CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-446

Medical Review(s)

Douglas C. Throckmorton, M.D.
Office of the Center Director, HFD-001

Food and Drug Administration
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Memorandum

DATE: 12.21.04

FROM: Douglas C. Throckmorton, M.D., Acting Deputy Director,
Center for Drug Evaluation and Research, HFD-001

SUBJECT: Scheduling recommendation for Pregabalin
NAME OF DRUG: Lyrica (pregabalin) capsules
SPONSOR: Pfizer Global Research and Development

DOCUMENTS USED FOR MEMO

1. 74-day letter for NDAs 21-446 and 21-723, dated January 01, 2004.
2. Controlled Substances Staff (CSS) memorandum to Bob Rappaport, regarding proposed scheduling, by Katherine Bonson, Ph.D., dated March 24, 2004.
3. Controlled Substances document 'Dispute Resolution Issues' by Michael Klein, Ph.D., dated September 29, 2004.
4. Basis for the recommendation for control of Pregabalin Schedule IV on the Controlled Substances Act (CSA), by Katherine Bonson, Ph.D., and Michael Klein, Ph.D., dated 11.16.04.
5. Approvable letter for NDA 21-446, pregabalin for the treatment of neuropathic pain, dated July 29, 2004.
6. FDA meeting minutes from meeting held April 13, 2004, minutes dated May 17, 2004.
7. FDA Statistical Reviews of study 098.
8. FDA 'Individual Assessment of Subjective Measures from Study 098' and 'Pregabalin Abuse Liability Study (1008-098) Summary of Individual Subject Responses Relative to Placebo' (both documents undated).
9. National Institute on Drug Abuse (NIDA) recommendation regarding scheduling decision, by Frank Vocci, Ph.D., dated August 31, 2004.
10. Memorandum on post-marketing reports of potential abuse with Gabapentin, from Lopa Thambi, Pharm. D., Division of Drug Risk Evaluation, HFD-430, dated Sept 21, 2004.
11. Title 21, United States Code, Controlled Substances Act, sections 811(b) and (c).
12. Report submitted as a part of NDA 21-446 on 'Abuse Liability Assessment of Pregabalin in Recreational Sedative/Alcohol Users' by Chris-Ellyn Johanson, Ph.D.
13. NDA 21-446, section 2.5.5.6.5 (Dependence Potential, Tolerance and Withdrawal).
14. Pfizer Dispute Resolution request, dated July 16, 2004.
15. Pfizer slides set 'Galson Briefing' dated October 1, 2004 ('draft').
16. Pfizer slides set 'Galson Briefing' dated October 1, 2004.
17. Pfizer slide set 'Risk Management' dated October 1, 2004.
18. Pfizer submission to NDA 21-446, dated July 16, 2004.
19. Information on Emergency Room visits and DAWN data for neurontin (gabapentin), alprazolam and hydrocodone.

20. Transcript for the April 28, 1998 FDA Drug Abuse Advisory Committee meeting.

CONCLUSIONS AND RECOMMENDATIONS

This memorandum constitutes my recommendation that pregabalin marketing should be controlled in Schedule V of the Controlled Substances Act, 21 USC section 811 (b). The available data are sufficient to conclude that a substantial abuse potential exists for this drug product. In particular, the data are consistent with a product that could have substantial potential for intermittent abuse related to the euphorigenic properties of pregabalin. The data are also sufficient to conclude that pregabalin has a lower risk of abuse than products currently in Schedule IV, supporting its placement into Schedule V.

BACKGROUND AND OVERVIEW

The outline of the arguments for scheduling is summarized in other parts of the record, as are the arguments made by Pfizer to address each of these arguments. Both the CSS staff and the sponsor have commented in multiple documents about various aspects of the pregabalin database, complicating my task at summarizing the written record, and the reader is referred to these documents where appropriate below for fuller details. Overall, while there is broad agreement about the data in this case, there exist some differences about how to interpret these data in areas that are critical to the determination of the abuse potential and the scheduling decision. What follows is an attempt to summarize the two sides, and to make a final recommendation about each piece of the 'puzzle' that is used, in the end, to determine the abuse potential of pregabalin. I will also need to address a proposal made by Pfizer in the meeting with the Agency on October 1, 2004: that the abuse potential of pregabalin... 'is better addressed by risk management plan'.

By way of reference, I'll start by listing the eight factors pertaining to the scheduling of drugs under 21 USC 811 (c):

1. The drug's actual or relative potential for abuse.
2. Scientific evidence of the drug's pharmacological effects, if known.
3. The state of current scientific knowledge regarding the drug or substance.
4. Its history and current pattern of abuse.
5. The scope, duration, and significance of abuse.
6. What, if any, risk there is to public health.
7. The drug's psychic or physiologic dependence liability.
8. Whether the drug or substance is an immediate precursor of a substance already controlled.

The reader is referred to the separate 8-factor analysis conducted by the Controlled Substances Staff (CSS)[1].

Pfizer makes the following set of arguments[2] against the scheduling of pregabalin, beginning with the observation that pregabalin is not pharmacologically related to any known drug with recognized substantial abuse potential:

1) Importance of the Pharmacological Properties of New Drugs For drugs that are related to known drugs of abuse (e.g., barbiturates, opiates), factor 2 (on the drug's pharmacological effect) will weigh heavily when making the decision about the abuse potential. For a drug that is not pharmacologically-related to another drug with know abuse potential, the 8-point analysis is 'less well-adapted to identify abuse potential...'.
2) Use of 'Isolated' Evidence of CNS Activity to Conclude Substantial Abuse Potential Because pregabalin is not pharmacologically-related to another scheduled drug, 'isolated' evidence of CNS activity (e.g., euphoria, reinforcing behavior) is less significant than it would be otherwise (per the sponsor, 'do not have added probative significance here...').
3) Use of 'Isolated' Evidence of CNS Activity to Conclude Substantial Abuse Potential Absent a shared pharmacology with known drugs of abuse, the available evidence of CNS activity does not rise to the level of substantial evidence of abuse potential.
4) Observed CNS Effects from other Non-Scheduled Drugs The available evidence of CNS activity is similar to reported effects of other drugs that are not scheduled.

[1] Basis of recommendation for Control of Pregabalin in Schedule IV of the Controlled Substances Act (CSA).
[2] October 26, 2004 submission.

5) Proposed Post-Marketing Surveillance to Detect Abuse Potential A post-marketing surveillance system can be put into place that will adequately detect an abuse liability.

In the body of this review below, I will discuss each of these arguments in turn. I will also discuss the Scheduling of pregabalin.

1) Importance of the Pharmacological Properties of New Drugs

As Pfizer points out in their October 26, 2004 submission, one important factor is the known pharmacology of the drug and related compounds. I agree that when a new drug is pharmacologically related to drugs with known abuse potential (e.g., barbiturates, opiates), this factor will be important when making the decision about the abuse potential. In the present case, again as pointed out repeatedly by the sponsor, pregabalin is not pharmacologically related to any drug with accepted abuse potential (it is structurally-related to Gabapentin, an unscheduled approved drug; a drug with some evidence abuse post-marketing that is currently being evaluated). However, I disagree strongly with Pfizer's assertion that the 8-factor analysis is 'less well-adapted to identify abuse potential for new drugs that are not pharmacologically related to known drugs of abuse, since the potential for abuse cannot be extrapolated and must be proven scientifically.' (October 26, 2004 submission, page 4). The development and methods of specific parts of the 8-point analysis has been discussed by other[3,4]. It has been remarked that abuse liability assessment is best suited to detecting risks of abuse by the addict community (and less good at predicting abuse by patients taking the drug therapeutically)[2]. From my reading of previous scheduling recommendations on other products, however, I find no evidence that the pharmacology of the new drug is given the pivotal role ascribed to it by Pfizer. Instead, I take the 8 parts of the analysis as all providing relevant information necessary to make an informed prediction as to the abuse potential for a new drug. Where a drug is not related pharmacologically to a drug of abuse is a part of that making that prediction (which is not the same thing as saying the 8-factor analysis is 'less well-adapted'). It is also not accurate that pregabalin is not related to other drugs with known abuse potential, if by that is meant the pharmacodynamic effects of the product. As discussed below, the CNS effects of pregabalin do resemble those of established drugs of abuse.

2) Use of 'Isolated' Evidence of CNS Activity to Conclude Substantial Abuse Potential

In this part of the argument I have little disagreement with the substance of the sponsor's argument as I understand it from their submissions. Each drug needs to be evaluated on its own, based on the totality of the 8-factor analysis, and the evidence must make a coherent case for a substantial abuse potential. In their most recent submission, the sponsor warns against the use of 'isolated observations' of CNS activity to support scheduling for compounds that do not share a pharmacology of concern. If by 'isolated', the sponsor means 'inconsistent' or 'contradictory' evidence of CNS activity not supported by other evidence from the 8-factor analysis, I agree with them. Regardless of the presence or absence of data relating the drug's pharmacology to a previously scheduled drug, such data cannot be taken, on its own, as an adequate level of evidence to recommend scheduling. The data on the CNS effects of pregabalin are, however, still relevant and still capable of supporting a scheduling decision when consistent and robust. As I'll go into in the next section, I believe the data on the CNS effects of pregabalin are not 'isolated' and do tell a consistent story supporting a substantial abuse potential.

3) Evidence of CNS Activity for Pregabalin

The next piece to be considered is the strength of the evidence that pregabalin has CNS activity of concern (*i.e.*, indicating an abuse potential). I believe that both the CSS staff and the sponsor have had ample opportunity to make their cases regarding the various assessments of the CNS effects of pregabalin. Further, while the data have been substantially agreed to, differences about their interpretation remain, differences remain that I cannot resolve here. Below, I'll discuss each of the various parts of the abuse liability assessment, summarizing what I have concluded about the data. The difficulty is that in the field of abuse liability assessment the FDA, DEA and sponsors are called to make critical decisions about abuse liability using trials that are typically conducted in small, and sometime heterogeneous numbers of subjects (either animal or human). This isn't criticism of the science; rather it is a recognition of the potentially ambiguous nature of these data and the likelihood that differences of

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[3] Principles of initial experimental drug abuse liability assessment in humans. Griffiths, R.R., et al. Drug and Alcohol Dependence, (2003) 70:S41-S54.

[4] Assessment of abuse liability of drugs in humans: a methodological survey. Foltin, R.W. and Fishman, M.W. (1991) Drug Alcohol Dependence (1991) 28:3-48

opinion, like those expressed in the various documents attached to this decision, will occur As a side-comment, this is an area that seems ripe for a thoroughgoing look back at the various methodologies, to seek to improve the science of future abuse liability assessments.

Pre-Clinical Assessment of Reinforcing Behavior

The pivotal pre-clinical study was the study assessing whether monkeys would 'self-administer' pregabalin more than saline vehicle. There were two studies performed[5], each that used 4 monkeys While the relevance of the finding varies, the conclusion from the sponsor's slides seems sufficient: 'Pregabalin is transiently and sporadically self-administered at rates greater than vehicle but substantially lower than active comparators.' The sponsor asserts, in the same slide set, that this finding is 'well-described phenomena in the literature' but offers no reference in support. I'm left to conclude that there is some animal evidence of transient reinforcing behavior with pregabalin.

Clinical Assessment: Euphoria in the Clinical Trials and the Abuse Liability Study (Study '098')

Here again, while there is disagreement about how to interpret some aspects of the database, there are some things that are agreed on by both the CSS and the sponsor.

1. 'Euphoria' as an adverse event (AE) observed in the controlled trials

Both the sponsor and the CSS agree that Euphoria as an adverse event was reported by a higher percentage of patients taking pregabalin than patients not taking pregabalin[6]. The overall rate quoted by the sponsor for controlled trials was 3.7% compared with 0.5% of placebo patients[7]. I agree that the exact nature of this signal is not clear[8], but it is clear that for some patients in these trials pregabalin had significant CNS activity. This activity persisted for some considerable time after onset (median duration of euphoria was 7 days), but resolved during continued use of pregabalin. People who reported euphoria did not report it as an AE when presented with pregabalin a second time. The sponsor's conclusion that this is evidence that the 'euphoria' does not occur consistently in a given is somewhat problematic, since the data are for spontaneously reported AEs.

There's another important point to make about the appearance of euphoria as an adverse events in clinical trials. It seems that euphoria is an uncommon adverse event for approved drugs. Where it is reported in labeling, the rates appear to be lower than the rates reported for pregabalin.

2. Abuse Liability Study ('098')

The clinical trials, discussed above, found evidence of CNS activity for pregabalin in populations taking it for therapeutic intent (*i.e.*, euphoria). The clinical Abuse Liability Study looks for similar activity in a separate population: drug and alcohol abusers. As an abuser population, they're a 'sensitive' population to CNS activity of drugs, making it possible to use a smaller number of subjects (15 subjects in this case). This study used a standard design for studies of this kind: the new drug is compared with a scheduled product and placebo in a randomized, double blind, crossover study. The subjects are asked a series of questions about the effects of the test substances aimed at assessing the CNS properties of the new drug. The use of the 'positive' control (the controlled substance) in these studies allows a comparison with it and the new drug, but also provides a means to make sure the study is valid (that is, that is can detect a drug with CNS activity if it is present). In the present study, diazepam was used as the control, and was not differentiated from placebo on one scale (making that portion of the testing invalid). Overall, however, pregabalin and diazepam differentiated from placebo consistently. In this regard, the conclusions

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[5] Discussed in section 1.1.1.2 of the sponsor's Scientific Assessment of Abuse Potential and starting on page 16 of Dr. Bonson's review dated March 24, 2004. It is also summarized in the slides submitted by the sponsor for the October 1, 2004 briefing (slide 8).

[6] Discussed beginning on page 7 of Dr. Bonson's review dated March 24, 2004, and in section 1.1.1 of the sponsor's Scientific Assessment of Abuse Potential.

[7] The incidence does not order by dose, see Dr. Bonson's review dated March 24, 2004, table 1, page 8 of her review. However, she reported that the higher the initial dose (several of the trials titrated up to the stable dose), the higher the incidence of 'euphoria'.

[8] 'Euphoria' as an Adverse Event as a preferred term was composed of many other words used by investigators to describe their patient's sensations: high, stoned, elation, elevated mood and drugged among others. See the sponsor's list table 2.7.4 Appendix ALL.010 for full list.

drawn by the investigator who conducted the study are worth reviewing[9]. Dr. Johanson concluded that the testing for the low dose of pregabalin (200 mg) tested 'was similar to the profile for the 15-mg dose of diazepam in that the majority of the participants identified it as a sedative.' The high dose of pregabalin (450 mg) had more 'stimulant-like' effects than did high-dose diazepam, but resembled it in scales related to what Dr. Johanson called 'drug-taking behavior' (e.g., 'Good Drug Effect' and 'High')[10]. The effect of pregabalin had a slightly delayed onset relative to diazepam, but the delay was on the order of only an hour or so. I believe this study, with all its flaws, reinforces the findings of the larger patient database from the other clinical trials, and suggests that pregabalin has a potential for euphorigenic activity in susceptible populations.

There is another aspect of the study that bears comment. A drug with potent euphoric properties (as the high dose of pregabalin appears to have in this study) would have less of an abuse liability if that 'high' was paired consistently with a 'low'. Per the CSS analyses, this was not the case for pregabalin, and euphoria in many of the drug and alcohol abusers was not consistently coupled to any dysphoric signals.

3. Withdrawal/Habituation

Another aspect of the 8-factor analysis is determining if there is a withdrawal syndrome associated with the use of the drug (which would favor habituation). This is discussed in the reviews[11]. Here, I part somewhat from the conclusions of the CSS staff. While the pattern of adverse events that were reported following abrupt discontinuation of pregabalin are consistent with a withdrawal syndrome (*e.g.*, diarrhea, insomnia, headache), these events are reported at rates lower than that for a scheduled drug with a classic discontinuation syndrome[12]. This suggests a lower level of concern for pregabalin in this regard. The sponsor also administered a 'Physician Withdrawal Checklist' (PCW) to patients in a group of short-term trials and in one long-term study (8 months, study 088). The scores for all trials were <10, somewhat lower than those of scores associated with benzodiazepines (drugs with a well-described withdrawal syndrome). The sponsor ascribed the scores on the PCW to increases in anxiety as the patients came off a drug they viewed as 'effective'... whether or not this is true, a severe withdrawal syndrome does not appear to be a prominent feature of pregabalin. This, coupled with the evidence of tolerance to the euphoric effects of pregabalin with repeated doses (in animals and in the clinical trials), reduces my concerns about any risk of abuse following chronic use. There was also no evidence for dose-escalation (a potential sign of drug-seeking behavior) in the clinical trials. Overall, then, while there is evidence for a withdrawal syndrome with pregabalin, I believe it is less substantial than that of other drugs currently in Schedule IV, and is not coupled to evidence of dose-escalation in the clinical trials.

4. Miscellaneous CNS activities of Pregabalin

Pregabalin has other CNS activities than the changes in 'mood' discussed above. These appear not to be the subject of disagreement. For instance, pregabalin impaired task performance and prolonged time to task completion in healthy volunteers[13]. The CSS staff concluded that the former effect was synergistic with lorazepam when the two are administered together. These results add additional evidence of CNS activity for pregabalin.

4) Observed CNS Effects from other Non-Scheduled Drugs

The last, critical point that the sponsor has made is that there is a substantial published literature on the abuse evaluation of drugs. The sponsor has identified several drugs that are not scheduled but have some data the sponsor believes is similar to the signals seen with pregabalin. CSS also reviewed the data presented by the sponsor in their November 16, 2004 submission. The sponsor in their October 26, 2004 submission specifically raised the following drugs:

Buproprion

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[9] Abuse Liability Assessment of Pregabalin (CI-1008) in Recreational Sedative/Alcohol Users, by C. Johanson, Ph.D., submitted to NDA 21-446, page 24 to 26 of the report.

[10] See the discussion on page 23 of her review.

[11] The sponsor's NDA 21-446, section 2.5.5.6.5 (Dependence Potential, Tolerance and Withdrawal)

[12] See sponsor's slide set dated 10.1.04, slide 24.

[13] Study #1008-076 and #1008-078. See CSS consult on abuse potential of pregabalin by Dr. Bonson, dated 3.24.04.

Pfizer points out that bupropion has several features that would suggest that might suggest abuse potential, including enhanced self-administration in animals and liking in human abuse liability studies. CSS staff has reviewed the data for bupropion. In the human abuse liability study, bupropion exhibited less 'liking' than the positive control in the study (amphetamine), a finding that was interpreted as suggesting a lower level of risk for abuse. In addition, buproprion is a compound with a complex regulatory history with regard to scheduling. Various international bodies have recommended that it be scheduled.

Clonidine

Pfizer reports that clonidine enhanced self-administration in animals, a finding the CSS staff contested[14]. Clonidine is a product that was developed and approved as an antihypertensive. It has other prominent and dose-limiting effects (*e.g.*, hypotension) that would severely limit any notions of abuse. This is simply not a credible example to raise in this context.

Ephedrine/Pseudoephedrine

Pfizer reports that ephedrine causes enhanced self-administration in monkeys, at rates greater than placebo but less than the comparator (cocaine, amphetamine). Like clonidine, it has prominent physiological effects (tachycardia, hypertension, sweating) that would limit abuse. It is, however, structurally related to amphetamines and the full evidence of its abuse potential should be examined.

Dextromethorphan

Pfizer lays out substantial evidence that dextromethorphan has substantial abuse potential. In fact, there is credible evidence of its abuse in the U.S. today, including the mixing of powdered dextromethorphan with alcohol. It is exempted in the Controlled Substances Act from control, or it would certainly be considered for scheduling.

Diphenhydramine

Pfizer submitted portions of several studies that were not otherwise available to the CSS staff. Those portions suggested that diphenhydramine maintains increased self-administration in monkey and baboons when substituted for cocaine, but the papers were not available for review. The sponsor also reported clinical data from a human abuse liability study including diphenhydramine, diazepam, and placebo. In this study, the diazepam and diphenhydramine both had similar effects on various 'liking' scales, an observation Pfizer used to assert that 'human abuse liability studies have great sensitivity but low specificity and thus can have low predictive value for actual abuse in the community.' Unfortunately, diphenhydramine also had high scores on the dysphoria scale (especially 'did not like'), an effect not shared with diazepam. This would, of course, limit its attractiveness as a drug of abuse.

Gabapentin

Gabapentin is pharmacologically similar to pregabalin of course, and is not scheduled. Unfortunately for this argument, gabapentin is being diverted to illicit use (where it has been called 'Vitamin G'), and its potential for abuse is being re-evaluated[15].

Tramadol

This is another product with some features that resemble pregabalin in terms of the level of evidence of abuse potential at the time of approval. It is also not scheduled. It was approved with a risk management program, but unfortunately, diversion and abuse emerged almost immediately after marketing and has continued to be a problem. A recommendation to schedule tramadol is under active consideration by CSS and DEA.

Nicotine Nasal Spray (NNS)

Pfizer reports from the Advisory Committee on Nicotine Nasal Spray. The review staff and the Advisory committee recommended scheduling for NNS, a decision that was ultimately not followed. Dr. Bonson ascribes this to public policy (the desire not to have the product for smoking cessation harder to get than cigarettes).

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[14] See memorandum by Katherine Bonson, Ph.D., dated 11.16.04, page 6.

[15] See recent consultation by Office of Drug Safety, by Lopa Thambi, dated 9.17.2004. She concludes that there is inadequate AERS reporting data of illicit use for 'euphoric' purposes to warrant labeling changes.

To summarize, I think that none of these examples offered by the sponsor offer substantial support for a choice not to schedule pregabalin. Several of the drugs (clonidine, ephedrine, diphenhydramine) are relatively old and have prominent physiological effects that would limit their use in abuse Others present cautionary tales (*i.e.*, drugs that aren't schedule but have some evidence of abuse requiring additional measures): dextromethorphan and tramadol. Others, notably Gabapentin and bupropion we have some concerning signals, and simply don't know enough about their use post-marketing to know if a problem exists or not. None of these drugs, then, provide clear precedent to apply in this case.

5) Proposed Post-Marketing Surveillance to Detect Abuse Potential

There is relatively little to say about the possible use of post-marketing surveillance in the case of pregabalin. The CSS staff has looked to all of the tools available for post-marketing surveillance to better understand the use of psychoactive drugs after approval, but relying on postmarketing (as an alternative to scheduling) demands that there be less than 'substantial' evidence of abuse potential. As discussed above, based on the available data I do not believe this is the case for pregabalin. Additionally, for one prominent case where this tack was chosen (tramadol), the postmarketing experience has been problematic. While this is not a reason to 'avoid' the use of post-marketing surveillance in the present case, it does remind us how important it is to make the best scheduling choices possible I do believe the post-marketing risk assessment has an

SUMMARY

Based on the data summarized above, I believe there is a consistent, credible case that pregabalin possesses substantial potential risk for abuse. The case begins with pre-clinical data showing increased self-administration when pregabalin is first presented to monkey, an effect that wanes fairly quickly (which I take to likely reflect the development of tolerance). Clinically, a similar pattern is seen, with euphoria in patients and 'drug-liking' behavior in addicts when first presented with pregabalin. This 'drug-liking' behavior was seen using more than one metric of such behavior, and was similar to what was seen with the active control (diazepam). This clinical effect is not offset consistently by any dysphoric effects that would offset this effect of pregabalin. It is true that the onset of the euphoric actions for pregabalin are delayed in onset compared with diazepam, the difference (1 hour) would not be consequential if the drug were taken illicitly for its acute euphoric effects. This euphoric effect of pregabalin was not off-set by any consistently identified dysphoric effects that might mitigate concerns about abuse. Similarly, the development of tolerance with repeated doses (agreed to by all reviewers) would not protect against intermittent, acute use illicitly.

So, what is the best course given these data? First, I believe a strong case for substantial abuse potential exists for pregabalin, and scheduling under 21 USC 811 (c) is appropriate, based on the pharmacological properties of pregabalin observed in the clinical and pre-clinical trials. I do, however, disagree with the CSS staff regarding the placement of pregabalin into Schedule IV. The CSS staff recommendation to place pregabalin into Schedule IV is based largely on the abuse liability trial (098), where the effects of pregabalin were similar to those seen with diazepam in an addict population. I believe diazepam and pregabalin have other relevant differences, however, differences that reduce the abuse liability of pregabalin, and support its inclusion into Schedule V:

1) Data on the chronic effects of pregabalin that are less concerning than data for the drugs in Schedule IV. For pregabalin, there is rapid loss of 'euphoric' effect in the therapeutic trials, matching the rapid decline in self-administration in pre-clinical studies. As discussed above, I believe the data also suggest that there are fewer withdrawal effects following discontinuation of pregabalin than other products that are currently in Schedule IV (especially benzodiazepines). I recognize one important weakness of these data—we don't have data on whether abusers of pregabalin will become habituated or have a significant withdrawal syndrome, as all the data are from therapeutic trials. These data are almost never obtained pre-approval, and will need to come from post-marketing data collection.
2) Second, pregabalin is not related pharmacologically (by which is meant structurally) to products with known abuse liability (a point the sponsor has made repeatedly), in contrast to the other products listed in Schedule IV. The absence of this association does not guarantee that pregablin will be free from abuse potential (as I believe the 098 study supports the overall conclusion that there is a substantial risk). What it does is support a conclusion that the risk is lower than that for a novel benzodiazepines, with known association with products of known abuse potential in Schedule IV. From my perspective, this means that, given the other available data we can support a less restrictive scheduling decision (V), coupled with the post-marketing follow-up suggested by the sponsor. This will give us flexibility to respond appropriately as additional data are collected, either to deschedule the product or to increase the level of restriction on its use (i.e., reschedule to Schedule IV), depending on what we learn after pregabalin is marketed.
3) Finally, placement of pregabalin into Schedule V will not reduce our ability to detect abuse should it occur in the postmarketing, and to react accordingly.

Placing pregabalin into Schedule V would best balance the available data, indicating the need for scheduling, and the need to remain flexible to respond to post-marketing data as they emerge. It would

also make pregabalin available for its indicated purposes, an important therapeutic area in need of additional therapeutic options.

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/s/

Doug Throckmorton
12/20/04 10:11:09 PM
MEDICAL OFFICER

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Addendum to the Medical Officer Review of the NDA

NDA: 21-446
Drug Name: LYRICA (pregabalin) capsules
Sponsor: Pfizer, Inc.
Type of Submission: Response to request for information (made June 17 2004)
Date of Receipt: June 24, 2004
Reviewer: Mwango Kashoki, MD MPH
Team Leader: Celia Winchell, MD
Project Manager: Lisa Malandro

Additional evaluation of adverse events data

Review of the Applicant's data found that treatment with pregabalin was associated with peripheral edema. Whereas 6% of patients treated with pregabalin reported peripheral edema, only 2% of the placebo group reported this adverse event. The risk of peripheral edema was highest in patients with neuropathic pain (postherpetic neuralgia, 12%; pain associated with diabetic peripheral neuropathy, 9%) compared to other treatment populations (epilepsy, 4%; generalized anxiety disorder, 2%).

In addition to a history of postherpetic neuralgia and pain associated with diabetic peripheral neuropathy, other risk factors associated with peripheral edema were age > 65 years and a BMI ≥ 38 (patients with generalized anxiety disorder only). Another possible risk factor was patients' concomitant medication.

Oral hypoglycemics are one of the mainstays of treatment of diabetes. They include the insulin-sensitizing thiazolidinediones, which are ligands for peroxisome proliferator activated receptors (PPARs). Thiazolidinediones include pioglitazone, troglitazone, and rosiglitazone. 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. The results are provided in the tables that follow.

Table 1 shows that, 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 1: 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)

Table 2 (below) shows the frequency of edema, weight gain, and heart failure among patients in all controlled trials of pregabalin. The majority of the patients who took a PPAR comprised patients with DPN. Nevertheless, the table shows similar results as those seen 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.

Conclusion:
Concomitant treatment of pregabalin and PPARs appears to result in an additive effect, and possibly a synergistic effect, on peripheral edema. Concomitant treatment also may increase the risk of congestive heart failure.

Regulatory action:
The Sponsor should include language in the pregabalin label describing the increased risk of peripheral edema with concomitant use of a thiazolidinedione.

Table 2: Summary of Adverse Events of Heart Failure, Edema, and Weight Gain Controlled Trials – All Indications

	Number of Patients (%)				
Adverse Event	**Placebo**	**50 mg/day PGB**	**75 mg/day PGB**	**150 mg/day PGB**	**200 mg/day PGB**
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, Jun 23 2004, NDA 21-446)

Table 2 (continued): Summary of Adverse Events of Heart Failure, Edema, and Weight Gain Controlled Trials – All Indications

Adverse Event	Number of Patients (%) 300 mg/day PGB	400 mg/day PGB	450 mg/day PGB	600 mg/day PGB	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, Jun 23 2004, NDA 21-446)

CC: Original IND, HFD-170 Division File, B. Rappaport, Mwango A. Kashoki, Lisa Malandro (Project Manager)

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/s/

Mwango Kashoki
7/1/04 04:47:38 PM
MEDICAL OFFICER

You've ok'd this for DFS

Celia Winchell
7/16/04 04:47:49 PM
MEDICAL OFFICER
I concur with Dr. Kashoki.

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

MEMORANDUM

DATE: June 3, 2004

TO: File, NDA 21-446

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

RE: Supervisory Review of NDA 21-445
Lyrica (pregabalin)
Pfizer

1 BACKGROUND

NDA 21-446 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 has been accorded priority review status, and therefore, the first action on this application will address specifically the safety and efficacy of Pregabalin in the treatment of the pain associated with diabetic neuropathy.

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.

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 studies in the application vary somewhat from the current recommendations, notably with respect to duration. In addition, the Division agreed to allow the sponsor to defer until Phase 4 the evaluation of nerve conduction velocity/neural integrity, now required as a safety assessment for neuropathic pain drugs, because partial clinical hold imposed late in development delayed the conduct of these studies. These agreements were made in view of the drug's potential to meet an unmet medical need for a serious medical condition that lacks other approved treatments.

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

This application is based on the available results for 11 US controlled clinical trials, 16 non-US controlled clinical trials, 1 uncontrolled non-US clinical study, and pharmacokinetic data from 20 clinical trials. The clinical studies of the effectiveness and

safety of this product in the diabetic neuropathy population, as well as safety information from the post-herpetic neuralgia population 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 Gerard Boehm, M.D. The application has also been reviewed by Ling Chen, 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. In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

2 EFFECTIVENESS

2.1 Overview

Evidence of efficacy has been submitted in the clinical studies 1008-014; 1008-029, and 1008-131. Secondary analyses providing additional supportive evidence of effectiveness for selected doses and regimens have been submitted in clinical study 1008-149. A non-supportive study using both placebo and active control (Study 1008-040) provided no support for efficacy claims. An additional study halted early due to the imposition of clinical hold was not analyzed for efficacy.

The table below briefly summarizes the features of the studies reviewed for efficacy.

Protocol # and Title	Design
1008-014 "A double blind, placebo-controlled trial of pregabalin for treatment of painful diabetic peripheral neuropathy"	29 centers (US and Canada), randomized, double-blind, placebo-controlled, parallel groups **N** = 246 **Dose**: 150 vs 600 mg/day vs placebo (given in 3 divided doses, TID) **Duration**: 8 weeks (2-week titration, 6 weeks fixed dose phase) **Result: Evidence of efficacy for 600 mg/day, given as three divided doses with 2 week titration.** **Some support for 150 mg/day based on secondary analyses.**
1008-029 "A 5-week, double-blind, placebo-controlled trial of 3 dosages of pregabalin (75, 300, and 600 mg/day) for treatment of patients with diabetic peripheral neuropathy"	45 US centers, randomized, double-blind, placebo-controlled, parallel groups N = 337 **Dose:** 75 vs 300 vs 600 mg/day vs placebo (given in 3 divided doses, TID) **Duration:** 5 weeks (1-week titration*, 4-week fixed dose period) *600 mg group only; others not titrated **Result: Evidence of efficacy for 300 mg/day, given as three divided doses, and 600 mg/day, given as three divided doses with 1 week titration.**
1008-131 "An 8-week, double-blind, placebo-controlled trial of pregabalin (300 mg/day) for relief of pain in patients with painful diabetic peripheral neuropathy"	25 US centers, randomized, double-blind, placebo-controlled, parallel groups N = 146 **Dose:** 300 mg/day vs placebo (given in 3 divided doses, TID) **Duration:** 8 weeks (no titration) **Result: Evidence of efficacy for 300 mg/day, given as three divided doses without titration.**
1008-149 "A 12-week, randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) for relief of pain associated with Diabetic Peripheral Neuropathy"	58 centers (Europe, Australia, South Africa), randomized, double-blind, placebo-controlled, parallel groups N = 384 **Dose:**150 vs 300 vs 600 mg/day* vs placebo (given in 2 divided doses, BID) **Duration:** 12 weeks (1-week titration, 11 weeks fixed dose phase) *600 mg used only in patients with CrCl >60 mL/min **Result: Not supportive based on primary analyses by reviewer. Some support for 600 mg/day in secondary analyses.**
1008-040 "A placebo-controlled trial of pregabalin and amitriptyline for treatment of painful diabetic peripheral neuropathy"	49 centers (Europe, Australia, and South Africa), randomized, double-blind, placebo-controlled, parallel groups N = 256 **Dose:** 600 mg/day vs amitriptyline 75 mg/day vs placebo (given in 3 divided doses, TID) **Duration**: 9 weeks (2 weeks titration, 6 weeks at fixed dose, 1 week withdrawal) **Result: not supportive; some evidence of efficacy for amitriptyline providing assurance of assay sensitivity.**

The table below summarizes the results of the three studies demonstrative of efficacy, showing the change in pain score and the responder rate based on reviewers' computation of these figures:

Protocol	RxGrp	Δ pain score	P value	% responders	P value
014	PBO	-0 98		12.9%	
	600	-1 99	0.0008	29.3%	.0041
029	PBO	-1.26		16.5%	
	300	-2.10	.005	38.3%	.0005
	600	-2.20	.003	36.6%	.0010
131	PBO	-0 59		7.14%	
	300	-1.79	0.0005	32.9%	.0233

Note: only treatment arms showing superiority over placebo are illustrated

2.2 Population

All studies had similar inclusion and exclusion criteria. To be eligible, subjects were required to be adults with a diagnosis of diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years, hemoglobin A1c levels ≤11%, with a minimum pain score of at least 40 mm on the VAS of the short-form McGill Pain Questionnaire at baseline and at randomization, and an average daily pain score of at least 4 on a Likert scale over the week prior to randomization. Subjects were excluded for other significant diseases and conditions, including but not limited to abnormal ECG, creatinine clearance below 60 mL/min, and depressed white blood cell count. (Study 1008-149 allowed enrollment of subjects with creatinine clearance of at least 30 mL/min, but only subjects with creatinine clearance of at least 60 mL/min could be treated with the 600 mg/day dose.) Notably, subjects with previous non-response to another, structurally similar, Pfizer product used commonly off-label for DPN, gabapentin (Neurontin), were excluded from participation in studies 1008-029, 1008-131, and 1008-149, while subjects with previous non-response to either gabapentin or amitriptyline were excluded from Study 1008-040. After partial clinical hold was imposed, the protocol for Study 1008-149 was amended to delete this exclusion.

