/day
196 Intl	Pro., MC, R, DB, PC trial of pregabalin given as a BID regimen. Only patients with CLcr > 60 mL/min were treated with the highest PGB dose	PGB: 275 Placebo: 93	Titration: 1 wk Fixed dose: 12 wks	150 mg/day 300 mg/day 600 mg/day

BID: twice daily; CLcr: creatinine clearance; DB: double blind; Intl: international; MC: multicenter; PC: placebo controlled; PGB: pregabalin; Pro: prospective; TID: three times daily; wk: week

6.3 Detailed Review of Trials

6.3.1 Protocol 1008-045: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin (150 and 300 mg/d) in patients with postherpetic neuralgia

6.3.1.1 Objective/Rationale

To assess the efficacy and safety of 150- and 350 mg/d of pregabalin compared to placebo in patients with PHN

6.3.1.2 Overall design

This Phase 3 study was designed as an international, multi-center, multiple-dose, randomized, double-blind, parallel, placebo-controlled trial

6.3.1.3 Study population and procedures

6.3.1.4 Treatment duration: 8 weeks (1-week titration; 7-week fixed dose period)

6.3.1.5 Entry criteria

Enrollment of 240 subjects (80 per treatment arm) was planned.

Subjects were eligible if they met the following criteria:

- Age ≥ 18 years
- Pain ≥ 6 months and ≤ 5 years after the healing of herpes zoster skin rash
- At baseline and randomization: score ≥ 40 mm on the Visual Analog Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ)
- Completion of at least 4 daily pain diaries during the baseline phase
- At randomization: score ≥ 4 over the last 7 days on the daily Likert pain rating scale
- Normal chest x-ray within 2 years prior to the baseline visit
- Women at risk of pregnancy: appropriate contraception and negative serum pregnancy test (at baseline and randomization)

Subjects were excluded for:

- Previous neurolytic or neurosurgical therapy for PHN
- Presence of other severe pain that may confound assessment or self-evaluation of pain due to PHN
- Skin conditions in the affected dermatome that could alter sensation;
- Failure to respond to previous treatment with gabapentin (Neurontin) for postherpetic neuralgia at ≥ 1200-mg/day dose
- Clinically significant hepatic, respiratory, hematological illnesses, or cardiovascular disease
- Abnormal 12-lead ECG
- WBC <2500/ mm^3, neutrophil count <1500/ mm^3, platelet count <100 x10^3/mm^3
- Immunocompromised state (i.e., conditions known to be associated with an immunocompromised state);
- Clinically significant or unstable medical or psychological conditions that would compromise participation in the study
- Creatinine clearance < 30 mL/min (estimated from serum creatinine);

- Malignancy
- History of illicit drug or alcohol abuse in the past 2 years
- Use of prohibited medications 1 in the absence of appropriate washout periods

6.3.1.6 Study medications

The study drug comprised capsules containing placebo, 25-, or 100-mg pregabalin. Subjects randomized to the 2 pregabalin arms were to be titrated to the full dose over a 7-day period. These subjects were to initially receive 75 mg/d, and then increased to the target dose in 75 mg/d increments:

	Week 1 (Titration period)			Weeks 2 to 8
Treatment arm	Days 1-3	Day 4 + Day 5	Day 6 + Day 7	(Fixed dose period)
Placebo	Placebo	Placebo	Placebo	Placebo
150 mg/d	75 mg/d	150 mg/d	150 mg/d	150 mg/d
300 mg/d	75 mg/d	150 mg/d	225 mg/d	300 mg/d

Permitted medications:

Class of Medication	Examples	Minimum Period on Medication Prior to Visit V1
Analgesics	Non-narcotic, e.g., dolobid	Patients were to be on a stable regimen. Therapy could not be initiated during the study.
	Acetaminophen	Allow up to six 500-mg tablets daily
	Narcotic, e.g., opioids	Stable for 30 days; narcotics could not be initiated during the study
Anti-inflammatories	NSAIDs	Patients were to be on a stable regimen. Therapy could not be initiated during the study.
	Aspirin	Up to 1 aspirin tablet (□325 mg) daily for myocardial infarction and stroke prophylaxis
Antidepressants	Tricyclics, serotonin-specific reuptake inhibitors	Stable for 30 days; therapy could not be initiated during the study
Benzodizaepine		Intake of short-acting benzodiazepines, at stable dose, for night sedation was allowable. The dose was not to be changed during the double-blind phase of the study

The following medications were to be prohibited during the study (in the absence of a pre-defined washout period):

- Medications commonly used for relief of postherpetic neuralgia (e.g. benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, amantandine) – washout of ≥ 14 days prior to Visit 1
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topirmate, gabapentin) - washout of ≥ 14 days prior to Visit 1
- Vigabatrin and miscellaneous (hydroxychloroquine, deferoxamine, thioridazine) – patients on these medications were ineligible for the study

6.3.1.7 Study procedures

Study visits

There were to be 7 clinic visits. The first visit (V1) would be the screening visit, and the second visit (V2) would occur at the end of the 1-week baseline phase. V2 was also to be the day of

randomization and initiation of study drug. Thereafter, subjects would be assessed at 1 week (V3) and then at 2 to 3-week intervals (V4, 5, and 6). A safety follow-up visit (V7) would occur at Study Week 9.

Baseline
During this phase, eligible subjects were to complete daily pain and sleep interference diaries. Subjects who completed at least 4 pain diaries and had an average pain score of at least 4 would then be randomized to study drug at V2.

Treatment phase
Patients randomized to either of the 2 pregabalin arms were to be titrated to the target dose over a 1-week period. Patients unable to attain the target dose were to be withdrawn from the study. During clinic visits, subjects would be evaluated for pain, sleep quality, laboratory changes, physical status, and any adverse effects. At V6/Terminiation visit, additional assessments regarding quality of life, depression, and overall improvement would be made. Patients could then opt to continue in the open-label extension study of pregabalin 150 mg/d in patients with chronic pain (Protocol 1008-061). Patients who did not participate in the extension study were to complete a safety follow-up visit one week later. A patient was to be considered as having completed the study if they received 8 weeks of double blind treatment and attended the Visit 6/Termination visit.

Table 6.3.3.4: Time and Events Schedule: Protocol 1008-045

Study Phase:	Baseline	Double-Blind Treatment					
Week:	WK1	Randomization	WK1	WK3	WK5	WK8	WK9
Clinic Visit:[a]	V1	V2	V3	V4	V5	V6 Term[b]	V7 Follow-Up[c]
Observation/Procedure							
Informed Consent	X						
Inclusion/Exclusion	X	X					
Medical History	X						
Physical Exam	X		X[d]		X[d]	X	
Abbreviated Neurological Exam	X					X	
SF-MPQ	X	X	X	X	X	X	
Daily Diaries (Pain, Sleep)	X ---------->	X ---------->	X ------->	X ------->	X ------>	X	
Global Impression of Change (Clinician & Patient)						X	
SF-36 QOL		X				X	
Zung Self-Rating Depression Scale		X				X	
Adverse Events		X	X	X	X	X	X[e]
Prior and Concurrent Medications	X	X	X	X	X	X	X[e]
Study Medication Dosing/Dispensing		X	X	X	X	X[e]	
Clinical Labs:							
Hematology and Chemistry	X		X	X		X	X[e]
Urinalysis	X					X	X[e]
Serum Pregnancy	X			X		X	
Study Medication Plasma Concentration						X	
Chest X-ray	X[f]						
12-Lead ECG	X		X		X	X	

[a] Telephone contact will be made with the patients twice weekly during the titration phase to ensure completion of daily diaries. Should the patient experience an adverse event during titration or during double-blind, an extra visit can be scheduled. Between subsequent visits, telephone contact will be made weekly to ensure compliance with study procedures.
[b] Whenever patient withdraws from or completes the study
[c] For patients who do not enter Study 1008-061; this visit occurs 1 week after termination visit.
[d] Vital signs only
[e] Dispense open-label medication for patients continuing on to Protocol 1008-061.
[f] Chest x-ray must be taken at baseline visit if none available in the past 2 years

(Applicant's Appendix A.1, RR 720-04356, P. 147)

6.3.1.8 Efficacy parameters

- *Daily pain score*, as measured on an 11-point Likert numerical scale – 0 is "no pain" an d10 is the "worst possible pain"
- *Short Form McGill Pain Questionnaire (SF-MPQ)* which comprises
  - a standard 100 mm visual analog scale (VAS)
  - a Present Pain Intensity (PPI) scale : a 6-point categorical scale from 0 (no pain) to 5 (excruciating pain)
  - 15 pain descriptors, each rating pain on a 4-point categorical scale from 0 (no pain) to 3 (severe pain)
- *Daily diary of sleep interference*: 11-point Likert-type numerical rating scale from 0 (pain did not interfere with sleep) to 10 (pain completely interfered; patient was unable to sleep due to pain)
- *Clinical Global Impression of Change (CGIC):* a 7-point scale from 1 (very much improved) to 7 (very much worse)
- *Patient Global Impression of Change (PGIC):* a 7-point scale from 1 (very much improved) to 7 (very much worse)

- *SF-36 Health Survey Questionnaire (SF-36 QOL):* 36-item questionnaire measuring physical and social function, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception
- *Zung Self-Rating Depression Scale:*20-item questionnaire assessing affective, somatic, pyschomotor, and psychological aspects of symptoms of depression.

6.3.1.9 Statistical Analysis

Patient population

The population for the primary analysis was to be the *(modified) intent-to-treat* population, which included all randomized patients who took at least 1 dose of study medication.

Data would also be analyzed for the *per protocol* population (randomized subjects without major protocol violations). The results of these analyses were to be considered supportive, and used only for the interpretation of the main statistical analysis.

Primary efficacy outcome

The primary efficacy parameter was to be the weekly mean pain score, computed from the last 7 pain scores in the daily patient diary. The primary efficacy outcome was to be the endpoint weekly mean pain score, where "endpoint" was the last 7 pain diary entries while the patient was on study medication.

The primary analysis would compare the endpoint weekly mean pain score to the baseline (the mean of the last 7 pain scores preceding visit V2) using ANCOVA, with treatment and cluster in the model, and screening mean pain score as the covariate. Using Hochberg's approach, the p-values for the high dose versus placebo and low dose versus placebo comparisons would be ranked from larger to smaller. The larger (i.e., less significant) of the p-values would be evaluated at the $p = 0.05$ level. If it is not statistically significant, the smaller p value was to be evaluated for statistical significance at the $(0.05)/2 = 0.025$ level.

Supplemental analyses of the primary efficacy outcome

- Mean pain score for each week separately
- Change in weekly mean pain score from baseline to endpoint, and to each week separately

Secondary efficacy outcomes

- SF-MPQ (sensory, affective, VAS, PPI,, and total scores) at weeks 1, 3, 5, and 8
- Mean sleep interference score, weekly and at endpoint
- Global impression of change (by subject and investigator)
- SF-36 QOL, change from baseline to endpoint
- Zung Self-Rating Depression Scale,

No adjustments were to be made for testing multiple parameters. Due to the large number of secondary and supplemental analyses being performed, some significant results were expected to occur by chance alone. Undue consideration was not to be given to any particular significant

difference; rather, interpretation of the results would be based on patterns of significant differences.

Interim analyses
No interim analyses were planned.

6.3.1.10 Protocol amendments
Amendment 1
November 11, 1998
- The minimum allowable age for entry into the study was changed from 18 to 19 years. This was because in Austria, the age of majority is 19 years.
- A urinary dipstick pregnancy test was added to visit V5, due to investigator requests for pregnancy testing every 4 weeks.

Amendment 2
November 16, 1999
- The informed consent form was modified to include the potential risk of tumors, based on the non-clinical findings of hemangiomas and hemangiosarcomas in mice.

Although not specifically described as a protocol amendment, the Applicant states that "there was a general agreement reached at Investigators' Meetings to allow patients with pain lasting more than 5 years to enter the trial" (Applicant's Appendix A.9, RR 720-04356, 1008-045, P. 314).

6.3.1.11 **Study Results**

6.3.1.12 Subject characteristics

The trial was conducted from February 17, 1999 to June 16, 2000. A total of 53 centers in Europe and Australia participated.

6.3.1.13 Enrollment by Center
The table below shows the number of patients who were randomized at each center

Table 6.3.1.13: Enrollment by center – Protocol 045

No. Patients Randomized Per Center	Center Number
0	007, 017, 036, 056, 076
1	013, 031, 032, 071, 072
2	006, 012, 016, 040, 050, 067, 069, 073, 075, 077, 081
3	0.8, 030, 038, 046
4	010, 014, 015, 042, 051, 055, 060, 064
5	011, 033, 047, 053, 062, 063, 066, 068
6	034, 043
8	041
9	054, 074
10	003, 065, 070
12	002, 035
17	052
18	001

(Adapted from Applicant's Table 1, RR 720-04356, 1008-045, P. 15)

6.3.1.14 Protocol violations

The Applicant identified 105 patients who had protocol violations, and identified 51 as being eligibility exceptions. These violations are separate from the protocol variations demonstrated by subjects excluded from the *per protocol* population. The specific types of protocol violations are detailed below:

	Number of patients			
Violation	**Total**	**Placebo**	**Pregabalin 150 mg/d**	**Pregabalin 300 mg/d**
Ongoing malignancy	8	1	3	4
History of malignancy	24	5	10	9
Pain > 5 years	54	23	13	18
Pain < 6 months	1	0	0	1
Creatinine clearance < 30 mL/min	3	1	1	1
Prohibited medications	7	3	3	1
Abnormal chest x-ray at baseline	6	1	1	4
VAS < 40 mm at visit V1	1	1	0	0
Abnormal ECG at baseline	1	0	1	0
Platelets < 100 x10^3/mm^3	1	1	0	0
Total violations	*105*	*36*	*32*	*37*

(Adapted from Applicant's Appendix A.9, RR 720-04356, P. 311-314)

Of note, there were 2 placebo patients (Patient 010003 [site 010] and Patient 040001 [site 040]) who, at study termination, had detectable levels of pregabalin in their plasma. The Applicant did not find an explanation for this. I believe that there are three possible causes for this finding: the patients were mistakenly provided with pregabalin by the study site; the patients took medication from a study participant who was randomized to pregabalin; or there was contamination at laboratory where drug levels were being analyzed.

In my opinion, the protocol violations that could impact the primary efficacy outcome are:

- Pain > 5 years – patients with pain (and therefore neuropathy) of longstanding duration may be less likely to benefit from treatment than patients who have had pain for a relatively short time.
- Creatinine clearance < 30 mL/min – these patients would experience greater overall exposure to the drug and therefore might have greater treatment benefit than patients with normal CLcr
- Use of prohibited medications – patients may experience a decrease in pain due to the prohibited medication, and not necessarily due to treatment with study drug
- VAS < 40 mm at V1 – these patients have relatively minimal pain and so if a small improvement in pain occurred with study treatment, it would be difficult to detect

There were equal numbers of patients in each of the treatment groups who had violations with respect to CLcr, duration of pain, and use of prohibited medications. Also, only 1 patient had a VAS score < 40 mm. Therefore, the overall effect of this pattern of violations is not expected to have a significant impact on the interpretation of the results.

6.3.1.15 Protocol variations

Pfizer states that there were 33 patients who were excluded from the *per protocol* population due to variations from the study protocol:

	Number of patients*			
Variation	**Total**	**Placebo**	**Pregabalin 150 mg/d**	**Pregabalin 300 mg/d**
Significant change of supposed stable concurrent medication	20	5	8	7
Inappropriate washout of prior medication or change during baseline	12	1	7	4
Study medication compliance < 75%	1	1	-	-
Concurrent prohibited medication continued during study	1	-	1	-

* Patients could have more than 1 variation.
(Adapted from Applicant's Appendix A.8, RR 720-04356, 1008-045, P. 308-310)

Although Pfizer believes these patients had "variations" from the protocol, I consider them to have had protocol violations. While the change in stable concurrent medication might tend to bias the study in favor of the affected arm, there were equal numbers of patients with these changes across all treatment arms. Also, the numbers of patients with the other variations was relatively small. Therefore, the overall effect of this pattern of violations is not expected to have a significant impact on the interpretation of the results.

6.3.1.16 Blinding
Pfizer did not describe any instances when the study blind was broken.

6.3.1.17 Subject disposition
The table shows patient disposition, and the reasons for early withdrawal from the study. Of the 307 patients who entered the baseline phase, 69 did not complete 238 this. Reasons for withdrawal from the baseline phase were not meeting study criteria (n = 54) or "other administrative" reasons (n 15).

A total of 238 patients were randomized and all took at least 1 dose of study medication. These patients comprised the ITT population. There were 61 subjects in the placebo arm, 71 in the 150 mg/d arm, and 60 in the 300 mg/d arm. Overall, 46 subjects withdrew from the study during the double-blind treatment phase. More patients withdrew from the placebo group due to lack of efficacy than did subjects in either of the pregabalin groups. The most frequent reason for withdrawal was adverse effects, and this was greater for the 300 mg/d group (16%) than the 150 mg/d (11%) and placebo groups (10%). No deaths occurred during the 7-weeks of treatment.

Table 6.3.4.6: Patient disposition, Protocol 1008-045

[Number (%) of Patients]

Disposition N,(%)	Placebo	Pregabalin		All Patients
		150 mg/day	300 mg/day	
Entered Baseline Phase				307[a]
Completed Baseline Phase				238 (77.5)
Withdrawn During Baseline Phase:				69 (22.5)
Did Not Meet Criteria				54 (17.6)
Other				15 (4.9)
Randomized	81	81	76	238
Intent-To-Treat	81	81	76	238
Completed Study	61 (75.3)	71 (87.7)	60 (78.9)	192 (80.7)
Withdrawn During Treatment Phase:	20 (24.7)	10 (12.3)	16 (21.1)	46 (19.3)
Adverse Event	8 (9.9)	9 (11.1)	12 (15.8)	29 (12.2)
Lack of Compliance	2 (2.5)	0 (0)	1 (1.3)	3 (1.3)
Lack of Efficacy	7 (8.6)	0 (0)	1 (1.3)	8 (3.4)
Other	3 (3.7)	1 (1.2)	2 (2.6)	6 (2.5)
Entered Open Label[b]	52 (64.2)	52 (64.2)	53 (69.7)	157 (66.0)

[a] Includes 2 patients that were re-screened.

[b] Number is taken from patient status at end of double-blind. Because of delay in approval of the open-label study by Ethics Committees and other factors, 3 patients listed here never took open-label study medication.

(Applicant's Table 10, RR 720-04356, 1008-045, P. 41)

6.3.1.18 Extent of exposure/Dosing information

Overall, 178 of the 238 patients (74.8%) completed at least 8 weeks of treatment with study medication. This number is different from the Applicant's number of patients who completed the study (n = 192, 81%). Pfizer says that this is because completion of the study was determined independently of the number of weeks a patient was exposed to study medication. Due to scheduling issues, patients may have completed earlier than Day 56, resulting in exposure to study medication of <8 weeks. Of note, the protocol-specified definition of a study "completer" was completion of 8 weeks of double-blind treatment and attendance of the V6/Termination visit.

Drug exposure appeared to be lower for the placebo group: 75% of patients who received 300 mg/day, 78% of patients who received 150 mg/day, and 72% of patients who received placebo had at least 8 weeks of exposure. More than 80% of patients in each treatment group received at least 5 weeks of study medication.

Table 6.3.4.7: Patient exposure to medication, Protocol 1008-045

Total Exposure Time, N(%)[b]	Placebo (N= 81)		Pregabalin 150 mg/day (N = 81)		Pregabalin 300 mg/day (N = 76)		Pregabalin Total (N = 157)	
≥1 Day	81	(100.0)	81	(100.0)	76	(100.0)	157	(100.0)
≥1 Week	79	(97.5)	80	(98.8)	76	(100.0)	156	(99.4)
≥2 Weeks	75	(92.6)	77	(95.1)	72	(94.7)	149	(94.9)
≥3 Weeks	72	(88.9)	76	(93.8)	66	(86.8)	142	(90.4)
≥4 Weeks	68	(84.0)	74	(91.4)	65	(85.5)	139	(88.5)
≥5 Weeks	67	(82.7)	73	(90.1)	62	(81.6)	135	(86.0)
≥6 Weeks	63	(77.8)	72	(88.9)	61	(80.3)	133	(84.7)
≥7 Weeks	61	(75.3)	71	(87.7)	61	(80.3)	132	(84.1)
≥8 Weeks	58	(71.6)	63	(77.8)	57	(75.0)	120	(76.4)

[a] Zero dose days during study are included in summary of patient exposure to study medication.
[b] The total exposure time includes titration and fixed-dose phases.

(Applicant's Table 9, RR 720-04356, 1008-045, P. 40)

6.3.1.19 Demographics

The majority of patients in the study were white (99%), and slightly more than half were women (55%). The mean age of the population was 72 (± 10.2) years, with a range of 32 to 96 years. The majority of patients (75%) were between the ages of 60 and 85 years. The pregabalin 150 mg/d group had slightly more men than the other treatment groups, and the placebo group had fewer patients aged 18-64 years than did the two pregabalin groups. The pregabalin 300 mg/d group had a slightly lower mean creatinine clearance (54.5 mL/min) than did the 150 mg/d groups placebo (58 mL/min and 60 mL/min, respectively). There was no difference with respect to body weight across the 3 treatment arms.

Postherpetic neuralgia history

The placebo group had a longer mean duration of PHN (45 months) than the pregabalin 150 mg/d and 300 mg/d groups (41 months each). The trigeminal, cervical, and thoracic regions were most commonly affected in each of the treatment groups, however more patients in the placebo and pregabalin 300 mg/d groups had pain in the thoracic region (54% and 58% respectively), compared to the 150 mg/d group (40%). Mean baseline pain scores were not appreciably different across the groups (score of 6.6 for the placebo group; score of approximately 7 for patients in the pregabalin groups).

I do not believe that these treatment group differences would significantly impact the primary efficacy outcome.

Table 6.3.4.8.a: Summary of patient characteristics (ITT population) – Protocol 045

Characteristic		PBO	Pregabalin			All Patients
		N = 81	150 mg/day N = 81	300 mg/day N = 76	Total N = 157	N = 238
Sex, N (%)	N	81	81	76	157	238
	Male	37 (45.7)	39 (48.1)	31 (40.8)	70 (44.6)	107 (45.0)
	Female	44 (54.3)	42 (51.9)	45 (59.2)	87 (55.4)	131 (55.0)
	Premenopausal	2 (4.5)	2 (4.8)	1 (2.2)	3 (3.4)	5 (3.8)
	Postmenopausal	42 (95.5)	40 (95.2)	44 (97.8)	84 (96.6)	126 (96.2)
Race, N (%)	N	81	81	76	157	238
	White	81 (100.0)	79 (97.5)	76 (100.0)	155 (98.7)	236 (99.2)
	Black	0 (0.0)	2 (2.5)	0 (0.0)	2 (1.3)	2 (0.8)
Age Categories, N(%)	N	81	81	76	157	238
	18-64 years	12 (14.8)	18 (22.2)	17 (22.4)	35 (22.3)	47 (19.7)
	≥65 years	69 (85.2)	63 (77.8)	59 (77.6)	122 (77.7)	191 (80.3)
Age (years)	N	81	81	76	157	238
	Mean (STD)	73.2 (10.3)	71.3 (10.1)	71.9 (10.3)	71.6 (10.2)	72.2 (10.2)
	Median	74.0	73.0	74.0	74.0	74.0
	Range	36 to 96	43 to 88	32 to 90	32 to 90	32 to 96
Estimated Creatinine Clearance At Baseline (mL/min)	N	81	81	76	157	238
	Mean (STD)	60.46 (18.53)	62.89 (20.31)	58.87 (20.96)	60.94 (20.66)	60.78 (19.92)
	Median	58.00	60.00	54.50	56.00	58.00
	Range	31.0 to 104.0	31.0 to 116.0	23.0 to 158.0	23.0 to 158.0	23.0 to 158.0
Height (cm)	N	80	81	76	157	237
	Mean (STD)	165.96 (8.98)	165.03 (8.83)	164.84 (11.21)	164.94 (10.02)	165.28 (9.68)
	Median	165.50	165.00	165.00	165.00	165.00
	Range	145.0 to 185.5	145.0 to 182.8	138.0 to 189.0	138.0 to 189.0	138.0 to 189.0
Weight (kg)	N	81	81	76	157	238
	Mean (STD)	72.03 (13.96)	71.55 (13.10)	68.50 (13.48)	70.08 (13.33)	70.74 (13.55)
	Median	72.00	70.00	67.50	69.50	70.00
	Range	42.0 to 108.0	41.0 to 101.0	42.0 to 102.8	41.0 to 102.8	41.0 to 108.0

(Applicant's Table 7, RR 720-0356, 1008-045, P. 38)

Table 6.3.4.8.b: Summary of postherpetic neuralgia history (ITT population) – Protocol 045

	Placebo	Pregabalin		All Patients
		150 mg/day	300 mg/day	
Duration of Postherpetic Neuralgia(months)[a]				
N	81	81	76	238
Mean (STD)	44.8 (46.3)	40.9 (41.8)	40.7 (42.1)	42.1 (43.3)
Median	32	29	30.5	30.5
Range	0.0 to 267.0	5.0 to 243.0	1.0 to 215.0	0.0 to 267.0
Predominantly Affected Dermatomal Region. N(%)	81	81	76	238
Trigeminal	19 (23.5%)	25 (30.9%)	16 (21.1%)	60 (25.2%)
Cervical	9 (11.1%)	12 (14.8%)	13 (17.1%)	34 (14.3%)
Thoracic	44 (54.3%)	32 (39.5%)	44 (57.9%)	120 (50.4%)
Lumbar	6 (7.4%)	11 (13.6%)	3 (3.9%)	20 (8.4%)
Sacral	3 (3.7%)	1 (1.2%)	0 (0.0%)	4 (1.7%)
Baseline Mean Pain Score				
N	81	81	76	238
Mean (STD)	6.6 (1.6)	6.9 (1.7)	7.0 (1.6)	6.8 (1.6)
Median	6.7	7.1	7	7
Range	4.0 to 10.0	4.0 to 10.0	4.0 to 10.0	4.0 to 10.0

[a] Duration is obtained by dividing a number of days by 30.44 and rounding it to the lowest integer.

(Applicant's Table 8, RR 720-0356, 1008-045, P. 39)

Concomitant medications

Approximately 88% of placebo patients took medications either concurrently or within 30 days prior to initiation of study drug, compared to 96% and 95% of patients in the pregabalin 150- and 300 mg/d groups. The most frequently used medication was paracetamol (acetaminophen).

When use of only concurrent medications was evaluated, Pfizer found that more patients in the pregabalin groups (96% in the pregabalin 150 mg/d and 92% in the pregabalin 300 mg/d) took medications during the study, compared to the placebo group (85%). The most commonly concurrently used medications were acetylsalicylic acid (11% placebo, 17% pregabalin 150 mg/d, 14% pregabalin 300 mg/d), amitriptyline (15% placebo, 14% pregabalin 150 mg/d, 19% pregabalin 300 mg/d), acetaminophen (16% placebo, 22% pregabalin 150 mg/d, 18% pregabalin 300 mg/d) and tramadol (9% placebo, 16% pregabalin 150 mg/d), 17% pregabalin 300 mg/d).

Overall, the proportions of patients using these various medications was similar across treatment groups, and is therefore not expected to have an effect on the primary analysis.

6.3.1.20 Applicant's efficacy results

6.3.1.21 Overview

Pfizer found that both the pregabalin 150- and 300 mg/d groups showed a statistically significance difference in mean pain scores at endpoint, compared to the placebo group. That is, patients in both pregabalin groups had significantly less pain than patients treated with placebo. Improved pain scores were noted starting at Week 1. The pregabalin groups also differed from the placebo group with respect to several secondary outcomes, including the proportion of responders at endpoint, as well as the SF-MPQ VAS and PPI scores at endpoint.

6.3.1.22 Primary Efficacy outcome

The primary efficacy outcome was the endpoint mean pain score, defined as the mean of the last 7 entries of the daily pain diary while the patient was on study medication. The Applicant's analysis found improvement (i.e. decreases) in mean pain scores for all 3 treatment groups, with the greatest improvement in the pregabalin 300 mg/d group. The ANCOVA results, where the baseline score was included as a covariate, showed that both the mean pain scores for the pregabalin 150- and 300 mg/d treatment groups were significantly different from placebo. The endpoint mean pain scores for the two pregabalin groups were not statistically different from each other.

Table 6.3.5.2.a: Mean pain score: Descriptive statistics – Protocol 045

Time point	Placebo			Pregabalin 150 mg/day			Pregabalin 300 mg/day		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	81	6.6 (1.6)	4, 10	81	6.9 (1.7)	4, 10	76	7.0 (1.6)	4, 10
Endpoint[b]	81	6.2 (2.3)	1.3, 10	81	5.2 (2.5)	0.1, 10	76	4.9 (2.5)	0, 10
Change[c]	81	-0.5 (1.7)	-6.1, 3.1	81	-1.7 (2.0)	-8.4, 1.9	76	-2.1 (2.4)	-9, 1.9

[a] Baseline = Last 7 available scores before taking study medication, up to and including Day1.
[b] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.
[c] Change is from Baseline to Endpoint
(Applicant's Table 11, RR 720-04356, 1008-045, P. 44)

Table 6.3.5.2.a: Endpoint[a] mean pain score: ANCOVA results – Protocol 045

Treatment	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin Placebo)			
				Difference	95% CI	Undadjusted p-Value	Adjusted[b] p-Value
Placebo	81	6.33	0.22				
Pregabalin 150	81	5.14	0.22	-1.20	(-1.81, -0.58)	0.0002	0.0002
Pregabalin 300	76	4.76	0.23	-1.57	(-2.20, -0.95)	0.0001	0.0002
PGB 150 vs. PGB 300	-	-	-	-0.38	(-1.00, 0.24)	0.2323	0.2323

0.2323 SE = Standard error; CI = Confidence interval.
[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.
[b] Adjustment based on Hochberg's procedure for the 2 pair-wise comparisons versus placebo
(Applicant's Table 12, RR 720-04356, 1008-045, P. 44)

Supplemental analyses of the primary efficacy variable

Mean pain scores at endpoint: Per protocol population

As noted in Section 6.3.4.4, Pfizer found that 33 patients had protocol violations and excluded them from the Per Protocol population. Therefore, there were 205 patients, 86% of the ITT population: 65 patients (86%) in the 300 mg/day pregabalin group, 67 patients (83%) in the 150 mg/day pregabalin group, and 73 patients (90%) in the placebo group.

Based on the ANCOVA results, the endpoint mean pain scores for the Per Protocol patient population were similar to the scores for the ITT population: 6.31 for the placebo group, 5.1 for the 150 mg/d group, and 4.66 for the 300 mg/d group. The endpoint mean pain scores for both the 150 and the 300 mg/day pregabalin group were significantly better than the placebo group (p-value = 0.0004 and 0.0002, respectively). The 2 pregabalin treatment groups did not differ significantly from each other on endpoint mean pain scores (p-value = 0.2072) (See Applicant'

Mean pain scores: Weekly scores and Change from baseline

Based on Pfizer's week-by-week descriptive statistics, the mean pain scores generally decreased for all treatment groups as the study progressed. Both the 300 and the 150 mg/day pregabalin group had significantly improved pain scores compared to placebo at Weeks 1 through 8. Further analysis with ANCOVA, as well as analysis of the change in mean pain score from baseline, and at each week separately found similar results.

6.3.1.23 Applicant's secondary efficacy analysis

Results of the secondary efficacy outcomes were to be interpreted based on the *pattern* of significant differences, and not on individual significant findings. This was because the protocol did not call for adjustments due to testing of multiple parameters, and because some significant results were expected by chance alone.

- *SF-MPQ (sensory, affective, VAS, PPI, and total scores)*

Descriptive statistics from the English version of the SF-MPQ showed that, in general, the sensory, affective, and total scores tended to decrease (improve) over the course of the study. The pregabalin treatment groups showed somewhat greater decreases in all 3 scores than the placebo group. Similar results were seen with the other languages, with the exception that the placebo group scores increased (worsened) slightly over the course of the study for the Dutch and German patients.

Both the 150- and the 300 mg/day pregabalin groups had better mean VAS scores compared to the placebo treatment group at each time point (Weeks 1, 3, 5, 8, and at endpoint). The pregabalin groups had PPI scores that differed from placebo only at Week 1.

- *Mean sleep interference score, weekly and at endpoint*

A comparison of sleep interference scores at each week and at endpoint revealed a statistically significant improvement for patients in both pregabalin 300 and 150 mg/day groups compared to patients in the placebo group. The pregabalin groups had a larger drop in mean sleep interference scores from baseline to Week 1 and then the scores decreased slightly throughout the remainder of the study. The sleep interference scores for the placebo group decreased slightly throughout the study, without a large drop from baseline to Week 1.

- *Global impression of change (by subject and investigator)*

More patients (40%) in the pregabalin 300 mg/day group reported scores of "very much improved" or "much improved" compared to patients in the pregabalin 150 mg/day and placebo groups (31% and 14%, respectively). Similar findings were noted for the investigator ratings of patient improvement. Only the differences between the PGIC for pregabalin 300 mg/day groups vs. the placebo group reached statistical significance. The CGIC for both pregabalin groups was significantly better than placebo.

- *SF-36 QOL, change from baseline to endpoint*

Higher (more favorable) mean scores were reported for the 300 mg/day pregabalin group for each of the 8 domains and for the 150 mg/day pregabalin group for each of the domains except for Physical Role Limitations. Both the 300 and 150 mg/day pregabalin groups were significantly better than placebo in the Mental Health domain. In addition, the 300 mg/day pregabalin group was significantly better than placebo in the Bodily Pain and in the Vitality domains.

- *Zung Self-Rating Depression Scale,*

The Zung Self-Rating Depression Scale index scores were reduced (improved) in all 3 treatment groups at termination, with greater reductions in the pregabalin treatment groups than in the placebo group. The 300 mg/day pregabalin group was significantly improved compared to placebo (Table 27). There was a significant treatment by language interaction

6.3.1.24 Unplanned Analyses

Mean pain score: Weekly scores and change from baseline using LOCF analysis techniques

Weekly mean pain scores were also analyzed using a LOCF technique, with the last non-missing, post-randomization weekly mean pain score carried forward to Week 8 for those patients withdrawing early from the study. Both the 300 and the 150 mg/d pregabalin groups were statistically significantly improved compared to placebo at Weeks 1 through 8

Proportion of responders

Patients who had a 50% decrease in mean pain score from baseline to endpoint were defined as responders. There was a statistically significantly higher proportion of responders in both the 300 mg/d pregabalin group (28%) and the 150 mg/d pregabalin group (26%) compared to placebo (10%).

Table 6.3.5.4.a: Results of analysis of responder status – Protocol 045

Treatment group	Number assessed	Number of responders (%)	Treatment Comparisons (Pregabalin Placebo) Unadjusted p-Value[a]	Adjusted p-Value[b]	Breslow Day Test for the Homogeneity of the Odds Ratio
Placebo	81	8 (9.9)			
Pregabalin 150	81	21 (25.9)	0.006	0.006	0.513
Pregabalin 300	76	21 (27.6)	0.003	0.006	0.146

[a] P-Value based on the results of the Cochran-Mantel-Haenszel procedure, adjusting for center
[b] Adjustment based on Hochberg's procedure
(Applicant's Table 16, RR 720-04356, 1008-045, P. 52)

Time to being a sustained responder
The Applicant defined a sustained responder as "a randomized patient who attained a 50% or greater reduction from baseline to 1 of the weekly mean pain scores and maintained this reduction to the endpoint mean pain score if the patient withdrew early or to Week 8 otherwise." Descriptive statistics showed that more patients in both the pregabalin 150- and 300 mg/d groups were sustained responders by Week 2. Thereafter, no considerable difference between the 150 mg/d group and the placebo group was apparent.

Table 6.3.5.4.b: Summary of time to being a sustained responder – Protocol 045

Time to Being Sustained Responder[a], N (%)	Placebo (N = 7)		Pregabalin 150 mg/d (N = 20)		Pregabalin 300 mg/d (N = 14)	
Within 07 days	1	(14.3)	2	(10.0)	1	(7.1)
Within 14 days	1	(14.3)	4	(20.0)	6	(42.9)
Within 21 days	1	(14.3)	7	(35.0)	7	(50.0)
Within 28 days	3	(42.9)	8	(40.0)	9	(64.3)
Within 35 days	4	(57.1)	9	(45.0)	10	(71.4)
Within 42 days	4	(57.1)	11	(55.0)	11	(78.6)
Within 49 days	6	(85.7)	14	(70.0)	12	(85.7)
Within 56 days	7	(100.0)	20	(100.0)	14	(100.0)

[a] Patients with no postbaseline data are not taken into account.
(Applicant's Table 17, RR 720-04356, 1008-045, P. 52)

However, using a log rank test stratified on cluster, Pfizer found a statistically significant difference for the 150 mg/d group vs. placebo (p-value [adjusted based on Hochberg's procedure] = 0.0114), The difference for the 300 mg/d vs. placebo comparison did not reach statistical significance (p-value = 0.070).

FDA-requested analyses
At the FDA's request, the Applicant conducted the following additional analysis to provide more information on the primary outcome measure, and to test its robustness.

- Endpoint mean pain score: Baseline Observation Carried Forward (BOCF) analysis
  Using the Patient Status information from the CRF, Pfizer identified 46 patients who did not complete the study. The baseline mean pain score was used instead of the endpoint mean

pain score in the ANCOVA, and the endpoint mean pain scores for the pregabalin groups were again statistically different from placebo:

Table 6.3.5.4.c: Endpoint mean pain scores: Results of ANCOVA with BOCF – Protocol 045

				Treatment comparisons (Pregabalin – Placebo)			
Treatment	N	Least Squares Means	SE	Difference	95% CI	Unadjusted p-value	Adjusted p-value
Placebo	81	6.32	0.22				
Pregabalin 150	81	5.20	0.21	-1.12	(-1.718-0.522)	0.0003	0.0004
Pregabalin 300	76	5.21	0.22	-1.11	(-1.723-0.502)	0.0004	0.0004
SE = Standard error; CI = Confidence interval							
Endpoint = Last 7 available scores while on study medication, up to and including day after last dose							
Adjustment based on Hochberg's procedure							

(Applicant's Table E1, Appendix D.23, RR 720-04356, 1008-045, P. 1889)

- Endpoint mean pain score: Removing subjects who took prohibited medications or unstable concurrent medications

  Pfizer stated that the patient population that results from the removal of patients who took prohibited or unstable concurrent medications is similar to the Per Protocol population (see Section 6.3.5.2 – Supplemental analyses of the primary efficacy outcome). Therefore the results for this analysis should be the same as those for the Per Protocol population.

- Endpoint mean pain score: Removing subjects with somnolence or dizziness

  Since somnolence, an apparent effect of pregabalin, might decrease the reliability of the reported of pain scores, the Applicant was asked to conduct efficacy analyses on the subset of patients who did not report somnolence following treatment with study medication. Pfizer elected to evaluate the effect of both dizziness and somnolence on the efficacy outcome.

  A total of 71 patients (17 placebo, 20 pregabalin 150 mg/day and 34 pregabalin 300 mg/day) reported TESS adverse events of dizziness and/or somnolence at some time during the study. After removing these patients from the ITT population, the ANCOVA of weekly mean pain at endpoint again showed a statistically significant difference in mean pain scores between both pregabalin groups and the placebo group.

- Longitudinal analysis of the pain scale

  A longitudinal analysis was performed on the observed values of the weekly mean pain score using ANCOVA, with treatment, cluster, creatinine clearance strata, baseline pain and week as fixed effect terms in the model. In addition, the model was run again with a treatment by week interaction term included.

  There was evidence of a treatment by week interaction (p=0.0019). The weekly contrasts were quantitatively, and not qualitatively different. All weekly contrasts resulted in significant treatment effects favoring the two pregabalin treatment groups over placebo. The interaction effects ANCOVA model also yielded statistically significant overall differences for pregabalin 300 mg/d and pregabalin 150 mg/d in comparison to placebo (p=0.0002 for both comparisons based on Hochberg's procedure).

- Analysis of measures of skin hypersensitivity: Allodynia and Hyperalgesia
  Allodynia and hyperalgesia were measured in 233 patients (79 placebo, 80 pregabalin 150 mg/d, and 74 pregabalin 300 mg/d) at baseline and at endpoint. Neither allodynia nor hyperalgesia was statistically significantly associated with treatment.

6.3.1.25 Reviewer's analysis of efficacy

There are several problems with the Applicant's statistical approach to determining efficacy in this study.

First, the primary efficacy outcome, the final weekly mean pain score, was defined as the mean of last 7 available pain scores. Although this definition appropriately captures subjects' pain scores during the pre-specified last week of treatment, it also inappropriately captures pain scores for subjects who may not have completed the full duration of treatment.

Second, the primary analysis method was a last observation carried forward (LOCF) method. LOCF is problematic way of handling missing data because it imputes a favorable score for patients who experience some drug benefit, but drop out due to adverse events. The FDA's recommended BOCF analysis is preferred since it imputes the less favorable score for all patients who have no drug benefit, and who discontinue drug due to intolerable effects. Unfortunately, the Applicant did not appropriately conduct the BOCF analysis. BOCF required that the Applicant assign baseline pain scores for all patients who did not have any observations during the final week of the study (that is, subjects who did not complete the entire treatment period). Instead, the Applicant assigned baseline scores for only those patients who did not complete all study visits and procedures. As such, subjects who, for example, withdrew from the study after 6 weeks of treatment, but completed the Week 8 (V6/Termination) assessments, were incorrectly labeled as study completers and their last available mean scores used in the analysis.

In order to analyze the data more appropriately, I redefined the study endpoint as the last week of treatment with study medication (Week 8). Subjects withdrew from the study prematurely were considered "non-completers." Subjects who did not withdraw were "completers." Among the completers, there were some patients who did not complete a full 8 weeks of treatment and therefore had missing data at study endpoint. Subjects who did not complete a pain diary each day also had missing data for those days. To address this issue of missing data, the Statistical Reviewer, Dr. Joan Buenconsejo, conducted a BOCF analysis of the ITT population as follows:

- For patients who withdrew from the study for any reason: the baseline pain score was assigned instead of the weekly mean pain score
- For patients who did not withdraw from the study: weekly mean pain scores were calculated as the average of the available pain scores for that week. Therefore, if a patient had 7 daily pain scores for a given week, those 7 scores were used to calculate the average. Similarly, if a subject had only 2 daily scores for a given week, only those to 2 scores were used to calculate the week's mean pain score. Study weeks were defined as follows:

Week	Days
1	2 – 8
2	9 – 15
3	16 – 22
4	23 – 29
5	30 – 36
6	37 – 43
7	44 – 50
8	51 – 57

Primary Efficacy Outcome

Mean Pain Score – Weekly and at Endpoint

Based on Dr. Buenconsejo's analysis, all of the treatment groups showed a decrease (improvement) in endpoint mean pain score at study endpoint (Week 8). Descriptive statistics suggested that the improvement was seen starting at Week 1. Greater decreases in pain score were seen in the pregabalin 150 mg/d group (change in score = -1.65) and the 300 mg/d group (change in score = -1.66) at Week 8, compared to the placebo group (change in score = -0.5).

Table 6.3.6.a: Descriptive statistics: Mean pain score by Study Week – Protocol 045

	Placebo N=81	PGB 150 N=81	PGB 300 N=76
Baseline[1]	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Week 1	6.39 (1.8)	6.07 (2.0)	6.17 (2.0)
Week 2	6.33 (1.8)	5.80 (2.2)	5.59 (2.2)
Week 3	6.33 (1.9)	5.68 (2.2)	5.69 (2.3)
Week 4	6.30 (1.9)	5.72 (2.2)	5.57 (2.3)
Week 5	6.16 (2.0)	5.58 (2.4)	5.42 (2.3)
Week 6	6.18 (2.1)	5.58 (2.3)	5.33 (2.4)
Week 7	6.09 (2.1)	5.47 (2.3)	5.38 (2.4)
Week 8	6.14 (2.2)	5.28 (2.5)	5.32 (2.6)
Endpoint[2]	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1

[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose (as defined by the Applicant)

The change in mean pain score from baseline to Week 8 for each of the pregabalin groups was compared to that of the placebo group. The pair-wise comparisons of the changes in mean pain score for the 150 mg/d and 300 mg/d groups to the placebo group reached statistical significance (p-values = 0.0005 each)

Table 6.3.6.b: Change in mean pain scores, ANCOVA– Protocol 045

	Placebo	Pregabalin 150	Pregabalin 300
Baseline[1]	6.64 (1.6)	6.93 (1.7)	6.98 (1.6)
Endpoint[2]	6.15 (2.1)	5.31 (2.5)	5.34 (2.6)
Change[3]	0.50 (1.5)	1.63 (2.0)	1.64 (2.3)
ls means	0.53 (0.2)	1.65 (0.2)	1.64 (0.2)
p-value[4]		0.0004	0.0004
Week 8[5]	6.14 (2.2)	5.28 (2.5)	5.32 (2.6)
Change[6]	0.51 (1.5)	1.63 (2.01)	1.66 (2.4)
ls means	0.54 (0.2)	1.65 (0.2)	1.66 (0.2)
p-value[4]		0.0005	0.0005

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose
[3] Change= Baseline – Endpoint
[4] using Hochberg's test of difference from control (placebo)
[5] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[6] Change= Baseline – Week 8

Dr. Buenconsejo also conducted an ANCOVA of weekly pain scores and endpoint mean scores based on the above BOCF method of imputation. Although there was a significant difference between the pregabalin groups and the placebo group at each week and at endpoint, the difference in mean pain scores between the treatment groups was more pronounced starting at Week 2. At Week 1, there was only a minimal reduction (-0.6) in mean pain scores among the pregabalin-treated groups and the placebo group. This observation could be attributed to the fact that subjects underwent dose titration during Week 1, and only began the fixed dose regimen at Week 2.

Table 6.3.6.b: ANCOVA of Mean Pain Score by Study Week – Protocol 045

	Placebo N=81	PGB 150 N=81		PGB 300 N=76	
	Mean* (SD)	Mean (SD)	P value	mean (SD)	P value
Week 1	6.6 (0.1)	6.0 (0.1)	0.0017	6.1 (0.1)	0.0053
Week 2	6.5 (0.2)	5.7 (0.2)	0.0005	5.5 (0.2)	<0.0001
Week 3	6.5 (0.2)	5.6 (0.2)	<0.0001	5.6 (0.2)	<0.0001
Week 4	6.5 (0.2)	5.6 (0.2)	0.0002	5.4 (0.2)	<0.0001
Week 5	6.3 (0.2)	5.5 (0.2)	0.0015	5.3 (0.2)	0.0002
Week 6	6.4 (0.2)	5.5 (0.2)	0.0017	5.2 (0.2)	<0.0001
Week 7	6.2 (0.2)	5.4 (0.2)	0.0038	5.3 (0.2)	0.0010
Week 8	6.3 (0.2)	5.2 (0.2)	0.0004	5.2 (0.2)	0.0005
Endpoint[1]	6.3 (0.2)	5.2 (0.2)	0.0003	5.2 (0.2)	0.0004

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose
* Least square mean pain score

Dr. Buenconsejo assessed the sensitivity of the above analyses of the weekly mean pain scores using three other methods to extrapolate for missing data:

- Patients who withdrew from the study (non-completers) were assigned the baseline pain score for each week.

Patients who did not withdraw (completers) who had > 4 missing observations for a given week were assigned a weekly score based on the previous week's average pain score (LOCF).
Completers who had < 4 missing observations in a week were assigned the average of the available pain scores.

- Non-completers were assigned the baseline pain score for each week.
  Completers who had missing observations during a given week were assigned the previous week's average pain score for each missing observation (LOCF). The pain scores for that week were averaged to get the mean pain score for the week
- Average pain scores were calculated for non-completers until the week they dropped out of the trial. Thereafter, baseline mean pain scores were assigned for each week.

Each of these methods yielded similar results to the primary analysis method (see Dr. Buenconsejo's review).

Analysis of responder rates

To further characterize the effect of pregabalin on patients' pain, a comparison of the proportions of patients who had a favorable response to treatment (treatment 'responders') was done using the BOCF data. Study non-completers were considered to be non-responders. Similar to the Applicant, I defined a responder as a patient who had at least a 50% decrease in pain from baseline to study endpoint (Week 8). Other cut-offs were (10% to 100%) were used to define a treatment responder and proportions of responders at these cut-offs were compared across groups. Patient response to drug over time (i.e. at each week) was also evaluated.

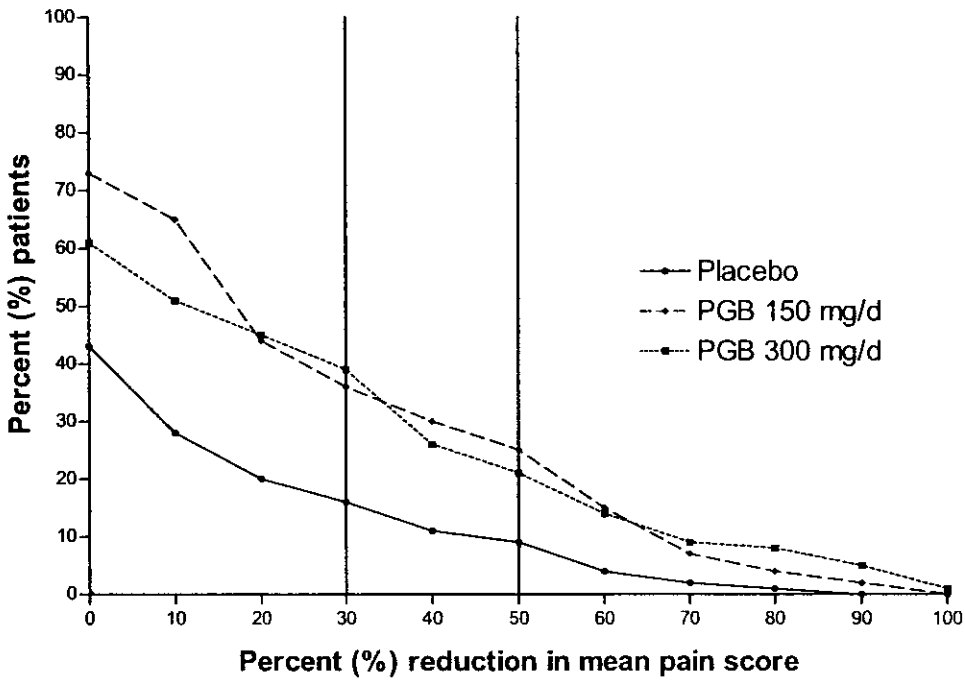
Responder rates at Endpoint

Table 6.3.6.c and Figure 1 show that, based on a definition of ≥ 50% decrease in pain, there were more patients in the pregabalin 150 mg/d group (25%) and the 300 mg/d group (21%) who were responders, compared to the placebo group (18%). At lower cut-offs for treatment response, treatment response was also greater in the 150 mg/d group than in the 300 mg/d.

Table 6.3.6.c: Percent change in endpoint mean pain score by dose – Protocol 045

	TOTAL		PLACEBO		PGB150		PGB300	
	Total	%	Total	%	Total	%	Total	%
Any increase	39	16%	19	23%	11	14%	9	12%
None	59	25%	27	33%	11	14%	21	28%
> 0 % decrease	140	59%	35	43%	59	73%	46	61%
≥ 10%	115	48%	23	28%	53	65%	39	51%
≥ 20%	86	36%	16	20%	36	44%	34	45%
≥ 30%	72	30%	13	16%	29	36%	30	39%
≥ 40%	53	22%	9	11%	24	30%	20	26%
≥ 50%	**43**	**18%**	**7**	**9%**	**20**	**25%**	**16**	**21%**
≥ 60%	26	11%	3	4%	12	15%	11	14%
≥ 70%	15	6%	2	2%	6	7%	7	9%
≥ 80%	10	4%	1	1%	3	4%	6	8%
≥ 90%	6	3%	0	0%	2	2%	4	5%
=100%	1	0%	0	0%	0	0%	1	1%

Figure 1: Response profile at endpoint – Protocol 045



Responder rates at each week separately

Using definitions (cut-offs) of treatment response that ranged from a 10% to 80% reduction in pain, Dr. Buenconsejo compared the proportion of responders at each week. At each week, and at each definition of responder, the proportions of responders were greater in the pregabalin groups than in the placebo group. Using a definition of 50% reduction in pain, there was no apparent difference in responder rates between the pregabalin 150- and 300 mg/d groups (Figure 2), regardless of the study week. Using a definition of 60% to 80% reduction in pain, treatment with pregabalin 300 mg/d appeared to yield more responders, compared to 150 mg/d, at each study week (Figures 3 and 4). However, as shown in Table 6.3.6.c, there were very few patients in each study group who met these criteria. Based on a definition of response as a 50% reduction in mean pain score, a difference in treatment response between pregabalin and placebo groups could be seen at Week 2, and the difference persisted throughout the study (Figure 5).

Figure 2: Patients with 50% decrease in pain from baseline by study week – Protocol 045

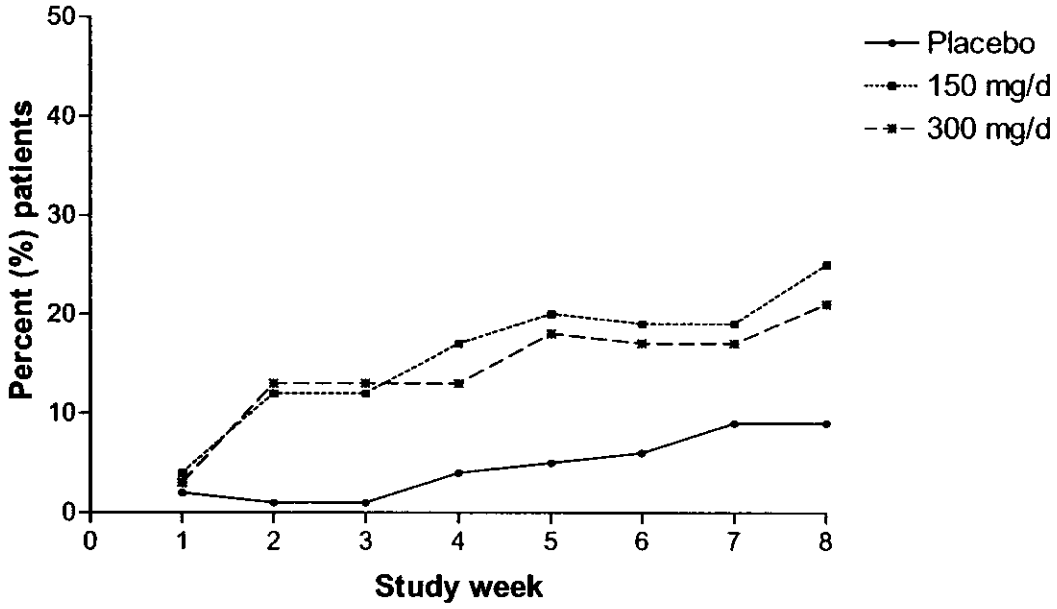


Figure 3: Patients with 60% decrease in pain from baseline by study week – Protocol 045

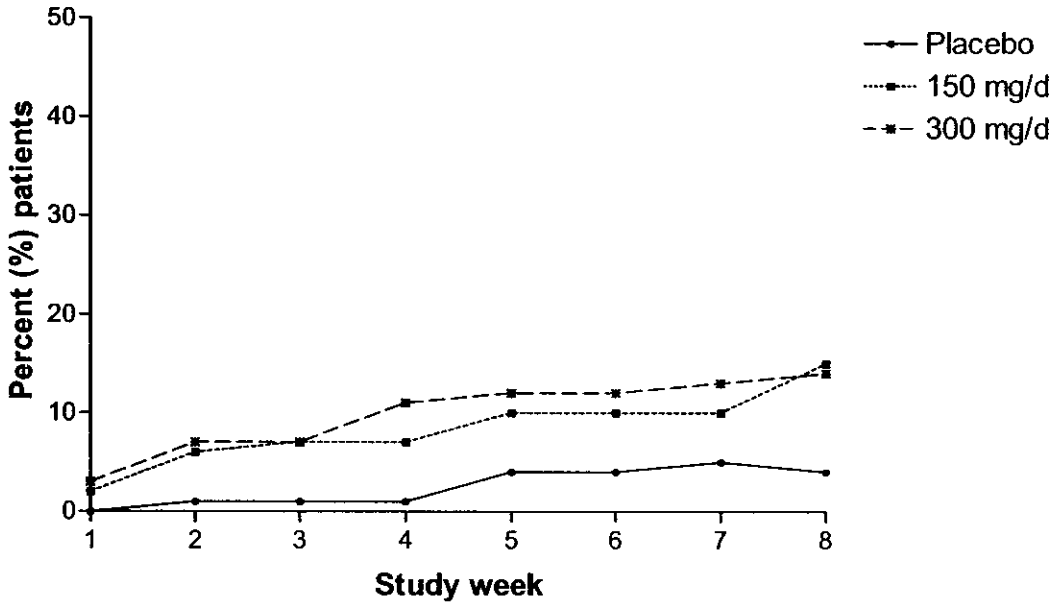
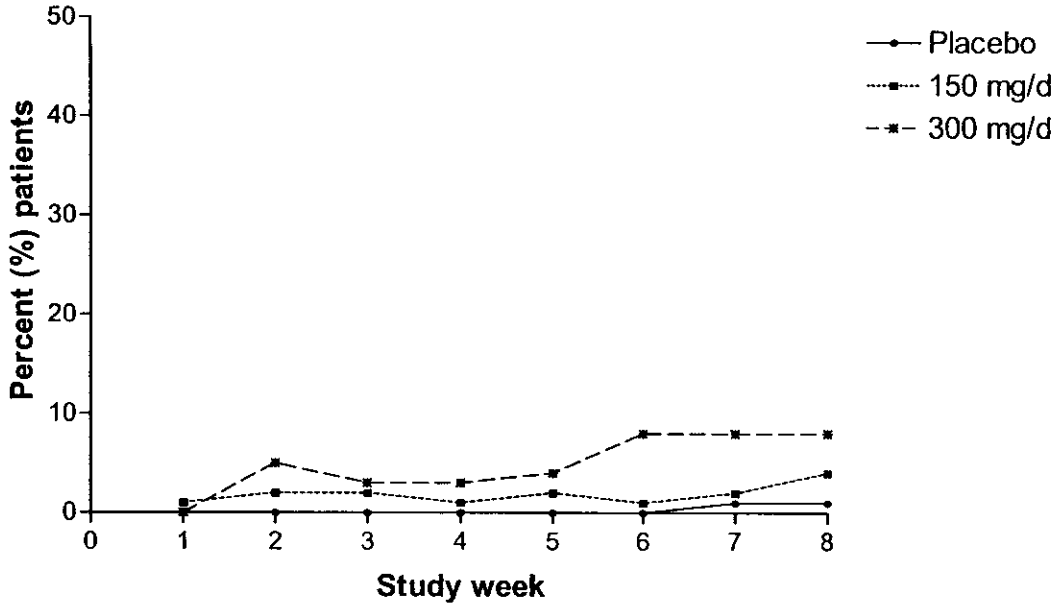
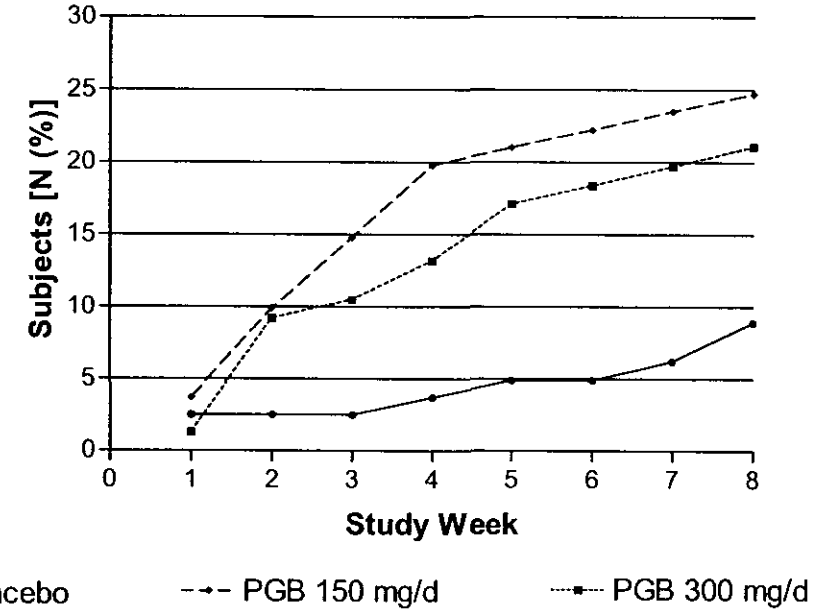


Figure 4: Patients with 80% decrease in pain from baseline by study week – Protocol 045



There were 43 study completers who met the definition of response as a 50% reduction in mean pain score. Figure 5 presents the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 8). The graph shows an increasing trend of responders, suggesting that patients treated with pregabalin who did not respond to treatment early in the study (Weeks 1-4) could potentially still respond by week 5. This was particularly true for patients in the pregabalin 150 mg/d group. There was no apparent trend in treatment response over time for patients in the placebo group.

Figure 5: Proportion of treatment responders (≥ 50% decrease in pain), by study week – Protocol 045



6.3.1.26 **Conclusions regarding efficacy data – Protocol 045**

Both the Applicant's and the Agency's analyses show that treatment with pregabalin 150 mg/d and 300 mg/d (administered in 3 divided doses) resulted in a decrease in pain due to postherpetic neuralgia. The Agency's analysis further showed that more patients in the pregabalin groups responded to treatment compared to the placebo group. Treatment with pregabalin 150 mg/d appeared to yield a greater treatment response than treatment with 300 mg/d.

6.3.2 Protocol 1008-127: An 8-week, double-blind, placebo-controlled, parallel group study of pregabalin in patients with postherpetic neuralgia

6.3.2.1 Objective/Rationale

To evaluate the efficacy and safety of pregabalin compared to placebo in relieving pain in patients with postherpetic neuralgia.

6.3.2.2 Overall design

This was a Phase 2/3, multi-center, multiple dose, randomized, double-blind, parallel, placebo-controlled trial comparing pregabalin to placebo. It was conducted in the United States.

6.3.2.3 Study population and procedures

6.3.2.4 Treatment duration:

8 weeks (1-week titration; 7-week fixed dose period)

6.3.2.5 Entry criteria

The trial would enroll 152 patients (76 in the pregabalin arm; 76 in the placebo arm).

Eligibility criteria were similar to those for Protocol 1008-045 (see Section 6.3.3.2), with the following exceptions:

Inclusion criteria:

- Pain ≥ 3 months after the healing of herpes zoster skin rash
- Normal chest x-ray within 2 years prior to baseline visit OR stable x-ray (i.e. x-ray without significant change from previous exam)

Exclusion criteria

- Malignancy within the previous 2 years

6.3.2.6 Study medications

The study drugs comprised capsules containing placebo or pregabalin 50-, 100-, or 200 mg. Subjects randomized to the pregabalin arm were to be titrated to the full dose over a 7-day period. Dosing would begin at 150 mg/d, and then increased to the target dose as shown below:

	Week 1 (Titration period)			Weeks 2 to 8
Treatment arm	Days 1-3	Day 4 + Day 5	Day 6 + Day 7	(Fixed dose period)
Placebo	Placebo	Placebo	Placebo	Placebo
300 mg/d	150 mg/d	300 mg/d	300 mg/d	300 mg/d
600 mg/d	150 mg/d	300 mg/d	300 mg/d	600 mg/d

Permitted medications were the same as for Protocol 1008-045 (see Section 6.3.3.3), except patients were not allowed to take short-acting benzodiazepines.

Prohibited medications were the same as for Protocol 1008-045 (see Section 6.3.3.3). Additional prohibited medications (in the absence of a pre-defined washout period) were:

- Local/topical agents for relief of postherpetic neuralgia – washout of ≥ 7 days prior to Visit 1
- Injections for relief of pain (e.g. local anesthetics, steroids) – washout of ≥ 1 month for epidural; ≥ 1 week for IM or subcutaneous
- Potential retinotoxins (e.g. hydroxychloroquine, thioridazine, deferoxamine, vigabatrin – patients on these medications were ineligible for the study

6.3.2.7 Study procedures

The protocol specified 6 clinic visits. Visit 1 (V1) would be the screening visit which, and V2 would occur at the end of the 1-week baseline period during which baseline physical, ophthalmologic, and laboratory measurements would be obtained. Also, subjects would complete daily pain and sleep interference diaries. Subjects who completed at least 4 pain diaries and had an average pain score of at least 4 would then be randomized to study drug (placebo or pregabalin) at V2. Patients who were ineligible for randomization (screen failures) were to have the following information collected: demographics; reason for not entering double-blind treatment; and SAEs or withdrawals due to AEs.

Randomization was to be blocked into 2 strata based on the creatinine clearance of each patient in the pregabalin group. Patients with a creatinine clearance >60 mL/min would be treated with 600 mg/d, whereas patients with a creatinine clearance of 30 - 60 mL/min would take 300 mg/d. Study drug would be increased to the target dose over a 1 week period (as described above) at the end of which patients would attend V3. Patients unable to maintain the target dose were withdrawn from the study.

Following V3, patients would be assessed at 2-3 week intervals (V4, 5, and 6). During clinic visits patients would be evaluated for pain, sleep quality, laboratory changes, physical status, and any adverse effects. AT V6/Termination, additional assessments including ophthalmology exam, quality of life, mood, and overall improvement would be made. Subjects not continuing in the open-label extension study Protocol 1008-134 would attend safety follow-up visit at Study Week 9 (V7/FU).

Table 6.4.2.7: Timetable of visits and procedures – Protocol 127

Study Phase:	Baseline (1 Week)	Double-Blind Treatment (8 Weeks)					
Clinic Visit No.:	V1	V2	V3	V4	V5	V6[c]	(V7/FU[c])
End of Study Week[a]:	Screening	Randomization	1	3	5	8	9
Day:	--	-1	7	21	35	56	63
Observation/Procedure							
Informed Consent	X						
Inclusion/Exclusion	X----------X						
Medical History	X						
Physical Examination	X			X (vitals)		X	
Abbreviated Neurological Examination	X					X	
12-Lead ECG	X					X	
SF-McGill Pain Questionnaire (SF-MPQ)	X	X	X	X	X	X	
Daily Diaries (Pain and Sleep)	X----------->X						
Clinical Labs:							
Pregnancy Test (serum)	X			X		X	
Hematology, Chemistry	X			X		X	X
Urinalysis	X[g]					X	X
Study Medication Plasma Concentration				X		X	
Visual Examinations[d]	X					X	
Chest X-ray[e]	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Study Medication Dosing/Dispensing		X	X	X	X	X[f]	
Global Impression of Change (Clinical and Patient)						X	
SF-36 Health Survey		X				X	
Profile of Mood States (POMS)		X				X	
MOS-Sleep Scale (Exploratory)		X				X	

[a] Telephone contact will be made with the patients at least once between each visit (V2-V6) to ensure compliance with study procedures and assess adverse events. Should the patient experience an adverse during double-blind, an extra visit can be scheduled.
[b] Whenever patient withdraws from or completes the study
[c] For patients who do not enter Study 1008-134; this visit occurs 1 week after termination visit.
[d] Examination/testing preferably by the same ophthalmologist at V1, V6/Term: 120-point Humphrey visual screening with the quantified defects routine, best-corrected Snellen visual acuity, dilated ophthalmoscopy (direct or indirect).
[e] Chest x-ray must be taken at baseline visit if none available in the past 2 years.
[f] Dispense open-label medication for patients continuing on to Protocol 1008-134.
[g] A 24-hour urine sample may be collected for potential inclusion if estimated serum creatinine clearance <30 mL/min.

(Applicant's Table 5, RR 720-04457, 1008-127, P. 27)

6.3.2.8 Efficacy parameters-

Efficacy parameters were the same as for Protocol 1008-045 (See Section 6.3.3.5) except patients were not assessed with the Zung Self-Rating Depression Scale. Also, these additional measures were utilized:

- *Profile of Mood States:* 65 descriptors of subject's mood, each rated on a 5-point scale from 0 (not at all) to 4 (extremely)
- *Medical Outcomes Study (MOS)-Sleep Scale:* 12-item questionnaire assessing various constructs of sleep including snoring, somnolence, sleep disturbance, optimal sleep, sleep adequacy, quantity of sleep, and awaken short of breath or with headache

6.3.2.9 Statistical Analysis

Patient population

Data would be analyzed for the ITT population only (i.e. all randomized patients who took at least 1 dose of study medication).

Primary efficacy outcome

Similar to Protocol 1008-045 (See Section 6.3.1.9), the primary efficacy parameter was the weekly mean pain score (the average of the last 7 pain scores), and the primary efficacy outcome was the endpoint weekly mean pain score, where the "endpoint" was the last 7 pain diary entries while the patient was on study medication.

The primary analysis would compare the final weekly mean pain score between the pregabalin and placebo groups using analysis of covariance (ANCOVA) with treatment, center, and creatinine clearance strata in the model and the baseline mean pain score as covariate.

Supplemental analyses of the primary efficacy outcome
These were to be the same as for Protocol 1008-045. An additional analysis was a comparison of the proportion of responders between pregabalin and placebo, adjusting for treatment center.

Secondary efficacy outcomes
These would be the same as for Protocol 1008-045. Also:

- POMS, change from baseline to endpoint
- MOS, change from baseline to endpoint

No adjustments would be made for testing multiple outcome measures.

Interim analyses
No interim analyses were planned

6.3.2.10 Protocol amendments
Pfizer did not describe any protocol amendments.

6.3.2.11 Study results

6.3.2.12 Subject characteristics
The study was initiated on December 17 1999, and ended on May 11, 2000. A total of 29 centers in the United States participated in the trial

6.3.2.13 Enrollment by Center
The number of patients enrolled at each center is shown in the table below:

Table 6.3.2.13: Enrollment by center – Protocol 127

No. Patients Randomized Per Center	Center Number
0	009
1	019, 022
2	014
3	006, 025, 021, 029
4	007, 008, 013,
6	003, 010
7	001, 004
8	002, 030, 031
9	015, 018
10	023
11	026
13	017
14	011, 024
15	028

One site, Site No. 009, received study medication, but did not enroll any patients.

6.3.2.14 Protocol violations
Whereas Pfizer stated that there were 36 patients with protocol violations. I identified 37 such patients:

Table 6.3.2.14: Protocol violations – Protocol 127

	Number of Patients			
Violation	Total	Placebo	Pregabalin 300	Pregabalin 600
Baseline mean pain score < 4	1	-	-	1
VAS score < 40 mm	2	2	-	-
V4 lab test not done	7	4	-	3
Patient randomized before receipt of V2 FSH results	5	2	1	2
Inappropriate washout of prohibited medications or unstable regimen of restricted medications	12	6	-	6
Abnormal ECG	4	-	2	2
Malignancy within the past 2 years	1	-	1	-
Randomization to incorrect creatinine clearance stratum (i.e. randomization to incorrect pregabalin dose)	5	3	2	-
Total violations	37	17	6	14

(Adapted from Applicant's Appendix A.8, RR 720-04457, 1008-127, P. 262-67)

In my opinion, the protocol violations that could potentially impact the primary efficacy outcome are:

- Inappropriate washout of prohibited medications/unstable regimen of restricted medications – patients may experience a decrease in pain due to the prohibited medications, and not due to treatment with study drug

  However, equal numbers of placebo and pregabalin patients demonstrated this violation, and so the bias was evenly distributed across treatment groups.

- Randomization to the incorrect pregabalin dose (300 mg/d instead of 600 mg/d). The 2 patients with this violation could theoretically have had a lower pregabalin exposure compared to patients with a low creatinine clearance who were treated with 300 mg/d. Thus, the incorrectly dosed patients could have had less drug benefit, and worse pain scores, and would have lowered the overall mean pain score for the group.

  However, since the numbers of patients with this violation is small (n=2), the impact of this violation on the outcome is believed to be minimal.

The other violations are not expected to have a significant impact on the interpretation of the results because they are relatively irrelevant to the efficacy outcome or occurred in low numbers.

6.3.2.15 Blinding
Pfizer did not report that the study blind was broken.

6.3.2.16 Subject disposition
Patient disposition, and reasons for premature withdrawal from the study are shown in the table below. Of the 245 patients who entered the baseline phase, 72 did not complete this phase.

Reasons for withdrawal from the baseline phase included not meeting study criteria (n=57), withdrawal of consent (n=13) and "other" (n=2).

There were 173 patients randomized to study drug and who took at least one dose of study medication: 84 in the placebo group, and 89 in the "pregabalin" group. Of the patients randomized to pregabalin, 29 patients had a creatinine clearance (CLcr) ≥ 30 mL/min and ≤ 60 mL/min; there were 60 patients with a CLcr > 60 mL/min. However, 30 patients were randomized to pregabalin 300 mg/d, and 59 were randomized to 600 mg/d (exposure data). That is, one patient was treated with 300 mg/d instead of 600 mg/d. This is consistent with the protocol violation described in Section 6.3.2.14.

A total of 41 patients withdrew from the study during the double-blind treatment phase. The most frequent reason for withdrawal from the placebo group was 'lack of efficacy' (7%), while the most patients in the pregabalin group withdrew due to adverse events (31%). Adverse events were the most common reason for withdrawal for all study population. There were no deaths during the double-blind treatment phase.

Table 6.3.2.16: Patient disposition – Protocol 127

	[Number (%) of Patients]		
	Treatment Group		
Disposition N,(%)	Placebo	Pregabalin	All Patients
Entered Baseline Phase			245
Completed Baseline Phase			173 (70.6)
Withdrawn During Baseline Phase:			72 (29.4)
Did not meet criteria			57 (23.3)
Other			2 (0.8)
Patient withdrew consent			13 (5.3)
Randomized	84	89	173
Intent-to-Treat	84	89	173
Completed Study	74 (88.1)	58 (65.2)	132 (76.3)
Withdrawn During Treatment Phase:	10 (11.9)	31 (34.8)	41 (23.7)
Adverse Event	4 (4.8)	28 (31.5)	32 (18.5)
Lack of Compliance	0 (0)	2 (2.2)	2 (1.2)
Lack of Efficacy	6 (7.1)	0 (0)	6 (3.5)
Patient withdraws consent	0 (0)	1 (1.1)	1 (0.6)
Entered Open Label Treatment	63 (75.0)	62 (69.7)	125 (72.3)

a Those who withdrew early from the study could elect to enter open-label treatment.
(Applicant's Table 10, RR 720-04457, 1008-127, P. 39)

6.3.2.17 Extent of exposure/Dosing information

Pfizer found that, of the 173 randomized patients, 87 (50.2%) patients completed at least 8 weeks of treatment with study drug. Pfizer explains the difference in total exposure to study drug for 8 weeks from the number of study completers as being due to the fact that patients often had their termination visit prior to completing a full 56 days of exposure. Study completion was defined as

completion of all the visits and procedures described in and was determined independently of the number of weeks that a patient was exposed to study medication.

Pfizer stated that approximately 52% of pregabalin-treated patients and 49% of placebo patients had ≥ 8 weeks' of drug exposure. In general, drug exposure was greater for the placebo group compared to the pregabalin group for up to 7 weeks of treatment.

Table 6.3.2.17.a: Applicant's Analysis of patient drug exposure – Protocol 127

Total Exposure Time[a]		[Number (%) of Patients] Treatment Group			
		Placebo (N= 84)		Pregabalin (N= 89)	
		N of Pts	(%)	N of Pts	(%)
≥	1 Day	84	(100.0)	89	(100.0)
≥	1 Week	83	(98.8)	85	(95.5)
≥	2 Weeks	82	(97.6)	78	(87.6)
≥	3 Weeks	78	(92.9)	76	(85.4)
≥	4 Weeks	76	(90.5)	68	(76.4)
≥	5 Weeks	75	(89.3)	65	(73.0)
≥	6 Weeks	74	(88.1)	60	(67.4)
≥	7 Weeks	73	(86.9)	57	(64.0)
≥	8 Weeks	41	(48.8)	46	(51.7)

a Days on which patients received 0 dose are included in summary of patient exposure to study medication.

(Applicant's Table 9, RR 720-04457, 1008-127, P. 38)

I reanalyzed patient's drug exposure based on actual dose of medication received (placebo, 300 mg/d or 600 mg/d). As described above, there were 84 patients in the placebo group, 30 in the 300 mg/d group, and 59 patients in the 600 mg/d group. I found that 165 patients participated in the fixed-dose phase of the trial (83 in the placebo group, 25 in the 300 mg/d group, and 57 in the 600 mg/d group). That is, 165 patients tolerated the titration to the target dose and entered into the fixed-dose phase. Exposure data for the patients are shown in the table below. My analysis shows that more placebo patients took study drug for at least 7 weeks compared to either of the pregabalin groups. Similar proportions of patients in the two pregabalin groups were exposed to study medication.

Table 6.3.2.17.b: Reviewer's Analysis of patient drug exposure – Protocol 127

Total exposure, time N (%)	Placebo [N (%)] (N = 84)	Pregabalin [N (%)] 300 mg/d (N = 30)	Pregabalin [N (%)] 600 mg/d (N=59)
≥ 1 day	84 (100%)	30 (100%)	59 (100%)
≥ 1 week	83 (98.81)	25 (83.33)	52 (88.1)
≥ 2 week	77 (91.67)	23 (76.67)	50 (84.7)
≥ 3 week	76 (90.48)	22 (73.33)	45 (76.3)
≥ 4 week	75 (89.29)	21 (70.00)	42 (71.2)
≥ 5 week	74 (88.1)	19 (63.33)	40 (67.8)
≥ 6 week	72 (85.71)	16 (53.33)	36 (61.0)
≥ 7 week	38 (45.24)	5 (16.67)	15 (25.4)
≥ 8 week	1 (1.19)	0 (0.00)	1 (1.7)

6.3.2.18 Demographics
Pfizer found that the patient population was comprised primarily of whites (95%), and slightly more than half was women (53%). The mean age was 72 (± 10.9) years, and most patients (82%) were 65 years or older. There were more women in the pregabalin group (58%) compared o the placebo group (48%). The two groups were similar with respect to age.

The mean baseline creatinine clearance (CLcr) for the population was 76 mL/min, with most patients (68%) having a CLcr > 60 mL/min. The pregabalin group had a lower mean CLcr (73 mL/min) compared to the placebo group (80 mL/min). The proportions of patients with a CLcr > 60 mL/min was similar for the two groups (67% of the pregabalin group, versus 70% of the placebo group).

Postherpetic neuralgia history
The mean duration of PHN was similar across groups (approximately 3 years), with the thoracic, trigeminal, and lumbar dermatomal regions being the most commonly affected areas. However, more patients in the placebo group had the trigeminal area affected than did patients in the pregabalin group (26% vs. 20%). The mean baseline pain score for the population was 6.4, and was similar for both groups (6.4 for the placebo group, and 6.3 for the pregabalin group).

Dr. Buenconsejo calculated the mean baseline pain score for patients treated with placebo, 300- and 600 mg/d, and found that patients randomized to pregabalin 300 mg/d had the highest pain score, while patients in the 600 mg/ day group had the lowest.:

	Placebo N = 84	Pregabalin 300 mg/d N = 30	Pregabalin 600 mg/d N = 59
Baseline mean pain score	6.43	6.60	6.13

The potential effect of this difference in baseline pain score on the primary efficacy outcome was controlled for by including baseline mean pain score as a covariate in the ANCOVA.

Table 6.3.2.18.a: Summary of patient characteristics, ITT population – Protocol 127

Characteristic		Treatment Group		
		Placebo N=84	Pregabalin N=89	All Patients N=173
Sex, N (%)	N	84	89	173
	Male	44 (52.4)	37 (41.6)	81 (46.8)
	Female	40 (47.6)	52 (58.4)	92 (53.2)
	Premenopausal	3 (7.5)	2 (3.8)	5 (5.4)
	Postmenopausal	37 (92.5)	50 (96.2)	87 (94.6)
Race, N (%)	N	84	89	173
	White	82 (97.6)	82 (92.1)	164 (94.8)
	Hispanic	1 (1.2)	6 (6.7)	7 (4.0)
	Asian or Pacific Islander	1 (1.2)	1 (1.1)	2 (1.2)
Age Categories, N (%)	N	84	89	173
	18 - 64 years	17 (20.2)	15 (16.9)	32 (18.5)
	>= 65 years	67 (79.8)	74 (83.1)	141 (81.5)
Age (years)	N	84	89	173
	Mean (STD)	70.5 (11.3)	72.4 (10.5)	71.5 (10.9)
	Median	73.0	74.0	73.0
	Range	31 to 90	34 to 100	31 to 100
Estimated Creatinine at Baseline (mL/min)	N	84	89	173
	Mean (STD)	80.33 (27.29)	72.85 (27.53)	76.49 (27.59)
	Median	78.50	72.00	74.00
	Range	32.0 to 147.0	24.0 to 178.0	24.0 to 178.0
Creatinine Clearance Strata, N (%)	N	84	89	173
	Low	25 (29.8)	30 (33.7)	55 (31.8)
	Normal	59 (70.2)	59 (66.3)	118 (68.2)
Height (cm)	N	84	88	172
	Mean (STD)	168.92 (9.77)	166.09 (10.74)	167.47 (10.35)
	Median	168.00	164.75	165.40
	Range	147.0 to 190.5	141.0 to 190.5	141.0 to 190.5
Weight (kg)	N	84	88	172
	Mean (STD)	79.76 (16.73)	74.81 (13.40)	77.23 (15.27)
	Median	77.50	73.85	75.90
	Range	29.1 to 136.8	52.7 to 112.4	29.1 to 136.8

(Applicant's Table 7, RR 720-04457, 1008-127, P. 36)

Table 6.3.2.18.b: Summary of postherpetic neuralgia history, ITT population – Protocol 127

	Treatment Group		
	Placebo N=84	Pregabalin N=89	All Patients N=173
Duration of Postherpetic Neuralgia (Months)			
N	84	89	173
Mean (STD)	34.4 (36.7)	33.3 (35.4)	33.8 (35.9)
Median	18.5	21	19
Range	3.0 to 151.0	3.0 to 187.0	3.0 to 187.0
Predominantly-Affected Dermatomal Region, N(%)			
Trigeminal	22 (26.2%)	18 (20.2%)	40 (23.1%)
Cervical	6 (7.1%)	9 (10.1%)	15 (8.7%)
Thoracic	41 (48.8%)	42 (47.2%)	83 (48.0%)
Lumbar	11 (13.1%)	16 (18.0%)	27 (15.6%)
Sacral	4 (4.8%)	4 (4.5%)	8 (4.6%)
Baseline Mean Pain Score			
N	84	89	173
Mean (STD)	6.4 (1.5)	6.3 (1.4)	6.4 (1.5)
Median	6.4	6.1	6.3
Range	4.0 to 10.0	3.7 to 9.1	3.7 to 10.0

(Applicant's Table 8, RR 720-04457, 1008-127, P. 37)

Concomitant medications

Prior (within the previous 30 days) and concurrent medications were used by 98% of patients in the placebo and pregabalin groups. The most commonly used medications were:

Medication	Placebo (% patients)	Pregabalin (% patients)
Acetylsalicylic acid	33	32
Paracetamol (acetaminophen)	17	14
Ibuprofen	11	15
Gabapentin	12	12
Furosemide	8	14
Levothyroxine	17	21
Tocopherol	13	14
Atenolol	7	11
Atorvastatin	6	11
Multiviatamins	20	20

(Adapted from Applicant's Appendix C.1, RR 720-04457, 1008-127, P. 288)

The proportions of patients using each of these mediations was approximately similar between treatment groups., and therefore the use of a concomitant medication should have little or no effect on the primary efficacy outcome.

6.3.2.19 Applicant's efficacy results

6.3.2.20 Overview

Per Pfizer's analysis, the "pregabalin" treatment arm had a statistically significant decrease in mean pain score at endpoint, compared to the placebo arm. Pfizer found that the improvement in mean pain score for the "pregabalin" group was evident at Week 1. There were also statistical differences between the "pregabalin" and placebo groups with respect to several; secondary outcomes including the proportion of treatment responders, mean sleep interference score, and global impression of change.

6.3.2.21 Primary efficacy outcome

The primary efficacy outcome was the endpoint mean pain score (the mean of the last 7 entries on of the daily pain diary, while the patient was on study medication). Pfizer found that both the pregabalin and placebo treatment groups had an improvement (decrease) in their mean pain scores at endpoint. The mean changes from baseline to endpoint, were greater for patients in the pregabalin group than the placebo group. Using the ANCOVA model, the endpoint mean pain score was statistically significantly different, pregabalin over placebo.

Table 6.3.2.21.a: Mean pain score: Descriptive statistics – Protocol 127

Time point	Placebo			Pregabalin		
	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
Baseline[a]	84	6.4 (1.5)	4, 10	89	6.3 (1.4)	3.7, 9.1
Endpoint[b]	84	5.3 (2.6)	0, 10	88	3.6 (2.3)	0, 9.6
Change[c]	84	-1.1 (2.0)	6.6, 3.9	88	-2.7 (2.1)	-7.3, 2.4

SD = Standard deviation

a Baseline = Last 7 available scores before taking study medication, up to and including Day 1.

b Endpoint = Last 7 available scores while on study medication, up to and including day after last dose

c Change is from baseline to endpoint

(Applicant's Table 11, RR 720-04457, 1008-127, P. 42)

Table 6.3.2.21.b: Endpoint mean pain score: ANCOVA results – Protocol 127

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
				Difference	95% CI	p-value
Placebo	84	5.29	0.24			
Pregabalin	88	3.60	0.24	-1.69	(-2.33, -1.05)	0.0001

SE = Standard error; CI = Confidence interval

Endpoint = last 7 available scores while on study mediation (if less than 7, then whatever scores are available)

(Applicant's Table 12, RR 720-04457, 1008-127, P. 43)

Supplemental analyses of the primary efficacy variable

Mean pain scores: Weekly scores and change from baseline

Pfizer computed mean pain scores for each of the 8 treatment weeks and found that the pregabalin treatment group had a considerable decrease in mean pain score at Week 1 (decrease from 6.3 to 4.7), and at Week 2 (decrease from 4.7 to 3.9). This low score varied only slightly for the remaining weeks of the study. The weekly mean pain score for the placebo group decreased

more gradually during the course of the study, from 6.4 to 5.3 at study endpoint. Pfizer's analysis of weekly mean pain scores between the treatment groups revealed differences that were statistically significant, favoring pregabalin over placebo at every time point

Proportion of responders

A responder was defined as a subject who had a 50% decrease in mean pain score from baseline to endpoint. Using an LOCF imputation strategy, Pfizer found that the proportion of responders in the pregabalin treatment group was 50%, compared to 20% in the placebo group, a difference that was statistically significant.

Table 6.3.2.21.c: Results of analysis of responder status – Protocol 127

Treatment Group	No. Assessed	Responders, (N,%)	p-value[a]
Placebo	84	17 (20.2)	
Pregabalin	88	44 (50.0)	0.001

a p-value based on the results of the Cochran-Mantel-Haenszel procedure, adjusting for center and creatinine clearance strata.
(Applicant's Table 15, RR 720-04457, 1008-127, P. 46)

6.3.2.22 Applicant's secondary efficacy analysis

Results of the secondary efficacy outcomes were to be interpreted on the pattern of significant differences, and not in individual significant findings. This was because the protocol did not call for adjustments for testing of multiple parameters.

- *SF-MPQ (sensory, affective, VAS, PPI, and total scores)*

The largest effect of pregabalin treatment was seen on 2 of the 4 affective descriptors (fearful and punishing-cruel). Less than half of the percentage of patients who reported each of those at randomization reported these descriptors at endpoint. In the placebo group, the frequency of patients reporting a given pain descriptor was not reduced by 50% for any pain descriptor.

Overall, pregabalin treatment was associated with a greater decrease (improvement) in VAS, PPI, sensory and total scores over the course of the study, compared to placebo treatment. These differences in scores, at endpoint and each study week, reached statistical significance.

- *Mean sleep interference score, weekly and at endpoint*

The mean sleep interference score decrease considerably at Week 1 for the pregabalin group, where as the placebo group's score decreased to a lesser amount. At each study week, and at study endpoint, the pregabalin group's sleep score was lower than the placebo group's, and the differences were statistically significant.

- *Global impression of change (by subject and investigator)*

The percentage of patients in the pregabalin group reporting improvement in the global impression of change (very much improved, much improved, or minimally improved) was 84%, where as 26% of patients in the placebo group reported these changes. The percentage of pregabalin-treated patients reporting worsening of their overall status from study start (4%) was

less than that of the placebo-treated patients (14%). There was a statistically significant difference (p = 0.001) in the PGIC response of the pregabalin group in comparison with the placebo group. Similar findings were noted for the investigator ratings of patient improvement.

- *SF-36 QOL change from baseline to endpoint*

Higher (more favorable) mean scores were reported for the pregabalin group compared with the placebo group in each of the 8 health domains of the SF-36 Health Survey. However, the differences in scores between treatment groups reached statistical significance in only the Bodily Pain and General Health Perception domains

- *POMS, change from baseline to endpoint*

POMS scores of the pregabalin-treated patients were more favorable for each mood state compared to scores of the placebo patients. However, the differences in the groups' scores failed to reach statistical significance.

- *MOS, change from baseline to endpoint*

Compared to the placebo group, only the mean scores of the subscales sleep disturbance, awaken short of breath or with headache, quantity of sleep, sleep adequacy, and overall sleep problems of the pregabalin group were improved. The differences reached statistical significance. A post-hoc logistic regression analysis performed on the Optimal Sleep subscale showed no statistically significant differences from placebo in comparing optimal sleep at randomization and at termination.

6.3.2.23 Unplanned Analyses

Pfizer conducted the following additional analyses at the Agency's request, to provide more information on the primary outcome measure:

BOCF analysis of the endpoint mean pain score

Based on the Patient Status information from the CRF, Pfizer found 40 patients who did not complete the study. Fore these patients, the baseline mean pain score was used instead of the endpoint mean pain score in the ANCOVA. Pfizer found that there was a statistically significant difference between placebo and pregabalin with respect to the endpoint mean pain score.

Table 6.3.2.23: Endpoint mean pain scores: Results of ANCOVA with BOCF – Protocol 127

				Treatment Comparisons (Pregabalin – Placebo)		
Treatment	N	Least Squares Means	SE	Difference	95% CI	p-value
Placebo	84	5.15	0.23			
Pregabalin	88	4.36	0.24	-0.79	(-1.44, -0.15)	0.0166

SE = Standard error; CI = Confidence interval

[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

(Applicant's Table E1, RR 720-04457, 1008-127, App D3)

Endpoint mean pain score: Removing subjects with somnolence or dizziness

A total of 54 patients (14 receiving placebo and 40 pregabalin) reported TESS adverse events of dizziness and/or somnolence at some time during the study. The primary analysis of weekly mean pain at endpoint was repeated after removing these patients. The results of this ANCOVA showed a significant difference between pregabalin and placebo, consistent with those seen in the primary analysis.

Longitudinal analysis of the pain scale

There was evidence of a treatment by week interaction (p=0.0237), but the weekly contrasts were only quantitatively, and not qualitatively different; all weekly contrasts resulted in a significant treatment effect favoring pregabalin. The interaction effects ANCOVA model also yielded a significant overall difference for pregabalin 300mg/day in comparison to placebo (p=0.0001).

Analysis of measures of skin hypersensitivity: Allodynia and Hyperalgesia

A total of 169 patients (84 placebo, 85 pregabalin) had allodynia measurements at baseline and endpoint. There were 170 patients (84 placebo, 86 pregabalin) who had hyperalgesia measurements. Neither allodynia nor hyperalgesia was significantly associated with treatment.

Proportion of patients who took rescue medication

The only concurrent pain medication allowed during the study was acetaminophen (up to 4 g/d). In the placebo group, 13 (15.5%) patients took acetaminophen as compared to 11 (12.4%) in the pregabalin group. Pfizer concluded that since the proportion of patients taking acetaminophen was smaller within the pregabalin group compared to the placebo, acetaminophen usage was unlikely to affect the results.

Additionally, Pfizer identified 5 patients took prohibited medications for pain. The proportion of patients taking prohibited pain medications was also similar among the treatment groups and was therefore believed to not likely have an effect on the results.

6.3.2.24 Reviewer's analysis of efficacy

The same problems with the Applicant's statistical analysis of efficacy exist for this protocol, as were discussed for Protocol 045 (See Section 6.3.6, Reviewer's analysis of efficacy). Therefore, the data were reanalyzed using the preferred definition of study endpoint (the last week of treatment with study medication) and completion of study, as well as imputation of missing data using the BOCF method, as already described.

Another limitation of the Applicant's analysis of this study was that, rather than compare actual dosing groups (placebo, pregabalin 300 mg/d, and pregabalin 600 mg/d), the Applicant compared the results of only the placebo- and "pregabalin"-treated patients. The Applicant preformed this latter comparison on the assumption that exposure (and hence effect) of 600 mg/d in patients with CLcr > 60 mL/min would be the same as that of 300 mg/d in patients with a CLcr ≤ 60 mL/min.

To test this assumption of comparable efficacy of 300 mg/d in patients with a relatively low creatinine clearance, compared to 600 mg/d in patients with a relatively high creatinine clearance, I first divided subjects into treatment groups, based on dose of medication received (0-, 300-, or 600 mg/d). There were 84 patients in the placebo group, 30 patients in the 300 mg/d group, and 59 in the 600 mg/d group.

Using the same BOCF strategy, Dr. Buenconsejo then calculated the mean pain score for the treatment groups at each study week, and at endpoint. In addition, a comparison of the proportion of treatment responders in each group was performed.

Primary efficacy outcome
Mean Pain Score – Weekly and at Endpoint
Assessment of baseline scores by dose group showed that the pregabalin 600 mg/d group had the lowest baseline score (6.13) compared to the 300 mg/d group (6.6) and placebo group (6.43). All of the treatment groups had a decrease in endpoint mean pain score at the redefined endpoint, Week 8. Descriptive statistics suggest that similar decreases in score from baseline to endpoint occurred in the 600 mg/d group (change in score = -1.89) and 300 mg/d group (change = 1.84). These decreases were larger than in the placebo group (change = -1.18).

Mean pain scores improved for all groups as early as Week 1, with greater improvement seen in each of the pregabalin groups. Throughout each week, patients in the 600 mg/d group had lower scores than either the 300 mg/d and placebo groups.

Table 6.3.2.24.a: Reviewer's analysis: Descriptive statistics, mean pain score by study week, BOCF method – Protocol 127

	Placebo N=84	PGB300/600 N=89	PGB 300 N=30	PGB 600 N=59
Baseline[1]	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Week 1	6.01 (1.8)	5.15 (1.8)	5.37 (1.7)	5.04 (1.8)
Week 2	5.80 (1.9)	4.66 (2.0)	5.20 (1.9)	4.39 (2.0)
Week 3	5.64 (2.1)	4.46 (2.2)	5.09 (2.2)	4.14 (2.1)
Week 4	5.60 (2.2)	4.58 (2.2)	5.01 (2.1)	4.36 (2.2)
Week 5	5.48 (2.3)	4.49 (2.3)	4.81 (2.3)	4.33 (2.3)
Week 6	5.49 (2.4)	4.46 (2.2)	4.85 (2.3)	4.26 (2.2)
Week 7	5.44 (2.6)	4.50 (2.3)	4.86 (2.3)	4.31 (2.3)
Week 8[2]	5.20 (2.6)	4.42 (2.4)	4.85 (2.5)	4.21 (2.4)
Endpoint[3]	5.25 (2.5)	4.42 (2.4)	4.76 (2.4)	4.24 (2.4)

[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

ANCOVA of the weekly and endpoint mean pain scores was performed. Treatment, cluster, creatinine clearance stratum, and baseline pain score were included in the analysis. The ANCOVA showed a statistically significant difference between the 600 mg/d and placebo groups in each weekly mean pain score, starting at Week 1. A difference in pain scores between the 300 mg/d and placebo was evident only at Weeks 1 and 2. However, due to the small number of patients in this group, the results for the 300 mg/d group should be interpreted cautiously.

Table 6.3.2.24.b: Reviewer's analysis: ANCOVA, mean pain score by study week (BOCF) – Protocol 127

	Placebo N=84	PGB 300 N=30		PGB 600 N=59	
	Mean (SD)	mean (SD)	P value[1]	mean (SD)	P value[1]
Week 1	5.94 (0.1)	5.26 (0.2)	0.0121	5.27 (0.2)	0.0019
Week 2	5.71 (0.2)	5.00 (0.3)	0.0306	4.56 (0.2)	<0.0001
Week 3	5.54 (0.2)	4.91 (0.3)	0.0999	4.34 (0.2)	<0.0001
Week 4	5.54 (0.2)	4.93 (0.3)	0.1126	4.55 (0.2)	0.0013
Week 5	5.41 (0.2)	4.71 (0.4)	0.1007	4.48 (0.3)	0.0066
Week 6	5.41 (0.2)	4.78 (0.4)	0.1229	4.39 (0.3)	0.0019
Week 7	5.34 (0.2)	4.75 (0.4)	0.1769	4.41 (0.3)	0.0087
Week 8[2]	5.08 (0.2)	4.62 (0.4)	0.3334	4.28 (0.3)	0.0333
Endpoint[3]	5.14 (0.2)	4.61 (0.4)	0.2346	4.36 (0.3)	0.0302

[1] using pair-wise comparison test
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers

Dr. Buenconsejo assessed the sensitivity of the above analyses using other methods to extrapolate for missing data (see Section 6.3.1.25). There was no difference in the endpoint mean pain score results using each of those methods.

To further assess whether pregabalin treatment is associated with an improvement in pain score, Dr. Buenconsejo compared the change in mean pain score from baseline to Week 8 and Endpoint (as defined by the Applicant) for each of the pregabalin groups to that of the placebo group. The pair-wise comparisons of 300 mg/d showed no significant difference from placebo at either Week 8 or Endpoint. However, the change in scores for the 600 mg/d group was significantly greater than for placebo:

Table 6.3.2.24.c: Reviewer's analysis: Change in mean pain scores at Week 8 and Endpoint, ANCOVA[1] (BOCF) – Protocol 127

	Placebo	Pregabalin 300/600	Pregabalin 300	Pregabalin 600
Baseline[2]	6.43 (1.5)	6.29 (1.4)	6.60 (1.4)	6.13 (1.4)
Endpoint[3]	5.25 (2.5)	4.42 (2.4)	4.76 (2.4)	4.24 (2.4)
Change[4]	1.18 (1.9)	1.87 (2.2)	1.84 (2.6)	1.89 (2.1)
LS means	1.21 (0.2)	1.93	1.75 (0.4)	2.00 (0.3)
p-value[5]		0.0137	0.2346	0.0302
Week 8[6]	5.20 (2.6)	4.42 (2.4)	4.85 (2.5)	4.21 (2.4)
Change[7]	1.25 (1.9)	1.85 (2.2)	1.74 (2.6)	1.90 (2.1)
LS means	1.28 (0.2)	1.96	1.73 (0.4)	2.07 (0.3)
p-value[5]		0.0224	0.3334	0.0333

[1] Analysis includes treatment, center, and creatinine clearance strata (for pregabalin 300/600 only group) as fixed effects, with baseline mean pain score as covariate, and the interaction between baseline pain score and treatment.
[2] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline pain score for non-completers
[4] Change= Baseline – Endpoint

[5] Using Dunnett's test of difference from control (placebo)
[6] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[7] Change= Baseline – Week 8

The use of rescue medication and/or prohibited medications was evaluated, given that patients taking these medications could possibly report less pain, compared to patients not taking the medications. Of the 173 patients in the ITT population, 26 patients (14 placebo, 4 in the 300 mg/d group, and 8 in the 600 mg/d group) patients took rescue medication. The majority of patients (n=21) took rescue medications throughout the study, where as 3 subjects took rescue medication from the middle to the end of the study. One patient took rescue medication no more than twice during the middle of the trial, and another patient took rescue medication during the baseline period only.

None of the 26 patients' scores varied from the day before or after rescue medication was taken. Three of the 26 subjects dropped out due to lack efficacy, all 3 of which had taken rescue medication throughout their time in the study. Three other subjects withdrew from the study due to an adverse event, 2 of who also took rescue medication throughout their trial participation.

Based on these findings, it was concluded that the use of rescue medication would not bias the efficacy findings, and no further analyses that incorporated rescue medication as a factor were conducted.

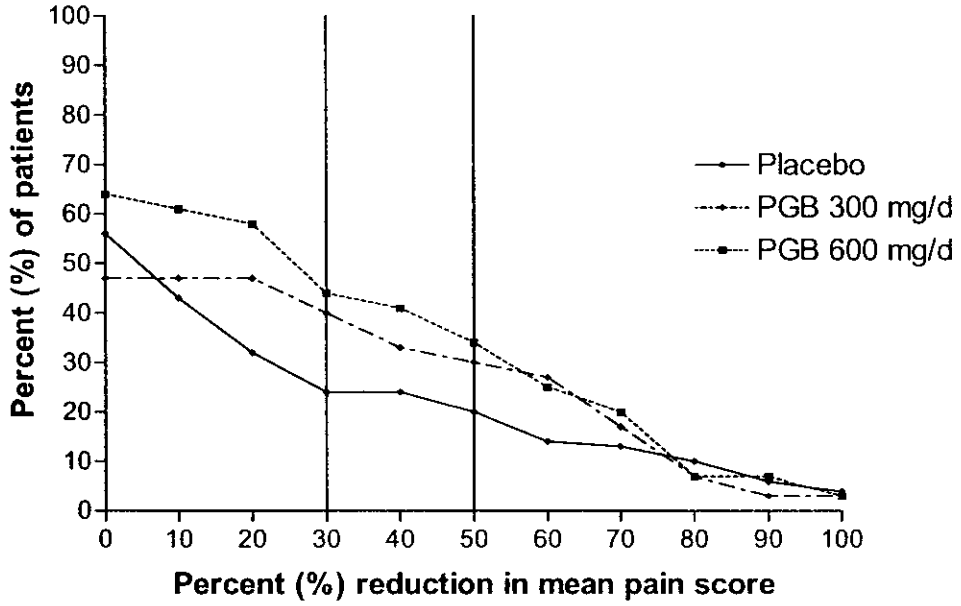
Analysis of responder rates
As another evaluation of the effect of pregabalin on patient's pain, a comparison of the proportions of patients who had a favorable response to treatment (treatment 'responders') was performed using the BOCF data. Responders were defined as patients who had at least a 50% decrease in pan from baseline to Week 8. The proportion of responders in each dose group was also determined for each study week.

Responder rates at Endpoint
The proportions of patients with ≥ 50% decrease in pain score from baseline to Study Endpoint in the pregabalin 300- and 600 mg/d groups were 30% and 34% respectively, compared to 27% of the placebo patients. At lower cut-offs for the definition of treatment response (i.e. < 50% decrease in pain), the pregabalin groups also had higher proportions of responders compared to placebo. At cut-off values of 80-100% decrease in pain, the placebo group had more responders than either of the pregabalin groups.

Table 6.3.2.24..d: Reviewer's Analysis: Percent change in endpoint mean pain score by dose – Protocol 127

	PLACEBO		PGB300		PGB600	
Change in pain	**Total**	**%**	**Total**	**%**	**Total**	**%**
Any increase	16	19.1	3	10.0	3	5.1
None	21	25.0	13	43.3	18	30.5
> 0 % decrease	47	56.0	14	46.7	38	64.4
≥ 10%	36	42.9	14	46.7	36	61.0
≥ 20%	27	32.1	14	46.7	34	57.6
≥ 30%	20	23.8	12	40.0	26	44.1
≥ 40%	20	23.8	10	33.3	24	40.7
≥ 50%	**17**	**20.2**	**9**	**30.0**	**20**	**33.9**
≥ 60%	12	14.3	8	26.7	15	25.4
≥ 70%	11	13.1	5	16.7	12	20.3
≥ 80%	8	9.5	2	6.7	4	6.8
≥ 90%	5	6.0	1	3.3	4	6.8
=100%	3	3.6	1	3.3	2	3.4

Figure 6: Reviewer's Analysis: Response profile at endpoint – Protocol 127



Responder rates at Week 8

There were greater proportions of patients in pregabalin 300- and 600 mg/d groups (33% and 36%, respectively) who had ≥ 50% decrease in pain score from baseline to Week 8 than in the placebo group (24%). This is similar to what was noted when responder rates at Study Endpoint were evaluated (see above). At lower cut-offs for the definition of treatment response (i.e. < 50% decrease in pain), the pregabalin groups again higher proportions of responders compared to placebo, with the highest proportions seen for the pregabalin 600 mg/d group.

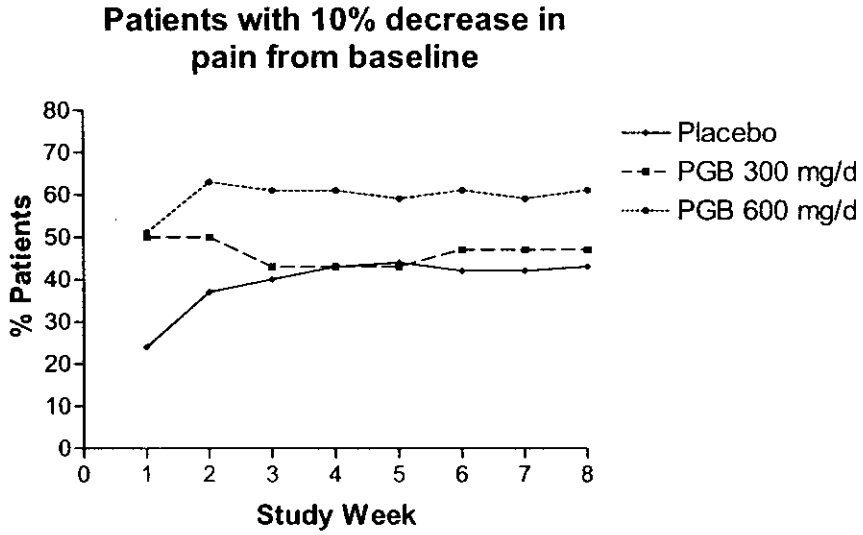
Table 6.3.2.24..e: Reviewer's Analysis: Percent change in Week 8 mean pain score by dose – Protocol 127

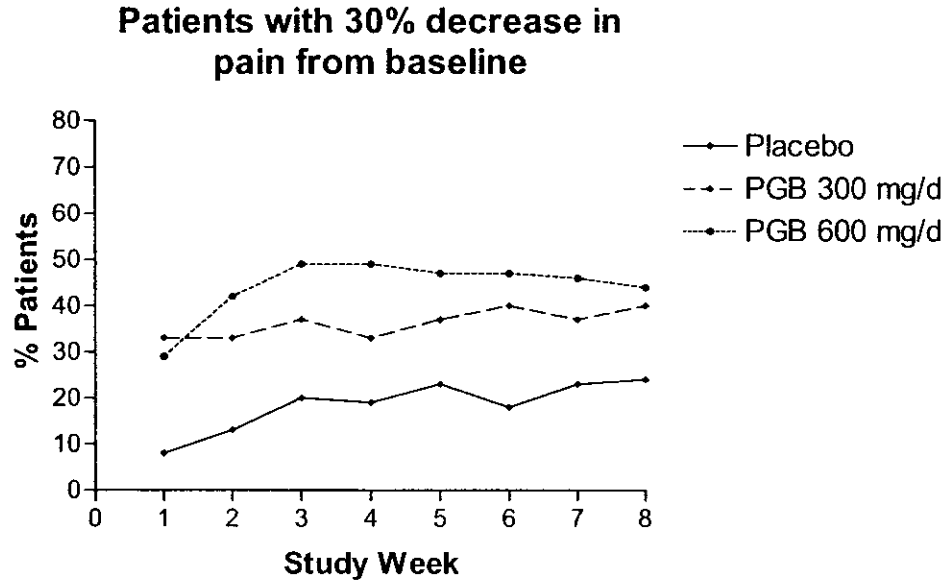
	PLACEBO		PGB300		PGB600	
Change in pain	**Total**	**%**	**Total**	**%**	**Total**	**%**
Any increase	14	17%	2	7%	3	5%
None	18	21%	13	43%	18	31%
> 0 % decrease	52	62%	15	50%	38	64%
≥ 10%	43	51%	14	47%	37	63%
≥ 20%	29	35%	14	47%	35	59%
≥ 30%	24	29%	12	40%	29	49%
≥ 40%	23	27%	10	33%	25	42%
≥ 50%	**20**	**24%**	**10**	**33%**	**21**	**36%**
≥ 60%	17	20%	9	30%	17	29%
≥ 70%	15	18%	7	23%	13	22%
≥ 80%	11	13%	5	17%	6	10%
≥ 90%	10	12%	3	10%	6	10%
=100%	4	5%	1	3%	2	3%

Responder rates at each week separately

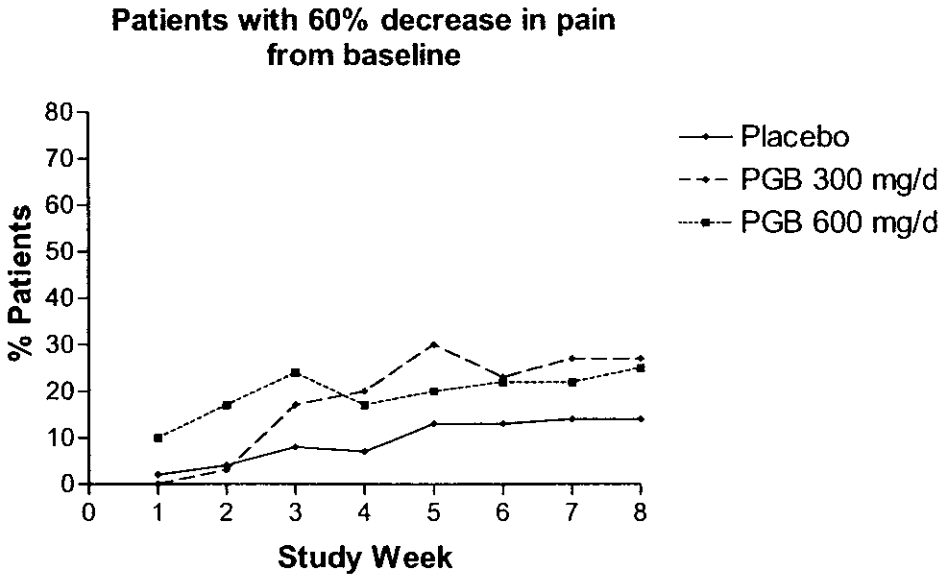
Using definitions (cut-offs) of treatment response that ranged from 10% to 80% reduction in pain, Dr. Buenconsejo compared the proportion of responders at each week. At definitions of treatment response of < 50% decrease in pain, and at each study week, the proportions of responders in the pregabalin groups were greater than in the placebo group (Figure 7). At cut-offs of 50 and 60%, and at each study week, the pregabalin groups had more treatment responders than the placebo group. At a cut-off of 70%, the difference between active and placebo groups was less pronounced, particularly at study weeks 7 and 8. At a cut-off of 80%, the placebo group had at least as many treatment responders, beginning around study week 6 (Figure 8).