2.3 Design and Endpoints

The designs differed slightly in duration, as well as timing and frequency of efficacy assessments. Studies 1008-014 and 1008-029 featured three on-treatment visits at 2 week intervals for assessment of efficacy. Study 1008-131 featured four on-treatment visits at intervals of 2-3 weeks. Study 1008-040 incorporated two visits during the fixed-dose phase, occurring at three-week intervals, while Study 1008-149 called for three monthly visits during the fixed-dose phase. All studies required subjects to complete daily diaries of pain ratings and ratings of the degree to which pain interfered with sleep.

The following measures of patient pain and function were used in all studies:

- *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)
- *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

The Profile of Mood States (POMS), EuroQOL, and Hospital Anxiety and Depression Scale were also used in some studies.

2.4 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 available 7 pain diary entries while the patient was on medication. 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 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. However, Drs. Kashoki and Chen identified significant flaws in the sponsor's analysis and completed their own analysis of the data using the Agency's preferred approach.

As noted in Dr. Kashoki's review:

[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 fails to take into account differential drop-out from treatment groups. The FDA's recommended BOCF analysis is preferred since it does take differential drop-out into account. Unfortunately, the Sponsor did not appropriately conduct the BOCF analysis. BOCF required that the Sponsor 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 Sponsor 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 5 weeks of treatment, but completed the Week 6 (V5/Termination) assessments, were incorrectly labeled as study completers and their final mean scores used in the analysis.

The Statistical Reviewer, Dr. Ling Chen, conducted a BOCF analysis on the ITT population. In this analysis, the primary endpoint was defined as follows:

- If a patient completed the full duration of the study, and provided pain scores for the all 7 days of the last week of the study, then the endpoint was defined as the mean of the last week's pain diary scores.
  - If a patient completed the full duration of the study, but had missing pain scores during the last week of the study, the missing data was replaced with the mean of the baseline scores. The mean endpoint score was then the mean of these and the actual recorded pain scores.
- If a patient dropped out of the study before the last week of the study, then the endpoint was the mean of the baseline scores.

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 Chen. The results of other analyses are documented in the primary reviews.

2.5 Results

The results of the five efficacy trials, as documented in Dr. Kashoki's review, are briefly summarized below:

2.5.1 Protocol 1008-014: A double blind, placebo-controlled trial of pregabalin for treatment of painful diabetic peripheral neuropathy

As noted above, this was a randomized, double-blind, placebo-controlled, parallel groups study conducted at 26 centers in US and 3 centers in Canada. A total of 396 subjects with diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years, hemoglobin A1c levels ≤11%, meeting minimum requirements for baseline levels of pain, were enrolled in the baseline phase, and 246 subjects were subsequently randomized to pregabalin 150 mg/day vs 600 mg/day vs placebo (given in 3 divided doses) and treated for 8 weeks (2-week titration, 6 weeks fixed dose phase).

2.5.1.1 Demographics and Patient Disposition

The demographics of the treatment groups (patients randomized) at baseline differed somewhat with respect to diabetic history and treatment. In the placebo group, 85% had Type II diabetes, while in the pregabalin 600 mg/day group, 98% had Type II diabetes.

More of the placebo patients used insulin (55%) than in the pregabalin groups (38% each), and fewer used oral hypoglycemics (61% in placebo group vs. 78% in the pregabalin 600 mg/day group). Pain scores, however, were similar at baseline.

Patient disposition is illustrated in the table below, adapted from Dr. Kashoki's review:

Patient Disposition in Study 1008-014, Number (%) of Patients

Disposition	Placebo	Pregabalin 150 mg/day	Pregabalin 600 mg/day	All patients
Entered baseline phase				396
Completed baseline phase				246 (62%)
Withdrawn during baseline phase				150 (38%)
Adverse Event				3 (1%)
Did not meet criteria				135 (34.%)
Other*				12 (3%)
Randomized	85	79	82	246
Completed study	72 (85%)	75 (95%)	72 (88%)	219 (89%)
Withdrawn during treatment phase	13 (15%)	4 (5%)	10 (12%)	27 (11%)
Adverse event	4 (5%)	2 (3%)	7 (9%)	13 (5%)
Lack of efficacy	1 (1%)	0 (0)	1 (1%)	2 (1%)
Other**	8 (9%)	2 (3%)	2 (2%)	12 (5%)

(Sponsor's Table 11, RR 720-04236, 1008-014, P. 36)

*

** 4 patients were lost to follow-up (3 in the placebo group, 1 in the pregabalin 150 mg/day group)
3 patients withdrew consent (1 in the placebo group, 2 in the pregabalin 150 mg/day group)
1 patient (pregabalin 600 mg/day) began prohibited pain medication due to facial trauma
1 patient (placebo) had significant abnormalities on fundoscopic examination
1 patient (placebo) withdrew early due to jury duty
1 patient (placebo) withdrew due to familial responsibilities
1 patient (pregabalin 600 mg/day) entered the open-label study early

Protocol violations deemed significant by the primary reviewer included two subjects in the pregabalin 600 mg/day group who did not complete double-blind treatment but were apparently not classified as dropouts. In addition, nine subjects randomized to pregabalin 600 mg/day and two randomized to pregabalin 150 mg/day did not have a stable dose of medication during the protocol-specified fixed-dose phase. One placebo subject and one pregabalin 600 mg/day subject did not meet the minimum pain requirement for entry. Use of prohibited pain medication was also noted in three placebo subjects, two pregabalin 150 mg/day subjects, and one pregabalin 600 mg/day subject.

Use of prohibited pain medication would tend to bias the study in favor of the affected arm, but the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is not expected to have a significant impact on the interpretation of the results.

2.5.1.2 Efficacy Results

2.5.1.2.1 Mean Pain Scores at Endpoint

The sponsor's analysis, using LOCF imputation of missing values, showed improvement in mean pain scores for all three treatment groups, with the 600 mg/day pregabalin group showing the greatest decrease. The ANCOVA results showed that only the pregabalin 600 mg/day endpoint mean pain score was significantly better than that of the placebo group.

Mean pain scores at endpoint in Study 1008-014, using LOCF (Sponsor's Analysis)

		Placebo	PGB 150 mg/d	PGB 600 mg/d
Time point	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline	85	6.9 (1.6)	6.5 (1.3)	6.7 (1.7)
Endpoint	82	5.8 (2.2)	4.9 (2.2)	4.3 (2.7)
Change	82	-1.2 (1.8)	- 1.5 (1.8)	- 2.4 (2.4)

PGB: pregabalin SD: standard deviation
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
(Adapted from Sponsor's Table 12, RR 720-04326, P 37)

The sponsor also conducted an analysis identified as a BOCF analysis, which yielded similar results to the primary analysis: the scores of the pregabalin 600 mg/day group were significantly better than the scores for placebo group ($p = 0.0002$). However, as described above, Drs. Kashoki and Chen noted that the BOCF analysis had failed to account for all patients with missing data and to adjust accordingly. Therefore, the reviewers undertook a BOCF analysis using the ITT population which yielded the following results:

Mean pain scores at endpoint in Study 1008-014, using BOCF (Reviewers' Analysis)

		Placebo	PGB 150 mg/day	PGB 600 mg/day
Time point	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline*	85	6.90 (1.58)	6.43 (1.32)	6.73 (1.68)
Endpoint	85	5.92 (2.18)	5.01 (2.10)	4.74 (2.61)
Change	85	-0.98 (1.71)	-1.43 (1.66)	-1.99 (2.12)

* Baseline = the average of last 7 days prior to randomization
** Endpoint = the average of the last 7 days of the treatment period

The pairwise comparison of 600 mg/day vs placebo achieved statistical significance (.0008), but the comparison of 150 mg/day vs placebo did not.

2.5.1.2.2 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, the proportion of

responders in the 600 mg/day group (39%) was greater than that of the pregabalin 150 mg/day group (19%) or the placebo group (15%), and was significantly different from placebo (p = 0.002). The proportion of responders in the pregabalin 150 mg/day group was not significantly different from placebo. However, the calculation of change from baseline for the purposes of defining a responder in this analysis used the LOCF imputation strategy, which is considered inappropriate for this study. Therefore, Drs. Kashoki and Chen 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 unshaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this data presentation, 13% of the placebo group, 18% of the pregabalin 150 mg/day group, and 30% of the 600 mg/day group meet the definition of responder (50% reduction in pain). The effect of 600 mg/day is further highlighted by the differences in proportions of patients experiencing even greater degrees of improvement in pain. Considering either the overall responder rate, or an analysis which considered the difference in median percentage change from baseline (taking into account all degrees of response), statistical significance was demonstrated in the pairwise comparisons of 600 mg/day vs. placebo (p=.0041 for categorical responder analysis and p=.0003 for comparisons of median percentage change from baseline), but the comparison of 150 mg/day vs. placebo achieved statistical significance only when all degrees of improvement were taken into account (p=.0074 for comparison of median percentage change from baseline).

Percentage change in endpoint mean pain score by dose in Study 1008-014, BOCF analysis

Total	**85**	**79**	**82**
Pain Score	**Placebo**	**Pregabalin 150 mg/day**	**Pregabalin 600 mg/day**
	N (%)	**N (%)**	**N (%)**
Any increase	21 (24.71)	12 (15.19)	7 (8.54)
No change	12 (14.12)	7 (8.86)	12 (14.63)
> 0% decrease	52 (61.18)	60 (75.95)	63 (76.83)
≥ 10 % decrease	39 (45.88)	49 (62.03)	52 (63.41)
≥ 20 % decrease	25 (29.41)	36 (45.57)	41 (50.00)
≥ 30 % decrease	18 (21.18)	26 (32.91)	40 (48.78)
≥ 40 % decrease	15 (17.65)	19 (24.05)	33 (40.24)
≥ 50 % decrease	***11 (12.94)***	***14 (17.72)***	***24 (29.27)***
≥ 60 % decrease	6 (7.06)	11 (13.92)	16 (19.51)
≥ 70 % decrease	5 (5.88)	6 (7.59)	11 (13.41)
≥ 80 % decrease	4 (4.71)	4 (5.06)	9 (10.98)
≥ 90 % decrease	1 (1.18)	1 (1.27)	4 (4.88)
= 100% decrease	0 (0.00)	1 (1.27)	2 (2.44)

An additional analysis approach was also taken by Dr. Chen. In her analysis, patients who used rescue pain medication during the final week of the study were identified, and the pain score on the day rescue was used was replaced with the maximum baseline pain score, to represent the assumption that use of rescue pain medication signals an intolerable level of pain. Using this imputation strategy, there were more subjects in the

pregabalin 600 mg/day group (23.17%) who were treatment responders compared to the placebo group (8.24%). A total of 17.72% of the pregabalin 150 mg/day group were treatment responders, which was appreciably different from placebo.

2.5.1.2.3 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; and POMS. At endpoint, the differences in sensory, affective, and total pain scores of the SF-MPQ were significantly significant for the pregabalin 600 mg/day group compared to placebo, but not for the pregabalin 150 mg/day group. End point and weekly mean sleep interference score were significantly better for patients receiving 600 mg/day pregabalin than for those patients receiving placebo. The 150 mg/day treatment group was not significantly different from the placebo group. On the global impression assessments, more patients (52%) in the pregabalin 600 mg/day group reported scores of "very much improved" or "much improved" compared to patients in the pregabalin 150 mg/day and placebo groups (36% and 28%, respectively). Similar findings were noted for the investigator ratings of patient improvement. The differences between the pregabalin 600 mg/day and placebo groups reached statistical significance. SF-36 did not reveal differences between pregabalin and placebo in any domain other than bodily pain, and POMS scores did not reveal significant differences in changes from baseline.

2.5.1.3 Efficacy Conclusion, Study 1008-014

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 2-week titration period.

2.5.2 Study 1008-029: A 5-week, double-blind, placebo-controlled trial of 3 dosages of pregabalin (75, 300, and 600 mg/day) for treatment of patients with diabetic peripheral neuropathy

As noted above, this was a randomized, double-blind, placebo-controlled, parallel groups study conducted at 45 centers in the U.S. A total of 578 subjects with diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years, hemoglobin A1c levels ≤11%, meeting minimum requirements for baseline levels of pain, were enrolled in the baseline phase, and 338 subjects were subsequently randomized to pregabalin 75 mg/day, 300 mg/day, 600 mg/day, or placebo, given in three divided daily doses, and treated for 5 weeks (1 week titration, 4 week fixed dose period).

2.5.2.1 Demographics and Patient Disposition

The demographics of the treatment groups (patients randomized) at baseline differed somewhat with respect to diabetes history and treatment. In the placebo group, 86% had Type II diabetes, while in the pregabalin groups, 92%-94% had Type II diabetes. Mean duration of diabetes was, perhaps consequently, longer (11±10 yrs) in the placebo group compared to the active groups (about 9±years), and more of the placebo patients used insulin (48%) than in the pregabalin groups (39-41%) Pain scores, however, were similar at baseline.

Patient disposition is illustrated in the table below, adapted from Dr. Kashoki's review:

Subject Disposition in Study 1008-029

DISPOSITION N (%)	Placebo	Pregabalin (mg/day) 75	300	600	All Patients
Entered Baseline Phase					578
Completed Baseline Phase					338 (59%)
Withdrawn During Baseline.					240 (42%)
Adverse Event					2 (<1%)
Did Not Meet Criteria					212 (37%)
Other					26 (5%)
Randomized	97	77	82	82	338
Intent-to-Treat	97	77	81	82	337
Completed Study	89 (92%)	67 (87%)	79 (94%)	70 (86%)	302 (90%)
Withdrawn During Treatment Phase:	8 (8%)	10 (13%)	5 (6%)	12 (15%)	35 (10%)
Adverse Event	3 (3%)	2 (3%)	3 (4%)	10 (12%)	18 (5%)
Lack of Compliance	1 (1%)	1 (1%)	0	0	2 (1%)
Lack of Efficacy	2 (2%)	4 (5%)	0	0	6 (2%)
Other	2 (2%)	3 (4%)	2 (3%)	2 (2%)	9 (3%)
Entered Open Label	88 (91%)	67 (87%)	70 (86%)	70 (85%)	295 (85%)

(Sponsor's Table 13, RR 720-04242, 1008-029, P 45)

Protocol violations deemed significant by the primary reviewer included:

		Pregabalin		
	Placebo	75 mg/day	300 mg/day	600 mg/day
Did not meet minimum pain score for entry	3 (3%)	0	2 (2%)	2 (2%)
Another potential cause of neuropathy		2 (3%)		1 (1%)
Prohibited analgesics	4 (4%)	2 (3%)	1 (1%)	4 (5%)

Some violations (e.g. patients without minimum pain score required for entry) would tend to decrease the likelihood of the treatment showing efficacy, while others (prohibited analgesics) might give spurious positive results. The effect of enrolling patients with other possible causes of neuropathy is unknown, as it cannot be predicted whether these patients would be more or less likely to respond to pregabalin than patients with diabetic neuropathy. However, the distribution of violations, both those that bias a trial in favor of a particular arm and those that bias against, appears to be roughly equal across the arms of primary interest (i.e., placebo vs. 600 mg/day).

2.5.2.2 Efficacy Results

2.5.2.2.1 Mean Pain Scores at Endpoint

The sponsor's analysis, using LOCF imputation of missing values, showed that the endpoint mean pain score for the pregabalin 75 mg/day group [5.1 (± 2.5)] was not statistically significant from the placebo group [5.2 (± 2.2)] (p = 0.6267). However, there was a significant difference in the endpoint mean pain score for the pregabalin 300 mg/day group [3.6 (± 2.1)] and the pregabalin 600 mg/day group [3.5 (± 2.3)] compared to placebo (p = 0.001 each). The table below illustrates these data.

Mean pain scores at endpoint in Study 1008- 029, using LOCF (Sponsor's Analysis)

Time Point	Placebo		Pregabalin 75 mg/day		Pregabalin 300 mg/day		Pregabalin 600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	97	6.6 (1.5)	77	6.7 (1.3)	81	6.2 (1.4)	82	6.2 (1.5)
Endpoint	97	5.2 (2.2)	77	5.1 (2.5)	81	3.6 (2.1)	81	3.5 (2.3)
Change	97	-1.4 (1.9)	77	-1.5 (2.1)	81	-2.5 (1.9)	81	-2.7 (2.3)

(Adapted from Sponsor's Table 14, RR 720-04242, 1008-029, P. 47)

The sponsor also conducted an analysis identified as a BOCF analysis, which yielded results similar to the primary analysis. Pregabalin 300 mg/day and 600 mg/day, but not 75 mg/day, were statistically significantly superior to placebo in this analysis.

However, as described above, Drs. Kashoki and Chen noted that the BOCF analysis had failed to account for all patients with missing data and to adjust accordingly. Therefore, the reviewers undertook a BOCF analysis using the ITT population which yielded the following results:

Mean pain scores at endpoint in Study 1008-029, using BOCF (Reviewers' Analysis)

Time point	N	Placebo Mean (SD)	PGB 75 mg/day Mean (SD)	PGB 300 mg/day Mean (SD)	PGB 600 mg/day Mean (SD)
Baseline*		6.56 (1.57)	6.68 (1.32)	6.09 (1.38)	6.26 (1.44)
Endpoint**		5.30 (2.21)	5.32 (2.34)	3.99 (2.04)	4.06 (2.36)
Change		-1.26 (1.95)	-1.35 (1.94)	-2.10 (1.99)	-2.20 (2.24)

* Baseline = the average of last 7 days prior to randomization

** Endpoint = the average of the last 7 days of the treatment period

In the BOCF analysis without imputation for use of rescue mediation, the pregabalin 300- and 600 mg/day groups had significantly improved mean pain scores at endpoint compared to the placebo group (p = 0.005 and 0.003 respectively). There was no statistically significant difference between the pregabalin 75 mg/day and placebo groups.

2.5.2.2.2 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, the proportion of responders in the placebo group was 18%, while the responder rate in the active treatment groups were 22% in the 75 mg/day group, 46% in the 300 mg/day group, and 48% in the 600 mg/day group. The comparisons to placebo reached statistical significance for the 300 mg/day and 600 mg/day groups (p = .001 each) but not for the 75 mg/day group (p = 0.407).

However, the calculation of change from baseline for the purposes of defining a responder in this analysis used the LOCF imputation strategy, which is considered inappropriate for this study. Therefore, Drs. Kashoki and Chen 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 unshaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this data presentation, 16% of the placebo group, 15% of the pregabalin 75 mg/day group, 31% of the pregabalin 300 mg/day group, and 30% of the pregabalin 600 mg/day group met the definition of responder (50% reduction in pain). The effect of pregabalin, 300 or 600 mg/day, is further highlighted by the differences in proportions of patients experiencing even greater degrees of improvement in pain. Considering either the overall responder rate, or an analysis which considered the difference in median percentage change from baseline (taking into account all degrees of response), statistical significance was demonstrated in the pairwise comparisons of 600 mg/day vs. placebo (p=.0005 for categorical responder analysis and p=.0003 for comparisons of median percentage change from baseline), and 300 mg/day vs. placebo (p=.0010 for categorical responder analysis and p=.0009 for comparisons of median percentage change from baseline), but not 75 mg/day vs. placebo.

Percentage change in endpoint mean pain score by dose: BOCF analysis (Protocol 1008-029)

Total Pain Score	97 Placebo N (%)	77 Pregabalin 75 mg/day N (%)	81 Pregabalin 300 mg/day N (%)	82 Pregabalin 600 mg/dat N (%)
Any increase	15 (15.46)	12 (15.58)	8 (9.88)	5 (6.10)
No change	20 (20.62)	18 (23.38)	12 (14.81)	15 (18.29)
> 0% decrease	62 (63.92)	47 (61.04)	61 (75.31)	62 (75.61)
≥ 10 % decrease	49 (50.52)	40 (51.95)	56 (69.14)	59 (71.95)
≥ 20 % decrease	36 (37.11)	35 (45.45)	48 (59.26)	50 (60.98)
≥ 30 % decrease	28 (28.87)	26 (33.77)	42 (51.85)	41 (50.00)
≥ 40 % decrease	20 (20.62)	19 (24.68)	36 (44.44)	35 (42.68)
≥ 50 % decrease	***16 (16.49)***	***15 (19.48)***	***31 (38.27)***	***30 (36.59)***
≥ 60 % decrease	13 (13.40)	9 (11.69)	19 (23.46)	24 (29.27)
≥ 70 % decrease	8 (8.25)	5 (6.49)	13 (16.05)	14 (17.07)
≥ 80 % decrease	4 (4.12)	5 (6.49)	7 (8.64)	10 (12.20)
≥ 90 % decrease	1 (1.03)	1 (1.30)	4 (4.94)	4 (4.88)
= 100% decrease	1 (1.03)	0 (0.00)	1 (1.23)	4 (4.88)

An additional analysis approach was also taken by Dr. Chen. In her analysis, patients who used rescue pain medication during the final week of the study were identified, and the pain score on the day rescue was used was replaced with the maximum baseline pain score, to represent the assumption that use of rescue pain medication signals an intolerable level of pain. Using this imputation strategy, approximately 40% of subjects in all treatment groups had no change or an increase in their pain. However, more patients in the pregabalin 300 and 600 mg/day groups were treatment responders (27% and 20%, respectively), compared to patients in the placebo and pregabalin 75 mg/day groups (16% and 17% respectively). Imputation for use of rescue medication lowered the proportion of responders in all groups.

2.5.2.2.3 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; and POMS. At endpoint, the differences in VAS, PPI, sensory, affective, and total pain scores of the SF-MPQ were significantly significant for the pregabalin 300 mg/day and 600 mg/day group compared to placebo, but not for the pregabalin 75 mg/day group. End point and weekly mean sleep interference score were significantly better for patients receiving 300 mg/day or 600 mg/day pregabalin than for those patients receiving placebo. The 75 mg/day treatment group was not significantly different from the placebo group. On the global impression assessments, pregabalin 300 mg/day and 600 mg/day were statistically significantly superior to placebo while pregabalin 75 mg/day was not. SF-36 did not reveal differences between pregabalin and placebo in any domain other than

social functioning (600 mg/day and 300 mg/day superior to placebo) and vitality (300 mg/day and 75 mg/day superior to placebo). Note that adjustments for multiple comparisons were not made. POMS scores did not reveal significant differences in changes from baseline

2.5.2.3 Efficacy Conclusion, Study 1008-029

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 6 day titration period and for pregabalin, 100 mg t.i.d. (300 mg/day given as three divided doses), without titration.

2.5.3 Protocol 1008-040: A placebo-controlled trial of pregabalin and amitriptyline for treatment of painful diabetic peripheral neuropathy

As noted above, this was a randomized, double-blind, placebo-controlled, parallel groups study conducted at 49 centers in Europe, Australia, and South Africa. A total of 357 subjects with diabetic, distal, symmetrical, sensorimotor polyneuropathy for at least one year, hemoglobin A1c levels ≤11%, meeting minimum requirements for baseline levels of pain, were screened and 256 were subsequently randomized to pregabalin 600 mg/day, amitriptyline 75 mg/day, or placebo and treated for 9 weeks, comprising 2 weeks of titration, 6 weeks of stable dosing, and 1 week of taper.

2.5.3.1 Demographics and Patient Disposition

The demographics of the treatment groups (patients randomized) at baseline differed somewhat with respect to sex and age distribution. In the amitryptiline group, over 63% of the subjects were male, while the pregabalin group was more evenly distributed (52% male, 48% female). In the placebo group, 57% of subjects were male. The amitriptyline group also had the lowest enrollment of subjects ≥65 years, with 30%. The pregabalin and placebo groups enrolled 42% and 44% elderly subjects, respectively. With respect to diabetes history, 83% of the amitriptyline group had Type I diabetes while 87-88% of the pregabalin and placebo groups had Type I diabetes. The baseline mean pain score was slightly higher in the pregabalin group (6.9) than in the placebo (6.3) or amitriptyline (6.4) groups.

Patient disposition is illustrated in the table below, adapted from Dr. Kashoki's review:

Subject Disposition, Protocol 1008-040

Disposition N (%)	Placebo	Pregabalin	Amitriptyline	All Patients
Entered Baseline Phase				357
Completed Baseline Phase				256 (71.7)
Withdrawn During Baseline Phase:				101 (28.3)
Adverse Event				1 (0.3)
Did not meet entry criteria				84 (23.5)
Other/administrative reasons				16 (4.5)
Randomized	81	87	88	256
Intent-to-treat	81	86	87	254
Completed Titration and Fixed-Dose Phase	62 (76.5)	62 (72.1)	64 (73.6)	188 (74.0)
Withdrawn during Titration/Fixed Dose Phase:	19 (23.5)	24 (27.9)	23 (26.4)	66 (26.0)
Adverse Event	4 (4.9)	11 (12.8)	16 (18.4)	31 (12.2)
Lack of compliance	2 (2.5)	4 (4.7)	2 (2.3)	8 (3.1)
Lack of Efficacy	9 (11.1)	7 (8.1)	3 (3.4)	19 (17.5)
Other	4 (4.9)	2 (2.3)	2 (2.3)	8 (3.1)
V7/Follow-up, Not Done	9 (11.1)	14 (16.3)	15 (17.2)	38 (15.0)
Completed Withdrawal Phase	65 (80.2)	66 (76.7)	66 (75.9)	197 (77.6)
Withdrawn During Withdrawal Phase:	7 (8.6)	6 (7.0)	6 (6.9)	19 (7.56)
Adverse Event	1 (1.2)	0 (0)	0 (0)	1 (0.4)
Lack of Compliance	1 (1.2)	2 (2.3)	0(0)	3 (1.2)
Other	5 (6.2)	4 (4.7)	6 (6.9)	15 (5.9)
Entered Open Label	60 (74.1)	66 (76.7)	63 (72.4)	189 (74.4)

(Sponsor's Table 8, RR 720-30054 1008-040, P. 63)

Protocol violations deemed significant by the primary reviewer included two subjects in the amitriptyline group and one in the placebo group who used prohibited medications during the study; and two subjects in the placebo group and one in active group who did not meet the minimum pain criteria for entry. These violations would tend to operate in opposite directions in potential bias of the study; therefore they are unlikely to have an impact on interpretation of the data.

2.5.3.2 Efficacy Results

2.5.3.2.1 Mean Pain Scores at Endpoint

The sponsor's analysis, using LOCF imputation of missing values, showed that the endpoint mean score for the pregabalin group (4.1 (± 2.4) was not statistically different from the placebo group (4.5 (± 2.4)) ($p = 0.082$). There was a significant difference between endpoint mean score for the amitriptyline group compared to the placebo group.

There was an apparent improvement (decrease) in mean pain scores from baseline to endpoint across all treatment groups.

Mean pain scores at endpoint in Study 1008- 040, using LOCF (Sponsor's Analysis)

	Placebo		Pregabalin 600 mg/day		Amitriptyline 75 mg/day	
Time Point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	80	6.3 (1.6)	86	6.9 (1.6)	87	6.4 (1.6)
Endpoint	81	4.5 (2.4)	86	4.1 (2.4)	87	3.6 (2.4)
Change	80	-1.8 (2.5)	86	-2.8 (2.5)	87	-2.8 (2.6)

(Adapted by Primary Reviewer from Sponsor's Tables 12 and 13, RR 720-30054 1008-040, P. 74)

Additional analyses illustrated that the mean pain scores (using LOCF) were lower for both active treatment groups than for the placebo group at each week of treatment; mean scores were also lower for amitriptyline than for pregabalin at each week.

The sponsor also conducted an analysis identified as a BOCF analysis, which showed that neither the pregabalin nor the amitriptyline groups' mean pain score at endpoint was statistically different from the placebo group (p = 0.4697 and 0.0611, respectively).

The reviewers did not reanalyze the data using the preferred definition of BOCF, because the sponsor's less conservative approach did not demonstrate an effect of pregabalin.

2.5.3.2.2 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, that 30% of placebo-treated patients, 40% of pregabalin-treated patients, and 46% of amitriptyline-treated patients were responders. There was no statistically significant difference in the proportion of responders between the pregabalin and placebo groups (p = 0.239), but there was between the amitriptyline and placebo groups (p = 0.034).

The reviewers did not reanalyze the data using BOCF imputation, because the sponsor's approach did not demonstrate an effect of pregabalin.

2.5.3.2.3 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; and Hospital Anxiety and Depression Scale (HADS).

On the SF-MPQ, mean endpoint (week 8) VAS scores for the pregabalin group (39.5) and the amitriptyline group (37.4) were statistically significantly better than the placebo group's score (48.3) (p = 0.0142 and 0.0055 respectively). Only the amitriptyline group had significantly better PPI indices than the placebo group. Sensory, affective, and total scores showed a greater mean change from randomization to endpoint in the pregabalin and amitriptyline groups than in the placebo group. Mean sleep interference scores at

endpoint were statistically better for the pregabalin group (3.1) and the amitriptyline group (2.5) compared to placebo (3.8), ($p = 0.0023$ and 0.0003 respectively). On the global assessments, no statistically significant difference in the PGIC or the CGIC between the pregabalin group and the placebo group were observed, but the amitriptyline group did differ significantly from the placebo group for both measures ($p = 0.020$ and 0.003). On the SF-36, both active treatment groups were statistically significantly better than placebo in the physical functioning, bodily pain, mental health, and general health perception domains. On the HADS, there were statistically significant differences between both active groups and the placebo group with respect to anxiety only.

2.5.3.3 Efficacy Conclusion, Study 1008-040

This study did not provide evidence of efficacy for pregabalin, 200 mg t.i.d. (600 mg/day given as three divided doses), although demonstration of efficacy for amitriptyline provides assurance of assay sensitivity. However, secondary measures and week-by-week pain scores suggest a favorable effect of pregabalin.

2.5.4 Protocol 1008-131: An 8-week, double-blind, placebo-controlled trial of pregabalin (300 mg/day) for relief of pain in patients with painful diabetic peripheral neuropathy

As noted above, this was a randomized, double-blind, placebo-controlled, parallel group study conducted at 25 centers in the US. A total of 255 subjects with diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years, hemoglobin A1c levels ≤11%, meeting minimum requirements for baseline levels of pain, were enrolled in the baseline phase, and 146 subjects were subsequently randomized to pregabalin, 100 mg t.i.d. (300 mg/day) or placebo and treated for 8 weeks at a fixed dose (no titration).

2.5.4.1 Demographics and Patient Disposition

The demographics of the treatment groups (patients randomized) at baseline were similar with respect to age and sex. Racially, more of the placebo subjects (91%) were white compared to the pregabalin group (84%). Type I diabetes was more common among patients randomized to pregabalin (16%) than among patients randomized to placebo (10%). More subjects in the placebo group (86%) used oral antidiabetic medications than in the pregabalin group (75%). The proportion of subjects who used insulin was comparable (34% and 40%, respectively). Baseline mean pain scores were similar.

Patient disposition is illustrated in the table below, adapted from Dr. Kashoki's review:

Subject Disposition: Protocol 1008-131

	Placebo	Pregabalin 300 mg/day	Total
Entered baseline phase			225
Completed baseline phase			146
Withdrawn during baseline phase			79 (35.1)
Adverse event			1 (0.4)
Did not meet criteria			60 (26.7)
Lost to follow-up			1 (0.4)
Other / Administrative			7 (3.1)
Patient withdrew consent			10 (4.4)
Randomized	70	76	146
Intent-to-treat	70	76	146
Completed study	62 (88.6)	65 (85.5)	127 (87.0)
Withdrawn during treatment phase	8 (11.4)	11 (14.5)	19 (13.0)
Adverse event	2 (2.9)	8 (10.5)	10 (6.8)
Lack of compliance	1 (1.4)	2 (2.6)	3 (2.1)
Lack of efficacy	3 (4.3)	1 (1.3)	4 (2.7)
Lost to follow-up	1 (1.4)	0 (0.0)	1 (0.7)
Other	1 (1.4)	0 (0.0)	1 (0.7)
Entered open-label study	61 (87.1)	62 (81.6)	123 (84.2)

(Sponsor's Table 10, RR 720-04452, 1008-131, P. 37)

Protocol violations deemed significant by the primary reviewer included four subjects in the pregabalin group who failed to meet minimum baseline VAS pain scores. All of these would serve to bias the trial against showing an effect of pregabalin. In addition, 12 subjects (7 placebo and 5 pregabalin) took prohibited medication. This roughly even distribution renders it unlikely that these violations would affect the interpretation of study results.

2.5.4.2 Efficacy Results

2.5.4.2.1 Mean Pain Scores at Endpoint

The sponsor's analysis, using LOCF imputation of missing values, showed a statistically significant difference favoring pregabalin over placebo, as shown in the table below.

Mean pain scores at endpoint in Study 1008-131, using LOCF (Sponsor's Analysis)

Time Point	Placebo N	Placebo Mean (SD)	Pregabalin 300 mg/day N	Pregabalin 300 mg/day Mean (SD)
Baseline	70	6.1 (1.5)	76	6.5 (1.7)
Endpoint	69	5.3 (2.4)	75	4.0 (2.5)
Change	69	-0.8 (1.7)	75	-2.6 (2.6)

(from Table 6.6.3.1.2.b in Dr. Kashoki's review)

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

However, as described above, Drs. Kashoki and Chen noted that the BOCF analysis had failed to account for all patients with missing data and to adjust accordingly. Therefore, the reviewers undertook a BOCF analysis using the ITT population which yielded the following results:

Mean pain scores at endpoint in Study 1008-131, using BOCF (Reviewers' Analysis)

Time Point	Placebo N	Placebo Mean (SD)	Pregabalin 300 mg/day N	Pregabalin 300 mg/day Mean (SD)
Baseline	70	6.12 (1.48)	76	6.53 (1.66)
Endpoint	70	5.53 (2.16)	76	4.74 (2.45)
Change		-0.59 (1.47)		-1.79 (2.46)

Baseline = the last 7 days prior to randomization
Endpoint = the last 7 days of the treatment period

The BOCF analysis of the primary outcome, mean pain score during the last week of the study, found that the pregabalin 300 mg/day group had significantly improved pain compared to the placebo group ($p = 0.0005$).

2.5.4.2.2 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, the proportion of responders in the placebo group was 15%, while 40% of the pregabalin group were categorized as responders. This difference in the proportion of responders between the 2 treatment groups was statistically significant ($p = 0.001$).

However, the calculation of change from baseline for the purposes of defining a responder in this analysis used the LOCF imputation strategy, which is considered inappropriate for this study. Therefore, Drs. Kashoki and Chen 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 unshaded area, and various levels of response (50% reduction from baseline in pain and better) are illustrated. In this

data presentation, 7% of the placebo group and 33% of the pregabalin 300 mg/day group met the definition of responder (50% reduction in pain). The effect of pregabalin 300 mg/day is further highlighted by the differences in proportions of patients experiencing even greater degrees of improvement in pain. Considering either the overall responder rate, or an analysis which considered the difference in median percentage change from baseline (taking into account all degrees of response), statistical significance was demonstrated , with p=.0233 for the categorical responder analysis and p=.0010 for the comparison of median percentage change from baseline.