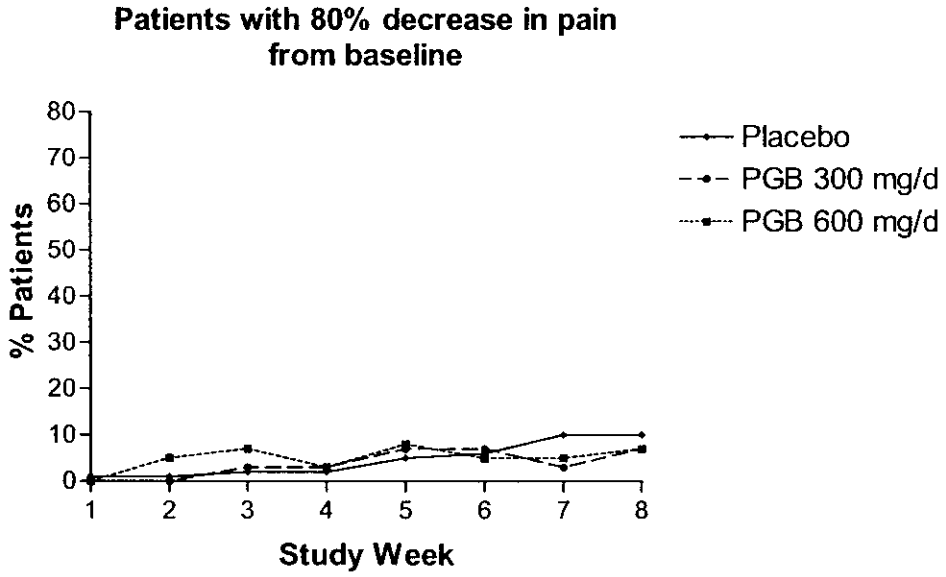
Figures 7 - 8: Patients with < 50% decrease in pain from baseline, by study week – Protocol 127





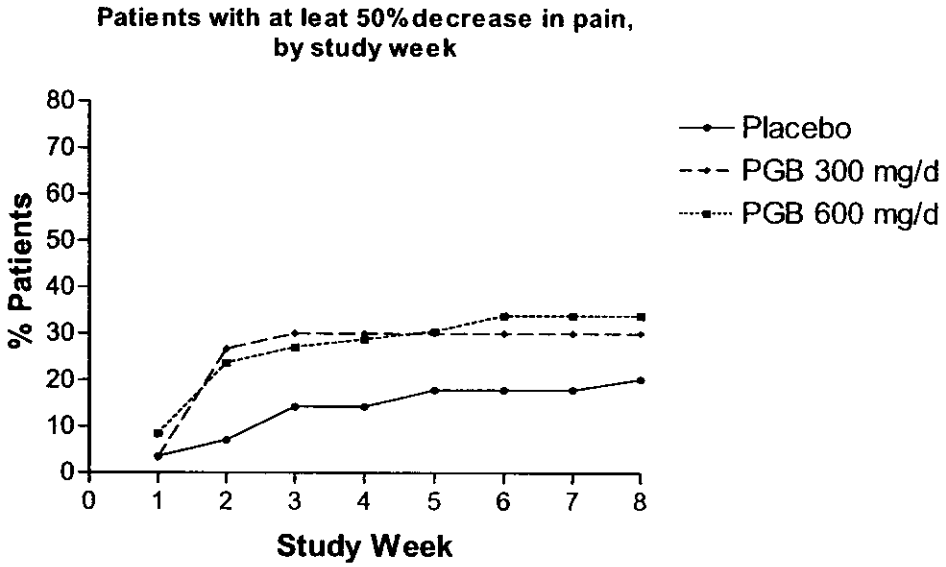
Figures 8-9: Patients with > 50% decrease in pain from baseline, by study week – Protocol 127





A total of 46 patients completed the study and had a 50% reduction in mean pain score at the end of the study. Figure 10 shows the distribution of these patients from the beginning to the end of the study. A difference in treatment response between the pregabalin and placebo groups was most evident at Week 2, and this difference persisted throughout the study. The data suggest that patients who do not respond to treatment with 600 mg/d in Week 2 are likely respond with continued treatment, up until Week 6. The likelihood of treatment response does not increase beyond Week 3 of treatment with pregabalin 300 mg/d. The proportion of treatment responders gradually increased over time for the pregabalin group, and was greatest between Weeks 1-3.

Figure 10: Reviewer's analysis: Proportion of treatment responders (50% decrease in pain), by study week – Protocol 127



6.3.2.25 Conclusions regarding efficacy data – Protocol 1008-127

The Applicant found that treatment with "pregabalin" resulted in a lower mean pain score at study endpoint than did treatment with placebo. After reanalyzing the effects of treatment on mean pain score by actual dose of study medication received (0-, 300-, or 600 mg/d), the Agency found that only treatment with pregabalin 600 mg/d resulted in a statistically significant difference in mean pain score, compared to placebo. However, the number of patients in the 300 mg/d group was small, and therefore there could have been insufficient power to detect a difference from placebo. On evaluation of the proportion of treatment responders across treatment groups, the Agency found that there were considerably more treatment responders in the pregabalin 300- and 600 mg/d groups, and that this difference persisted throughout the study. Also, the proportions of treatment responders in the pregabalin groups were similar. The responder analysis therefore gives some support of possible efficacy of treatment with pregabalin 300 mg/d.

6.3.3 Protocol 1008-196: A 13-week randomized, double-blind, multi-center, placebo-controlled study of pregabalin twice a day (BID) in the treatment of postherpetic neuralgia

6.3.3.1 Objective/Rationale

To evaluate the safety and efficacy of pregabalin (150-, 300-, or 300/600 mg/d) compared with placebo, given BID, for pain relief in patients with postherpetic neuralgia (PHN)

6.3.3.2 Overall design

This Phase 3 study was designed as an international, multi-center, multiple-dose, randomized, double-blind, parallel, 4-arm, placebo-controlled trial

6.3.3.3 Study population and procedures

6.3.3.4 Treatment duration: 13 weeks (1-week titration, 12-week fixed dose period)

6.3.3.5 Entry criteria

The protocol called for enrollment of 352patients (88 patients per treatment arm).

Eligibility criteria were similar to those for Protocol 1008-045 (see Section 6.3.1.5), with the following exceptions:

Inclusion criteria

- Pain ≥ 3 months after the healing of the herpes zoster rash
- Normal chest x-ray within 1 year prior to baseline, or stable x-ray without clinically significant change from the previous exam

Exclusion criteria

- Malignancy within the past 2 years, with the exception of basal cell carcinoma
- History of chronic hepatitis B, or C; *or* hepatitis B or C within the past 3 months; *or* HIV infection

6.3.3.6 Study medications

Study drug was pregabalin capsules containing 0, 75, 150, 200, and 300 mg. All subjects in the pregabalin groups would initially be dosed with 150 mg/d. Subjects in the 300- and 300/600 mg/d arms were to be titrated to the full dose over a 7 day period, with increases to the target dose in 75 to 150 mg increments.

Final Target Dose	**Day 1[a]** AM (mg)/ PM (mg)	**Day 2** AM (mg)/ PM (mg)	**Day 3** AM (mg)/ PM (mg)	**Day 4** AM (mg)/ PM (mg)	**Day 5** AM (mg)/ PM (mg)	**Day 6** AM (mg)/ PM (mg)	**Day 7** AM (mg)/ PM (mg)
Placebo	0/0	0/0	0/0	0/0	0/0	0/0	0/0
150 mg/day	0/75	75/75	75/75	75/75	75/75	75/75	75/75
300 mg/day	0/75	75/75	75/75	75/150	75/150	75/150	150/150
600 mg/day	0/75	75/75	75/150	150/150	200/200	200/300	300/300

[a] On Day 1 patients take 1 capsule in the evening only

Permitted medications were the same as for Protocol 1008-045 (see Section 6.3.3.3), except patients were allowed up to 4 g of acetaminophen per day.

Prohibited medications were the same as for Protocol 1008-045 (see Section 6.3.1.5), except patients were also not allowed to take long-acting benzodiazepines. Also, the washout period for prohibited anti-epileptics and medications commonly used to treat PHN was ≥ 7 days (the washout period was ≥ 14 days for Protocol 045).

6.3.3.7 Study procedures

The protocol specified 6 clinic visits. Visit 1 (V1) would be the screening visit which, and V2 would occur at the end of the 1-week baseline period during which baseline physical, ophthalmologic, and laboratory measurements would be obtained. Also, subjects would complete daily pain and sleep interference diaries. Subjects who completed at least 4 pain diaries and had an average pain score of at least 4 would then be randomized to study drug (placebo or pregabalin) at V2. Patients who were ineligible for randomization (screen failures) were to have the following information collected: demographics; reason for not entering double-blind treatment; and SAEs or withdrawals due to AEs.

Randomization to treatment groups was stratified by creatinine clearance (CLcr). Subjects would be randomized to the placebo, 150-, 300- or 300/600 mg/d treatment arms. The target dose for patients randomized to the 300/600 mg/d arm was to be dependent on creatinine clearance (CLcr). Patients with a CLcr >60 mL/min would be treated with 600 mg/d, whereas patients with a CLcr between 30 and 60 mL/min would take 300 mg/d. For patients in the 300- and 300/600 mg/d groups, study drug would be increased to the target dose over a 1 week period (as described above). One week after initiating study drug, patients would attend V3. Patients unable to maintain the target dose were withdrawn from the study.

Following V3, patients would be assessed in the clinic at 3-5 week intervals (V4, 5, and 6). Additionally, telephone contact would be made with the patients at least once between each visit to verify treatment compliance and ascertain if any AEs had occurred. During clinic visits patients would be evaluated for pain, sleep quality, laboratory changes, physical status, and any adverse effects. AT V6/Termination, additional assessments including ophthalmology exam, quality of life, mood, and overall improvement would be made. Subjects not continuing in the open-label extension study Protocol 1008-198 would attend safety follow-up visit at Study Week 14 (V7/FU).

Table 6.3.3.7: Time and Events Schedule: Protocol 1008-196

	Baseline (1 Week)	Double-Blind Treatment (12 Weeks)					FU (1 Week)
		Titration		Fixed dose			
End of Study Week:	Screening	Random	1	4	8	13	14
Study Day:	-8	1	8	29	57	92	99
Clinic Visit:[a]	1	2	3	4	5	6/Term[b]	7/FU[c]
Informed Consent	X[d]						
Inclusion/Exclusion	X	X					
Medical History	X						
Physical Exam Incl Edema Assessment	X		X[e]	X[e]	X[e]	X	
Abbreviated Neurological Exam	X					X	
SF-McGill Pain Questionnaire	X	X	X	X	X	X	
Daily Diaries (Pain, Sleep)	X	X	X	X	X	X	
Global Imp of Change (Clinical & Patient)						X	
MOS Sleep Scale		X				X	
SF-36		X				X	
EQ-5D		X	X[f]	X[f]	X[f]	X	
Adverse Events		X	X	X	X	X	X
Prior and Concurrent Medications	X	X	X	X	X	X	X
Study Medication Dosing/Dispensing		X	X	X	X		
Hematology/Chemistry/Urinalysis	X[g]			X		X[g]	
Pregnancy Test (Serum)	X			X		X	
12-Lead ECG	X					X	
Ophthalmologic Assessment[h]	X						
Patient Status — End of Baseline		X					
Patient Status — End of Double-blind Treatment Phase						X	
Chest X-Ray	X[i]						

[a] Telephone contact will be made with the patients at least once between each visit beginning after V2/Randomization and continuing until V6/Termination to ensure compliance with pain/sleep diaries and to assess adverse events.
[b] Whenever patient withdraws from or completes the study
[c] V7/Follow-up is only performed for patients not entering open-label Study 1008-198.
[d] At V1 or prior to washout of previous analgesics if applicable
[e] Vitals including weight and edema assessment
[f] VAS section only
[g] Estimated creatinine clearance is calculated at V1. Fasting lipid profiles are measured at V1 and V6/Termination only (if patient is not fasting at V1, the lipid profile should be measured at V2, before drug administration).
[h] Examination/testing by an ophthalmologist, as detailed in Appendix C
[i] Chest x-ray must be taken at baseline visit if none available in the 1 year prior to baseline.

(Applicant's Appendix A.1, RR 720-30191, 1008-196, P. 906)

6.3.3.8 Efficacy parameters

These were the same as for Protocol 045, except the Zung Self-Rating Depression Scale was not used. Additional efficacy measures were the

- *Medical Outcomes Study (MOS)-Sleep Scale:* 12-item questionnaire assessing various constructs of sleep including snoring, somnolence, sleep disturbance, optimal sleep, sleep adequacy, quantity of sleep, and awaken short of breath or with headache
- *EuroQOL Health State Profile (EQ-5D):* A questionnaire assessing 5 domains reflective of a patient's quality of life: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. It also includes a VAS that rates patients' current health state (where 0=worst health, and 100=best health)

6.3.3.9 Statistical Analysis

Patient population

Data would be analyzed for the ITT population only (i.e. all randomized patients who took at least 1 dose of study medication).

Primary efficacy outcome

Similar to Protocol 1008-045 (see Section 6.3.1.9), the primary efficacy parameter was the weekly mean pain score (the average of the last 7 pain scores), and the primary efficacy outcome

was the endpoint weekly mean pain score, where the "endpoint" was the last 7 pain diary entries while the patient was on study medication.

The primary analysis would compare the final weekly mean pain score between the each of the pregabalin and placebo groups using analysis of covariance (ANCOVA) with treatment, center cluster, and creatinine clearance strata in the model and the baseline mean pain score as covariate. The p-values from these 3 comparisons were to be ranked from largest to smallest. If the largest (i.e., least significant) of the p-values were less than 0.05 then all comparisons would be declared significant at the overall Type I error level of 0.05. Otherwise, if the next largest p-value were less than (0.05)/2 = 0.025, only the remaining 2 comparisons would be declared significant. Failing that, the final comparison would be considered significant if the smallest p-value is less than (0.05)/3 = 0.0167.

The study was to be considered positive if efficacy of at least 1 pregabalin group versus placebo were demonstrated with regards to the primary efficacy parameter.

Supplemental analyses of the primary efficacy outcome

- Comparison of the proportion of responders in each pregabalin group compared to the placebo group
- Comparison of endpoint mean pain scores of patients with expected plasma concentrations of pregabalin to the scores of those who received placebo.

  Patients with low creatinine clearance (between 30 and 60 mL/min) who received pregabalin 150 mg/day would be pooled with patients with creatinine clearance >60mL/min who received pregabalin 300 mg/day. These patients would form the 300 mg/day "adjusted dose" group. Likewise, the 600 mg/day adjusted dose group would consist of patients with low creatinine clearance who received pregabalin 300 mg/day and patients with creatinine clearance >60mL/min who received pregabalin 600 mg/day.

- Week 8 mean pain score (the mean of the last 7 available diary entries while on study medication)
- Mixed model repeated measures analysis using all available weekly mean pain scores as the response

Secondary efficacy outcomes

These would be the same as for Protocol 1008-045 except that endpoints would include:

- SF-MPQ (sensory, affective, VAS, PPI, and total scores) at weeks 1, 4, 8, 13, and the last observation for each score
- EQ-5D (index value and VAS AUC score), change from baseline to endpoint
- MOS, change from baseline to endpoint

No adjustments would be made for testing multiple parameters with the secondary and supplemental analyses. Instead, interpretation of the results would be based on the pattern of significant differences.

Interim analyses
No interim analyses were planned.

6.3.3.10 Protocol amendments
Pfizer reports one protocol amendment and 8 addenda. One of the addenda (Addendum F) was, in actuality, a protocol amendment and is described below (Amendment 2):

Amendment 1
November 9, 2001
Baseline and follow-up ophthalmologic assessments were removed from the protocol for all sites except those in Germany and France. Investigators in these two countries requested that the assessments continue to be performed. This amendment updated Appendix D and deleted Appendix G of the protocol.

Amendment 2
February 14, 2002
Baseline, Visit 4, and Visit 6/Termination clinic assessments would include the following laboratory tests:
- platelet associated VEGF (vascular endothelial growth factor)/PDGF (platelet-derived growth factor
- Platelet ultrastructure determination
- Urine bFGF (basic fibroblast growth factor)

This amendment affected only the German study sites.

Addenda
- Addenda A, D, and E (August 6, October 22, and November 13 2001): A baseline chest x-ray was not required, if one was not available at screening (All German sites; sites 106, 109, and 116 in the UK; site 902 in Austria, and site 410 in the Netherlands)
- Addendum B (August 7 2001): Pregnancy tests were to be done each month (Austrian sites only)
- Addendum C (September 21 2001): Patients with long-term benzodiazepine use (> 3 months) were to be excluded from the protocol (UK sites only, per the Multi-Research Ethics Committee requirements)
- Addendum G (March 26 2002): updated Appendix D and deleted Appendix G of the protocol (affected German sites only)

These protocol addenda are should not have an effect on the primary efficacy outcome.

6.3.3.11 Study outcome

6.3.3.12 Subject characteristics
The trial was initiated on November 9 2001 and was completed on October 30 2002. A total of 76 centers in Europe and Australia participated in the study.

6.3.3.13 Enrollment by Center

In the table below, the number of patients randomized at each center is listed:

Table 6.3.3.13: Enrollment by center – Protocol 196

No. Patients Randomized per Center	Center Number
1	113, 114, 120, 205, 206, 207, 308, 403, 657, 701, 706, 707, 712
2	111, 128, 208, 301, 305, 316, 321, 405, 501, 502, 503, 506, 702, 705, 710, 803, 808, 902
3	002, 101, 106, 107, 110, 116, 409, 650, 651, 804, 809, 901
4	012, 105, 108, 118, 119, 125, 303, 307
5	115, 202, 306
6	006, 112, 127, 323
7	008, 658407, 810
8	103
9	005, 121, 904
10	123, 402
11	007
12	010, 011
15	109
19	410
23	655
26	408

(Adapted from Applicant's Table 1, RR 720-30191, 1008-196, P. 36-37)

6.3.3.14 Protocol violations

Altogether, there were 105 patients with protocol violations. Pfizer sub-divided the violations as "eligibility exceptions" (n = 9), "protocol deviations" (n = 40) and "protocol violations" (n = 56). The specific types of violations are detailed below:

Table 6.3.3.14: Protocol violations – Protocol 196

		Number of Patients*			
Violation	**Total**	**Placebo**	**150 mg/d**	**300 mg/d**	**300/600 mg/d**
Eligibility exception (n = 9)					
Malignancy within 2 years	1	-	-	1	-
Use of prohibited medications	4	-	1	3	-
Clinically significant, but stable, respiratory disease	1	-	1	-	-
Abnormal ECG	1	-	-	-	1
No baseline chest x-ray	3	-	2	-	1
Protocol deviations (n = 40)					
Prohibited medication, without washout	17	5	3	4	5
PHN < 3 months	4	2	1	-	1
Unstable dosing of allowable medication	10	0	3	4	3
Use of prohibited medication	4	1	-	1	3
Incorrect dose for 1st six days (partial blind break)	2	-	1	1	-
Abnormal ECG	2	1	1	-	-
Lack of compliance	2	1	-	1	-
Continued malignancy	1	-	-	1	-

Table 6.3.3.14: Protocol violations – Protocol 196 (continued)

Violation	Total	Placebo	Number of Patients* 150 mg/d	300 mg/d	300/600 mg/d
Protocol violations (n = 56)					
Unstable dosing of allowable medication	29	6	6	7	10
Prohibited medication, without washout	8	2	1	3	2

Violation	Total	Placebo	Number of Patients* 150 mg/d	300 mg/d	300/600 mg/d
Baseline mean pain score < 4	9	2	4	2	1
Baseline VAS < 40 mm	3	-	1	1	1
VAS at randomization < 40 mm	3	1	2	-	-
Randomization to incorrect CLcr stratum	8	3	1	1	3
Prohibited medication	5	2	2	1	-
Abnormal ECG	1	1	-	-	-
PHN < 3 months	1	-	1	-	-
Incorrect dose of drug from Visit 5 to end of study	1	1	-	-	-

* Some patients had more than one violation, deviation, or eligibility exception
(Adapted from Applicant's Sections 9.3.1, 9.3.2.1, and 9.3.2.2, RR 720-30191, 1008-196, P. 400-406)

In my opinion, the protocol violations that could impact the primary efficacy outcome are:

- Use of prohibited medications, unstable dosing of allowable mediations – patients taking these medications could experience reduced pain as an effect of these medications, and not necessarily as an effect of study drug.
  However, there were approximately equal numbers of patients with these violations across all treatment arms, so the bias was evenly distributed.
- Randomization to the incorrect CLcr stratum – this violation is of greatest relevance for the pregabalin 300/600 mg arm, where doses would differ depending on the patient's renal function.
  However, the numbers of patients in this treatment arm who were incorrectly randomized is relatively small, and so the effect of this violation is not expected to be considerable.
- Low mean pain and VAS scores (< 4 and 40 mm, respectively) at baseline/randomization – a small improvement in pain as a result of study treatment would not be easy to detect in patients who do not have significant pain at study initiation.
  However, the numbers of patients with this violation are small and relatively evenly distributed across treatment groups.
- PHN duration < 3 months – these patients did not strictly meet criteria for a diagnosis of PHN. However, their duration of disease closely approximated 3 months, and therefore they were allowed to participate in the study. The small number of patients with this violation is not expected to significantly impact the study results.

6.3.3.15 Blinding

Pfizer broke the study blind for the following 4 patients:

- *Patient 011008*: Patient experienced an SAE of an anaphylactoid reaction. The patient had been treated with pregabalin 300 mg/d for 10 days.

- *Patient 206601*: This patient was hospitalized for facial and peripheral edema, dizziness, myasthenia, and somnolence on Study Day 16. The patient was taking pregabalin 300 mg/d and this was discontinued when he was hospitalized.
- *Patients 409003 and 409004*: The blind was partially broken due to an error in randomization to treatment arm. The 2 patients were dispensed the wrong medication on Study Day 1 due to an inversion of the medications by the hospital pharmacist. The error was discovered 5 study days after both patients had received the incorrect medication. The 2 patients had been stratified to different CLcr strata (Patient 409003 was included in the low CLcr strata and Patient 409004 included in the normal CLcr strata). The blind for the 2 patients was broken by the pharmacist, at the request of the investigator, because of the potential risk for the low CLcr patient. The pharmacist did not reveal the code to the investigator at this time and only indicated that the patients were randomized to receive different medications. Both patients were returned to their correct medication 6 study days after the error occurred.

6.3.3.16 Subject disposition

There were 435 patients who entered the baseline phase. Of these, 370 (85%) completed the phase. Reasons for withdrawal of the other 65 patients during baseline were: not meeting eligibility criteria (n = 48), adverse event (n = 1), and "other" (n = 16).

A total of 370 patients were randomized to study drug, but only 368 took at least one dose of study medication (the ITT population). There were 93 patients in the placebo group, 87 in the pregabalin 150 mg/d group, 98 in the 300 mg/d group, and 91 in the 300/600 mg/d group. Overall, 126 patients withdrew from the study during the treatment phase. Withdrawal due to lack of efficacy was greatest for the placebo group (24%). Lack of efficacy was also the most frequently reported reason for withdrawal among patients in the 150 m/d groups (18%). Comparable proportions of patients in the 300 mg/d group withdrew for lack of efficacy (13%) and adverse events (15%). Most patients (21%) in the pregabalin 300/600 mg/d group withdrew due to adverse events.

Table 6.3.3.16: Patient disposition – Protocol 196

Disposition N (%)	Placebo	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 300/600 mg/day	All Patients
Entered Baseline Phase					435
Completed Baseline Phase					370 (85.1)
Withdrawn During Baseline Phase[a]:					65 (14.9)
Adverse Event					1 (0.2)
Did Not Meet Criteria					48 (11.0)
Other					16 (3.7)
Entered Double-Blind (Randomized)	94	87	98	91	370
Intent-to-Treat Patients	93	87	98	90	368
Withdrawn During Treatment Phase:	34 (36.6)	26 (29.9)	36 (36.7)	30 (33.3)	126 (34.2)
Adverse Event	5 (5.4)	7 (8.0)	15 (15.3)	19 (21.1)	46 (12.5)
Lack of Compliance	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.1)	2 (0.5)
Lack of Efficacy	22 (23.7)	16 (18.4)	13 (13.3)	6 (6.7)	57 (15.5)
Other/Administrative	7 (7.5)	3 (3.4)	7 (7.1)	4 (4.4)	21 (5.7)
Completed Study	59 (63.4)	61 (70.1)	62 (63.3)	60 (66.7)	242 (65.8)
Entered Open Label (1008-198)	74 (79.6)	68 (78.2)	70 (71.4)	63 (70.0)	275 (74.7)

[a] The denominator for percentages of "Withdrawn during baseline" category and sub-categories is the number of patient entered in Baseline; the denominator for all other percentages is, respectively, for each column the number of ITT patients.

(Applicant's Table 10, RR 720-30191, 1008-196, P. 71)

6.3.3.17 Extent of exposure/Dosing information

Pfizer found that, of the 368 patients in the ITT population, 201 (54.6%) completed at least 13 weeks of treatment with study medication. This number is different from the 242 (66%) the Applicant identified as having completed the study. Pfizer does not provide an explanation for this, but I assume that the discrepancy is due to the same reason as the discrepancy in the other two protocols: completion of the study was determined independently of the number of weeks a patient was exposed to study medication. Due to scheduling of clinic visits, patients may have completed the trial earlier than Day 91, resulting in exposure of < 13 weeks.

Pfizer found that approximately 53% of placebo patients and 55% of pregabalin patients had ≥ 13 weeks of drug exposure. Also, 72% of patients in both the placebo and combined pregabalin groups took study drug for at least 8 weeks. Over the duration of the study, drug exposure was comparable across the 4 treatment arms.

Table 6.3.3.17.a: Applicant's analysis: Patient exposure to study medication – Protocol 196

Total exposure time	Number and % of Patients									
	Placebo		Pregabalin							
			150 mg/d		300 mg/d		300/600 mg/d		All Pregabalin	
	[N=93]		[N=87]		[N=98]		[n=90]		[n+275]	
≥1 Day	93	(100.0)	87	(100.0)	98	(100.0)	90	(100.0)	275	(100.0)
≥1 Week	92	(98.9)	87	(100.0)	96	(98.0)	87	(96.7)	270	(98.2)
≥2 Weeks	88	(94.6)	83	(95.4)	92	(93.9)	81	(90.0)	256	(93.1)
≥3 Weeks	87	(93.5)	83	(95.4)	88	(89.8)	79	(87.8)	250	(90.9)
≥4 Weeks	84	(90.3)	80	(92.0)	84	(85.7)	75	(83.3)	239	(86.9)
≥5 Weeks	71	(76.3)	70	(80.5)	72	(73.5)	68	(75.6)	210	(76.4)
≥6 Weeks	69	(74.2)	66	(75.9)	71	(72.4)	66	(73.3)	203	(73.8)
≥7 Weeks	68	(73.1)	65	(74.7)	69	(70.4)	66	(73.3)	200	(72.7)
≥8 Weeks	67	(72.0)	65	(74.7)	69	(70.4)	64	(71.1)	198	(72.0)
≥9 Weeks	64	(68.8)	63	(72.4)	65	(66.3)	64	(71.1)	192	(69.8)
≥10 Weeks	61	(65.6)	62	(71.3)	62	(63.3)	63	(70.0)	187	(68.0)
≥11 Weeks	61	(65.6)	61	(70.1)	62	(63.3)	62	(68.9)	185	(67.3)
≥12 Weeks	60	(64.5)	60	(69.0)	60	(61.2)	59	(65.6)	179	(65.1)
≥13 Weeks	49	(52.7)	55	(63.2)	45	(45.9)	52	(57.8)	152	(55.3)
≥14 Weeks	9	(9.7)	4	(4.6)	8	(8.2)	5	(5.6)	17	(6.2)
≥15 Weeks	2	(2.2)	0	(0.0)	0	(0.0)	2	(2.2)	2	(0.7)

[a] Study days on which patient received zero dose during the study are included in the summary of patient exposure to study medication
(Applicant's Table 34, RR 720-30191, 1008-196, P. 116)

I tabulated the number of patients in each treatment group, based on actual dose of study medication received (0-, 150, 300, or 600 mg/d)., and not by treatment arm (as Pfizer did)., I first identified which patients in each treatment arm had a "normal" creatinine clearance (> 60 mL/min) or a "low" creatinine clearance (between 30 and 60 mL/min). For subjects in the 300/600 mg/d treatment arm, those subjects with a "low" creatinine clearance considered to have been treated with 300 mg/d. The subjects in that group with a "normal" creatinine clearance were treated with 600 mg/d.

Table 6.3.3.17.b shows, for the 370 patients who were randomized into the study, the actual dose of study medication received, based on creatinine clearance. As already described, 2 subjects did not take any study medication. Therefore, there were 368 patients in the ITT population.

Table 6.3.3.17.b: Reviewer's analysis: Dose of medication received, based on CLcr (Randomized population) – Protocol 196

	Assigned Treatment Group							
	Placebo [N = 93]		150 mg/d Pregabalin [N = 88]		300 mg/d Pregabalin [N = 99]		300/600 mg/d Pregabalin [N = 90]	
Creatinine clearance	Normal	Low	Normal	Low	Normal	Low	Normal	Low
Actual dose received (mg/d)	Placebo	Placebo	150	150	300	300	600	300
N	59	34	63	25	66	33	63	27

Pfizer also tabulated the number of patients within each treatment group that had a low or high creatinine clearance:

Table 6.3.3.17.c: Applicant's analysis: Dose of medication received, based on CLcr (Randomized population) – Protocol 196

Estimated Creatinine Clearance at Baseline	Placebo (N=93)		Pregabalin 150 mg/day (N=87)		Pregabalin 300 mg/day (N=98)		Pregabalin 300/600 mg/day (N=90)	
(mL/min)	Low	Normal	Low	Normal	Low	Normal	Low	Normal
N	31	62	26	61	33	65	26	64
Mean (STD)	50.0 (7.9)	90.2 (30.6)	51.5 (7.8)	84.1 (17.1)	50.0 (7.6)	88.2 (22.7)	49.9 (9.0)	87.1 (22.6)
Median	53	83.5	53	82	50	85	51.5	79.5
Range	32 to 60	44 to 229	36 to 71	61 to 126	37 to 69	61 to 201	33 to 62	47 to 152

[a] Creatinine clearance (CLcr) stratum was 'Normal' for patients with CLcr >60 mL/min, and 'Low' for patients with CLcr >30 and ≤60 mL/min.

(Applicant's Table 12, RR 30191, 1008-196, P. 77)

Whereas I found 88 and 99 in the randomized pregabalin 150- and 300-mg/d groups respectively, Pfizer noted 87 and 88 patients in the ITT population. After removing those 2 randomized patients who were not dosed with any study medication, my total number of patients in the 150- and 300 mg/d treatment arms are the same as Pfizer's. However, whereas I noted only 63 patients in the 300/600 mg/d group who had a normal CLcr, Pfizer counted 64 patients. It appears therefore that 1 patient with a normal CLcr was incorrectly dosed with pregabalin 300 mg/d. Similarly, with respect to the 150 mg/d group, Pfizer appears to have included one patient with normal CLcr in the "low" CLcr group.

Pfizer explained these discrepancies as follows: per the protocol, randomization was supposed to occur by stratification based on baseline CLcr. Patients with CLcr > were to randomized to a number between 1-1800, and patients with a CLcr ≤ 60 were to be randomized to a number between 2001 and 4000. However, there were 8 patients who were randomized to the incorrect CLcr stratum. Table 6.3.3.17.c therefore reflects the actual stratum to which patients were assigned. Pfizer correctly noted that the randomization errors would have no impact on the dose that patients in the 150- and 300-mg/d groups received. However, the error did affect the 3 patients in the 300/600 mg/d group who were incorrectly randomized.

6.3.3.18 Demographics

Per Pfizer's calculations, approximately 99% of the trial participants were white, and 54% were women. The mean age of the total population was 71 (± 10.6) years, with a range of 18 to 92 years. Most patients (76%) were aged ≥ 65 years. The pregabalin 300 mg/d group had the most males (55%), otherwise there were no considerable differences among the treatment arms with respect to race, age, weight or height. Also, the mean CLcr was relatively similar across treatment groups (approximately 75 mL/min). However, the placebo and pregabalin 300 mg/d groups had slightly more patients (about 33%)with a low CLcr compared to the other groups (approximately 30% of patients).

Table 6.3.3.18.a : Summary of patient characteristics – Protocol 196

		Placebo	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 300/600 mg/day	Any Pregabalin	All Patients
		N = 93	N = 87	N = 98	N = 90	N = 275	N = 368
Gender, N (%)		93	87	98	90	275	368
Male	n (%)	40 (43.0)	36 (41.4)	54 (55.1)	38 (42.2)	128 (46.5)	168 (45.7)
Female	n (%)	53 (57.0)	51 (58.6)	44 (44.9)	52 (57.8)	147 (53.5)	200 (54.3)
Premenopausal	n (%)	1 (1.9)	2 (3.9)	2 (4.5)	4 (7.7)	8 (5.4)	9 (4.5)
Postmenopausal	n (%)	52 (98.1)	49 (96.1)	42 (95.5)	48 (92.3)	139 (94.6)	191 (95.5)
Race, N (%)		93	87	98	90	275	368
White	n (%)	92 (98.9)	86 (98.9)	98 (100.0)	88 (97.8)	272 (98.9)	364 (98.9)
Black	n (%)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.1)	2 (0.7)	2 (0.5)
Other	n (%)	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.4)	2 (0.5)
Age Categories		93	87	98	90	275	368
18 to 64 Years	n (%)	20 (21.5)	20 (23.0)	25 (25.5)	23 (25.6)	68 (24.7)	88 (23.9)
≥65	n (%)	73 (78.5)	67 (77.0)	73 (74.5)	67 (74.4)	207 (75.3)	280 (76.1)
Age (Years)	n	93	87	98	90	275	368
	Mean	70.9	70.5	70.7	70.7	70.6	70.7
	(SD)	(10.4)	(9.3)	(11.9)	(10.6)	(10.7)	(10.6)
	Median	72.0	73.0	73.0	72.5	73.0	73.0
	Min, Max	42 to 89	38 to 88	18 to 92	38 to 90	18 to 92	18 to 92

(Applicant's Table 11, RR 720-30191, 1008-196, P. 75)

Table 6.3.3.18.b : Summary of patient characteristics – Protocol 196

		Placebo	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 300/600 mg/day	Any Pregabalin	All Patients
		N = 93	N = 87	N = 98	N = 90	N = 275	N = 368
Weight (kg)	n	93	87	98	90	275	368
	Mean	73.03	72.27	73.72	72.71	72.93	72.96
	(SD)	(15.95)	(14.72)	(14.07)	(14.72)	(14.45)	(14.82)
	Median	72.00	72.00	74.35	71.45	72.00	72.00
	Min, Max	36.0 to 154.0	44.8 to 111.1	45.0 to 111.0	44.5 to 105.8	44.5 to 111.1	36.0 to 154.0
Height (cm)	n	92	87	98	89	274	366
	Mean	164.24	163.70	167.39	164.83	165.39	165.10
	(SD)	(9.33)	(9.98)	(9.98)	(11.19)	(10.47)	(10.19)
	Median	164	164	168	162.3	164.75	164
	Min, Max	143.0 to 186.0	135.0 to 188.0	141.0 to 192.0	141.0 to 194.0	135.0 to 194.0	135.0 to 194.0
Estimated Baseline CLcr (mL/min)	n	93	87	98	90	275	368
	Mean	76.80	74.34	75.33	76.34	75.35	75.71
	(SD)	(31.68)	(21.13)	(26.26)	(25.90)	(24.55)	(26.50)
	Median	68.00	71.00	70.50	72.50	71.00	71.00
	Min, Max	[illegible]					1
CLcr Stratum	n	93	87	98	90	275	368
Low (30-60 mL/min)	n (%)	31 (33.3)	26 (29.9)	33 (33.7)	26 (28.9)	85 (30.9)	116 (31.5)
Normal (>60 mL/min)	n (%)	62 (66.7)	61 (70.1)	65 (66.3)	64 (71.1)	190 (69.1)	252 (68.5)

(Applicant's Table 11, RR 720-30191, 1008-196, P. 76)

Postherpetic neuralgia history

Pfizer found that the pregabalin 300 mg/d group had the longest mean duration of PHN (48 months) and the pregabalin 300/600 group had the shortest duration (34 months). The thoracic, trigeminal, cervical, and lumbar dermatomal regions were the most commonly affected in each of the treatment arms. The pregabalin 150 mg/d group had the lowest baseline mean pain score

(6.4) and the placebo group had the highest (6.8). Baseline mean pain scores for the other two treatment groups were approximately 6.7. The potential effect of the baseline mean pain score on the primary efficacy outcome is controlled for in the Applicant's ANCOVA.

Table 6.3.3.18.c : Summary of postherpetic neuralgia history (ITT population) – Protocol 196

	Placebo (N = 93)	Pregabalin 150 mg/day (N = 87)	Pregabalin 300 mg/day (N = 98)	Pregabalin 300/600 mg/day (N = 90)	All Patients (N = 368)
Duration of Postherpetic Neuralgia (months)					
N	93	87	98	90	368
Mean (SD)	43.4 (44.8)	36.3 (43.1)	48.2 (53.1)	34.1 (37.3)	40.7 (45.3)
Median	31	22	29	22.5	27
Range	2 to 263	2 to 224	3 to 262	2 to 180	2 to 263
Predominantly-Affected Dermatomal Region, N(%)					
Trigeminal	26 (28.0)	21 (24.1)	29 (29.6)	25 (27.8)	101 (27.4)
Cervical	10 (10.8)	13 (14.9)	9 (9.2)	9 (10.0)	41 (11.1)
Thoracic	45 (48.4)	39 (44.8)	45 (45.9)	42 (46.7)	171 (46.5)
Lumbar	10 (10.8)	10 (11.5)	11 (11.2)	10 (11.1)	41 (11.1)
Sacral	2 (2.2)	4 (4.6)	4 (4.1)	4 (4.4)	14 (3.8)
Baseline Mean Pain Score					
N	93	87	98	90	368
Mean (SD)	6.85 (1.49)	6.44 (1.58)	6.72 (1.41)	6.65 (1.44)	6.67 (1.48)
Median	7	6.57	6.93	6.71	6.79
Range	1.71 to 10.00	2.57 to 10.00	3.71 to 9.71	3.86 to 10.00	1.71 to 10.00

(Applicant's Table 13, RR 720-30191, 1008-196, P. 79)

Dr. Buenconsejo calculated the mean baseline pain score for:

- patients in the placebo group,
- patients with a low CLcr who took 150- or 300 mg/d,
- patients with a normal CLcr who took 300 mg/d, and
- patients with a normal CLcr who were treated with 600 mg/d.

She based her calculations on the stratum to which patients were randomized, not the patients' actual CLcr.

Table 6.3.3.18.d : Reviewer's Analysis: Summary of baseline mean pain score (ITT population) – Protocol 196

	Placebo	Pregabalin 150 mg/d		Pregabalin 300 mg/d		Pregabalin 600 mg/d
		Low[1]	Normal[2]	Low[1]	Normal[2]	Normal[2]
N	93	26	61	59	65	64
Mean (SD)	6.85 (1.49)	6.77 (1.72)	6.30 (1.51)	6.84 (1.42)	6.60 (1.44)	6.64 (1.42)
Median	7.0	7.0	6.29	7.0	6.86	6.66
Range	1.7 – 10.0	3.14 – 10.0	2.57 – 10.0	4.14 – 9.71	3.71 – 9.14	3.86 – 10.0

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

The table above shows that baseline mean pain scores were variable across groups. Patients in the pregabalin 150 mg/d group with a normal CLcr had the lowest baseline pain score (6.3), and patients in the placebo group had the highest score (6.8). This difference in baseline pain score could considerably affect the primary efficacy outcome. However, as noted above, the potential effect of the baseline mean pain score on the primary efficacy outcome is controlled for in the ANCOVA.

Concomitant medications
Prior (within the previous 30 days) and concurrent medications were used by 83% of the randomized patients. Of these patients, the most frequently used medication was acetylsalicylic acid (by 16% of patients). Concurrent medications were used by 305 of the 368 ITT patients (83%).

Pfizer found that, among the ITT population, 194 patients (53%) reported concurrent use of neuropathic pain medications. The 3 most frequently used medications for neuropathic pain were acetaminophen (85 patients, 23%), amitriptyline (44 patients, 12%), and tramadol (22 patients, 6%). Of the 85 patients who took acetaminophen, 22 patients (24%) were in the placebo group, 19 patients (22%) were in the 150 mg/day group, 19 patients (19%) were in the 300 mg/day group, and 25 patients (28%) were in the 300/600 mg/day group.

The frequency of use of these medications was approximately equally distributed across treatment groups. Therefore the potential bias on the primary efficacy outcome is equaled out.

Eighty-seven patients (24%) reported prior (within 30 days) and/or concurrent use of diuretic medications. The most frequently taken diuretic medications included furosemide (28 patients, 8 %), bendroflumethiazide (13 patients, 4%), and hydrochlorothiazide (12 patients, 3%).

The use of diuretic medications should impact only the interpretation of the incidence of any edema-related adverse effects of study drug, and not the primary efficacy outcome.

6.3.3.19 Applicant's efficacy results

6.3.3.20 Overview

Pfizer found that the mean pain score at endpoint was significantly lower for all pregabalin treatment arms (150-, 300-, and 300/600 mg/d) than for the placebo group. A significant difference in mean pain score from placebo was also noted for groups of patients with a similar expected exposure of pregabalin based on plasma concentrations. Secondary analyses of responder rates, sleep interference scores, and global impression of change were also significantly different between the placebo group and each of the pregabalin treatment arms.

6.3.3.21 Primary Efficacy outcome

The primary efficacy outcome was the endpoint mean pain score (the mean of the last 7 entries of the daily pain diary, while the patient was on study medication). Pfizer's analysis of the data showed that there was improvement (i.e. decrease) in mean pain scores for all treatment groups, both at Week 8 and at study endpoint. The greatest decrease in scores at these time points occurred in the pregabalin 300/600 mg/d group.

Table 6.3.3.21.a: Mean pain score: Descriptive statistics – Protocol 196

	Placebo		Pregabalin					
			150 mg/d		300 mg/d		300/600 mg/d	
Time point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	93	6.9 (1.5)	87	6.4 (1.6)	98	6.7 (1.4)	90	6.7 (1.4)
Week 8	65	5.7 (2.1)	66	4.6 (2.3)	68	4.6 (2.5)	64	4.0 (2.2)
Week 8 endpoint	93	6.2 (2.2)	87	5.0 (2.3)	98	5.0 (2.5)	88	4.4 (2.4)
Endpoint	93	6.2 (2.3)	87	5.1 (2.6)	98	5.0 (2.6)	88	4.3 (2.6)
Change from baseline to Week 8 endpoint	93	-0.7 (1.8)	87	-1.5 (1.9)	98	-1.7 (2.1)	88	-2.3 (2.3)
Change from baseline to Endpoint	93	-0.6 (2.0)	87	-1.4 (2.1)	98	-1.7 (2.3)	88	-2.4 (2.5)

Baseline = last 7 available pain scores before taking study medication, up to and including Day 1. If less than 7 scores were available, then the baseline consists of all scores that were available

Week 8 endpoint = Last 7 available scores, up to and including Day 57. If less than 7 scores were available, then the endpoint consisted of all scores that were available

Endpoint = Last 7 available pain scores while on study medication, up to and including the day after the last dose. If less than 7 scores were available, then Endpoint consisted of all scores that were available

(Adapted from Applicant's Section 9.1.10, RR 720-30191, 1008-196, P. 228-231)

Using the ANCOVA model, the endpoint mean pain score for all pregabalin treatment groups was significantly lower than the placebo group's score:

Table 6.3.3.21.b: Mean pain score: Descriptive statistics – Protocol 196

Treatment (mg/day)	N	Least-Squares Means	SE	Treatment Comparisons (Pregabalin — Placebo)			
				Difference	95% CI	Unadjusted p-Value	Adjusted[b] p-Value
Placebo	93	6.14	0.23				
PGB 150 mg	87	5.26	0.24	-0.88	(-1.53, -0.23)	0.0077	0.0077
PGB 300 mg	98	5.07	0.23	-1.07	(-1.70, -0.45)	0.0008	0.0016
PGB 300/600 mg	88	4.35	0.24	-1.79	(-2.43, -1.15)	0.0001	0.0003
Interactions treatment by:							
• Cluster (Generalizability)		p = 0.2965					
• CLcr Stratum		p = 0.3991					
• Baseline Score		p = 0.4771					

SE = Standard error; CI = Confidence interval; PGB = Pregabalin.

[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, CLcr stratum and the baseline score value as covariate).

[b] Adjustment based on Hochberg's procedure.

(Applicant's Table 16, RR 720-30191, 1008-196, P. 85)

Supplemental analyses of the primary efficacy variable

Mean pain scores at endpoint: Patients with similar expected plasma drug concentrations

As described in Section 6.3.3.9, Pfizer hypothesized that the plasma concentration of patients with a low CLcr and treated with 150 mg/d would be the same as the plasma concentration of

patients with a normal CLcr who were treated with 300 mg/d. These patients were pooled to form the "*300 mg/d adjusted dose group*." Similarly, the "*600 mg/d adjusted dose group*" consisted of patients with low CLcr who received pregabalin 300 mg/day, and patients with a normal CLcr who received pregabalin 600 mg/day. The analysis compared the endpoint mean pain scores of the 2 adjusted dose groups with placebo using an ANCOVA model with the baseline mean pain score as the covariate. Patients with a normal who took 150 mg/day were not included in the analysis.

A statistically significant difference was seen in the comparison of endpoint mean pain scores based on expected plasma concentrations for both the adjusted 300 mg/day (p = 0.0098) and 600 mg/day (p = 0.0002) pregabalin treatment groups:

Table 6.3.3.21.c: Endpoint mean pain scores of groups with expected similar plasma concentrations (ANCOVA) – Protocol 196

Table 4. Endpoint [a] Mean Pain Scores by Groups of Patients with Expected Similar Plasma Concentrations: Results of Analysis of Covariance: Intent-to-Treat Analysis

				Treatment Comparisons (Pregabalin – Placebo)			
Treatment Group	N	Least Squares Means	SE	Difference	95% CI	Unadjusted p-Value	Adjusted p-Value [b]
Placebo	93	6.27	0.23				
Adj. PGB 300 mg	91	5.43	0.24	-0.84	(-1.48, -0.20)	0.0098	0.0098
Adj. PGB 600 mg	121	4.51	0.20	-1.76	(-2.36, -1.15)	0.0001	0.0002

SE = Standard error; CI = Confidence interval
[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, Creatinine clearance stratum and the baseline score value as covariate).
[b] Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

(Applicant's Table 4, Appendix E2.24, RR 720-30191, 1008-196, P. 2541)

Proportion of responders

Patients with a 50% decrease in mean pain score from baseline to endpoint were considered to be responders. The greatest proportion of responders was in the 300/600 mg/day treatment group (37.5%), followed by the 300 and 150 mg/day treatment groups (26.5% and 26.4%, respectively). All 3 pregabalin treatment groups (150, 300, 300/600 mg/day) had a significantly greater proportion of responders as compared with placebo (7.5%) (p = 0.001 for all treatment groups).

Table 6.3.3.21.d: Results of analysis of responder status (LOCF method) – Protocol 196

Treatment group (mg/d)	Number assessed	Number of responders (%)	Treatment comparisons (pregabalin - placebo	
			Unadjusted p-value [a]	Adjusted p-value [b]
Placebo	93	7 (7.5)		
Pregabalin 150 mg/d	87	23 (26.4)	0.001	0.001
Pregabalin 300 mg/d	98	26 (26.5)	0.001	0.001
Pregabalin 300/600 mg/d	88	33 (37.5)	0.001	0.001

a: p-value based on the results of the CMH procedure, adjusting for center and CLcr strata
b: Adjustment based on Hochberg's procedure
(Applicant's Table 19, RR 720-30191, 1008-196, P. 88)

6.3.3.22 **Applicant's secondary efficacy analysis**

Results of the secondary efficacy analyses were to be interpreted based on the pattern of significant differences, and not on individual significant findings. This was because the protocol did not include adjustments for testing of multiple parameters

- *SF-MPQ (sensory, affective, VAS, PPI, and total scores)*

SF-MPQ scores at Endpoint

Due to heterogeneity of the SF-MPQ across languages, these parameters were analyzed for only English speaking patients. At study endpoint, all 3 pregabalin treatment groups (150, 300, 300/600 mg/day) had improved sensory, affective, and total scores compared to the placebo group. The 300- and 300/600 mg/d groups had better endpoint VAS scores than the placebo group. Finally, only the 300/600 mg/d group showed a significantly improved PPI score at endpoint compared to placebo.

SF-MPQ scores at Weeks 1, 4, 8, and 13

At Weeks 1, 4, 8, and 13, all pregabalin groups had significantly better sensory and total scores than the placebo group. Only the 300- and 300/600 mg/d groups had better affective scores at these four time points compared to the placebo group. The 150 mg/d group's affective score was no different from placebo at Week 4 only.

With respect to the weekly VAS scores, all pregabalin groups were significantly better than the placebo group at Week 1, but only the 300/600 mg/d group was also better than at Week 13. The 300- and 300/600 mg/d groups' VAS scores at Week 8 were also significantly improved compared to placebo.

The 300/600 mg/d group was the only one whose PPI scores were different from placebo at Week 13. Otherwise, Statistically significant differences were seen favoring all 3 pregabalin treatment groups at Weeks 1, 4, and 8.

- *Mean sleep interference score, weekly and at endpoint*

A comparison of mean sleep interference scores both weekly and at endpoint showed statistically significant improvement for patients in all 3 pregabalin treatment groups (150, 300, 300/600 mg/day) compared to the placebo patients.

- *MOS: Sleep scale scores - Change from baseline to endpoint*

The optimal sleep subscale was analyzed using logistic regression, and the other 6 MOS subscales were analyzed using ANCOVA. All 3 pregabalin treatment groups (150, 300, 300/600 mg/day) had a more favorable mean score for Sleep Disturbance and the Overall Sleep Problem Index, compared to placebo. In addition, the 300/600 mg/day pregabalin treatment group had better Quantity of Sleep scores than the placebo group. Otherwise, there were no significant differences across groups for the other Sleep Subscales

- *Global impression of change*

The percentage of patients reporting very much and much improvement in global impressions of change was 36% for 300/600 mg/day pregabalin, 27% for 300 mg/day pregabalin, and 23% for 150 mg/day pregabalin, and16% for the placebo group. Only the PGIC scores of the 150- and 300/600 mg day groups were significantly different from placebo.

The percentage of clinicians reporting very much and much improvement in global impressions of change was 38% for 300/600 mg/day pregabalin, 25% for 300 mg/day pregabalin, and 25% for 150 mg/day pregabalin when compared with 17% in the placebo group The difference in the CGIC response for only the 300/600 mg/day pregabalin treatment group reached statistical significance.

- *SF-36 Health survey, change from baseline to endpoint*

In general, the pregabalin groups had higher (more improved) scores than the placebo group. However, only the change in scores with respect to the Bodily Pain domain for the 300/600 mg/d group were significantly better than placebo.

- *EQ-5D: Utility and VAS scores, change from baseline to endpoint*

All 3 pregabalin treatment groups (150, 300, and 300/600 mg/day) had significantly improved EQ-5D Utility and VAS AUC scores when compared to the placebo group

6.3.3.23 Unplanned Analyses

Mean pain score at endpoint: Per protocol population

Pfizer repeated analysis of the primary efficacy out come using the Per Protocol population. Using the ANCOVA model, the endpoint mean pain scores from the 150, 300, and 300/600 mg/day pregabalin treatment groups were all significantly different from the placebo treatment group, favoring pregabalin ($p = 0.0213$, $p = 0.0128$, and $p = 0.0003$, respectively)

Endpoint mean pain score -BOCF analysis

For the 126 patients that Pfizer identified as not completing the study, the mean pain score at endpoint was analyzed using the baseline score as the endpoint score. All 3 of the pregabalin treatment groups (150, 300, and 300/600 mg/day) were significantly different from placebo, favoring pregabalin:

Table 6.3.3.23: Endpoint mean pain scores: Results of ANCOVA with BOCF – Protocol 196

Treatment Group	N	Least Squares Means	SE	Treatment Comparisons (Pregabalin - Placebo) Difference	95% CI	Unadjusted p-Value	Adjusted p-Value [b]
Placebo	93	6.22	0.22				
PGB 150 mg	87	5.35	0.23	-0.87	(-1.48, -0.27)	0.0051	0.0102
PGB 300 mg	98	5.52	0.21	-0.70	(-1.29, -0.11)	0.0201	0.0201
PGB 300/600 mg	88	4.89	0.23	-1.33	(-194, -0.73)	0.0001	0.0003

SE = Standard error; CI = Confidence interval
[a] Based on LS Means using ANCOVA model (including effects for treatment, cluster, Creatinine clearance stratum and the baseline score value as covariate).
[b] Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

(Applicant's Table 12 in Appendix E.2.24, RR 720-30191, P. 2545)

Endpoint mean pain score –Removing subjects with somnolence or dizziness
The primary analysis of endpoint mean pain scores was repeated after removing patients who reported dizziness and/or somnolence to address the potential for bias resulting from unblinding due to central nervous system (CNS) side effects. All 3 of the pregabalin treatment groups (150, 300, and 300/600 mg/day) were significantly improved pain scores compared to the placebo group.

Endpoint mean pain score at Week 8
ANCOVA showed that the of the mean pain scores at Week 8 of each of the pregabalin groups (150, 300, and 300/600 mg/day) were significantly mean pain scores of the placebo group ($p = 0.0040$, $p = 0.0010$, and $p = 0.0003$, respectively)

Weekly mean pain score: Repeated measures analysis
A pair-wise comparison of each pregabalin dose versus placebo was performed at each time point. All 3 of the treatment groups (150, 300, and 300/600 mg/day) showed a significant difference from placebo, favoring pregabalin. Pfizer states that the difference was apparent starting at Week 1, and was maintained through to the end of the study (Week 13).

Analysis of measures of skin hypersensitivity: Allodynia and Hyperalgesia
Allodynia and hyperalgesia were measured in 344 patients (91 placebo, 81 pregabalin 150 mg/d, 88 pregabalin 300 mg/d, and 84 pregabalin 300/600 mg/d) at baseline and at endpoint. The difference in occurrence of neither allodynia nor hyperalgesia was not significantly different from placebo for any pregabalin group.

6.3.3.24 Reviewer's analysis of efficacy

The same problems with the analysis methods present in protocols 045 and 127 are present in this protocol (See Section 6.3.1.9, Reviewer's analysis of efficacy).

In addition, instead of comparing groups based on actual dose of study medication received (as determined by creatinine clearance, for the 300/600 mg/d group), the Applicant compared the results of only the assigned treatment groups. However, as shown in the tables (b) and (c) in Section 6.3.3.17, patients in the 300/600 mg/d group who had a low CLcr and who were treated

with 300 mg/d, were "the same" as patients in the 300 mg/d group who also had a low CLcr and were treated with 300 mg/d. That is, these subjects had similar exposure to pregabalin 300 mg/d. Therefore, they should be combined into a single group for analysis of efficacy, and should not be analyzed separately, as done by the Applicant.

Since several patients were incorrectly randomized to study drug, efficacy data could not be analyzed based on patients the dose patients should have received, as determined by their CLcr. Instead, Dr. Buenconsejo reanalyzed the data based on the actual dose that patients were administered. The re-categorized analysis groups were as follows:

	Placebo	Pregabalin 150 mg/d		Pregabalin 300 mg/d		Pregabalin 600 mg/d
Creatinine clearance		Low	Normal	Low	Normal	Normal
No. patients	93	26	61	59	65	64

Using the same BOCF imputation strategy as employed for Protocol 045, Dr. Buenconsejo then calculated the mean pain score for the treatment groups at each study week. Study endpoint was redefined as the last 7 days while patients were on study medication. In addition, a comparison of the proportion of treatment responders in each group was performed.

Primary efficacy outcome

Mean pain score – weekly and at endpoint

All treatment groups showed an improvement (i.e. decrease) in mean pain score at Week 8, 13, and at the redefined study endpoint. Descriptive statistics (see Table 6.3.3.24 below) suggest that mean pain scores improved for all groups as early as Week 1, with greater improvement seen in the pregabalin 150 mg/d – "high" CLcr group. Throughout each week, this group had the lowest pain scores, followed by the pregabalin 600 mg/d ("high" CLcr) group.

Table 6.3.3.24.a: Reviewer's analysis: Descriptive statistics, mean pain score by study week, BOCF method – Protocol 196

	Mean Pain Score					
	Placebo	PGB 150		PGB 300		PGB 600
Study Week		Low[2]	High[3]	Low[2]	High[3]	High[3]
Baseline[4]	6.85 (1.5)	6.77 (1.7)	6.30 (1.5)	6.84 (1.4)	6.60 (1.4)	6.64 (1.4)
Week 1	6.68 (1.7)	6.08 (2.2)	5.38 (1.9)	5.80 (1.7)	5.78 (1.9)	5.76 (1.8)
Week 2	6.53 (1.8)	6.00 (2.1)	5.33 (1.9)	5.57 (2.0)	5.51 (2.0)	5.18 (2.1)
Week 3	6.51 (1.8)	6.01 (2.1)	5.17 (1.9)	5.55 (2.1)	5.50 (2.2)	4.99 (2.2)
Week 4	6.54 (1.8)	5.88 (2.3)	5.11 (2.0)	5.62 (2.0)	5.25 (2.3)	4.97 (2.3)
Week 5	6.55 (1.7)	5.73 (2.3)	4.94 (2.1)	5.73 (2.0)	5.41 (2.3)	4.76 (2.4)
Week 6	6.42 (1.9)	5.71 (2.3)	4.86 (2.1)	5.64 (2.1)	5.46 (2.2)	4.95 (2.3)
Week 7	6.38 (1.9)	5.88 (2.3)	4.79 (2.1)	5.64 (2.1)	5.40 (2.3)	4.85 (2.5)
Week8	6.31 (2.1)	5.83 (2.3)	4.75 (2.2)	5.57 (2.1)	5.33 (2.4)	4.81 (2.5)
Week9	6.37 (2.0)	5.77 (2.2)	4.84 (2.2)	5.65 (2.1)	5.44 (2.3)	4.77 (2.5)
Week10	6.42 (2.0)	5.63 (2.4)	4.88 (2.4)	5.71 (2.1)	5.47 (2.3)	4.64 (2.6)
Week11	6.36 (2.1)	5.72 (2.2)	4.91 (2.6)	5.61 (2.1)	5.38 (2.4)	4.67 (2.7)
Week12	6.38 (2.2)	5.72 (2.3)	4.80 (2.5)	5.51 (2.2)	5.47 (2.3)	4.73 (2.7)
Week13	6.42 (2.1)	6.02 (2.1)	4.78 (2.6)	5.56 (2.2)	5.40 (2.4)	4.72 (2.8)
Week8 Endpoint[5]	**6.28 (2.1)**	**5.83 (2.3)**	**4.75 (2.2)**	**5.58 (2.1)**	**5.33 (2.4)**	**4.76 (2.5)**
Endpoint[6]	**6.30 (2.2)**	**5.90 (2.2)**	**4.82 (2.6)**	**5.46 (2.3)**	**5.42 (2.4)**	**4.69 (2.7)**

[1]Weekly pain score= Average of the available scores per week for completers, and baseline mean pain scores for non-completers
[2]Low = creatinine clearance is between 30 and 60 mL/min
[3]Normal = creatinine clearance >60 mL/min
[4] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[5] Week 8= Average of the last 7 available scores up to day 57, and baseline mean pain scores for non-completers at week 8 and onwards
[6] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain
score for non-completers

ANCOVA of the weekly and endpoint mean pain scores showed that all pregabalin groups had a statistically significant difference in pain score compared to pregabalin at Week 1. However, patients in the pregabalin 150 mg/d group who had a low CLcr did not consistently show a statistically significant difference in scores throughout each week, whereas the other treatment groups did (Table 6.3.3.24.b).

The differences in mean pain scores between the pregabalin and placebo groups at study week 8 and at endpoint were evaluated. There was no statistically significant difference from placebo for patients with a low CLcr who were in the pregabalin 150 mg/d group at either Week 8 or at endpoint. Also, the mean score for the pregabalin 300 mg/d-normal CLcr group was not significantly different from the placebo group's score at endpoint (Table 6.3.3.24.c and d).

Table 6.3.3.24.b: Reviewer's analysis: ANCOVA, mean pain score by study week (BOCF) – Protocol 196

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin – Placebo)		
			Differences	p-value[2]	p-value[3]
Week 1					
Placebo	6.51 (0.1)	0.16 (0.1)			
PGB 150-Low[4]	5.97 (0.2)	0.71 (0.2)	-0.54	0.0311	0.0311
PGB 150-High[5]	5.74 (0.1)	0.93 (0.1)	-0.77	<0.0001	0.0004
PGB 300-Low[4]	5.64 (0.1)	1.04 (0.1)	-0.87	<0.0001	0.0004
PGB 300-High[5]	5.87 (0.1)	0.80 (0.1)	-0.64	0.0005	0.0010
PGB 600	5.82 (0.1)	0.86 (0.1)	-0.69	0.0002	0.0006
Week 2					
Placebo	6.40 (0.2)	0.26 (0.2)			
PGB 150-Low[4]	5.93 (0.3)	0.73 (0.3)	-0.47	0.1593	0.1593
PGB 150-High[5]	5.65 (0.2)	1.02 (0.2)	-0.75	0.0027	0.0054
PGB 300-Low[4]	5.46 (0.2)	1.21 (0.2)	-0.94	0.0002	0.0008
PGB 300-High[5]	5.60 (0.2)	1.07 (0.2)	-0.80	0.0010	0.0030
PGB 600	5.23 (0.2)	1.44 (0.2)	-1.17	<0.0001	0.0005
Week 3					
Placebo	6.37 (0.2)	0.30 (0.2)			
PGB 150-Low[4]	5.90 (0.3)	0.77 (0.3)	-0.47	0.1766	0.1766
PGB 150-High[5]	5.49 (0.2)	1.18 (0.2)	-0.88	0.0007	0.0021
PGB 300-Low[4]	5.40 (0.2)	1.27 (0.2)	-0.97	0.0003	0.0012
PGB 300-High[5]	5.60 (0.2)	1.07 (0.2)	-0.77	0.0027	0.0054
PGB 600	5.04 (0.2)	1.63 (0.2)	-1.33	<0.0001	0.0005
Week 4					
Placebo	6.40 (0.2)	0.27 (0.2)			
PGB 150-Low[4]	5.77 (0.3)	0.90 (0.3)	-0.63	0.0922	0.0922
PGB 150-High[5]	5.41 (0.2)	1.25 (0.2)	-0.99	0.0004	0.0012
PGB 300-Low[4]	5.51 (0.2)	1.15 (0.2)	-0.89	0.0018	0.0036
PGB 300-High[5]	5.34 (0.2)	1.33 (0.2)	-1.06	0.0001	0.0004
PGB 600	4.99 (0.2)	1.68 (0.2)	-1.41	<0.0001	0.0004
Week 5					
Placebo	6.41 (0.2)	0.25 (0.2)			
PGB 150-Low[4]	5.63 (0.3)	1.04 (0.3)	-0.78	0.0366	0.0366
PGB 150-High[5]	5.26 (0.2)	1.41 (0.2)	-1.15	<0.0001	0.0004
PGB 300-Low[4]	5.61 (0.2)	1.06 (0.2)	-0.80	0.0044	0.0088
PGB 300-High[5]	5.51 (0.2)	1.16 (0.2)	-0.90	0.0010	0.0030
PGB 600	4.80 (0.2)	1.87 (0.2)	-1.61	<0.0001	0.0004

Table 6.3.3.24.b: Reviewer's analysis: ANCOVA, mean pain score by study week (BOCF) – Protocol 196 (continued)

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin – Placebo)		
			Differences	p-value[2]	p-value[3]
Week 6					
Placebo	6.28 (0.2)	0.40 (0.2)			
PGB 150-Low[4]	5.58 (0.3)	1.09 (0.3)	-0.70	0.0765	0.0765
PGB 150-High[5]	5.17 (0.2)	1.50 (0.2)	-1.11	0.0002	0.0008
PGB 300-Low[4]	5.62 (0.2)	1.06 (0.2)	-0.66	0.0261	0.0522
PGB 300-High[5]	5.55 (0.2)	1.13 (0.2)	-0.73	0.0109	0.0327
PGB 600	4.96 (0.2)	1.72 (0.2)	-1.32	<0.0001	0.0005
Week 7					
Placebo	6.26 (0.2)	0.41 (0.2)			
PGB 150-Low[4]	5.76 (0.4)	0.91 (0.4)	-0.50	0.2165	0.2165
PGB 150-High[5]	5.10 (0.2)	1.58 (0.2)	-1.16	0.0001	0.0004
PGB 300-Low[4]	5.54 (0.2)	1.13 (0.2)	-0.72	0.0186	0.0372
PGB 300-High[5]	5.51 (0.2)	1.16 (0.2)	-0.75	0.0107	0.0321
PGB 600	4.86 (0.2)	1.81 (0.2)	-1.40	<0.0001	0.0004
Week 8					
Placebo	6.18 (0.2)	0.50 (0.2)			
PGB 150-Low[4]	5.71 (0.4)	0.97 (0.4)	-0.47	0.2643	0.2643
PGB 150-High[5]	5.06 (0.2)	1.61 (0.2)	-1.12	0.0004	0.0016
PGB 300-Low[4]	5.47 (0.3)	1.20 (0.3)	-0.71	0.0277	0.0544
PGB 300-High[5]	5.44 (0.2)	1.23 (0.2)	-0.74	0.0164	0.0492
PGB 600	4.82 (0.2)	1.85 (0.2)	-1.36	<0.0001	0.0005
Week 9					
Placebo	6.22 (0.2)	0.44 (0.2)			
PGB 150-Low[4]	5.63 (0.4)	1.04 (0.4)	-0.59	0.1423	0.1423
PGB 150-High[5]	5.16 (0.2)	1.51 (0.2)	-1.06	0.0005	0.0020
PGB 300-Low[4]	5.53 (0.2)	1.14 (0.2)	-0.69	0.0243	0.0486
PGB 300-High[5]	5.54 (0.2)	1.13 (0.2)	-0.68	0.0200	0.0486
PGB 600	4.81 (0.2)	1.86 (0.2)	-1.41	<0.0001	0.0005
Week 10					
Placebo	6.28 (0.2)	0.39 (0.2)			
PGB 150-Low[4]	5.50 (0.4)	1.17 (0.4)	-0.78	0.0604	0.0604
PGB 150-High[5]	5.20 (0.2)	1.47 (0.2)	-1.08	0.0006	0.0024
PGB 300-Low[4]	5.60 (0.2)	1.07 (0.2)	-0.68	0.0306	0.0604
PGB 300-High[5]	5.57 (0.2)	1.10 (0.2)	-0.71	0.0192	0.0576
PGB 600	4.67 (0.2)	1.99 (0.2)	-1.61	<0.0001	0.0005

Table 6.3.3.24.b: Reviewer's analysis: ANCOVA, mean pain score by study week (BOCF) – Protocol 196 (continued)

Treatment	Least-Squares Mean (SE)	Change from baseline LS mean (SE)	Treatment Comparisons (Pregabalin – Placebo)		
			Differences	p-value[2]	p-value[3]
Week 11					
Placebo	6.23 (0.2)	0.44 (0.2)			
PGB 150-Low[4]	5.58 (0.4)	1.10 (0.4)	-0.65	0.1446	0.1446
PGB 150-High[5]	5.20 (0.3)	1.48 (0.3)	-1.03	0.0021	0.0084
PGB 300-Low[4]	5.52 (0.3)	1.15 (0.3)	-0.71	0.0357	0.0714
PGB 300-High[5]	5.48 (0.2)	1.19 (0.2)	-0.75	0.0226	0.0678
PGB 600	4.68 (0.3)	1.99 (0.3)	-1.55	<0.0001	0.0005
Week 12					
Placebo	6.27 (0.2)	0.41 (0.2)			
PGB 150-Low[4]	5.59 (0.4)	1.09 (0.4)	-0.68	0.1372	0.1372
PGB 150-High[5]	5.10 (0.3)	1.58 (0.3)	-1.17	0.0007	0.0028
PGB 300-Low[4]	5.44 (0.3)	1.24 (0.3)	-0.83	0.0163	0.0489
PGB 300-High[5]	5.56 (0.3)	1.19 (0.3)	-0.71	0.0333	0.0666
PGB 600	4.75 (0.3)	1.93 (0.3)	-1.52	<0.0001	0.0005
Week 13					
Placebo	6.28 (0.2)	0.40 (0.2)			
PGB 150-Low[4]	5.87 (0.4)	0.82 (0.4)	-0.41	0.3705	0.3705
PGB 150-High[5]	5.10 (0.3)	1.59 (0.3)	-1.18	0.0007	0.0028
PGB 300-Low[4]	5.41 (0.3)	1.27 (0.3)	-0.87	0.0131	0.0393
PGB 300-High[5]	5.52 (0.3)	1.17 (0.3)	-0.76	0.0252	0.0504
PGB 600	4.77 (0.3)	1.91 (0.3)	-1.51	<0.0001	0.0005

Table 6.3.3.24.c: Reviewer's analysis: ANCOVA, mean pain score at Week 8 (BOCF) – Protocol 196

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.11	0.20			
PGB 150							
Low[4]	26	6.77	5.79	0.38	-0.31	0.4461	0.4461
Normal[5]	61	6.30	5.00	0.25	-1.11	0.0006	0.0024
PGB 300							
Low[4]	59	6.84	5.22	0.26	-0.89	0.0066	0.0174
Normal[5]	65	6.60	5.29	0.24	-0.82	0.0087	0.0174
PGB 600	64	6.64	4.74	0.25	-1.37	<0.0001	0.0005

[1] Week 8= Average of available scores between day 51 to day 57, except when subject dropped out before or during that week then it will be baseline pain score
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the six pair-wise comparisons versus placebo
[3]Low = creatinine clearance is between 30 and 60 mL/min
[4]Normal = creatinine clearance >60 mL/min

Table 6.3.3.24.d: Reviewer's analysis: ANCOVA, mean pain score at Endpoint (BOCF) – Protocol 196

Treatment	N	Baseline Mean	Least-Squares Mean	SE	Treatment Comparisons (Pregabalin – Placebo)		
					Differences	p-value[2]	p-value[3]
Placebo	93	6.85	6.19	0.22			
PGB 150							
Low[4]	26	6.77	5.76	0.41	-0.43	0.3514	0.3514
Normal[5]	61	6.30	5.12	0.27	-1.07	0.0020	0.0080
PGB 300							
Low[4]	59	6.84	5.38	0.27	-0.81	0.0194	0.0582
Normal[5]	65	6.60	5.54	0.26	-0.65	0.0532	0.1064
PGB 600	64	6.64	4.72	0.26	-1.47	<0.0001	0.0005

[1] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose for completers, and baseline mean pain score for non-completers
[2] unadjusted p-value
[3] Adjustment based on Hochberg's procedure for the two pair-wise comparisons versus placebo
[4]Low = creatinine clearance is between 30 and 60 mL/min
[5]Normal = creatinine clearance >60 mL/min

As described earlier, Pfizer hypothesizes that, for patients with a low CLcr, exposure to a given dose of pregabalin would be the same as the exposure of twice the pregabalin dose in patients with a normal CLcr. Therefore, for example, exposure to 150 mg/d in patients with a low CLcr would the same as exposure to 300 mg/d in patients with a normal CLcr. Consequently, Pfizer believes, the efficacy of those doses should be similar.

The above results show that, at up to 8 weeks of treatment with pregabalin, an improvement in mean pain score can be seen, except for patients with a low CLcr who are treated with 150 mg/d. This Week 8 finding therefore does not support Pfizer's theory of similar efficacy based on similar drug exposure. However, at study endpoint, there is no difference in mean pain scores for both the patients with a low CLcr who are treated with 150 mg/d, and the for patients with a normal CLcr who are treated with 300 mg/d, lending weight to Pfizer's hypothesis. Finally, Tables 6.3.3.24 c and d also show that, for patients with a normal CLcr, treatment with pregabalin 600 mg/d is efficacious at either time point. However, treatment with 300 mg/d is not efficacious, regardless of CLcr status.

As performed for the previous two protocols, Dr. Buenconsejo assessed the sensitivity of the analyses using other methods to extrapolate for missing data and obtained similar results using each of those methods.

The use of rescue medication and/or prohibited medications was evaluated, given that patients taking these medications could possibly report less pain, compared to patients not taking the medications. There were 27 patients who took prohibited medications, and 94 who took the allowable rescue medication for pain:

Table 6.3.3.24.e: Use of rescue/prohibited medications – Protocol 196

Treatment group	[Number (%) of patients] Prohibited medication, N = 27	[ITT population = 338] Rescue medication, N = 94
Placebo, N = 93	6 (6.4)	24 (25.8)
PGB 150 – low CLcr, N = 26	3 (11.5)	8 (30.8)
PGB 150 – normal CLcr, N = 61	3 (4.9)	13 (21.3)
PGB 300 – low CLcr, N = 59	5 (8.5)	17 (28.8)
PGB 300 – normal CLcr, N = 65	5 (7.7)	18 (27.7)
PGB 600 – normal CLcr, N = 64	5 (7.8)	14 (21.9)

Of the 94 patients who took rescue medication, 77 patients (82%) took it throughout the study, 8 patients took rescue medication during the latter half of the study, and 1 patient used rescue medication only during the baseline period. The daily mean pain scores of the 94 patients were evaluated, and showed no considerable variability with respect to the day before or after the day rescue medication was taken.

Nine of the 94 subjects (9.6%) dropped out of the study due to an adverse event, 8 of who had taken rescue medication until the day they dropped out of the trial. Another 14 subjects (14.9%) dropped out due to lack of efficacy, 12 of whom took rescue medication throughout the their trial participation. Based on these findings, the use of rescue medication is not believed to have had an effect on the mean pain score. No further analyses were conducted that included the use of rescue medication as a factor.

Analysis of responder rates

To further evaluate the effect of pregabalin treatment on patients' pain, the proportion of patients who had a favorable response to treatment (treatment 'responders') was performed, using the BOCF method of data imputation. Responders were defined as patients who had at least a 50% decrease in pain from baseline. The proportions of responders at Weeks 8, 13, and study endpoint were determined.

Responder rates at Week 8

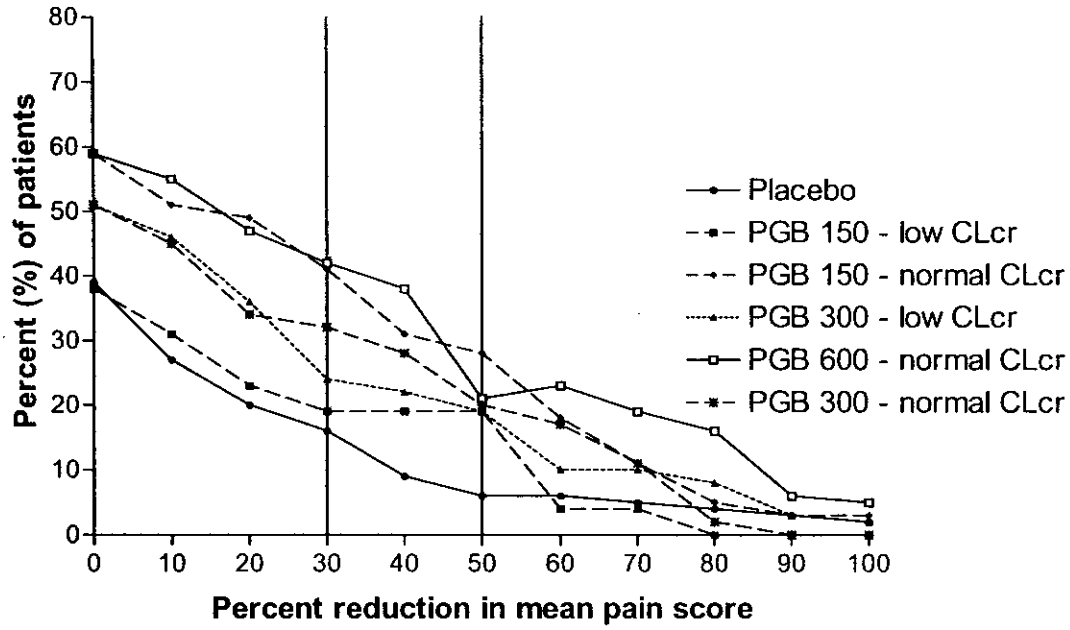
Table 6.3.3.24.f displays the proportion of patients with various decreases in pain score from baseline to Week 8 for each of the treatment groups. At lower cut-offs for the definition of treatment response (i.e. < 50% decrease in pain), there were more patients with a favorable response in each of the pregabalin groups (except for the 150 mg/d-low CLcr group) than in the placebo group. A similar result was seen for the proportion of treatment responders (i.e. patients with a ≥ 50% decrease in pain): the proportion of treatment responders was greatest in the pregabalin 600 mg/d group (30%), followed by the 300mg/d-normal CLcr (23%), 150 mg/d-normal CLcr groups (21%), and 300 mg/d-low CLcr (17%). There was no appreciable difference in treatment responders between the placebo group (6%) and the 150 mg/d-low CLcr group (8%). At higher cut-off values (60-80% decrease in pain), only the pregabalin 600 mg/d group consistently had more patients with a favorable treatment response.

Table 6.3.3.24.f: Reviewer's analysis: Percent change in mean pain score by treatment dose, from baseline to Week 8 – Protocol 196

	PLACEBO		PGB 150[1]		PGB 150[2]		PGB 300[1]		PGB 300[2]		PGB 600	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	18	19%	2	8%	5	8%	2	3%	8	12%	3	5%
None	39	42%	13	50%	17	28%	26	44%	23	35%	22	34%
> 0 % decrease	36	39%	11	42%	39	64%	31	53%	34	52%	39	61%
≥ 10%	27	29%	8	31%	36	59%	27	46%	31	48%	36	56%
≥ 20%	22	24%	8	31%	31	51%	21	36%	22	34%	33	52%
≥ 30%	18	19%	5	19%	26	43%	15	25%	21	32%	24	38%
≥ 40%	8	9%	5	19%	18	30%	13	22%	17	26%	22	34%
≥ 50%	**6**	**6%**	**2**	**8%**	**13**	**21%**	**10**	**17%**	**15**	**23%**	**19**	**30%**
≥ 60%	3	3%	2	8%	10	16%	7	12%	12	18%	14	22%
≥ 70%	3	3%	2	8%	6	10%	3	5%	7	11%	11	17%
≥ 80%	3	3%	1	4%	2	3%	1	2%	2	3%	8	13%
≥ 90%	1	1%	1	4%	0	0%	0	0%	0	0%	4	6%
=100%	1	1%	0	0%	0	0%	0	0%	0	0%	1	2%

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Figure 10: Reviewer's analysis: Response profile at Week 8

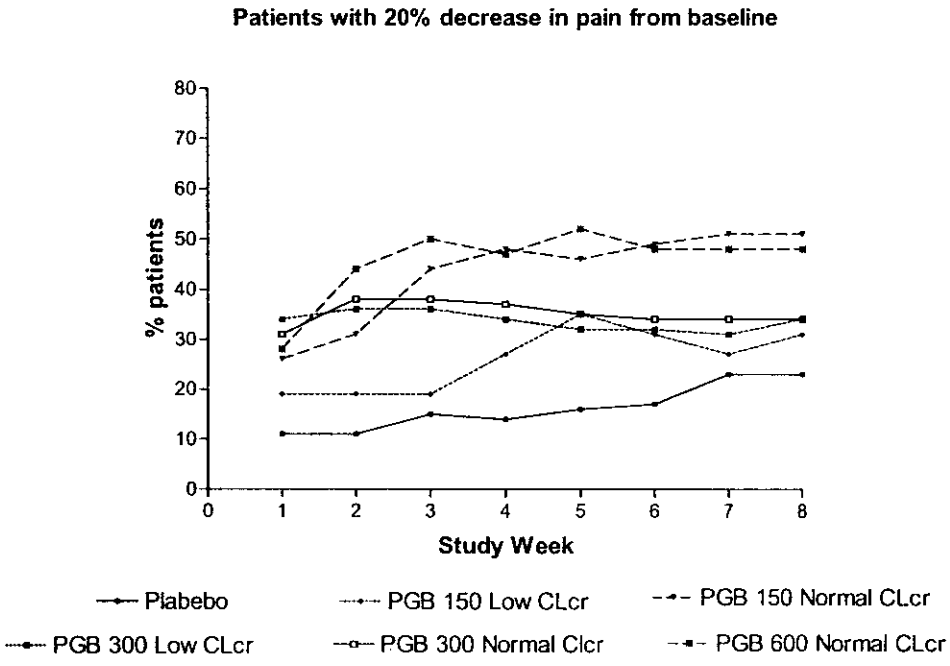


Responder rates at each week separately

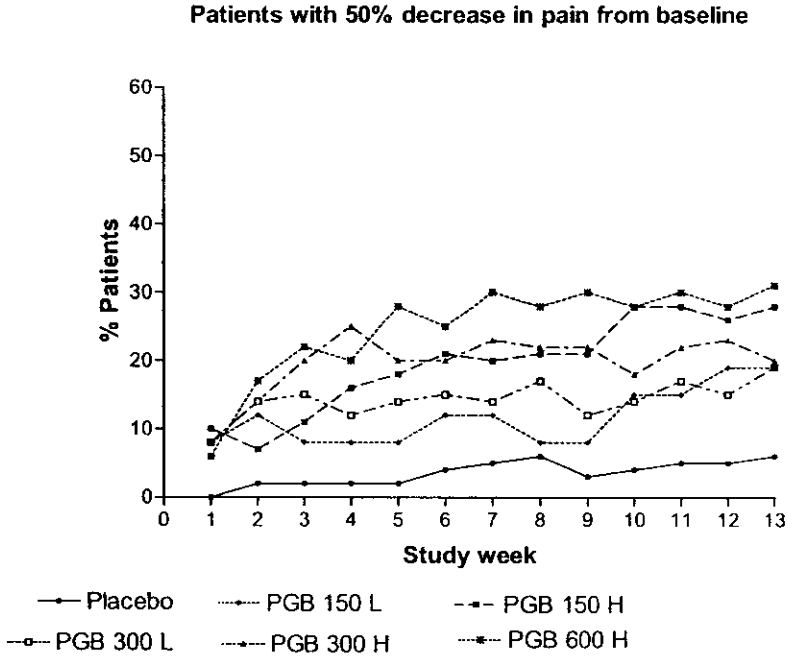
Using definitions (cut-offs) of treatment response that ranged from 10-80% reduction in pain, Dr. Buenconsejo compared the proportions of responders at each week. At definitions of treatment response < 50% decrease in pain, and at each study week, the proportions of responders in the pregabalin groups were greater than in the placebo group. The proportions of treatment responders in the 150 mg/d-lowCLcr were similar to those in the 600mg/d-normal CLcr, and were greater than each of the other treatment groups, at each study week. (Figure 11).

At a cut-off of 50% decrease in pain, all pregabalin groups had more treatment responders than the placebo group at Week 1, and the proportions were relatively similar. However, by Week 2, the proportions of treatment responders in the pregabalin groups were different, with the greatest in the 600 mg/d-normal CLcr group. Between Weeks 5 and 9, the most treatment responders were in the 600 mg/d-normal CLcr group, followed by the 150 mg/d-normal CLcr and 300 mg/d-normal CLcr groups. By Week 10, the proportions of responders in the 600 mg/d-normal CLcr and 150 mg/d-normal CLcr groups were similar, and greater than the other treatment groups (Figure 12).

Figures 11: Patients with < 50% decrease in pain from baseline, by study week – Protocol 196

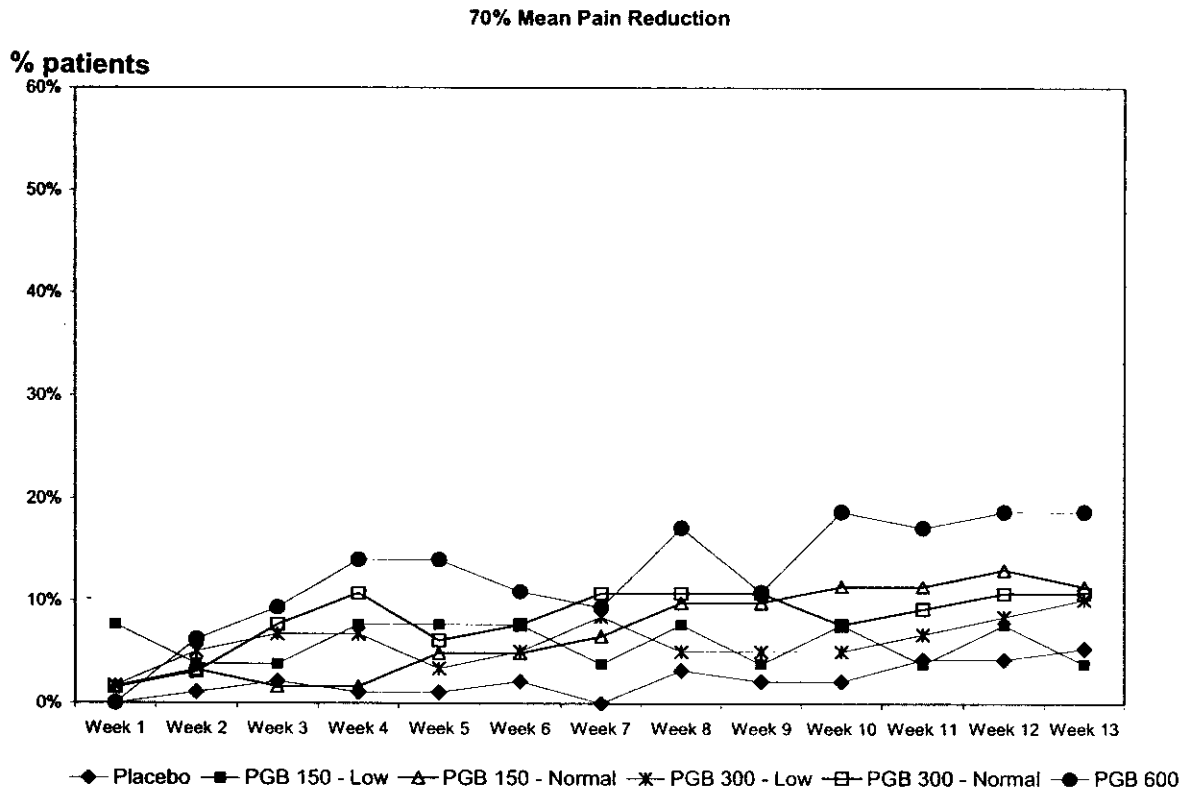


Figures 12: Patients with 50% decrease in pain from baseline, by study week – Protocol 196



At higher cut-offs (60-80% decrease in pain), only the pregabalin 600 mg/d-normal CLcr group had considerably more treatment responders than the placebo group. The proportions of treatment responders in the other pregabalin groups gradually approached that of the placebo group (Figure 13).

Figures 13: Patients with 70% decrease in pain from baseline, by study week – Protocol 196



Treatment responders at Week 13

Table 6.3.3.24.g displays the proportion of patients with various decreases in pain score from baseline to Week 13 for each of the treatment groups. At lower cut-offs of treatment response, there were more patients in the pregabalin groups who had an improvement in pain, compared to the placebo group, with the exception of the 150 mg/d-low CLcr group. The same was true at higher cut-offs for the definition of treatment response. However, all pregabalin groups, including the 150 mg/d-low CLcr group, had considerably greater proportions of treatment responders (≥ 50% decrease in pain from baseline) than the placebo group did. The pregabalin 600 mg/d-normal CLcr group had the highest proportion of treatment responders (31%), followed by the pregabalin 150 mg/d-normal CLcr group (28%).

A total of 72 subjects completed the study and had a 50% reduction in mean pain score by Week 13. Figure 13 shows the distribution of these patients from Week 1 to 13. A difference in treatment response was most evident at Week 2, and the difference persisted throughout the

study. As was seen at Week 8, there were more treatment responders in the pregabalin 600 mg/d-normal CLcr and 150 mg/d-normal CLcr groups than in the other treatment groups. At Week 10 and beyond, the difference in responder rates between these two groups was negligible.

The data suggests that patients in the pregabalin 600 mg/d-normal CLcr and 150 mg/d-normal CLcr groups who do not respond to in Week 2 are likely to respond with continued treatment, up to Week 5. The likelihood of treatment response with continued treatment beyond Week 6 does not increase appreciably for the pregabalin 300 mg/d-normal CLcr. Finally, the likelihood of treatment response to 150 mg/d in patients with a low CLcr increases considerably after approximately 9 weeks of treatment.

Figure 13: Reviewer's Analysis: Proportion of treatment responders (50% decrease in pain), by study week – Protocol 196

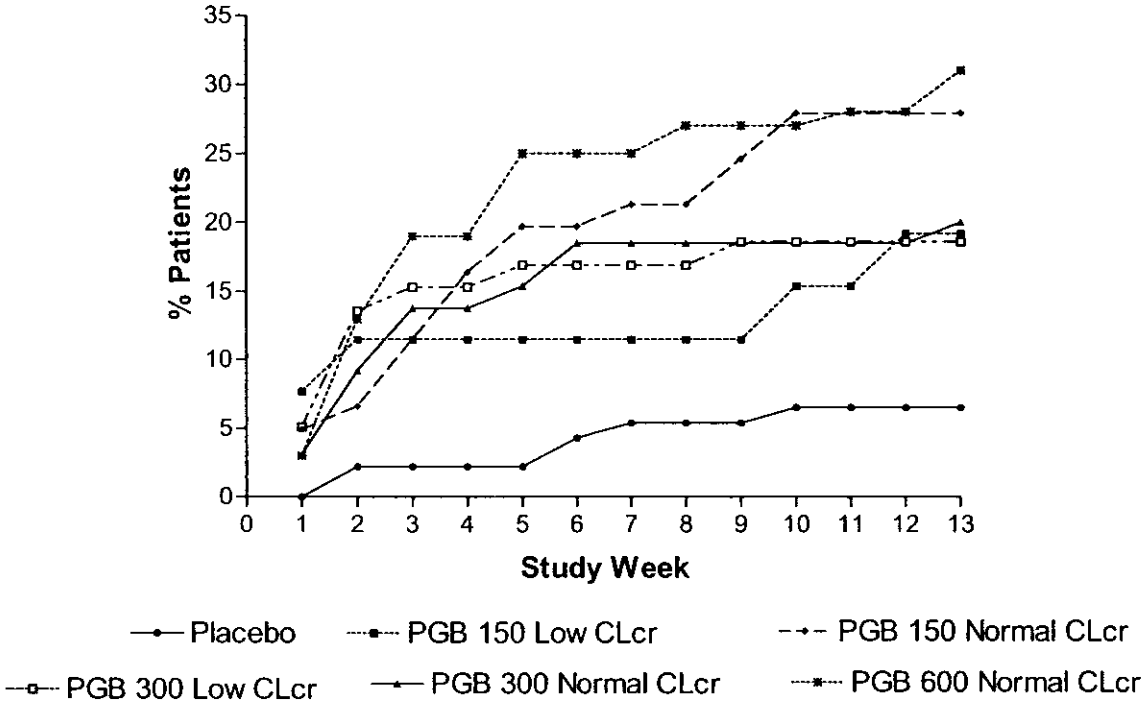


Table 6.3.3.24.g: Reviewer's analysis: Percent change in mean pain score by treatment dose, from baseline to Week 13 – Protocol 196

	PLACEBO		PGB150-L		PGB150-H		PGB300-L		PGB300-H		PGB600	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	26	28%	2	8%	9	15%	2	3%	8	12%	6	9%
None	36	39%	14	54%	16	26%	27	46%	24	37%	20	31%
> 0 % decrease	36	39%	10	38%	36	59%	30	51%	33	51%	38	59%
≥ 10%	25	27%	8	31%	31	51%	27	46%	29	45%	35	55%
≥ 20%	19	20%	6	23%	30	49%	21	36%	22	34%	30	47%
≥ 30%	15	16%	5	19%	25	41%	14	24%	21	32%	27	42%
≥ 40%	8	9%	5	19%	19	31%	13	22%	18	28%	24	38%
≥ 50%	**6**	**6%**	**5**	**19%**	**17**	**28%**	**11**	**19%**	**13**	**20%**	**20**	**31%**
≥ 60%	6	6%	1	4%	11	18%	6	10%	11	17%	15	23%
≥ 70%	5	5%	1	4%	7	11%	6	10%	7	11%	12	19%
≥ 80%	4	4%	0	0%	3	5%	5	8%	1	2%	10	16%
≥ 90%	3	3%	0	0%	2	3%	2	3%	0	0%	4	6%
=100%	2	2%	0	0%	2	3%	1	2%	0	0%	3	5%

6.3.3.25 **Conclusions regarding efficacy data – Protocol 1008-196**

The Applicant found that patients in the pregabalin 150-, 300-, or 300/600 mg/d groups had a significantly lower mean pain score at Week 8 and study endpoint than did patients in the placebo treatment group. Similarly, Pfizer found that there were significantly more treatment responders in each of the pregabalin groups than in the placebo group.

After reanalyzing the effects of treatment on mean pain score the by the actual dose of study medication received, as determined by creatinine clearance, the Agency found that after 8 weeks of treatment, there was no statistically significant difference from placebo for only those patients with a low CLcr who were in the pregabalin 150 mg/d group. When the mean pain scores at study endpoint (week 13) were evaluated, neither the 150 mg/d-low CLcr or the 300 mg/d-normal CLcr showed a significant difference from placebo.

On evaluation of the proportion of treatment responders (patients with ≥ 50% decrease in pain from baseline), the Agency found that there were many more responders in the pregabalin groups, compared to the placebo group, and this difference persisted throughout the trial. The most responders were in the 600 mg/d-normal CLcr and 150 mg/d-normal CLcr groups, followed by the 300 mg/d-low and –normal CLcr groups, respectively. The responder analysis therefore supports the relative lack of efficacy of treatment with 150 mg/d in patients with a low CLcr, and suggests that treatment with 300 mg/d in patients with a normal CLcr is efficacious.

6.3.4 Efficacy in patients with low creatinine clearance

As previously described, subjects in protocols –127 and –196 were randomized to pregabalin with stratification according to their creatinine clearance. Although not initially done for the protocol –045, this study's efficacy data were reanalyzed after dividing the patients in the pregabalin according to their creatinine clearance (see Appendix). Efficacy of pregabalin, as assessed by mean pain score at endpoint and treatment responder status, is summarized below:

Table 6.3.4.a: Efficacy of pregabalin by CLcr/drug dose - Protocols 045, 127 and 196

		Pregabalin dose – CLcr category				
Study/ Endpoint	**Placebo**	**150-L**	**150-N**	**300-L**	**300-N**	**600-N**
Protocol 045						
Mean pain score at endpoint	6.3	4.9*	5.5	5.7	4.6*	
Responder rate (%)e	9	29	21	11	35	
Protocol 127						
Mean pain score at endpoint	5.14	-	-	4.61	-	4.36*
Responder rate (%)e	20	-	-	30		34
Protocol 196 (week 8)						
Mean pain score	6.11	5.79	5.0*	5.22*	5.29*	4.74*
Responder rate (%)e	6	8	21	17	23	30
Protocol 196 (week 13)						
Mean pain score at endpoint	6.19	5.76	5.12*	5.38	5.54	4.72*
Responder rate (%)e	6	19	28	19	20	31

AE = adverse event L = Low CLcr (30-60 mL/min) N = CLcr > 60 mL/min Responder = patient with ≥ 50% decrease in pain from baseline
* statistically significantly different from placebo

Of note, protocol –196 was a 13-week study. Therefore, efficacy was evaluated both at endpoint and at Week 8.

The table above shows that replicated efficacy of pregabalin 150- and 300 mg/d in patients with low creatinine clearance, as determined by the mean pain score at endpoint, has not been shown. In contrast, these doses appear to be efficacious in patients with CLcr > 60 mL/min.

The table also shows that the frequency of treatment responders in the placebo group varied by study. Therefore, assessment of superiority of pregabalin treatment over placebo was done within studies, and not across studies. The studies were inconsistent with regards to whether treatment of pregabalin (150- or 300 mg/d) in patients with low creatinine clearance resulted in a greater proportion of treatment responders. However, pregabalin treatment in patients with CLcr > 60 mL/min resulted in more patients with a treatment response compared to placebo therapy.

Consequently, the data presented in the table do not support Pfizer's hypothesis that similar drug exposure would result in comparable efficacy. Pfizer theorized that, since pregabalin is cleared by the kidneys, exposure to a given dose of drug in patients with low creatinine clearance (30-60 mL/min), would be similar to the exposure of twice as much drug in patients with normal creatinine clearance (> 60 mL/min). For example, exposure of 300 mg/d in patients with low creatinine clearance would be the same as that of 600 mg/d in patients with normal creatinine clearance. Pfizer concluded that similar exposure would result in similar efficacy. Our analysis does not show this.

One reason why the low creatinine clearance groups did not show a difference from placebo could be that the size of these groups was insufficient to show a difference from placebo, with respect to mean pain scores. The relatively higher proportions of responders in these pregabalin groups compared to placebo lends support to the argument that the drug is efficacious in those groups, and perhaps if the groups were larger, a significant difference in mean pain score could be achieved.

An alternative reason for the differences the apparent lack of efficacy of pregabalin in the low creatinine clearance groups could be related to patient characteristics. Not surprisingly, patients in the low creatinine clearance group were older than the patients with normal creatinine clearance:

Table 6.3.4.b: Mean age of patients in PHN efficacy trials, by CLcr and drug dose

		Treatment group Mean Age, years (ITT population)						
	Placebo	75 mg/d		150 mg/d		300 mg/d		600 mg/d
CLcr		L	N	L	N	L	N	N
Protocol –030	71.3	76.6	69.0	77.0	64.8	-	-	-
Protocol -045	73.2	-	-	78.3	63.8	76.7	65.1	-
Protocol -127	70.5	-	-	-	-	78.2	-	69.5
Protocol –196	70.7	-	-	77.0	67.8	78.4	66.8	67.4

L: low creatinine clearance; N: normal creatinine clearance For details on protocol 030, see section 7.5

Based on the Division's BOCF method of imputing for missing data, the older patients who also had a low CLcr had a similar treatment effect as did patients given placebo. Under the BOCF method, patients who did not complete the study were assigned a baseline score. It was possible that more of the older patients in the low CLcr groups did not complete the study and were assigned their baseline score, than patients in the normal creatinine or the placebo groups. As a result, the mean pain scores would be higher in the low CLcr groups, and the proportion of treatment responders would be lower. That is, efficacy of pregabalin in this group would not be apparent.

To further examine this possibility, the disposition data were evaluated to see if there was a difference with respect to dropout rates and reasons for dropouts across the groups:

Table 6.3.4.c: Disposition – by actual dose administered/creatinine clearance grouping Protocol – 045

	Placebo	PGB 150-L	PGB 150-N	PGB 300-L	PGB 300-N
ITT (N)	81	42	39	45	31
Completed Study [N (%)]	61 (75.3)	36 (85.7)	35 (89.7)	30 (66.7)	30 (96.8)
Withdrawn [N (%)]:					
Adverse Event	8 (9.9)	6 (14.3)	3 (7.7)	12 (26.7)	0 (0.0)
Lack of Compliance	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)
Lack of Efficacy	7 (8.6)	0 (0.0)	0 (0.0)	1 (2.2)	0 (0.0)
Patient withdrew consent	3 (3.7)	0 (0.0)	1 (2.6)	2 (4.4)	0 (0.0)

Table 6.3.4.d: Disposition – by actual dose administered/creatinine clearance grouping Protocol – 127

	Placebo	PGB 300	PGB600
ITT	84	30	59
Completed Study [(n (%)]	74 (88.1)	17 (56.7)	41 (69.5)
Withdrawn [N (%)]:			
Adverse Event	4 (4.8)	11 (36.7)	17 (28.8)
Lack of Compliance	0 (0.0)	1 (3.3)	1 (1.7)
Lack of Efficacy	6 (7.1)	0 (0.0)	0 (0.0)
Patient withdrew consent	0 (0.0)	1 (3.3)	0 (0.0)

Table 6.3.4.e: Disposition – by actual dose administered/creatinine clearance grouping Protocol – 196

	Placebo	PGB 150-L	PGB 150-N	PGB 300-L	PGB 300-N	PGB 600
ITT	93	26	61	59	65	64
Completed Study	59 (63.4)	15 (57.7)	46 (75.4)	35 (59.3)	43 (61.1)	44 (68.8)
Withdrawn:						
Adverse Event	5 (5.4)	5 (19.2)	2 (3.3)	13 (22.0)	7 (10.8)	14 (21.9)
Lack of Compliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.6)
Lack of Efficacy	22 (23.7)	5 (19.2)	11 (18.0)	9 (15.2)	9 (13.8)	1 (1.6)
Patient withdrew consent	7 (7.5)	1 (3.8)	2 (3.3)	2 (3.4)	5 (7.7)	4 (6.3)

Overall, fewer patients in the low creatinine groups completed the trials compared to patients with a normal creatinine clearance. The most frequent reason for discontinuation among patients

with low creatinine clearance was adverse events, and these occurred with higher frequency than in patients with a normal creatinine clearance. As already discussed, patients in the low creatinine groups were older than the other patients were. The relatively high rate of withdrawal due to adverse events suggests intolerability of the drug for this sub-group of patients. Specific causes for withdrawal are tabulated in Table 6.3.4.f below:

Table 6.3.4.f: AEs leading to withdrawal/discontinuation, by CLcr and drug dose – PHN controlled trials (protocols 30, 45, 127, & 196)

Body system	Preferred term	Placebo		75-L		75-N		150-L		150-N		300-L		300-N		600-N		Low CLcr		High CLcr	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Nervous system	Dizziness	3	0.87	0	0	0	0	3	2.83	2	1.38	6	4.48	1	1.04	8	6.5	9	3.18	11	2.72
	Somnolence	1	0.29	0	0	0	0	1	0.94	1	0.69	7	5.22	1	1.04	9	7.32	8	2.83	11	2.72
	Confusion	1	0.29	0	0	0	0	1	0.94	0	0	0	0	1	1.04	7	5.69	1	0.35	8	1.98
	Ataxia	0	0	0	0	0	0	0	0	0	0	3	2.24	1	1.04	3	2.44	3	1.06	4	0.99
	Hallucinations	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2.44	0	0	3	0.74
	Abnormal gait	0	0	0	0	0	0	0	0	0	0	2	1.49	0	0	2	1.63	2	0.71	2	0.49
	Speech disorder	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	2	1.63	1	0.35	2	0.49
	Anxiety	0	0	0	0	0	0	0	0	1	0.69	0	0	0	0	1	0.81	0	0	2	0.49
	Diplopia	0	0	0	0	0	0	0	0	1	0.69	0	0	0	0	1	0.81	0	0	2	0.49
	Nervousness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1.63	0	0	2	0.49
	Vertigo	0	0	0	0	0	0	1	0.94	0	0	1	0.75	0	0	0	0	2	0.71	0	0
Body as a whole	Asthenia	1	0.29	1	2.33	0	0	1	0.94	0	0	1	0.75	0	0	1	0.81	3	1.06	1	0.25
Digestive system	Dry mouth	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	3	2.44	0	0	3	0.74
	Constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1.63	0	0	2	0.49
Metabolic/ nutritional disorders	Peripheral edema	1	0.29	0	0	0	0	0	0	0	0	3	2.24	0	0	3	2.44	3	1.06	3	0.74
	Edema	0	0	0	0	0	0	1	0.94	0	0	1	0.75	0	0	2	1.63	2	0.71	2	0.49
Special senses	Abnormal vision	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	2	1.63	1	0.35	2	0.49
	Blurred vision	0	0	0	0	0	0	0	0	0	0	1	0.75	1	1.04	1	0.81	1	0.35	2	0.49

* The COSTART preferred term used to code for this AE was "amblyopia"

Table 6.3.4.f shows that more patients with a low creatinine clearance than patients with a normal creatinine clearance withdrew because of dizziness, somnolence, and edema. As was described in my previous review of pregabalin (N 21-446), and as is described in Section 7 below, these are adverse effects commonly associated with pregabalin treatment.

In summary, the data suggest that older patients and/or patients with a low creatinine clearance do not tolerate pregabalin well as patients with normal creatinine clearance, primarily due to effects known to be associated with the drug. Consequently, patients discontinue treatment and are less likely to benefit from treatment.

6.4 Efficacy Conclusions

Based on the Agency's analyses, three clinical trials show the efficacy of pregabalin as treatment for postherpetic neuralgia. Two trials showed efficacy of a TID dosing regimen, and one trial showed efficacy of BID dosing. Treatment with pregabalin 300-, and 600 mg/d was shown reduce the mean pain score at study endpoint, compared to treatment with placebo. Similar results were noted when the proportion of patients with a treatment "response" (a decrease in of at least 50% from baseline) was compared across pregabalin and placebo groups.

Efficacy of pregabalin appeared to be limited by CLcr. Patients with a low creatinine clearance were less able to tolerate the adverse effects of the drug, and subsequently discontinued treatment. This was true regardless of the size of the pregabalin dose (75-, 150- or 300 mg/d). Patients with a normal creatinine clearance were more likely to experience significant improvement in pain, particularly at the higher doses (300- and 600 mg/d)

A favorable treatment response was observed with both a BID and TID dosing regimen.

7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

Exposure

Per the initial NDA integrated safety database, 9469 patients have been exposed to pregabalin during clinical pharmacology trials and Phase 2/3 trials in various indications. The integrated safety database for this application is comprised of 8666 subjects who participated in Phase 2/3 trials in epilepsy (EPI), generalized anxiety disorder (GAD), postherpetic neuralgia (PHN), pain due to diabetic neuropathy (DPN), chronic [redacted] pain, osteoarthritis, fibromyalgia, acute mania, panic disorder, and social anxiety disorder. With respect to patients with postherpetic neuralgia, a total of 1111 patients have received at least one dose of pregabalin. To date, 212 and 48 subjects with PHN have been exposed to the proposed marketed doses (300- and 600 mg/day), for at least 6 months, and 1 year, respectively. While the long-term exposure for the PHN population is low, exposure based on the total population is adequate to meet ICH guidelines for patient exposure.

Deaths

A total of 55 deaths occurred in patients included in the integrated safety database. Considering only those deaths that occurred within 30 days of last pregabalin exposure, the mortality risk was 0.5%. Deaths were generally cardiac-related, and consistent with causes of death in older populations. The exception was the epilepsy population, where deaths were also associated with seizure activity. There was no clear association between the use of pregabalin and death.

Serious adverse events

Overall, the incidence of SAEs in all controlled studies was similar between all pregabalin-treated patients (2.3%) and placebo patients (2.1%). The most commonly occurring SAEs included accidental injury, chest pain, angina pectoris, myocardial infarction, congestive heart failure, and pneumonia. A different pattern was seen when only the PHN population was considered. In this population, treatment with pregabalin did not appear to convey a slightly greater risk of SAEs. The most common SAE was cerebral ischemia.

SAEs of interest, and for which an alternate possible cause is not apparent, were anaphylactoid reaction, acute renal failure, leukemoid reaction, macrocytic anemia, edema, abscess, cellulitis, accidental injury, visual field defect, abnormal LFTs, cholestatic jaundice, cardiomyopathy, and pulmonary fibrosis.

Common (non-serious) adverse events

CNS-related AEs - particularly dizziness, somnolence, ataxia, vertigo, confusion, abnormal thinking, and euphoria - were the most frequently occurring non-serious AEs,. Additionally, edema (face, generalized, or peripheral) was also extremely common. The incidence of common AEs appeared to be dose-related.

Adverse events of interest

Compared to placebo patients, patients treated with pregabalin more frequently reported blurred vision, diplopia and "abnormal vision". Similar results were seen when data from only the PHN

population were examined. The risk of blurred vision appeared to be dose dependent. Finally, the incidence of peripheral edema and infection was higher for patients in the pregabalin groups compared to placebo.

Laboratory values
The most notable differences between treatment groups with respect to mean changes from baseline were an increase in creatinine kinase, and a decrease in platelet count among pregabalin-treated patients, compared to placebo patients. These changes were evident in the overall population, and in the DPN population alone. The increase in creatinine kinase was greatest in the epilepsy population, and therefore the increase noted in the overall population may be reflective of seizure-related changes in that population. A clinical pharmacology study, conducted to explore the theory that hemangiomas associated with pregabalin treatment developed as a consequence of drug-induced changes in platelet parameters, showed no significant effect of pregabalin on platelet aggregation and activation. This study's findings therefore also did not provide a possible mechanism for the observed decrease in platelet count in clinical trials.

Vital signs, weight, ECGs
There were no differences in vital signs between placebo and pregabalin groups with respect to mean changes from baseline, or in the proportion of subjects who had clinically significant changes from baseline. Across indications, weight gain was higher among pregabalin-treated patients and was greatest among patients treated with pregabalin 600 mg/d. Weight gain and edema did co-occur, however edema alone does not explain all of the weight gain. With the exception of a mild increase in PR interval, pregabalin did not appear to have a clinically significant effect on ECG parameters.

7.2 Materials Utilized in the Review

Refer to my review of NDA 21-446, "pregabalin as treatment for pain associated with diabetic peripheral neuropathy) for details regarding all of the materials upon which the safety review was based.

Briefly, 53 trials were submitted for safety analyses in the NDA and the safety update. They explored the following indications: epilepsy, [redacted] fibromyalgia, [redacted], generalized anxiety disorder (GAD), [redacted], postherpetic neuralgia (PHN), pain due to diabetic neuropathy (PDN), [redacted].

Pfizer presented the pregabalin safety data using 2 major groupings. "Group 1" data comprised 30 Phase 2/3 double-blind, placebo-controlled studies in the indications listed above. These studies were considered the primary source for safety because they were placebo-controlled and had the largest exposure to the pregabalin doses that are proposed for marketing. Data from Group 1 studies were subdivided by the indications being sought (GAD, epilepsy, postherpetic neuralgia, and pain due to diabetic peripheral neuropathy), as well as by other exploratory indications. "Group 2" data included all controlled and uncontrolled studies.

Additional safety data were collected from 28 Phase 1 studies and 3 acute dental pain trials. However these data were not included in the integrated safety database but were instead put in the integrated clinical pharmacology database (locked on June 4, 2001). One additional clinical pharmacology study to assess platelet function in healthy volunteers (Study A0081022) was included in the application, but this study was not included in the integrated clinical pharmacology database because it completed after the cutoff date for the integrated safety database.