Percentage change in endpoint mean pain score by dose: BOCF analyis, Protocol 1008-131

Total N	**70**	**76**
Pain Score	**Placebo** **N (%)**	**Pregabalin 300 mg/day** **N (%)**
Any increase	26 (37.14)	9 (11.84)
No change	7 (10.00)	9 (11.84)
> 0% decrease	37 (52.86)	58 (76.32)
≥ 10 % decrease	27 (38.57)	52 (68.42)
≥ 20 % decrease	22 (31.43)	40 (52.63)
≥ 30 % decrease	18 (25.71)	34 (44.74)
≥ 40 % decrease	8 (11.43)	28 (36.84)
≥ 50 % decrease	***5 (7.14)***	***25 (32.89)***
≥ 60 % decrease	1 (1.43)	18 (23.68)
≥ 70 % decrease	0 (0.00)	12 (15.79)
≥ 80 % decrease	0 (0.00)	6 (7.89)
≥ 90 % decrease	0 (0.00)	4 (5.26)
= 100% decrease	0 (0.00)	4 (5.26)

An additional analysis approach was also taken by Dr. Chen. In her analysis, patients who used rescue pain medication during the final week of the study were identified, and the pain score on the day rescue was used was replaced with the maximum baseline pain score, to represent the assumption that use of rescue pain medication signals an intolerable level of pain. Using this imputation strategy, lower decreases in pain were demonstrated across both groups. One quarter of patients in each group reported no change in their pain, and more patients in the placebo group (31%) reported an increase in their pain by the end of the study compared to the pregabalin group (13%). There were more treatment responders in the pregabalin 300 mg/day group than in the placebo group.

2.5.4.2.3 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; and POMS. On the SF-MPQ, the endpoint and weekly mean VAS and PPI scores were consistently lower for the pregabalin group than for the placebo group. Analysis of the differences in weekly VAS scores found statistically significant differences at all time-

points. The PPI scores for the pregabalin group were significantly different from placebo at all weeks except Week 8. Analysis of sleep interference scores between the treatment groups showed statistically significant differences that favored pregabalin over placebo at every weekly timepoint. On the global assessments, 67% of patients in the pregabalin group reported improvement (very much improved, much improved, or minimally improved), compared to 39% of the placebo patients. Similarly, clinicians reported that 67% of pregabalin-treated patients were improved, compared to 39% of placebo patients. These differences were statistically significant. SF-36 showed no differences apart from the bodily pain domain. On the POMS, favorable effects were noted on measures of tension/anxiety and total mood disturbance.

2.5.4.3 Efficacy Conclusion, Study 1008-131

This study provides evidence of efficacy for pregabalin, 100 mg t.i.d. (300 mg/day given as three divided doses).

2.5.5 Protocol 1008-149: A 12-week, randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) for relief of pain associated with Diabetic Peripheral Neuropathy

As noted above, this was a randomized, double-blind, placebo-controlled, parallel groups study conducted at 58 centers in Europe, Australia, and South Africa, with centers in Poland providing 42% of patients . A total of 512 subjects with diabetic, distal, symmetrical, sensorimotor polyneuropathy for at least one year, hemoglobin A1c levels ≤11%, meeting minimum requirements for baseline levels of pain, were enrolled in the baseline phase, and 396 subjects were subsequently randomized to placebo, pregabalin 150 mg/day, pregabalin 300 mg/day, or pregabalin 600 mg/day, administered in two divided doses (BID), and treated for 12 weeks (including 1 week titration for 300 mg/day and 600 mg/day groups).

It should be noted that, as originally proposed, this study was to enroll a total of approximately 100 patients, who were to be pooled with a planned, identical study to be conducted in the U.S. However, the U.S. study was halted due to the imposition of partial clinical hold when animal findings of hemangiosarcoma were reported. Subsequently, in March 2001, the protocol was amended to stipulate enrollment of 352 subjects, and a revised statistical analysis plan omitting the plan to pool data with the U.S. study was developed. In addition, the protocol was amended to allow enrollment of subjects who had previously failed treatment with gabapentin. (Notably, the partial hold allowed enrollment into U.S. study *only* subjects who had failed treatment with gabapentin.) Approximately 6 months later, in November 2001, a regulatory decisions in some participating countries[1] resulted in a change in inclusion/exclusion criteria that required the premature discontinuation of 11 subjects from the study; these subjects were replaced to reach the desired sample size and were excluded from the efficacy analysis. The "modified intent-to-treat" (MITT) population identified by the sponsor (correctly) omits these 11 patients and is considered the appropriate population for analysis in the

[1] Details about this regulatory decision have been vague; additional clarification has been requested from Pfizer

discussion below.

Another feature of note in this protocol is that, unlike the other efficacy studies in the development program, this protocol permitted enrollment of subjects with creatinine clearance <60 mL/min. Subjects with creatinine clearance of at least 30 mL/min were eligible, but those with creatinine clearance <60 could not be treated with 600 mg/day pregabalin. Although the protocol specified stratified randomization, with those with creatinine clearance <60 mL/min to be randomized to placebo, 150 mg/day, or 300 mg/day, the procedure for assignment to treatment actually used appears to have permitted this group to be randomized to any dose, but those assigned to the 600 mg/day group were, instead, treated with 300 mg/day. In the data presentations below, this group was designated by the sponsor as the "300/600 mg/day" group. However, as noted by the reviewers, overall the study treated 23 subjects whose creatinine clearance was 30-60 mL/min with 300 mg/day pregabalin, and for the purposes of analysis designated some of these as members of the 300 mg/day group and others as members of the 300/600 mg/day group although these groups were treated *with the same dose*. Therefore, the reviewers' analysis attempted to address this. However, in presentations of demographics, patient disposition, and other aspects of the sponsor's analysis, the groups are displayed as grouped by the sponsor.

2.5.5.1 Demographics and Patient Disposition

The demographics of the treatment groups (patients randomized) at baseline differed somewhat with respect to sex, race, and age distribution. The proportion of male subjects ranged from 53% in the placebo group to 60% in the 300/600 mg/day group, and the proportion of white subjects ranged from 99% in the placebo group to 94% in the 300/600 mg/day group. The enrollment of subjects age 65 and over ranged from 26% in the 300 mg/day group to 34% in the placebo group. In the modified intent-to-treat population (after removal of the 11 subjects discontinued due to regulatory action), demographic features for each group were very similar to those in the corresponding group in the ITT population. The majority of subjects (85%) in the MITT population had Type 2 diabetes. The proportion of subjects with Type 2 diabetes was similar across treatment groups. More subjects in the pregabalin 150 mg/day group used insulin (74.2%) than subjects in the pregabalin 300 and 300/600 groups, and the placebo groups respectively (70.8%, 71.4%, and 68.8%, respectively). There were 237 subjects (62%) who reported prior (within 30 days) and/or concurrent use of an oral antidiabetic medication. More subjects in the pregabalin 300/600 mg/day group used an oral antidiabetic drug (64.3%) than subjects in the pregabalin 150 and 300 groups, and the placebo groups respectively (58.8%, 62.5%, and 61.3%, respectively).

The baseline mean pain score was slightly higher in the pregabalin 300/600 mg/day group (6.6, ± 1.4) compared to the scores of the pregabalin 150 and 300 mg/day groups and the placebo group (6.2, 6.4, and 6.4 respectively)

Patient disposition is illustrated in the table below, adapted from Dr. Kashoki's review:

Subject Disposition, Protocol 1008-149

	Placebo	Pregabalin (mg/day), N (%)			All Patients
	N (%)	150	300	300/600	N (%)
Entered baseline					512
Withdrawn during baseline [a]					116 (22.7)
Did not meet entry criteria					74 (14.5)
Adverse event					2 (0.4)
Other/Administrative					40 (7.8)
Entered double-blind (randomized) phase	97	99	99	101	396
Intent-to-treat population	96	99	99	101	395
Withdrawn during the Treatment phase	17 (17.7)	17 (17.2)	20 (20.2)	23 (22.8)	77 (19.5)
Lack of compliance	0 (0.00)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Lack of efficacy	11 (11.5)	8 (8.1)	5 (5.1)	3(3.0)	27 (6.8)
Adverse event	3 (3.1)	5 (5.1)	11 (11.1)	13 (12.9)	32 (8.1)
Withdrawn after MoH/EC decision	3 (3.1)	2 (2.0)	3 (3.0)	3(3.0)	11 (2.8)
Other/Administrative	0 (0.0)	2 (2.0)	1 (1.0)	3 (3.0)	6 (1.5)
Completed the study	79 (82.3)	82 (82 8)	79 (79.8)	78 (77.2)	318 (80.5)
Entered open-label study	85 (88.5)	85 (85.9)	78 (78.8)	82 (81.2)	330 (83.5)

(Sponsor's Table 9, RR 720-30080, 1008-149, P. 69)

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

MoH = Ministry of Health; EC = Ethics Committee

Protocol violations of significance included seven patients listed as "incorrect diagnosis" and an additional five subjects who did not fully meet the diagnostic criteria stipulated for entry. (Individuals not fully meeting criteria were described as "eligibility exceptions" rather than protocol violations.) These included 3 in the placebo group, 2 in the 150 mg/day group, 2 in the 300 mg/day group, and 5 in the 300/600 mg/day group. In addition, 14 subjects did not meet minimum pain criteria at entry. These included 1 in the placebo group, 4 in the 150 mg/day group, 2 in the 300 mg/day group, and 5 in the 300/600 mg/day group. Study medication non-compliance was also noted as a violation for 1 subject in the 300 mg/day group and 2 in the 300/600 mg/day group. Overall, both of these violations/exceptions would tend to bias the study away from finding a difference in favor of the affected treatment group, and the distribution of these types of violations/exceptions creates, if anything, a bias against the 300/600 mg/day group.

Use of prohibited study medication was recorded in 8 subjects, roughly evenly across groups (1 in the placebo group, 2 in the 150 mg/day group, 2 in the 300 mg/day group, and 3 in the 300/600 mg/day group).

2.5.5.2 Efficacy Results

2.5.5.2.1 Mean Pain Scores at Endpoint

The sponsor's analysis, using LOCF imputation of missing values, showed that there was a statistically significant difference in the endpoint mean pain score for the pregabalin 300/600 mg/day group [3.7 (± 2.2)] compared to the placebo group [4.4 (± 2.3)] (p = 0.0054). The other active treatment groups were not significantly better than placebo. The Sponsor's analysis using the ITT and Per Protocol populations yielded similar results to those of the MITT population.

Mean pain scores at endpoint in Study 1008- 149 (MITT), using LOCF (Sponsor's Analysis)

Time Point	Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 300/600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	93	6.4 (1.5)	97	6.2 (1.4)	96	6.4 (1.3)	98	6.6 (1.5)
Endpoint	93	4.5 (2.3)	96	4.1 (2.3)	96	4.4 (2.2)	98	3.7 (2.2)
Change	93	-1.9 (2.1)	96	-2.1 (2.4)	96	-2.1 (2.1)	98	-3.0 (2.4)

(Adapted by Dr. Kashoki from Sponsor's Table 18, RR 720-30080, 1008-149, P. 84)

The sponsor also conducted an analysis identified as a BOCF analysis. None of the pregabalin treatment groups was statistically significantly different from placebo using this imputation strategy.

However, as described above, Drs. Kashoki and Chen noted that the BOCF analysis had failed to account for all patients with missing data and to adjust accordingly. Therefore, the reviewers undertook a BOCF analysis using the MITT population. In addition, the reviewers noted that:

> Additionally, the Sponsor's interpretation of treatment efficacy for all subjects in the pregabalin 300/600 mg/day group is incorrect. The Sponsor concluded that because the 300/600 mg/day treatment arm showed greater improvement in pain from placebo, then treatment with either 300 or 600 mg/day (where dosing is dependent on creatinine clearance) is effective. This conclusion is incorrect because it fails to take into account that the 13 subjects in the 300/600 treatment arm who had a creatinine clearance ≤ 60 mL/min and received 300 mg/day of drug, were exactly the same as the 10 subjects with low creatinine clearance who were randomized to the pregabalin 300mg/day arm (see Table 6.7.3.4.d). Data analysis showed that treatment for all subjects in this latter arm was not significantly different from placebo.
>
> Consequently, the data were reanalyzed after reassigning the aforementioned 13 subjects to the 300 mg/day treament arm, and grouping them with the 10 subjects who also had a low creatinine clearance. The data were analyzed separately for subjects with a creatinine clearance > 60 mL/min, and for subjects with a creatinine clearance ≤ 60 mL/min but ≥ 30 mL/min.

The reviewers' BOCF analysis of the data for subjects with a creatinine clearance > 60 mL/min showed that none of the pregabalin treatment groups had a significantly different mean pain score at study endpoint compared to placebo. The p-values for the difference in median percentage changes for the pregabalin 150, 300, and 600 mg/day groups were 0.54, 0.39, and 0.08 respectively (1-sided alpha = 0.0083). The BOCF analysis was repeated after factoring the use of rescue medications during the final week of the study,

and yielded similar results.

2.5.5.2.2 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, the percent of responders in the MITT population was 46% in the 300/600 mg/day pregabalin group, 33% in the 300 mg/day pregabalin group, and 34% in the 150 mg/day pregabalin group, compared with 30% in the placebo group. There was a statistically significantly greater proportion of responders for the 300/600 mg/day pregabalin group when compared with the placebo group ($p = 0.036$).

However, the calculation of change from baseline for the purposes of defining a responder in this analysis used the LOCF imputation strategy, which is considered inappropriate for this study. Therefore, Drs. Kashoki and Chen recalculated change from baseline using the BOCF strategy and tabulated the results as shown below.

% of Subjects with Change from Baseline Pain of ≥50%, BOCF analysis, Study 1008-149

	Proportion of Responders (%)			
		Pregabalin		
Creatinine clearance	**Placebo**	**150 mg/day**	**300 mg/day**	**600 mg/day**
> 60 mL/ min	25	30	28	36
≤ 60 mL/min	33	25	22	-

from Dr. Kashoki's review

The table shows that a considerable proportion (25-33%) of subjects in the placebo group responded to treatment. This proportion is considerably larger than the placebo response observed in other studies. The table also illustrates that the effect seen in the "300/600 mg/day group" should not be inappropriately attributed to both 600 mg/day in patients with creatinine clearance of 60 mL/min or more *and* 300 mg/day in patients with creatinine clearance between 30-60 mL/min. In fact, this latter group did not show efficacy, with a response rate notably lower than placebo.

An additional analysis approach was also taken by Dr. Chen. In her analysis, patients who used rescue pain medication during the final week of the study were identified, and the pain score on the day rescue was used was replaced with the maximum baseline pain score, to represent the assumption that use of rescue pain medication signals an intolerable level of pain. Using this imputation strategy, responder rates are shown below.

% of Subjects with Change from Baseline Pain of ≥50%, BOCF analysis (with imputation of pain scores due to use of rescue medication), Study 1008-149

	Proportion of Responders (%)			
		Pregabalin		
Creatinine clearance	Placebo	150 mg/day	300 mg/day	600 mg/day
> 60 mL/ min	21	29	24	35
≤ 60 mL/min	33	17	18	-

from Dr Kashoki's review

2.5.5.2.3 Secondary endpoints

Secondary endpoints analyzed included SF-MPQ (sensory, affective, VAS, PPI, and total scores); Sleep interference; global impression (patient and clinician); Medical Outcomes Study--Sleep Scale Score, SF-36 Health Survey; VAS area under the curve (AUC) score and the single index value score calculated from the EuroQol Health State Profile (EQ-5D)

On the SF-MPQ, there was a statistically greater change from baseline to study endpoint with respect to the VAS score for the 300/600 mg/day pregabalin group compared to the placebo group. A statistically significant decrease was seen for the endpoint PPI when all pregabalin treatment groups were compared to placebo. Comparisons of the SF-MPQ sensory, affective, and total scores at endpoint (English-speaking patients only) favored the 300/600 mg/day pregabalin treatment group over placebo. The mean sleep interference scores for the 300/600 mg/day pregabalin group was significantly different from placebo from Week 1 through Week 12. Neither of the other pregabalin treatment groups was statistically different from the placebo group. On the global assessments, more than 50% of subjects and investigators provided ratings of "very much" and "much" improvement for the pregabalin 300/600 mg/day vs 33% and 34% of subjects and investigators, respectively, in the the placebo group. The differences in these ratings reached statistical significance. On the Medical Outcomes Study Sleep Scale, results were mixed with the pregabalin groups reporting more favorable scores on some outcomes compared to placebo. Only the sleep adequacy scale demonstrated a statistically significant difference in favor of pregabalin 300/600 mg/day. No domains on the SF-36 health survey demonstrated statistically significant differences. EQ-5D utility scores for all pregabalin treatment groups were statistically significantly better when compared with the placebo treatment group. Statistical significance was not reached for the EQ-5D VAS and VAS AUC for any dose of pregabalin.

2.5.5.3 Efficacy Conclusion, Study 1008-149

This study provides some support for pregabalin, 300 mg b.i.d. (600 mg/day) in patients with creatinine clearance of ≥60 mL/min, only when the last-observation-carried-forward method is used to impute missing data. Because LOCF is particularly misleading when rates of discontinuation for adverse events differ across treatment groups, it is notable that the rate of dropout for adverse events was 3% in the placebo group vs. 13% in the pregabalin 300/600 mg/day group. The BOCF strategy is preferable in this situation,

because it avoids carrying forward a score which may have represented adequate pain relief in the face of intolerable side effects, a clinical scenario which cannot be called successful treatment. Using the BOCF strategy, evidence of efficacy is not maintained. Secondary measures and analyses, however, are consistent with an overall favorable effect of pregabalin and does not contradict the positive findings in Studies 014, 029, and 131.

This study does not provide support for any dose in subjects with lower creatinine clearance.

2.6 Exploration of Characteristics of Responders

Because of the drug's significant safety concerns (potential carcinogenicity, ophthalmologic effects, and possible skin effects), it was proposed by the CDER Management panel at the Regulatory Briefing that the product might be limited through labeling to use in refractory cases. However, the product was not studied in refractory cases, and, in fact, subjects refractory to gabapentin were specifically excluded from participation. Further exploration of the characteristics of responders is difficult because of the format of the data. Additional data have been requested of Pfizer to facilitate this analysis.

However, using Dr. Chen's BOCF imputations performed on the datasets from the supportive pivotal trials, 131, 014, and 029, I was able to explore the data to determine whether baseline pain severity predicted response. This was a concern for two reasons. First, although a minimum pain score of 4 on a 10 point scale was required for entry, had the responder analysis been driven primarily by patients reducing from a pain score of 4 to a pain score of 2, the overall clinical impact of the drug would have been less compelling. Furthermore, if only patients with mild pain responded, the limitation of the product to patients only with greater severity or more refractory pain might have selected *out* the very patients who were likely to benefit, rendering the risk/benefit ratio unfavorable.

Therefore, I examined the distribution of pain scores at baseline for responders and non-responders, using the definition of responder as carried out by Dr. Chen in her BOCF analysis. I also plotted the baseline pain score against the percent reduction in pain at endpoint, again, using Dr. Chen's calculations.

As shown below, the patients with a favorable response to pregabalin seem to be distributed across the range of baseline pain scores, and there appears to be no relationship between baseline pain score and percent change from baseline at endpoint. In the tabulation of baseline pain scores, approximately 3 subjects with baseline pain scores <4 were deleted to render the axes similar for ease of comparison. The overall size of the groups (549 non-responders vs. 165 responders) should be borne in mind while examining these tabulations.

Figure: Distribution of Baseline Pain Scores

Responders

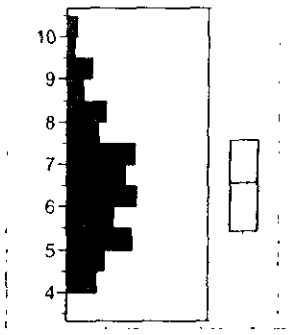
Quantiles

100 0%	maximum	10.000
99.5%		10.000
97 5%		9.829
90 0%		8.400
75.0%	quartile	7.286
50 0%	median	6.143
25.0%	quartile	5 155
10.0%		4 429
2.5%		4.000
0.5%		4.000
0 0%	minimum	4 000

Moments

Mean	6.3371429
Std Dev	1.4680374
Std Err Mean	0.1142866
upper 95% Mean	6.5628056
lower 95% Mean	6.1114801
N	165

Non-Responders



Quantiles

100.0%	maximum	10.000
99.5%		10.000
97.5%		9.839
90.0%		8.714
75.0%	quartile	7 571
50.0%	median	6.571
25 0%	quartile	5 429
10 0%		4.714
2.5%		4.161
0.5%		4.000
0.0%	minimum	4.000

Moments

Mean	6 6114581
Std Dev	1.4627676
Std Err Mean	0.0624294
upper 95% Mean	6.7340883
lower 95% Mean	6.4888278
N	549

Figure: All subjects, studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF

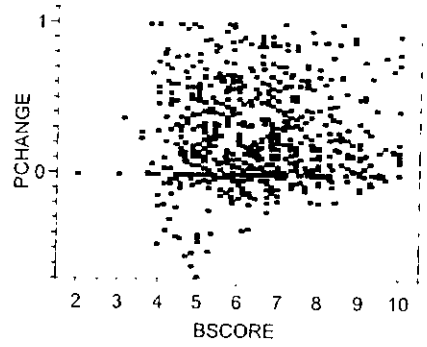


Figure: Responders, Studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF

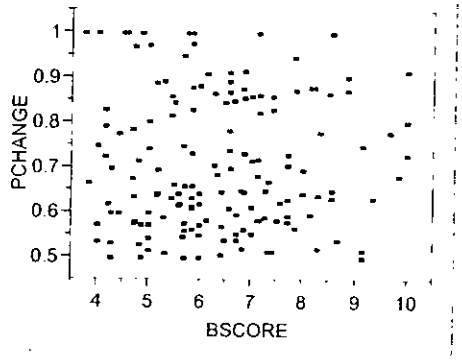
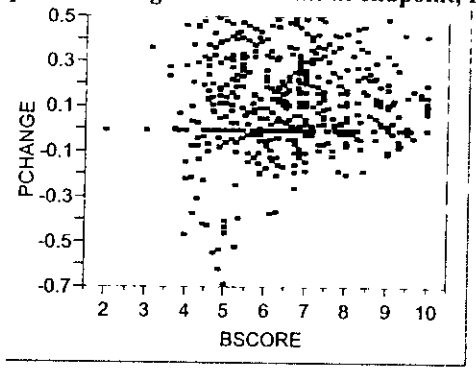


Figure: Non-responders, Studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF



2.7 Overall Efficacy Conclusion

The data submitted provide substantial evidence that pregabalin, at doses of 300-600 mg/day, given in three divided doses, is more effective than placebo in relieving the pain associated with diabetic peripheral neuropathy in patients with creatinine clearance ≥60 mL/min. However, there appears to be no benefit of 600 mg/day over 300 mg/day.

3 SAFETY

In a safety database of sufficient size and using suitable safety monitoring procedures, pregabalin is associated with nervous system abnormalities (dizziness, somnolence, changes in mental status, motor changes, and vertigo) edema, blurred vision, dry mouth, constipation, and dyspepsia. Approximately 13% of DPN subjects discontinued due to adverse events, most commonly for dizziness and somnolence. 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 DPN population were noted. Other safety concerns of note include ophthalmologic effects which require further study for complete characterization, and animal findings of dermatopathy for which no clinical correlation has been identified.

3.1 Exposure

The overall exposure to pregabalin for DPN was adequate to characterize the safety profile and met ICH requirements. 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 DPN program, a total of 1413 patients received at least one dose of pregabalin. To date, 289 subjects have been treated with pregabalin 600 mg/day (the highest proposed marketed dose) for at least 6 months, and 201 for at least 1 year.

A dose-by-duration table for the doses proposed for marketing was constructed by Dr. Kashoki and is shown below (from her review)

Exposure to pregabalin by dose and duration, Controlled and Uncontrolled studies, DPN vs. All Indications

	Pregabalin dose			
	300 mg/day (N = 6969) N(%)		600 mg/day (N = 3333) N(%)	
Duration	DPN [N=1413]	ALL [N=8666]	DPN [N=1413]	ALL [N=8666]
≥4 wks	657	2 423	571	2 514
≥ 8 wks	467	1 537	458	1 999
≥ 12 wks	339	1 041	370	1 550
≥ 26 wks	215	526	289	1106
≥ 52 wks (1 year)	102	193	201	664
≥ 78 wks (1.5 years)	52	83	149	484
≥ 104 wks (2 years)	22	32	49	263

3.2 Deaths

No deaths reported appear to be clearly associated with pregabalin. The overall mortality rate in controlled trials, when deaths occurring within 30 days of medication discontinuation were considered, were similar between pregabalin-treated and placebo-treated groups.

3.2.1 Overall database

Mortality in the overall safety database was reviewed by Drs. Boehm and Kashoki.

Dr. Boehm noted: 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). Six 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.

Dr. Boehm notes that these small numbers render comparison difficult, and overall, there does not appear to be a pregabalin effect on mortality rate in controlled trials.

Similarly, no indication of elevated mortality risk was observed in the uncontrolled studies. 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 (NDA Section 2.5.5.2.2, p.94).

Pfizer provided the following table that summarizes the deaths by indication for the integrated safety database.

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.

(Sponsor'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.

3.2.2 Diabetic Peripheral Neuropathy database

As indicated in the table above, there were 17 deaths in patients with DPN, making the total mortality for subjects in DPN studies 1.2% (17/1413). The mortality rate for these trials was 11.9/1000 PY (17/1421PY).

Using the patient narratives, CRFs, datasets, and patient profiles, Dr. Kashoki constructed summaries of the clinical details for the DPN study deaths. All 17 patients who died had been treated pregabalin. Three subjects died while taking medication during controlled trials, while 1 subject died after prematurely discontinuing medication during the controlled trial. Thirteen subjects died while participating in uncontrolled studies. The majority of deaths were cardiac related (arrhythmia, cardiac arrest, heart failure, and myocardial infarction; n = 2 each). Four deaths were due to unknown causes. The remaining deaths were from respiratory failure (n = 3), cancer (n = 1) and sudden death (n = 1). One death, although occurring 1.5 years after treatment was discontinued, was related to an adverse event possibly attributable to pregabalin.

Patient 015001 (Study 1008-033)

Patient 015001, Study 1008-033, a 72-year-old white woman with painful diabetic neuropathy and a family history of leukemia was hospitalized for cognitive changes on Study Day 386 (3 days post treatment) of open-label pregabalin. Study medication consisted of pregabalin 600 mg/day for 375 days. The patient participated in a previous Study 1008-029 and received pregabalin 600 mg/day for 37 days. The patient was diagnosed with a low platelet count on Study Day 320, and medication was temporarily discontinued until Study Day 335. On study day 356 she developed pancytopenia, and myelodysplasia (leukemoid reaction), and on Day 383, the pregabalin was interrupted due to a low platelet count. On Day 867 she was diagnosed with myelodysplastic syndrome. She died on Study Day 941 (519 days post-treatment). Total exposure to the study medication was 420 days.

For this subject, an association with pregabalin is possible, although myelodysplastic syndrome is not uncommon in elderly 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. Adverse events were cited as the reason for early termination in approximately 13% of subjects in the overall population and 9% of the DPN population. In the DPN population, dizziness, somnolence, and headache emerged as the most common adverse event-related reasons for discontinuation.

3.3.1 Overall Database

As shown in the tables below, constructed by Dr. Kashoki from the sponsor's data, 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%.

Patient disposition – Controlled trials, All indications

Patient Status	Placebo [N = 2384]*		Pregabalin [N = 5508]*	
	N	%	N	%
Completed Treatment [1]	1733	72.69	3770	68.45
Reasons for discontinuation				
Adverse Event	164	6.88	701	12.73
Lack of Efficacy [2]	287	12.04	272	4.94
Lack of Compliance	41	1.72	101	1.83
Patient withdraws consent	39	1.64	73	1.33
Lost to Follow-Up	45	1.89	84	1.53
Significant improvement	0	0.00	2	0.04
Other	197	8.26	387	7.03

* N = all subjects exposed to pregabalin
[1] Completion of the Termination Visit was considered indicative of completion of study treatment
[2] "Lack of Efficacy" includes indication-specific criteria for study withdrawal

Patient disposition – Uncontrolled trials, All indications

	Pregabalin, [N = 5459]* N (%)	
Patient Status	**Sponsor**	**Reviewer**
Ongoing at data cutoff	962 (17.6)	962 (17.6)
Completed study [1]	479 (8.8)	497 (9.1)
Reasons for discontinuation		
Adverse event	774 (14.2)	760 (13.9)
Lack of efficacy	934 (17.1)	912 (16.7)
Lack of compliance	213 (3.9)	212 (3.8)
Other	2097 (38.4)	2149 (39.4)

* Number exposed to pregabalin in uncontrolled trials

3.3.2 Diabetic Peripheral Neuropathy Database

Within the DPN trials specifically, approximately 20% of the placebo-treated patients and 25% of the pregabalin-treated patients in controlled trials discontinued study participation prematurely. As illustrated in Dr. Kashoki's table, below, more pregabalin-treated subjects withdrew due to adverse events (9%) compared to placebo patients (4%). Almost twice as many placebo patients (6%) withdrew because of lack of efficacy compared to pregabalin patients (3%). Lack of efficacy and "other" were the most common reasons for premature discontinuation in the placebo-treated patients (accounting for 29% and 48% of discontinuations, respectively), adverse events and "other" were the most common reasons among the pregabalin-treated patients, accounting for 48% and 35% of discontinuations, respectively.

Patient disposition, DPN controlled trials

Patient status	Placebo N	[N = 459]* %	All Pregabalin N	[N = 979]* %
Completed	365	79.52	732	74.77
Reason for discontinuation				
Adverse Event	17	3.70	86	8.78
Lack of Efficacy	27	5.88	33	3.37
Lack of Compliance	4	0.87	10	1.02
Lost to Follow-Up	1	0.22	0	0.00
Other [1]	45	9.80	118	12.05

* N = number of subjects exposed to pregabalin

1 "Other" includes withdrawal of consent, loss to follow-up, and early termination of the study per the FDA, or failure to meet requalification criteria

The table below lists adverse events that led to premature discontinuation of treatment at an incidence of at least 0.2% among subjects treated with pregabalin during DPN controlled trials. Only dizziness, somnolence, and headache were cited with a frequency of more than 1%.

Table 7.4.3.3: Adverse events reported as reason for discontinuation, by decreasing frequency - DPN controlled trials

Preferred term	Placebo N	[N=459] %	All pregabalin N	[N=979] %
Dizziness	3	0.65	34	3.47
Somnolence	0	0.00	27	2.76
Headache	4	0.87	11	1.12
Asthenia	1	0.22	8	0.82
Amblyopia	1	0.22	8	0.82
Dry mouth	0	0.00	7	0.72
Nausea	3	0.65	7	0.72
Confusion	1	0.22	7	0.72
Peripheral edema	1	0.22	6	0.61
Accidental injury	0	0.00	4	0.41
Infection	0	0.00	4	0.41
Ataxia	0	0.00	4	0.41
Neuropathy	1	0.22	4	0.41
Tremor	0	0.00	4	0.41
Constipation	1	0.22	3	0.31
Diarrhea	1	0.22	3	0.31
Incoordination	1	0.22	3	0.31
Thinking abnormal	0	0.00	3	0.31

3.4 Serious Adverse Events

3.4.1 Overview

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. Several cases of traumatic injury are plausibly linked to pregabalin's CNS effects, and one case of leukemoid reaction (ultimately fatal) lacks alternative explanation and raises concern because of pregabalin's hematologic effect (albeit primarily upon platelets). An unexplained case of rhabdomyolysis raises concern because of pregabalin's observed effect on creatine kinase. However, leukemoid reactions are not uncommon in the elderly. Further evaluation of the effect of preabalin on CK by Dr. Boehm did not yield clear evidence of causality in the case of rhabdomyolysis.

3.4.2 Overall Database

Pfizer pooled the safety data from the Phase 2/3 clinical trials in the following ways:
•*Across Indications*: (1) all controlled studies alone and (2) all controlled and open-labelextension studies combined
•*By Indication*: (1) controlled studies alone, (2) uncontrolled studies alone (ie, open-label extensions of the controlled studies), and (3) combined controlled and uncontrolled

studies.

The details of how the events were assigned to a dose level or to a controlled/uncontrolled study when occurring in a patient who participated in both (i.e. a controlled study and its open-label extension) are described in detail in Dr. Kashoki's review.

Per Dr. Kashoki's review,

> Pfizer reports that there have been 726 (8.4%, 726/8666) pregabalin subjects with one or more serious adverse events in the integrated safety database (Summary of Clinical Safety, p.40). The rate of experiencing on or more SAEs in the integrated safety database is 113/1000PY (726/6393PY).
>
> The table belows 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%).

In the table below (from Dr. Kashoki's review), NeP represents the combined neuropathic pain databases.

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 nonneuropathic pain studies and other psychiatry studies.
(Adapted from Sponsor's Table 16, RR-REG 720-30199, P. 40)

3.4.2.1 SAEs in controlled studies

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)

3.4.2.2 SAEs in combined controlled and uncontrolled studies

In the combined controlled trials and uncontrolled trials database, there was no SAE that occurred at a frequency of at least 1% in pregabalin subjects. The most commonly reported SAEs in the combined controlled trials and uncontrolled trials database were accidental injury (0.9%, 78/8666), pneumonia (0.5%, 39/8666), chest pain (0.3%, 29/8666), congestive heart failure (0.3%, 29/8666), myocardial infarction (0.3%, 29/8666) and angina pectoris (0.3%, 22/8666)

Tabulations of all SAEs are included in Dr. Kashoki's review as Tables **7.4.5.1.b and** 7.4.5.1.c .

Assessments of relatedness were undertaken by Drs. Boehm and Kashoki. Pfizer provided a listing of all SAEs experienced by pregabalin treated subjects in any of their safety databases, and Dr. Boehm reviewed this list to identify subjects with SAEs coded to preferred terms of potential importance. Dr. Boehm identified subjects with the following SAEs: Kidney function abnormal (5) acute kidney failure (4), kidney failure (1), creatinine increased (1), nephrosis (1), nephritis (1), glomerulitis (1), pancreatitis (4), necrotizing pancreatitis (1), cardiomyopathy (3), cholestatic jaundice (2), jaundice (1), abnormal LFT (3), allergic reaction (2), anaphylactoid reaction (2), rash (2), Stevens Johnson Syndrome (1), CPK increased (3), myopathy/rhabdomyolysis (2), acidosis (1), face edema (1), leukopenia (1), pancytopenia (1), lung fibrosis (3), and pulmonary hypertension (1). Dr.Boehm read the narratives for these events and identified those with alternative explanations. The summaries for these events presumed unattributable to study drug are provided in the appendix to Dr. Kashoki's review.

Dr. Kashoki augmented the list of terms of interest identified by Dr. Boehm (see above) to detect SAE's of specific relevance to the diabetic population. Because of a pre-clinical signal of dermatopathic effects, and the vulnerability of the diabetic population (and the DPN population in particular) to skin ulcers, Dr. Kashoki expanded Dr. Boehms' list to

include select dermatologically-related terms that would suggest a wound or infections origin. Preferred terms were abcess, cellulitis, cyst, exfoliative dermatitis, fungal dermatitis, furunculosis, healing abnormal, injection site reaction, joint disorder, mouth ulceration, osteomyelitis, peridontal abcess, peripheral gangrene, pustular rash, pyogenic arthritis, sepsis, skin atrophy, skin disorder, skin ulcer, and vesigulobullous rash. Additionally, subjects who had allergic, anaphylactoid, or unevaluable reactions were identified. Cases suggestive of a relationship to study drug, or cases without other plausible explanation, are discussed in Dr. Kashoki's and Dr. Boehm's reviews and tabulated below.