Although safety data was obtained from 2 Phase 2/3 studies that were conducted in Japan, this information was also not included in the integrated safety database. The studies were conducted in patients with postherpetic neuralgia (Study 3J) and trigeminal neuralgia (Study 4J). Both studies were prematurely terminated at the time of the clinical hold in the US. As a result, the number of patients in each study (31 and 34, respectively) was relatively small. Synopses of the study show that there were no deaths, and only 3 patients with SAEs (accidental injury; nausea/vomiting/dizziness; malaise). Non-serious AEs were otherwise not remarkable from other trials. Based on this information, as well as the relatively large size of the safety data obtained from Western sites, Pfizer chose to evaluate the Japanese studies independently and not include them in the integrated safety database.

There were no secondary sources for safety data since all of the Applicant's safety data were derived from studies conducted under the IND.

7.2.1 Approach to Safety Review/Methods

The objective of the safety review was to ascertain the effects of pregabalin, first on all exposed patients and then on patients with postherpetic neuralgia (PHN). Some aspects of the review of the overall database were conducted by Dr. Gerard Boehm, of DNDP (HFD 120). Since the database was comprised of trials for multiple indications, data from these studies were not pooled for several analyses. the incidence of common adverse events (AEs) and the frequency of select AEs of interest within the PHN population were specifically examined.

Using the electronic Summary of Clinical Safety (SCS) submission, the 120-day Safety Update, and responses to specific reviewer questions, I reviewed the identified treatment emergent adverse events. In the clinical trials, adverse events were elicited by open-ended questions. Pfizer coded adverse event terms to the preferred terms using the COSTART thesaurus, IVth edition.

I evaluated the adverse event data for accuracy. For selected events (e.g. edema and blurred vision), I reviewed the coding of a sample of those events in more detail by examining the CRFs, electronic data sets, narratives, and study report listing to verify that the coded terms accurately reflected the described events. Due to the large size of the database, I limited the sample to adverse events that led to dropout in DPN controlled trials. Based on this audit, the Applicant's preferred terms appeared appropriate with the exception of "amblyopia" and "angioma." The Applicant coded all verbatim terms describing blurry vision to the preferred term "amblyopia," which is incorrect. For the purposes of my review, I re-coded "amblyopia" to "blurred vision." Also, the Applicant coded events of 'angioma' and 'cherry angioma' under "cardiovascular system" instead of "neoplasms."

I reviewed the death narratives for all study subjects who died and summarized the clinical details for selected deaths. In addition, I reviewed the CRFs, narrative summaries, data sets, and study reports for a subset of SAEs, select AEs that led to premature study withdrawal, and AE preferred terms that were suggestive of AEs of interest.

Finally, I reviewed the results of Pfizer's AE risk calculations, as well as laboratory and vital sign data analyses. Unfortunately, due to the formatting of the data, I was unable to conduct additional analyses of extreme lab outliers, blood pressure outliers, and QTc data.

7.3 Description of Patient Exposure

7.3.1 Number of subjects exposed

Pfizer reported that 9469 subjects have received at least 1 dose of pregabalin. All subjects in Phase 2/3 studies used the immediate release (IR) formulation capsules, with pregabalin strengths of 25, 50, 75, 100, 150, 200, or 300 mg. There were 21 subjects in other studies who received pregabalin as either solution or modified-release formulation. I calculated that there were 9480 subjects exposed in total. My evaluation of subject exposure to pregabalin by dosage form and clinical study is shown below:

Table 7.3.1.a: Total number of subjects exposed to pregabalin

Study Type	No. subjects exposed
Integrated phase 2/3 database*	8, 666
Japanese phase 2/3 studies	51
pain studies	267
Integrated phase 1/clinical pharmacology database**	440
Japanese phase 1/clnical pharmacology studies	36
Clinical pharmacology study of platelet function	20
Total	9, 480

* Includes both controlled and open-label extension trials
** Includes patients who received pregabalin in solution or modified-release form

Using information from the integrated safety database, I calculated subjects' exposure to pregabalin in controlled and uncontrolled trials, for PHN as well as all indications:

Table 7.3.1.b: Exposure to pregabalin, uncontrolled and controlled studies

Indication	Controlled Trials		Uncontrolled trials
	Placebo	Pregabalin	Pregabalin
All Indications	2 384	5 508	8 666
PHN	398	852	793

Like Pfizer, I found that 852 subjects were exposed to pregabalin during controlled trials. However, whereas Pfizer found that 735 subjects were treated with pregabalin during uncontrolled trials (SCS, Table 48, RR-REG 720-30199, P. 111), using the NEWDOSE.xpt data set I calculated that there 793 such subjects.

7.3.2 Duration of exposure

Duration of exposure - All indications

Pfizer summarized all pregabalin exposure (all indications) by treatment dose, for both controlled studies (n = 5508), as well as combined controlled and uncontrolled trials (n = 8666). The tables below show that there were 411 subjects (7.5%, 411/5508) in the controlled trials that were treated with 600 mg/day for at least 3 months. Pfizer found that approximately 2415 subjects (28%) in both controlled and uncontrolled studies were exposed to pregabalin for at least 1 year, and 939 subjects (11%) for at least 2 years.

Table 7.3.1.c: Exposure to pregabalin, Controlled studies – All indications

Table 4. Summary of Exposure to Pregabalin: Controlled Studies—All Indications (009, 011, 014, 017, 021, 022, 025, 026, 029, 030, 031, 032, 034, 040, 045, 080, 081/153, 083, 085, 087, 092, 094, 104, 105, 127, 131, 132, 149, 173, 196)

[Number of Patients (%)]

Total Exposure Time[a]	Total Daily Dose of Pregabalin in mg/day (Regimen)									
	150 (BID) N=357	150 (TID) N=807	200 (BID) N=208	300 (BID) N=460	300 (TID) N=764	400 (BID) N=360	450 (TID) N=501	600 (BID) N=551	600 (TID) N=1251	Any Dose[b] N=5508
≥1 day	357(100.0)	807(100.0)	208(100.0)	460(100.0)	764(100.0)	360(100.0)	501(100.0)	551(100.0)	1251(100.0)	5508(100.0)
≥1 week	348(97.5)	782(96.9)	202(97.1)	427(92.8)	728(95.3)	337(93.6)	470(93.8)	506(91.8)	1165(93.1)	5212(94.6)
≥2 weeks	327(91.6)	761(94.3)	189(90.9)	386(83.9)	700(91.6)	318(88.3)	453(90.4)	465(84.4)	1082(86.5)	4917(89.3)
≥4 weeks	291(81.5)	714(88.5)	166(79.8)	334(72.6)	653(85.5)	289(80.3)	410(81.8)	428(77.7)	953(76.2)	4463(81.0)
≥6 weeks	261(73.1)	436(54.0)	146(70.2)	296(64.3)	474(62.0)	269(74.7)	318(63.5)	395(71.7)	619(49.5)	3298(59.9)
≥8 weeks	250(70.0)	257(31.8)	87(41.8)	275(59.8)	365(47.8)	126(35.0)	196(39.1)	295(53.5)	465(37.2)	2396(43.5)
≥10 weeks	232(65.0)	120(14.9)	53(25.5)	245(53.3)	123(16.1)	59(16.4)	65(13.0)	260(47.2)	305(24.4)	1540(28.0)
≥12 weeks	171(47.9)	88(10.9)	5(2.4)	196(42.6)	59(7.7)	1(0.3)	4(0.8)	212(38.5)	190(15.2)	975(17.7)

[a] Study days on which patients received zero dose during the study are included. The total exposure time includes titration and fixed-dose phases.
[b] Includes other doses of pregabalin (eg, 50 or 75 mg/day).

(Applicant's Table 4, RR-REG 720-30199, P. 22)

Table 7.3.1.d: Applicant's summary of exposure to pregabalin: Combined Controlled and Uncontrolled Studies, All Indications

Total Exposure Time[a]	Number (%) of Patients Any Dose Pregabalin N=8666
≥12 weeks	5,095(58.8)
≥24 weeks	4,010(46.3)
≥36 weeks	3,223(37.2)
≥52 weeks	2,415(27.9)
≥104 weeks	939(10.8)
≥156 weeks	284(3.3)

[a] Study days on which patients received zero dose during the study are included.
(Applicant's Table 5, RR-REG 720-30199, P. 22)

To verify the findings of the above table, I recalculated the total exposure to pregabalin for both controlled and uncontrolled trials. My analysis found considerably fewer subject exposures per time period, compared to the Applicant. These differences may be due to differences in how the duration (in weeks) was calculated, and/or in rounding off the total duration of exposure. My findings are shown in the table below:

Table 7.3.1.e: Reviewer's analysis of total pregabalin exposure: Combined controlled and uncontrolled Studies, All indications

Total Exposure Time[a]	Number (%) of Patients Any Dose Pregabalin N=8666
≥ 1 day	8 666 (100)
≥ 1 week	7 981 (92.1)
≥ 2 weeks	7 598 (87.7)
≥ 3 weeks	7 244 (83.6)
≥ 4 weeks	6 646 (76.7)
≥ 8 weeks	5 211 (60.1)
≥ 12 weeks	4 037 (46.6)
≥ 16 weeks	3 531 (40.7)
≥ 24 weeks	2 931 (33.8)
≥ 26 weeks (6 mos)	2 732 (31.5)
≥ 52 weeks (1 year)	1 332 (15.3)
≥ 78 weeks (1.5 years)	824 (9.6)
≥ 104 weeks (2 years)	427 (4.9)
≥ 156 weeks (3 years)	110 (1.27)

[a] Study days on which patients received zero dose during the study are included.

Duration of exposure – PHN trials

The overall safety database for all pregabalin development programs includes 8666 individuals who were exposed to pregabalin and are included in the integrated safety database. In the PHN program, a total of 852 patients received at least one dose of pregabalin in controlled trials, and an additional 259 patients who had been treated with placebo participated in open-label extensions. Therefore, the total PHN population exposed to pregabalin was 1111 (SCS, RR-REG 720-301999, P. 111). Using the NEWDOSE.xpt data set, I determined how many subjects in the PHN trials were exposed to the proposed marketed doses (300- and 600 mg/day) for at least 1 year (Table 7.3.1.f). Based on that data set, I found that 1126 PHN patients were exposed to pregabalin: 212 and 48 subjects were exposed to the proposed marketed doses (300 and 600 mg) for at least 6 months and one year, respectively.

While long-term exposure for the PHN population is low, exposure based on the total population (i.e. all treated populations) is adequate to characterize the safety profile and met ICH requirements..

Table 7.3.1.f: Exposure to pregabalin by dose and duration, Controlled and Uncontrolled studies, PHN vs. All Indications

	Pregabalin dose			
	300 mg/day		600 mg/day	
Duration	PHN [n=1126] N	ALL*[n=8666] N	PHN [n=1126] N	ALL*[n=8666] N
≥ 1 day	1119		486	
≥4 wks	518	2 423	330	2 514
≥ 8 wks	299	1 537	251	1 999
≥ 12 wks	210	1 041	195	1 550
≥ 24 wks	104		108	
≥ 26 wks	88	526	99	1106
≥ 52 wks (1 year)	20	193	28	664
≥ 78 wks (1.5 years)	11	83	20	484
≥ 104 wks (2 years)	3	32	5	263

* ALL: All subjects exposed to pregabalin

Of the total exposed population (n = 8666), 6969 patients took at least one dose of pregabalin 300 mg, and 3333 patients took at least one dose of pregabalin 600 mg. There were 1126 PHN patients who took at least one dose of pregabalin.

7.3.3 Exposure: Demographics

Of the 5508 patients who were treated with pregabalin during all controlled studies, 53.6% were women and 88.1% were white. Patient age ranged from 12 to100 years, with a mean of 49 years. There were 1205 (21.9%) patients who were at least 65 years old. By indication, 33.2% of pregabalin-treated patients were enrolled in neuropathic pain studies(17.8% DPN and 15.4% PHN), 13.8% in epilepsy studies, 20.9% in GAD studies, 19.4% in other chronic pain studies, and 12.7% in other psychiatry studies. Characteristics of the 8666 patients treated with pregabalin in the combined controlled and uncontrolled studies were similar to those in the controlled studies (SCS, APP. 8 & 9).

7.4 Safety Findings from Clinical Studies

7.4.1 Deaths

7.4.1.1 Deaths in the overall integrated safety database

Pfizer provided the following table that summarizes the deaths by indication for the integrated safety database.

Table 7.4.1.1.a. Summary of Deaths by Indication: Combined Controlled and Uncontrolled Studies All Indications

Data in the Integrated Clinical Safety Database (All Chronic Controlled and Uncontrolled Studies)	DPN	PHN	Epilepsy	GAD	All Studies[a]
Median Age (Years)	60	73	38	38	47
% of Patients ≥65	32.3%	79.1%	1.9%	2.5%	19.3%
N Treated With PGB	1413	1111	1613	1962	8666
Number (%) of Deaths	17 (1.2%)	19 (1.7%)	14 (0.9%)	1(0.05%)	55(0.6%)
Patient-Years of Exposure	1421	649	2461	626	6394
Deaths/1000 Patient-Years	11.9	29.3	5.6	1.6	8.6

[a] Includes patients from non-neuropathic pain studies and other psychiatric disorders.
(Applicant's Table 15, RR-REG 720-30199, P. 39)

This table demonstrates that the mortality risk was not uniform across indications, with the highest mortality risk observed in the post-herpetic neuralgia and diabetic neuropathy study groups. This table also demonstrates the differences in ages of the different study populations. The pain indication study groups were comprised of older individuals compared to the epilepsy and anxiety study populations.

Pfizer reported that, as of the cutoff date for the integrated safety database (2/14/03), there were 55 deaths in subjects treated with pregabalin. The mortality risk was therefore 0.63% (55/8666) and the mortality rate was 8.6/1000PY (55/6393PY). Pfizer noted that not all of these deaths occurred within 30 days of last pregabalin exposure (Summary of Clinical Safety p.38). Considering only those deaths occurring within 30 days of last pregabalin exposure, the mortality risk was 0.5% (43/8666) and the mortality rate was 6.7/1000PY (43/6393PY).

Pfizer found that 6 pregabalin deaths (0.1%, 6/5508) and one placebo death (0.04%, 1/2384) occurred during controlled trials. The mortality rate for pregabalin subjects in controlled trials was 7.9/1,000PY (6/790 PY) compared to 3/1,000PY (1/336PY) for placebo subjects. I reviewed all deaths during controlled trials to evaluated whether there was an association with study treatment:

Table 7.4.1.1.b. Summary of deaths during all controlled studies - All indications

Patient ID	Trial	Treatment group	Cause of death	StudyDay of last dose	StudyDay of death
040-072020	DPN	600 mg/d	Sudden death; Follow-up labs on Day 78 showed increased alk phos, bilirubin, CK, and BUN	Day 7	Day 85
149-391002	DPN	300 mg/d	Heart failure	Day 21	Day 21
149-415019	DPN	150 mg/d	Myocardial infarction in the setting of a gastrointestinal bleed	Day 5	Day 18
173-319003	DPN	600 mg/d	Died following onset pulmonary congestion with chest pain and tachycardia	Day 21	Day 65
181-002003	GAD	400 mg/d	Suicide	Day 2	Day 45
045-010002	PHN	300 mg/d	Myocardial infarction	Day 18	Day 143
045-066001	PHN	Placebo	Myocardial infarction	Day 46	Day 47

There were 3 deaths that occurred within 30 days of dosing during controlled trials – 2 among pregabalin-treated patients, and 1 among placebo patients. Consequently, the mortality rate for pregabalin patients can be considered to be 2.5/1000 PY (2/790 PY), which is not considerably different from the placebo mortality rate (3/1000 PY). Furthermore, in each of the 2 deaths among pregabalin-treated patients, there was an alternate possible explanation for the death. Together with the observation that the other deaths occurred greater than 30 days of last pregabalin dose, the data suggest that treatment with pregabalin did not confer a greater risk of death, even though the overall proportion of deaths was greater in the pregabalin group than in the placebo group.

Forty-nine deaths occurred during uncontrolled trials. The mortality rate for uncontrolled trials was 8.7/1,000PY (49/5633PY). Pfizer applied the age specific death rates from the US population (2001) to the open label study population to calculate a standardized mortality ratio (SMR). The SMR was 0.85 (95% CI 0.74, 1.32) which Pfizer interpreted as supporting the conclusion that the number of deaths observed in the open label study population was similar to that expected given the patients age, gender and follow up time (SCS, Section 2.5.5.2.2, p.94). Agency review of the deaths in uncontrolled trials also found that deaths were associated with a brief treatment duration and a relatively long latency between last dose of pregabalin and death.

Unlike Pfizer, I found that there were 57 deaths among patients exposed to pregabalin. Similar to Pfizer, I counted 14 deaths in the epilepsy population, 17 deaths in the DPN population, and 1 death in the GAD population. However, I noted 20 deaths in the PHN population (compared to Pfizer's 19), and 5 deaths in other treatment populations (compared to Pfizer's 4). The number of deaths in the safety database, and their cause are listed below.

Table 7.4.1.1.c. Cause-specific deaths: All studies, all indications

Cause of death	No patients	Cause of death	No patients
Myocardial infarction/myocardial ischemia/cardiac arrest	13	Pulmonary embolus	2
Cancer	6	Sudden death	2
Unknown	5	Cardiogenic shock	1
Seizure-related	4	COPD*	1
Heart failure*	4	Fall	1
Pneumonia *	4	Gastrointestinal bleed	1
Respiratory failure	3	Pulmonary hypertension*	1
Multiple organ failure*	3	Septicemia	1
Cardiomyopathy (ischemic/dilated)	2	Suicide	1
Cerebral hemorrhage	2		

* 1 death each occurred in trials other than EPI, DPN, GAD, and PHN
(Safety Update summary, Appendix ALL.14, P. 369-383)

The table shows that the majority of deaths were cardiac-related, and occurred in the DPN and PHN populations. The study investigators did not attribute any of the deaths to study medication. I find that there was 1 death that did not have a clear alternate etiology. This death is discussed below:

Patient 012-084102
This was a 68 year old male with a history of partial seizures. He suffered a fall on Study Day 828 of open-label treatment with pregabalin 600 mg/day. Details regarding the fall are not available. On Study Day 830 he was hospitalized for a perinephric hematoma and pericardial effusion. Hospital course was complicated by renal failure, pleural effusions, and need for ventilatory support. He died on Study Day 834. Autopsy revealed bilateral adrenal hemorrhage, left renal infarct with massive perinephric hematoma, and bilateral pleural effusions.

It is possible that the patient suffered the fall during a seizure. Alternatively, the patient could have fallen due to known adverse effects of pregabalin, specifically dizziness, somnolence, ataxia, and/or incoordination. The autopsy is consistent with renal hemorrhage due to injury, and the patient's renal failure could be due to ensuing tissue infarction. Due to the renal failure, the patient could have developed volume overload, manifest by pleural effusions. In my opinion, therefore, the cause of death was a fall, possibly due to adverse effects of pregabalin.

For a detailed discussion of all deaths in the integrated safety database, please refer to my clinical review of N 21-446 (pregabalin as treatment for pain due to diabetic peripheral neuropathy (DPN)). A comprehensive list of narratives of patient deaths is located in the Appendix.

Deaths from ongoing studies/not included in the integrated safety database
Pfizer reported 10 additional (1 placebo, 9 pregabalin) deaths that are not included in the integrated safety database. These deaths occurred in patients in ongoing blinded studies, or were reported to the Applicant's serious adverse event database but not entered into the clinical trial safety database (SCS, p.39). The reported causes of death for the 10 patients are summarized in the my clinical review of N-21-446. None of the deaths appeared attributable to study medication.

7.4.1.2 Deaths in the PHN population

Whereas Pfizer identified 19 deaths in patients with PHN, I identified 20 deaths in such patients. Therefore, the total mortality for subjects in PHN studies was 1.8% (20/1111). The mortality rate for these trials was 30.8/1000 PY (20/649PY). One subject (placebo patient) died during participation in a controlled trial, and another died following premature withdrawal from a controlled trial. . Both patients died due to a myocardial infarct. An additional 18 subjects died during PHN uncontrolled trials,.

The majority of deaths were cardiac related (n = 9). Four deaths were due to cancer and 4 deaths due to pneumonia. Deaths in PHN trials are listed below. Summaries of patient deaths were constructed using the patient narratives, CRFs, data sets, and patient profiles and are in the Appendix. None of the deaths is indicative of a clear association with pregabalin treatment.

Table 7.4.1.2: Deaths in PHN Trials

Body System	Cause of Death	No. Patients
Cardiovascular	Myocardial infarct	5
	Cardiac arrest	2
	Cardiogenic shock	1
	Ischemic cardiomyopathy	1
Gastrointestinal	Gastrointestinal bleed	1
	Pancreatic necrosis	1
Neoplasm	Throat cancer	1
	Renal cell carcinoma	1
	Metastatic carcinoma (unknown primary)	1
	Small cell carcinoma	1
Pulmonary	Pulmonary embolus	1
	Respiratory failure	1
	Pneumonia	3

7.4.2 Assessment of dropouts

7.4.2.1 Pattern of dropouts – All controlled trials

The tables below provide an enumeration of subjects who prematurely discontinued treatment in controlled and uncontrolled trials of pregabalin. The reasons for discontinuation were categorized on the basis of the investigator's judgment of the single most important reason for withdrawal on the "Patient Status" form of the CRF. Tables 7.4.2.1 and 7.4.2.2 list the patient disposition for patients treated with pregabalin in all controlled and uncontrolled trials, respectively. Note that fewer patients are reported as withdrawn due to adverse events than those on the Adverse Event form of the CRF. Therefore, withdrawals due to AEs are summarized in the adverse event tables (see Section 7.4.6).

The assessment of premature withdrawal from all controlled studies is shown in Table 7.4.2.1. I found that there were 2 patients (pregabalin-treated) who discontinued study participation due to significant improvement in pain, where as Pfizer identified none. Also, while Pfizer found 557 pregabalin-treated patients who withdrew due to "other" reasons, I found 555. The table shows that, in all the controlled trials, slightly more placebo patients completed the trials than patients

treated with pregabalin. Placebo patients dropped out more frequently for lack of efficacy than did pregabalin patients. Conversely, more pregabalin-treated patients dropped out due to adverse events.

Table 7.4.2.1: Patient disposition – Controlled trials, All indications

Patient Status	Placebo N	[N = 2384]* %	Pregabalin N	[N = 5508]* %
Completed Treatment [1]	1782	(74.7)	3942	(71.6)
Reasons for discontinuation				
Adverse event [2]	158	(6.6)	731	(13.3)
Lack of efficacy	155	(6.5)	183	(3.3)
Significant improvement	0	(0.00)	2	(0.04)
Lack of compliance	39	(1.6)	95	(1.7)
Other [3]	250	(10.5)	555	(10.1)

1 Completion of the Termination Visit was considered indicative of completion of study treatment
2 Per the Patient Status CRF; more patients were reported as withdrawn due to AEs on the Adverse Event CRF and are therefore summarized in the adverse event tables
3 Includes patients who were withdrawn due to early termination of study per the FDA, patients lost to follow-up, and patients who withdrew consent
(Adapted from Pfizer's Summary of Clinical Safety, Table 19, p. 50)

7.4.2.2 Pattern of dropouts - All uncontrolled trials

Table 7.4.2.2 shows my results regarding subject disposition of subjects in all uncontrolled trials. Using the stat.xpt data set, I first identified all uncontrolled trials, and then I determined the disposition status based on information from the Termination Visit. I found that there were 4530 subjects who had disposition data on Termination Visit forms. Adding this value to the 962 subjects that Pfizer reports were ongoing in clinical trials at the time of data cut off, gives a total of 5492 subjects whose study participation status was known – a total that exceeds the 5459 subjects that were exposed to pregabalin in open label studies, and for whom Pfizer provided disposition data (SCS, Table 20). One reason for the discrepancy could be that Pfizer determined patient disposition using data from the last available Patient Status form, and not just the Termination Visit form.

Table 7.4.2.2: Reviewer's Analysis, Patient disposition – Uncontrolled trials, All indications

Patient Status	Pregabalin, [N = 5459]* N (%) Sponsor	Pregabalin, [N = 5492]* N (%) Reviewer
Ongoing at data cutoff	962 (17.6)	962 (17.5)
Completed study [1]	479 (8.8)	497 (9.0)
Reasons for discontinuation		
Adverse event [2]	774 (14.2)	760 (13.8)
Lack of efficacy	934 (17.1)	912 (16.6)
Lack of compliance	213 (3.9)	212 (3.9)
Other [3]	2097 (38.4)	2149 (39.1)

* Number exposed to pregabalin in uncontrolled trials

1 Study completion was defined as completion of the study Termination Visit CRF

2 Adverse event includes subjects who were listed as "other" in the stat.xpt data set: 3 patients had abnormalities on eye exam, and 1 patient experienced weight gain

3 Other includes

- patients who were withdrawn due to early termination of the study per FDA, country's regulatory/ethics committee, or who individually failed requalification criteria
- Patients who were lost to follow-up
- Withdrew consent (e.g. due to reported tonicities in non-clinical studies)
- Did not meet individual study relapse criteria

7.4.2.3 Dropouts in PHN trials

Controlled PHN trials

Disposition data for PHN controlled trials show that all 1250 subjects who were randomized to study treatment completed Termination Visit forms of the CRF (placebo = 398, pregabalin = 852). Based on the data from these forms, I found that more pregabalin-treated subjects withdrew due to adverse events (14%) compared to placebo patients (7%). Approximately 10% of placebo patients withdrew because of lack of efficacy compared to 5% of pregabalin patients. Slightly fewer pregabalin patients completed PHN controlled studies than placebo patients did (Table 7.4.2.3.a).

Table 7.4.2.3.a: Patient status at study end – All PHN placebo controlled trials

Status	All Patients [N=1250]		Placebo [N=398]		Pregabalin 75 mg/d [N=84]		150 mg/d [N=302]		300 mg/d [N=312]		600 mg/d [N=154]		All Pregabalin [N=852]	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Completed	802	64.16	273	68.59	79	94.05	208	68.87	157	50.32	85	55.19	529	62.09
Adverse Event	149	11.92	26	6.53	2	2.38	29	9.6	51	16.35	41	26.62	123	14.44
Lack of Compliance	9	0.72	2	0.5	0	0	2	0.66	3	0.96	2	1.3	7	0.82
Lack of Efficacy	79	6.32	41	10.3	0	0	18	5.96	19	6.09	1	0.65	38	4.46
Other*	210	16.8	56	14.07	3	3.57	45	14.9	81	25.96	25	16.23	154	18.08
Patient withdrew consent	1	0.08	0	0	0	0	0	0	1	0.32	0	0	1	0.12

* Other includes termination of the study by the sponsor due to partial clinical hold, withdrawal of patient consent, and loss to follow-up. One patient (ISSPTID 196-126005) was listed as "other" but was withdrawn due to a suicide attempt.

Dropouts - Uncontrolled PHN trials

Of the 793 patients I identified as having participated in PHN uncontrolled trials, 568 completed the Termination Visit form of the CRF. More patients withdrew due to adverse events (19%) than for lack of efficacy (13%).

Table 7.4.2.2.b: Patient status at study end – All PHN uncontrolled trials

Patient status	Patients Total N = 793* N (%)
Completed	54 (6.8)
Adverse Event	149 (18.8)
Did not meet criteria	1 (0.1)
Did not meet relapse criteria	3 (0.4)
Lack of Compliance	22 (2.8)
Lack of Efficacy	103 (13.0)
Lost to Follow-Up	8 (1.0)
Other**	221 (27.9)
Patient withdrew consent	7 (0.9)

* Total is based on my analysis of the exposure data set (NEWDOSE.xpt)

** Other includes termination of the study by the sponsor due to partial clinical hold, withdrawal of patient consent, and loss to follow-up. Also, 3 patients (0.4%) reported insufficient pain to warrant continued treatment

7.4.2.4 Adverse events associated with dropout – PHN controlled trials

The number of patients withdrawing from PHN controlled trials due to specific adverse events is shown in Table 7.4.2.4. Dizziness, somnolence, confusion, peripheral edema, and ataxia were the most frequently reported adverse events that led to discontinuation of study participation among study patients, and occurred with much greater frequency in pregabalin patients compared to placebo patients. The highest dose of pregabalin (600 mg/d) was associated with more adverse events than the other treatment groups. Patients who withdrew and were taking

600 mg/d also reported facial edema, hallucinations, abnormal gait, vision abnormalities (diplopia, blurred vision), and headache with greater frequency than the other treatment groups.

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Table 7.4.2.4: Adverse events leading to withdrawal from controlled PHN trials (events occurring in ≥ 2 pregabalin-treated patients)

AE	Placebo N = 398		75 mg/d N = 84		150 mg/d N = 302		300 mg/d N = 312		600 mg/d N = 154		ALL PGB N = 852	
	N	%	N	%	N	%	N	%	N	%	N	%
Dizziness	3	0.75	0	0	11	3.64	12	3.85	12	7.79	35	4.11
Somnolence	1	0.25	0	0	6	1.99	12	3.85	10	6.49	28	3.29
Confusion	1	0.25	0	0	2	0.66	5	1.6	8	5.19	15	1.76
Peripheral edema	1	0.25	0	0	2	0.66	5	1.6	5	3.25	12	1.41
Ataxia	0	0	0	0	1	0.33	5	1.6	4	2.6	10	1.17
Asthenia	2	0.5	1	1.19	4	1.32	2	0.64	2	1.3	9	1.06
Abnormal gait	0	0	0	0	0	0	4	1.28	4	2.6	8	0.94
Face edema	2	0.5	0	0	1	0.33	2	0.64	2	1.3	5	0.59
Headache	2	0.5	0	0	2	0.66	0	0	3	1.95	5	0.59
Hallucinations	0	0	0	0	0	0	1	0.32	4	2.6	5	0.59
Nausea	3	0.75	0	0	2	0.66	2	0.64	0	0	4	0.47
Blurred vision*	1	0.25	0	0	1	0.33	2	0.64	1	0.65	4	0.47
Dry mouth	1	0.25	0	0	0	0	0	0	4	2.6	4	0.47
Edema	0	0	0	0	1	0.33	1	0.32	2	1.3	4	0.47
Speech disorder	0	0	0	0	0	0	2	0.64	2	1.3	4	0.47
Pain	1	0.25	1	1.19	2	0.66	0	0	0	0	3	0.35
Abnormal vision	0	0	0	0	0	0	1	0.32	2	1.3	3	0.35
Constipation	0	0	0	0	0	0	1	0.32	2	1.3	3	0.35
Diplopia	0	0	0	0	1	0.33	0	0	2	1.3	3	0.35
Thinking abnormal	2	0.5	0	0	0	0	1	0.32	1	0.65	2	0.23
Nervousness	1	0.25	0	0	0	0	0	0	2	1.3	2	0.23
Syncope	1	0.25	0	0	1	0.33	1	0.32	0	0	2	0.23
Ventricular extrasystoles	1	0.25	0	0	2	0.66	0	0	0	0	2	0.23
Anxiety	0	0	0	0	1	0.33	0	0	1	0.65	2	0.23
Myasthenia	0	0	0	0	1	0.33	1	0.32	0	0	2	0.23
Vertigo	0	0	0	0	1	0.33	1	0.32	0	0	2	0.23

* The COSTART term used to code for this adverse event was "amblyopia"

7.4.3 Serious adverse events

Pfizer pooled the safety data from the Phase 2/3 clinical trials in the following ways:
A*cross Indications*: (1) all controlled studies alone and (2) all controlled and open-label extension studies combined
B*y Indication*: (1) controlled studies alone, (2) uncontrolled studies alone (i.e., open-label extensions of the controlled studies), and (3) combined controlled and uncontrolled studies.

The controlled data were considered the primary safety data source, and displayed doses of 150- to 600 mg/day with pooling of BID and TID regimens. Doses of 50 and 75 mg/day (studied in epilepsy and neuropathic pain, respectively) were considered ineffective; and therefore were included in the "all pregabalin" analyses. The primary presentation for adverse event summaries reflects the randomized (fixed) dose.

During the open-label extension studies, adverse events were reported on open-label forms and were entered into the open-label databases (separate from the databases for the preceding double-blind studies). In some cases, however, the adverse event start dates suggested that they began during the preceding double-blind study. Therefore if, prior to the double-blind database closure and randomization code release, the adverse event was confirmed as having started during the double-blind study, the adverse event was removed from the open-label database and entered to the double-blind database. If the start dates were not resolved prior to double-blind database closure and randomization code release, the adverse event remained in the open-label database regardless of the start date. As a result, such adverse events were included only in summaries of combined double-blind and open-label data.

7.4.3.1 Overview of SAEs - All indications

The table below shows that the overall incidence of serious adverse events in the controlled studies was similar between all pregabalin-treated (2.3%) patients and placebo-treated (2.1%) patients. With respect to the individual indications, patients in the controlled DPN (3.9%), PHN, (3.3%), and epilepsy studies (3.8%) had similar incidences of adverse events, whereas the incidence in the GAD population was lower (0.6%). The relative risk (pregabalin vs. placebo), however, shows that the SAE risk was greatest for patients in the DPN and PHN populations (RR > 1.0), and that the SAE risks for GAD and epilepsy were < 1. The table also shows that that in the combined controlled and uncontrolled studies, incidences of SAEs were similar among the DPN (17.3%), PHN (13.1%), and epilepsy (13.0%) populations and lower in the GAD population (1.9%).

Table 7.4.4.1.a: Overview of SAEs by indication

	N(%) of Patients With Serious Adverse Events]					
	DPN	**PHN**	**NeP**	**Epilepsy**	**GAD**	**All Studies[a]**
Completed Controlled						
Placebo	**N = 459**	**N = 398**	**N = 857**	**N = 294**	**N = 484**	**N = 2384**
	11 (2.4)	10 (2.5)	21 (2.5)	13 (4.4)	6 (1.2)	49 (2.1)
All PGB	**N = 979**	**N = 852**	**N = 1831**	**N = 758**	**N = 1149**	**N = 5508**
	38 (3.9)	28 (3.3)	66 (3.6)	29 (3.8)	7 (0.6)	129 (2.3)
Relative risk	*1.63*	*1.32*	*1.44*	*0.86*	*0.5*	*1.1*
Combined DB/OL	**N = 1413**	**N = 1111**	**N = 2524**	**N = 1613**	**N = 1962**	**N = 8666**
	244 (17.3)	145 (13.1)	389 (15.4)	210 (13.0)	38 (1.9)	726 (8.4)

N = Total number of patients in the patient population.
[a] Includes serious adverse events in non-neuropathic pain studies and other psychiatry studies.
(Adapted from Applicant's Table 16, RR-REG 720-30199, P. 40)
The Appendix contains a list of SAEs occurring in at least 1 patient

7.4.3.2 SAEs all controlled trials – All indications

There were 129 pregabalin subjects (2.3%, 129/5508) and 49 placebo subjects (2.1%, 49/2384) who experienced one or more SAEs during controlled trials. The rate of experiencing one or more SAEs was 163.3/1000PY (129/760PY) for pregabalin subjects and 145.8/1000PY (49/336PY) for placebo subjects. There was no specific SAE that occurred at a frequency of at least 1% in pregabalin subjects in the integrated safety database controlled trials. The most commonly occurring SAE among pregabalin subjects in controlled trials was accidental injury (pregabalin 0.3%, 19/5508, placebo 0.0%, 1/2384). The other SAEs occurring in at least five pregabalin subjects in controlled trials were chest pain (pregabalin 0.2%, 9/5508, placebo 0.1%, 3/2384), pneumonia (pregabalin 0.1%, 6/5508, placebo 0.1%, 2/2384), congestive heart failure (pregabalin 0.1%, 5/5508, placebo 0.1%, 2/2384), and myocardial infarction (pregabalin 0.1%, 5/5508, placebo 0.1%, 2/2384) (See Appendix).

7.4.3.3 SAEs in all uncontrolled trials – All indications

In the uncontrolled (open label) trials, accidental injury was the only SAE that occurred at a frequency of at least 1%. Other commonly reported SAEs in the open-label trials were pneumonia (0.6%, 33/5459), congestive heart failure (0.5%, 26/5459), myocardial infarct (0.4%, 24/5459), chest pain (0.4%, 21/5459), and cellulitis (0.3%, 18/5459). The SAEs that occurred in at least 0.15% of patients in open-label trials are shown provided in the Appendix.

7.4.3.4 SAEs - All PHN controlled trials

The SAE risk for pregabalin-treated subjects in PHN controlled trials was 3.3% (28/852), and 2.5% (10/398) for placebo-treated subjects. The relative risk of an SAE among pregabalin-treated subjects was 1.32. The SAEs that occurred in more than 2 patients in pregabalin-treated patients are listed in the table that follows. A complete list of SAEs is located in the Appendix.

There was no SAE that occurred in more than 1% of pregabalin subjects. The most common SAE was cerebral ischemia (pregabalin 0.35%, placebo 0.25%).

Table 7.4.4.3: Serious adverse events – PHN controlled trials

Body system	Preferred term	Placebo [N = 398]		All pregabalin [N = 852]	
		N	%	N	%
Body as a whole	Chest pain	0	0.00	2	0.23
	Pain	0	0.00	2	0.23
Cardiovascular system	Cerebral ischemia	1	0.25	3	0.35
	Ventricular extrasystoles	1	0.25	2	0.23
Respiratory system	Pneumonia	0	0.00	2	0.23
Urogenital system	Urinary tract infection	0	0.00	2	0.23

There were no SAEs of acute hepatic failure, acute renal failure, rhabdomyolysis, or aplastic anemia in PHN controlled trials. There were several SAEs coded to preferred terms of interest including anaphylactoid reaction, cellulitis, face edema, leukopenia, lung fibrosis, lymphoma like reaction, and peripheral edema (n = 1, each). The SAEs that are suggestive of a relationship with pregabalin are listed below:

Lung fibrosis

045 066002 This 62 year old male with post herpetic neuralgia discontinued pregabalin on study day 44 for severe dizziness which resolved two days after stopping pregabalin. Approximately forty days after stopping pregabalin, he was hospitalized for heart failure and possible pulmonary fibrosis. The narrative reported that the subject recovered from both events.

Anaphylactoid reaction

196 011008 This 67 year old female with a history of post herpetic neuralgia, coronary artery disease, pacemaker insertion, duodenal ulcer, hypertension and osteoporosis experienced anaphylaxis on study day 10 of double blind pregabalin treatment (pregabalin 300 mg/day). Concomitant medications included naproxen, Paracetamol, aspirin, sotalol, ranitidine, ascorbic acid, multivitamins, and salmon calcitonin. Study medication was stopped on study day 11. On study day 12, the subject complained of facial edema, lower left leg edema, burning pain of the left shank, and warmth of the skin. She was hospitalized and noted to have facial and periorbital edema, erythema of the right side of the face, left leg edema with pain, erythema of the left leg, high blood pressure, tachycardia, and dyspnea. The events were reported as recovered on study day 12.

Peripheral edema, face edema

Patient 206001 (Study 1008-196), an 81-year-old white woman with post- herpetic neuralgia, experienced edema of the left and right foot (edema peripheral), dizziness, drowsiness, muscle weakness of lower limbs, and facial edema (face edema) on Study Day 16 of blinded pregabalin therapy (300 mg/day). History is significant for deterioration in renal function.

As noted in Section 7.4.2.3 (Table 7.4.2.3.a) one patient in protocol 1008-196 withdrew from the trial due to a suicide attempt. This AE was not associated with pregabalin treatment, since the patient was being treated with placebo. The patient's narrative is below:

Overdose

Patient 126005 (Study 1008-196), a 49-year-old white man with a history of depression and previous medication overdoses who was taking placebo daily for post- herpetic neuralgia was admitted to the emergency room for an intentional overdose of phenytoin and paracetamol on Study Day 2. He recovered that same day and placebo treatment continued.

7.4.3.5 All PHN uncontrolled trials

There were 112 patients (14.1%; 112/793) in PHN uncontrolled trials who reported a serious adverse event. SAEs reported by at least 2 patients are listed in the table below. The most common SAE was accidental injury (1.8%), followed by pneumonia (1%), myocardial infarction (0.8%), congestive heart failure, and syncope (0.6%, each). The complete list of SAEs in uncontrolled PHN trials is located in the Appendix.

Table 7.4.4.4.a: List of SAEs in PHN uncontrolled trials.

Body system	Preferred term	Number (N) of patients	Percent (%) of patients
Body as a whole	**Accidental injury**	**14**	**1.77**
	Carcinoma	**5**	**0.63**
	Chest pain	3	0.38
	Cyst	2	0.25
	Infection	2	0.25
	Viral Infection	2	0.25
Cardiovascular system	**Myocardial infarct**	**6**	**0.76**
	Congestive heart failure	**5**	**0.63**
	Syncope	**5**	**0.63**
	Angina pectoris	4	0.50
	Atrial fibrillation	4	0.50
	Heart failure	4	0.50
	Coronary artery disorder	3	0.38
	Heart arrest	3	0.38
	Cerebrovascular accident	2	0.25
	Coronary occlusion	2	0.25
	Ventricular extrasystoles	2	0.25
Digestive system	Gastrointestinal hemorrhage	4	0.50
	Colitis	3	0.38
	Gastroenteritis	3	0.38
	Cholelithiasis	2	0.25
	Intestinal obstruction	2	0.25
	Rectal hemorrhage	2	0.25
Metabolic and nutritional disorders	**Dehydration**	**5**	**0.63**
Respiratory system	**Pneumonia**	**8**	**1.01**
	Lung disorder	3	0.38
Special senses	Retinal edema	2	0.25
Urogenital system	Urinary tract infection	4	0.50
	Breast carcinoma	2	0.25
	Kidney function abnormal	2	0.25
	Prostatic disorder	2	0.25

SAEs in the uncontrolled PHN trials that coded to preferred terms of interest (and that are not listed above) are provided in the table below. There were no SAEs of acute hepatic failure, rhabdomyolysis, or aplastic anemia.

Table 7.4.4.4.a: Select SAEs, occurring in < 2 pregabalin-treated patients - PHN uncontrolled trials.

SAE	Any Dose Pregabalin [N = 793] N (%)
Acute kidney failure	1 (0.13)
Creatinine increased	1 (0.13)
Lymphoma-like reaction	1 (0.13)
Necrotizing pancreatitis	1 (0.13)
Pancreatitis	1 (0.13)
Shock	1 (0.13)
Thrombocytopenia	1 (0.13)
Visual field defect	1 (0.13)
Retinal disorder	1 (0.13)

After reviewing the narratives and CRFs for these patients, I found that the following SAEs did not have a clear alternative explanation, and therefore were possibly related to pregabalin:

Pancreatitis

030 131005 This 80 year old female with post herpetic neuralgia was hospitalized for pancreatitis on study day 147 of open label pregabalin treatment. Total duration of pregabalin was 184 days. Concomitant medications included paroxetine, lorazepam, doxepin, dextropropoxyphene and paracetamol/hydrochloride. On study day 92, her amylase was 77 U/L. While hospitalized, her lipase and amylase were increased (not specified). The narrative described no gall bladder inflammation and the abdominal CT and MRI were negative. She recovered without sequelae.

Visual field defect

Patient 120004 a 68-year-old Hispanic woman with postherpetic neuralgia developed medically significant visual field defect (primarily the superior fields) on Study Day 119 (open-label). History includes pseudoexfoliation syndrome of right eye, cataracts of both eyes, and peripheral drusen in both eyes. Open label study medication consisted of pregabalin 100 mg/day for 119 days and it was discontinued, and was preceded by double blind treatment with pregabalin 150 mg/day for 34 days. Total exposure to study medication was therefore 153 days. She had a normal baseline Humphrey 120 point screening test 8 days prior to double-blind study (missed 0 point in the left and 1 point in the right eye). At the Termination Visit of that study, 17 points were missed in the left eye and 4 points were missed in the right eye. A repeat eye exam on Study Day 119 showed the patient missed 25 points in the left eye and 8 points in the right eye. A Goldmann perimetry test on the same day confirmed the visual field defect. The defect appears more pronounced in the left eye. A repeat Humphrey perimetry performed on Study Day 133 (14 days post-treatment) showed significant resolution of the superior field defects. All points missed on Study Day 119 were not missed on the repeat testing on Study Day 133. Despite the variability of these results, it is the impression of the ophthalmologist that the field defect represents a true change in sensitivity of the left pre-chiasmal visual pathway.

Retinal disorder

Patient 034001, an 81-year-old white man with postherpetic neuralgia was diagnosed with medically significant macular degeneration on or about Study Day 238 of open-label pregabalin. History includes polyneuropathy. Study medication consisted of pregabalin 150 mg/day, which was continued. The patient participated in a previous study (1008-045) and received pregabalin 300 mg/day (per end of study code break) for 58 days. Total exposure to pregabalin was approximately 296 days. The patient's macular degeneration was not diagnosed prior to the start of the study. He has not yet recovered.

7.4.3.6 Serious Adverse Events in ongoing studies/not listed in the integrated safety database

As of 14 February 2003, 100 additional serious adverse events occurred in ongoing, blinded studies (or their open-label extensions) that were not included in the integrated safety database. Additionally, 60 patients with serious adverse events were reported to ARISg database but not the Oracle Clinical database as of the 14 February 2003 cutoff.

Pfizer also stated that 31 adverse events reported on double-blind forms were received after database lock of the double-blind study and treatment code release and therefore were not entered into the Oracle Clinical database. They are found in the Appendix. Pfizer considered the pattern of these events as reflective of the pattern in the overall population (mainly cardiac, vascular, or CNS events and carcinomas), or within the individual indications.

7.4.4 Common adverse events

7.4.4.1 Common adverse events - All PHN controlled trials

To examine the common adverse event profile for pregabalin, only the controlled studies of patients with postherpetic neuralgia (controlled PHN studies) were pooled. These studies were selected for the following reasons:

- Controlled studies allow for comparison of rates between active- and placebo-treated subjects.
- Subjects in the GAD, PHN, DPN, and epilepsy trials differed considerably with respect to age and health characteristics. Therefore, I considered it inappropriate to pool these studies for comparison of rates of common AEs.
- Subjects with PHN were older and more vulnerable to treatment effects; therefore they were the most sensitive population for detection of pregabalin-related adverse effects.

Although the studies differ with respect to treatment duration, these pooling of the PHN controlled studies was felt to be otherwise reasonable because they were placebo-controlled and of similar design.

I found that, of the 1250 patients in PHN controlled trials, 858 reported at least 1 adverse event. Table 7.4.5.1 lists the non-serious adverse events reported by at least 1% of all pregabalin-treated patients in the controlled PHN trials. Overall, adverse events of the nervous system were most frequently reported. Specifically, dizziness (26%) and somnolence (16%) were the most common, with relative risks of 2.7 and 3.1 respectively. Other nervous system AEs included motor effects (ataxia, abnormal gait, incoordination), change in mental status (confusion, abnormal thinking, amnesia) and speech abnormalities ("speech disorder).

The third most frequently reported non-serious AE was peripheral edema (12% in the pregabalin group vs. 4% in the placebo group). Face edema and "edema" in general were also more common in the pregabalin group than in the placebo group. Similarly, weight gain occurred more frequently in pregabalin-treated patients (4%) compared to placebo patients (0.3%). Also, infection, blurred vision (coded as "amblyopia"), diplopia, and accidental injury were more frequent among the pregabalin group than in the placebo group. Finally, there were gastrointestinal effects of dry mouth and constipation.

Table 7.4.5.1: Non-serious AEs in PHN controlled trials

Body system	Term	Placebo N = 398		75 mg/d N = 84		150 mg/d N = 302		300 mg/d N = 312		600 mg/d N = 154		All PGB N = 852	
		N	%	N	%			N	%	N	%	N	%
Body as a whole	Infection	17	4.27	12	14.29	26	8.33	23	7.37	6	3.9	67	7.86
	Headache	21	5.28	4	4.76	28	8.97	14	4.49	13	8.44	59	6.92
	Pain	15	3.77	3	3.57	12	3.85	18	5.77	7	4.55	40	4.69
	Asthenia	16	4.02	3	3.57	15	4.81	8	2.56	8	5.19	34	3.99
	Accidental injury	10	2.51	3	3.57	8	2.56	11	3.53	8	5.19	30	3.52
	Flu syndrome	7	1.76	2	2.38	5	1.6	9	2.88	2	1.3	18	2.11
	Face edema	3	0.75	0	0	5	1.6	3	0.96	5	3.25	13	1.53
	Abdominal pain	12	3.02	0	0	2	0.64	5	1.6	2	1.3	9	1.06
Digestive system	Dry mouth	11	2.76	6	7.14	21	6.73	19	6.09	23	14.94	69	8.1
	Constipation	9	2.26	3	3.57	14	4.49	17	5.45	8	5.19	42	4.93
	Diarrhea	16	4.02	2	2.38	13	4.17	13	4.17	7	4.55	35	4.11
	Nausea	16	4.02	1	1.19	8	2.56	7	2.24	4	2.6	20	2.35
	Vomiting	5	1.26	1	1.19	3	0.96	10	3.21	4	2.6	18	2.11
	Flatulence	4	1.01	2	2.38	4	1.28	5	1.6	5	3.25	16	1.88
	Dyspepsia	6	1.51	0	0	3	0.96	4	1.28	3	1.95	10	1.17
Metabolic and nutritional disorders	Peripheral edema	14	3.52	0	0	27	8.65	48	15.38	25	16.23	100	11.74
	Weight gain	1	0.25	1	1.19	5	1.6	17	5.45	10	6.49	33	3.87
	Edema	4	1.01	0	0	3	0.96	7	2.24	9	5.84	19	2.23
Musculoskeletal system	Myasthenia	0	0	1	1.19	3	0.96	4	1.28	2	1.3	10	1.17
Nervous system	Dizziness	38	9.55	9	10.71	55	17.63	99	31.73	57	37.01	220	25.82
	Somnolence	21	5.28	7	8.33	37	11.86	56	17.95	38	24.68	138	16.2
	Ataxia	2	0.5	1	1.19	6	1.92	17	5.45	14	9.09	38	4.46
	Abnormal gait	2	0.5	0	0	6	1.92	12	3.85	13	8.44	31	3.64
	Confusion	1	0.25	1	1.19	6	1.92	9	2.88	10	6.49	26	3.05

Table 7.4.5.1: Non-serious AEs in PHN controlled trials (continued)

Body system	Term	Placebo N = 398		75 mg/d N = 84		150 mg/d N = 302		300 mg/d N = 312		600 mg/d N = 154		All PGB N = 852	
Nervous system	Thinking abnormal	6	1.51	0	0	5	1.6	5	1.6	9	5.84	19	2.23
	Incoordination	0	0	2	2.38	5	1.6	4	1.28	4	2.6	15	1.76
	Amnesia	0	0	0	0	3	0.96	4	1.28	6	3.9	13	1.53
	Insomnia	7	1.76	0	0	2	0.64	7	2.24	1	0.65	10	1.17
	Speech disorder	0	0	0	0	1	0.32	4	1.28	5	3.25	10	1.17
Respiratory system	Pharyngitis	5	1.26	0	0	8	2.56	3	0.96	1	0.65	12	1.41
	Rhinitis	8	2.01	1	1.19	2	0.64	3	0.96	6	3.9	12	1.41
	Bronchitis	3	0.75	0	0	4	1.28	3	0.96	4	2.6	11	1.29
	Dyspnea	3	0.75	0	0	3	0.96	6	1.92	1	0.65	10	1.17
	Sinusitis	4	1.01	0	0	2	0.64	5	1.6	3	1.95	10	1.17
	Cough increased	4	1.01	0	0	4	1.28	3	0.96	2	1.3	9	1.06
Skin and appendages	Rash	12	3.02	2	2.38	6	1.92	9	2.88	8	5.19	25	2.93
Special senses	Blurred vision*	10	2.51	1	1.19	15	4.81	16	5.13	14	9.09	46	5.4
	Diplopia	0	0	0	0	5	1.6	6	1.92	6	3.9	17	2
	Abnormal vision	1	0.25	0	0	3	0.96	5	1.6	8	5.19	16	1.88
	Eye disorder	1	0.25	0	0	4	1.28	2	0.64	3	1.95	9	1.06
Urogenital system	Urinary tract infection	6	1.51	0	0	8	2.56	6	1.92	5	3.25	19	2.23
	Urinary incontinence	0	0	0	0	3	0.96	3	0.96	3	1.95	9	1.06

* The COSTART preferred term used to describe this adverse event was "amblyopia"

The list of all non-serious AEs was reviewed to identify AEs that coded to preferred terms of potential importance, occurring in less than 1% of pregabalin-treated patients but in greater frequency than in placebo patients. The following select AEs were identified.

Non-serious AE of interest	% All pregabalin	% Placebo
Euphoria	0.94	0
Vertigo	0.94	0
Hallucinations	0.82	0
BUN increased	0.7	0.5
Creatinine phosphokinase increased	0.59	0
Amylase increased	0.59	0
Thrombocytopenia	0.47	0
Liver function tests abnormal	0.35	0.25
Tongue edema	0.23	0
Heart failure	0.12	0
Kidney function abnormal	0.12	0

The table suggests that other nervous system AEs (euphoria, vertigo, hallucinations) were again more frequent in the pregabalin-treated patients. Additional AEs that appeared to occur more commonly in the pregabalin group were thrombocytopenia, tongue edema and increased amylase. Although pregabalin-treated patients reported more edema than placebo patients did, the risk of non-serious heart failure was not considerably increased. Also, the risk of renal and hepatic abnormalities appeared comparable to the placebo group. There was no apparent greater risk of non-serious skin ulcer, cellulitis, rash, jaundice, myopathy, pancytopenia, leukopenia, or visual field defects.

7.4.4.2 Common adverse events - All PHN uncontrolled trials

There were 793 subjects who participated in open-label PHN trials. Of these, 602 patients (75.9%) reported at least one non-serious AE. The Appendix shows that the most common non-serious AEs were similar to those occurring in controlled PHN trials: dizziness (23%), peripheral edema (16%), somnolence (16%), weight gain (9%), and blurred vision (6%). Other frequent AEs were accidental injury (12%), ataxia (6%) and dry mouth (8%).

7.4.5 Select AEs of interest

As described in my review of N21-446, pregabalin for the treatment of pain associated with diabetic peripheral neuropathy (DPN), reports of skin-, vision-, and edema-related adverse events underwent additional investigation. This was due to findings of dermatopathy in animal studies (rats, mice, and monkeys), as well as reports of peripheral edema and vision abnormalities during early clinical studies. The possibility of a toxic effect on skin and vision in patients with PHN was of less concern than for patients with DPN, since patients with PHN do not have the vulnerabilities to skin and eye disorders that diabetes confers. However, the relatively advanced age of patients with PHN puts them at risk for cardiovascular disease and certain eye disorders, which could be made worse by a potential toxic effect of pregabalin on these organ systems.

7.4.5.1 Vision-related AEs

All indications – controlled trials

Querying of the integrated safety database using the term "special senses" and then selecting for eye-related disorders found that there were 704 patients who reported one of the following eye-related AEs: abnormal vision, amblyopia (verbatim term "blurry vision"), diplopia, or visual field defect. Blurred vision corresponds to a loss in visual acuity. The frequency of these AEs by treatment group is shown in the table below. There were more pregabalin-treated patients who experienced these AEs than patients in the placebo group, and this is suggestive of a causal role of pregabalin.