Indication	Event	Comment
DPN	Pulmonary fibrosis, 71 y.o. M	Took pregabalin 500 mg/day x 73 days, then d/c; hospitalization for pulmonary fibrosis on study day 184
PHN	Heart failure and possible pulmonary fibrosis, 62 y.o. M	forty days after stopping pregabalin
DPN	Leukemoid reaction, 72 y.o. F	Low platelet count diagnosed on study day 320; subsequent pancytopenia and myelodysplasia after drug reinstituted. Drug d/c but pt dx myelodysplastic syndrome ~15 months post-d/c and died shortly thereafter
DPN	Macrocytic anemia, 62 y.o. M	Macrocytic anemia dx on study day 64 during hospitalization for SOB and edema
DPN	Edema, 52 y.o. M	Hospitalized for bilateral lower extremity edema on day 492 of open-label tx with pregabalin 600 mg/d
PHN	Edema, peripheral and face, 81 y.o. F	Bilateral foot edema and facial edema developed on study day 16 of pregabalin 300 mg/d
PHN	Pancreatitis, 80 y.o. F	hospitalized on study day 147 of open label pregabalin
PHN	Anaphylactoid reaction, 67 y.o. F	anaphylaxis on study day 10 of double blind pregabalin treatment (pregabalin 300 mg/day). Study medication was stopped on study day 11; events were reported as recovered on study day 12.
DPN	Acute renal failure, 71 y.o. M	Hospitalized after a fall (possible syncope) on study day 8 of open-label pregabalin; Cr 4.2 mg/dL BUN 78 mg/dL, K^+ 5.1, recovered and continued in study*
DPN	Acute renal failure, rhabdomyolysis, 31 y.o. F	study drug was stopped on study day 59 for adverse events
DPN	Acute renal failure, 62 y.o. F	Hospitalized on open label study day 301; Cr 5.4, K^+ 7.9, recovered and continued in study*
DPN	Abscess, 52 y.o. M	Hospitalized for groin abscess after 1172 days of treatment at doses from 75-500 mg/d

DPN	Cellulitis, 69 y.o. F	Hospitalized for bilateral lower extremity edema and cellulitis and bilateral urticaria of arms after 92 days of pregablin exposure of pregabalin at 75-450 mg/d. Edema began Study day 15 and progressed.
DPN	Cellulitis, 69 y.o. M	Hospitalized on day 42 of open-label pregabalin 600 mg/d for cellulitis of right leg which began as infection of an ulcer of the great toe.
DPN	Cellulitis, 46 y.o. F	Hospitalized twice for cellulitis, once on study day 50 and once on study day 177 of open label pregabalin 600 mg/d
Epilepsy	Accidental injury/fall, 63 y.o. M	Fell and fractured leg on study day 44 while taking pregabalin 600mg/day BID, hospitalized. Withdrew from the study but subsequently re-enrolled in the open label extension
Epilepsy	Accidental injury/fall, 37 y.o. M	Hospitalized for injury on day 34 of pregabalin 600 mg/day; reported drowsiness.
GAD	Accidental injury/fall, 71 y.o. F	Patient fell and fractured wrist in context of dizziness on study day 5 during dose titration; dose at event was 300 mg/d
GAD	Accidental injury, 43 y.o. M	Patient required surgery after injuring finger while chopping wood on day 31 of pregabalin 400 mg/d; had reported difficulty concentrating on study day 13.
PHN	Visual field defect, 68 y.o. F	"Medically significant" visual field defect in superior fields noted on day 153 of pregabalin
PHN	Macular degeneration, 81 y.o. M	Macular degeneration diagnosed after approximately 296 days of pregabalin treatment.

Epilepsy	Abnormal LFT's, 44 y.o. M	Pt with normal baseline labs developed AST 585U/L, ALT 840 U/L, total bilirubin 0.5mg/dL and ALP 440U/L on study day 56 of pregabalin. Drug was withdrawn and f/u labs included AST 30U/L, ALT 52U/L, total bilirubin 0.3mg/dL and ALP 172U/L on day 112. Subsequent re-challenge in OL extension; values on day 28 included ALT 71U/L, AST 39U/L, ALP 293U/L, and total bilirubin 0.4mg/dL; on day 38, ALT was 466U/L, AST 148U/L, ALP 291U/L and total bilirubin was 0.3mg/dL. Study drug appears to have been continued at 600 mg/d, with final lab values (~day 243) ALT 57U/L, AST 28U/L, ALP 292U/L and total bilirubin 0.4mg/dL.
Epilepsy	Cholestatic jaundice, Confusion, 64 y.o. M	Cholestatic jaundice diagnosed in context of hospitalization for confusion on study day 13 after escalating course of CNS symptoms including ataxia, tremors, and headache with positive challenge/dechallenge; hospitalized for supervised taper due to encephalopathic sx (confusion, visual hallucinations). Diagnosis of cholestatic jaundice reported but no lab values reported.
GAD	Cardiomyopathy, 39 y.o. M	Pt presented with chest pain and SOB, dx with cardiomyopathy on day 9 of pregabalin 600 mg/d; no etiology established although viral syndrome recorded within week prior to event.

*This patient had previous and/or subsequent pregabalin exposure without apparent effect on Creatinine

3.4.3 Diabetic Peripheral Neuropathy Database

3.4.3.1 Controlled Trials

The Sponsor reported that 3.9% (38/979) of pregabalin-treated patients and 2.4% (11/459) placebo subjects in controlled DPN trials experienced at least one SAE. As shown in the table below, chest pain was the most common SAE (pregabalin 0.5%, placebo 0.2%), followed by accidental injury (pregabalin 0.4%, placebo 0%). Congestive heart failure, myocardial infarction, infection, and pneumonia each occurred with a frequency of 0.3% in pregabalin-treated subjects, and these frequencies were not considerably different from the placebo group. The table below shows the SAEs that occurred in at least 0.2% of pregabalin-treated patients in controlled DPN trials.

SAEs in controlled DPN trials

Body system	Preferred term	Placebo N	[N=459] %	All PGB N	[N=979] %
Body as a whole	Chest pain	1	0.22	5	0.51
	Accidental injury	0	0.00	4	0.41
	Infection	1	0.22	3	0.31
Respiratory system	Pneumonia	1	0.22	3	0.31
Cardiovascular system	Congestive heart failure	1	0.22	3	0.31
	Myocardial infarct	0	0.00	3	0.31
	Angina pectoris	0	0.00	2	0.20
	Cerebrovascular accident	0	0.00	2	0.20
Respiratory system	Dyspnea	0	0.00	2	0.20
Metabolic and nutritional disorders	Hypoglycemia	0	0.00	2	0.20
Digestive system	Vomiting	0	0.00	2	0.20

SAEs that coded to preferred terms of interest (as identified by Dr. Boehm) in pregabalin subjects were acute kidney failure, kidney function abnormal, jaundice, macrocytic anemia, myopathy, and skin ulcer (n = 1, each). Only one case was suggestive of a relationship to study drug, while the remaining SAEs, upon review by Dr. Kashoki, appeared to have alternate explanations for the events. The single event deemed possibly related involved a 31 year-old female (subject **149 430001)** with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension who developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject

was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatine kinase to 124 U/L. and she was discharged on study day 72.

3.4.3.2 Combined controlled and uncontrolled trials

Among the pregabalin-treated subjects in combined controlled and uncontrolled DPN studies, 17.3% (244/1413) experienced at least one SAE. Congestive heart failure, myocardial infarct, and chest pain were reported by more than 1% of subjects in DPN. There were several SAEs that coded to preferred terms of interest:

SAEs in DPN combined trials that coded to preferred terms of interest

SAE	Any Dose Pregabalin [N = 1413] N (%)
Acute kidney failure	3 (0.2)
Kidney function abnormal	3 (0.2)
Kidney failure	1 (0.1)
Nephrosis	1 (0.1)
Lung disorder	2 (0.1)
Lung edema	1 (0.1)
Lung fibrosis	1 (0.1)
Pancreatitis	2 (0.1)
Liver function tests abnormal	1 (0.1)
Cholestatic jaundice	1 (0.1)
Jaundice	1 (0.1)
Edema	1 (0.1)
Generalized edema	1 (0.1)
Leukemoid reaction	1 (0.1)
Macrocytic anemia	1 (0.1)
Megaloblastic anemia	1 (0.1)
Pancytopenia	1 (0.1)
Allergic reaction	1 (0.1)
Anaphylactoid reaction	1 (0.1)
Myopathy	1 (0.1)
Cellulitis	12 (0.8)
Skin ulcer	7 (0.5)
Abcess	4 (0.3)
Peripheral gangrene	3 (0.2)
Healing abnormal	1 (0.1)
Joint disorder	1 (0.1)
Osteomyelitis	1 (0.1)
Pyogenic arthritis	1 (0.1)
Rash	1 (0.1)
Sepsis	1 (0.1)

(Dr. Kashoki's table 7.4.4.3.1.B:)

All of the corresponding CRFs were reviewed to ascertain whether there was a relationship to study drug. Events assessed as related, or lacking in alternative explanation are summarized in the table in the section on the overall database above. The events include:

Pulmonary fibrosis, 71 y.o. M
Leukemoid reaction, 72 y.o. F
Macrocytic anemia, 62 y.o. M
Edema, 52 y.o. M
Acute renal failure, 71 y.o. M
Acute renal failure, rhabdomyolysis, 31 y.o. F
Acute renal failure, 62 y.o. F
Abscess, 52 y.o. M
Cellulitis, 69 y.o. F
Cellulitis, 69 y.o. M
Cellulitis, 46 y.o. F

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.

Also as discussed above, non-clinical studies in mice, rats, and monkeys demonstrated pregabalin-associated dermatopathy. Since patients with diabetes are at significant risk for injury, poor wound healing, and ulceration, Dr. Kashoki queried the AE database to explore whether skin-related adverse events possibly associated with pregabalin were seen in this population. The following terms were used in this search: ulcer, wound, cellulitis, infection, necrosis, erythema, (delayed) healing, abcess, dermatitis, peripheral gangrene, healing abnormal, osteomyelitis, sepsis, and urticaria.

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.

Furthermore, because of the specific vulnerability of the population, Dr. Kashoki examined the database for evidence of effects of pregabalin on glycemic control.

The entire safety database, and then data from all DPN trials, were evaluated for the frequency of the following AEs (serious or non-serious): dermatological AEs, eye-related AEs, and metabolic AEs (hyper-or hypoglycemia and edema).

3.5.1 Neoplastic Events

Three subjects in the overall safety database reported vascular neoplasms. One was coded as "angiolieomyoma," one as "angioma," and one as "cherry angiomas." Further detail provided by Pfizer at Agency request did not suggest causality.

3.5.2 Dermatologic Events

3.5.2.1 Overall Database

The entire safety database was queried for dermatological AEs. A total of 1366 subjects in the entire safety database reported a skin- or appendage-related AE. There were 300 reports of skin-related AEs when patients were taking either placebo or no study medication at all. There were 1259 reports when patients were taking pregabalin.

Rash was the most commonly reported AE, occurring with greater frequency among patients taking pregabalin 600 mg/day (3.2%) compared to those not taking pregabalin (2.18%). Similarly, subjects on pregabalin 600 mg/day reported skin disorders (0.6%) and skin ulcers (0.7%) more often than subjects taking either placebo or no study medication at all (0.2% and 0.04%, respectively). Because uncontrolled trials are included in this database, it is difficult to distinguish a drug effect from an effect of time on study.

3.5.2.2 Diabetic Peripheral Neuropathy Database

In the overall database, including both controlled and uncontrolled trials, there were 272 subjects with pain due to diabetic peripheral neuropathy who reported a skin-related AE. There were 46 reports of these AEs in patients on placebo or no study medication at all, and 289 reports when subjects were taking pregabalin. Rash was the most commonly reported dermatological AE, and skin ulcer was the next most common. Rash, skin ulcer, eczema, dry skin, nail and other "skin disorders" were reported in more subjects with DPN while taking pregabalin than while taking placebo or no study drug. However, these findings may be due to the longer time on study for patients taking pregabalin in open-label studies.

Skin ulcers were of particular interest, due to the preclinical findings of skin lesions occurring across species and routes of administration. Skin ulcers occurred with similar frequency in pregabalin and placebo groups in the controlled trials, but in the controlled and uncontrolled database combined, they occurred with greater frequency among subjects taking ≥ 300 mg/day with an apparent dose-dependency when "dose at onset" was used to assign the event to a dose. However, an analysis of ulcer-free survival time suggested that the differences in time on study can account for the observed effect. Nevertheless, the possibility of clinical correlation to the animal findings is of particular concern in this population, with impaired wound healing.

3.5.3 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."

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. Given the existing retinal complications of diabetes, an adverse drug effect of pregabalin on the retina is of particular concern in the diabetic population.

3.5.4 Glycemic Control

Looking specifically at the DPN database (to avoid dilution of the effect by inclusion of non-diabetic populations), Dr. Kashoki observed that both hyperglycemia and hypoglycemia, reported as adverse event terms, were more frequent in the pregabalin-treated patients than in placebo-treated patients. In controlled trials, lasting 6-12 weeks, adverse event reports of impaired glucose control were uncommon. Hyperglycemia was reported by 1.3% of the pregabalin-treated patients in controlled trials, vs. 0.65% of placebo-treated patients, while hypoglycemia was reported by 1.7% of pregabalin-treated patients and 1.1% of placebo-treated patients.

In the combined database of controlled and uncontrolled trials, Dr. Kashoki identified 53 patients who reported hyperglycemia and 46 subjects who reported hypoglycemia. Three patients had a serious episode of hyperglycemia, and six subjects experienced serious episodes of hypoglycemia, none of which was likely related to study drug.

3.5.5 Male Fertility

In animal studies, pregabalin was shown to have reproductive toxicity in males. Pfizer conducted a study in male human volunteers to evaluate the effect of pregabalin on reproductive function in humans. Pfizer concluded that this study, study #072, demonstrated that [

]

[redacted] (Proposed label language.) Dr. George Benson, HFD-580, reviewed study 072 and associated animal data, and concluded that, due to small sample size and study design, Study 072 does not provide reasonable reassurance that pregabalin has no adverse effect on human reproductive function. Dr. Benson noted that an additional clinical trial should be performed if a portion of the target population is younger men of reproductive age and potential, and provided suggestions for study design. (See Dr. Benson's review.)

3.6 Common Adverse Events

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

The table below lists, by body system, the non-serious adverse events reported by more than 1% of pregabalin-treated patients in the controlled DPN studies. Overall, nervous system abnormalities were the most common AEs. Specifically, dizziness (21.4%) and somnolence (12.2%) were the most frequent (relative risks of 4.7 each). Other CNS AEs included changes in mental status (confusion, abnormal thinking, euphoria), motor effects (gait abnormalities, incoordination, tremor, ataxia), and vertigo. Another notable common AE was edema, which occured in 13.5% of pregabalin-treated patients. Also, amblyopia and vision abnormalities occurred with greater frequency than in placebo patients. Finally, there were gastrointestinal effects of dry mouth, constipation, and dyspepsia.

Adverse Events in DPN controlled trials

		Pregabalin dose at which AE occurred (mg/d)											
Body system	**Preferred term**	**Placebo**	**[N=459]**	**75**	**[N=77]**	**150**	**[N=221]**	**300**	**[N=321]**	**600**	**[N=369]**	**All PGB**	**[N=979]**
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Body as a whole	Headache	41	8.93	5.00	6.49	13	5.88	23	7.17	29	7.86	70	7.15
	Infection	33	7.19	5.00	6.49	18	8.14	29	9.03	16	4.34	68	6.95
	Asthenia	12	2.61	3.00	3.90	4	1.81	14	4.36	27	7.32	48	4.90
	Pain	20	4.36	4.00	5.19	9	4.07	10	3.12	19	5.15	42	4.29
	Accidental injury	16	3.49	4.00	5.19	6	2.71	7	2.18	18	4.88	35	3.58
	Back pain	3	0.65	0.00	0.00	5	2.26	4	1.25	8	2.17	17	1.74
	Chest pain	5	1.09	2.00	2.60	3	1.36	4	1.25	4	1.08	13	1.33
	Face edema	2	0.44	0.00	0.00	2	0.90	3	0.93	8	2.17	13	1.33
	Flu syndrome	11	2.40	1.00	1.30	1	0.45	3	0.93	7	1.90	12	1.23
Digestive system	Dry mouth	5	1.09	2.00	2.60	4	1.81	15	4.67	24	6.50	45	4.60
	Constipation	6	1.31	0.00	0.00	5	2.26	13	4.05	22	5.96	40	4.09
	Diarrhea	23	5.01	4.00	5.19	6	2.71	6	1.87	13	3.52	29	2.96
	Nausea	26	5.66	1.00	1.30	5	2.26	12	3.74	9	2.44	27	2.76
	Flatulence	6	1.31	2.00	2.60	0	0.00	7	2.18	10	2.71	19	1.94
	Vomiting	7	1.53	1.00	1.30	3	1.36	7	2.18	4	1.08	15	1.53
	Dyspepsia	4	0.87	0.00	0.00	3	1.36	5	1.56	6	1.63	14	1.43
Metabolic and nutritional disorders	Peripheral edema	12	2.61	3.00	3.90	13	5.88	31	9.66	48	13.01	95	9.70
	Weight gain	2	0.44	0.00	0.00	9	4.07	12	3.74	23	6.23	44	4.49
	Edema	0	0.00	0.00	0.00	4	1.81	13	4.05	7	1.90	24	2.45
	Hypoglycemia	5	1.09	1.00	1.30	6	2.71	5	1.56	4	1.08	16	1.63
	Hyperglycemia	3	0.65	1.00	1.30	2	0.90	5	1.56	4	1.08	12	1.23
Musculoskeletal system	Leg cramps	8	1.74	1.00	1.30	0	0.00	4	1.25	5	1.36	10	1.02
Nervous system	Dizziness	21	4.58	6.00	7.79	19	8.60	77	23.99	108	29.27	210	21.45
	Somnolence	12	2.61	3.00	3.90	13	5.88	42	13.08	61	16.53	119	12.16
	Neuropathy	16	3.49	7.00	9.09	4	1.81	7	2.18	20	5.42	38	3.88

Nervous system	Ataxia	6	1.31	5.00	6.49	2	0.90	7	2.18	17	4.61	31	3.17
	Vertigo	5	1.09	1.00	1.30	4	1.81	8	2.49	13	3.52	26	2.66
	Confusion	3	0.65	0.00	0.00	3	1.36	7	2.18	12	3.25	22	2.25
	Euphoria	1	0.22	0.00	0.00	1	0.45	11	3.43	6	1.63	18	1.84
	Incoordination	2	0.44	1.00	1.30	1	0.45	6	1.87	7	1.90	15	1.53
	Thinking abnormal	0	0.00	1.00	1.30	0	0.00	3	0.93	11	2.98	15	1.53
	Tremor	0	0.00	1.00	1.30	3	1.36	4	1.25	6	1.63	14	1.43
	Abnormal gait	0	0.00	1.00	1.30	0	0.00	2	0.62	10	2.71	13	1.33
	Insomnia	4	0.87	1.00	1.30	3	1.36	3	0.93	6	1.63	13	1.33
	Reflexes decreased	8	1.74	3.00	3.90	1	0.45	4	1.25	5	1.36	13	1.33
	Amnesia	1	0.22	2.00	2.60	2	0.90	0	0.00	8	2.17	12	1.23
	Nervousness	1	0.22	0.00	0.00	2	0.90	3	0.93	5	1.36	10	1.02
Respiratory system	Bronchitis	6	1.31	2.00	2.60	3	1.36	2	0.62	7	1.90	14	1.43
	Dyspnea	3	0.65	2.00	2.60	0	0.00	6	1.87	6	1.63	14	1.43
	Pharyngitis	5	1.09	0.00	0.00	2	0.90	5	1.56	4	1.08	11	1.12
Skin and appendages	Rash	8	1.74	0.00	0.00	1	0.45	2	0.62	7	1.90	10	1.02
Special senses	Amblyopia	7	1.53	2.00	2.60	3	1.36	9	2.80	21	5.69	35	3.58
	Abnormal vision	1	0.22	1.00	1.30	1	0.45	4	1.25	5	1.36	11	1.12
Urogenital system	Urinary tract infection	6	1.31	0.00	0.00	2	0.90	4	1.25	6	1.63	12	1.23

Dr. Kashoki also identified identify AEs that occurred in less than 1% of pregabalin-treated patients, but which coded to preferred terms of potential importance. The following select AEs were identified:

AE of interest	% Pregabalin	% Placebo
Creatinine clearance decreased*	0.41	0.22
Creatinine increased	0.1	0.0
Kidney function abnormal	0.1	0.0
Liver function tests abnormal	0.2	0.0
Pancreatitis	0.1	0.0
Cellulitis	0.41	0.0
Mouth ulceration	0.31	0.0

* Relative risk = 1.9

3.7 *Explorations to Identify Potential Tolerability Differences Across Dosing Regimens*

All controlled DPN protocols except for 1008-131 incorporated a titration phase. The safety data for these trials were evaluated to see if there were differential rates of dropouts, non-serious adverse events, and dropouts due to these non-serious adverse events. Titration is generally employed to improve tolerability, and this exploration was undertaken to establish whether the expectation of improved tolerability was borne out. Dr. Kashoki compared overall dropout rates, which revealed that the overall dropout rate for titrated trials (15.9%) was, in fact, higher than that for non-titrated trials (13%). Similarly, the rates of dropout due to AEs were 6.8% (10/146) in non-titrated trials, and 11.7% in titrated trials.

However the non-titrated trial was associated with almost twice the rate of dizziness and somnolence (36% and 20%) than the non-titrated trials (19% and 10%, respectively). Lack of drug titration was also associated with a greater frequency of euphoria (5% vs. 0%). Otherwise, rates of non-serious AEs was similar between titrated and non-titrated controlled DPN studies.

3.8 *Explorations to Identify Potential Tolerability Differences Due to Impaired Renal Function*

All trials enrolled patients with mild renal impairment, requiring a creatinine clearance of only 60 mL/min for entry (50-80 mL/min is considered "mild" impairment). One trial enrolled subjects with creatinine clearance as low as 30 mL/min (moderate impairment). Dr. Kashoki examined the data but did not note an increase in adverse effects associated with moderate renal impairment, possibly because of the small numbers of patients enrolled.

3.9 Laboratory data

In their analysis of lab data for the integrated safety database, Pfizer calculated mean changes from baseline for all analytes and based on those results provided additional discussion of platelet and CPK outliers. The mean change analyses compared subjects' last lab result prior to initiating study medication in any study (baseline) to their last available non-follow up result (endpoint). Dr. Kashoki examined the descriptive comparisons of laboratory data provided by the sponsor, which included tabulations of mean changes from baseline in various lab parameters, and tabulations of patients with "low" and "high" 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. Dr. Kashoki's review focused on results of controlled trials, and presented analyses of uncontrolled trials when appropriate.
The most notable differences between treatment groups from Pfizer's analysis of the mean changes from baseline was an increase in creatinine kinase and a decrease in platelets among pregabalin treated patients compared to placebo patients.

3.9.1 Platelets

3.9.1.1 Measures of Central Tendency

Considering the change from baseline to end of treatment, pregabalin-treated subjects experienced a mean decrease in platelets of 9.5 x $10^3/\mu L$ compared to 0.3 x $10^3/\mu L$ in placebo patients. Analyses of the mean decrease in platelet values between pregabalin and placebo patients in the overall database found that the decreases were statistically significant across all treatment groups. The mean changes ranged from -5.348 x $10^3/\mu L$ in the pregabalin 150 mg/day group to -12.3 x $10^3/\mu L$ in the pregabalin 450 mg/day group. Pfizer reported that in the combined controlled and uncontrolled studies across all indications, the mean decrease in platelet counts (-5.325 x 10_3 /L) was similar in magnitude to that observed in the controlled studies.

Dr. Kashoki examined the data for the DPN population specifically and noted that the mean decreases in platelets (-9.546 x $10^3/\mu L$, all pregabalin) were consistent with the changes observed in the overall population.

3.9.1.2 Outliers

In the overall database of controlled trials, a total of 1.6% (36/2224) placebo patients and 3.2% (162/5142) pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and < 150 x $10^3/mm^3$. Low platelet counts (≤ 100 x10 $3/mm^3$) occurred in 0.4% of placebo-treated patients and 0.9% of pregabalin-treated patients, although no patient had a very low platelet count (≤ 10 x $10^3/mm^3$). 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).

Pfizer reported that in the combined controlled and uncontrolled studies across all indications, a decrease in platelets occurred in 5.4% (424/7851) of patients. A total of 114 patients had a post-baseline platelet count ≤ 100 x 10^3/mm^3. For most 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. but neither event was considered serious nor led to withdrawal.

Dr. Boehm identified 120 patients with a platelet count <100,000/mm^3, and reviewed their laboratory values in depth. His review did not reveal a clear association between the decrease and development of bleeding abnormalities.

3.9.1.3 Specific studies of platelet function

Relevant to the pre-clinical findings of angiosarcomas in mice, which Pfizer attributed to a species-specific effect on endothelial cells, platelet activation, and platelet aggregation, Pfizer conducted specific clinical pharmacology studies in healthy volunteers to evaluate the effect of pregabalin on platelet function and did not find an effect.

3.9.2 Creatine Kinase

3.9.2.1 Measures of Central Tendency

Pregabalin-treated subjects experienced a mean increase in creatinine kinase from baseline to endpoint of 9.7 U/L compared to 4.8 U/L for placebo patients in the controlled studies. In the combined controlled and uncontrolled studies, Pfizer found that the mean increase in creatine kinase (12.42 U/L) was similar in magnitude to that observed in the controlled studies. In the combined controlled and uncontrolled studies, Pfizer found increases in creatine kinase occurred in 1.9% (103/5352) of patients with CK measurements.

Pfizer examined change from baseline to maximum value, at Agency request, and found a mean increase of 27.9 U/L in the placebo group and 60.13 U/L in the pregabalin group. All clinical populations showed a difference between placebo and pregabalin groups, with the pregabalin group showing mean increases in the range of 2x – 3x that of the placebo group. Highest values for both placebo and pregabalin groups were seen in the epilepsy population, while the DPN and PHN populations had the lowest values. For the DPN population, the mean change from baseline to maximum value was 13.17 U/L in the placebo group, and 32.41 U/L in the pregabalin group.

To assess change in CK over time, Dr. Boehm analyzed the CK mean changes by study visit for the pooled epilepsy controlled trials (chosen because all study durations and test intervals were identical across trials in this dataset). This analysis revealed that the mean CK increases from baseline relative to placebo were present early, varied over the course of the study, and did not suggest dose response for the studied doses.

Outliers

In the overall database of controlled trials, Pfizer reported that 1.7% (62/3742) of pregabalin subjects and 0.8% (12/1529) of placebo subjects had a post baseline creatine kinase greater than 3x ULN. Pfizer found that 10.5% (397/3781) of pregabalin subjects and 8.1% (125/1544) of placebo subjects had a "high" creatine kinase lab result (≥340U/L in males, ≥180U/L in females) at any time. Furthermore, 0.7% (28/3781) of pregabalin subjects and 0.3% (5/1544) of placebo subjects had a "very high" creatine kinase result (≥1000U/L). Dr. Boehm reanalyzed the data taking into consideration only subjects with normal CK at baseline, and found that overall, 0.9% (27/2944) of pregabalin subjects and 0.4% (5/1223) placebo subjects with a normal baseline CK had a post-baseline CK greater than 3x ULN; 6.7% of pregabalin subjects and 5.6% of placebo subjects had a "high"CK result, and 0.5% of pregabalin and 0.2% of placebo subjects had a "very high" CK. In the DPN population, 0.6% (3/517) of pregabalin subjects and 0/252 placebo subjects with a normal baseline CK had a post-baseline CK greater than 3x ULN; 3.6% (28/503) of pregabalin subjects and 4% (11/241) of placebo subjects had a "high"CK result, and 0.2% (1/524) of pregabalin and 0/253 of placebo subjects had a "very high" CK.

Examination of shift tables shows that, across all populations, more pregabalin-treated patients who had a baseline CK of < 2x ULN had an increase in CK to >2x ULN (3%) than did placebo patients (1.3%). There were more patients in the DPN population who experienced this change (5.4% pregabalin vs. 1.3% placebo) compared to the epilepsy (3.5% vs. 1.6%) and GAD populations (2.1% vs. 1%).

There were 81 patients who had a CK >5 x ULN. Dr. Boehm requested that Pfizer determine which of these subjects also had recorded AEs that were suggestive of myopathy (e.g. muscle weakness, muscle pain, etc.). Pfizer identified 12 such subjects, and Dr. Boehm identified a 13th. Of these, 6 had abnormalities suggestive of a relationship to pregabalin treatment, although 3 of the 6 experienced resolution of their symptoms despite continued treatment with pregabalin.

Among subjects who had a creatine kinase result >3x ULN or >1000U/L, four also had evidence of renal dysfunction (increase in creatinine >0.2mg/dL). Pfizer noted that three of four had evidence of renal dysfunction at baseline and experienced further increase in creatinine that were temporally associated with the increase in creatine kinase. The fourth subject had an elevated creatine kinase at baseline and both creatine kinase and creatinine increased during the study (both analytes returned to normal after stopping pregabalin). An additional subject who had elevations in creatine kinase and creatinine but was not included in the lab database because the lab values were from a local laboratory. This subject reportedly had a non-serious adverse event of rhabdomyolysis concurrent with anemia, hepatitis C, type II diabetes mellitus, hypokalemia, hyponatremia, and hypotension and a serious AE of cellulitis; fever of 107 F and renal dysfunction (increased creatinine). Creatinine and creatine kinase returned to normal within two weeks while the subject continued on pregabalin.

Overall, increases in CK tended to occur early in treatment, and were 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 rhabdomyolosis or renal failure associated with increased CK.

3.9.3 Lab parameters of particular importance to diabetic population

Dr. Kashoki also looked closely at the data related to glycemic control and renal function (creatinine) in the DPN population and noted that there was no clear indication that pregabalin-treated patients were at greater risk for potentially clinically significant increases in glucose or creatinine compared with placebo-treated patients. In the adverse events database, although adverse events associated with renal function were reported in a higher proportion of pregabalin-treated than placebo-treated subjects, the overall numbers were small.

AE of interest	% Pregabalin	% Placebo
Creatinine clearance decreased*	0.41	0.22
Creatinine increased	0.1	0.0
Kidney function abnormal	0.1	0.0
Hyperglycemia	1.3	0.65
Hypoglycemia	1.7	1.1

In the laboratory values database, in controlled DPN trials, the proportion of patients with a decrease in estimated creatinine clearance of at least 15% was similar between pregabalin (10.9%) and placebo (11.3%). High (2.0 mg/dL) serum creatinine values were observed in 3.2% of the controlled and uncontrolled DPN population, and no DPN patients had a very high (6 mg/dL) creatinine value. No effect on serum glucose was noted.

3.10 Vital Signs

Weight, heart rate and blood pressure were measured in all clinical trials, however the latter two 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. 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. 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).

3.11 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.

Within the DPN studies, the distribution of weight gain from baseline to last observation is tabulated below:

Cumulative distribution of weight gain by dose – DPN controlled studies

		Pregabalin Dose, mg/day (BID and/or TID)				
	Placebo	75	150	300	600	Any Dose
Percent Change	N=459	N=77	N=212	N=321	N=369	N=979
N at Risk*	444	73	207	309	358	947
Increase						
>=7	6 (1.4)	3 (4.1)	7 (3.4)	12 (3.9)	27 (7.5)	49 (5.2)
>=10	2 (0.5)	1 (1.4)	2 (1.0)	3 (1.0)	4 (1.1)	10 (1.1)
>=15	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	1 (0.3)	3 (0.3)
>=20	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

(Sponsor's Appendix ALL.135, Summary of Clinical Safety, P. 7366)

Exploration of edema (reported as a drug-related AE) as a possible explanation for weight gain revealed that approximately 13% (51 of 401) of pregabalin-treated patients in the overall database with weight gain had a concurrent adverse event of edema. None of

the 38 of placebo-treated patients with ≥7% weight gain had concurrent edema. DPN and PHN patients with ≥ 7% weight gain had the highest incidence of concurrent edema (30.6% and 26.8%, respectively). The epilepsy population had a lower incidence of edema and ≥ 7% weight gain (8.3%), whereas the GAD population had no overlap between weight gain and peripheral edema.

3.12 ECGs

ECG data were collected in 28 clinical trials. Both placebo and pregabalin patients, were included in the analysis, as long as they had an ECG at baseline and during the treatment period which were analyzed by a central reader. Two summary reports for combined ECG data were provided; one report compiled data from 2876 pain patients, 850 epileptic patients, and 1019 psychiatric patients, while the second included data from various other "psychiatry" studies. . At the Division's request, Pfizer also calculated the percentage of patients who had shifts from baseline to maximum value in ventricular rate, as well as PR, QRS, and QTc intervals. Pregabalin did not appear to have a clinically significant effect on QT intervals. Slightly more patients (2.8%) in the pregabalin group had a shift in the PR interval from normal to 'high' compared to 2.1% in the placebo group. The percentage of patients with an absolute post-baseline PR ≥220 msec and a maximum increase in PR ≥ 40 msec (0.005%) was the same for the pregabalin 600 mg/day group (5/966) as the placebo group (6/1160). The percentage of any pregabalin-treated patients meeting these PR criteria was 0.002%. The frequency of AV block first degree was the same (0.1%) in placebo- treated and pregabalin-treated patients. In the DPN group, the results were similar to the overall group.

However, no formal evaluation in a clinical pharmacology setting was undertaken, nor has the potential for HERG channel inhibition by pregabalin been evaluated. The lack of this evaluation is noted by the Office of Clinical Pharmacology and Biopharmaceutics in their review and identified as a deficiency requiring further investigation.

3.13 Safety Update

A safety update encompassing 1617 additional patient exposures (including 273 in controlled studies) was submitted during the review cycle and reviewed with primary attention to additional information regarding deaths and serious adverse events. An additional 13 deaths are reported in the Safety Update, 8 of which occurred during trials that are now complete, and 5 that occurred in trials that are ongoing. None of the deaths was without possible alternate cause, except perhaps for a case of accidental head injury following a fall (patient 904-5 in protocol 1008-198) which could plausibly have been related to pregabalin's CNS effects. However, the patient was elderly and had a history of falls. The Safety update includes information on SAEs occurring in 54 additional patients. Of the 54 patients, there were 19 patients (2 placebo, 17 pregabalin) who who experienced a SAE during a completed controlled trial or its open label extension. Among these 19 patients, notable SAEs were acute renal failure and symptoms of pregabalin drug withdrawal, both of which occured in the same individual.

3.14 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 will be prepared by the CSS, and the drug may not be marketed, even if approved, until the DEA has completed consideration and implementation of any scheduling action.