Table 7.4.4.1.a: Select vision AEs – Controlled trials, all indications

					Number of Patients (%)							
					Total pregabalin daily dose (mg/d)							
Preferred term	**Placebo N=2308**		**All PGB N=5508**		**150 N=1164**		**300 N=1224**		**450 N=501**		**600 N =1802**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Abnormal vision	12	0.50	101	1.83	16	1.37	20	1.63	4	0.80	51	2.83
Blurred vision*	51	2.14	361	6.55	54	4.64	68	5.56	36	7.19	164	9.10
Diplopia	12	0.50	113	2.05	17	1.46	24	1.96	7	1.40	60	3.33
Visual field defect	18	0.76	53	0.96	14	1.20	12	0.98	4	0.80	19	1.05

All PGB includes other doses of pregabalin (50, 75, 200, and 400 mg/d)
*The COSTART preferred term was "amblyopia"

Controlled PHN trials

Table 7.4.5.1.b lists the eye-related AEs that were reported during PHN controlled trials. One hundred and twenty five patients reported an eye-related AE (21 placebo patients; 114 pregabalin patients). Only one AE was described as "serious" (See Serious Adverse Events, above). As was noted for the total population of patients evaluated, the most commonly reported vision-related AE was blurry vision. It occurred with greater frequency among pregabalin treated patients (5%) than placebo patients (2%), and appeared to be dose-dependent. Other eye-related AEs that were more common in the pregabalin group were diplopia and "abnormal vision." The

frequency of visual field defects, although highest in the 600 mg/d group, was lower for the overall pregabalin group (0.23%) than for the placebo group (0.5%).

Table 7.4.5.1.b: Vision AEs – PHN controlled trials

Preferred term	Placebo [N=398]		75 mg/d [N=84]		150 mg/d [N=302]		300 mg/d [N=312]		600 mg/d [N=154]		All PGB [N=852]	
	N	%	N	%	N	%	N	%	N	%	N	%
Blurred vision*	10	2.51	1	1.19	15	4.97	16	5.13	14	9.09	46	5.40
Diplopia	0	0.00	0	0.00	5	1.66	6	1.92	6	3.90	17	2.00
Abnormal vision	1	0.25	0	0.00	3	0.99	5	1.60	8	5.19	16	1.88
Eye disorder	1	0.25	0	0.00	4	1.32	2	0.64	3	1.95	9	1.06
Eye pain	3	0.75	1	1.19	1	0.33	3	0.96	0	0.00	5	0.59
Conjunctivitis	3	0.75	1	1.19	1	0.33	0	0.00	1	0.65	3	0.35
Retinal disorder	1	0.25	0	0.00	2	0.66	1	0.32	0	0.00	3	0.35
Blepharitis	0	0.00	0	0.00	1	0.33	1	0.32	0	0.00	2	0.23
Glaucoma	0	0.00	0	0.00	0	0.00	2	0.64	0	0.00	2	0.23
Lacrimation disorder	1	0.25	0	0.00	0	0.00	2	0.64	0	0.00	2	0.23
Visual field defect	2	0.50	0	0.00	0	0.00	0	0.00	2	1.30	2	0.23
Abnormality of accommodation	0	0.00	0	0.00	1	0.33	0	0.00	0	0.00	1	0.12
Blindness	0	0.00	0	0.00	0	0.00	0	0.00	1	0.65	1	0.12
Cataract specified	1	0.25	1	1.19	0	0.00	0	0.00	0	0.00	1	0.12
Dry eyes	1	0.25	0	0.00	0	0.00	1	0.32	0	0.00	1	0.12
Eye hemorrhage	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00	1	0.12
Hyperacusis	0	0.00	0	0.00	1	0.33	0	0.00	0	0.00	1	0.12
Keratitis	0	0.00	0	0.00	1	0.33	0	0.00	0	0.00	1	0.12
Ptosis	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00	1	0.12
Refraction disorder	0	0.00	0	0.00	1	0.33	0	0.00	0	0.00	1	0.12

* The COSTART preferred term used to code this AE was "amblyopia"

7.4.5.2 Metabolic adverse events: Edema

Controlled trials – All indications

Pfizer found that across all controlled studies, the overall incidence of peripheral edema in patients treated with pregabalin was 6.1% compared with 1.8% in placebo-treated patients. By indication, the incidence of peripheral edema was higher in the neuropathic pain population (10.4%) compared with epilepsy (4.2%) and GAD (1.9%) patients. Both the incidence of peripheral edema (DPN 9.4% and PHN 11.5%) and relative risk (DPN 3.9 and PHN 3.3) were similar between patients with DPN and PHN. The incidence of peripheral edema was increased relative to placebo starting at the pregabalin 150-mg/day dose, with higher incidences at doses of 300 mg/day and above. Results were similar when the terms "generalized edema" and "edema" were included. Peripheral edema led to discontinuation of study medication in less than 1% of patients, most of who were enrolled in neuropathic pain studies.

Table 7.4.5.2: Frequency of peripheral edema, by dose group – All controlled trials

	[n (%)of Patients With Peripheral Edema]						
	Pregabalin Total Daily Dose in mg/day (BID and/or TID)						
Placebo	**150**	**200**	**300**	**400**	**450**	**600**	**Any Dose[a]**
All Studies[b]							
N=2384	N=1164	N=208	N=1224	N=360	N=501	N=1802	N=5508
42 (1.8)	56* (4.8)	4 (1.9)	109* (8.9)	7 (1.9)	25* (5.0)	131* (7.3)	336* (6.1)
DPN							
N=459	N=212	-	N=321	-	-	N=369	N=979
11 (2.4)	13* (6.1)	-	30* (9.3)	-	-	46* (12.5)	92* (9.4)
PHN							
N=398	N=302	-	N=312	-	-	N=154	N=852
14 (3.5)	24* (7.9)	-	49* (15.7)	-	-	25* (16.2)	98* (11.5)
Epilepsy							
N=294	N=185	-	N=90	-	-	N=395	N=758
6 (2.0)	6 (3.2)	-	3 (3.3)	-	-	22* (5.6)	32 (4.2)
GAD							
N=484	N=210	N=78	N=91	N=186	N=178	N=406	N=1149
2 (0.4)	3 (1.4)	2 (2.6)	1 (1.1)	5* (2.7)	5* (2.8)	6 (1.5)	22 (1.9)

* Significantly different from placebo based on odds ratio or Fisher s exact p-value
[a] Includes all other doses of pregabalin (i.e., 50 and 75 mg/day).
[b] Includes other non-neuropathic pain studies and other psychiatry studies.
(Adapted from Applicant's Table 36, Summary of Clinical Safety, P. 88)

Risk factors for peripheral edema

1. Age and BMI

PHN patients aged >65 years and DPN patients aged 65 to 74 years were more likely to experience peripheral edema. Also, GAD patients with a BMI ≥ 28 were at a higher risk for developing peripheral edema (SCS, P. 88)

2. Concomitant use of a PPAR

a) Controlled DPN trials

Thiazolinediones, which are ligands for peroxisome proliferator activated receptors (PPARs), are commonly used antidiabetic medications. Since PPAR drugs can cause peripheral edema, the Applicant was asked to compare the rates of edema, weight gain, and heart failure in patients taking a PPAR drug, to the rates in patients not taking a PPAR drug.

Among controlled trials of pain associated with diabetic peripheral neuropathy, the frequency of peripheral edema greater among patients taking a PPPAR than among those not taking a PPAR. The risk of peripheral edema was 6 times greater for pregabalin patients taking a PPAR, compared to placebo patients who were taking a PPAR (19% compared to 3%). Among

pregabalin-treated patients, more patients taking a PPAR reported peripheral edema and congestive heart failure, compared to pregabalin-treated patients who were not taking a PPAR.

Table 7.4.5.3.a:Summary of Adverse Events of Heart Failure, Edema, and Weight Gain Controlled Diabetic Neuropathy Studies (Protocols 014, 029, 040, 131, 149, 173)

	Number of Patients (%)					
Adverse Event	**Placebo**	**75 mg/day PGB**	**150 mg/day PGB**	**300 mg/day PGB**	**600 mg/day PGB**	**All PGB**
DPN Non-PPAR						
Preferred Term	N=399	N=62	N=195	N=279	N=323	N=859
Congestive heart failure	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Edema	0 (0.0)	0 (0.0)	4 (2.1)	13 (4.7)	7 (2.2)	24 (2.8)
Peripheral edema	9 (2.3)	2 (3.2)	10 (5.1)	24 (8.6)	33 (10.2)	69 (8.0)
Weight gain	2 (0.5)	0 (0.0)	8 (4.1)	9 (3.2)	18 (5.6)	35 (4.1)
DPN PPAR						
Preferred Term	N=60	N=15	N=17	N=42	N=46	N=120
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)	1 (2.2)	3 (2.5)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral edema	2 (3.3)	1 (6.7)	3 (17.6)	6 (14.3)	13 (28.3)	23 (19.2)
Weight gain	0 (0.0)	0 (0.0)	1 (5.9)	3 (7.1)	5 (10.9)	9 (7.5)
Percent of DPN Patients reporting PPAR Use	13.1%	19.5%	8.0%	13.1%	12.5%	12.3%

DPN: diabetic peripheral neuropathy
(Applicant's Table, Jun 23 2004, NDA 21-446)

2b) Controlled trials – all indications

Among subjects in all controlled trials of pregabalin, the majority of the patients who took a PPAR comprised patients with DPN. Nevertheless, similar results regarding edema and other related AEs were seen as those in controlled DPN trials. Treatment with a PPAR was associated with a greater frequency of peripheral edema and congestive heart failure, and the risk of peripheral edema was approximately 6 times greater for patients also treated with pregabalin (see Appendix).

3. Concomitant use of tocopherol (vitamin E)

Tocopherol is commonly used for its anti-oxidant effects. The drug exerts this effect by up-regulating peroxisome proliferator activated receptor (PPAR) gamma (γ) expression. Tocopherol is similar in structure to the PPARγ ligands, the thiazolinediones. Thiazolinediones are known to cause peripheral edema. Therefore, data from controlled PHN trials were evaluated to determine the effect of concomitant use of tocopherol and pregabalin on edema. The effect of concomitant therapy on other AEs related to edema (heart failure and weight gain) was also evaluated.

3a) Controlled PHN trials

Table 7.4.5.3.b shows that in controlled PHN trials, there were 120 patients (38 placebo, 82 pregabalin) who took tocopherol concurrently with study medication. Overall the frequency of tocopherol use was similar across placebo and pregabalin groups (9.5% and 9.6%, respectively).

Compared to the other edema-related AEs, peripheral edema occurred most frequently. The incidence of peripheral edema among placebo patients was similar, regardless of whether placebo patients were or were not taking (3% vs. 4%, respectively). The incidence of peripheral edema among pregabalin-treated patients was considerably higher than among placebo patients, but did not differ considerably between those taking tocopherol (12%) and those not taking tocopherol (11%). The relative risk of peripheral edema among pregabalin-treated patients taking tocopherol was 4.7 times greater than placebo patients taking tocopherol. The relative risk of peripheral edema for pregabalin-treated patients not taking tocopherol was slightly lower (RR = 3.7).

Table 7.4.5.3.b: Summary of adverse events of heart failure, edema, or weight gain – PHN controlled studies

		Number of Patients (%) Pregabalin dose				
Adverse Event	**Placebo**	**75 mg/d**	**150 mg/d**	**300 mg/d**	**600 mg/d**	**All PGB**
PHN Non-Tocopherol						
Preferred Term	N=360	N=65	N=281	N=289	N=135	N=770
Congestive heart failure	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Heart failure	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Edema	5 (1.4)	0 (0.0)	3 (1.1)	7 (2.4)	8 (5.9)	18 (2.3)
Face edema	3 (0.8)	0 (0.0)	5 (1.8)	3 (1.0)	4 (3.0)	12 (1.6)
Peripheral edema	13 (3.6)	0 (0.0)	23 (8.2)	45 (15.6)	20 (14.8)	88 (11.4)
Generalized edema	1 (0.3)	0 (0.0)	4 (1.4)	1 (0.3)	2 (1.5)	7 (0.9)
Weight gain	1 (0.3)	1 (1.5)	5 (1.8)	16 (5.5)	8 (5.9)	30 (3.9)
PHN Tocopherol						
Preferred Term	N=38	N=19	N=21	N=23	N=19	N=82
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	1 (1.2)
Face edema	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (5.3)	2 (2.4)
Peripheral edema	1 (2.6)	0 (0.0)	1 (4.8)	4 (17.4)	5 (26.3)	10 (12.2)
Generalized edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight gain	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	2 (10.5)	3 (3.7)
Percent of PHN Patients reporting Tocopherol Use	9.5%	22.6%	7.0%	7.4%	12.3%	9.6%

(Applicant's Table, based on all patients in the Safety Update integrated data set, Jul 29, 2004)

Other edema-related AEs such as heart failure and weight gain occurred with a very low incidence in both pregabalin and placebo groups, and no appreciable difference in incidence was noted between patients who were or were not taking tocopherol.

3b) All controlled trials – all indications

As depicted in Table 7.4.5.3.c below, slightly fewer patients in the pregabalin group (7%) took tocopherol than in the placebo group (8%). Again, peripheral edema was the most commonly occurring AE among pregabalin-treated patients compared to the placebo patients. Also, the incidence of peripheral edema was higher among pregabalin patients who were taking tocopherol (8.3%) compared to those who were not (5.9%). A similar result was seen when the incidence of peripheral edema was compared among placebo patients who were taking tocopherol (2.5%) and those who were not (1.7%). No considerable differences were noted with regards to the incidences of heart failure and weight gain.

Reviewer's conclusions regarding risk factors for peripheral edema:

Advanced age (≥ 65 years) and a high BMI confer increased risk of peripheral edema. Concomitant treatment of pregabalin and PPARs appears to result in an additive effect, and possibly a synergistic effect, on peripheral edema. Concomitant treatment with pregabalin and a PPAR may also increase the risk of congestive heart failure. Data from the overall safety database suggest that tocopherol may slightly increase the risk of peripheral edema, however this conclusion could not be drawn from the data from PHN controlled trials.

Table 7.4.5.3.c: Summary of adverse events of heart failure, edema, or weight gain – All controlled studies, all indications

	Number of Patients (%)						Number of Patients (%)				
		Pregabalin					Pregabalin				
Adverse Event	Placebo	50 mg/d	75 mg/d	150 mg/d	200 mg/d	Adverse Event	300 mg/d	400 mg/d	450 mg/d	600 mg/d	All PGB
All Indications: Non-Tocopherol						**All Indications: Non-Tocopherol**					
Preferred Term	N=2187	N=85	N=134	N=1083	N=202	**Preferred Term**	N=1110	N=349	N=473	N=1676	N=5112
Congestive heart failure	2 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	Congestive heart failure	1 (0.1)	0 (0.0)	0 (0.0)	3 (0.2)	5 (0.1)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	Heart failure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Edema	8 (0.4)	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)	Edema	23 (2.1)	0 (0.0)	2 (0.4)	22 (1.3)	56 (1.1)
Face edema	8 (0.4)	1 (1.2)	0 (0.0)	9 (0.8)	1 (0.5)	Face edema	6 (0.5)	0 (0.0)	2 (0.4)	24 (1.4)	43 (0.8)
Peripheral edema	37 (1.7)	1 (1.2)	3 (2.2)	53 (4.9)	3 (1.5)	Peripheral edema	98 (8.8)	6 (1.7)	24 (5.1)	115 (6.9)	303 (5.9)
Generalized edema	1 (0.0)	0 (0.0)	0 (0.0)	6 (0.6)	0 (0.0)	Generalized edema	10 (0.9)	0 (0.0)	5 (1.1)	14 (0.8)	35 (0.7)
Weight gain	18 (0.8)	1 (1.2)	1 (0.7)	39 (3.6)	5 (2.5)	Weight gain	59 (5.3)	18 (5.2)	31 (6.6)	137 (8.2)	291 (5.7)
All Indications: Tocopherol						**All Indications: Tocopherol**					
Preferred Term	N=197	N=3	N=27	N=81	N=6	**Preferred Term**	N=114	N=11	N=28	N=126	N=396
Congestive heart failure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Congestive heart failure	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Edema	1 (0.9)	0 (0.0)	1 (3.6)	3 (2.4)	5 (1.3)
Face edema	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Face edema	3 (2.6)	0 (0.0)	0 (0.0)	1 (0.8)	4 (1.0)
Peripheral edema	5 (2.5)	0 (0.0)	0 (0.0)	3 (3.7)	1 (16.7)	Peripheral edema	11 (9.6)	1 (9.1)	1 (3.6)	16 (12.7)	33 (8.3)
Generalized edema	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Generalized edema	3 (2.6)	0 (0.0)	0 (0.0)	1 (0.8)	4 (1.0)
Weight gain	1 (0.5)	0 (0.0)	0 (0.0)	2 (2.5)	0 (0.0)	Weight gain	4 (3.5)	1 (9.1)	2 (7.1)	11 (8.7)	20 (5.1)
Percent of All Patients Reporting Tocopherol Use	8.3%	3.4%	16.8%	7.0%	2.9%	**Percent of All Patients Reporting Tocopherol Use**	9.3%	3.1%	5.6%	7.0%	7.2%

(Applicant's Table, based on all patients in the Safety Update integrated data set, Jul 29, 2004)

7.4.5.3 Infection

Controlled PHN trials

The frequency of the COSTART preferred term "infection" was higher among pregabalin-treated patients (8%) compared to placebo patients (4%), relative risk = 2. Infection rates were greater at lower doses of pregabalin (14% in the 75 mg/d group, 8% in the 150 mg/d group), than at higher doses (7% in the 300 mg/d group; 4% in the 600 mg/d group). Of note, in the PHN trials, separate COSTART terms were used to code for the adverse events "urinary tract infection" and "flu syndrome", both of which are types of infection. As shown in Table 7.4.5.1, the frequency of non-serious cases of "urinary tract infection" was slightly higher in the pregabalin groups than in the placebo group (2.2% vs. 1.5%, relative risk = 1.5). There was no appreciable difference between pregabalin and placebo groups with respect to "flu syndrome."

To further evaluate the apparent increased risk of infection associated with pregabalin treatment, data were analyzed where "infection" was included the COSTART preferred term, or in the actual AE text. I calculated that a total of 135 patients, the majority of whom were in study 1008-196 (n = 51), reported 151 infections. The most commonly occurring infections were the "cold" (n = 54), urinary tract infection (UTI) (n = 31), and upper respiratory infection (URI) (n = 34). The frequency of each type of infection, by treatment group and occurring in more than 1 patient, is shown in table 7.4.5.3.a.

The table shows that among the infections occurring in > 1 patient, "cold", UTI, and URI occurred more frequently in pregabalin-treated patients than in placebo patients. The relative risks of "cold", URI, and UTI were 1.3, 1.8, and 1.9 respectively. Approximately three times as many patients in the 75 mg/d group had a "cold" compared to placebo patients (11% vs. 4%). A dose-response relationship was suggested for only the urinary tract infection.

I compared the within-study rates of "cold", URI, and UTI for each of the controlled PHN studies (see Table 7.4.5.3.b). I found that frequencies of "cold" and UTI in the placebo groups fell within a narrow range across studies (3.2-3.6% for "cold"; 0.0-1.1% for UTI), whereas the rate of URI among the placebo groups was quite variable (0.0-3.6%). The frequency of URI in the pregabalin groups were also quite variable both within and across studies. In general, the frequency of "cold" among pregabalin groups was greater than those in the placebo groups, without evidence of a dose-response relationship. Overall, the frequencies of UTI in the pregabalin groups were only slightly higher than in the placebo groups.

Infection - Uncontrolled PHN trials

There were 141 patients (17.8%) in PHN uncontrolled studies had an infection (based on either the COSTART preferred term "infection" or the actual AE text). A total of 47 patients (5.9%) reported a UTI, 45 patients (5.7%) had a URI, and 20 patients (2.5%) had a cold. These frequencies are generally in the range that was observed among pregabalin-treated patients in PHN controlled trials.

Table 7.4.5.3.a: Frequency of infections (≥ 2 patients) – PHN controlled trials

Infection type	Total N = 1250		Placebo N = 398		75 mg/d N = 84		150 mg/d N= 302		300 mg/d N = 312		600 mg/d N = 154		ALL PGB N = 852	
	N	%	N	%	N	%	N	%	N	%	N	%		
"Cold"	54	4.3	14	3.5	9	10.8	14	4.6	16	5.1	3	1.9	40	4.7
Urinary tract infection (UTI)	31	2.5	6	1.5	0	0.0	9	3.0	9	2.9	7	4.5	25	2.9
Upper respiratory infection (URI)	34	2.7	7	1.8	2	2.4	13	4.3	8	2.6	4	2.6	27	3.2
Viral infection	5	0.4	1	0.3	1	1.2	3	1.0	0	0.0	0	0.0	4	0.5
Dermal infection	4	0.3	1	0.3	0	0.0	3	1.0	0	0.0	0	0.0	3	0.4
Eye infection	3	0.2	0	0.0	0	0.0	0	0.0	1	0.3	2	1.3	3	0.4
Ear infection	3	0.2	1	0.3	0	0.0	0	0.0	0	0.0	2	1.3	2	0.2
Stomach/intestinal virus	3	0.2	3	0.8	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Tooth/gum infection	2	0.2	0	0.0	0	0.0	1	0.3	0	0.0	1	0.6	2	0.2

"Cold" includes the following terms: cold, head cold, cold symptoms, sinus cold, common cold, cough & cold and cold virus
UTI includes: kidney infection, UTI symptoms, bacteria in urine, increased WBC in U/A, urosepsis
URI includes nose infection, sinus infection, chest virus, and chest infection
Dermal infection includes: infection of face, finger infection, infected leg ulcer, infection left forearm

Table 7.4.5.3.b: Frequency of "cold", URI, and UTI in each of the PHN controlled trials

	Percent (%) patients					
Protocol/ Infection type	**Placebo**	**75 mg/d**	**150 mg/d**	**300 mg/d**	**600 mg/d**	**All PGB**
1008-030						
Cold	3.4	10.7	3.6	-	-	7.1
URI	0.0	2.4	7.1	-	-	4.8
UTI	1.1	0.0	1.2			0.6
1008-045						
Cold	2.4	-	1.2	2.6	-	1.9
URI	0.0	-	0.0	2.6	-	1.3
UTI	0.0	-	3.7	2.6	-	3.2
1008-127						
Cold	3.6	-	-	0.0	0.0	0.0
URI	3.6	-	-	10.0	5.1	6.7
UTI	0.0	-	-	13.3	1.7	5.6
1008-196						
Cold	3.2	-	6.9	4.8	1.6	4.7
URI	2.2	-	5.7	1.6	1.6	2.9
UTI	1.1	-	2.3	0.8	6.3	2.5

Infection – Other controlled trials
To evaluate whether the apparent increased risk of infection in the PHN studies was also observed in the total population, I evaluated the frequency of this AE among patients in all controlled trials (all indications). Also, to determine whether the apparent increased risk was related to age, I reviewed the frequency of infection among DPN population which, like the PHN population, was comprised of older patients.

a) All controlled trials, all indications
The frequency of the COSTART preferred term "infection" in all controlled studies (all indications) was evaluated. Per Pfizer's analysis, 7.7% of placebo patients reported an infection, compared to 8.2% of pregabalin-treated patients. The highest rates of "infection" occurred in the 200- and 400-mg/d groups (14% and 10%, respectively). However, a dose-response relationship was not seen. The frequencies of the other COSTART preferred terms that are consistent with infection (e.g. "urinary tract infection," "gastroenteritis", "abscess", "cellulitis", "fever") were not different between pregabalin and placebo groups (SCS, Appendix ALL.023, RR-REG 720-30199, P. 236-7).

b) DPN controlled trials
The frequency of infection was 7% for both the placebo and pregabalin groups. The pregabalin 150- and 300- mg/d groups had slightly more patients with infection (8% and 9%, respectively). The frequency of UTI was considered separately, and again no difference was observed between placebo and pregabalin groups (1% in each group).

The age range of patients in the DPN controlled studies was relatively wide (21 to 87 years) and therefore the mean age of the DPN patients was considerably younger than that of the PHN population (approximately 60 years vs. 72 years). Therefore, for more appropriate comparison

of infection rates, and to ascertain whether advanced age conferred an increased risk of infection, the frequency of infection was compared for those DPN and PHN subjects aged ≥ 65 years:

Table 7.4.5.3.c: Rates of infection in DPN and PHN controlled studies, by age category

Study population/ Age category		Placebo [N (%)]	Pregabalin [N (%)]
Diabetic peripheral neuropathy			
	Age ≥ 65 years	9 (5.7)	24 (7.5)
	Age < 65 years	25 (8.3)	47 (7.1)
Postherpetic neuralgia			
	Age ≥ 65 years	26 (8)	78 (11.8)
	Age < 65 years	6 (8.1)	25 (13.1)

The table above shows that, for the DPN population, treatment with pregabalin did not appear to confer increased risk of infection, for either age category. However, for the PHN population, treatment with pregabalin was associated with a higher risk of infection compared to treatment with placebo (approximately 12.5% vs. 8%) and this was true for both age categories.

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Reviewer's conclusions about the risk of infection: Overall, the risk of "infection" appears to be greater for the PHN population that is treated with pregabalin. Specifically, UTI and URI infections are most commonly associated with pregabalin therapy. The risk is does not appear to be dose-dependent, or associated with age.

7.4.6 Laboratory data

Using data from both controlled and uncontrolled Phase 2/3 studies, Pfizer calculated mean changes in laboratory values from baseline to endpoint for each pregabalin group compared to the change in the placebo group. Also, clinically important changes in values, shifts from baseline to endpoint, and extreme outliers were evaluated. The 'baseline' value was considered the last value obtained on or before Day 1 of therapy, and the 'endpoint' value was the last available non-follow-up value. (Values taken > 14 days after the last dose of study medication were considered follow-up values.) At the Agency's request, Pfizer also calculated mean changes in laboratory values from baseline to maximum value. Additionally, shift tables were later submitted that showed the number and percent of patients who had normal, above normal, and below normal lab values at baseline and at endpoint. I focused on results of controlled trials, and presented analyses of uncontrolled trials when appropriate.

Of note, upon auditing of the Oracle Clinical (OC) database, Pfizer noted errors in the OC reference range table and in unit conversions. Corrections were made, and applied to the data used in the SCS. The corrections resulted changes in the reference ranges in the lab data view for several ongoing and completed studies – that is, the summary laboratory output for several studies does not mach these individual clinical study reports.

Additionally, although some glucose measurements were labeled as 'fasting' or 'non-fasting', all glucose measurements should be considered 'non fasting,' except values from protocols 1008-132, 149, 173, and 196 which specified fasting samples at some visits. Also, for 249 patients in trials 1008-127 and 1008-131 had baseline and open-label lab samples analyzed by different laboratories. Therefore, their values are excluded from the change from baseline analysis. Creatine kinase and lipid measurements were added later in the course of the pregabalin clinical program. Finally, for controlled trials, the dosages shown in summary tables indicate the treatment group to which subjects were randomized, not the actual dose taken on the day of the laboratory assessment (See SCS, Appendix ALL.11).

7.4.6.1 Laboratory mean changes: All controlled trials, all indications

Please see my review of N 21-446 (pregabalin for treatment of the pain associated with DPN) for a detailed discussion of the mean laboratory changes across all treatment populations.

In summary, the most notable differences between treatment groups in Pfizer's analysis of the mean changes from baseline to study endpoint, and from baseline to maximum value, were an increase in creatinine kinase (CK) and a decrease in platelets among pregabalin treated patients compared to placebo patients.

Creatinine kinase

When the mean change in CK from baseline to study endpoint was calculated, the pregabalin-treated subjects had a mean increase in CK of 9.7 U/L compared to 4.8 U/L for placebo patients. A comparison of the mean change in CK from baseline to maximum value also showed greater differences for the pregabalin group than the placebo group. Subjects treated with pregabalin had a mean increase in CK of 60.1 U/L, compared to 27.9 for placebo subjects. This finding of an elevated CK associated with pregabalin treatment is of concern considering the potential for renal injury with treatment.

The increase in creatinine kinase did not appear to be dose-related, and was not consistent across the treatment populations. The greatest mean change in CK from baseline to endpoint occurred in the epilepsy population, and was substantially less in the GAD population (considered to be the healthiest treatment group). Similar results were noted when the mean change from baseline to maximum value was analyzed (see Table 7.4.6.1 below). Therefore it is possible that mean increase in CK seen in the overall safety database was driven by changes in the epilepsy population.

Table 7.4.6.1: CK Mean Change from Baseline to Maximum Value, Controlled Trials

Indication/Database	**Placebo** (U/L)	**Pregabalin** (U/L)
Overall	27.90	60.13
Diabetic Peripheral Neuropathy	13.17	32.41
Post Herpetic Neuralgia	15.53	27.57
Epilepsy	45.77	107.79
GAD	19.41	64.10

Dr. Boehm used CK data from the epilepsy population to assess when the CK changes were occurring. He found that the mean CK increases from baseline relative to placebo were present

early, and varied over the course of the study. Again, there was no suggestion of a dose-response relationship.

At the Agency's request, Pfizer prepared shift tables of CK from baseline to maximum value for the overall population, and for each indication. Across all populations, more pregabalin-treated patients who had a baseline CK of < 2x ULN had an increase in CK than did placebo patients. There were more patients in the DPN population who experienced this change (5.4%) compared to the epilepsy (3.5%) and GAD populations (2.1%). There were no considerable differences in the numbers of placebo versus pregabalin patients with baseline CK values > 2x ULN who had experienced increases in CK values. Treatment with the higher doses (450, 600 mg/d) appeared to convey the most risk (Appendix All_sft.03). Again, the epilepsy population was at greatest risk for pregabalin-associated CK abnormalities (Appendix Epi_sft.03).

Platelets
The mean decrease in platelets for placebo patients was only 0.3 x $10^3/\mu L$ compared to 9.5 x $10^3/\mu L$ for pregabalin patients. However, evaluation of the mean change in platelet value from baseline to lowest (minimum) value found that the pregabalin group had an even greater decrease in platelets (-19.91 x $10^3/\mu L$), compared to the placebo group (-11.26 x $10^3/\mu L$) (Applicant's Table1.MIN.ALL.). Pfizer calculated that 1.6% (36/2224) placebo patients and 3.2% (162/5142) pregabalin patients experienced a potentially clinically significant decrease in platelets at study endpoint, defined as 20% below baseline value and < 150 x $10^3/mm^3$ (Applicant's Appendix ALL.090).

Thrombocytopenia was reported as an adverse event in 0.1% of placebo-treated patients and 0.3% of all pregabalin-treated patients, and the adverse event ecchymosis was reported in similar percentages of placebo- and pregabalin-treated patients (0.6% and 0.5%, respectively).

7.4.6.2 Laboratory changes – All uncontrolled trials, all indications

Creatinine kinase
In the combined controlled and uncontrolled studies, Pfizer found that the mean increase in creatine kinase from baseline to study endpoint (12.42 U/L) was similar in magnitude to that observed in the controlled studies. Increases in creatine kinase occurred in 1.9% (103/5352) of patients with CK measurements.

There were 81 patients who had a CK >5 x ULN. Of these, Pfizer identified 12 patients who reported AEs that were suggestive of myopathy. In total, 6 patients had CK abnormalities that were suggestive of a relationship to pregabalin treatment. Two patients experienced symptomatic CK elevations during double-blind treatment (Patient 085-416002 and 032-322019), and their values returned to normal upon discontinuation of treatment. Three of the 6 patients had relative resolution of their CK values despite continued treatment with pregabalin, including Patient 010-008124 who had elevated CK and rhabdomyolosis in the setting of cellulitis. Two of the 6 patients were diagnosed with fibromyalgia around the time of the CK abnormalities. However, fibromyalgia does not usually cause CK abnormalities.

To further examine instances of extreme CK elevation, Dr. Boehm assessed the summaries of the CPK data for the 5 placebo, and 28 pregabalin subjects in controlled trials who had a CPK≥1,000. The pregabalin group includes 12 subjects who had a CPK elevation that appeared to decrease or resolve with continued pregabalin treatment. For the remaining 16 subjects, the CPK≥1,000 was either the only on-treatment CK measurement for the subject, or the CK was increasing at the time of the last on treatment measurement.

In the controlled trials, the risk for CK≥1,000 was higher for pregabalin subjects (0.7%, 28/3781) compared to placebo subjects (0.3%, 5/1544). For some subjects, CK abnormalities were present at baseline. Also, CK elevations were present in the placebo treated subjects (illustrative of the background occurrence of CK elevations). As already mentioned, there were subjects who developed marked CK elevations on pregabalin that resolved with continued treatment. A number of subjects had their marked CK abnormality as their only on-treatment test or their last on-treatment test.

To put these CK abnormalities in perspective, Dr. Boehm reviewed the medical data for rosuvastatin, a recently approved treatment for elevated cholesterol. The safety data for this drug showed CK elevations (CK > 5x ULN) and cases of rhabdomyolysis, both of which resulted in limiting of the maximum recommended dose (80mg dose was not approved). The frequency of this level of CK elevation in combined controlled and uncontrolled rosuvastatin trials was 2.4% in the 80 mg dose group, and 0.5% in the 5-40 mg dose group. Also, the risk for CK elevations >5x ULN associated with symptoms of myopathy was 0.09% (5/5544) in the combined lower dose groups compared to 1.1% (14/1314) in the 80mg group.

With respect to the pregabalin combined trials, the frequency of CK elevation > 5xULN was 1.1% for all doses, and approximately 0.03% of patients (2/6776) with CK > 5 x ULN also had myopathy that was likely due to pregabalin treatment.. The frequency of this level of CK increase, as well as the proportion of patients with both a high CK and myopathy, are lower than those for the unapproved 80 mg dose of rosuvastatin.

Reviewer Conclusion: The data show that treatment with pregabalin is associated with a moderate increase in CK which does not appear to be dose-related, and was greatest in the epilepsy population. Increases in CK tend to occur early in treatment, and are generally not very large. Among the relatively few patients who had extreme increases in CK (> 5 x ULN), there were 2 patients for whom discontinuation of pregabalin was required, and 3 patients whose CK values resolved despite continued treatment. There was no clear evidence of rhabdomyolysis or renal failure associated with increased CK.

Platelets

Pfizer found that in all uncontrolled studies, the mean decrease in platelet counts (-5.325 x 10^3 /L) was similar in magnitude to that observed in the controlled studies. A decrease in platelets occurred in 5.4% (424/7851) of patients.

Pfizer identified 114 patients who had a post-baseline platelet count ≤ 100 x $10^3/mm^3$, and noted that for most other patients, the low platelet counts were transient and/or below normal at baseline. There was no apparent pattern of consistent decreases in WBCs, hematocrit, or

hemoglobin. All patients with adverse events of thrombocytopenia, thrombocytopenic purpura, purpura, petechiae were reviewed for any bleeding adverse events. Two patients (Patient 010_008125 and Patient 034_026008) reported concurrent bleeding, and the former withdrew due to the AE.

At Dr. Boehm's request, Pfizer provided a listing of all pregabalin-treated subjects with a platelet count <100,000. Dr. Boehm identified 120 patients who met the criterion, 113 of whom had an on-treatment platelet count ≤100,000. The majority of these 113 patients had a platelet count > 50,000. Patients with on-treatment counts of < 30,000 had only solitary episodes of this, and all had additional counts > 100 000. . Eleven of the 120 subjects had one or more AE terms suggestive of bleeding. For many of these events, the bleeding AE did not occur on days when platelet counts were checked. The platelet counts nearest to the bleeding AE did not suggest a relationship for most of these subjects. Only one patient (Subject 030-131014) had a strong temporal relationship between the AE (bruising) and an on-treatment platelet count of 13, 000.

A total of 31 subjects had baseline counts of ≥ 100 000, but later had one or more on-treatment counts < 100 000. All of these 31 patients' baseline platelet counts were below the lower limit of normal (140 000 or 150 000) for the study laboratories that performed the analyses.

Overall, the data show that treatment with pregabalin is associated with a slight decrease in platelet count. The data do not show a clear association between the decrease and development of bleeding abnormalities

7.4.6.3 Analysis of Liver Function Tests – All controlled trials, all indications

There were no considerable differences between placebo and pregabalin groups with respect to changes in mean AST, ALT, and total bilirubin from baseline to study endpoint. Analysis of the mean change from baseline to maximum value showed similar results:

Table 7.4.7.2: Change from Baseline to Maximum value in AST, ALT, and total bilirubin

Test Name	Units	Placebo	All PGB
AST	U/L	2.0618	3.7051
ALT	U/L	2.9742	4.5279
Total bilirubin	mg/dL	0.0506	0.0424

(Adapted from Applicant's Table 1.MAX.ALL (submitted March 16, 2004)

At the Agency's request, Pfizer identified all subjects with extremes in AST and/or ALT (> 3x ULN), and total bilirubin (≥ 2 mg/dL). There were 56 subjects who had a total bilirubin of ≥2mg/dL, 6 of whom also had an AST and or ALT >3x ULN. After reviewing these 6 subjects' data and narratives, Dr. Boehm noted that each of the cases had an alternate possible explanation for the observed abnormalities.

7.4.6.4 Laboratory mean changes – PHN controlled trials

Table 7.4.6.4.a displays the clinical laboratory parameters for which there was a statistically significant difference in mean change from baseline to study endpoint between placebo and any pregabalin treatment group in the controlled DPN studies.

The Tables 7.4.6.4.a to c show that, similar to the overall population, the most marked differences between the placebo and pregabalin groups were with respect to mean changes in platelets and creatinine kinase from baseline to study endpoint. The pregabalin group had a mean decrease in platelets (-12.7 x $10^3/\mu L$) compared to mild increase in the placebo group (-0.2 x $10^3/\mu L$). In addition, the pregabalin group showed an increase in creatine kinase (7.8 U/L), compared to a slight increase in the placebo group (2.1 U/L). When the mean change in platelets from baseline to minimum value was analyzed, there was a considerable difference between placebo (-11.1 x $10^3/\mu L$) and pregabalin (-23.3 x $10^3/\mu L$) (Applicant's Table1.MIN.PHN, submitted March 16 2004). A sizeable difference between groups was also seen with respect to the mean in creatinine kinase from baseline to maximum value (15.5 U/L for the placebo group, compared to 27.6 U/L for the pregabalin group) (Applicant's Table1.MAX.PHN, submitted March 16 2004).

Table 7.4.6.4.a: Mean change from baseline for clinical laboratory parameters with a statistically significant difference between pregabalin and placebo – PHN controlled trials

Test Name	Units	Placebo	PGB 150 mg/day	PGB 300 mg/day	PGB 600 mg/day	All PGB[a]
Hemoglobin	g/dL	-0.137	**-0.274**	**-0.274**	-0.189	**-0.25**
Hematocrit	%	-0.538	**-0.881**	-0.78	-0.716	**-0.78**
WBC	x^{103}/μ^L	-0.024	**-0.204**	**-0.307**	-0.259	**-0.268**
Differential-Neutrophils	%	-0.038	**-1.076**	**-1.371**	-1.016	**-1.187**
Absolute Neutrophils	x^{103}/μ^L	-0.014	**-0.174**	**-0.281**	-0.22	**-0.239**
Differential Lymphocytes	%	-0.005	**1.2044**	**1.1882**	0.603	**1.0703**
Differential Eosinophils	%	-0.025	**0.1105**	0.1736	**0.354**	**0.1963**
Platelets	x^{103}/μ^L	-0.214	**-8.264**	**-14.61**	**-21.31**	**-12.7**
CK-Creatine Kinase	U/L	2.1081	**5.372**	**7.7455**	**12.853**	**7.7847**
Creatinine Clearance Estimated	mL/min	-1.047	**1.7293**	2.3333	-3.08	0.0739
Uric Acid	mg/dL	0.0171	**0.1632**	**0.2529**	**0.2732**	**0.2048**
Albumin	g/dL	-0.024	**-0.077**	**-0.104**	**-0.075**	**-0.085**
Total Protein	g/dL	-0.052	**-0.11**	**-0.143**	-0.065	**-0.112**
Alkaline Phosphatase	U/L	-1.074	0.6296	**7.1163**	**3.1133**	**3.3923**
LDL Cholesterol	mg/dL	-6.86	-10.87	**-2.14**	-6.549	-5.829
Sodium	mEq/L	-0.059	-0.04	0.093	**0.6133**	0.0975
Calcium	mg/dL	0.0042	**-0.113**	**-0.113**	-0.041	**-0.099**
Amylase	U/L	-2.097	-2.037	**0.209**	**-1.94**	-0.838
Chloride	mEq/L	0.5725	0.6263	**1.0864**	**1.4333**	**0.917**
Urine Specific Gravity	--	0	-0.001	0	**-0.001**	-0.001

Values in **bold** = Statistically significantly different ($p < 0.05$) from placebo by Wilcoxon Rank-Sum test.
[a] Includes all other doses of pregabalin (i.e., 75 mg/day).
(Applicant's Table 82, SCS, RR-REG 720-30199, P. 159)

Table 7.4.6.4.b: No. and % of patients with changes in specific lab values – PHN controlled trials

Test Name	Direction of Change	Placebo %	Placebo No.	Placebo Total	150 %	150 No.	150 Total	300 %	300 No.	300 Total	600 %	600 No.	600 Total	All PGB %	All PGB No.	All PGB Total
Platelets	Decrease	1.0	4	387	2.4	7	296	1.3	4	300	3.4	5	148	2.8	23	826
	Increase	1.0	4	387	2.0	6	296	0.7	2	300	0.0	0	148	1.0	8	826
CK – creatinine kinase	Increase	0.4	1	259	0.0	0	164	0.4	1	224	0.7	1	150	0.4	2	562
Creatinine	Increase	1.3	5	393	2.0	6	297	2.6	8	302	0.7	1	150	1.8	15	832
Uric acid	Increase	0.5	2	393	0.0	0	297	1.3	4	301	0.7	1	150	0.6	5	832
BUN	Increase	3.3	13	393	3.7	11	297	8.0	24	301	2.7	4	1.5	4.8	40	831
Bilirubin - total	Increase	1.0	4	393	1.4	4	296	0.3	1	301	0.0	0	150	1.0	8	830
Albumin	Decrease	0.0	0	393	0.0	0	297	0.0	0	301	0.0	0	150	0.0	0	831
Total protein	Decrease	0.8	3	393	0.7	2	297	0.0	0	301	0.0	0	150	0.4	3	831
	Increase	0.0	0	393	0.0	0	297	0.0	0	301	0.0	0	150	0.1	1	831

(Adapted from Applicant's Appendix PHN.072, RR-REG 720-30199, SCS, P. 10004-8)

Table 7.4.6.4.c: Summary of changes from baseline to maximum/minimum value for specific laboratory tests – PHN controlled trials

Test Name	Units	Placebo N	Placebo Mean	Placebo Med	Placebo Min	Placebo Max	All pregabalin N	All pregabalin Mean	All pregabalin Med	All pregabalin Min	All pregabalin Max
Platelets (to min value)	$\times^{10^3}/\mu^L$	387	-11.06	-10	-139	176	826	-23.27	-21	-199	168
Creatinine kinase (to max value)	U/L	259	15.529	8	-181	463	562	25.571	17	-366	735

(Adapted from Applicant's Table1.MIN.PHN and Table1.MAX.PHN, March 24, 2004)

7.4.6.5 Laboratory mean changes – PHN uncontrolled trials

In the open-label PHN studies, an increase in mean creatine kinase from baseline to study endpoint was observed (15.623 U/L), which was consistent with the controlled PHN studies. One patient (0.9%) had a potentially clinically significant increase in creatine kinase during open-label treatment. With regard to platelets, the mean (-12.64×103/μL) decrease in platelet count from baseline to study endpoint was also similar to that of the controlled studies. Out of 558 patients, 45 (8.1%) had potentially clinically significant decreases in platelet values at study endpoint, and 3 (0.5%) had potentially clinically significant increases (Applicant's Appendices PHN.083, 084, 086).

7.4.7 Vital signs

Heart rate and blood pressure were measured in all clinical trials, however they were assessed with variable subject positioning. Respiratory rate was measured only in epilepsy studies. Similar to analyses of laboratory values, the baseline value was the last value obtained prior to therapy and the endpoint value was the last available non-follow-up value. Pfizer summarized vital signs data for the ITT population, and evaluated changes from baseline. At the Division's request, Pfizer also provided summaries of mean changes in vital signs from baseline to maximum and minimum value, as well as shift tables to identify extreme outliers.

Controlled trials – All indications

In the placebo group, 1.5% (37/2384) of patients met criteria for clinically important changes from baseline, compared to 1.2% (70/5508) of pregabalin patients. The data showed no differences between pregabalin- and placebo treatment groups with respect to abnormalities in heart rate, blood pressure, or respiratory rate. Also, there was no apparent association between dose and change in vital signs (Applicant's Appendices ALL_sft.01, ALL_chg.01).

PHN controlled trials

Similar to the data from the combined controlled trials, data from the PHN controlled trials showed no substantial difference between placebo and pregabalin patients with respect to heart rate or blood pressure (Applicant's Appendices PHN.087-094, PHN_sft.01, PHN.chg.01).

7.4.8 Weight

Refer to my review of N 21-446 (pregabalin for treatment of pain associated with DPN) for a detailed discussion of the weight data.

All clinical trials included an assessment of patients' weight. Similar outlier analyses and shifts from baseline to maximum and minimum value were conducted as for the vital signs data.

7.4.8.1 Controlled studies – All indications

Using a LOCF analysis, Pfizer found that the mean change in weight from baseline to endpoint was 0.3 kg for the placebo patients, and 1.6 kg for pregabalin patients. An evaluation of change in weight from baseline to any time showed that 12.6% of patients treated with pregabalin had an

increase in weight, compared to 2.4% of placebo patients. Furthermore, among patients with a normal body mass index (BMI) at baseline, 2.2% of placebo patients versus 4.6% of pregabalin patients experienced an increase in BMI (Applicant's Appendices ALL_sft.01, All_chg.01).

The overall incidence of ≥7% weight gain (from baseline to last observation) was higher among pregabalin-treated patients (7.7%) than placebo-treated patients (1.7%), with the highest incidence in patients treated with pregabalin 600 mg/day (11.6%) (Table 7.4.9). The 12-week controlled epilepsy studies had the highest overall incidence of weight gain (18.0%) and strongest dose response.

Table 7.4.8.1.a: Summary of ≥ 7% weight gain (baseline to last observation)[a] by indication: Controlled studies

	[n (%)of Patients With ≥7% Weight Gain]							
Indication	Pregabalin Total Daily Dose in mg/day (BID and/or TID)							
	Placebo	150	200	300	400	450	600	Any Dose[b]
All Studies[c]	N=2233	N=1122	N=175	N=1158	N=320	N=470	N=1701	N=5181
	38 (1.7)	53* (4.7)	4 (2.3)	81* (7.0)	22* (6.9)	33* (7.0)	198* (11.6)	401* (7.7)
NeP	N=831	N=505	--	N=612	--	--	N=507	N=1775
	13 (1.6)	18* (3.6)	--	40* (6.5)	--	--	41* (8.1)	105* (5.9)
DPN	N=444	N=207	--	N=309	--	--	N=358	N=947
	6 (1.4)	7 (3.4)	--	12* (3.9)	--	--	27* (7.5)	49* (5.2)
PHN	N=387	N=298	--	N=303	--	--	N=149	N=828
	7 (1.8)	11 (3.7)	--	28* (9.2)	--	--	14* (9.4)	56* (6.8)
Epilepsy	N=292	N=181	--	N=87	--	--	N=385	N=737
	6 (2.1)	15* (8.3)	--	12* (13.8)	--	--	102* (26.5)	133* (18.0)
GAD	N=428	N=195	N=64	N=79	N=170	N=162	N=374	N=1044
	6 (1.4)	2 (1.0)	0 (0.0)	1 (1.3)	12* (7.1)	5 (3.1)	22* (5.9)	42* (4.0)

* Significantly different from placebo based on odds ratio
[a] N at risk = the number of patients with both baseline and termination/LOCF weight.
[b] Includes all other doses of pregabalin (ie, 50 and 75 mg/day).
[c] Includes other nonneuropathic pain and other psychiatry studies.

Most patients who had a clinically significant increase in weight during the controlled studies gained no more than 10% of their body weight. More patients treated with 600 mg/day had increases greater than 7% compared with other treatment. However, 46 of the 72 patients with ≥10% increases in the pregabalin 600 mg/day group were from the controlled epilepsy studies groups). The relative risk of weight gain among pregabalin-treated subjects was highest in the epilepsy population (8.6) compared to the DPN, GAD, and PHN populations (2.9, 3.7, and 3.7, respectively) (SCS, Appendix ALL.154, Table 31 P.82).

7.4.8.2 Weight - PHN controlled trials

Among PHN patients in controlled trials, 1.6% of placebo-treated patients had an increase in their weight from baseline to anytime in the study, compared to 13.1% of pregabalin-treated patients (Applicant's Appendix PHN.chg.01). Similarly, 1.8% of placebo patients versus 6.8%% of pregabalin patients had an increase in weight (≥ 7% increase in weight) from baseline to study

termination. This magnitude of weight increase occurred more frequently among patients treated with 300- and 600 mg/d (9% of patients) compared to patients treated with pregabalin 75-or 150 mg/d (4% of patients) or with placebo (2% of patients) (Appendix PHN.099, SCS P. 10120). Analyses of shifts in BMI from "normal" at baseline to "high" at any time in the trial found that 2.6% of placebo patients had an increase, compared to 5.0% of pregabalin patients (Applicant's Appendices PHN_sft.01 and DPN_chg.01).

The cumulative distribution of weight gain in controlled PHN trials is shown in the table below. Treatment with pregabalin conferred a greater risk of weight gain, and a dose dependent association was suggested. Subjects taking the higher dose of pregabalin (300 or 600 mg/day) appeared to suffer the greatest risk of weight increases > 7%.

		Pregabalin Dose, mg/day (BID and/or TID)				
	Placebo	75	150	300	600	Any Dose
Percent Change	**N=398**	**N=84**	**N=302**	**N=312**	**N=154**	**N=852**
N at Risk*	387	78	298	303	149	828
Increase						
>=7	7 (1.8)	3 (3.8)	11 (3.7)	28 (9.2)	14 (9.4)	56 (6.8)
>=10	3 (0.8)	1 (1.3)	4 (1.3)	6 (2.0)	6 (4.0)	17 (2.1)
>=15	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.7)	3 (0.4)
>=20	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>=25	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*N at risk = the number of patients with both baseline and termination/LOCF weights recorded
Applicant's Appendix ALL.136, P. 7367

There were no apparent risk factors for weight gain, other than treatment with pregabalin. Co-occurrence of edema did not fully account for the observed weight gain.

7.4.9 ECG

Refer to my review of N 21-446 (pregabalin for treatment of pain associated with DPN) for a detailed discussion of the ECG data.

Overview

Overall, pregabalin treatment had no clinically significant findings for ECG parameters. Pregabalin had no consistent effect on QTc, QRS, or ventricular rate. Premature ventricular contractions (PVCs) did not occur more commonly in pregabalin-treated than placebo-treated patients in the combined pain trials, epilepsy trials, short -term GAD trials, or relapse-prevention trials. In the DPN sub-population, PVCs occurred more commonly in pregabalin-treated patients, but there was no clear dose relationship of pregabalin with PVCs.

Across all studies pregabalin was associated with a statistically significant but clinically insignificant mean increase in PR interval (3-6 msec) at doses ≥300 mg/day. The incidence of cardiovascular adverse events was similar among pregabalin-treated and placebo-treated patients. Generally, pregabalin treatment was not associated with significant cardiac-associated sequelae (SCS, P. 69). Of note, Pfizer has not conducted any formal studies to evaluate the effects of pregabalin on cardiac function.

7.4.9.1 ECG data – PHN trials

Initially, Pfizer did not summarize separately the ECG data for the neuropathic pain models (PHN and DPN). Instead, all studies of neuropathic and non-neuropathic pain that were analyzed by Pfizer's central reader (Studies 014, 029, 030, 031, 032, 040, 104, 105, 127, and 131) were pooled for analysis. In this pooled pain population, there were no dose-related trends in mean maximum changes in QRS, QTc, or ventricular rate.

The pooled ECG data showed that the mean maximum change in PR interval tended to increase with higher pregabalin doses. The largest mean maximal increase, observed in the pregabalin 600 mg/day group, was 3.4 msec more than in the placebo group. Based on Pfizer's medical review, there were no clinically important ECG findings related to pregabalin treatment in Studies 149 and 173 (DPN trials) or Studies 045, 132, and 196 (PHN trials) - these trials were not analyzed by the central reader (SCS, P. 163).

At the Division's request, Pfizer calculated mean changes of these parameters from baseline to maximum value for the PHN population only. Changes in ECG parameters were presented by assigned treatment dose, and comparisons made to placebo:

Table 7.4.9.1.a: Summary of ECG changes from baseline to maximum value – controlled PHN studies

Parameter	Placebo		75 mg/d		150 mg/d		300 mg/d		600 mg/d		All PGB	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
PR interval	143	2.49	78	6.46	72	8.01	18	10.33	32	5.69	200	7.25
QRS interval	148	0.59	81	1.48	77	1.53	18	4.11	33	0.79	209	1.62
Ventricular rate	151	-0.31	81	1.15	78	0.81	18	-4.39	33	-4.3	210	-0.31
QTc interval	148	2.46	81	3.47	77	3.1	18	-3.39	33	-1.15	209	2.01

(Adapted from Applicant's Table Max_PHN.pdf, submitted April 9 2004)

The table above shows that the PR interval appeared to increase with ascending doses of pregabalin (except the 600 mg/d dose), with the largest change from baseline seen at the 300 mg/d dose. An adverse effect on the QTc interval was not apparent from these data.

A comparison of the proportion of PHN patients in controlled trials who had a change from normal PR interval at baseline to "high" PR interval at study endpoint gave similar results to the overall treated population. More pregabalin-treated patients than placebo patients had a change from normal PR interval at baseline to "high" (6.5% vs. 2.1%, respectively). Otherwise, there was no difference with respect to shifts from normal QRS and QTc intervals, or ventricular rate, between the two groups (Applicant's Appendix phn_sft.02).

In PHN controlled trials, there were 6 patients who experienced heart block, only 1 case of which was considered "serious" (Table 7.4.9.1.b). The frequency of heart block in the placebo group was 0.3% (1/398), which was not considerably different from the frequency in the pregabalin group (0.6%, 5/852). The serious case of 2nd degree heart block was not believed to be associated with pregabalin treatment.

Table 7.4.9.1.b: List of patient sin PHN controlled trials that experienced heart block

ISSPTID	AE text	Treatment group	Serious AE
196_005001	VARIABLE HEARTBLOCK	Placebo	No
127_014007	1ST DEGREE AV BLOCK	300 mg/day PGB TID	No
127_015004	ECG-1ST DEGREE AVB	300 mg/day PGB TID	No
127_017018	1 DEGREE AV BLOCK ON EKG	600 mg/day PGB TID	No
196_108003	FIRST DEGREE AV BLOCK	300 mg/day PGB BID	No
132_130006	1ST DEGREE A-V BLOCK	300 mg/day PGB BID	No
	2ND DEGREE A-V BLOCK	300 mg/day PGB BID	Yes

The frequency of heart block in uncontrolled trials was also determined. Four patients in the uncontrolled trials experienced AV block, two of who had this AE during controlled trials. None of the reports of AV block were considered "serious".

Table 7.4.9.1.c: List of patient sin PHN uncontrolled trials that experienced heart block

ISSPTID	**AE text**	**Serious AE**
127_015004	ECG-1ST DEGREE AVB	No
127_017018	1 DEGREE AV BLOCK ON EKG	No
127_023002	PRIMARY AV BLOCK	No
132_128012	FIRST DEGREE AV BLOCK	No

Reviewer's conclusions: Treatment with pregabalin is associated with an increase in PR interval, but not on QT or QRS intervals, or on ventricular rate. The effect on the PR interval does not appear to be dose-related. The data do not show an increased risk of heart block with pregabalin treatment.

7.5 MISCELLANEOUS STUDIES

7.5.1 Other PHN efficacy studies

The following two studies also evaluated the safety and efficacy of pregabalin as treatment for postherpetic neuralgia. However, these studies were considered inadequate because they were of insufficient duration (Protocols 030 and 132), failed to show efficacy of pregabalin on the Applicant's analysis (Protocol 030), or had too few patients for adequate study power (Protocol 132).

7.5.1.1 Protocol 1008-030: A 5-week, double-blind, placebo-controlled, parallel-group study of pregabalin (75 and 150 mg/d) in patients with postherpetic neuralgia

This was a 5-week, multi-center study conducted across 29 centers in the United States, from October 14 1998 to July 26 1999. The objective was to evaluate the safety and efficacy of two dosing regimens of pregabalin (25 mg TID or 50 mg TID) vs. placebo in patients with postherpetic neuralgia. Adult patients (age ≥ 18 years) with pain persisting more than 3 months after healing of the herpes zoster rash, and with a score of ≥ 40 mm on the VAS at randomization were enrolled into the study. A total of 256 patients were randomized, and 255 took at least one dose of study drug (88 in the placebo group, 84 in the 75 mg/d group, and 84 in the 150 mg/d group).

Pfizer found that at endpoint, no statistically significant differences existed in the comparison of either pregabalin group with the placebo group for any parameter. Descriptive statistics showed that mean pain scores decreased for the pregabalin 150 mg/day, 75 mg/day, and placebo groups as the study progressed, with the largest decreases occurring between baseline and Week 1. There were no statistically significant differences in responder rates between groups.

7.5.1.2 Protocol 1008-132: A 12-week, randomized, double-blind, multi-center, placebo-controlled study of pregabalin twice a day (BID) in the treatment of postherpetic neuralgia

A total of 38 centers in the United States enrolled patients into this study, which was initiated on November 15 2000, but was prematurely terminated on February 12 2001. The study was terminated due to the FDA's imposition of a partial clinical hold on all trials of pregabalin in patients with neuropathic pain.

Eligibility criteria were similar to those of Protocol 1008-196. Also, patients were randomized to the actual dose of study drug based on their creatinine clearance: patients in the 300/600 mg/d group were treated with 300 mg/d if their creatinine clearance was between 30 and 60 mL/min. Patients with a creatinine clearance > 60 mL/min were treated with 600 mg/d. There were 217 randomized patients, 216 of whom took at least one dose of study drug (51 in the 150 mg/d group, 62 in the 300 mg/d group, and 51 in the 300/600 mg/d group) (the ITT population). Two patients completed the trial.

Data were analyzed for the ITT population. Pfizer compared each of the active groups (150, 300, or 300/600 mg/day) to placebo. Comparisons were not made on actual dose of pregabalin received. Compared with placebo, all 3 dose regimens administered BID demonstrated efficacy based on the primary efficacy measure endpoint mean pain scores for relief of pain associated with postherpetic neuralgia. A statistically significant difference was also seen in the comparison of endpoint mean pain scores based on expected There was a statistically significant proportion of responders (defined as the number of patients reporting at least 50% improvement in pain at endpoint compared with baseline) in each pregabalin treatment group compared with the placebo group. Percent of responders for pregabalin 300/600 mg/day was 32%, pregabalin 300 mg/day was 24.3%, and pregabalin 150 mg/day was 13.7%, compared with 1.9% in the placebo group.

7.5.2 Other studies in patients with pain

The Applicant submitted reports for the following pain studies that were not considered as supportive of efficacy in PHN, but did contribute to the safety data for pregabalin:

Protocol number	Indication/treatment population
031	Osteoarthritis
032	Chronic low back pain
060	Chronic cervical radiculopathy
104	Chronic low back pain
105	Fibromyalgia
183	Chronic cervical radiculopathy

8 Literature Review for Safety

Pfizer did not provide any published literature in support of the safety of pregabalin.

9 Postmarketing Surveillance

Pregabalin was only recently approved for marketing in Europe (April 2004). There are no post-marketing data for review.

10 Safety Update

The original NDA submission had a data cut-off date of February 14, 2003. The four-month safety update was submitted on February 23, 2004. It includes data from four trials that were not included in the original NDA, as well as information from ongoing, long-term, open-label extension studies that was collected between February 14 and October 10 2003. The four trials are listed below:

Protocol No.	Indication	Pregabalin (N)	Placebo (N)
1008-155	DPN/PHN (controlled trial)	DPN: 201 PHN: 72	65
1008-166	DPN/PHN Open-label extension	50	
108-093/192	Panic relapse prevention (controlled trial)	190	

Of the controlled trials, only 1008-155 was completed prior to the cut-off date for the Safety Update (October 10, 2004).

In its presentation of data in the Safety Update, Pfizer uses three general categories: "NDA data", "New data" and "All Safety Update data." "New data" includes information from both newly exposed patients, and new data from ongoing patients. "All Safety Update data" is a combination of the original NDA data and the New data, as well as any correction that were made to the data after the February 14 2003 cutoff date.

10.1 Exposure

As of the cut-off date for the Safety Update, there were 273 additional patients exposed to pregabalin during controlled clinical trials. These patients were enrolled in Protocol 1008-155, a placebo-controlled trial evaluating the effects of pregabalin on neuropathic pain (DPN (n=201) and PHN (n=72)). The total number of patients exposed to pregabalin during controlled trials was therefore 5,781 (compared to 5,508 in the original NDA),

Among combined controlled or uncontrolled trials, 1617 additional patients received at least one dose of pregabalin, making a total of 9278 patients exposed to pregabalin among combined trials (compared to 8666 in the original NDA).

Table 10.1 shows the source and number of patients who were exposed to study drug, using both the initial NDA data and the new exposure data:

Table 10.1: Safety Update: Exposure - All trials

	Placebo NDA Data	Placebo New Data	Placebo Safety Update #1 Data	ALL PGB NDA Data	ALL PGB New Data	ALL PGB Safety Update #1 Data
Clinical Phase 2/3 Integrated Safety Database						
Controlled Studies	2384	65	2449	5508	273	5781
Neuropathic Pain	857	65	922	1831	273	2104
Diabetic Neuropathy	459	48	507	979	201	1180
Postherpetic Neuralgia	398	17	415	852	72	924
Epilepsy (Adjuvant Therapy in Partial Seizures)	294	0	294	758	0	758
Generalized Anxiety Disorder	484	0	484	1149	0	1149
Other *	749	0	749	1770	0	1770
Other Chronic Pain	416	0	416	1068	0	1068
Other Psychiatry	333	0	333	702	0	702

Table 10.1: Safety Update: Exposure - All trials (continued)

	Placebo NDA Data	Placebo New Data	Placebo Safety Update #1 Data	ALL PGB NDA Data	ALL PGB New Data	ALL PGB Safety Update #1 Data
Clinical Phase 2/3 Integrated Safety Database						
Controlled and Uncontrolled Studies				8666	1617	9278
Neuropathic Pain				2524	958	2864
Diabetic Neuropathy				1413	597	1650
Postherpetic Neuralgia				1111	361	1214
Epilepsy (Adjuvant Therapy in Partial Seizures) **				1613	344	1613
Generalized Anxiety Disorder ***				1962	14	1962
Other *				2567	301	2839
Other Chronic Pain				1364	21	1364
Other Neuropathic Pain #				28	0	28
Other Psychiatry $				1175	280	1447

* Other includes chronic pain, other neuropathic pain, and other psychiatry studies that are not summarized separately but are included when all indications are combined (overall profile of pregabalin).
** Includes comparator-controlled, 8-day monotherapy trial (Study 007) and its adjunctive therapy OL extension (Study 008).
*** Includes Study 088, a long-term, placebo-controlled, relapse prevention/sustained efficacy study in GAD.
# Other NeP includes Study 060 (cervical radiculopathy), Study 160 (sleep in NeP), and their OL extensions (Studies 183 and 174, respectively).
$ Includes the following long-term, placebo-controlled, relapse prevention/sustained efficacy studies: Study 082 (social anxiety disorder (SAD)) and Study093/192 (panic disorder).
(Applicant's Table 1, Safety Update, P. 11)

10.2 Deaths

The data on deaths are provided from two sources, i.e., the Oracle clinical database and the ARISg database. The Oracle clinical database provides summaries and listings of deaths that occurred in the completed, double blind studies and their open-label extensions. The Adverse Reaction Information System, global (ARISg) provides summaries and listings for deaths that occurred in the ongoing, double blind studies and their open-label extensions. In addition, ARISg contains data from open-label extensions of completed double blind studies that did not get entered into Oracle database as of the data cutoff for the Safety Update (10 October 2003).

The NDA's initial integrated safety database (the Oracle Clinical Database) described 55 deaths that occurred among pregabalin-treated patients. In the Safety Update, Pfizer reports 13 additional deaths among clinical trial participants. Of these 13 deaths, 8 occurred during trials that are now complete: 7 deaths occurred in pregabalin-treated patients, and 1 death occurred in a patient who did not take pregabalin (Table 10.2.a). The other 5 deaths occurred in trials that are ongoing.

Table 10.2.a: Safety Update: Deaths included in the Oracle Database by the Safety Update cut-off date

PT ID	Protocol/ Treatment	Narrative
149-48003	165 PGB 600 mg/d	Myocardial infarction on Study Day 317 of open label treatment
155-033004	166 PGB	Myocardial infarction on Study Day 222 of open-label treatment
155-074020	155 PGB 600 mg/d	Diabetic acidosis; hypovolemic shock; cardiac arrest on Study Day 22 of double-blind treatment
155-132002	166 PGB 450 mg/d	Myocardial ischemia on Study Day 63 of open label treatment
155-038003	166 PGB 600 mg/d	Cerebral stroke on Study day 411 of open label treatment
155-106008	155 PGB	Worsened COPD on Study Day 33 of double-blind treatment
155-136003	166 PGB	Cerebrovascular accident on Study Day 506 of open label treatment
196-008002	198 PGB 600 mg/d	Myocardial infarction on Study Day 219 of open label treatment
196-705001	198 PGB 300 mg/d	Metastatic carcinoma on Study Day 263 of open label treatment
009-045013	10 PGB 375 mg/d	Cardiopulmonary arrest on Study Day 1053
012-084102	12 PGB 600 mg/d	Death
034-027017	35 PGB	Aspiration following seizure on Study Day 1355
192-027006	192 PGB	Endocarditis, septicemia, with multiple organ failure on Study Day 245

(Applicant's Appendix ALL.16, Safety Update, P. 385 -400)

Of note, at the time of the NDA filing, 8 of the 13 deaths had been reported to the ARISg database (but not the Oracle Clinical database). Therefore, these 8 deaths were listed in the original Summary of Clinical Safety, but were not included in the integrated safety database. The 8 deaths occurred in the following subjects: Patients 155_033004, 155_038003,155_074020, 155_106008, 155_132002, 192_027006, 009_045013 and 196_008002 (SCS Tables ALL.51, ALL.289). Consequently, of the 13 deaths, the 5 deaths that were not reported in the NDA at all were:

Table 10.2.b: Safety Update: New Deaths (not previously reported to the ARISg or Oracle databases)

Patient Identification	Protocol Number	Days from Last Dose to Death	Preferred Term for Cause of Death
012_084102	1008-012	Unknown	Unknown
034_027017	1008-035	55	Respiratory disorder
149_484003	1008-165	1	Myocardial infarct
155_136003	1008-166	136	Cerebrovascular accident
196_705001	1008-198	17	Carcinoma

(Applicant's Appendix Table 10, Safety Update, P. 23)

In addition to the above deaths, I found that there were 8 other deaths that were listed in the ARISg Database, but which were not reported to the Oracle Clinical Database before the Safety Update deadline of October 10 2003. The deaths were are briefly described in Table 10.2.c.

Table 10.2.c: Listing of patients with deaths reported to the ARISg database, but not to the updated Oracle Database, as of the Safety Update cut-off date

Protocol No.	PT ID	Preferred Term
1008-035	22-012	Aspiration
1008-061	003-3	Cardiomyopathy NOS; Sepsis NOS
1008-198	904-5	Head injury
1008-114	112-6	Unknown
1008-164	126-1	Epileptic seizures, drowning
1008-112	145-4	Possible suicide
1008-114	147-3	High grade lymphoma
1008-100	477-33	Myocardial ischemia

(Applicant's Tables 11 and 12, Safety Update, P. 23; Appendix ALL18.1, P. 403)

Consequently, there have been a total of 21 additional deaths that occurred which were not included in the initial integrated safety database at the time of NDA filing.

None of the deaths was without possible alternate cause, except perhaps for the case of accidental head injury following a fall (patient 904-5 in protocol 1008-198).

Protocol 1008-198 Subject Identification Number: 904-5
Head Injury Head Injury
This 83-year-old white female with a history of postherpetic neuralgia, myocardial infarction, dizziness, and falls. The subject was initially enrolled in a the double-blind study 1008-196 and was treated with placebo for 95 days. The subject continued in extension study 1008-198 and was administered pregabalin 150 - 300 mg/day until Study Day 417. On that day, she fell from a staircase and suffered a severe head injury. (intracerebral, subarachnoid and subdural hematoma). The subject died on Study Day 424. The cause of death was reported as head injury caused by the fall. No autopsy results were available.

It is not stated whether the fall occurred in the setting of somnolence or dizziness related to pregabalin treatment. However, this patient was elderly and had a history of falls, so it is possible that her death was not a result of adverse effects of pregabalin treatment.

10.3 Serious adverse events
As discussed earlier regarding the data on deaths, serious adverse event (SAE) data are provided from two sources, i.e., the Oracle clinical database and the ARISg database.

SAES in completed double-blind trials and their open-label extensions
There were 854 subjects from completed trials who experienced an SAE and were included in the Safety Update Oracle database. In comparison, in the original NDA database, 714 subjects were noted to have had an SAE. Also, there were 54 patients from completed trials who had an SAE reported to the ARISg database, but not to the Oracle database, as of the cut-off date for the

Safety Update. Consequently, in total, the Safety Update contains SAE information for an additional 194 participants of completed trials.

With respect to completed controlled trials for all indications, there were 19 additional patients (2 placebo, 17 pregabalin) who had an SAE and whose data were added to the integrated (Oracle) safety database. The SAEs that occurred in more than one pregabalin-treated participant in a controlled trial are listed below (data from both the original NDA and the Safety Update are compared):

Table 10.3: Safety Update: Summary of SAEs by decreasing frequency – Completed controlled trials, all indications

Preferred Term	Placebo NDA Data N=2384	Placebo Safety Update #1 Data N=2449	ALL PGB NDA Data N=5508	ALL PGB Safety Update #1 Data N=5781
Accidental injury	0 (0.0)	0 (0.0)	16 (0.3)	16 (0.3)
Chest pain	3 (0.1)	3 (0.1)	8 (0.1)	9 (0.2)
Pneumonia	2 (0.1)	2 (0.1)	6 (0.1)	7 (0.1)
Angina pectoris	2 (0.1)	2 (0.1)	3 (0.1)	5 (0.1)
Cholecystitis	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)
Confusion	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)
Congestive heart failure	2 (0.1)	2 (0.1)	4 (0.1)	4 (0.1)
Dizziness	0 (0.0)	0 (0.0)	3 (0.1)	4 (0.1)
Myocardial infarct	2 (0.1)	2 (0.1)	4 (0.1)	4 (0.1)
Cellulitis	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Cerebral ischemia	1 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Coronary artery disorder	1 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)
Diabetes mellitus	0 (0.0)	0 (0.0)	1 (0.0)	3 (0.1)
Dyspnea	1 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)
Hypesthesia	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Infection	1 (0.0)	1 (0.0)	3 (0.1)	3 (0.1)
Pain	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Suicide attempt	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Urinary tract infection	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)
Deep thrombophlebitis	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Fever	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Gastroenteritis	1 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.0)
Hypoglycemia	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Kidney calculus	1 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)
Myopathy	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Peripheral edema	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Somnolence	1 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)
Syncope	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Ventricular extrasystoles	1 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)
Vomiting	0 (0.0)	1 (0.0)	2 (0.0)	2 (0.0)

* = SAE that occurred in more than one of the patients treated with pregabalin in the cumulative SU#1 data.
Source Data: Appendix ALL.20
(Applicant's Table 13, Safety Update, P. 25)

The table shows that even after inclusion of the additional SAE data, there was no considerable difference between pregabalin and placebo groups with respect to SAE type or frequency.

Safety Update: Treatment-related SAEs
Pfizer considered the following SAEs to likely be associated with pregabalin treatment:

Patient ID	Protocol No.	AE text
031-1	174	67 yo F with DPN. Adenocarcinoma of the liver diagnosed on Study Day 885 of open-label treatment with PGB 600 mg/d. Pt had no history of risk factors for liver cancer.
147-7	114	16 yo F with partial seizures. Seizure exacerbation of Study Day 7 of blinded treatment.
001-6	125	41 yo M with neuropathic pain Weight gain, Hyponatremia, pitting edema, sedation, thrombocytopenia - Study Day 29 of treatment with pregabalin, up to 600 mg/d
112-23	164	36 yo M with partial seizures Worsening depression with aggression – Study Day 45 of open label treatment (pregabalin 600 mg/d) Increased seizures – Study day 59
136-3	166	88 yo M with postherpetic neuralgia Accidental fall in the setting of somnolence – Study Day 262 of open label treatment with 300 mg/d Hospitalization for chest infection, discontinuation of study drug – Study Day 500 Death following cerebrovascular accident – Post therapy day 8
152-4	197	49 yo F with neuropathic pain Deep vein thrombosis – Study Day 428 of open label treatment, pregabalin 450 mg/d

Note that the death of Patient 1008-166-136-6 is included in the new data on deaths (See Table 10.2.b)

SAEs in completed neuropathic pain trials
Pfizer noted 3 that there were 3 patients in the completed neuropathic pain trial 1008-155 that had a newly reported SAE added to the Safety Update:

Patient ID	Protocol No.	AE text	Preferred term
155-106007	155	Dysarthria	Dysarthria
155-109005	155	Dizziness	Dizziness
155-138018	155	Petiachial rash on calves Increased sodium Increased creatinine Increased urea Henoch-Schoenlein rash on both legs	Petichial rash Hypernatremia Creatinine increased BUN increased Purpura

(Applicant's Table 14, Safety Update, P. 26)

With respect to controlled neuropathic pain trials, the overall rate of SAE occurrence among placebo patients was 2.2% within the original NDA and 2.3% in the Safety Update. In comparison, patients treated with pregabalin had an SAE frequency of 3.5% in the original NDA and 3.8% in the cumulative Safety Update data. Thus, the additional data did not considerably affect the SAE frequency for either placebo or pregabalin groups, or the difference in SAE frequency between the groups. Also, the data did not suggest a meaningful difference in SAE occurrence within any body system (Safety Update, P. 45)

11 DRUG WITHDRAWAL, ABUSE, AND OVERDOSE EXPERIENCE

Refer to my review of N 21-446 (pregabalin for the treatment of pain associated with DPN) for a detailed discussion of drug withdrawal, abuse, and overdose experience with pregabalin.

Drug withdrawal

In summary, the potential discontinuation effects of pregabalin were evaluated in nonclinical models, clinical pharmacology trials, and in the Phase 2/3 psychiatry trials using 2 methods, discontinuation-emergent signs and symptoms (DESS) and the Physician's Withdrawal Checklist (PWC). Discontinuation effects were also evaluated prospectively in one 8-week DPN study (Study 040) and one study in healthy volunteers (Study 072). The data show that subjects who abruptly discontinue, or cease pregabalin treatment over a short duration, commonly experience insomnia, headache, nausea, and diarrhea. The Controlled Substance Staff (CSS) believes this describes a withdrawal syndrome, and indicates the presence of physical dependence.

Abuse

Euphoria was a common adverse event, occurring in 3.7% (205/5508) of pregabalin-treated patients and 0.5% (11/2384) placebo-treated patients in controlled trials. Investigator terms referring to euphoria included elation, elevated mood, excessive happiness, increased drive, increased sense of well-being, being "high", "stoned", or "intoxicated." The incidence of euphoria in controlled studies varied by indication, and was greatest in the GAD population (as many as 12% of patients treated with 400 mg/d dose reported to Euphoria). Rates in the DPN, PHN and epilepsy populations were relatively similar (1-2%).

Based on the results of a clinical abuse potential study with sedative/alcohol abusers, CSS believed the subjective responses to pregabalin (200 and 450 mg) were similar or greater than the responses to 15-and 30 mg of diazepam. Also, CSS considered the self-administration study of in animals to be indicative of a reinforcing effect. Therefore, CSS recommends that pregabalin be a controlled substance (Schedule IV).

Overdose

The data suggest that doses of > 600 mg are associated with similar adverse effects as those experienced when recommended doses are taken, including somnolence and dizziness. Immediate lethality secondary to overdoses is not apparent from the data.

12 ADEQUACY OF SAFETY TESTING

As per the Safety Update, 9278 patients have had at least 1 dose of pregabalin, 1650 of who were enrolled in PHN trials. Also, a total of 2701 patients (29.1%) have been exposed to pregabalin for at least 1 year. Data from the initial NDA submission showed that more than 300 patients were exposed to the proposed marketed doses of pregabalin for more than 6 months, and 201 patients were exposed to the highest dose (600 mg/d) for at least 1 year.

During both controlled and open-label trials, subjects were assessed for effects on physical and laboratory parameters, as well as adverse events, every 2-4 weeks. Overall, the extent of exposure, as well as the types and frequency of patient monitoring are adequate for determination of pregabalin's safety profile.

13 LABELING SAFETY ISSUES AND POSTMARKETING COMMITMENTS

Following review of pregabalin as treatment for pain due to diabetic peripheral neuropathy, the following were identified as post-marketing (phase 4) commitments:

- Completion of an adequate and well-controlled clinical study or studies to better assess the ophthalmologic toxicity of pregabalin.
- Completion of an in vitro study of the propensity of pregabalin to induce CYP-enzyme metabolism.
- Completion adequate and well-controlled clinical studies to assess the effect of pregabalin on nerve conduction velocity (NCV).

At the time of this review, no postmarketing commitments were identified for the postherpetic neuralgia indication.

14 DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The proposed marketing dose for the treatment of PHN is 150 mg BID (300 mg/d) and 200 mg BID (600 mg/d). Although only a single trial evaluating the efficacy of a BID regimen was conducted, consistency with the findings from TID studies supports the use of a BID regimen. The pharmacokinetic data show that pregabalin can be administered with or without meals.

15 USE IN SPECIAL POPULATIONS

15.1 Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of the Applicant's Analyses.

With respect to the total safety database, there were slightly more female subjects than male (53% vs. 47%). Most subjects were Caucasian (87.5%), 5% were Black or Hispanic, and 1.4% were Asian or Pacific Islander. Most patients were 17-64 years of age (80.4%), with a mean age of 47.9 years for the total exposed populations. Subjects younger than 18 years of age were excluded from DPN and PHN trials, but were enrolled in GAD and epilepsy trials. Exposure in this demographic group was smaller than other groups in the total safety population, but adequate for the respective populations. Consequently, further exploration of drug safety in this demographic does not appear to be necessary.

With respect to the PHN population, the overwhelming majority of subjects were Caucasian (98%). Therefore it is not possible to draw conclusions about the effect of race on the efficacy of pregabalin for this indication. There were slightly more female patients than male (53% vs. 47%); nevertheless, pregabalin appears to be effective in both men and women. Approximately 89% of patients studied were ≥ 65 years, with a median age of 73. years. Exposure in this age group was therefore appropriate.

15.2 Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

Pediatric data has not been submitted regarding use in patients with postherpetic neuralgia. In previous interactions with the Division, Pfizer requested a full waiver of pediatric studies for this indication. The waiver was granted. The waiver of pediatric studies is consistent with previous Agency decisions for other products intended to treat postherpetic neuralgia.

15.3 Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

Use in pregnancy or in lactating women has not been evaluated. Non-clinical showed decreased fetal body weight, post-natal survival, and delay in developmental landmarks. There was also evidence of maternal toxicity with higher pregabalin doses. Also, pregabalin has been detected in the milk of lactating rats. These findings suggest that pregabalin not be used during pregnancy or lactation, until further data showing safety are available.

Studies in renal impairment are included in the NDA and indicate a need for dose adjustment in renal impairment, as well as the need for supplemental dosing following hemodialysis (See Section 3). Since renal clearance decreases with age, dose adjustment may also be indicated in elderly patients with decreased renal function.

The lack of a need for studies in hepatic impairment has already been discussed in the NDA (See Section 3).

16 Conclusions, Recommendations, and Labeling

16.1 Conclusions Regarding Safety and Efficacy

The data provided in this application show that pregabalin, at doses of 300- and 600 mg/d, administered in either two or three divided doses, is efficacious in reducing pain associated with postherpetic neuralgia, in patients with a creatinine clearance > 60 mL/min.

The data do not suggest an association between pregabalin and a specific SAE. Nevertheless, there is evidence that treatment with pregabalin is primarily associated with CNS adverse effects. Dizziness and somnolence are the most frequently occurring reactions, and were the most common reasons for discontinuation of treatment. Other CNS effects are changes in mental status (confusion, abnormal thinking, and euphoria), ataxia/incoordination, and vertigo. Non-CNS effects include edema, blurring of vision, visual field defects, weight gain, dry mouth, and

constipation. "Accidental injury" was also occurred more frequently among pregabalin treated patients.

The vision-related effects of pregabalin are of concern, especially for the postherpetic neuralgia population. Patients with postherpetic neuralgia tend to be older and are therefore already at considerable risk of certain eye disorders and vision loss. Addition of the apparent visual effects of pregabalin could add considerably to these patients' morbidity. . At present, Pfizer has not adequately characterized the effects of pregabalin on vision.

Development of edema in patients with postherpteic neuralgia is also of concern, given that these patients tend to be older and therefore more likely to have cardiac-related disease. The edema could lead to worsened heart function. Another worrisome potential effect is the development of severe edema in patients who are also taking a thiazolinedione for diabetes. These patients could develop or experience worsening heart failure.

Pregabalin is also associated with decreases in platelet count and increases in creatinine kinase. Although the data did not show any clear clinical correlates to these effects, the potential for pregabalin to cause adverse events such as thrombocytopenia or acute renal failure remains.

The non-clinical studies show that pregabalin is carcinogenic. There was no clinical correlation with the findings of hemangiomas and hemangiosarcomas in mice, however this is to be expected, given the relatively brief period over which subjects were observed.

Finally, because pregabalin is cleared via the kidneys and because older patients such as those with postherpetic neuralgia experience a decline in renal function over time, these patients will progressively be exposed to higher systemic levels of pregabalin and will be more likely to experience adverse effects.

16.2 Recommendations on Approvability

The data support efficacy of pregabalin (300- and 600 mg/d) in patients with CLcr > 60 mL/min. Efficacy for patients with lower creatinine clearance values was not apparent, possibly because most of these patients could not tolerate their doses and therefore discontinued treatment.

The data also show that the for the 300 mg/d dose, the risk of an adverse event related to pregabalin treatment is slightly greater than the likelihood of a favorable treatment outcome (i.e. ≥ 50% decrease in pain). The likelihood of an improvement in pain is greater for the 600 mg/d dose, but only for those patients who are able to tolerate treatment with pregabalin.

As already noted, patients with postherpetic neuralgia are older, and are therefore likely to have the health conditions typical of advancing age: osteoporosis, unsteadiness of gain, and poor vision. Treatment with pregabalin, with its adverse effects on vision, mental status, gait, and coordination, could therefore potentially lead to serious injury. Since the risk adverse effects is greater at higher doses of pregabalin, the potential for injury could increase with increasing doses. The data regarding the incidence of accidental injury lend weight to this argument.

Together, these data suggest that pregabalin is efficacious in only a subset of patients with postherpetic neuralgia (i.e. those patients with a creatinine clearance > 60 mL/min). While efficacy is greater at the highest proposed dose (600 mg/d), even fewer patients appear able to tolerate this dose and experience a good treatment effect.

Comparison of the frequency of treatment responders (i.e. patients with ≥ 50% decrease in pain from baseline) and the frequency of adverse events shows that patients who have a favorable treatment outcome are at equal or greater risk of experiencing one or more of the common adverse effects of pregabalin. Furthermore, although increased efficacy is observed at higher doses, so are greater adverse events.

Overall, the risk of adverse effects of treatment approach or exceed the likelihood of treatment benefit. Finally, the risk of ophthalmologic effects of pregabalin are currently of uncertain clinical significance, yet are of considerable concern in this patient population.

Ultimately, because of the limited efficacy of this product, the risks of adverse effects, and the availability of other approved therapy for postherpetic neuralgia, I do not recommend approval of this application.

I recommend further studies to characterize the effects of pregabalin on the visual system.

With respect to the carcinogenic and teratogenic effects, as well as the effects on platelets and creatinine kinase, I recommend that the risks of these effects be addressed in the product label, when and if the pregabalin is eventually approved.

16.3 Labeling

In anticipation of possible future approval pregabalin for this indication, I reviewed the draft labeling as proposed by the Applicant, starting with the Clinical Studies section. Where indicated, I included the actual language proposed and any suggested revisions. Otherwise, I make general comments regarding which segments of the label will need to be revised.

CLINICAL STUDIES

Neuropathic pain associated with ...herpes zoster (postherpetic neuralgia)

Comments regarding any secondary analyses should be deleted, as explained below.

Postherpetic neuralgia studies

Pfizer calculated treatment effects (change in pain score) using the LOCF method whereas the Agency used the more appropriate BOCF method. Consequently, values regarding the absolute change in mean pain score, as well as the p- will need to be revised per the Agency's analyses. P-values values for the comparisons of the difference from placebo, or based on an analysis of responder rates, should not be included.

Descriptions of the time to favorable drug effect should be based on the Agency's analyses for each study.

Pfizer provides information regarding changes in scores using the Patient Global Impression of Change (PGIC). This measure is entirely subjective and prone to bias, therefore its value is questionable. Also, the PGIC was one of numerous secondary and supplemental analyses for which Pfizer did not make any adjustments for testing multiple parameters, and for which any significant differences would not be given any undue consideration. Therefore, the PGIC, as well as the other secondary parameters, should not be included in the label.

Figure 3, a graph of the proportion of responders, is redundant and should be deleted.

Figure 4 should be revised to include data from only the 3 PHN efficacy trials, and data based on the Agency's BOCF analyses of the percentage of patients with reduction in pain.

PRECAUTIONS

The Applicant should adopt the language proposed by the Agency upon its review of the product label for pregabalin as treatment for pain due to diabetic peripheral neuropathy (N 21-446). This language describes the most concerning adverse drug effects for prescribers, as well as the drug information that should be conveyed to patients:

Ophthalmologic Effects

In controlled studies, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo. In prospectively planned ophthalmologic testing, pregabalin was associated with increased frequency of visual disturbances (i.e., reduction in visual acuity and visual fields) compared to placebo. Patients should be informed that if changes in vision occur, they should notify their physician. Patients treated with LYRICA should have their visual acuity and field of vision routinely monitored. For patients who are already routinely monitored for other ocular conditions including diabetes, consideration should be given to increasing the frequency and nature of the ophthalmologic monitoring and to include visual field testing.

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, and diarrhea. Pregabalin should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Dizziness and Somnolence

Dizziness and somnolence were reported by 26% and 16% — respectively of patients treated with pregabalin in controlled studies in neuropathic pain associated with postherpetic neuralgia — These events began shortly after the initiation of therapy and generally occurred more frequently at higher doses. Dizziness and somnolence were mostly mild to moderate in intensity and led to withdrawal for 4% and 3% — of patients, respectively. For the remaining patients who experienced dizziness and somnolence, these events resolved in a majority of cases with continued dosing. Patients taking LYRICA should be counseled that dizziness and somnolence may impair their ability to perform potentially hazardous tasks (e.g., driving). (See **PRECAUTIONS-Information for Patients**)

Weight Gain

In controlled clinical trials of neuropathic pain associated with postherpetic neuralgia — — the incidence of weight gain was 7% — in the pregabalin group, compared to 2% — in the placebo group. Few patients — withdrew from the controlled trials due to weight gain. Among the patients who experienced significant weight gain, less than one-third also reported

peripheral edema. Therefore, the weight gain may be partially, but not completely, explained by pregabalin-associated edema.

Peripheral Edema

LYRICA should be used with caution in patients with edema. In controlled clinical trials of neuropathic pain associated with postherpetic neuralgia, the incidence of peripheral edema was 12% in the pregabalin group, compared to 4% in the placebo group. These events of peripheral edema were mostly mild to moderate in intensity and led to withdrawal in 1.4% of pregabalin-treated patients and less than 1% of placebo patients. There was no evidence of hemodilution or changes in any laboratory parameters indicative of underlying organ dysfunction.

In these short-term trials of patients, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. However, since there are limited data on patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

Increased reports of weight gain and edema were observed in patients taking both LYRICA and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and fluid retention, possibly exacerbating or leading to heart failure, caution should be exercised when co-administering LYRICA with these agents.

Laboratory Changes

Pregabalin treatment was associated with an elevation in creatinine kinase. Mean changes in creatinine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatinine kinase at least three times the upper limit of normal.

Pregabalin treatment was also associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x $10^3/\mu L$, compared to 11 x $10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 10^3/\mu L$.

Information for Patients

- Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician. (See **PRECAUTIONS section)**
- Patients should be counseled that LYRICA may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual, and/or motor performance adversely.
- Patients should be counseled that LYRICA may cause peripheral edema and weight gain.
- Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain, which may increase the risk of heart failure.

- Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.
- Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.
- Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding.

ADVERSE REACTIONS

Most common adverse events in all controlled clinical studies

The term "amblyopia" is an inaccurate and potentially misleading term for the adverse event of blurred vision. Therefore, "blurred vision" should be used when describing this particular visual adverse effect. The rates of common adverse events, as well as the rates of discontinuation due to adverse events should be revised to reflect the numbers seen on the Agency's review of the data.

Adverse events from controlled neuropathic pain studies in postherpetic neuralgia

Table 1 should be replaced with the table generated upon the Agency's review of these data

DRUG ABUSE AND DEPENDENCE:

The controlled substance class should be revised. Also, the description of the data from the human and animal studies should reflect the findings of CSS.

Controlled substance class: [ ] LYRICA is a Schedule IV controlled substance.

OVERDOSAGE

Again, the Applicant should adopt the language proposed by the Agency upon its review of the product label for N 21-446.

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest reported accidental overdose of pregabalin during the clinical development program was 15,000 mg and there were no notable clinical consequences. There is limited experience with overdose of pregabalin. In clinical studies, some patients took as much as 2400 mg/d. The types of adverse events experienced by patients exposed to higher doses (≥ 900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.
[ ]

]

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and

observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up to date information on the management of overdose with pregabalin.

Hemodialysis

[

]

Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND ADMINISTRATION

I propose the following language for this section of the label:

LYRICA™ is given orally with or without food

[

]

When discontinuing LYRICA, taper gradually over a minimum of 1 week.

Language regarding dosing in patients with renal impairment should be the same as that proposed by the agency upon its review of n 21-446.

Appears This Way
On Original

17 APPENDIX

17.1 Appendix 1: Deaths in epilepsy, GAD, and DPN trials

NARRATIVES OF DEATHS IN EPILEPSY TRIALS

007-000601 This 68 year old female with partial seizures was taking pregabalin 200mg/d and had a total of 1098 days of pregabalin when she experienced a seizure, fell down, aspirated, and died. The coded cause of death was respiratory disorder. She was found dead in her home and the death certificate listed aspiration and seizure disorder as causes of death. An autopsy was not performed. Concomitant medications included phenytoin, rofecoxib, and ibuprofen.

007-001704 This 24 year old male who was taking pregabalin 600mg/d and had a total of 511 days of pregabalin at the time of the event died and death was attributed to airway obstruction. The coded cause of death was lung disorder. The narrative noted that the subject experienced a seizure followed by vomiting and difficulty breathing. Another episode of vomiting and a second seizure followed this and he was noted to be cyanotic. CPR was begun and he was transported to an ED. He was unresponsive and asystolic. It was one day from last dose until death.

009-004001 This 84 year old male with a history of coronary artery disease, atrial fibrillation, hypertension, diabetes, congestive heart failure and stomach cancer who was taking pregabalin 600mg/d and had a total of 713 days of pregabalin exposure when he experienced cerebral artery occlusion, pneumonia, and brainstem hemorrhage. The coded cause of death was intracranial hemorrhage. The subject was admitted to a hospital for pneumonia with hemoptysis, cerebral artery occlusion, and corticoadrenal insufficiency. While hospitalized he experienced a brainstem hemorrhage and exam noted he was unresponsive with fixed, dilated pupils. Concomitant medications included levetiracetam, fludricortisone acetate, furosemide, hydrocortisone, omeprazole, and acetylsalicylic acid. It was 3 days from last dose until death.

009-042003 This 56 year old female with a history of rheumatic fever, myokymia (involuntary rippling of the muscles at rest), hypertension, atrial fibrillation, and seizure disorder was taking pregabalin and had a total of 545d exposure. She experienced staph endocarditis, sepsis, respiratory failure, and cerebral hemorrhage. The coded cause of death was cerebral hemorrhage. It was nine days from last dose until death. She had a history of rheumatic fever and underwent mitral and aortic valve replacement surgery on study day 407. She subsequently presented with fever, chills and nausea and had positive blood cultures. She was treated with vancomycin and gentamicin. Vancomycin was switched to cefazolin due to lack of improvement and a declining mental status. On open label study day 459 she experienced cerebral hemorrhage and died.

010-045102 This 42 year old male with a history of partial seizures, hypertension, hypercholesterolemia, cervical spondylosis, back pain, and migraine was taking pregabalin 600mg/d and had been taking pregabalin for 974 days. He died and death was attributed to a heart attack. The coded cause of death was cardiovascular disorder. The subject was taking pregabalin at the time of death. The narrative noted that the subject had a brother who died of a heart attack (age "30's"). Concomitant medications included carbamazepine, oxcarbazepine, tiagabine, levetiracetam, lisinopril, simvastatin, cyclobenzaprine, diazepam, amitriptyline, ranitidine, butalbital with aspirin and caffeine. The narrative noted that this subject experienced elevated liver enzymes (ALT, AST in 300's) that were attributed to simvistatin and that resulted in discontinuation of simvistatin.

011-066001 This 47 year old male with a history of complex partial seizures, with secondary generalization, intelligence deficit, cerebral malformations, basal cell carcinoma, cutaneous abscesses, guanine/thymine elevation, anemia, fibromas, Sprengel's deformity corrected (congenital elevation of the scapula), macroglossia, and hypoalbuminemia was taking pregabalin 300mg/d and had been taking pregabalin for 607 days. He experienced somnolence, cough, fever, bronchitis, and cardiovascular arrest. The coded cause of death was heart arrest. He was taking pregabalin on the day of death. The narrative noted that on study day 582 the subject experienced fever, increased cough, wheezing and rhonchi that were treated with amoxicillin/clavulanate and acetylcysteine. On open label study day 583 he was found dead in bed by his caregiver. No autopsy report was provided. Concomitant medications included valproic acid, carbamazepine, clobazam, hyoscine, phenolphthalein, and paraffin.

011-070011 This 60 year old male with a history of complex partial and secondary general seizures, alcohol and tobacco abuse and recent weight loss was taking pregabalin 600mg/d at the time of the event and had been taking pregabalin for 211 days. He died and his AEs included metastatic carcinoma, abdominal ascites, dyspnea, painful left shoulder, confusion, and abnormal liver function. The coded cause of death was carcinoma. This subject was diagnosed with metastatic

adenocarcinoma on study day 128. The narrative noted that at baseline the ALT, AST and ALP were elevated and that on study day 113, the AST was slightly elevated (29 u/L) and the ALP was elevated (900u/L). A CT on study day 128 demonstrated that the liver had extensive metastatic disease and that the lung had metastases bilaterally. He withdrew from

Narratives of deaths in epilepsy trials (continued)

011-070011 (continued)
the open label study on day 170 and died 21 days later.

012-084102 This 68 year old male with a history of partial seizures, closed head injury and hypertension was taking pregabalin 600mg/d and had been taking pregabalin for 828 days. He died and the coded cause of death was fall. It was 45 days from last dose until death. He was assessed at a hospital following a fall on study day 828. There was no information about the events preceding the fall and no description of the distance or circumstances of the fall itself. He was sent home but returned to the hospital two days later and was diagnosed with a perinephric hematoma and a pericardial effusion. He underwent a pericardiocentesis. His condition deteriorated and two days later he developed bilateral pleural effusions that were treated by thoracentesis. On study day 833 he was treated with external ventilation (BIPAP). He developed a large pleural effusion and abdominal distension. The effusion was drained. He developed renal failure. Study medication was stopped. He died on study day 875 and the investigator felt the death was due to renal failure. An autopsy documented chronic liver disease, ileus, bilateral adrenal hemorrhage, bilateral pleural effusion, possible ARDS, fibrous pericarditis with cardiomegaly, left renal infarct with massive perinephric hematoma.

012-084108 This 74 year old male with epilepsy, hyperlipidemia, angina, hypertension and s/p CABG was taking pregabalin 300mg/d and had been taking pregabalin for 34 days. On study day 7 he was hospitalized for weakness, inability to stand, disorientation, hallucinations, and reduced alertness. His pregabalin dose was reduced from 450mg/d to 300mg/d. On study day 10 he was diagnosed with a urinary tract infection and possible pulmonary edema. He was treated with ampicillin and gentamicin. He developed septicemia and died on study day 34. The cause of death listed on the death certificate was pulmonary embolism.

012-084122 This 77 year old female with a history of epilepsy, hypertension, arrhythmia, pulmonary emboli, angina, diabetes mellitus, cerebral hemorrhage, and digitalis toxicity was taking pregabalin 375mg/d and had been taking pregabalin for 495 days. She died and the coded cause of death was sepsis. She was taking pregabalin on the day of death. During the study she was hospitalized for digitalis toxicity (screening phase) myocardial infarction (study day 8), DVT (study day 42), fall (study day 111) and loss of consciousness (study day 418). On study day 495 she experienced life threatening sepsis of unknown origin. The narrative noted that she lost consciousness that evening. Hospital labs included a WBC count of 19.6 neutrophils of 17.54 and AST=65U/L. Two days later, WBC count was 24.4 neutrophils 20.15 and AST 3100U/L. The listed cause of death was septicemia.

034-001008 This 52 year old female with mental retardation, spastic cerebral palsy, bilateral benign breast cyst removal, hypothyroidism, migraine headaches and constipation was taking pregabalin 600mg and had been taking pregabalin for 931 days. She died and the coded cause of death was sudden death. It was one day from last dose until death. This adult home resident returned to the home from vacation and went to bed. A caregiver heard her get up and go to the bathroom several times during the night. She was found dead in her bed the next morning. Concomitant medications included carbamazepine, tiagabine, alendronate sodium, citalopram, docusate, ergocalciferol, levothyroxine, paracetamol/dichloralphenazone/isometheptene, polycarbophil, and urea hydrogen peroxide.

034-015002 This 44 year old male with intractable partial seizures, status epilepticus, post ictal psychosis, and incomplete right bundle branch block was taking pregabalin 600mg and had been taking pregabalin for 1174 days. He died and the coded cause of death was convulsion. The subject was taking pregabalin on the day of death. The narrative noted that this subject experienced a witnessed prolonged generalized tonic clonic seizure that resulted in death. No autopsy was performed. Concomitant medications included phenytoin and levetiracetam.

034-025004 This 23 year old male with a history of partial seizures, sickle cell anemia, and thrombocytopenia died and the narrative listed sudden unexpected death in epilepsy as the cause of death. This subject had received a total of 605 days of pregabalin (92 in RCT, 513 in open label). The subject was found dead on the floor by his father. An autopsy noted mild concentric LVH. Concomitant medications were valproate, topiramate, hydrochlorothiazide/triamterene, desonide, clindamycin, and ketoconazole.

035-022105 This 55 year old male with a history partial seizures, myocardial infarction x 2, and intermittent chest pain, was found dead by his mother. An autopsy was not performed and cause of death was attributed to respiratory failure secondary to congestive heart failure and cardiomyopathy. He had received a total of 499 days of pregabalin treatment. Concomitant medications included phenytoin, paroxetine, metoprolol, trazodone, and cerivastatin.

NARRITIVES OF DEATHS IN PAIND DUE TO DIABETIC PERIPHERAL NEUROPATHY (DPN) TRIALS

Deaths during or after controlled trials

040-072020 A 63-year-old Asian man with history of painful diabetic peripheral neuropathy, congestive heart failure, hypertension, gout, ischemic heart disease and quadruple coronary bypass surgery. The patient had 7 days of treatment with pregabalin 200 mg/day, after which he was lost to follow-up and was withdrawn from the study due to noncompliance and nonattendance. He completed a termination visit on Study Day 78. Blood samples obtained at that visit revealed evidence of biliary disfunction (alkaline phophatase361 U/L, total bilirubin 2.3 mg/dL, AST 16 U/L, ALT 13 U/L) and worsening renal function compared with baseline (BUN 68.9 mg/dL, creatinine 1.88 mg/dL, creatinine clearance 46 mL/min, sodium 129 mEq/L). In addition, amylase and creatine kinase were mildly elevated (135 U/L and 84 U/L, respectively). The patient died suddenly 7 days later ,on Study Day 85 (78 days post-treatment). An autopsy was not performed and the body was cremated.

149-415019 A 66-year old white woman with considerable medical history: painful peripheral diabetic neuropathy, hypertension, angina pectoris, cholelithiasis, hypercholesterolaemia,c ataract, and recent myocardial infarction. She had received 6 days of treatment with pregabalin 150mg/day when she developed gastrointestinal hemorrhage with tarry stools. She was hospitalized and received 960 ml blood and furosemide 40mg/day IV. Endoscopy (on Study Day 8 or 12) showed two erosions in the oesophagus, fresh clots in the stomach, and gastric muscle with blood extravasation. On Study Day 14, icterus was observed, and ultrasonography confirmed cholelithiasis. On Study Day 18, suffered an acute myocardial infarction and resuscitation was unsuccessful. Autopsy showed healed myocardial infarct (antero-posterior), left ventricular hypertrophy, and coronary atheromatosis.

149-387005 A 65-year old white woman with painful peripheral diabetic neuropathy, hypertension, diabetic retinopathy, a deep veinthrombosis and chronic anxiety. She was treated with pregabalin 300 mg/day for 21 days, when she suffered cardiac failure and died. No further information is provided regarding the circumstances surrounding the patient's death.

173-319003 A 54-year-old Hispanic man with painful diabetic peripheral neuropathy and hypertension. He was treated with pregabalin 600 mg/day for 20 days and 300 mg/day on study day 21 when he was withdrawn from the study due to the FDA's imposition of a partial hold on pregabalin investigation in humans. The patient completed a termination visit, which was notable for the a normal ECG and the absence of peripheral edema. He was hospitalized for chest pain and dyspnea on Study Day 58. After admission, the patient's condition improved, however, he developed a tachycardia and congestion of the lungs and expired on Study Day 65 (44 days post-treatment).

Deaths during or after uncontrolled trials

014-012019 A 54-year-old black woman with a history significant for painful diabetic peripheral neuropathy, hypertension (controlled), arthritis of both knees, mild respiratory problems during childhood, gout, pedal edema, and an abnormal electrocardiogram at screening visit. On Study Day 672 of open-label pregabalin (Protocol 1008-015), the patient had nausea, vomiting, and progressive shortness of breath. On Study Day 673 the patient was unable to ambulate to the bathroom. Her family called Emergency Medical Services and ACLS protocol was administered. She suffered cardiopulmonary arrest in the ambulance and was pronounced dead in the emergency department.

The patient had been treated with pregabalin 600 mg/day for 50 days in the double-blind trial 1008-014. She entered the open label trial 1008-015 during which study medication consisted of pregabalin 300 mg/day for 38 days,and then pregabalin 150 mg/day for 630 days. There were 4 days on which the patient took no study medication. Total exposure to the study medication was 722 days

014-013009 A 46-year-old white man with a history of painful diabetic peripheral neuropathy, hypertension and alcoholism. He died at home of unknown causes on Study Day 300 of open-label pregabalin. He was an assembly worker, single, and lived alone. His mother and father died at ages 70 and 60, respectively, from diabetes and heart disease. The investigator

learned of the patient's death through an obituary in the newspaper. Examination of the decomposed body estimated death to have occurred 1 week prior to discovery. There was no evidence of foul play and death. An autopsy was not performed and the body was cremated.

Narratives of deaths in DPN trials (continued)

Patient 014-013009 (continued)

At baseline, an electrocardiogram showed evidence of a septal myocardial infarction of indeterminate age. The patient last saw his primary care physician on Study Day 257 for a routine check-up of his diabetes and hypertension. The investigator last saw the patient on Day 259. An electrocardiogram performed at this visit was unchanged compared to the baseline tracing. Routine laboratory tests at this visit included serum chemistries, complete blood count (CBC) with differential, and urinalysis. The only abnormalities were elevated glucose (136 mg/dL), alkaline phosphatase (305 IU/L), and aspartate transaminase (AST 42 IU/L) measures. The baseline AST and alkaline phosphatase measures prior to starting open-label medication were 47 IU/L and 253 IU/L respectively. The patient was last seen for his eye exam per protocol request on Day 263.

Prior to the open-label study, 1008-015, the patient participated in Study 1008-014 and received placebo for 44 days. In 1008-015, the patient received pregabalin 300 mg/day-575 mg/day for 117 days, and then 600 mg/day for 183 days. Total exposure to study medication was 300 days.

014-013023 A67-year-old white man with a history of painful diabetic peripheral neuropathy, myocardial infarction and arrhythmias. Shortly before his death, the patient presented to his cardiologist with complaints of chest pain and arm pain of a3-week duration. A cardiolite/rest thallium study showed evidence of a high inferior wall infarction with apical, inferior wall, and septal myocardial ischemia. The patient died from an acute myocardial infarction on Study Day 232 of open-label pregabalin. Total exposure to pregabalin was 232 days (open-label treatment with pregabalin 300 mg/day to 600 mg/day for 175 days, followed by pregabalin 400 mg/day for 57 days). In the preceding double blind trial, Study 1008-014, the patient received placebo for 45 days.

014-015009 A 46-year-old white woman with painful diabetic neuropathy, morbid obesity, hypertension, non-pitting edema, and atrial flutter requiring cardioversion due to overuse of decongestants. She was hospitalized for cellulitis of the left leg on open-label Study Day 50 (open-label). The patient was treated with dicloxacillin andcefazolin sodium and recovered. Total pregabalin exposure was 88 days (pregabalin 600 mg/day for 40 days in Study 1008-014, and pregabalin 600 mg/day for 48 days in open-label Study 1008-015).. While hospitalized, the patient had 3 days of missed medication.

The patient was hospitalized again for cellulitis on Study Day 177. Study medication was still pregabalin 600 mg/day, with only 1 day of treatment 400 mg/day and 12 days of missed medication. Total exposure to study medication was 217 days. The patient recovered.

On Study Day 431, the patient was hospitalized again for supraventriculartachycardia and atrial flutter. The patient reportedly signed herself out of the hospital against medical advice while still in atrial flutter and tachycardia and on antiocagulation therapy. Between this and the previous hospitalization, study medication consisted of varying doses of pregabalin 300 mg/day-600 mg/day. Pregabalin was apparently discontinued on Study Day 445 when the patient died from dilated cardiomyopathy. A co-worker reported the patient's demise. At the time of her death, total exposure to study medication was 485 days..

While on pregabalin, the patient had ongoing adverse events of weight gain and tachycardia. She also complained of a recent episode of shortness of breath. A chest x-ray revealed an increase in heart size but not heart failure. An echocardiogram did not reveal any clots or holes, but one fast chamber. An autopsy was performed and the cause of death was determined to be dilated cardiomyopathy.

029_021010 A 75-year-old white man with painful diabetic peripheral neuropathy and hypertension was hospitalized for angina (angina pectoris) and coronary arterydisease (coronary artery disorder) on Study Day 206 of open-label pregabalin. On Study Day 210, the patient underwent 5-vessel bypass surgery, then remained hospitalized due to atrial fibrillation, pneumothorax, questionable seizures,tracheotomy and ventilator dependency, and gastrointestinal dysfunction. The patient died 52 days post-study due to respiratory failure. Open label study medication consisted of pregabalin 300 mg/day for 206

days. The patient participated in a previous Study 1008-029, and received pregabalin 600 mg/day for 35 days, giving a total pregabalin exposure of 241 days. No other information regarding the death was available.

Narratives of deaths in DPN trials (continued)

029-032006 A 69-year-old white man with a history of painful diabetic neuropathy, hypertension, hyperlipidemia, chronic atrial fibrillation, cerebrovascular accident, myocardial infarction, and obesity. He was hospitalized for dyspnea secondary to

Patient 029-032006 (continued)
congestive heart failure on Study Day 208 of open-label pregabalin treatment. During the hospitalization he received no further pregabalin dosing. While hospitalized, he suffered an acute myocardial infarction with extension, was placed on a ventilator due to respiratory failure, He developed encephalopathy, shock, renal failure, anemia, and sepsis. The family discontinued supportive care and the patient expired on Study Day (33 days post-treatment). The patient had completed double-blind treatment with pregabalin 300 mg/day for 35 days, and then entered the open-label trial 1008-033. In the open-label trial, pregabalin exposure was as follows: 300 mg/day for 6 days, then 375 mg/day for 17 days, followed by 600 mg/day for 184 days. Total exposure to the study medication was 243 days.

029-037004 A 60-year-old white woman with a history of painful diabetic neuropathy, hypertension, hypothyroidism, and anxiety. . The narrative states that the patient died in her sleep on Study Day 232 of open-label pregabalin treatment. The autopsy listed the causes of death as cardiac arrhythmia , cardiac ischemia , and atherosclerotic heart disease. The study coordinator reported laboratory results as unremarkable. Study medication consisted of pregabalin 600 mg/day for 33 days (double-blind study 1008-029), and then open-label treatment first with pregabalin 200 to 600 mg/day for 79 days, followed by pregabalin 250 mg/day for 153. Total exposure to pregabalin was 265 days.

040-017006 A 70-year-old white man with painful diabetic peripheral neuropathy, hypertension, hyperuricemia and hypercholesterolemia. He developed a leg ulcer (skin ulcer) on Study Day 83 of open label pregabalin. The study investigator determined the leg ulcer to be severe in intensity. The patient was hospitalized on Study Day 202 for evaluation of the worsening ulcer of the lower right leg that also became gangrenous. On Study Day 204, he underwent elective surgery with multiple removal of necrotic tissue. On Study Day 285 the wound was covered with mesh. The patient was discharged on an unknown Study Day but had not yet recovered. He was re-admitted to the hospital on an unknown Study Day with a non-healing leg ulcer. Subsequent hospital course and treatment are unknown. On follow-up with the patient's general physician, it was learned that the patient died at home from unknown causes on an unknown day. It was speculated that death was due to apoplexy. An autopsy was not performed

Prior to the open-label study (1008-074), the patient participated in the double blind study 1008-040 and received placebo for 44 days. During 1008-074, study medication consisted of pregabalin 600mg/day and presumably was continued until the patient's death.