3.14.1 Withdrawal phenomena

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). Among the studies in which this information was collected was one DPN study, Protocol 1008-040. In that study, which featured a one week taper at the end of 8 weeks of treatment, DESS occurred in 10.5% of pregabalin-treated patients, 16% of placebo-treated patients, and 14% of amitriptyline-treated patients. However, across the entire database, which included studies incorporating drug tapers of 3-6 days, DESS were more common in pregabalin-treated than placebo-treated patients. The CSS concluded that that subjects who abruptly discontinue, or cease pregabalin treatment over a short duration, commonly experience insomnia, headache, nausea, and diarrhea. The CSS concluded that this constellation of symptoms describes a withdrawal syndrome, and indicates the presence of physical dependence.

3.14.2 Abuse Potential

Data relevant to the abuse potential of pregabalin included a specific laboratory study in sedative/alcohol abusers, animal studies using various models of self-administration, and the occurrence of side effects in clinical trials which suggest potential for the drug to be used for its psychic effects.

The laboratory study compared subjective responses of volunteers to different doses of pregabalin and diazepam. Although Pfizer interpreted the outcome differently, CSS review of this data concluded that subjective responses to pregabalin (200 mg and 450 mg) were similar to responses to diazepam, a Schedule IV substance.

Furthermore, CSS noted that euphoria was reported as an AE in clinical trials at a rate consistently higher in pregabalin-treated than placebo-treated subjects across indications.

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. Dr. Katherine Bonson, the CSS Pharmacology Reviewer, tabulated the incidence of "euphoria" in GAD and epilepsy trials:

	% Patients		
Pregabalin dose	GAD	Epilepsy	NeP*
150	0.5	0	1.0
200	10.3	-	-
300	3.3	2.2	2.4
400	4.8	-	-
450	11.8	-	-
600	2.5	1.0	1.5
All doses	4.5	0.8	1.4
Placebo	1.2	0.3	0

*Neuropathic pain

These findings, taken together with inconsistent but suggestive findings in the animal studies, led CSS to conclude that pregabalin should be a controlled substance.

3.14.3 Overdose

Dr. Kashoki identified 91 patients in the overall database who took pregabalin doses exceeding 600 mg/day. Doses ranged from as low as 625 mg to 2400 mg. "Overdose" durations ranged from 1 to 464 days.

There were 20 patients who reported taking >900 mg/d. Six patients took overdoses that ranged from 1500 mg to 8000 mg. Five overdoses were intentional and occurred in patients with epilepsy or GAD.

The maximum reported overdose, 15000 mg, reportedly resulted in no consequences; however, this overdose was not substantiated by blood levels or the dosing information recorded in the clinical study database (1700 mg was recorded).

Adverse events associated with overdose included accidental injury, headache, asthenia, dizziness, somolence, ataxia, blurred vision, confusion, peripheral edema, and diplopia. No deaths resulted from overdose.

4 CONCLUSION AND RECOMMENDATIONS

This application provides substantial evidence that pregabalin, at daily doses of 300-600 mg/day, given in three divided doses, is effective in reducing the pain associated with diabetic peripheral neuropathy for periods up to 8 weeks. The data suggest that the 600 mg/day dose may offer no benefit over the 300 mg/day dose, and the single 12-week study did not demonstrate efficacy at the end of the treatment period.

The safety data show that the nervous system abnormalities (dizziness, somnolence, changes in mental status, motor changes, and vertigo) were the most common AES.

Specifically, dizziness (21.4%) and somnolence (12.2%) were the most frequent. Also notable were edema (13.5%) blurred vision and dry mouth, constipation, and dyspepsia. Approximately 13% of DPN subjects 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. The diabetic population is already prone to retinal damage and vision loss due to the underlying disease, and may be at risk of debilitating consequences if exposed to a product which caused further ophthalmologic damage.

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 of dermatopathy, the diabetic population is uniquely vulnerable to adverse consequences of otherwise minor skin lesions, due to the poor wound healing associated with diabetes. A clinical correlation with the observed carcinogenicity in mice was not observed, as would be expected in a safety database encompassing exposures of largely brief duration.

Finally, the drug is renally eliminated, and patients with diabetic neuropathy typically also have diabetic nephropathy. These diabetic patients are likely to experience elevated systemic exposure to pregabalin at any given dose, making them especially vulnerable to the entire range of dose-dependent adverse effects of the drug; even at a fixed nominal dose, systemic exposure in a given patient may increase over time as renal function declines.

The animal carcinogenicity and dermatopathy, along with the ophthalmologic effects of pregabalin, taken together with the vulnerabilities of the diabetic population, call into question the risk/benefit ratio for the overall DPN population.

At a regulatory briefing on March 19, 2004, Center management considered the available information and concluded that it may be possible to define a population for whom the benefits of pregabalin outweigh the risks, and that the issues of carcinogenicity, dermatopathy, and visual effects could be handled with suitable warning language in labeling, although it was acknowledged that such warnings would be of a strong nature possibly involving a boxed warning. The panel proposed that dosing be limited to 300 mg/day and that the use of the product be limited to patients refractory to other treatment. However, it is not clear that the efficacy of the product can be assured in this population. In fact, patients refractory to neurontin (commonly used off-label) were specifically excluded from trial participation. Further exploration of the characteristics of responders is needed to determine whether there exists a population whose need for treatment is so

great as to warrant the various risks of pregabalin, and who can be reasonably expected to derive benefit. Exploration of the data available did not reveal any obvious way to limit the population. Furthermore, nerve conduction studies, which the Division had agreed to accept post-approval, may be needed pre-approval to completely delineate the risk/benefit relationship for pregabalin in DPN. It is also noted that the current Agency approach for products under development for this chronic illness require studies of 12 weeks' duration to establish efficacy. Pfizer was permitted to submit this application based on a single 12 week study, with confirmatory evidence from other, shorter studies. However, the single study of 12 weeks' duration (which, to further confound interpretation, used a different treatment regimen from the other studies) did not demonstrate efficacy at the end of treatment, calling into question the durability of the effect observed in clinical studies.

Although the application contains substantial evidence of efficacy of pregabalin in the treatment of pain due to diabetic peripheral neuropathy for periods up to 8 weeks, I recommend against approval of this application because it is not clear that the benefits of this product outweigh the risks in the intended population. If the application is approved, I recommend that Pfizer conduct post-approval studies to further delineate the ophthalmologic effects and the reproductive (male fertility) effects of pregabalin, and nerve conduction studies to demonstrate lack of direct neurotoxicity. The nature of the male fertility study has been described in Dr. Benson's review; recommendations for further ophthalmologic evaluation are in Dr. Chambers' review.

Until the ophthalmologic studies are carried out to the Agency's satisfaction, I recommend the label carry a warning about the potential for adverse effects on visual acuity and visual fields.

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/s/

Celia Winchell
6/3/04 11:27:11 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:	**May 21, 2004**
Medical Officer:	**Mwango A. Kashoki, M.D., M.P.H**
Project Manager:	**Lisa Malandro**

Table of Contents

Clinical Review of NDA 21-446

Executive Summary

1 RECOMMENDATIONS

1.1 Recommendations on Approvability

Pregabalin, at doses of 300 mg/d and 600 mg/d, administered in three divided doses, is efficacious in reducing pain associated with diabetic peripheral neuropathy. There does not appear to be a greater benefit of treatment with 600 mg/d compared to 300 mg/d. The safety of pregabalin in patients with diabetes is uncertain, given preclinical evidence of dermatopathy, as well as clinical reports of vision abnormalities associated with treatment. Together, these adverse effects represent a concerning level of risk in the diabetic population that is already at considerable risk of morbidity related to retinopathy and skin ulceration.

Based on the available data, therefore, approval of this application is not recommended. Further characterization of the dermatological and ophthalmologic effects of pregabalin is recommended.

1.2 Recommendations on Phase 4 studies and Risk Management Steps

Evaluation of nerve function in a 12 week, adequate and well-controlled study of pregabalin in patients with pain due to diabetic neuropathy (DPN) is required to demonstrate that efficacy in DPN does not correlate with accelerated nerve damage.

The Controlled Substances Staff has found that pregabalin has similar abuse liability as diazepam and has recommended that pregabalin be scheduled (Schedule IV). Risk management for pregabalin can therefore occur under the regulations of the Controlled Substances Act.

2 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.

2.1 Brief Overview of Clinical Program

Product name: Pregabalin
Route of administration: Oral

Indication: Management of pain associated with diabetic peripheral neuropathy

The application contained 5 efficacy trials, four of which were considered adequate and well-controlled (AWC). Three of the trials contributed to the finding of efficacy. These 3 trials were of variable duration (5-8 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 and 2 weeks. The four AWC trials included 252 placebo-treated subjects, 157 subjects treated with 300 mg/d, and 164 subjects treated with 600 mg/d. Overall exposure (both controlled and open-label DPN trials) to the highest dose was 289 patients for at least 6 months, and 201 patients for at least 1 year. Safety data were obtained from 53 phase 2/3 trials in multiple indications (epilepsy, osteoarthritis, fibromyalgia, chronic low back 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.

2.2 Efficacy

In three US efficacy studies the mean pain score for subjects randomized to pregabalin 300 and 600 mg/day, administered in three divided doses (TID) was lower than the mean pain score for patients randomized to placeob. Also, subjects treated with pregabalin were more likely than subjects treated with placebo to report a clinically significant decrease in pain due to diabetic peripheral neuropathy. The TID dosing regimen supported by the efficacy trials is different from the Applicant's labeling claim, [redacted] Although the Applicant submitted a single trial of BID dosing (Protocol 1008-149), this trial failed to show efficacy on our analysis of the primary endpoint, weekly mean pain score at the final week of the study. Another protocol (Protocol 1008-040) also failied to show a difference of pregabalin (200 mg TID) from placebo.

The three trials that showed efficacy were:

- **Protocol 1008-014**: "A double blind, placebo-controlled trial of pregabalin for treatment of painful diabetic peripheral neuropathy" – an 8 week comparison of placebo vs. pregabalin at 2 different doses in 246 patients
- **Protocol 1008-029**: "A 5-week, double-blind, placebo-controlled trial of 3 dosages of pregabalin (75, 300, and 600 mg/day) for treatment of patients with diabetic peripheral neuropathy"- a comparison of placebo vs. pregabalin at 3 different doses in 337 patients
- **Protocol 1008-131**: "An 8-week, double-blind, placebo-controlled trial of pregabalin (300 mg/day) for relief of pain in patients with painful diabetic peripheral neuropathy" – a comparison of placebo vs. 1 dose of pregabalin in 146 patients

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:

Protocol	Treatment group	Change in pain score	P value	% responders*
014	Placebo	-0.98	-	12.9
	Pregabalin 200 mg TID (600 mg d)	-1.99	< 0.001	29.3
029	Placebo	-1.26	-	16.5
	Pregabalin 100 mg TID (300 mg/d)	-2.10	< 0.001	38.3
	Pregabalin 200 mg TID (600 mg/d)	-2.20	< 0.001	36.6
131	Placebo	-0.59	-	7.14
	Pregabalin 100 mg TID (300 mg/d)	-1.79	< 0.001	32.9

* A responder was defined as anyone having ≥ 50% decrease in pain score from baseline

2.3 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 changes in mental status (confusion, abnormal thinking, and euphoria), ataxia/incoordination, and vertigo. Non-CNS effects include edema, blurring of vision, weight gain, dry mouth, and constipation. The available data do not suggest an association between pregabalin and a specific SAE, however one unexplained case of was identified and requires further investigation. Pregabalin is also associated with decreases in platelet count and increases in creatinine kinase, however there were no clinical correlates (e.g. thrombocytopenia, acute renal failure) to these 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.

The non-clinical finding of dermatopathy raises the concern of possible skin breakdown in humans, a particularly worrisome event for patients with diabetes who are already at risk for skin ulceration, poor wound healing, and subsequent amputation. While the available data did not establish an association between pregabalin treatment and skin ulcers in the DPN population, the absence of a comparator group exposed for a similar duration as the pregabalin group, does not rule out the possibility of a real effect. Furthermore, the mechanism and risk factors for skin changes have not been fully characterized.

Another concerning dermatologically-related effect is the development of edema. Edema is associated with decreased skin integrity and this, is again worriesome for diabetic patients who have a pre-existing risk for skin ulceration.
Additionally, the vision-related effects of pregabalin are raise another question regarding the relative safety of this product in the diabetic population. Patients with diabetes are

already at considerable risk of retinopathy and vision loss. The combined effects of long-standing disease and possible drug-induced vision changes could add considerably to these patients' morbidity. At present, Pfizer has not adequately characterized the effects of pregabalin on vision.

Finally, because pregabalin is cleared via the kidneys and because patients with diabetes experience decline in renal function over time, diabetic patients will progressively be exposed to higher systemic levels of pregabalin and will be more likely to experience adverse effects.

2.4 Dosing, Regimen, and Administration

The data support a TID dosing regimen. Pfizer submitted only one clinical trial (Protocol 1008-149) in support of efficacy of BID dosing in patients with pain due to diabetic neuropathy. However, this trial did not show that BID dosing of 150, 300, or 600 mg/day was effecacious in reducing pain. [redacted]

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

2.5 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.

2.6 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): [redacted]
- Dose: 25, 50, 75, 100, 150, 200, 225, and 300 mg capsules
- Regimens: 100mg (1 capsules) or 200 mg (2 capsules) p.o. T.I.D.
- Age groups: Adults;
  Studies in children waived/deferred

1.2 State of Armamentarium for Indication(s)

There are currently no FDA-approved pharmacological therapies for pain due to diabetic neuropathy. Clinical practice utilizes a variety of analgesics (e.g. NSAIDS, and benzodiazepines) or with antidepressants (tricyclic antidepressants, selective serotonin re-uptake inhibitors) and anticpileptic agents (gabapentin, carbamazepine), but without a finding of efficacy by the Agency based on a review of adequate and well-controlled trials.

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. In 2000, the Applicant proposed two parallel trials (1008-149 and -173) whose data would be combined to evaluate the effectiveness of b.i.d. dosing. When 1008-173 was prematurely terminated due to imposition of a partial clinical hold, Protocol 1008-149 was analyzed as a stand-alone study. Also, studies of < 12 weeks' duration could be filed, and studies to evaluate whether any observed efficacy was due to nerve damage could be conducted as a Phase 4 commitment.

Several milestones in the neuropathic pain development program are noted in the 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 a [ ] 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	None of the proposed efficacy studies was of ideal duration (12 wks) to show durability of effect. Patient exposure to the highest proposed dose was insufficient. 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-week trial of BID dosing in neuropathic pain, 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.
07/26/03	Meeting	For this NDA submission, a 12-week, adequate and well-controlled study demonstrating that efficacy in DPN does not correlate with accelerated nerve damage is required. The study can be completed as a Phase 4 commitment.
10/30/03	NDA submission	

1.4 Other Relevant Information

Pregabalin has never been marketed in any country.

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, gabapentin was associated with higher incidences of dizziness, somnolence, blurry vision, and peripheral edema.

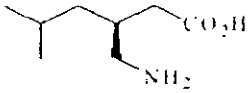
2 SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

Much of the material below is taken from the Applicant's NDA summary.

2.1 Chemistry, manufacturing and controls

Pregabalin is a white to off-white solid that is readily soluble in water. The oral capsules contain 25 or 100 mg of pregabalin.

Generic name: Pregabalin
Trade name: LYRICA™
Chemical name: (s)-3-(aminomethyl)-5-methylhexanoic acid
Alternative name (internal lab identification numbers): CI-1008; PD 0144723
Molecular formula: $C_8H_{17}NO_2$
Molecular weight: 159.23
Chemical structure:



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

2.2 Pre-clinical efficacy

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.

Pregabalin is active in rodent models of analgesic, anticonvulsant and anxiolytic activity. In rat models, pregabalin does not prevent behaviors in response to acute nociceptive pain, but it reduces behaviors caused in animals sensitized by inflammation or damage to sensory nerves (neuropathic pain). Pregabalin reduces both sensory and motor spinal reflexes induced by toe pinch in rats. However, this effect was pronounced only in rats that were previously inflamed by injection of an immune antigen or in rats with neuropathic pain from chronic constriction injury to the sciatic nerve. Pregabalin also is active in rodent models of visceral pain from manipulation of the gastrointestinal tract. Pregabalin reduces nociceptive spinal reflex activity in anesthetized rats particularly after inflammation or neuropathic damage. However, it does not alter behavioral responses to immediate nociceptive pain (heat or pressure). Instead, it reduces pain-related behaviors subsequent to inflammation or neuronal sensitization in rats. Pregabalin treatment

reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin prevents pain-related behaviors after intrathecal administration and reduces pain-related behavior caused by spinally administered neurotransmitters, suggesting that it acts directly on tissues of the spinal cord or brain.

Pregabalin is inactive at 38 commonly studied drug and neurotransmitter radioligand binding sites and it does not alter monoamine neurotransmitter uptake in isolated brain tissues. Pregabalin has no effect on the electrophysiology of GABA receptors or on glutamate or GABA synaptic transmission and it does not alter long-term synaptic potentiation in vitro.

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 Pre-clinical 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.

2.3.3 Genetic toxicology

Genotoxic potential was assessed in vitro and in vivo. Pregabalin was not mutagenic in bacteria using metabolic activation provided by mouse or rat liver. Pregabalin did not induce point mutations or structural chromosome aberrations in Chinese hamster ovary cells in vitro. Nor did pregabalin did not induce unscheduled Deoxyribonucleic acid (DNA) synthesis in mouse or rat hepatocytes and was not clastogenic in mouse or rat bone marrow in vivo.

2.3.4 Carcinogenicity

Pfizer reported that carcinogenic potential was evaluated in B6C3F1 and CD-1 mice and Wistar rats after 2 years of treatment. Pregabalin induced an increased incidence of hemangiosarcoma in male and female B6C3F1 mice at 1000 and 5000 mg/kg with associated AUC (0-24) range of 653 to 3840 mg·hr/mL. No statistically significant increase in hemangiosarcoma occurred in mice at 200 mg/kg with associated AUC (0-24) ranging from 140 to 153 µg.hr/mL. In CD-1 mice, an increased incidence of hemangiosarcoma was observed in males at 5000 mg/kg with associated AUC (0-24) of 3440 µg.hr/mL. Although not statistically significant, there was an increased incidence of hemangiosarcoma in females at 5000 mg/kg with an associated AUC (0-24) of 3150

µg.hr/mL. No statistically significant increase in hemangiosarcoma occurred in CD-1 mice at ≤ 1000 mg/kg with associated AUC(0-24) ≤558 µg x hr/mL. Pregabalin was not carcinogenic in 2 studies in male or female rats at doses up to 900 mg/kg with associated AUC(0-24) ≤ 2960 µg ×hr/mL.

Dr. Terry Peters (HFD 520) reviewed the carcinogenicity studies and associated pathology findings. She concluded that, based on the 2-year dietary carcinogenicity study in DC-1 mice, pregabalin elicited hemangiomas and hemangiosarcomas in a dose-related fashion. There were also changes in the myeloid:erythroid ratio in bone marrow, and significant increases in body weight and body weight gains. Dr. Peters stated that presence of active compound in the sera of the control animals of both sexes is of concern. A similar study in rats also showed effects on body weight, but no evidence of carcinogenic activity.

2.3.5 Reproductive toxicology

Fertility and early embryonic development and prenatal-postnatal toxicity were assessed in rats; embryo- fetal development was evaluated in mice, rats, and rabbits. Male fertility decreased at ≥ 1250 mg/kg, while sperm motility decreased at ≥ 250 mg/kg. Both of these changes were reversible and occurred at exposures > 20 times the mean human exposure [AUC(0-24) of 123 µg.hr/mL] at the maximum recommended clinical dose of 600 mg/d. Female fertility was unaffected up to 2500 mg/kg although estrus and diestrus stages were prolonged at ≥ 1250 mg/kg.

Pregabalin was not teratogenic in mice, rats, or rabbits. There was an increased incidence of closure of the jugal bone to maxilla was noted at ≥ 1250 mg/kg and closure of the nasal bones was observed at 2500 mg/kg in rats. Pfizer believes that these findings represent advanced ossification and not skeletal malformations. Pregabalin decreased fetal body weight in rats at 2500 mg/kg and in rabbits at 1250 mg/kg when given during organogenesis. In the prenatal-postnatal toxicity study, pregabalin induced maternal toxicity characterized by ataxia, hypoactivity, and tail dermatopathy at ≥ 50 mg/kg, dystocia at ≥ 1250 mg/kg, and abnormal maternal care at 2500 mg/kg. Fetal and neonatal survival decreased at ≥ 250 mg/kg, with no surviving offspring after Postnatal Day 3 at 2500 mg/kg. Developmental toxicity characterized by reduced offspring body weight occurred at ≥ 100 mg/kg. Acquisition of developmental landmarks was delayed at 1250 mg/kg, and maximum response elicited by acoustic startle was decreased in females at 250 and 1250 mg/kg. No developmental toxicity occurred at 50 mg/kg with associated AUC(0-24) of 241 mg·hr/mL. Pregabalin decreased fertility and litter size, and increased post-implantation loss in F_1 offspring of dams given 1250 mg/kg, but there were no drug-related external malformations in F_2 fetuses.

2.3.6 Special toxicology

Studies were conducted in juvenile rats to support clinical development in pediatric populations. Decreased body weight gain, but no deaths or clinical signs, occurred in 7- and 21-day-old rats given single oral doses up to 2500 mg/kg. Pregabalin given to rats beginning at 7 days of age for 7 weeks induced transient bruxism, hyperactivity, and decreased body weight gain at ≥ 50 mg/kg. There were no other drug-related findings.

Cmax values after 3 weeks of treatment were similar in adults (12 weeks old at study initiation) and juveniles (7 days old at study initiation); however, AUC (0-24) values in adults were approximately 1.7 times greater than in juvenile animals. Pregabalin had no affect on neuromuscular function or hearing in neurotoxicity studies. There were impairing effects on acclimation to stimuli, learning, and memory, and based on these results, pregabalin induced developmental neurotoxicity in juvenile rates at ≥ 250 mg/kg.

Pregabalin had no affect on sexual maturation, copulation, or fertility in juvenile male rats. At 500 mg/kg, epididymal weight, sperm motility, and the percentage of sperm with normal morphology decreased, and pre-implantation loss increased in untreated females mated with treated males. In females, pregabalin induced prolonged diestrus and decreased fertility at 250 and 500 mg/kg. No effects on fertility occurred at 50 mg/kg.

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Much of the text below is from the Pfizer's NDA summary.

3.1 Pharmacokinetics

Oral absorption is rapid and independent of dose. The absolute bioavailablity is ≥ 90%. Under fasting conditions and following single dose administration, Tmax ranges from 0.5-2 hours, and from 0.8-1.4 hours after multiple dose administration. Cmax and AUC increase with increasing doses, in a linear fashion. Although the rate of absorption was somewhat slower when taken with a meal (Tmax delayed by 1-2.6 hours and Cmax decreased by 25-29%), the extent of absorption (AUC) was similar. Thus, there is not anticipated to be an overall effect with regard to the efficacy or safety of pregabalin whether it is taken with or without food.

Dr. Sue Chih Lee, the Clinical Pharmacology Reviewer, considers that since the decrease in Cmax with food is moderate, and because there were no restrictions in clinical trials on how to take the drug with regard to food, pregabalin can be taken with or without food. Mean (%CV) PK parameter values following single- and multiple-dose administrations are presented in the table below:

Dosing Regimen	N	Cmax (• g/mL)	Tmax (hr)	AUC (• g.h/mL)
100 mg Single Dose	6	2.99 (16.2)	0.83	22.1[1] (16.8)
200 mg Single Dose	13	5.23 (27.0)	1.31	37.7[1] (16.3)
300 mg Single Dose	8	7.57 (16.4)	1.38	62.8[1] (9.3)
100 mg TID (q8h)	6	5.03 (21.3)	0.83	25.2[2] (23.0)
200 mg TID (q8h)	11	8.52 (14.8)	0.91	41.7[2] (12.8)
300 mg BID (q12h)	8	9.07 (10.5)	1.44	59.0[2] (6.4)

[1] $AUC_{0-\infty}$; [2] $AUC_{0-\tau}$

Pregabalin is water-soluble and has a volume of distribution of approximately 0.56 L/kg. The drug is not protein bound, therefore potential drug-drug interactions via the mechanism of displacement of protein-bound drug is not likely. In animal studies, pregabalin was shown to cross the blood brain barrier and placenta, and was present in the milk of lactating rats. There have been no human studies investigating the penetration or distribution of pregabalin within the CNS.

Pregabalin undergoes negligible metabolism and is primarily renally excreted (90%) as an unchanged compound. Renal clearance is approximately 72.7 mL/min, and steady state is achieved within 48 hours after multiple dosing. Since pregabalin is excreted via the kidneys, dosage adjustment for patients with renal impairment is indicated. Studies of 4-hour hemodialysis showed reduction in the plasma pregabalin concentration by

approximately 50% (52.3±13.8% on one occasion, and 54.8±9.2% on another). Therefore, a supplemental pregabalin dose immediately after hemodialysis is necessary.

Pregabalin does not inhibit any of the major CYP 450 enzymes (1A2, 2A6, 2C9, 2C19, 2D6, 2E1, or 3A4). The terminal half-life (t½) is approximately 6.3 hours, and is also independent of dose.

Effect of age
There were no formal clinical pharmacology studies conducted in subjects < 18 years old. Pfizer is of the opinion that the only factor that might alter the PK profile of pregabalin in adolescents from that in adults is renal function. Research has shown that there are age-related changes in glomerular filtration, and that renal excretion for individuals 12-17 years approximates that of adults. Therefore, the PK profile of pregabalin in that population should be similar to that of adults.

The only specific clinical pharmacology studies in individuals older than 65 years were conducted in Japanese subjects. Studies in healthy, young Japanese volunteers produced similar ADME results to those described above. When mean PK parameter values from elderly Japanese subjects were compared to those of healthy Japanese and non-Japanese subjects, there were differences in t½ and AUC, consistent with age-related changes in renal function. Pfizer conducted a population analysis of PK data and found that, after correction for creatinine clearance (CLcr), there were no age-related differences in pregabalin clearance. Therefore, once renal function has been considered, specific dosage adjustment based on age is not indicated.

Effect of race and gender
Population analyses did not reveal race-, menopausal- or gender associated differences in pregabalin clearance of volume of distribution after correction for creatinine clearance.

Renal impairment
Two studies were conducted to assess single dose pharmacokinetics of pregabalin (50 mg) in patients with renal impairment (CLcr 30-60 mL/min) and on hemodialysis (mean CLcr 13.6 mL/min). In subjects with renal impairment, Cmax, AUC, and t½ increased with decreasing renal function. Pfizer concluded that since the decreases in pregabalin total clearance (CL/F) and renal clearance (CLr) correlated with decreases in subjects creatinine clearance (CLcr), CLcr can be used to determine the appropriate pregabalin dose for patients with renal impairment. A CLcr of 50-60 mL/min corresponded with a CL/F of approximately half that observed in subjects with normal renal function. Therefore, Pfizer proposed that patients with a CLcr of 30-60 mL/min should have the total daily dose halved relative to that of patients with normal renal function. If renal function is halved again (CLcr 15-30 mL/min), the dose should be a quarter of the normal dose.

In subjects requiring hemodialysis, the mean t½ was 3 hours during dialysis, and 54.7 hours prior to dialysis. Dialysis is effective at removing pregabalin. Pfizer proposed

dosing in these patients to be adjusted according to CLcr, with a supplemental dose (25 to 100 mg) administered following every 4-hour hemodialysis treatment.

Hepatic impairment
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, as discussed above.

Drug-drug interactions
The following commonly administered drugs were evaluated to assess potential interactions with pregabalin:

- Antiepileptic drugs (AEDs): valproic acid, carbamazepine, lamotrigine, phenytoin
- Oral contraceptives: Ortho-Novum
- Gabapentin
- Ethanol
- Oxycodone
- Lorazepam (*see AED comment, above)*

Both specific studies and population analyses were conduced to evaluate the possible drug-drug interactions.

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

The pharmacodynamic effects of co-administration of pregabalin with lorazepam, ethanol, or oxycodone on CNS and performance tasks were evaluated.

Pregabalin + Lorazepam
Pfizer found that, when administered alone, neither pregabalin (300 mg q 12h) nor lorazepam (1 mg qd) produced clinically important respiratory depression. When pregabalin and lorazepam were co-administered, there were greater and longer deficits in task performance. For some response variables and at certain times, the deficits stemming from the combination treatment were not merely additive, but suggestive of a synergistic interaction. These possible interactions were most apparent among the reaction times, speed of performing tasks, and postural stability response variables.

Overall, pregabalin potentiated lorazepam related impairment of cognitive and gross motor function.

Pregabalin + oycodone
Administration of pregabalin (300 mg q 12h) and oxycodone (10 mg), either sperately or in combination, did not produce clinically important respiratory depression. Overall, the impairment of cognitive and gross motor function produced by pregabalin alone was minimally increased when pregabalin and oxycodone were co-administered. The combination treatment also resulted in improvements in self-rated contentment and calmness suggestive of a synergistic interaction for these parameters.

Pregabalin + ethanol
Ethanol (0.7 mg/kg) impaired cognition. The combination of pregabalin and ethanol prolonged reaction times by about 50 msec and had a greater effect on body sway (seen up to 2.5 hours post-dose) than ethanol alone.

Reviwer Comment: The doses of lorazepam, oxycodone, and ethanol used in these interaction studies were relatively low. Therefore these results suggest that even more considerable respiratory and CNS deficits would occur when higher oxycodone and/or pregabalin doses are administered.

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 for support of equivalency of effect, whether the drug is administered in a TID or BID regimen.

Dr. Sue Chih Lee, the Clinical Pharmacology Reviewer, reviewed the plasma concentration data and the Applicant's interpretation of the data. Based on the clinical efficacy trials, treatment with 100 mg TID regimen is efficacious. A plot of the concentration-time profile for this dosing regimen is shown below. Protocol 1008-149, thoe sole trial evaluating BID dosing, evaluated the efficacy of the following dosing regimens: 75-, 150-, and 300-mg BID. A plot of the concentration time-profile of the 300 mg BID regimen is also shown in the graph.

Based on a comparison of the minimum plasma concentrations for the 100 mg TID and 300 mg BID regimens, one would expect the 300 mg BID regimen to be efficacious. However, Protocol 1008-149 failed to show efficacy at all dose levels, including the 300-mg BID regimen. Therefore, pharmacokinetics alone is not able to explain the failure of Protocol 1008-199, at least for the 300 mg BID regimen.

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 pivotal efficacy studies for each proposed indication.
- *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 or safety databases. They include phase 2/3 trials conducted in Japan, [

]

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

4.2 Postmarketing Experience

Pregabalin has not yet been marketed in any country. It was approved for marketing in Europe in 2004.

5 CLINICAL REVIEW METHODS

5.1 Description of Review Conduct

The Applicant identified 4 trials as contributing to evidence of efficacy (1008-014, 029, -131, and -149) in treatment of pain due to diabetic peripheral neuropathy (DPN). 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. Trial 1008-040, although considered by the Applicant to be a failed study, was also reanalyzed in an effort to resolve the inconsistent efficacy results between this study and trials 1008-014 and 108-029. A sixth trial, 1008-173, 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).

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.

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 efficacy trials that were conducted in the US. Sites that had the largest enrollment and/or the greatest treatment-by-center interaction were identified for audit. One site each was audited for trials for Protocols 1008-014 and 029. Two sites were audited for trial 1008-131 was audited because this was the only Phase 3 study, and therefore its results were considered very relevant for approval of efficacy. DSI elected to conduct a "for cause" audit an additional site involved in trial 1008-131 because of reports of inconsistent data from other studies in which the site investigator was involved (Site 105, [ ]

No international sites were audited. This was because the international study 1008-040 failed, and trial 1008-149 was not considered a pivotal trial. Although 1008-149 showed a treatment-by-country effect where none of the active treatment groups at Polish sites was significantly different from placebo, this was not considered reason enough to warrant an audit of any of the involved sites.

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 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 67 (out of 1058) investigators involved in DPN trials did not provide financial disclosure information. Of all the investigators who provided complete or incomplete disclosure forms (Form 3454), there were 25 who reported significant financial interest:

Protocol [ ] _____
Dr. [ ] (sub-investigator, Site —) reported financial interest because his pension plans included 1500 shares of Warner-Lambert stock. Site — randomized 15 patients (6.1%).

Protocol [ ] __

Dr. [redacted] (sub-investigator, site — reported financial interest because [redacted] estate owns 2,150 shares of Warner-Lambert common stock. Site — randomized 13 patients (3.8%).

Protocol [redacted]
Dr. [redacted] (PI, site — reported financial interest because of a predicted excess of $25,000 for compensation [redacted] and lecturing for honoraria. Site — randomized 3 patients (2.0%).

Protocol [redacted]
[redacted] (PI, site — reported financial interest because he holds stock (ordinary shares) in Pfizer, and will be involved in a Pfizer-sponsored study of diabetes and will receive AUS $30,000 annually for 5 years. Two patients (0.5%) were randomized into the study.

Protocol [redacted]
Dr. [redacted] (PI, site — reported financial interest for receipt of $20,000 "for salary of research nurse." (This amount is below the threshold of $25,000). Five patients (2.1%) were randomized into the study.

Protocol [redacted]
Dr. [redacted] (sub-investigator, site — reported financial interest because he holds 1,150 shares of Pfizer. Site — randomized 9 patients (4.1%)

Dr. [redacted] (sub-investigator, site —, reported financial interest because he received payments > $25,000 for consulting with Pfizer. Site — randomized 5 patients (2.3%) into the study.

Dr. [redacted] (sub-investigator, site — reported financial interest because he owns a " Royalty Initial Investment $54,000" and receives monthly Royalty. Site — randomized 5 patients (2.3%) into the study.

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

Dr. [redacted] (sub-investigator, site — reported financial interest because he owns 1800 shares of Pfizer. Nine patients (4.1%) were randomized into the study.

Protocol [redacted]
Dr. [redacted] (PI, Site — and Dr. [redacted] (sub-investigator, Site — both reported financial interest because they receive honoraria for another pregabalin study, [redacted] Neither investigator knew whether the honoraria exceeded $25,000. Five (1.7%) patients from this site were randomized into the study.

Dr. [redacted] (PI, site [redacted] reported financial interest due to periodic financial support from Parke-Davis for research other than that related to clinical trials. Site [redacted] randomized 5 patients into the study (1.7%).

Protocol [redacted]

Dr. [redacted] (sub-investigator, site [redacted] reported financial interest [redacted] Parke-Davis and has stock options through that company's retirement plan. Although Dr. [redacted] also noted proprietary interest in pregabalin, compensation influenced by the study outcome, and significant equity interest in Warner-Lambert, Pfizer believes that only the last financial interest applies. Site [redacted] enrolled 14 patients (4.5%).

Dr. [redacted] (PI, site [redacted] holds 200 shares in Warner-Lambert. Although he reported proprietary interest in pregabalin, Pfizer believes that it is more correct to state that Dr. [redacted] "significant equity interest in the Applicant". Site [redacted] enrolled 5 patients (1.6%).

Dr. [redacted] (sub-investigator, site [redacted] reported that she would receive compensation via an educational grant ($60,000) that Park-Davis would make to the [redacted] to decrease the retail cost of an epilepsy textbook [redacted] Site [redacted] enrolled 5 patients (1.6%).