040-017008 A 71-year-old white man with history significant for painful diabetic peripheral neuropathy. The subject had a prostate biopsy on or about Study 36 of open-label treatment with pregabalin, but the results were not reported. On Study Day 289, he presented with somnolence and disorientation and was hospitalized for a hypercalcemic crisis. Imaging showed metastases in the lungs and liver. A biopsy of the liver showed tumor infiltration classified as adenocarcinoma. The skeleton was not affected. Immunohistochemical investigation of the tumor tissue for PSA was negative. It could not be determined whether the primary tumor was prostate carcinoma or of another origin. Following treatment, the patient recovered from the hypercalcemic crisis. He was subsequently treated with gemcitabine however his health status worsened. He developed macrohematuria and died from adenocarcinoma of liver (hepatoma), tumor infiltration of lung (carcinoma of lung) and prostate carcinoma on Study Day 305.

Study medication consisted of received pregabalin (600 mg/day) for 62 days (double-blind study 1008-040), followed by open-label treatment with pregabalin 600 mg/day which was discontinued on the day the patient died. Total pregabalin exposure, therefore, was 367 days.

040-072002 A 65-year-old woman with painful diabetic peripheral neuropathy and an increase in mass (4kg) around the time of study participation. On approximately Study Day 392 of open label pregabalin treatment, the patient experienced bleeding

per rectum described as"fresh" bleeding. A sigmoidoscopy and biopsy were performed, and the biopsy showed cancer of the colon (Study Day 408). The patient was scheduled for an ultrasound and a partial colectomy, date unknown. She died on Study Day 434 of unspecified causes.

Narratives of deaths in DPN trials (continued)

Open-label study medication consisted of pregabalin 600 mg/day and was discontinued on Study Day 433. Previously, the patient participated in the double blind study 1008-040, and received pregabalin 600 mg/day for 63 days. There were 9 days between the studies, that the patient did not receive any of the studymedication. Total exposure to the study medication was approximately 495 days.

040-111006 A 75-year-old white man with painful diabetic peripheral neuropathy, hypertension, cerebral apoplexy and pacemaker insertion. The patient died from heart failure on Study Day 12 of open-label pregabalin treatment (300 mg/day). He had discontinued pregabalin on Study Day 5. Previous pregabalin treatment was during the double-blind trial 1008-040, when he received pregabalin 600 mg/day for 64 days. Total exposure to pregabalin at the onset of the event was 70 days.

131-114002 A 77-year-old white woman with painful diabetic peripheral neuropathy, coronary artery disease and occlusion, cardiomegaly, congestive heart failure, and hypothyroidism . On Study Day 16 of open-label pregabalin treatment (300 mg/day), the patient developed dyspnea. She discontinued pregabalin, and was hospitalized on Study Day 17. On the day of admission, she suffered a cardiac arrest and she died on Study Day 18. She had previously participated in the double-blind study 1008-131 and received placebo for 56 days. Total exposure to pregabalin was therefore 16 days.

149-387006 A 77-year-old white man in Germany with a history of painful diabetic peripheral neuropathy, hypertension, and amputation of the left index finger secondary to chronic osteitis. Approximately one month prior to beginning the open-label study (1008-165), the patient developed cellulitis of the right leg, which was treated with flucloxacillin and amoxicillin. The cellulitis did not improve, and he was hospitalized on Study Day 19 for gangrene of the 2nd and 3 rd toes of the right foot. Examination showed that the dorsalis pedis pulse was still palpable and sensory motor function was still intact. On Study Day 22, the patient underwent an amputation of the 2nd and 3rd metatarsals. He was treated with oral, intravenous and intramuscular antibiotics, amoxycillin/clavulanate potassium, clavulanic acid and gentamicin, and recovered by Study Day 27. On Study Day 34, the patient was reported to have died in his sleep(sudden death)

The patient was previously enrolled in the blinded study 1008-149, and received pregabalin 600 mg/day for 86 days. After transition to the open-label study, medication consisted of pregabalin 150 mg/day, and was discontinued on Study Day 33. Total pregabalin exposure was 119 days.

17.2 Appendix 2: Deaths in PHN trials

Appendix 2: Deaths in PHN trials

Deaths in controlled trials

Deaths not likely related to pregabalin

Patient 045_010002, This was an 85-year-old woman with a history of postherpetic neuralgia, gastritis/gastric ulcer and sciatica. She was randomized to pregabalin 300 mg/day and took study medication for 18 days but was withdrawn from the study due to a low creatinine clearance. Around after Day 143 (at least 125 days post treatment), she had a myocardial infarction and died.

Patient 045_066001 A 74-year-old white man with postherpetic neuralgia and a history of gout, psoriasis, carcinoma of the rectum, and irregular heart rate. He was randomized to placebo and his last dose of study medication was taken on Day 46, the day before his death. Approximately 2 weeks prior, the patient complained of dizziness. On Study Day 47, he reportedly awakened from sleep because of vomiting vomiting and then died. The CRF states that the cause of death was a myocardial infarction.

Deaths in uncontrolled trials

Deaths not likely to be related to pregabalin

Patient 030_10100 A 64-year-old white man with postherpetic neuralgia had history significant for coronary artery disease, coronary artery bypass surgery, hypertension, hypercholesterolemia, ectopic atrial rhythm and left ventricular hypertrophy with repolarization abnormality. The patient participated in a previous Study 1008-030, and received pregabalin 150 mg/day for 35 days and then entered open-label treatment (1008-033) with pregabalin 225 mg/day for an unknown amount of days. The patient had his last visit on Study Day 19 and he was considered lost to follow-up. On approximately Study Day 215 of open-label pregabalin (an unknown number of days post-treatment), he had a myocardial infarction ascribed to his underlying atherosclerotic heart disease. He wasfound dead by a family member.

Patient 030_107003 An 82 year-old white man with postherpetic neuralgia and hypertension. On Study Day 164 of open-label treatment, he presented with vomiting, gastrointestinal bleeding and an abdominal obstruction. He then had a cardiac arrest during the aspiration of vomitus. He was intubated and resuscitated. His blood pressure was unable to be maintained without support over the next 24 hours. He was never sufficiently stabilized to perform diagnostic procedures and was placed on a ventilator. He died on Study Day 165 from gastrointestinal bleeding. . The patient previously participated in Study 1008-030 and received pregabalin 75 mg/day for 36 days. He then entered open-label treatment (1008-033) with pregabalin titrated up to 400 mg/day for 164 days and was discontinued on hospital admission. Total exposure was 200 days.

Patient 030_126012, Study 1008-033, a 75-year-old white woman with a history of postherpetic neuralgia and previous throat cancer with radiation therapy. The patient participated in a previous study (Study 1008-030) and received a placebo for 35 days then entered open label treatment. . Study medication consisted of pregabalin 450 mg/day which was continued even after diagnosis on Study Day 518 of recurrent throat cancer. On Study Day 553 she died due to the throat cancer.

Patient 030_126026, An 81-year-old white man with a history of postherpetic neuralgia, MI, CABG, CHF, and pacemaker insertion. He participated in the controlled study (Study 1008-030) and received placebo for 37 days, then entered open label treatment during which he took varying doses of pregabalin 50-525 mg/day for 255 days, followed by pregabalin 600 mg/day for 182 days. On Study Day 437, the patient died while in sleep. Cause of death was described as ischemic cardiomyopathy (myocardial ischemia).

Patient 030_130003, An 85-year-old white man with a significant medical history: postherpetic neuralgia, includes non-insulin-dependent diabetes mellitus and congestive heart failure. The patient participated in a previousStudy

DEATHS IN PHN TRIALS (CONTINUED)

1008-030 and received placebo for 39 days. Open label medication consisted of pregabalin 300 mg/day. The patient developed congestive heart failure on Study Day 93, and study medication was discontinued on Day 94. He died on Study Day 114 days (21 days post treatment). The death certificate listed cardiovascular arrest and congestive heart failure as causes of death.

Patient 030_130005, Study 1008-033, an 84-year-old white woman with postherpetic neuralgia was diagnosed with metastatic renal cell carcinoma (carcinoma) considered medically significant on Study Day 747 of open-label pregabalin. The patient participated in a previous study (Study 1008-030) and received pregabalin 75 mg/day (dates unknown). She died on Study Day 814.

Patient 030_133002, a 72 year-old white man with postherpetic neuralgia and significant cardiac history (coronary artery disease, malignant ventricular arrhythmias, congestive heart failure), chronic obstructive pulmonary, and interstitial edema. The patient previously participated in Study 1008-030 and received placebo for 51 days. Open label treatment was pregabalin 150 mg/day..He died n Study day 51, and the death certificate listed the immediate cause of death as cardiorespiratory arrest secondary to bowel obstruction.

Patient 045_002003, an 84-year-old white woman with postherpetic neuralgia. The patient participated in a previous study (Study 1008-045) and received placebo for 56 days, then open label treatment with pregabalin350 mg/day for 288 days. Pregabalin discontinued due to lack of efficacy and the patient withdrew from the study on Study Day 294. She was diagnosed with brain metastases on Study Day 359 of open label treatment. (72 days posttreatment) and died on Study Day 393 (105 days posttreatment).

Patient 045_030003 (Study 1008-061), a 74-year-old white man with a history significant for postherpetic neuralgia, 2 episodes of pulmonary embolism, and pneumosilicosis. She received 56 days of placebo during the preceding double-blind study (Study 1008-045) and then pregabalin450 mg/day and was discontinued on Study Day 240 when she developed hemoptysis. She had an acute pulmonary embolus and died on Study Day 250

Patient 045_052013, a 66-year-old white woman with postherpetic neuralgia, cholecystectomy and hyperglycemia. The patient received pregabalin 300 mg/day for 56 days in double-blind trials, and then open lablel treatment with 25 to 275 mg/day for 114 days, followed by pregabalin 225 mg/day. She was hospitalized for hepatic abscess on Study Day 236, recovered, and then was rehospitalized on Study Day 733 for vesicular lithiasis (pancreas disorder). She subsequently died due after ERCP and treatment in the ICU on Study Day 738. Autopsy findings were disseminated intravascular coagulation (DIC) syndrome and hemorrhagicnecrotic acute pancreatitis, and cause of death was multiple organ failure syndrome following pancreatic necrosis.

Patient 045_053005, an 85-year-old white man with postherpetic neuralgia. The patient participated in a previous Study 1008-045 and received placebo. Opn label.study medication consisted of by varying doses of pregabalin (75 to 250 mg/day for 118 days), followed by pregabalin300 mg/day for 277 days, which was discontinued. He was hospitalized for a myocardial infarct, renal insufficiency, and acute pulmonary edema (lung edema) on Study Day 395, and developed cardiogenic shock (shock) on Study Day 396. He died on Study Day 397

Patient 045_054008, a 69-year-old white man with postherpetic neuralgia, prostatectomy, and prostatitis. This patient had received placebo in a double blind trial. Open label treatment was by various doses of pregabalin (100-500 mg/day) for 407 days, followed by pregabalin 200 mg/day for 296 days. He was hospitalized on Study Day 705 for pneumonia, acute respiratory insufficiency and acute renal insufficiency, then died on Study Day 708. The cause of death was reported as pneumonia, acute respiratory insufficiency, and acute renal insufficiency.

Patient 045_060002, a 76-year-old white woman with postherpetic neuralgia. History includes angina, myocardial infarction, and rheumatic fever. The patient participated in a previous study (Study 1008-045) and received pregabalin 300 mg/day for 14 days. She then received open label treatment with variable pregabalin doses (75 to 150 mg/day). The patient had a non-serious fall (Study Day 119), hallucinations, and confusion, and withdrew from the study on Study Day 120. On Day 181 she was hospitalized for a diverticular bleed. On Study Day 183, she had

DEATHS IN PHN TRIALS (CONTINUED)

a myocardial infarction and died. The death certificate identified the cause of death as myocardial infarction due to gastrointestinal bleeding.

Patient 045_064001, a 56-year-old white man with postherpetic neuralgia and significant cardiac history: hypertension, tobacco abuse, obesity, atherosclerosis, and coronary artery thrombosis. He received 63 days of 150 mg/day of pregabalin in a preceding double-bind study (Study 1008-045), then open label treatment with various doses of pregabalin (150-450 mg/day) for 251 days, followed by pregabalin 525 mg/day for 56 days. Total exposure to pregabalin was 370 days. H died died due to a myocardial infarction on Study Day 435, 128 days posttreatment.

Patient 045_065002, a 67-year-old white man with postherpetic neuralgia. He received placebo during double blind trial, and then open-label pregabalin (150-450 mg/day) for 56 days, followed by 600 mg/day for 124 days. On study day 180 he was hospitalized for symptoms due to liver metastases secondary to small cell carcinoma. Study medication was discontinued upon hospitalization. He died on Study Day 244.

Patient 127_002010 (Study 1008-134), a 90-year-old white woman with postherpetic neuralgia,was hospitalized for pneumonia on Study Day 255 of open-label pregabalin treatment. Thepatient died from pneumonia on Study Day 258. History included hypertension, right bundle branch block and peripheral vascular disease. Study medication consisted of varying doses ofpregabalin 225-300 mg/day for 256 days. The patient had participated in a previousdouble-blind Study 1008-127, and received placebo for 56 days. Concomitant medicationconsisted of ibuprofen and valsartan hydrochlorothiazide. A computed tomography scan wasnegative for a cerebral vascular event.

Patient 127_011005, an 81-year-old white woman with postherpetic neuralgia, bronchiectasis and chronic bronchitis. She received placebo in a double blind trial, then pregabalin 250 mg/day. She was hospitalized for pneumonia and exacerbation of chronic obstructive pulmonary disease on Study Day 78 and pregabalin was discontinued. She was discharged on Study Day 82, but was not considered recovered from these events. On On Study Day 116, the patient lost consciousness at home and was transported to the hospital, where cardiopulmonary resuscitation (CPR) and defibrillation wer eattempted but failed. She died due to pneumonia

Patient 196_127004, a 73-year-old white man in the United Kingdom with postherpetic neuralgia, bronchitis, chronic obstructive airways disease, pneumonia, depression, transient ischemic attacks and duodenal ulcers. He received pregabalin150 mg/day for 36 days during double-blind study, then 375 mg/day. On Study Day 152, the patient was hospitalized for elective right total knee replacement surgery. Study medication was stopped the day of surgery. Following surgery, the patient's status deteriorated between Study Day 153 and Study Day 154. On Study Day 154, the patient experienced respiratory failure and respiratory arrest. He subsequently died.

17.3 Appendix 3: Serious AEs – All controlled trials, all indications

Summary of SAEs in ≥ 3 pregabalin-treated patients (0.1%) by decreasing frequency, All controlled studies

	[Number of Patients (%)]							
Preferred Term	**Placebo N = 2384**	**150 mg/day PGB N = 1164**	**200 mg/day PGB N = 208**	**300 mg/day PGB N = 1224**	**400 mg/day PGB N = 360**	**450 mg/day PGB N = 501**	**600 mg/day PGB N = 1802**	**All PGB[a] N = 5508**
Accidental injury	1 (0.0)	2 (0.2)	0 (0.0)	3 (0.2)	3 (0.8)	0 (0.0)	11 (0.6)	19 (0.3)
Chest pain	3 (0.1)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	3 (0.2)	9 (0.2)
Pneumonia	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.2)	3 (0.2)	6 (0.1)
Congestive heart failure	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)	5 (0.1)
Myocardial infarct	2 (0.1)	1 (0.1)	0 (0.0)	3 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	5 (0.1)
Angina pectoris	2 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	4 (0.1)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.1)	4 (0.1)
Cerebral ischemia	1 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Cholecystitis	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Confusion	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Coronary artery disorder	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.3)	0 (0.0)	1 (0.1)	3 (0.1)
Dyspnea	1 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Hypesthesia	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Infection	2 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Kidney calculus	1 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Pain	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Suicide attempt	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	3 (0.1)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Total SAEs	**49 (2.1)**	**25 (2.1)**	**1 (0.5)**	**33 (2.7)**	**5 (1.4)**	**4 (0.8)**	**55 (3.1)**	**129 (2.3)**

SAE = Serious adverse event.

[a] Includes other doses of pregabalin (e.g., 50 or 75 mg/day). Dose is total daily dose in mg/day given BID or TID.

17.4 Appendix 4: Serious AEs – All uncontrolled trials, all indications

Summary of SAEs in ≥ 0.15% of patients - All uncontrolled studies

Body system	Preferred term	No. Pts	% total
Body as a whole	**Accidental injury**	62	1.14
	Chest pain	21	0.38
	Cellulitis	18	0.33
	Infection	15	0.27
	Abscess	11	0.2
	Carcinoma	10	0.18
	Overdose	10	0.18
	Sepsis	8	0.15
Cardiovascular system	Congestive heart failure	26	0.48
	Myocardial infarct	24	0.44
	Angina pectoris	18	0.33
	Coronary artery disorder	15	0.27
	Syncope	15	0.27
	Cerebrovascular accident	14	0.26
	Atrial fibrillation	10	0.18
	Deep thrombophlebitis	8	0.15
	Heart failure	8	0.15
	Pulmonary embolus	8	0.15
Digestive system	Cholelithiasis	11	0.2
	Gastrointestinal disorder	11	0.2
	Gastrointestinal hemorrhage	9	0.16
Musculoskeletal system	Arthrosis	9	0.16
	Depression	15	0.27
	Convulsion	8	0.15
Respiratory system	Pneumonia	33	0.6
	Lung disorder	11	0.2
Special senses	Visual field defect	8	0.15
Urogenital system	Urinary tract infection	9	0.16
	Breast carcinoma	8	0.15

17.5 Appendix 5: List of serious AEs in controlled PHN trials

Appendix 5: List of serious AEs in controlled PHN trials

Body system	Preferred term	Placebo [N = 398]		All pregabalin [N = 852]	
		N	%	N	%
Body as a whole	Abscess	1	0.25	0	0.00
	Accidental injury	0	0.00	1	0.12
	Anaphylactoid reaction	0	0.00	1	0.12
	Cellulitis	0	0.00	1	0.12
	Chest pain	0	0.00	2	0.23
	Face edema	0	0.00	1	0.12
	Infection	1	0.25	0	0.00
	Overdose	1	0.25	0	0.00
	Pain	0	0.00	2	0.23
Cardiovascular system	Angina pectoris	1	0.25	0	0.00
	Atrial arrhythmia	0	0.00	1	0.12
	AV block	0	0.00	1	0.12
	Cerebral ischemia	1	0.25	3	0.35
	Cerebrovascular accident	0	0.00	1	0.12
	Congestive heart failure	0	0.00	1	0.12
	Digitalis intoxication	0	0.00	1	0.12
	Left heart failure	0	0.00	1	0.12
	Myocardial infarct	1	0.25	1	0.12
	Myocardial ischemia	1	0.25	0	0.00
	Occlusion	0	0.00	1	0.12
	Syncope	0	0.00	1	0.12
	Thrombophlebitis	0	0.00	1	0.12
	Ventricular extrasystoles	1	0.25	2	0.23
	Ventricular tachycardia	0	0.00	1	0.12
Digestive system	Cholecystitis	0	0.00	1	0.12
	Gastroenteritis	0	0.00	1	0.12
	Pancreatitis	1	0.25	0	0.00
Hemic and lymphatic system	Leukopenia	0	0.00	1	0.12
	Lymphoma like reaction	0	0.00	1	0.12
Metabolic and nutritional disorders	Edema	1	0.25	0	0.00
	Hypokalemia	0	0.00	1	0.12
	Peripheral edema	0	0.00	1	0.12
Musculoskeletal system	Myasthenia	0	0.00	1	0.12
Nervous system	Confusion	0	0.00	1	0.12
	Dizziness	0	0.00	1	0.12
	Hypesthesia	0	0.00	1	0.12
	Somnolence	0	0.00	1	0.12
Respiratory system	Asthma	0	0.00	1	0.12
	Dyspnea	0	0.00	1	0.12
	Lung fibrosis	0	0.00	1	0.12
	Pneumonia	0	0.00	2	0.23
Special senses	Glaucoma	0	0.00	1	0.12
Urogenital system	Urinary tract infection	0	0.00	2	0.23
	Uterine hemorrhage	1	0.25	0	0.00

17.6 Appendix 6: Serious AEs in uncontrolled PHN trials

Appendix 6: List of serious AEs in uncontrolled PHN trials

Body system	Preferred term	No. patients (N)	Percent patients (%)
Body as a whole	Accidental injury	14	1.77
	Carcinoma	5	0.63
	Chest pain	3	0.38
	Cyst	2	0.25
	Infection	2	0.25
	Viral Infection	2	0.25
	Abscess	1	0.13
	Accidental overdose	1	0.13
	Asthenia	1	0.13
	Cellulitis	1	0.13
	Flu syndrome	1	0.13
	Generalized edema	1	0.13
	Hernia	1	0.13
	Neoplasm	1	0.13
	Shock	1	0.13
Cardiovascular system	Myocardial infarct	6	0.76
	Congestive heart failure	5	0.63
	Syncope	5	0.63
	Angina pectoris	4	0.50
	Atrial fibrillation	4	0.50
	Heart failure	4	0.50
	Coronary artery disorder	3	0.38
	Heart arrest	3	0.38
	Cerebrovascular accident	2	0.25
	Coronary occlusion	2	0.25
	Ventricular extrasystoles	2	0.25
	Aortic stenosis	1	0.13
	Arteriosclerosis	1	0.13
	Bradycardia	1	0.13
	Cardiovascular disorder	1	0.13
	Carotid thrombosis	1	0.13
	Cerebral ischemia	1	0.13
	Cerebrovascular disorder	1	0.13
	Deep thrombophlebitis	1	0.13
	Myocardial ischemia	1	0.13
	Pulmonary embolus	1	0.13
	Sinus bradycardia	1	0.13
	Supraventricular extrasystoles	1	0.13
	Supraventricular tachycardia	1	0.13
Digestive system	Gastrointestinal hemorrhage	4	0.50
	Colitis	3	0.38
	Gastroenteritis	3	0.38
	Cholelithiasis	2	0.25
	Intestinal obstruction	2	0.25
	Rectal hemorrhage	2	0.25

Body system	Preferred term	No. patients (N)	Percent patients (%)
Digestive system	Diarrhea	1	0.13
	Esophageal stenosis	1	0.13
	Gastritis	1	0.13
	Nausea	1	0.13
	Nausea and vomiting	1	0.13
	Necrotizing pancreatitis	1	0.13
	Pancreatitis	1	0.13
	Stomach ulcer	1	0.13
Hemic and lymphatic system	Lymphoma like reaction	1	0.13
	Thrombocytopenia	1	0.13
Metabolic and nutritional disorders	Dehydration	5	0.63
	Creatinine increased	1	0.13
	Hypokalemia	1	0.13
	Hyponatremia	1	0.13
Musculoskeletal system	Joint disorder	1	0.13
	Musculoskeletal congenital anomaly	1	0.13
	Myalgia	1	0.13
	Tendon rupture	1	0.13
Nervous system	Ataxia	1	0.13
	CNS neoplasia	1	0.13
	Confusion	1	0.13
	Depression	1	0.13
	Incoordination	1	0.13
	Movement disorder	1	0.13
	Neuralgia	1	0.13
	Neuropathy	1	0.13
	Speech disorder	1	0.13
	Vertigo	1	0.13
Respiratory system	Pneumonia	8	1.01
	Lung disorder	3	0.38
	Asthma	1	0.13
	Bronchitis	1	0.13
	Hemoptysis	1	0.13
	Lung edema	1	0.13
	Pharyngitis	1	0.13
	Respiratory disorder	1	0.13
Skin and appendages	Skin melanoma	1	0.13
Special senses	Retinal edema	2	0.25
	Retinal disorder	1	0.13
	Visual field defect	1	0.13
Urogenital system	Urinary tract infection	4	0.50
	Breast carcinoma	2	0.25
	Kidney function abnormal	2	0.25
	Prostatic disorder	2	0.25
	Acute kidney failure	1	0.13
	Bladder carcinoma	1	0.13
	Cystitis	1	0.13
	Endometrial carcinoma	1	0.13
	Prostatic carcinoma	1	0.13
	Urinary retention	1	0.13

17.7 Appendix 7: Serious AEs in ongoing studies/not included in the integrated safety database

A total of 31 adverse events reported on double-blind forms were received after database lock of the double-blind study and treatment code release and therefore were not entered into the Oracle Clinical database. They are listed below:

Indication	Study	PTID	Treatment Group	AE text	Preferred Term
Epilepsy	007	1102	Gabapentin	Resting tremor	Tremor
	007	1501	600 mg/day	Dizziness/vertigo	Vertigo, dizziness
	009	36005	600 mg/day	Scalp laceration	Accidental injury
	009	36007	Placebo	Increased appetite, drowsiness	Increased appetite, drowsiness
	009	45015	600 mg/day	Weight gain	Weight gain
	034	8003	600 mg/day	Nausea	Nausea
	034	2209	50 mg/day	Imbalance when walking, rapid weight gain (22lbs in 2 wks)	Abnormal gain, weight gain
	034	27007	300 mg/day	Dizziness	Dizziness
	034	37001	Placebo	Decreased sensitivity in toes	Paresthesia
	034	56006	Placebo	Fractured left ankle	Accidental injury
Pain	014	14015	600 mg/day	Neck pain	Neck pain
	029	28012	300 mg/day	Dry cough	Cough incrased
	030	127005	75 mg/day	Intermittent hyperkalemia	Hyperkalemia
	030	130008	75 mg/day	Sl. Disorientation	Confusion
	031	203003	600 mg/day	Peripheral vasculitis	Vasculitis
	032	331002	Placebo	Disorientation	Confusion
	040	17006	Placebo	Onychomycosis	Infection
	045	2011	150 mg/day	Bladder infection	Cystitis
	104	408010	450 mg/day	Incontinence, lack of concentration	Urinary incontinence, thinking abnormal
	104	419003	Placebo	Sweating	Sweating
	104	421016	300 mg/day	HA – L side	Headache
	105	505028	Placebo	Stabbing intermittent chest pain	Chest pain
	105	526018	450 mg/day	Flu symptoms (x 2 episodes)	Flu syndrome
	131	113020	Placebo	Dizziness	Dizziness
Psych	017	5050	600 mg/day	R thigh numbness	Hypesthesia
	083	306015	450 mg/day	Weight gain	Weight gain

(Adapted from Sponsor's Appendix ALL.12, RR-REG 720-30199, P. 1161)

Pfizer considered the pattern of these events as reflective of the pattern in the overall population (mainly cardiac, vascular, or CNS events and carcinomas), or within the individual indications.

SAEs from Ongoing Epilepsy trials/ SAEs not included in the Integrated Safety Database
Dr. Bohem identified 25 additional subjects who received either pregabalin or blinded treatment in epilepsy trials who experienced SAEs. The SAEs were similar to those identified in patients in the integrated safety database. There were no events of hepatic failure, acute renal failure, rhabdomyolysis, blood dyscrasias or serious skin reactions for pregabalin treated or blinded therapy treated subjects from these epilepsy trials

SAEs from Ongoing GAD trials/ SAEs not included in the Integrated Safety Database
Dr. Boehm found that 5 patients enrolled in ongoing controlled GAD studies not in the integrated safety database[1] experienced SAEs that were reported to Pfizer by 2/14/03. These SAEs are listed in Appendix All066 (SCS, p. 3916). The SAEs are listed by Pfizer as chest pain; ventricular tachycardia; proctorrhagia, anemia, and intermittent second degree atrioventricular block (all experienced by one patient); fall, dizziness, and drowsiness (all experienced by one patient); and right big toe ulcer, progression of chronic arteritis, and right great toe infection (all experienced by one patient). Since treatment of patients in these studies was still blinded, Pfizer did not report whether the patients who experienced these SAEs were receiving pregabalin or placebo.

In addition, there were six patients with SAEs in open-label GAD studies that were reported to the sponsor's ARISg database but not the Oracle Clinical Database as of February 14, 2003. According to patient narratives and case report forms, all of these SAEs occurred in patients who had previously been enrolled in study 090/152, an ongoing study not in the integrated safety database being conducted among elderly patients with GAD. Their treatment assignments in this preceding study remain blinded. The SAEs, which are listed in Appendix ALL289 (SCS, p. 7674), were coded to the WHOART preferred terms atrial fibrillation; bronchiectasis (investigator's term: worsening of bronchiectasis); hypoxia and other and unspecified neoplasms (investigator's terms: hypoxemia and pancreatic mass); synovitis (investigator's term: inflamed Baker's cyst right knee); dizziness (investigator's term: faintness); and angioedema (investigator's term: Quincke's disease).

Ongoing neuropathic pain trials

Ogoing studies included in the NDA safety database, but for which some data were obtained after the cut-off date:

PROTOCOL NUMBER	DESIGN
1008-061	OPEN-LABEL EXTENSION OF 1008-045 (PHN)
1008-074	OPEN-LABEL EXTENSION OF 1008-040 (DPN)
1008-165	OPEN-LABEL EXTENSION OF 1008-149 (DPN)
1008-197	OPEN LABLEL STUDY OF REFRACTORY PATIENTS FROM STUDIES 015, 033, 132, 134, 173, 174 (DPN AND PHN)
	OPEN-LABEL EXTENSION OF 1008-196 (PHN)

[1] Study 090/152, a placebo-controlled study being conducted among elderly patients with GAD, is the only ongoing GAD study not in the integrated safety database described by Pfizer in table 135 (Summary of clinical safety, p.241; see attached table 2), in which ongoing studies not in the phase 2/3 integrated safety database are listed. Two additional studies for psychiatric indications are also described in this table—study 091 for panic disorder and study 093/192 for panic relapse prevention.

SAEs reported after the cut off date - PHN trials included in the NDA safety database

There were 17 patients in on-going DPN trials who had SAEs that were not included in the integrated safety database (Applicant's Appendix ALL.289). As noted above, the SAEs were coded to WHOART preferred terms and included and were as follows:

WHOART Preferred Term	No. Patients*
Pneumonia	4
Cerebrovascular disorder	3
Peripheral ischemia	2
Abcess	1
Arthralgia	1
Bacterial infection	1
Breast neoplasm (female)	1
Cardiac failure, pulmonary edema, drug toxicity	1
Hyperglycemia	1
Myocardial infarction	1
Other and unspecified neoplasms	1
Withdrawal syndrome	1

* some patients may have experienced more than one AE; Patients enrolld in trial 197 were not included

SAEs reported after the cut off date - PHN trials included in the NDA safety database

A total of 16 patients had SAEs that were not included in the safety database before the cut-off date:

WHOART Preferred Term	No. Patients*
Atrial fibrillation	2
Back pain	1
Carcinoma	1
Cardiac failure congestive	1
Cellulitis	1
Cerebrovascular accident	1
Chronic lymphocytic leukemia NOS	1
Chronic myeloid leukemia	1
Dyspnea	1
Gastroenteritis	1
Hematemesis	1
Hepatocellular damage	1
Hyperglycemia	1
Lyme disease	1
Nosocomial infection	1
Polyarthritis	1

* some patients may have experienced more than one AE; Patients enrolld in trial 197 were not included

Trial 1008-197 evaluated the efficacy of pregabalin in treating "refractory" DPN and PHN patients. Seven patients in this trial had an SAE that was not reported prior to the cut-off date. The appendix does not distinguish how many DPN and PHN patients had an SAE, so these data are presented seperately.

WHOART Preferred Term	No. Patients
Coronary artery occlusion	1
Diverticulum NOS	1
Bladder cancer NOS	1
Transient ischemic attack	1
Hip fracture	1
Gastroenteritis viral NOS	1

These additional SAEs from studies included in the clinical safety database are notable for the reports of leukemia (n=2), hepatic damage (n=1), and cellulitis (n=1). No information is provided that enables for better determination of an association with pregabalin treatment.

Ongoing neuropathic pain studies that were not included in the NDA safety database
There were 2 on-going trials of pregabalin as treatment for patients with pain due to DPN and PHN that were not included in the integrated safety database. Trial 1008-155 was a controlled study of different titration schemes in patients with either DPN or PHN. Trial 166 was an uncontrolled open-label trial in patients with either DPN or PHN. Notable SAEs during the trials are shown in the table below (all of the patients were taking pregabalin at the time of the SAE):

Protocol	Event Term	No. Patients*
1008-155 (controlled)	Diabetic decompensation	2
	AV block	1
	Confusion	1
	Dizziness	1
	Henoch-Schonlein rash	1
	Hyperglycemia	1
	Increased creatinine	1
	Increased INR	1
	Metabolic acidosis	1
	Petichial rash	1
	Quincke edema	1
	Worsening venous insufficiency	1
1008-166 (open label)	Hyperkalemia	2
	Accidental fall	1
	Cramping in arms and legs	1
	Disorientation	1
	Generalized convulsion	1
	Infected diabetic foot	1
	Muscle pain	1
	Myoclonus	1
	Necrosis of the femoral head	1
	Somnolence	1
	Withdrawal reaction	1
	Worsening hypertension	1

17.8 Appendix 8: Non-serious AEs in uncontrolled PHN trials

Appendix 8: List of non-serious AEs in uncontrolled PHN trials

Body system	Adverse event	No. patients	Percent (%) of patients
Body as a whole	Accidental injury	91	11.48
	Asthenia	65	8.20
	Infection	64	8.07
	Pain	57	7.19
	Headache	44	5.55
	Back pain	33	4.16
	Flu syndrome	28	3.53
	Abdominal pain	26	3.28
	Chest pain	14	1.77
	Face edema	10	1.26
Cardiovascular system	Hypertension	21	2.65
Digestive system	Dry mouth	61	7.69
	Constipation	50	6.31
	Nausea	49	6.18
	Diarrhea	37	4.67
	Vomiting	21	2.65
	Dyspepsia	18	2.27
	Gastrointestinal disorder	12	1.51
	Anorexia	11	1.39
	Flatulence	11	1.39
Metabolic and nutritional disorders	Peripheral edema	130	16.39
	Weight gain	68	8.58
	Hypercholesteremia	11	1.39
	Edema	9	1.13
	Hyperglycemia	9	1.13
Musculoskeletal system	Arthritis	23	2.90
	Arthralgia	17	2.14
	Myasthenia	11	1.39
Nervous system	Dizziness	181	22.82
	Somnolence	128	16.14
	Ataxia	49	6.18
	Abnormal gait	25	3.15
	Reflexes decreased	25	3.15
	Amnesia	24	3.03
	Thinking abnormal	22	2.77
	Insomnia	20	2.52
	Confusion	19	2.40
	Vertigo	19	2.40
Body system	**Adverse event**	**No. patients**	**Percent (%) of patients**
Nervous system	Anxiety	17	2.14
	Tremor	17	2.14

	Paresthesia	15	1.89
	Depression	14	1.77
	Nervousness	14	1.77
	Hypesthesia	12	1.51
	Incoordination	12	1.51
	Speech disorder	11	1.39
	Twitching	11	1.39
	Hyperesthesia	9	1.13
	Euphoria	8	1.01
Respiratory system	Sinusitis	20	2.52
	Pharyngitis	19	2.40
	Dyspnea	17	2.14
	Rhinitis	14	1.77
	Lung disorder	12	1.51
	Bronchitis	9	1.13
Skin and appendages	Rash	46	5.80
	Sweating	14	1.77
	Pruritus	11	1.39
	Skin disorder	10	1.26
Special senses	Amblyopia	49	6.18
	Abnormal vision	19	2.40
	Diplopia	14	1.77
	Visual field defect	12	1.51
	Cataract specified	10	1.26
	Retinal disorder	9	1.13
	Eye pain	8	1.01
Urogenital system	Urinary tract infection	33	4.16
	Cystitis	13	1.64
	Urinary incontinence	12	1.51
	Impotence	11	1.39

17.9 Appendix 9: Comparison of the frequency of heart failure, edema, and weight gain in patients who did or did not take a PPAR – All controlled trials

Appendix 9: Summary of adverse events of heart failure, edema, and weight gain – All controlled trials, all indications

		TESS Number of Patients (%)			
		Pregabalin			
Adverse Event	**Placebo**	**50 mg/day**	**75 mg/day**	**150 mg/day**	**200 mg/day**
All Indications: Non-PPAR					
Preferred Term	N=2316	N=87	N=146	N=1144	N=208
Congestive heart failure	2 (0.1)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Edema	8 (0.3)	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)
Peripheral edema	40 (1.7)	1 (1.1)	2 (1.4)	53 (4.6)	4 (1.9)
Weight gain	19 (0.8)	1 (1.1)	1 (0.7)	40 (3.5)	5 (2.4)
All Indications: PPAR					
Preferred Term	N=68	N=1	N=15	N=20	N=0
Congestive heart failure	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 -
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 -
Edema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 -
Peripheral edema	2 (2.9)	0 (0.0)	1 (6.7)	3 (15.0)	0 -
Weight gain	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 -
Percent of All Patients Reporting PPAR Use	2.9%	1.1%	9.3%	1.7%	0.0%

(Applicant's Table, submitted June 25 2004)

Appendix 9: Summary of adverse events of heart failure, edema, and weight gain – All controlled trials, all indications (continued)

Adverse Event	Number of Patients (%) Pregabalin 300 mg/day	400 mg/day	450 mg/day	600 mg/day	All PGB
All Indications: Non-PPAR					
Preferred Term	N=1176	N=360	N=500	N=1752	N=5373
Congestive heart failure	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	3 (0.1)
Heart failure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)
Edema	24 (2.0)	0 (0.0)	3 (0.6)	25 (1.4)	61 (1.1)
Peripheral edema	102 (8.7)	7 (1.9)	25 (5.0)	118 (6.7)	312 (5.8)
Weight gain	60 (5.1)	19 (5.3)	32 (6.4)	143 (8.2)	301 (5.6)
All Indications: PPAR					
Preferred Term	N=48	N=0	N=1	N=50	N=135
Congestive heart failure	2 (4.2)	0 -	0 (0.0)	1 (2.0)	3 (2.2)
Heart failure	0 (0.0)	0 -	0 (0.0)	0 (0.0)	0 (0.0)
Edema	0 (0.0)	0 -	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral edema	7 (14.6)	0 -	0 (0.0)	13 (26.0)	24 (17.8)
Weight gain	3 (6.3)	0 -	1 (100.0)	5 (10.0)	10 (7.4)
Percent of All Patients Reporting PPAR Use	3.9%	0.0%	0.2%	2.8%	2.5%

(Applicant's Table, submitted June 25 2004)

17.10 Appendix 10: AEs leading to withdrawal from PHN controlled trials, by CLcr and dose of drug (Protocols 30, 45, 127, & 196)

Body system	Preferred term	Placebo		75-L		75-N		150-L		150-N		300-L		300-N		600-N		Low CLcr		High CLcr	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Body as a whole	Asthenia	1	0.29	1	2.33	0	0	1	0.94	0	0	1	0.75	0	0	1	0.81	3	1.06	1	0.25
	Face edema	1	0.29	0	0	0	0	0	0	0	0	1	0.75	0	0	1	0.81	1	0.35	1	0.25
	Generalized edema	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Headache	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Pain	1	0.29	0	0	1	2.44	0	0	0	0	0	0	0	0	0	0	0	0	1	0.25
	Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0	1	1.04	0	0	0	0	1	0.25
	Accidental injury	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Anaphylactoid reaction	0	0	0	0	0	0	0	0	0	0	0	0	1	1.04	0	0	0	0	1	0.25
	Chest pain	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Lab test abnormal	0	0	0	0	0	0	0	0	0	0	0	0	1	1.04	0	0	0	0	1	0.25
	Malaise	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
Cardiovascular system	Cerebral ischemia	1	0.29	0	0	0	0	1	0.94	0	0	0	0	0	0	0	0	1	0.35	0	0
	Syncope	0	0	0	0	0	0	0	0	1	0.69	1	0.75	0	0	0	0	1	0.35	1	0.25
	Bradycardia	0	0	0	0	0	0	1	0.94	0	0	0	0	0	0	0	0	1	0.35	0	0
	Cerebrovascular accident	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
	Heart failure	0	0	0	0	0	0	1	0.94	0	0	0	0	0	0	0	0	1	0.35	0	0
Digestive system	Dry mouth	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	3	2.44	0	0	3	0.74
	Vomiting	2	0.58	0	0	0	0	0	0	0	0	0	0	1	1.04	0	0	0	0	1	0.25
	Constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1.63	0	0	2	0.49
	Dyspepsia	1	0.29	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
	Nausea	2	0.58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Anorexia	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Diarrhea	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Gastrointestinal disorder	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Increased salivation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25

	Pancreatitis	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemic and lymphatic system	Lymphoma like reaction	0	0	0	0	1	2.44	0	0	0	0	0	0	0	0	0	0	0	0	1	0.25
Metabolic/ nutritional disorders	Peripheral edema	1	0.29	0	0	0	0	0	0	0	0	3	2.24	0	0	3	2.44	3	1.06	3	0.74
	Edema	0	0	0	0	0	0	1	0.94	0	0	1	0.75	0	0	2	1.63	2	0.71	2	0.49
Musculoskeletal system	Leg cramps	0	0	0	0	0	0	1	0.94	0	0	0	0	0	0	0	0	1	0.35	0	0
	Myasthenia	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
	Rheumatoid arthritis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
Nervous system	Dizziness	3	0.87	0	0	0	0	3	2.83	2	1.38	6	4.48	1	1.04	8	6.5	9	3.18	11	2.72
	Somnolence	1	0.29	0	0	0	0	1	0.94	1	0.69	7	5.22	1	1.04	9	7.32	8	2.83	11	2.72
	Confusion	1	0.29	0	0	0	0	1	0.94	0	0	0	0	1	1.04	7	5.69	1	0.35	8	1.98
	Ataxia	0	0	0	0	0	0	0	0	0	0	3	2.24	1	1.04	3	2.44	3	1.06	4	0.99
	Abnormal gait	0	0	0	0	0	0	0	0	0	0	2	1.49	0	0	2	1.63	2	0.71	2	0.49
	Hallucinations	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	2.44	0	0	3	0.74
	Speech disorder	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	2	1.63	1	0.35	2	0.49
	Thinking abnormal	2	0.58	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Anxiety	0	0	0	0	0	0	0	0	1	0.69	0	0	0	0	1	0.81	0	0	2	0.49
	Nervousness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1.63	0	0	2	0.49
	Vertigo	0	0	0	0	0	0	1	0.94	0	0	1	0.75	0	0	0	0	2	0.71	0	0
	Depression	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Emotional lability	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Euphoria	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
	Hypertonia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Incoordination	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Insomnia	1	0.29	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Libido decreased	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Stupor	0	0	0	0	0	0	1	0.94	0	0	0	0	0	0	0	0	1	0.35	0	0
Respiratory system	Asthma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25

Respiratory system	Voice alteration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
Skin and appendages	Pruritus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Rash	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
Special senses	Abnormal vision	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	2	1.63	1	0.35	2	0.49
	Amblyopia	0	0	0	0	0	0	0	0	0	0	1	0.75	1	1.04	1	0.81	1	0.35	2	0.49
	Diplopia	0	0	0	0	0	0	0	0	1	0.69	0	0	0	0	1	0.81	0	0	2	0.49
	Deafness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Tinnitus	0	0	0	0	0	0	0	0	0	0	1	0.75	0	0	0	0	1	0.35	0	0
Urogenital system	Impotence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25
	Kidney function abnormal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.81	0	0	1	0.25

17.11 Appendix 11: Protocol 1008-045: Reanalysis of efficacy based on treatment group and creatinine clearance

Protocol 045 specified that patients with a creatinine clearance (CLcr) > 30 mL/min would be randomized to treatment with placebo, pregabalin 150 mg/d or pregabalin 300 mg/d. Randomization to study drug would not be stratified by CLCr.

As previously noted, in protocols 127 and 196, patients were randomized to study treatment depending on their CLcr. Patients with a CLcr of 30-60 mL/min would receive lower doses of pregabalin (150- or 300 mg/d), while patients with a CLcr > 60 mL/min could receive either 300- or 600 mg/d. Sections 6.3.2, 6.3.3, and 6.3.4 discuss the variability in efficacy of the various doses of pregabalin, depending on patients' CLcr. Given these findings, the Division evaluated whether the observed efficacy of pregabalin in trial 045 would change if the data were reanalyzed after dividing patients in the pregabalin group according to their creatinine clearance ("low CLcr" = 30-60 mL/min; "normal CLcr" = > 60 mL/min).

Results

Among the 81 patients initially randomized to pregabalin 150 mg/d, there were 42 patients with a low CLcr and 39 with a normal CLcr. Out of the 76 patients in the 300 mg/d group, 45 had a low CLcr and 31 had a normal CLcr. When the mean pain score at endpoint was calculated, only the pregabalin 150 mg/d-low CLcr and the 300 mg/d-normal CLcr groups showed a significant difference from placebo (Appendix 11.Table1). The same was true when the change in mean pain score from baseline to endpoint was calculated (Appendix 11.Table2).

Evaluation of the proportion of treatment responders at endpoint (patients with ≥ 50% decrease in pain from baseline) found that 3 of the 4 pregabalin had considerably higher proportions of treatment responders compared to the placebo group. The greatest proportion of responders was seen in the pregbalin 600 mg/d-normal CLcr group (35%), followed by the 150 mg/d-low CLcr group (29%), and the 150 mg/d-normal CLcr group (21%). There was essentially no difference in treatment responders between the 300 mg/d-low CLcr group (11%) and the placebo group (9%) (Appendix 11.Table3 and Figure1).

Across all treatment groups, 43 patients completed the study and had a treatment response. The distribution of these patients over the duration of the study is illustrated in Figure 2 below. There is an increasing trend in treatment responders for all pregabalin groups compared to the placebo group, with the steepest trends observed for the 600 mg/d-normal CLcr group and the 150 mg/d-low CLcr groups. The graph shows that a treatment effect (greater than that for placebo) occurs around the 2nd week of treatment for these 2 groups, and around the 3rd week for the 150 mg/d-normal CLcr and the 300 mg/d-low CLcr groups. Finally, the graph suggests that the likelihood of treatment response does not increase with beyond 3 weeks of treament with 300 mg/d in patients with a low CLcr.

Appendix 11.Table1: Least square mean pain score by dose/CLcr (BOCF) – ITT population

	Placebo N=81	PGB 150-Low N=42		PGB 150-Normal N=39		PGB 300-Low N=45		PGB 300-Normal N=31	
	Mean (SD)	mean (SD)	P value[1]	Mean (SD)	P value[1]	mean (SD)	P value[1]	Mean (SD)	P value[1]
Week 1	6.6 (0.1)	5.7 (0.2)	0.0008	6.3 (0.2)	0.1797	6.2 (0.2)	0.1606	5.8 (0.2)	0.0078
Week 2	6.5 (0.2)	5.3 (0.2)	0.0003	6.2 (0.2)	0.1867	5.8 (0.2)	0.0098	5.0 (0.3)	0.0003
Week 3	6.5 (0.2)	5.3 (0.2)	0.0004	5.9 (0.2)	0.0253	5.7 (0.2)	0.0034	5.4 (0.3)	0.0012
Week 4	6.5 (0.2)	5.4 (0.2)	0.0003	5.9 (0.2)	0.0293	5.7 (0.2)	0.0102	5.0 (0.3)	0.0003
Week 5	6.3 (0.2)	5.3 (0.3)	0.0051	5.7 (0.3)	0.0378	5.6 (0.3)	0.0378	4.8 (0.3)	0.0004
Week 6	6.4 (0.2)	5.2 (0.3)	0.0018	5.8 (0.3)	0.0799	5.6 (0.3)	0.0450	4.6 (0.3)	0.0004
Week 7	6.2 (0.2)	5.0 (0.3)	0.0024	5.8 (0.3)	0.1678	5.6 (0.3)	0.1284	4.7 (0.3)	0.0004
Week 8[2]	6.3 (0.2)	4.9 (0.3)	0.0006	5.5 (0.3)	0.0716	5.7 (0.3)	0.0716	4.5 (0.4)	0.0004
Endpoint[3]	6.3 (0.2)	4.9 (0.3)	0.0003	5.5 (0.3)	0.0587	5.7 (0.3)	0.0587	4.6 (0.3)	0.0003

[1] using Hochberg's test of difference from control (placebo)
[2] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[3] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose

Appendix 11.Table2: Change in Mean Pain Scores: Results of Analysis of Covariance

	Placebo	PGB150-Low	PGB150-Normal	PGB300-Low	PGB300-Normal
Baseline[1]	6.64 (1.6)	7.02 (1.7)	6.84 (1.6)	6.96 (1.7)	7.00 (1.6)
Endpoint[2]	6.15 (2.1)	5.14 (2.5)	5.48 (2.4)	5.83 (2.4)	4.62 (2.6)
Change[3]	0.50 (1.5)	1.88 (1.9)	1.36 (2.1)	1.13 (1.7)	2.38 (2.8)
lsmeans	0.52 (0.2)	1.94 (0.3)	1.32 (0.3)	1.20 (0.3)	2.28 (0.3)
p-value[4]		0.0003	0.0587	0.0587	0.0003
Week 8[5]	6.14 (2.2)	5.07 (2.5)	5.49 (2.5)	5.83 (2.4)	4.57 (2.7)
Change[6]	0.51 (1.5)	1.89 (1.9)	1.35 (2.1)	1.13 (1.7)	2.44 (2.9)
lsmeans	0.54 (0.2)	1.97 (0.3)	1.32 (0.3)	1.19 (0.3)	2.33 (0.4)
p-value[4]		0.0006	0.0716	0.0716	0.0004

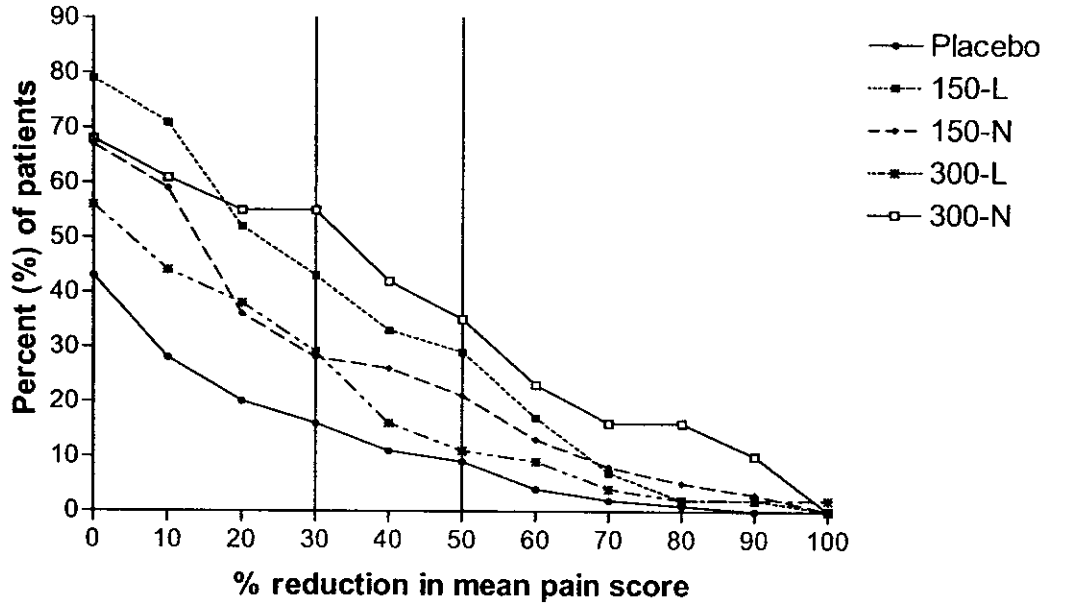
[1] Baseline = Last 7 available scores before taking study medication, up to and including Day 1
[2] Endpoint= Last 7 available scores while on study medication, up to and including day after last dose
[3] Change= Baseline – Endpoint
[4] using Hochberg's test of difference from control (placebo)
[5] Week 8= baseline mean pain score for non-completers, and average of day 51 to day 57 pain scores for completers
[6] Change= Baseline – Week 8

Appendix 11.Table3: Percentage change in Endpoint mean pain score by dose using new treatment assignment based on creatinine clearance (BOCF) – ITT population

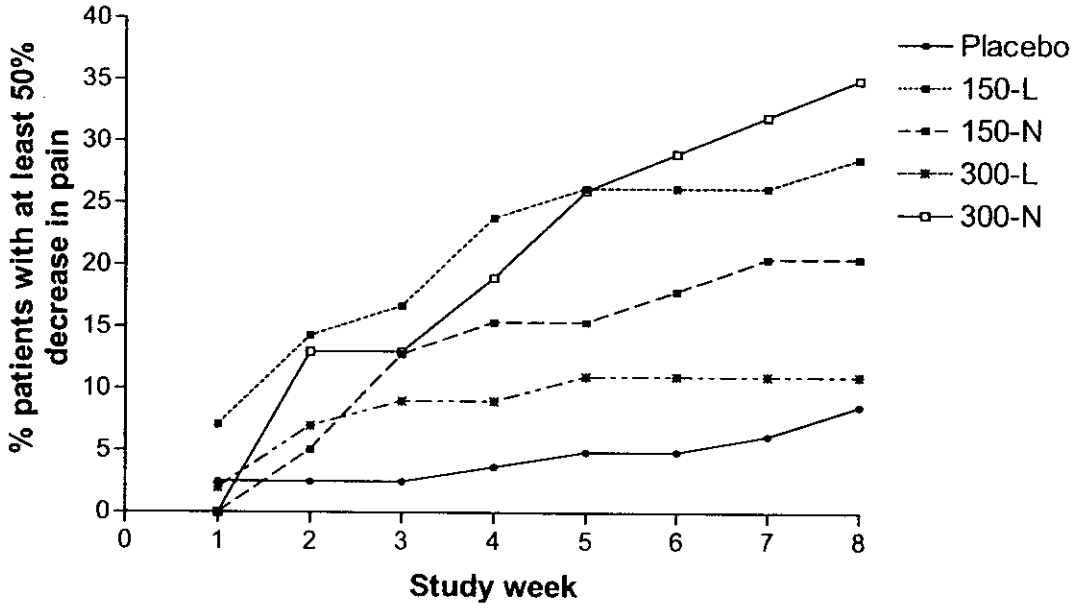
	TOTAL		PLACEBO		PGB 150[1]		PGB 150[2]		PGB 300[1]		PGB 300[2]	
	Total	%	Total	%	Total	%	Total	%	Total	%	Total	%
Any increase	39	16%	19	23%	3	7%	8	21%	4	9%	5	16%
None	59	25%	27	33%	6	14%	5	13%	16	36%	5	16%
> 0 % decrease	140	59%	35	43%	33	79%	26	67%	25	56%	21	68%
≥ 10%	115	48%	23	28%	30	71%	23	59%	20	44%	19	61%
≥ 20%	86	36%	16	20%	22	52%	14	36%	17	38%	17	55%
≥ 30%	72	30%	13	16%	18	43%	11	28%	13	29%	17	55%
≥ 40%	53	22%	9	11%	14	33%	10	26%	7	16%	13	42%
≥ 50%	**43**	**18%**	**7**	**9%**	**12**	**29%**	**8**	**21%**	**5**	**11%**	**11**	**35%**
≥ 60%	26	11%	3	4%	7	17%	5	13%	4	9%	7	23%
≥ 70%	15	6%	2	2%	3	7%	3	8%	2	4%	5	16%
≥ 80%	10	4%	1	1%	1	2%	2	5%	1	2%	5	16%
≥ 90%	6	3%	0	0%	1	2%	1	3%	1	2%	3	10%
=100%	1	0%	0	0%	0	0%	0	0%	1	2%	0	0%

[1]Low = creatinine clearance is between 30 and 60 mL/min
[2]Normal = creatinine clearance >60 mL/min

Appendix 11.Figure1: Response profile at endpoint – Protocol 045



Appendix 11.Figure2: Proportion of treatment responders by study week



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Mwango Kashoki
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Celia Winchell
8/6/04 10:36:35 AM
MEDICAL OFFICER
I concur with Dr. Kashoki's review overall, but differ with her concerning the recommended regulatory action. See my memo.