Dr. [redacted] (sub-investigator, site [redacted] reported financial interest because he received a speaker honorarium. Site 033 enrolled 8 patients (2.6%).

Protocol [redacted]

Dr. [redacted] (sub-investigator, site [redacted] reported financial interest because Warner-Lambert expressed interest in funding a clinical trial for which Dr. [redacted] is a co-PI. One patient (0.2%) was randomized into the trial.

Dr. [redacted] (PI, site [redacted] reported financial interest because he owns 708 shares of Warner Lambert. Site [redacted] randomized 7 patients (1.5%) into the study.

Dr. [redacted] (PI, [redacted] reported financial interest due to Sponsor contributions of $20,000 to her institution to support symposia, $7,000/year for participation as a board member on the [redacted] and $3,000 for speaking engagements. Ten patients (2.2%) were randomized into the study.

Dr. [redacted] (sub-investigator, site [redacted] reported financial interest to due future receipt of funds for animal trials using gabapentin. Site [redacted] randomized 1 patient (0.2%) into the study.

Protocol [redacted]

Dr [redacted] (PI, site [redacted] reported financial interest because he received payments exceeding $25,000 for consulting and speaker fees, and for training investigative sites. A total of 37 (13.4%) patients from this site were randomized into this study.

Dr. [redacted] (sub-investigator, site [redacted] reported financial interest because he, his wife, or dependent children own Warner-Lambert stock of approximately $50,000. Site [redacted] randomized 6 patients (1.8%) into the study.

Protocol [redacted]
Dr. [redacted] (PI, sites [redacted] reported financial interest because he received payments exceeding $25,000 for consulting and speaker fees, and for training investigative sites. A total of 12 patients (2.6%) from site [redacted] and 11 patients (2.4%) from site [redacted] were randomized into this study. The total number of patients enrolled by this investigator was 23 (5.1%).

Summary:
The financial disclosure information from Pfizer appears adequate, based on the available information. One investigator reported financial interest and enrolled a considerable number of patients that could potentially influence the study outcome (Dr. [redacted] protocols [redacted]

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6 INTEGRATED REVIEW OF EFFICACY

6.1 *Brief Statement of Conclusions*

In three US efficacy studies, the mean pain score for subjects randomized to pregabalin 300 and 600 mg/day, administered in three divided doses (TID) was lower than the mean pain score for patients randomized to placebo. Also, subjects randomized to pregabalin 300 and 600 mg/day were more likely than subjects randomized to placebo to report a decrease in pain due to diabetic peripheral neuropathy. The dosing regimen is different from the Applicant's labeling claim, [ ] TID dosing. The Applicant submitted a single trial of BID dosing (Protocol 1008-149), however this trial failed to show efficacy on our analysis of the primary endpoint.

6.2 General Approach to Review of the Efficacy of the Drug

Five efficacy studies were provided for review with full study reports and primary data sets. Two were non-US studies (1008-040 and 1008-149). 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, 1008-173, 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 DPN efficacy database:

Prot	Design	No. of subjects (ITT)	Treatment Duration	PGG Dose
014	Pro., MC, R, DB, PC trial of 2 doses of pregabalin given as a TID regimen	PGB: 161 Placebo: 85	Titration: 2 wks Fixed dose: 6 wks	150 mg/day 600 mg/day
029	Pro., MC, R, DB, PC trial of 3 doses of pregabalin given as a TID regimen vs. amitriptyline	PGB: 240 Placebo: 97	Titration: 1 wk Fixed dose: 4 wks	75 mg/day 300 mg/day 600 mg/day
040	Pro., MC, R, DB, PC trial of 1 dose of pregabalin given as a TID regimen vs. amitriptyline	PGB: 86 Placebo: 81 Amitriptyline: 87	Titration: 2 wks Fixed dose: 6 wks Withdrawal: 1 wk	600 mg/day
131	Pro., MC, R, DB, PC trial of 1 dose of pregabalin given as a TID regimen vs. amitriptyline	PGB: 76 Placebo: 70	Fixed dose: 8 wks	300 mg/day
149	Pro., MC, R, DB, PC trial of 3 dose of pregabalin given as a BID regimen vs. amitriptyline	PGB: 299 Placebo: 96	Titration: 1 wk Fixed dose: 11 wks	150 mg/day 300 mg/day 600 mg/day

6.3 Protocol 1008-014: A double blind, placebo-controlled trial of pregabalin for treatment of painful diabetic peripheral neuropathy

6.3.1 Protocol

6.3.1.1 Objective/Rationale

The aim of the study was to determine the safety and efficacy of pregabalin (150 or 600 mg/day) given in 3 divided doses (TID) compared to placebo for treatment of pain associated with diabetic peripheral neuropathy.

6.3.1.2 Overall Design

This was a Phase 2/3 prospective, multicenter, randomized, double-blind, placebo-controlled, parallel group study of pregabalin and placebo in 240 subjects with painful diabetic neuropathy.

6.3.1.3 Study Population and Procedures

6.3.1.3.1 Treatment Duration

8 weeks (2-week titration, 6 weeks fixed dose phase)

6.3.1.3.2 Entry Criteria

The protocol called for enrollment of 240 subjects from 20- 30 sites in the United States and Canada. There were to be 80 subjects per treatment group.

To be eligible, subjects were required to meet the following criteria:

- Age ≥ 18 years
- Diagnosis of diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years
- Hemoglobin A1c ≤ 11%
- Score of ≥ 40 mm on the VAS of the Short Form McGill Pain Questionnaire (SF-MPQ) at screening and randomization
- Completion of at least 4 daily pain diaries at randomization
- Average daily pain score of ≥ 4 over the past 7 days prior to randomization

Subjects were excluded for:

- Serious hepatic, respiratory, or hematologic illness; unstable cardiovascular disease or symptomatic peripheral vascular disease
- History of pernicious anemia, untreated hypothyroidism, chronic hepatitis B, hepatitis B within the past 3 months, or HIV infection
- Neurologic disorders unrelated to diabetic neuropathy
- Skin conditions in the area affected by the neuropathy that could alter sensation

- Other severe pain that may confound assessment or self evaluation of the pain due to diabetic neuropathy
- Amputation, other than toes
- Serious or unstable medical or psychological disease (including substance abuse within the last year) that may compromise study participation
- Clinically significant abnormalities on dilated fundoscopic exam, visual field testing, or visual acuity testing
- Abnormal ECG or abnormality found on 2-minute rhythm strip
- Creatinine clearance (CLcr) ≤ 60 mL/min (estimated from serum creatinine)
- WBC < 2500/mm^3; neutrophil count < 1500/mm^3, platelet count < 100 x 10^3/mm^3
- Use of :
  - Analgesics (other than acetaminophen or aspirin (see below))
  - Antidepressants (other than SSRIs), anticonvulsants, or neuroleptics within the 14 to 30 days prior to randomization
  - any concomitant medication that could alter the effectiveness of the study medication within the 14 to 30 days prior to randomization
  - hydroxychloroquine, desferrioxamine, thioridazine or vagabatrin at any time (due to potential irreversible retinotoxicity)
- Previous treatment with pregabalin

6.3.1.3.3 Study Medications

Study drug was placebo or pregabalin capsules (25- and 100 mg). Subjects were randomized (in blocks of 6) to placebo, pregabalin 150 mg/day, and pregabalin 600 mg/day. Study drug was administered in three divided doses (TID). All subjects randomized to active drug were to begin at a dose of 25 mg, with the dose increased in 25-mg increments to the target dose, over a 2-week period.

Subjects' medications for diabetes control were to remain stable during the study. They were allowed to use the following medications:

- Acetaminophen, ≤ 3 g daily
- SSRIs (as long as dose remained stable both during and 30 days prior to the study)
- Aspirin (≤ 325 mg daily, for prophylaxis of MI and transient ischemic attacks)

The protocol disallowed concomitant pain medications within the last 14 or 30 days during the study that might affect painful diabetic neuropathy. Additionally, subjects were not allowed to use pro-arrhythmic drugs. A complete list of prohibited medications is shown below:

1 day prior to randomization	Not allowed during the last 30 days of the study	Not allowed during the last 30 days of the study	Absolutely disallowed
Antihistamines Macrolide antibiotics	Tricyclic antidepressants Narcotics Benzodiazepines Other Schedule II Medications Skeletal muscle relaxants Capsaicin Mexiletine Dextromethorphan Tramadol	Antiepileptic medications NSAIDS	Pro-arrhythmic drugs - phenothiazines - antiarrhythmics - pteridine Fatty acid supplements Evening primrose oil Myoinositol Chromium picolinate

6.3.1.3.4 Study Procedures

The protocol specified 5 clinic visits, and 1 follow-up visit. The first visit (V1) would occur during screening and the second (V2) at the end of the 1-week baseline phase. Subjects were to be randomized at V2. Thereafter, subjects were to be evaluated every 2 weeks (V3, V4, and V5/Termination). A safety-follow-up visit was required for all subjects not entering the extension study, Protocol 1008-015.

Randomized subjects were to begin treatment at Visit 2 (V2). After the 2-week titration to the target dose, the dose was to be maintained for the final 4 weeks of the study. Subjects who went 7 consecutive days without taking any study medication were withdrawn from the study. A patient was defined as having completed the study if s/he received 6 weeks of double-blind treatment (V5/Termination visit.

Table 6.3.1.3.4 illustrates the planned schedule of assessments (see below)

6.3.1.3.5 Efficacy Parameters

The following measures of patient pain and function were to be utilized:

- *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)

- *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
- *Profile of Mood States (PMOS)*: 65 descriptors of subject's mood, each rated on a 5-point scale from 0 (not at all) to 4 (extremely)

Table 6.3.1.3.4: Time and Events Schedule

Timetable of Study Visits and Procedures and Dosing Titration Schedule

Observation/ Procedure ⇩	Study Phase: / End of Study Week: / Clinic Visit*:	Baseline WK-1 1	Double-Blind Treatment WK0 2	WK2 3	WK4 4	WK6 5/Term[a]	WK 7 Follow-Up[b]
Inclusion/Exclusion		X					
Medical History		X					
Physical Exam		X	X[c]	X[c]	X[c]	X	
Abbreviated Neurological Exam		X				X	
Peripheral Sensory Exam		X				X	
SF-McGill Pain Questionnaire		X	X	X	X	X	
Daily diaries (Pain, Sleep)		X	X	X	X	X	
Global Imp of Change (Clinical & Patient)						X	
SF-36			X			X	
Profile of Mood States (POMS)			X			X	
Adverse Events			X	X	X	X	X
Prior and Concurrent Medications		X	X	X	X	X	
Study Medication Dosing			X	X	X	X	X
Clinical Labs							
Hematology		X		X	X	X	
Hemoglobin A_{1C}		X				X	
B12/folate, SPEP, T4/TSH		X					
Chemistry		X		X	X	X	
Urinalysis		X				X	
Serum Pregnancy		X			X	X	
Study Medication Plasma Conc.		X		X	X	X	
ECG With 2-Minute Rhythm Strip		X		X	X	X	
Dilated Fundoscopic Examination[d]		X			X	X	
Vision Function Testing[d]		X			X	X	

[a] Whenever patient withdraws from or completes the study
[b] Complete after study termination for patients who do not enter Study 1008-015
[c] Orthostatic blood pressure and heart rate - supine and standing
[d] Examination/testing by an ophthalmologist at Visits 1, 4, 5/Term
* Telephone contact will be made with the patients twice weekly throughout the study to ensure completion of daily diaries.

(Applicant's Appendix A.1, RR 720-04236, 1008-014, P. 132)

6.3.1.3.6 Pharamcokinetics

The protocol stipulated collection of blood samples at screening and at the Weeks 2, 4, and 6/termination visits for determination of pregabalin plasma concentrations.

6.3.1.3.7 Statistical Analysis

6.3.1.3.7.1 Patient Population

The *intent-to-treat (ITT)* population was defined as all randomized subjects who received at least 1 dose of study medication was the primary population for analysis. For each analysis, the primary comparison was 600 mg pregabalin versus placebo. The secondary comparison was to be 150 mg pregabalin versus placebo.

6.3.1.3.7.2 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 defined as the *final weekly mean pain score*. The primary analysis was to compare the final weekly mean pain score using ANCOVA, with treatment and center in the model, and the baseline mean pain score as a covariate.

6.3.1.3.7.3 Supplemental Analyses of the Primary Efficacy Outcome

- Mean pain score for each week separately
- Change in mean pain score from baseline, and at each week separately

6.3.1.3.7.4 Secondary Efficacy Outcomes

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) at Weeks 2, 4, and 6, and at endpoint (i.e. last available score)
- Mean sleep interference score, weekly and at study endpoint
- Change in mean sleep interference score, from baseline to endpoint and each week
- Global impression of change (by subject and investigator)
- SF-36 quality of life change from baseline
- POMS change from baseline

6.3.1.3.7.5 Interim Analyses

No interim analyses were planned.

6.3.1.4 Protocol Amendments

Amendment 1

December 9, 1998

Changes were made to the eye examination procedures and laboratory parameters. Also, cardiac exclusion criteria were clarified, and changes were made to administrative personnel.

6.3.2 Study Results

6.3.2.1 Study Conduct/Outcome

6.3.2.1.1 Subject characteristics

The first patient was randomized on 03/27/98, and the last observation was recorded on 03/18/99. A total of 26 centers in the US and 3 centers in Canada (centers 018, 021, and 028) participated in the study.

6.3.2.1.2 Enrollment by Center

Of the 246 subjects who were randomized, 16 were from the three Canadian centers. Approximately 55% of the subjects were enrolled at 7 centers. Enrollment was distributed among centers as listed in the table below:

Table 6.3.2.1.2: Subject Enrollment, by Center – Protocol 014

No. Subjects Randomized	No. Centers	Center Numbers	No. Subjects Randomized	No. Centers	Center Numbers
0	1	003	11	2	002, 024
1	2	023, 029	12	1	013
2	2	025, 028*	15	1	019
3	5	007, 008, 009, 022, 027	18	1	004
4	3	006, 010, 020	19	2	016, 017
5	2	005, 018*	20	1	026
8	2	001, 014	21	1	012
9	1	021*	22	1	015
10	1	011			

* Canadian sites

(Adapted from Applicant's Table 1, RR 720-04236, 1008-014, P. 12)

6.3.2.1.3 Protocol Violations

The Applicant states that 30 subjects at 16 study sites had protocol violations, with 1 to 7 violations reported per site. Table 6.3.2.1.3 below illustrates the number and types of protocol violations for this study.

Table 6.3.2.1.3: Protocol Violations, Protocol 014

Violation	Pregabalin 150 mg/day	Pregabalin 600 mg/day	Placebo
Diabetes < 1 year	5	-	-
Creatinine clearance ≤ 60 mL/min at V1	2	2	-
Baseline mean pain score < 4	-	1	1
Neutrophil count < 1500/mm3	-	-	2
History of pernicious anemia	-	-	1
Abnormal ECG	1	1	1
Completed < 6 weeks of double blind treatment	-	2	-
Did not stay on stable dose during fixed phase	2	9	-
Total	10	15	5

(Source: Appendix A.8, RR 720-04236, 1008-014, P. 269)

I consider that the protocol violations that might actually impact the primary efficacy outcome to be as follows:

- Incomplete double-blind treatment (< 6 weeks) reasons for non-completion might be related to lack of efficacy of study drug; or the patient could have ceased taking study drug due to AEs, despite reasonable treatment of pain
  - Patient 002009 (pregabalin 600 mg/day; 34 days of treatment)
  - Patient 010004 (pregabalin 600 mg/day, 23 days of treatment)
- Baseline mean pain score < 4 -- if a small improvement in pain occurred with therapy, it would be difficult to detect
  - Patient 012012 (placebo; baseline score = 2)
  - Patient 012003 (pregabalin 600 mg/day, baseline score = 3.9)
- Unstable study drug dose during the fixed-dose phase -- these subjects did not receive a full 6 weeks of treatment at the target dose, and their scores may not be representative of adequate treatment
  - Patients 009004 and 013022 (pregabalin 150 mg/d)
  - Patients 004003, 011014, 012008, 015029, 016020, 017019, 019006, 021013, and 027003 (pregabalin 600 mg/day)

Furthermore, I noted the following additional protocol violations:

- Continued use of prohibited medications that might themselves improve pain due to diabetic neuropathy
  - Patient 002002 (placebo; clonazepam)
  - Patient 026008 (placebo; Excedrin PM)
  - Patient 012016 (pregabalin 150 mg/day; naproxen)
  - Patient 012015 (pregabalin 150 mg/day; pyridoxine hydrochloride)
  - Patient 012003 (pregabalin 600 mg/day; propoxyphene)
- Insufficient washout of a prohibited medication
  - Patient 013014 (placebo; Excedrin PM)

Use of prohibited pain medication would tend to bias the study in favor of the affected arm, but the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is therefore not expected to have a significant impact on the interpretation of the results.

6.3.2.1.4 Blinding

The Applicant does not describe any instances of premature breaking of the study blind.

6.3.2.1.5 Subject Disposition

The table below shows patient disposition, and reasons for early withdrawal from the study. A total of 396 subjects were enrolled, and 150 were removed during the baseline phase. Reasons for removal were not meeting entry criteria (n = 135), experiencing and adverse event (n = 3), and "other" (n = 12).

All of the 246 randomized subjects took at least 1 dose of study medication and were included in the ITT population. There were 85 subjects in the placebo arm, and 79 and

82 subjects in the pregabalin 150- and 600 mg/day groups, respectively. Overall, 27 subjects (11%) in the ITT population were withdrawn from the study during the double-blind treatment phase. More patients were withdrawn from the placebo group due to "other" reasons (n = 9; 9.4%) compared to 2 subjects each in the pregabalin 150 and 600 mg/day groups (2.5% and 2.4%, respectively). The most common reason for withdrawal from the pregabalin 600 mg/day group was adverse effects (8.5%), compared to 2.5% and 4.7% in the pregabalin 150 mg/day and placebo groups respectively. No deaths occurred during the 6-week treatment phase.

Table 6.3.2.1.5: Patient Disposition, Number (%) of Patients – Protocol 014

Disposition	Placebo	Pregabalin 150 mg/day	Pregabalin 600 mg/day	All patients
Entered baseline phase				396
Completed baseline phase				246 (62.1)
Withdrawn during baseline phase				150 (37.9)
Adverse Event				3 (0.8)
Did not meet criteria				135 (34.1)
Other*				12 (3.0)
Randomized	85	79	82	246
Completed study	72 (84.7)	75 (94.9)	72 (87.8)	219 (89.0)
Withdrawn during treatment phase	13 (15.3)	4 (5.1)	10 (12.2)	27 (11.0)
Adverse event	4 (4.7)	2 (2.5)	7 (8.5)	13 (5.3)
Lack of efficacy	1 (1.2)	0 (0)	1 (1.2)	2 (0.8)
Other**	8 (9.4)	2 (2.5)	2 (2.4)	12 (4.9)

(Applicant's Table 11, RR 720-04236, 1008-014, P. 36)

* Data regarding specific reasons for withdrawal during the baseline phase are not provided

**Other: 4 patients were lost to follow-up (3 in the placebo group, 1 in the pregabalin 150 mg/day group)
3 patients withdrew consent (1 in the placebo group, 2 in the pregabalin 150 mg/day group)
1 patient (pregabalin 600 mg/day) began prohibited pain medication due to facial trauma
1 patient (placebo) had significant abnormalities on fundoscopic examination
1 patient (placebo) withdrew early due to jury duty
1 patient (placebo) withdrew due to familial responsibilities
1 patient (pregabalin 600 mg/day) entered the open-label study early

6.3.2.1.6 Extent of Exposure/Dosing Information

Table 6.3.2.1.6 shows the exposure duration across treatment groups. Drug exposure appeared to be lower for the placebo group, compared to either of the active treatment groups. Overall, 185 of the 246 patients (75.2%) completed at least 6 weeks of therapy. This number is different from the Applicant's number of patients who completed the study (n = 219, 89%). The Applicant states that this is because completion of the study was determined independently of the number of weeks a subject was exposed to study medication. Due to visit scheduling, some patients may have completed the study earlier than Day 42, resulting in < 6 weeks total exposure. Completion of the study was defined as "completion of all study visits and procedures". Note that this definition is different

from that stipulated in the protocol, where study completion was defined as receipt of 6 weeks of double-blind treatment (V5/Termination visit).

Table 6.3.2.1.6: Patient Exposure to Medication, Protocol 014

Total Exposure Time[b]	Placebo (N = 85)		Pregabalin 150 mg/day (N = 79)		Pregabalin 600 mg/day (N = 82)		Pregabalin Total (N =161)	
	N	(%)	N	(%)	N	(%)	N	(%)
≥1 Day	85	(100.0)	79	(100.0)	82	(100.0)	161	(100.0)
≥1 Week	82	(96.5)	79	(100.0)	82	(100.0)	161	(100.0)
≥2 Weeks	82	(96.5)	79	(100.0)	80	(97.6)	159	(98.8)
≥3 Weeks	76	(89.4)	75	(94.9)	75	(91.5)	150	(93.2)
≥4 Weeks	74	(87.1)	75	(94.9)	73	(89.0)	148	(91.9)
≥5 Weeks	73	(85.9)	75	(94.9)	71	(86.6)	146	(90.7)
≥6 Weeks	64	(75.3)	62	(78.5)	59	(72.0)	121	(75.2)

a Study days on which patients received zero dose during the study are included in the summary of patient exposure to study medication.
b The total exposure time includes titration and fixed-dose phases.
(Applicant's Table 10, RR 720-04236, 1008-014, P. 35)

6.3.2.1.7 *Demographics*

The tables that follow show the demographic and baseline characteristics of the 3 treatment groups. The majority of subjects in the ITT population were male (61%) and Caucasian (84%). The mean age of the population was 57 (± 9.7) years, with the majority of patients between the ages of 18 and 64 years (76%). The treatment groups differed with respect to gender, race, and mean weight. The pregabalin 150 mg/day group had a larger proportion of men and Caucasians compared to the placebo and pregabalin 600 mg/day groups. The mean weight of the subjects in the placebo group was lower than that of the other treatment groups. This reviewer does not consider that either of these differences would significantly impact the primary efficacy outcome.

Diabetes and neuropathic pain history

While most patients in the study had Type 2 diabetes (91%), the treatment groups varied with respect to the proportion of patients with this form of the disease (85% in the placebo group, 91% in the pregabalin 150 mg/day group, and 98% in the pregabalin 600 mg/day group). The mean duration of diabetes for the population was 9.4 years, and the baseline mean pain score was 6.7. The baseline mean pain score was similar across treatment groups.

More people in the placebo group used insulin (55%) compared to the pregabalin 150 and 600 mg/day groups (38% each). The proportion of subjects who used oral antidiabetic medication also varied across treatment groups (61% in the placebo group, 68% in the pregabalin 150 mg/day group, and 78% in the pregabalin 600 mg/day group). Again, these differences are not expected to significantly impact the primary analysis.

Concomitant medications

The Applicant states that allowable medications for neuropathic pain were taken in accordance with the protocol by 21% of patients in the 600 mg/day group, 17% of patients in the 150 mg/day group, and 21% of patients in the placebo group. Specifically, acetaminophen was the most commonly used medication, with similar frequency of use (approximately 15% of subjects) among the treatment groups.

Recall that the protocol disallowed use concomitant pain medications during the last 14 or 30 days of the study that might affect painful diabetic neuropathy. These medications included tricyclic antidepressants, benzodiazepines, tramadol, antiepileptics, and NSAIDs. The data show that only 16 subjects (6 in the placebo group, 2 in the pregabalin 150 mg/day group, and 8 in the pregabalin 600 mg/day group) used these medications within the allowable time periods of the study. These patients are not expected to considerably affect the study results.

6.3.3 Efficacy Results

6.3.3.1 Applicant's Primary Efficacy Analysis

6.3.3.1.1 Overview

The Applicant found that the pregabalin 600 mg/day group was statistically significantly different from the placebo group with respect to the primary outcome, the mean pain score at endpoint. That is, subjects in the 600 mg/day group had significantly less pain than those in the placebo group. Similar results were noted upon several secondary outcomes including the responder rate, as well as the SF-MPQ VAS and PPI scores at endpoint. There was no difference between pregabalin 150 mg/day and placebo with respect to either the primary or secondary outcomes.

6.3.3.1.2 Primary Efficacy Outcome

The primary efficacy outcome was the endpoint mean pain score. The Applicant's analysis showed improvement in mean pain scores for all 3 treatment groups, with the 600 mg/day pregabalin group showing the greatest decrease. The ANCOVA results showed that only the pregabalin 600 mg/day endpoint mean pain score was significantly better than that of the placebo group.

Table 6.3.3.1.2.a: Mean pain scores at endpoint, Descriptive Statistics – Protocol 014

		Placebo	PGB 150 mg/d	PGB 600 mg/d
Time point	**N**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline	85	6.9 (1.6)	6.5 (1.3)	6.7 (1.7)
Endpoint	82	5.8 (2.2)	4.9 (2.2)	4.3 (2.7)
Change	82	-1.2 (1.8)	- 1.5 (1.8)	- 2.4 (2.4)

PGB: pregabalin SD: standard deviation

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

(Adapted from Applicant's Table 12, RR 720-04326, P. 37)

Table 6.3.3.1.2.b: Endpoint mean pain interference, ANCOVA - Protocol 014

				Treatment Comparisons (PGB – Placebo)		
Treatment	N	Least Squares Mean	SE	Difference	95% CI	Adjusted p-value*
Placebo	82	5.55	0.23			
PGB 150	79	5.11	0.24	-0.440	(-1.080, 0.199)	0.1763
PGB 600	82	4.29	0.23	-1.264	(-1.890, -0.639)	0.0002

* Adjustment based on Hochberg's procedure
(Adapted from Applicant's Table 13, RR 720-04326, P. 38)

6.3.3.1.3 Supplemental Analyses of the Primary Efficacy Variable

Weekly mean pain scores

Descriptive statistics suggest that the mean pain scores for the pregabalin groups progressively decreased over the duration of the study, while the scores for the placebo group reached a plateau at Week 3. Further analysis with ANCOVA revealed that the pregabalin 150 mg/day group's weekly scores were not different from the placebo group. The weekly mean pain scores for the pregabalin 600 mg/day group were better than the placebo group's, except at Week 1. Analysis of the change in mean pain score from baseline, and at each week separately found similar results.

6.3.3.2 Applicant's Secondary Efficacy Analyses

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)*

At end point, as well as at Weeks 2, 4, and 6, the 600 mg/day pregabalin treatment group had a significantly better mean VAS score ($p = 0.0002$) and mean PPI score ($p = 0.0002$) compared to the placebo treatment group. The 150 mg/day pregabalin treatment group mean total score was not significantly different from those of the placebo group in either the mean VAS score ($p = 0.2058$) and mean PPI score ($p = 0.2836$) at any of those time points.

Most of the pain descriptors were chosen by at least 50% of the patients at randomization. At endpoint, the percentage of patients who reported gnawing, sickening, fearful, and punishing-cruel descriptors was less than half the percentage reported at randomization. The frequency of reporting of any pain descriptor was not decreased by 50% in either the placebo or pregabalin 150 mg/day groups.

At endpoint, the differences in sensory, affective, and total pain scores were significantly significant for the pregabalin 600 mg/day group compared to placebo, but not for the pregabalin 150 mg/day group. Similar results were seen upon analysis of the SF-MPQ sensory and total scores at Weeks 2, 4, and 6. At Week 4, there was no significant difference in affective scores between the pregabalin 600 mg/day and placebo groups.

- *Mean sleep interference score, weekly and at study endpoint*
  The mean sleep interference scores for all 3 treatment groups decreased by end point, and the 600 mg/day pregabalin group showed the greatest decrease. End point and weekly mean sleep interference score were significantly better for patients receiving 600 mg/day pregabalin than for those patients receiving placebo. The 150 mg/day treatment group was not significantly different from the placebo group. Similar results were noted when the change in mean sleep interference score, from baseline to endpoint and each week, was analyzed.

- *Global impression of change (by subject and investigator)*
  More patients (52%) in the pregabalin 600 mg/day group reported scores of "very much improved" or "much improved" compared to patients in the pregabalin 150 mg/day and placebo groups (36% and 28%, respectively). Similar findings were noted for the investigator ratings of patient improvement. The differences between the pregabalin 600 mg/day and placebo groups reached statistical significance.

- *SF-36 quality of life change from baseline*
  Results for both the 600 mg/day and the 150 mg/day pregabalin groups were significantly better than placebo in the bodily pain domain, but not in any of the other 7 health domains.

- *POMS change from baseline*
  There were no significant differences between the 600 mg/day pregabalin group and placebo or between the150 mg/day pregabalin group and placebo for any of the 7 mood disturbances.

6.3.3.3 Unplanned Analyses

Responder rate
Patients who had at least a 50% reduction in mean pain score from baseline to endpoint were considered to be responders. The proportion of responders in the 600 mg/day group (39%) was greater than that of the pregabalin 150 mg/day group (19%) or the placebo group (15%), and was significantly different from placebo ($p = 0.002$). The proportion of responders in the pregabalin 150 mg/day group did not reach statistical significance

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 analysis*
  Based on information from the Patient Status case report form, the Applicant identified 24 subjects as not having completed the study. The baseline mean pain score for these subjects was used instead of the endpoint mean pain score in the ANCOVA. This analysis yielded similar results to the primary analysis: the scores of the pregabalin 600 mg/day group were significantly better than the scores for placebo group ($p = 0.0002$).

Note that disposition data show that 27 subjects (and not 24) withdrew from the study prior to the end of the treatment period (see Table 6.3.2.1.5). The Applicant provides no explanation for the discrepancy between these numbers.

- *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. There were 53 subjects (5 receiving placebo, 11 receiving pregabalin 150 mg/day, and 37 receiving pregabalin 600 mg/day) who reported treatment emergent signs and symptoms (TESS) events of dizziness and or/somnolence during the study. The primary analysis was repeated after removing these patients, and showed that patients in the pregabalin 600 mg/day group had significantly greater improvements in pain ($p = 0.0102$) compared to placebo patients.

- *Longitudinal analysis*
  A longitudinal analysis was performed on the observed values of the weekly mean pain scores using ANCOVA with treatment, center, baseline pain, and week as fixed effect terms in the model. The model was run again including a treatment-by-week interaction term. Because there was evidence of a treatment-by-week interaction, an ANCOVA model using treatment-by-week effect was used. The results of this analysis were consistent with the primary analysis.

- *Analysis of allodynia*
  Table 6.3.3.3 shows that the 600 mg/day pregabalin group showed the largest percentage of patients with improvement in allodynia. Sixty-four percent of the patients from the 600 mg/day pregabalin group at risk at baseline experienced no allodynia at termination, compared to 57% from the 150 mg/day pregabalin group and 23% from the placebo group.

Table 6.3.3.3: Incidence of allodynia – Protocol 014

		Termination		Allodynia	
	Baseline	Yes		No	
	Allodynia	N	(%)	N	(%)
Placebo	Yes (N = 22)	17	(77.3%)	5	(22.7%)
	No (N = 55)	1	(1.8%)	54	(98.2%)
Pregabalin 150 mg/day	Yes (N = 23)	10	(43.5%)	13	(56.5%)
	No (N = 53)	1	(1.9%)	52	(98.1%)
Pregabalin 600 mg/day	Yes (N = 28)	10	(35.7%)	18	(64.3%)
	No (N = 53)	2	(3.8%)	51	(96.2%)

a Termination = Last available (non follow-up) record.
(Applicant's Table 36, RR 720-04236, 1008-014, P. 1923)

- *Rescue Medication*
  Subjects were allowed to take acetaminophen (up to 3 g per day) for pain. There were 13 subjects in the placebo group (15%) who took acetaminophen compared to 12 (15%) in the pregabalin 150 mg/day group, and 13 (16%) in the 600 mg/day group. The Applicant states that since the proportion of patients taking acetaminophen was similar across groups, use of rescue medication was unlikely to affect the results.

6.3.3.4 Reviewer's Analyses

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 fails to take into account differential drop-out from treatment groups. The FDA's recommended BOCF analysis is preferred since it does tale differential drop-out into account. 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 5 weeks of treatment, but completed the Week 6 (V5/Termination) assessments, were incorrectly labeled as study completers and their last available mean scores used in the analysis.

The Statistical Reviewer, Dr. Ling Chen, conducted a BOCF analysis on the ITT population. In this analysis, the primary endpoint was defined as follows:

- If a patient completed the full duration of the study, and provided pain scores for the all 7 days of the last week of the study, then the endpoint was defined as the mean of the last week's pain diary scores.
  - If a patient completed the full duration of the study, but had missing pain scores during the last week of the study, the missing data was replaced with the mean of the baseline scores. The mean endpoint score was then the mean of these and the actual recorded pain scores.
- If a patient dropped out of the study before the last week of the study, then the endpoint was the mean of the baseline scores.

Based on Dr. Chen's BOCF analysis, all of the groups showed an improvement in mean pain score:

Reviewer's analysis: Endpoint mean pain scores – Protocol 014

Time point	N	Placebo Mean (SD)	PGB 150 mg/day Mean (SD)	PGB 600 mg/day Mean (SD)
Baseline*	85	6.90 (1.58)	6.43 (1.32)	6.73 (1.68)
Endpoint	85	5.92 (2.18)	5.01 (2.10)	4.74 (2.61)
Change	85	-0.98 (1.71)	-1.43 (1.66)	-1.99 (2.12)**

* Baseline = the average of last 7 days prior to randomization
** Endpoint = the average of the last 7 days of the treatment period
*** p- value = 0.0008

The pairwise comparison of 600 mg/day vs placebo achieved statistical significance (.0008), but the comparison of 150 mg/day vs placebo did not. Furthermore, analysis of the difference in the median percent change in pain score from baseline found that both the 150 mg/day and the 600 mg/day treatment groups were statistically different from placebo ($p = 0.0074$ and $p = 0.0003$ respectively, 1-sided alpha = 0.0125).

The BOCF analysis was repeated after factoring in the use of acetaminophen (rescue medication for pain) during the final week of the study. Use of rescue was considered to assist in determining whether the effects seen were due to study treatment or to the analgesic effects of acetaminophen. In this analysis, if a patient took an analgesic rescue medication (either allowable or prohibited) during the last week of the study , the pain score for that day was replaced by the maximum of the baseline scores (if the diary pain score was lower than the maximum baseline score). The mean pain score at endpoint was then calculated.

There was relatively little difference in the percentage of subjects in the in the pregabalin 150 and 300 mg/day groups who used rescue medication during the last week of treatment (16% and 17% respectively), compared to the placebo group (19%). BOCF analysis showed that there was no significant difference between the placebo and the pregabalin 150 mg/day groups ($p = 0.0137$, 1-sided alpha = 0.0125). However, the pregabalin 600 mg/day group remained significantly different from placebo ($p = 0.014$, 1-sided alpha = 0.0125). The significance level of the difference was decreased upon consideration of rescue medication, suggesting that some of the observed treatment effect was due to use of rescue.

The responder analysis was also repeated based on the BOCF analysis. A responder was defined as a patient who had at least 50% reduction in mean pain score from baseline to endpoint. The results are shown below:

Percentage change in endpoint mean pain score by dose: BOCF analysis – Protocol 014

Total Pain Score	85 Placebo N (%)	79 Pregabalin 150 mg/day N (%)	82 Pregabalin 600 mg/d N (%)
Any increase	21 (24.71)	12 (15.19)	7 (8.54)
No change	12 (14.12)	7 (8.86)	12 (14.63)
> 0% decrease	52 (61.18)	60 (75.95)	63 (76.83)
≥ 10 % decrease	39 (45.88)	49 (62.03)	52 (63.41)
≥ 20 % decrease	25 (29.41)	36 (45.57)	41 (50.00)
≥ 30 % decrease	18 (21.18)	26 (32.91)	40 (48.78)
≥ 40 % decrease	15 (17.65)	19 (24.05)	33 (40.24)
≥ 50 % decrease	***11 (12.94)***	***14 (17.72)***	***24 (29.27)***
≥ 60 % decrease	6 (7.06)	11 (13.92)	16 (19.51)
≥ 70 % decrease	5 (5.88)	6 (7.59)	11 (13.41)
≥ 80 % decrease	4 (4.71)	4 (5.06)	9 (10.98)
≥ 90 % decrease	1 (1.18)	1 (1.27)	4 (4.88)
= 100% decrease	0 (0.00)	1 (1.27)	2 (2.44)

The table above shows that a greater proportion of subjects in the pregabalin 600 mg/day group were treatment responders, compared to the other two groups. Furthermore, there was only a small difference in the proportion of responders between the placebo and the pregabalin 150 mg/day group.

The percent change in endpoint mean pain score by dose group was recalculated using the BOCF analysis as well as the maximum baseline pain score imputation for rescue medication. Again, there were more subjects in the pregabalin 600 mg/day group (23.17%) who were treatment responders compared to the placebo group (8.24%). A total of 17.72% of the pregabalin 150 mg/day group were treatment responders, which was appreciably different from placebo. This analysis showed that imputation for use of rescue medication lowered the proportion of responders in all groups.

An analysis of pain score for only those patients who did not report somnolence was not conducted. This was because it is believed that retrospective reports of somnolence, given at study visits, might or might not have any impact whatsoever on the reliability of what were intended to be contemporaneous (diary-based) reports of pain. The temporal relationship is not even known, and furthermore, subjects would have to be extremely sleepy to be confused about their pain. On confused the other hand, subjects who reported being drowsy from time to time could have had those events coded as "somnolence."

6.3.3.5 Conclusions Regarding Efficacy Data - Protocol 014

Both the Applicant's and the Agency's analyses showed that treatment with pregabalin 600 mg/day (administered in 3 divided doses) was better than placebo for the treatment of pain due to diabetic neuropathy. Only the Agency's BOCF analysis found that treatment with pregabalin 150 mg/day was better than placebo. This result was not supported when the data were analyzed after imputation for use of rescue medication.

6.4 Protocol 1008-029: A 5-week, double-blind, placebo-controlled trial of 3 dosages of pregabalin (75, 300, and 600 mg/day) for treatment of patients with diabetic peripheral neuropathy

6.4.1 Protocol

6.4.1.1 *Objective/Rationale*

The purpose of this study was to assess the safety and efficacy of 3 dosages of pregabalin (75, 300, and 600 mg/day) compared with placebo for symptomatic relief of painful, diabetic sensorimotor polyneuropathy

6.4.1.2 Overall Design

This Phase 2/3 study was designed as a multicenter, multiple-dose, randomized, double-blind, parallel, placebo-controlled trial.

6.4.1.3 *Population and Procedures*

6.4.1.3.1 Treatment Duration: 5 weeks (1-week titration, 4-week fixed dose period)

6.4.1.3.2 Entry Criteria:

A total enrollment of 320 subjects was planned (80 subjects in each arm).

To be eligible, subjects were required to meet the following criteria:

- Age ≥ 18 years
- Type 1 or 2 diabetes mellitus
- Diagnosis of diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years
- Hemoglobin A1c of ≤ 11%
- Score of ≥ 40 mm on the Visual Analog Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at the baseline and randomization visits
- Completion of at least 4 daily pain diaries during the baseline phase, and had an average daily pain score of ≥ 4 over the previous 7 days on the Likert-type pain Rating Scale at randomization
- Normal chest x-ray within 2 years prior to the Baseline Visit
- Women at risk of pregnancy: appropriate contraception and negative serum pregnancy test

Subjects were excluded for:

- Clinically significant or unstable hepatic, respiratory, hematological, endocrine, immunological, cardiovascular, peripheral vascular, thyroid, or psychological condition
- History of pernicious anemia, untreated hypothyroidism, chronic hepatitis B, hepatitis B within 3 months, or HIV infection
- Malignancy
- Creatinine clearance ≤ 60 mL/min

- WBC < 2500/mm^3; neutrophil count x 1500 mm^3; platelet count < 100 x 103/mm^3
- Abnormal ECG or abnormality on 2 minute rhythm strip
- Failure to respond to previous treatment with gabapentin (Neruontin®) at doses ≥ 1200 mg/day for treatment of pain associated with diabetic neuropathy
- Neurologic disorder unrelated to diabetic neuropathy that could confuse the assessment of neuropathic pain
- Skin conditions in the area affected by the neuropathy that could alter sensation
- Other severe pain that may confound assessment on self-evaluation of the pain due to diabetic neuropathy
- Amputations other than toes
- Clinically significant abnormalities on best-corrected Snellen visual acuity, dilated ophthalmoscopy, or 120-point Humphrey visual screening with the quantified defects routine
- Use of prohibited medications (listed below), in the absence of appropriate washout periods

Study Medication:
The study drug was capsules containing placebo, 25, or 100-mg pregabalin. The protocol called for blocked randomization of subjects (in groups of 8) to placebo, 75 mg/day, 300 mg/day or 600 mg/day (given in TID dosing). Subjects randomized to the 600 mg/day arm were to be titrated to the full dose over the 6 day titration period. Patients randomized to 75 and 300 mg/day were to begin study drug at the full dose without titration. Subjects unable to attain the target (fixed) dose were to be withdrawn from the study.

Permitted Medications:
Subjects were allowed to take an aspirin (≤ 325 mg/day) for myocardial infarction and stroke prophylaxis, antidepressants (as long as they had been on a stable regimen within the last 30 days prior to screening and did not initiate therapy during the study), and acetaminophen (≤ 3g daily).

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

Class of Medication	*Washout period*
Pro-arrhythmics	Not applicable [a]
Anti-arrhythmics	Not applicable [a]
Macrolide antibiotics	Not to be taken with antihistamines
Antihistamines	Not to be taken with macrolide antibiotics
Medications commonly used for relief of neuropathic pain (e.g. benzodiazepines, skeletal muscle relaxants, capsaicin, dextromethorphan)	30 days prior to Visit 1
Antiepileptics (including vigabatrin [b])	14 days prior to Visit 1

a Patients on these medications were ineligible for the study
b Patients on vigabtrin were ineligible for the study

6.4.1.3.3 Study Procedures

Study Visits

The protocol stipulated 5 study visits. The first 2 visits were to occur during screening and at the end of the baseline phase. During the treatment phase, subjects were to be evaluated after 1 week of fixed-dose treatment, and then every 2 weeks (Visits 3 to 5). A follow-up visit would occur 7 days after study termination, for subjects who did not enter the open-label study, Protocol 1008-033.

Screening

In addition to the meeting the criteria above, each patient needed to be stabilized on their antidiabetic medication before initiating study drug, and the antidiabetic medication was to remain unchanged for the duration of the study.

Baseline

Eligible subjects were to undergo a 1-week baseline phase during which they would enter pain and sleep ratings for the previous day into diaries each morning on arising. Subjects who completed at least 4 daily pain diaries during the baseline phase, and who had an average daily pain score of ≥ 4 over the previous 7 days were to be randomized to study drug.

Treatment

The placebo, pregabalin 75 mg/day, and pregabalin 300 mg/day treatment groups were to begin at their fixed dose on Day 1. Study medication was to be increased over 6 days for the pregabalin 600 mg/day group. Patients who were not able to attain or maintain the target dose were to be withdrawn from the study. From Day 7 of Week 1 onward, study medication was to remain at the fixed dose for all subjects. After Week 5, subjects were to have the option of entering an open-label extension study (Protocol 1008-33).

The protocol considered a patient to have completed the study if s/he received 5 weeks of double blind treatment and completed the V5/Termination visit.

Table 6.4.1.3: Time and Events Schedule – Protocol 029

Table 6: Timetable of Visits and Procedures

Study Phase	Baseline Week	Double-Blind Treatment (8 Weeks)				
End of Study Week	Screening	Randomization	1	3	8	[illegible]
Study Day		-1	7	21	56	42
Clinic Visit [a]	1	2	3	4	5 Term[b]	6
Observation/Procedure						
Informed Consent	X					
Inclusion Exclusion	X					
Medical History	X					
Physical Exam	X		X[c]		X	
Abbreviated Neurological Exam	X				X	
Peripheral Sensory Exam	X				X	
SF-McGill Pain Questionnaire	X	X	X	X	X	
Daily Diaries (Pain, Sleep)	X-----------	-X--------	-X-----	-X----	-X	
Global Imp of Change (Clinical & Patient)					X	
SF-36 QOL		X			X	
Profile of Mood States (POMS)		X			X	
Adverse Events		X	X	X	X	X
Prior and Concurrent Medications	X	X	X	X	X	X
Study Medication Dosing Dispensing		X	X	X	X[d]	
Clinical Labs						
Hematology, Chemistry, Urinalysis	X		X	X	X	X
Hemoglobin A1c	X				X	
B12, folate, SPEP, T4, TSH	X					
Pregnancy Test (Serum, Urine)[e]	X		X		X	
Study Medication Plasma Conc					X	
FSH	X				X	
Chest X-ray	X[f]					
12-lead ECG With 2-Minute Rhythm Strip	X		X		X	
Visual Examinations[g]	X				X	

[a] Telephone contact was made with the patients twice weekly during the titration phase to ensure completion of daily diaries and to assess adverse events. Extra visits were scheduled if a patient experienced an adverse event during titration or during double-blind. Between each subsequent visit up until V5 Termination, telephone contact was made to ensure compliance with study procedures.

[b] Follow-up visit only for patients who do not enter open-label Protocol 1008-033

[c] Whenever patient withdrew from or completed the study

[d] Vital signs only

[e] Medication was dispensed for patients entering into open-label Protocol 1008-033.

[f] Serum pregnancy test was done at V1, and urine pregnancy test at Visits 3 and 5/Termination.

[g] Chest x-rays were taken at baseline visit if none available in the 2 years prior to baseline

Examination-testing by an ophthalmologist at Visits 1 and 5/Termination. These included Dilated Ophthalmoscopy (direct or indirect), 120-point Humphrey visual field screening with the quantified defects routine, and best-corrected Snellen Visual Acuity.

(Applicant's Table 6, RR 720-04242, 1008-029, P. 28)

The following measures of patient pain and function were to be utilized:

- Daily pain score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Clinical Global Impression of Change (CGIC)
- Patient Global Impression of Change (PGIC)
- SF-36 Health Survey Questionnaire (SF-36 QOL)
- Profile of Mood States (PMOS
- Daily diary of sleep interference

6.4.1.3.4 Pharmacokinetics

At the Week 5/Termination Visit, all subjects were to provide a blood sample for measurement of plasma drug concentrations.

6.4.1.3.5 Statistical Analysis:

6.4.1.3.5.1 Patient population

The *intent-to-treat (ITT)* and the *safety* populations were to be all randomized subjects who received at least one dose of study medication.

6.4.1.3.5.2 Demographics

Baseline characteristics (demographics, type of diabetes, duration of polyneuropathy, and hemoglobin A1c level.) among treatment groups were to be compared using descriptive statistics.

6.4.1.3.5.3 Primary Efficacy Outcome

The primary efficacy outcome was to be the *endpoint mean pain score*, defined as the mean of the last 7 diary entries while on study medication.

The primary analysis would compare the final mean weekly pain score between the treatment groups using ANCOVA, with treatment and center in the model, and the respective baseline as a covariate. The comparisons of pregabalin 600 mg/day versus placebo, and 300 mg/day pregabalin versus placebo were to be considered primary. Using the Hochberg approach, the p-values from these comparisons were to be ranked. If the larger (i.e. less significant) of the p-values was equal to 0.05, then both the 600 and the 300 mg pregabalin comparisons were to be considered statistically significant. If the larger p-value were > 0.05, then the treatment group associated with the smaller p-value was to be evaluated for significance at the 0.025 level (0.05/2). The 75 mg pregabalin comparison with placebo was to be considered a secondary.

6.4.1.3.5.4 Supplemental analyses of the Primary Efficacy Variable

- Weekly mean pain score
- Change in pain score from baseline to endpoint

6.4.1.3.5.5 Secondary Efficacy Endpoints

- SF-McGill Sensory, Affective, Total, VAS, and PPI scores, at endpoint and at Weeks 1, 3, and 5 (endpoint)
- Mean sleep interference scores, at endpoint and at each week separately
- PGIC and CGIC at endpoint
- SF-36 QOL (8 domains)
- POMS (6 mood scales, total mood disturbance)

The secondary efficacy endpoints were to be analyzed using the same ANCOVA main effects model as the primary efficacy endpoint. The protocol did not stipulate any adjustments for testing multiple parameters. However, due to the large number of supplemental and secondary analyses performed, some significant results were likely to occur by chance alone. Undue consideration was therefore not to be given to any particular significant result; rather, interpretation of results was to be based on patterns of significant differences.

6.4.1.3.5.6 Interim analysis

An interim analysis was to be performed if enrollment were slow, or if information from the trial would be needed to plan other studies. The significance level for the final analysis was to be adjusted for a penalty of 0.001.

6.4.1.4 Protocol Amendments

None reported.

6.4.2 Study Results

6.4.2.1 Study Conduct/Outcome

6.4.2.1.1 Subject characteristics

The first patient was randomized on 08/21/98 and the last patient completed the study on 06/24/99. A total of 45 centers in the United States participated, however 1 center did not enroll any patients.

6.4.2.1.2 Enrollment by Center

Enrollment was distributed among the 45 study centers as listed in the table below. Seventy one (21%) of the 338 patients who entered the study came from 3 centers, while 202 (59.8%) came from 13 centers.

Table 6.4.2.1.3: Enrollment by Center – Protocol 029

# Subjects randomized	No. of Centers	Centers (by Center Number)
0	1	038
1	5	018, 023, 026, 034, 040
2	5	005, 011, 031, 042, 045
3	3	008, 013, 029
4	3	006, 024, 044
5	4	004, 010, 014, 020,
6	3	030, 032, 039
7	4	001, 019, 027, 041
8	2	015, 025
9	2	003, 037
10	1	021
11	1	007
12	4	002, 022, 033, 035
14	2	012, 016
17	2	017, 036
20	1	009
25	1	028
26	1	043

(Adapted from Applicant's Table 1, RR 720-04242, P. 13)

6.4.2.1.3 Protocol violations

The Applicant identified 55 randomized patients with protocol violations that could potentially impact the primary efficacy endpoint. Twenty patients were randomized to placebo (21% of the placebo group), 13 patients (17%) to pregabalin 75 mg/day, 11 patients (13%) to pregabalin 300 mg, and 11 patients (13%) were randomized to pregabalin 600 mg/day. The specific types of protocol violations are detailed in the table below:

Table 6.4.2.1.4: Protocol Violations – Protocol 029

Violation	Total	Pregabalin 75 mg/day	Pregabalin 300 mg/day	Pregabalin 600 mg/day	Placebo
Diabetes diagnosis < 1 year	7	1	3	2	1
Diabetes diagnosis > 5 years	3	1	1	-	1
Other potential cause of neuropathy: Pernicious Anemia	3	2	1	-	-
Inconsistent evidence of neuropathy	2	2	-	-	-
Baseline mean pain score < 4	7	-	2	2	3
Incomplete pain diary at baseline	2	-	1	1	-
Creatinine clearance < 60 mL/min	2	1	-	-	1
Neutrophils < 1500/mm^3	4	1	-	-	3
Platelets < 100 x 10^3/mm^3	3	1	-	-	2
Hgb A1c > 11%	1	1	-	-	-
Use of prohibited medications, *or* inappropriate washout	18	2	3	6	7

Table 6.4.2.1.4: Protocol Violations (continued)

Violation	Total	Pregabalin 75 mg/day	Pregabalin 300 mg/day	Pregabalin 600 mg/day	Placebo
Abnormal screening ECG	2	1	-	-	1
Medication noncompliance	1	-	-	-	1
Total	55	13	11	11	20

(Adapted from Applicant's Appendix A.8, RR 720-04242, 1008-029, P 290)

I consider that the protocol violations that would potentially impact the primary efficacy outcome to be from the following subjects:

- Patients who had a pain score < 4 at baseline (n = 7): if a small improvement in pain occurred with therapy, it would be difficult to detect
  - 015 015013 Placebo Score = 2.86
  - 021 021009 Placebo Score = 3.14
  - 033 033021 Placebo Score = 3.86
  - 012 012004 300 mg/day Score = 3.70
  - 017 017010 300 mg/day Score = 3.714
  - 003 003005 600 mg/day Score = 3.71
  - 033 033020 600 mg/day Score = 3.86
- Patients with another potential cause of neuropathy (i.e. pernicious anemia)
  - Patient 017028 (pregabalin 75 mg/day)
  - Patient 019008 (pregabalin 75 mg/day)
  - Patient 025006 (pregabalin 300 mg/day)
- Patients who used (or had an inappropriate washout of) prohibited medications that might themselves improve pain (n = 11)
  - Patient 002015 (placebo) continued to use quinidine
  - Patient 013004 (placebo) had only 11 days of washout of nortriptyline
  - Patient 002007 (placebo) continued to use mexiletine and ibuprofen
  - Patient 028006 (placebo) initiated diclofenac during the study
  - Patient 042001 (75 mg/day) had only 1-day washout of gabapentin, and used naprosyn
  - Patient 016009 (75 mg/day) initiated amitriptyline during the study
  - Patient 040003 (300 mg/day) received neurontin during baseline phase, and had inadequate washout of oxycodone
  - Patient 017003 (600 mg/day) continued to use salsalate during the study
  - Patient 035002 (600 mg/day) had only 11 days washout of sertraline
  - Patient 028002 (600 mg/day) started oxaprozin (NSAID) during the study
  - Patient 030001 (600 mg/day) initiated lorazepam during the study

While the use of prohibited pain medication would tend to bias the study in favor of the affected arm, the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is therefore not expected to have a significant impact on the interpretation of the results.

6.4.2.1.4 Blinding

The Applicant states that the blind was broken for Patient 044007, who was randomized to the placebo arm. This patient experienced a serious adverse event (allergic reaction with hives, itching, blotchy skin, emesis, and fainting) after receiving study drug for 4 days. Study drug was discontinued and the blind was broken on Study day 6. The SAE lasted 33 days.

6.4.2.1.5 Subject disposition

The disposition of the enrolled patients is detailed in Table 6.4.2.1.6 below. Five hundred and seventy eight patients were enrolled, and 240 were removed during the baseline phase. Of the 338 patients who were randomized, 337 received at least one dose of study medication (ITT population): 97 received placebo, 77 received pregabalin 75 mg/day, 81 received pregabalin 300 mg/day, and 82 received pregabalin 600 mg/day. The one patient who did not receive study medication and therefore was not included in the ITT population (Patient 017020 in the pregabalin 300 mg/day group), withdrew consent due to concern about an ECG abnormality.

Titration Phase

Only the 82 subjects randomized to pregabalin 600 mg/day underwent a 6-day titration phase. Of these, 3 patients withdrew during the titration phase: 1 subject (Patient 015007) was lost to follow-up, and the other two withdrew due to an AE (Patient 028021 experienced a headache, and Patient 007004 had bronchitis).

Treatment Phase

A total of 302 subjects completed the study. That is, of the 337 subjects who received study medication, 35 withdrew prior to the end of the fixed-dose phase: 8 (8.2%) from the placebo group, 10 (13%) from the pregabalin 75 mg/day group, 5 (6.2%) from the pregabalin 300 mg/day group, and 12 (14.6%) from the pregabalin 600 mg/day group. Adverse events most frequently led to withdrawal from the pregabalin 600 mg/day group [10 (12.2%)], whereas the most frequent cause of withdrawal from the placebo and pregabalin 75 mg/day groups was lack of efficacy [2 (2.1%) and 4 (5.2%), respectively]. A total of 295 patients (87.5%) entered the open-label follow-on study, Protocol 1008-033.

Table 6.4.2.1.6: Subject Disposition – Protocol 029

Disposition N (%)	Placebo	Pregabalin (mg/day) 75	300	600	All Patients
Entered Baseline Phase					578
Completed Baseline Phase					338 (58.5)
Withdrawn During Baseline:					240 (41.5)
Adverse Event					2 (0.3)
Did Not Meet Criteria					212 (36.7)
Other [1]					26 (4.5)
Randomized	97	77	82	82	338
Intent-to-Treat	97	77	81	82	337
Completed Study	89 (91.8)	67 (87.0)	79 (93.8)	70 (85.4)	302 (89.6)
Withdrawn During Treatment Phase:	8 (8.2)	10 (13.0)	5 (6.2)	12 (14.6)	35 (10.4)
Adverse Event	3 (3.1)	2 (2.6)	3 (3.7)	10 (12.2)	18 (5.3)
Lack of Compliance	1 (1.0)	1 (1.3)	0 (0.0)	0 (0.0)	2 (0.6)
Lack of Efficacy	2 (2.1)	4 (5.2)	0 (0.0)	0 (0.0)	6 (1.8)
Other [2]	2 (2.1)	3 (3.9)	2 (2.5)	2 (2.4)	9 (2.7)
Entered Open Label	88 (90.7)	67 (87.0)	70 (86.4)	70 (85.4)	295 (87.5)

(Applicant's Table 13, RR 720-04242, 1008-029, P. 45)

Other [1] Data regarding reasons for withdrawal during the baseline phase are not provided

Other [2]: 3 subjects were lost to follow-up (1 patient each in the in the pregabalin 75, 300, and 600 mg/day groups)

2 subjects withdrew consent (both patients were in the pregabalin 300 mg/day group)

1 subject (pregabalin 75 mg/day) underwent surgery and had to withdraw from the study

1 subject (pregabalin 600 mg/day) lacked transportation to attend clinic visits

1 subject (pregabalin 75 mg/day) was withdrawn due to "med. error"

1 subject (placebo) was withdrawn due to an "exclusionary lab"

Note: I noted an additional subject who withdrew due to "other" reasons. This subject (placebo) was described as having "unexpected difficulty with the study protocol and schedule"

6.4.2.2 Extent of exposure/Dosing information

The table below illustrates exposure duration across treatment groups. Drug exposure was similar across treatment groups, over the duration of the study. Overall, only 157 (65.4%) patients completed at least 5 weeks of therapy. This number is different from the number of study 'completers' (n = 302). The Applicant explains that the difference occurs because completion of study was defined as completion of all study visits and procedures (see Table 6.4.1.3). Due to visit scheduling, some patients may have completed the study earlier than Day 35, resulting in < 5 weeks' exposure to study drug. A slightly higher proportion of subjects in the placebo group (69.1%) had at least 5 weeks' exposure than subjects in the other treatment groups.

Note that this definition of study completion is different from that stipulated in the protocol, where completion was defined as receipt of 5 weeks of double-blind treatment and attendance of the V5/Termination visit.

Table 6.4.2.2: Drug Exposure[a] - Protocol 029

Total Exposure time [b]	Placebo (N = 97) N (%)	Pregabalin (mg/day) 75 (N = 77) N (%)	300 (N = 81) N (%)	600 (N = 82) N (%)	Pregabalin Total (N = 240) N (%)
≥ 1 Day	97 (100)	77 (100)	81 (100)	82 (100)	240 (100)
≥ 1 Week	95 (97.9)	76 (98.7)	79 (97.5)	78 (95.1)	233 (97.1)
≥ 2 Weeks	93 (95.9)	71 (92.2)	79 (97.5)	75 (91.5)	225 (93.8)
≥ 3 Weeks	90 (92.8)	69 (89.6)	78 (96.3)	72 (87.8)	219 (91.3)
≥ 4 Weeks	86 (88.7)	63 (81.8)	74 (91.4)	68 (82.9)	205 (85.4)
≥ 5 Weeks	67 (69.1)	50 (64.9)	54 (66.7)	53 (64.6)	157 (65.4)

(Applicant's Table 12, Section 5.3, RR 720-04242, P. 42)

a Days off drug during the study are included in summary of patient exposure to study medication

b The total exposure time includes titration and fixed-dose phases

6.4.2.3 Demographics

The table below illustrates demographic and baseline characteristics of the 4 treatment groups. There were 337 patients in the ITT population and the majority was male (59.9%) and Caucasian (94.4%). The mean age of the subjects was 59.9 (± 10.5) years, with a range of 26 to 85 years. The median age was similar across treatment groups. The median estimated creatinine clearance for the ITT population was 90.0 mL/min. The pregabalin 600 mg/day group had the lowest median creatinine clearance (87.4 mL/min) and the placebo group had the highest (97.7 mL/min).

Diabetes and Neuropathic Pain History

The tables below show that most subjects in the ITT population had Type 2 diabetes (90.8%). Slightly fewer subjects in the placebo group had Type 2 diabetes (85.6%) than subjects in the pregabalin 75, 300, and 600 mg/day groups (92.2%, 93.8%, and 92.7% respectively). The mean duration of diabetes in the population was 9.5 (± 8.4) years. Ninety five percent of patients reported prior (within 30 days) and /or concurrent use of antidiabetic medication. Forty two percent of the patients used insulin, and 73% used an oral antidiabetic medication. More subjects in the placebo group used insulin (48.5%) than subjects in the pregabalin 75, 300, and 600 mg/day groups (39%, 41%, and 39% respectively).

The distribution of neuropathic pain was similar across the treatment groups. The baseline mean pain score was 6.4 (± 1.4) for the total population. The baseline mean pain score was slightly higher in the placebo and pregabalin 75mg/day groups (6.6 and 6.7, respectively) compared to the pregabalin 300 and 600 mg/day groups, each of which had a score of 6.2.

Table 6.4.2.3.a: Patient Characteristics

Table 8. Summary of Patient Characteristics: Intent-to-Treat Population

Characteristic	PBO N = 97	PGB 75 N = 77	PGB 300 N = 84	PGB 600 N = 82	Total PGB N = 240	All Patients N = 337
Sex: N (%)	97	77	84	82	240	337
Male	59 (60.8)	43 (55.8)	48 (57.1)	52 (63.4)	143 (59.6)	202 (59.9)
Female	38 (39.2)	34 (44.2)	36 (42.9)	30 (36.6)	97 (40.4)	135 (40.1)
Premenopausal	8 (21.1)	6 (17.6)	9 (25.0)	2 (6.7)	17 (17.5)	25 (18.5)
Postmenopausal	30 (78.9)	28 (82.4)	27 (75.0)	28 (93.3)	80 (82.5)	110 (81.5)
Race: N (%)	97	77	84	82	240	337
White	91 (93.8)	74 (96.1)	79 (94.0)	77 (93.9)	227 (94.6)	318 (94.4)
Black	5 (5.2)	1 (1.3)	3 (3.6)	3 (3.7)	7 (2.9)	12 (3.6)
Hispanic	1 (1.0)	1 (1.3)	2 (2.4)	2 (2.4)	5 (2.1)	6 (1.8)
American Indian or Alaskan Native	0 (0)	1 (1.3)	0 (0)	0 (0)	1 (0.4)	1 (0.3)
Age Categories: N (%)	97	77	84	82	240	337
18-64 Years	66 (68.0)	48 (62.3)	59 (70.2)	49 (59.8)	156 (65.0)	222 (65.9)
≥65 Years	31 (32.0)	29 (37.7)	25 (29.8)	33 (40.2)	84 (35.0)	115 (34.1)
Age (years): N	97	77	84	82	240	337
Mean (STD)	57.8 (11.6)	61.3 (10.5)	59.0 (9.2)	62.0 (9.7)	60.8 (9.9)	59.9 (10.5)
Median	60.0	61.0	60.0	62.0	61.5	61.0
Range	20 to 77	34 to 85	30 to 77	29 to 80	29 to 85	20 to 85
Estimated Creatinine Clearance at Baseline (mL/min): N	97	77	81	82	240	337
Mean (STD)	98.74 (29.09)	97.53 (32.78)	101.93 (30.42)	94.16 (30.02)	97.86 (31.10)	98.11 (30.49)
Median	97.70	89.00	93.80	87.40	89.25	90.90
Range	42.0 to 199.1	56.3 to 229.6	62.3 to 225.4	53.7 to 199.4	53.7 to 229.6	42.0 to 229.6
Height (cm): N	97	77	81	82	240	337
Mean (STD)	173.78 (10.74)	171.40 (9.66)	173.55 (9.30)	172.15 (9.97)	172.38 (9.65)	172.79 (9.98)
Median	175.20	172.70	172.70	172.90	172.70	173.00
Range	149.8 to 195.6	137.2 to 189.2	152.4 to 193.0	149.9 to 196.0	137.2 to 196.0	137.2 to 196.0
Weight (kg): N	97	77	81	82	240	337
Mean (STD)	98.27 (20.27)	96.12 (19.91)	101.07 (21.07)	97.61 (18.71)	98.30 (19.94)	98.29 (20.00)
Median	96.40	93.10	95.90	92.25	94.30	94.50
Range	59.0 to 167.4	52.3 to 173.8	54.5 to 157.1	63.8 to 165.9	52.3 to 173.8	52.3 to 173.8

(Applicant's Table 8, RR720-04242, P. 38)

Table 6.4.2.3.b: Patient Characteristics: Diabetic & Neuropathic Pain history – Protocol 029

Table 9 Summary of Diabetic and Neuropathic Pain History Intent-To-Treat Population

	Placebo	Pregabalin (mg/day) 75	300	600	All Patients
	N 97	N 77	N 81	N 82	N 337
Diabetes Type, N(%)					
type 1	14 (14.4)	6 (7.8)	5 (6.2)	6 (7.3)	31 (9.2)
type 2	83 (85.6)	71 (92.2)	76 (93.8)	76 (92.7)	306 (90.8)
Duration of Diabetes (yrs)					
N	97	77	81	82	337
Mean (STD)	11.0 (9.9)	9.3 (7.8)	8.6 (7.8)	8.5 (7.1)	9.5 (8.4)
Median	8	7	7	6.5	7
Range	0.0 to 52.0	1.0 to 34.0	0.0 to 48.0	0.0 to 32.0	0.0 to 52.0
Distribution of Neuropathic Pain,* N (%)					
Pain Distribution					
Lower Extremities	97 (100.0)	77 (100.0)	81 (100.0)	82 (100.0)	337(100.0)
Thigh	21 (21.6)	15 (19.5)	14 (17.3)	18 (22.0)	68 (20.2)
Calf	61 (62.9)	45 (58.4)	41 (50.6)	43 (52.4)	190 (56.4)
Toe/Foot	97 (100.0)	77 (100.0)	80 (98.8)	82 (100.0)	336 (99.7)
Toe	80 (82.5)	61 (79.2)	68 (84.0)	68 (82.9)	277 (82.2)
Foot	97 (100.0)	76 (98.7)	78 (96.3)	82 (100.0)	333 (98.8)
Distribution of Neuropathic Pain,* N (%)					
Upper Extremities	44 (45.4)	36 (46.8)	29 (35.8)	34 (41.5)	143 (42.4)
Forearm	12 (12.4)	5 (6.5)	3 (3.7)	6 (7.3)	26 (7.7)
Finger/Hand	44 (45.4)	36 (46.8)	29 (35.8)	34 (41.5)	143 (42.4)
Finger	37 (38.1)	27 (35.1)	21 (25.9)	23 (28.0)	108 (32.0)
Hand	32 (33.0)	25 (32.5)	17 (21.0)	25 (30.5)	99 (29.4)
Baseline Mean Pain Score					
N	97	77	81	82	337
Mean (STD)	6.6 (1.5)	6.7 (1.3)	6.2 (1.4)	6.2 (1.5)	6.4 (1.4)
Median	6.7	6.6	6	6.3	6.4
Range	2.9 to 9.6	3.7 to 10.0	3.9 to 10.0	3.7 to 10.0	2.9 to 10.0

* More than one category per patient possible

(Applicant's Table 9, RR 720-04242, 1008-029, P. 38)

Antidiabetic Medications

Oral antidiabetic medications were taken by approximately 75% of the patients in the study, while insulin was taken by less than half of the patients. More subjects (48%) in the placebo group used insulin compared to the active treatment groups (39% of the pregabalin 75 and 600 mg/day groups, and 41% of the pregabalin 300 mg/day group). The antidiabetic medications were not expected to impact the outcome of the study. The majority of patients did not have any fluctuations in their diabetic regimens.

Neuropathic pain medications

Prior and/or concurrent neuropathic pain mediations were used by 69 (20%) of the patients in the study. Acetaminophen was used by 67% of these patients. Use of acetaminophen was similar across groups(14% of the placebo group, 16% of the pregabalin 75 mg/day group, and 14% of the pregabalin 300 mg/day group). Venlafaxine was the next commonly used neuropathic pain medication: 2% of the placebo subjects, 1% of the pregabalin 75 mg/day group, and 6% of the pregabalin 600 mg/day group. No patients in the pregabalin 300 mg/day group used venlafaxine.

6.4.3 Efficacy Results

6.4.3.1 Applicant's primary efficacy analysis

6.4.3.1.1 Overview:

The Applicant's analyses showed that the pregabalin 300 and 600 mg/day groups were significantly better than the placebo group with respect to the primary efficacy outcome, the endpoint mean pain score, as well as for several secondary outcomes. The pregabalin 75 mg/day group was not statistically different from the placebo group.

6.4.3.1.2 Applicant's Primary Efficacy Analysis: Mean Pain Scores at End Point

The tables below show that the endpoint mean pain score for the pregabalin 75 mg/day group [5.1 (± 2.5)] was not statistically significant from the placebo group [5.2 (± 2.2)] (p = 0.6267). However, there was a significant difference in the endpoint mean pain score for the pregabalin 300 mg/day group [3.6 (± 2.1)] and the pregabalin 600 mg/day group [3.5 (± 2.3)] compared to placebo (p = 0.001 each).

Table 6.4.3.1.2.a: Endpoint Mean Pain Scores: Descriptive Statistics – Protocol 029

Time Point	Placebo		Pregabalin 75 mg/day		Pregabalin 300 mg/day		Pregabalin 600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	97	6.6 (1.5)	77	6.7 (1.3)	81	6.2 (1.4)	82	6.2 (1.5)
Endpoint	97	5.2 (2.2)	77	5.1 (2.5)	81	3.6 (2.1)	81	3.5 (2.3)
Change	97	-1.4 (1.9)	77	-1.5 (2.1)	81	-2.5 (1.9)	81	-2.7 (2.3)

(Adapted from Applicant's Table 14, RR 720-04242, 1008-029, P. 47)

Table 6.4.3.1.2.b: Endpoint Mean pain Scores: Results of ANCOVA – Protocol 029

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug – Placebo) Difference	95% CI	p-value
Placebo	97	5.06	0.21			
Pregabalin 75 mg/day	77	4.91	0.24	-0.151	(-0.759, 0.458)	0.6267
Pregabalin 300 mg/day	81	3.80	0.23	-1.257	(-1.862, -0.651)	0.0001
Pregabalin 600 mg/day	81	3.60	0.23	-1.454	(-2.056, -0.852)	0.0001

(Adapted from Applicant's Table 15, RR 720-04242, 1008-029, P.48)

6.4.3.2 Supplemental analyses of the primary efficacy variable

Weekly mean pain score

The results of this analysis were similar to those for the primary efficacy outcome. Both the pregabalin 300 and 600 mg/day groups showed statistically better pain scores at each week than the placebo group. There was no statistical difference between the pregabalin 75 mg/day group and the placebo group at any of the study weeks.

Change in pain score from baseline to endpoint

The p-values and 95% CIs for the comparisons between pregabalin 75, 300, and 600 mg/day versus placebo were the same as those for the primary analysis.

6.4.3.3 Applicant's secondary efficacy analysis

SF-McGill Sensory, Affective, Total, VAS, and PPI scores, at Weeks 1, 3, and 5
The Week 1, 3, and 5 (endpoint) VAS and PPI scores for the pregabalin 300 and 600 mg/day groups were statistically better than the scores for the placebo group. No significant differences from placebo were seen for the 75 mg/day dose.

Similar results were noted with respect to the SF-MPQ scores for sensory, affective, and total pain descriptors.

Mean sleep interference scores, at endpoint and at each week separately
The weekly sleep interference scores for the pregabalin 300 and 600 mg/day groups were statistically better than the scores for the placebo group. The 75 mg/day dose was not significantly different from the placebo group.

PGIC and CGIC at endpoint
Analyses showed that the pregabalin 300 and 600 mg/day groups were significantly better than placebo with respect to these efficacy outcomes. The 75 mg/day dose was not significantly different from the placebo group.

SF-36 QOL, and POMS
Overall, there were no significant differences between any of the pregabalin groups and the placebo group with respect to POMS measures of mood disturbances. As regards the SF-36 Health Survey (QOL) questionnaire, analyses showed statistically significant differences among groups with respect to only 2 specific health domains. The 600 and 300 mg/day pregabalin groups were better than placebo in the social functioning domain, while the 300 and 75 mg/day groups were better in the vitality domain.

6.4.3.4 Unplanned analyses

Responder rate
A responder was defined as a patient who had ≥ 50% decrease in mean pain score from baseline to endpoint. There was a significantly higher proportion of responders in the pregabalin 600 mg/day and 300 mg/day groups (48% and 46%, respectively) compared to placebo (18%) ($p = 0.001$ each). The proportion of responders in the pregabalin 75 mg/day group (22%) was not significantly different from placebo ($p = 0.407$).

Percent reduction in mean pain score
The Applicant calculated the distribution of the percent mean pain score (in deciles) from baseline to endpoint. The Applicant states that while the proportion of responders was similar for the 300 and 600 mg/day groups, more patients in the 600 mg/day group achieved substantial (e.g. ≥50%) reductions in pain score compared to the 300 mg/day group (see Table 6.4.3.4 below):

Table 6.4.3.4: Distribution of Percent Reduction in Mean Pain Score from Baseline to Endpoint

Reduction in Mean Pain	Placebo N = 97	Pregabalin 75 N = 77	Pregabalin 300 N = 81	Pregabalin 600 N = 81
			Number (%) of Patients	
≥ 50%	*17 (18)*	*17 (22)*	*37 (46)*	*39 (48)*
≥ 60%	10 (10)	12 (16)	23 (28)	31 (38)
≥ 70%	6 (6)	7 (9)	13 (16)	22 (27)
≥ 80%	2 (2)	6 (8)	8 (10)	13 (16)
≥ 90 %	1 (1)	1 (1)	4 (50	6 (7)
≥ 100%	0 (0)	0 (0)	4 (5)	5 (6)

(Adapted from Applicant's Table 19, RR 720-04242, P. 54)

FDA-requested analyses

a) Baseline Observation Carried Forward (BOCF) Analysis

In this analysis of the primary endpoint, the baseline pain score was carried forward for any patient who did not complete the study. The Applicant states that 34 patients were identified as non-completers. Their baseline pain scores were used instead of the endpoint mean pain score in the ANCOVA. As shown in the table below, the BOCF analysis resulted in similar results as the primary analysis.

Table 6.4.3.4.a: Endpoint Mean Pain Scores: Results of ANCOVA with BOCF – Protocol 029

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug – Placebo) Difference	95% CI	p-value*
Placebo	97	5.11	0.22			
Pregabalin 75 mg/day	77	4.90	0.24	-0.21	(-0.835, 0.407)	0.4981
Pregabalin 300 mg/day	81	3.94	0.24	-1.16	(-1.783, -0.547)	0.0002
Pregabalin 600 mg/day	81	3.84	0.23	-1.27	(-1.884, -0.656)	0.0002

* Pvalue adjusted based on Hochberg's procedure; applies to pregabalin 300 and 600 mg/day groups only, per protocol

(Applicant's Table 1, Appendix D21, RR 720-04242 1008-029, P. 2)

Note that disposition data show that 35 subjects (and not 34) withdrew from the study prior to the end of the treatment period (see Table 6.4.2.1.6). The Applicant provides no explanation for the discrepancy between these numbers.

b) Mean pain scores at endpoint: ITT patients without dizziness or somnolence

The Applicant removed 95 patients (8 in the placebo group, 9 in the pregabalin 75 mg/day group, 35 in the 300 mg/day group, and 43 in the 600 mg/day group) who reported TESS AEs of dizziness and/or somnolence during the study. Repeat analysis of the primary endpoint resulted in similar results as the entire ITT population. However, the differences in scores between active and placebo groups were smaller, and the p-values were slightly less significant (see Table 6.4.3.4.b below).

Table 6.4.3.4.b: **Endpoint Mean Pain Scores: Results excluding patients with dizziness and/or somnolence – Protocol 029**

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug - Placebo) Difference	95% CI	p-value*
Placebo	89	5.16	0.22			
Pregabalin 75 mg/day	68	5.13	0.25	-0.03	(-0.674, 0.619)	0.9336
Pregabalin 300 mg/day	46	4.27	0.31	-0.89	(-1.635, -0.148)	0.0190
Pregabalin 600 mg/day	38	3.78	0.34	-1.38	(-2.171, -0.590)	0.00014

* P-value adjusted based on Hochberg's procedure; applies to pregabalin 300 and 600 mg/day groups only, per protocol

(Applicant's Table 2, Appendix D21, RR 720-04242 1008-029, P 1728)

c) Longitudinal analysis of the weekly mean pain scores

A longitudinal analysis was performed on the observed values of the weekly mean pain scores using ANCOVA, with treatment, center, baseline pain, and week as fixed effect terms. A repeat analysis was done using a treatment by week interaction term. Results were similar to those obtained in the primary analysis. There were no treatment-by-week interactions.

d) Analysis of absence of allodynia and hyperalgesia at endpoint, in subjects with these symptoms at baseline

A total of 327 patients (97%) had allodynia and hyperalgesia measurements at baseline: 95 in the placebo group, 75 in the pregabalin 75 mg/day group, 79 in the pregabalin 300 mg/day group, and 78 in the pregabalin 600 mg/day group.

Allodynia

There were 104 subjects (32%) with allodynia at baseline: 20 placebo patients (21%), 31 pregabalin 75 mg/day patients (41%), 26 pregabalin 300 mg/day patients (33%), and 27 pregabalin 600 mg/day patients (35%). The table below shows that at termination, allodynia appeared to be decreased in all treatment groups. Greater effects of treatment on allodynia appeared to be in the pregabalin 300- and 600 mg/day groups.

Table 6.4.3.4.c: Incidence of Allodynia, ITT Population

	Baseline Allodynia		Termination[a] Allodynia Yes n (%)		No n (%)
Placebo	Yes (N = 20)	15	(75.0%)	5	(25.0%)
	No (N = 75)	2	(2.7%)	73	(97.3%)
Pregabalin 75 mg	Yes (N = 31)	23	(74.2%)	8	(25.8%)
	No (N = 44)	2	(4.5%)	42	(95.5%)
Pregabalin 300 mg	Yes (N = 26)	17	(65.4%)	9	(34.6%)
	No (N = 53)	4	(7.5%)	49	(92.5%)
Pregabalin 600 mg	Yes (N = 27)	15	(55.6%)	12	(44.4%)
	No (N = 51)	0	(0.0%)	51	(100.0%)

a Termination = Last available (non follow-up) record.

(Applicant's Table 45, RR 720-04242, 1008-029, P. 98)

Hyperalgesia

There were 157 patients (30.8%) who had hyperalgesia measurements at baseline. Of these, hyperalgesia was present in 40 placebo patients (42%), 38 pregabalin 75 mg/day patients (51%), 38 pregabalin 300 mg/day patients (48%), and 41 pregabalin 600 mg/day patients (52%). The shift table below shows the incidence of allodynia at baseline and at study termination. Similar to the results regarding allodynia, there appeared to be greater decreases in hyperalgesia in the pregabalin 300- and 600 mg/day groups.

Table 6.4.3.4.c: Incidence of Hyperalgesia, ITT Population – Protocol 029

		Termination [a] Hyperalgesia	
		Yes	No
	Baseline Hyperalgesia	N (%)	N (%)
Placebo	Yes (N=40)	29 (72.5%)	11 (27.5%)
	No (N =55)	4 (7.3%)	51 (92.7%)
Pregabalin 75 mg	Yes (N=38)	30 (78.9%)	8 (21.1%)
	No (N=37)	3 (8.1%)	34 (91.9%)
Pregabalin 300 mg	Yes (N=38)	26 (68.4%)	12 (31.6%)
	No (N=41)	2 (4.9%)	39 (95 1%)
Pregabalin 600 mg	Yes (N=41)	26 (63.4%)	15 (36.6%)
	No (N=37)	1(2.7%)	36 (97.3%)

[a] Termination = Last available (non follow-up) record.
(Applicant's Appendix C 49, RR 720-04242, 1008-029, P. 637)

6.4.3.5 Reviewer's analyses

This study had similar deficiencies in its analysis plan as Protocol 1008-014. The Applicant's primary efficacy analysis was a comparison of the treatment groups' endpoint mean pain scores, where endpoint referred to the last week of the study. Additionally, the endpoint mean pain score was defined as the mean of the last 7 available pain scores. Also, the primary analysis method was a LOCF method, in which missing pain data were replaced with the last observed pain score. Finally, the Applicant's BOCF analysis was inappropriate because it assigned baseline scores for only those subjects who were identified as not having completed all study visits or the full duration of treatment.

Dr. Ling Chen reanalyzed the data using a BOCF method, with and without imputation of pain scores due to use of rescue medication. A responder analysis was also repeated based on the BOCF analysis (see Section 6.3.3.5).

Descriptive statistics showed that all of the treatment groups had an improvement in the mean pain score, and that the largest improvements in pain occurred in the pregabalin 300 and 600 mg/day groups. Comparisons of the change in mean pain score between pregabalin and placebo showed that treatment with doses of 300- and 600 mg/d reached statistical significance.

Reviewer's Analysis: Endpoint mean pain scores – Protocol 029

Time point	N	Placebo Mean (SD)	PGB 75 mg/day Mean (SD)	PGB 300 mg/day Mean (SD)	PGB 600 mg/day Mean (SD)
Baseline*		6.56 (1.57)	6.68 (1.32)	6.09 (1.38)	6.26 (1.44)
Endpoint**		5.30 (2.21)	5.32 (2.34)	3.99 (2.04)	4.06 (2.36)
Change		-1.26 (1.95)	-1.35 (1.94)	-2.10 (1.99) [a]	-2.20 (2.24) [b]

* Baseline = the average of last 7 days prior to randomization

** Endpoint = the average of the last 7 days of the treatment period

a P-value = 0.005

b P-value = 0.003

In the BOCF analysis without imputation for use of rescue mediation, the pregabalin 300- and 600 mg/day groups had significantly improved mean pain scores at endpoint compared to the placebo group (p = 0.0009 and 0.0003 respectively, 1-sided alpha = 0.0083). There was no statistically significant difference between the pregabalin 75 mg/day and placebo groups.

Approximately 13% of the pregabalin 75 mg group used rescue medication, 15% of the pregabalin 300 mg/day group, 18% of the 600 mg/day group, and 21% of the placebo group. Repeat BOCF analysis of the primary outcome after factoring in the use of rescue medication showed that there was no significant difference in mean pain score at endpoint between the placebo and pregabalin 75- and 600 mg/day groups (p = 0.46 and 0.02 respectively, 1-sided alpha = 0.0083). The differences remained significant for the pregabalin 300 mg/day group (p= 0.0048, 1-sided alpha = 0.0083).

As described earlier, a BOCF analysis of the endpoint mean pain score after removing patients with somnolence was not conducted (see Section 6.3.3.5).

A comparison of the proportion of responders in each treatment group was done based on the BOCF analysis, with and without imputation for use of rescue medication. The results are described below:

Reviewer's Analysis: Percentage change in endpoint mean pain score by dose: BOCF analysis - Protocol 1008-029

Total Pain Score	97 Placebo N (%)	77 Pregabalin 75 mg/day N (%)	81 Pregabalin 300 mg/day N (%)	82 Pregabalin 600 mg/d N (%)
Any increase	15 (15.46)	12 (15 58)	8 (9.88)	5 (6.10)
No change	20 (20.62)	18 (23.38)	12 (14 81)	15 (18.29)
> 0% decrease	62 (63.92)	47 (61.04)	61 (75.31)	62 (75.61)
≥ 10 % decrease	49 (50 52)	40 (51.95)	56 (69.14)	59 (71.95)
≥ 20 % decrease	36 (37.11)	35 (45 45)	48 (59.26)	50 (60.98)
≥ 30 % decrease	28 (28.87)	26 (33.77)	42 (51 85)	41 (50.00)
≥ 40 % decrease	20 (20.62)	19 (24.68)	36 (44.44)	35 (42.68)
≥ 50 % decrease	***16 (16.49)***	***15 (19.48)***	***31 (38.27)***	***30 (36.59)***
≥ 60 % decrease	13 (13.40)	9 (11.69)	19 (23.46)	24 (29.27)
≥ 70 % decrease	8 (8.25)	5 (6.49)	13 (16.05)	14 (17.07)
≥ 80 % decrease	4 (4.12)	5 (6.49)	7 (8.64)	10 (12.20)
≥ 90 % decrease	1 (1.03)	1 (1.30)	4 (4.94)	4 (4.88)
= 100% decrease	1 (1.03)	0 (0.00)	1 (1.23)	4 (4.88)

A greater proportion of subjects in the pregabalin 300 and 600 mg/day groups had a ≥ 50% decrease in their pain, compared to the other treatment groups. The difference between the proportion of responders in the placebo and pregabalin 75 mg/day groups was relatively small.

The percent change in endpoint mean pain score by dose group was recalculated using the BOCF method, as well as the maximum baseline score imputation for use of rescue medication. The results are shown in the table below:

Reviewer's Analysis: Percentage change in endpoint mean pain score by dose: BOCF analysis and maximum baseline score imputation for rescue medication - Protocol 029)

Total Pain Score	97 Placebo N (%)	77 Pregabalin 75 mg/day N (%)	81 Pregabalin 300 mg/day N (%)	82 Pregabalin 600 mg/d N (%)
Any increase	13 (13.4)	9 (11.69)	7 (8.64)	5 (6.10)
No change	36 (37.11)	26 (33.77)	23 (28.40)	29 (33.37)
> 0% decrease	48 (49.48)	42 (54.55)	51 (62.96)	48 (58.54)
≥ 10 % decrease	39 (40.21)	36 (46.75)	47 (58.02)	46 (56.10)
≥ 20 % decrease	30 (30.93)	32 (41.56)	40 (49.38)	38 (46.34)
≥ 30 % decrease	24 (24.74)	24 (31.17)	35 (43.21)	29 (35.37)
≥ 40 % decrease	17 (17.53)	17 (22.08)	32 (39.51)	23 (28.05)
≥ 50 % decrease	***15 (15.56)***	***13 (16.88)***	***27 (33.33)***	***20 (24.39)***
≥ 60 % decrease	13 (13.40)	8 (10.39)	19 (23.46)	15 (18.29)
≥ 70 % decrease	8 (8.25)	5 (6.49)	13 (16.05)	9 (10.98)
≥ 80 % decrease	4 (4.12)	5 (6.49)	7 (8.64)	6 (7.32)
≥ 90 % decrease	1 (1.03)	1 (1.30)	4 (4.94)	3 (3.66)
= 100% decrease	1 (1.03)	0 (0.00)	1 (1.23)	3 (3.66)

Approximately 40% of subjects in all treatment groups had no change or an increase in their pain. However, more patients in the pregabalin 300 and 600 mg/day groups were treatment responders, compared to patients in the placebo and pregabalin 75 mg/day groups. There was no sizeable difference in the proportion of responders in the placebo and pregabalin 75 mg/day groups. Imputation for use of rescue medication lowered the proportion of responders in all groups.

6.4.3.6 Conclusions Regarding Efficacy Data in Study - Protocol 029

The Agency's analyses of the primary outcome, mean pain score at endpoint were consistent with the Applicant's findings: treatment with pregabalin 300 and 600 mg/day improved pain, compared to treatment with placebo. Similarly, more patients treated with these two pregabalin doses were met the definition of treatment response, compared to patients in the placebo group.

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6.5 Protocol 1008-040: A placebo-controlled trial of pregabalin and amitriptyline for treatment of painful diabetic peripheral neuropathy

The Applicant considered this a failed study. However, because the Applicant's statistical analysis methods were not adequate to appropriately capture pregabalin's effect on pain, and because the findings of inefficacy of 300 mg/day contradicted other study results, the data were reanalyzed.

6.5.1 Protocol

6.5.1.1 Objective/Rationale

- To evaluate the efficacy of pregabalin (600 mg/day, 200 mg TID) and amytriptyline (75 mg/day, 25 mg TID) versus placebo in relieving pain
- To compare the effects of pregabalin and amitriptyline versus placebo on quality of life and mood of patients
- To assess the safety of pregabalin compared to placebo and amytriptyline

6.5.1.2 Overall Design

The study was to be a Phase 3, multi-center, multi-national, randomized, double-blind, parallel, placebo-controlled trial of single dose level of pregabalin and amitriptyline in adult patients with pain due to diabetic neuropathy.

6.5.1.3 Population and Procedures

6.5.1.3.1 Treatment Duration: 9 weeks (2 weeks titration, 6 weeks at fixed dose, 1 week withdrawal)

6.5.1.3.2 Entry Criteria

The protocol called for a total enrollment of 240 subjects (80 subjects in each arm).

Subjects who met the following criteria were eligible:

- Age ≥ 18 years
- Diagnosis of Type 1 or 2 diabetes mellitus for at least 1 year
- Hemoglobin A1c ≤ 11%
- Diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy due to diabetes for at least 1 year
- VAS score of ≥ 40 mm at baseline and randomization
- Completion of at least 4 daily pain diaries during the baseline phase, and had an average daily pain score of ≥ 4 over the previous 7 days on the Likert-type pain Rating Scale at randomization
- Normal chest x-ray within 2 years prior to the baseline visit

Subjects were to be excluded for:

- Clinically significant or unstable hepatic, respiratory, hematological, cardiovascular, peripheral vascular, thyroid, or psychological condition
- Abnormal ECG or abnormality on 2-minute rhythm strip
- Creatinine clearance ≤ 60 mL/min
- Failure to respond to previous treatment with gabapentin (Neruontin®) at doses ≥ 1200 mg/day, *or* amitriptyline at doses ≥ 75 mg/day for treatment of pain associated with diabetic neuropathy
- Neurologic disorder unrelated to diabetic neuropathy that could confuse the assessment of neuropathic pain
- Skin conditions in the area affected by the neuropathy that could alter sensation
- Any pain that may confound assessment on self-evaluation of the pain due to diabetic neuropathy
- Amputations other than toes
- Medical condition contraindicating treatment with amitriptyline
- History of pernicious anemia, untreated hypothyroidism, chronic hepatitis B or C, hepatitis B or C within the last 3 months prior to screening, or HIV infection
- Use of prohibited medications (listed below), in the absence of appropriate washout periods
- Malignancy
- Previous treatment with pregabalin
- WBC < 2500/mm^3, neutrophil count < 1500/mm^3, platelet count < 100 x 10^3/mm^3
- Contraindications to therapy with amitriptyline (e.g. hypertrophy of the prostate, untreated narrow-angle glaucoma, pyloric stenosis, paralytic ileus, acute retention of ureine, orthostatic hypotension)

Study Medication:
Subjects were to be randomized to study drug as follows: amitriptyline 75 mg/day, placebo, or pregabalin 600 mg/day. The maximum target dose was to be obtained following 2 weeks of upward titration. Subjects unable to attain the target (fixed) dose were to be withdrawn from the study. After completion of the 6-week fixed-dose period, study drug was to be gradually decreased over 1 week.

Titration scheme:

Treatment Arm	Day 1-8 Dose (mg/day)	Day 9-15 Dose (mg/day)	Day 16 Dose (mg/day)	Fixed Dose Phase Dose (mg/day)
Placebo	0	0	0	0
Amitriptyline	25	50	75	75
Pregabalin	200	400	600	600

During the 1-week withdrawal phase, study drug was to be decreased as follows:

Treatment Arm	Fixed dose phase mg/day	Day 1-3 mg/day	Day 4-6 mg/day	Day 7 mg/day
Placebo	0	0	0	0
Amitriptyline	75	50	25	0
Pregabalin	600	400	200	0

Permitted Medications:
The protocol allowed subjects to take acetaminophen (up to 3 g daily) for continued pain (rescue medication). Additionally, subjects were allowed to take aspirin (no more than 325 mg/day) for myocardial infarction and stroke prophylaxis. Benzodiazepines were also permitted, as long as the patients were on a stable regimen (at least 30 days) for sleep only.

Prohibited Medications:
Transcutaneous electrical nerve stimulation and the following medications were to be prohibited during the study (in the absence of the pre-defined washout period:

Drug Class	Examples [a]	Washout Phase
Medications commonly used for neuropathic pain	Skeletal muscle relaxants, capsaicin, dextromethorphan, fatty acid supplements, local anesthetics, alpha-lipoic acid, benzodiazepines (**except for stable bedtime dose**)	30 days prior to Visit 1
Antiepileptics	Valproic acid, carbamazepine	14 days prior to Visit 1
Antidepressants	Tricyclics including amitriptyline, SSRIs, MAO inhibitors	30 days prior to Visit 1
Analgesics	NSAIDs Opioids, tramadol	7 days prior to Visit 1 30 days prior to Visit 1
Miscellaneous	Hydroxychloroquine, deferoxamine, vigabatrin, thioridazine, myoinositol, chromium picolinate	Not applicable

[a] Patients on these medications were not eligible for this study
(Applicant's Table 3, RR 720-30054, 1008-040, P. 44)

6.5.1.3.3 Study Procedures

Screening
In addition to the meeting the entry criteria, each patient needed to be stabilized on their antidiabetic medication before initiating study drug, and the antidiabetic medication was to remain unchanged for the duration of the study. Also, patients needed to undergo withdrawal from prohibited medications.

Baseline
Eligible subjects were to undergo a 1-week baseline phase during which they would enter pain and sleep ratings for the previous day into diaries each morning on arising. Subjects who completed at least 4 daily pain diaries during the baseline phase, and who had an average daily pain score of ≥ 4 over the previous 7 days were to be randomized to study drug in blocks of 6.

Treatment
Subjects were to be randomized to placebo, pregabalin 600 mg/day, and amitriptyline 75 mg/day. Study medication was to be titrated to the target dose over 2 weeks. Thereafter, study medication was to remain at the fixed dose for 6 weeks for all subjects. At Week 9, subjects were to undergo withdrawal from study drug over 1 week. A patient was to be considered a study "completer" after s/he received 8 weeks of double-blind treatment and completed the Week 8/Termination visit. Subjects who completed the study were to be given the opportunity to enter an open-label extension trial, Study 1008-074.

Table 6.5.1.3.3: Time and Events Schedule – Protocol 040

Table 5. Timetable of Study Visits and Procedures

	Baseline (1 Week)	Up to Three Treatment Weeks					
		Titration			Fixed Dose		Withdrawal
End of Study Week	Screening	Randomization	1	2	4	8	9
Study Day	-	1	8	15	29	57[a]	63
Clinic Visit:[b]	1	2	3	4	5	6 Term	7 W/D
Informed Consent	X						
Inclusion/Exclusion	X						
Medical History	X						
Physical Exam	X					X	
Abbreviated Neurological Exam	X					X	
Peripheral Sensory Exam	X					X	
SF-McGill Pain Questionnaire	X	X	X	X	X	X	X
Daily Diaries (Pain, Sleep)	X	X	X	X	X	X	
Global Imp. of Change (Clinical & Patient)						X	
SF-36 Health Survey		X				X	
Hospital Anxiety and Depression Scale		X				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	X	
Clinical Labs							
Hematology, Chemistry, Urinalysis	X		X	X	X	X	X
Hemoglobin A_1	X					X	
B12/folate/SPEP/14TSH	X						
Pregnancy Test (Serum)	X		X		X		X
Study Medication Plasma Concentration						X	
EST	X					X	
12-Lead ECG With 2-Minute Rhythm Strip	X			X		X	
Chest X-ray	X						
Patient Status – End of Baseline		X					
Patient Status – End of Fixed Dose Phase						X	
Patient Status – End of Withdrawal							X

[a] Telephone contact was made with the patients twice weekly during the titration phase to ensure completion of daily diaries and to assess adverse events. If the patient experienced an adverse event during titration or during double-blind, an extra visit could have been scheduled. Between each subsequent visit up until V7 Follow-Up, telephone contact was made once weekly to ensure compliance with Study procedures.

[b] Whenever patient withdrew from or completed the study.

[c] Vital signs only.

[d] Chest X-ray must have been taken at baseline visit (or at least prior to randomization) if none available in the 2 years prior to baseline.

(Applicant's Table 5, RR 720-30054, 1008-040, P. 46)

The following measures of patient pain and function were to be utilized:

- Daily pain score
- Short Form McGill Pain Questionnaire
- Clinical Global Impression of Change (CGIC)
- Patient Global Impression of Change (PGIC)
- Daily diary of sleep interference
- SF-36 Health Survey Questionnaire (SF-36 QOL)
- *Hospital Anxiety and Depression Scale (HADS)*: rates the extent to which descriptors of anxiety and depression apply to the subject. Items are rated on a scale of 0 to 3, with at total possible score of up to 21.

6.5.1.3.4 Pharmacokinetics

At the Week 8/Termination Visit, all subjects were to provide a blood sample for measurement of study drug concentrations. Date and time of blood draw, as well ad date and time of last study medication dose were to be recorded prior to drawing blood.

6.5.1.3.5 Statistical Analysis

6.5.1.3.5.1 Patient Population

The *intent-to-treat (ITT)* and the *safety populations* were to be all randomized subjects who received at least one dose of study medication. Patients with no data for a given parameter at baseline or at the time point to be analyzed were to be excluded from analysis. The *per protocol* population was defined as all randomized patients without any major protocol violations.

6.5.1.3.5.2 Demographics

Baseline characteristics (demographics, type of diabetes, duration of polyneuropathy, and hemoglobin A1c level.) among treatment groups were to be compared using descriptive statistics.

6.5.1.3.5.3 Primary Efficacy Endpoint

The protocol specified the primary efficacy outcome as the *endpoint mean pain score*. This was defined as the mean of the last 7 diary entries while on study medication, including the entry on the day after the last dose in the titration/fixed dose phase. If fewer than 7 scores were recorded by end point (7-x), the last x scores from baseline were to be used, in addition to the available post-baseline scores, to determine the endpoint.

The primary comparison was to be between the pregabalin and placebo groups' final mean weekly pain scores (two-sided test, 5% level). An additional analysis was to be a comparison between treatment groups of the final weekly mean pain score.

6.5.1.3.5.4 Supplemental Analyses of the Primary Efficacy Variable

Supplemental analyses were to include

- Comparison across treatment groups of the final weekly mean pain score, using the Per Protocol population (i.e. all randomized patients without major protocol violations)
- Comparison across treatment groups of the weekly mean pain scores
- Estimates and comparison of treatment effects in the pregabalin and amitriptyline groups (exploratory analyses only)

For outcome measures collected in daily pain diaries (pain and sleep interference), the following additional scores were to be computed:

- Baseline Mean Score: Mean of the last 7 diary entries before taking study medication, including the entry on Day 1. If fewer than 7 scores were recorded during baseline, the available scores were used to determine a mean
- Weekly Mean Score
- Change From Baseline
- Responder Patients, where treatment responders were those patients with ≥ 50% reduction from baseline to endpoint mean pain scores

6.5.1.3.5.5 Secondary Efficacy Endpoints

- SF-McGill Sensory, Affective, Total, VAS, and PPI scores, at endpoint and at Weeks 1, 2, 5 and 8
- Mean sleep interference scores, at endpoint and at each week separately

- Change in mean sleep interference scores from baseline to endpoint, and to each week separately
- PGIC and CGIC
- SF-36 QOL scores
- HADS
- Number of days of Paracetamol (acetaminophen) use, and total intake (grams) of Paracetamol

All efficacy analyses were to use one principal comparison, pregabalin 600 mg/day versus placebo. The endpoint mean pain scores, SF-MPQ VAS and PPI scores, HADS scores, and SF-36 domains were to be analyzed using an ANCOVA main effects model, with treatment and cluster in the model, and the baseline mean pain score as a covariate. (Small centers (< 18 patients) were to be pooled into geographic clusters, and individual centers with ≥ 18 randomized patients were to be considered a cluster). Adjusted least squares means were to be obtained from the model and 95% confidence intervals on the difference in least squares means between pregabalin and placebo, and amytriptyline and placebo were to be constructed.

No adjustments were to be made for testing multiple parameters with the secondary and supplemental analyses. Due to the large number of analysis to be performed, significant results could occur by chance. Therefore, results were to be interpreted based on patterns of significant differences only.

Pharmacokinetics:
The protocol stipulated collection of blood samples at Visit 6/Termination Visit to determine plasma concentrations of study medications.

6.5.1.3.5.6 Interim Analysis

No interim analyses were planned.

6.5.2 Protocol Amendments

The Applicant identified no protocol amendments, and stated that there were 2 protocol addenda.

Addendum A – 11/11/99

- New information regarding toxicology data was added to the informed consent used at the 8 centers in Spain (centers - 045 through -052)

Addendum B – 12/21/99

- The minimum patient age was increased to 19 years
- All females of childbearing potential were to have a pregnancy test on a monthly basis
- The changes affected only the 4 Austrian centers (-080 through 083). In Austria, the age of adulthood is 19 years, and not 18 years.

This Reviewer considers Addendum B to be a protocol amendment that was specific only to the Austrian centers. The data show that no subjects aged less than 19 years were

randomized into the study prior to this addendum, and therefore the protocol change has no impact on the analysis of the data

6.5.3 Study Results

6.5.3.1 Study Conduct/Outcome

6.5.3.1.1 Subject characteristics

A total of 256 subjects were randomized into the study. The study began on September 6, 1999 and ended on December 14, 2000. A total of 114 investigators and 68 centers in Europe, Australia, and South Africa participated.

6.5.3.1.2 Enrollment by Center

Only 49 centers enrolled patients. The table below shows that most of the randomized subjects (47%) were from German sites. Several centers did not enroll any patients, while the South African site enrolled the largest number of subjects.

Table 6.5.3.1.2: Enrollment by Center - Protocol 1008-040

No. Patients Randomized per Center	Country	Center Number*
0	France	002, 006, 007, 008, 009, 010
	Germany	022, 030, 114
	Italy	040, 041
	UK	056, 057, 059, 061, 068
	Australia	078
	Austria	080
	Switzerland	087
1	Belgium	011
	Germany	032
	UK	063
2	Germany	027, 029, 031, 113
	Italy	036
	Spain	045, 046, 047
	UK	067
	Switzerland	086
3	Belgium	012
	Germany	018, 019, 025, 033, 110
	Spain	050
	Austria	083
4	France	001
	Germany	023
	Spain	048
	UK	069
	Australia	073
	Switzerland	088
5	Germany	034
	Spain	052
	Australia	075
	Austria	081

* Sites not listed were not shipped study drug

Table 6.5.3.1.2: Enrollment by Center: Protocol 1008-040 (continued)

No. Patients randomized/Center	Country	Center Number*
6	Germany	024, 028
	Italy	035
	Spain	049
	Australia	077, 079
7	Austria	082
8	Germany	026
	Italy	038
	UK	062
9	Germany	016, 076
10	Germany	111
12	Germany	020, 112
	Australia	074
16	Germany	017
18	South Africa	072

* Sites not listed were not shipped study drug
(Adapted from Applicant's Table 1, RR 720-30054, 1008-040, P. 31)

6.5.3.1.3 Protocol Violations

Table 6.5.3.1.3 below shows that there were 35 randomized subjects identified as having protocol violations that could potentially impact the primary efficacy variable. Eleven patients (13%) were randomized to pregabalin (n = 86), 10 patients (12%) were randomized to placebo (n = 81), and 14 patients (16%) were randomized to amitriptyline (n = 87). Two subjects had 2 violations each. The Applicant states that all 35 subjects were excluded from the analysis prior to data unblinding to yield a *Per Protocol* population of 221 patients.

Table 6.5.3.1.3: Protocol Violations (Protocol 1008-040)

Violation	Total	Pregabalin	Amitriptyline	Placebo
Inclusion/Exclusion criteria violations				
Symmetry of pain not confirmed	6	3	3	-
Baseline mean pain score < 4	4	1	2	1
No/insufficient washout period	9	3	3	3
Normal sensory exam	2	-	1	1
Use of prohibited medications	1	1	-	-
Noncompliance with study medication	9	3	2	4
No baseline data	1	-	1	-
No post-baseline data	3	1	2	-
Patient randomized twice	1	-	-	1

I consider that the only protocol violations that would potentially impact the primary efficacy outcome were from the following 11 subjects:

- 3 subjects who continued using prohibited medications during the study -> If a subject experienced pain relief with treatment, it would be difficult to know which drug (study medication or prohibited medication) to which efficacy should be ascribed.
  - Patient 012001 (placebo group) continued to use amitriptyline
  - Patient 074010 (amitriptyline group) continued to use baclofen and quinine
  - Patient 077003 (amitriptyline group) continued to use quinine

- 4 subjects who has a baseline mean pain score less than 4 -> Relatively small improvements in pain are less easily detected in patients with a minimal pain at baseline.
  - Patient 024005 (pregabalin group)
  - Patient 012001 (placebo group)
  - Patient 112011 (placebo group)
  - Patient 026008 (amitriptyline group)
- 1 subject who was randomized twice [Patient 026010 (placebo group)] -> In effect, this patient provided data for 2 patients.
- 3 Subjects who had no post-baseline data -> These subjects did not contribute data towards the primary efficacy outcome.
  - Patient 001005 (pregabalin group)
  - Patient 001003 (amitriptyline group)
  - Patient 049004 (amitriptyline group)

While the use of prohibited pain medication would tend to bias the study in favor of the affected arm, the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is therefore not expected to have a significant impact on the interpretation of the results.

6.5.3.1.4 Blinding

The Applicant states that the blind was broken for two patients, Patient 062006 and Patient 026009.

Patient 062006

The blind was broken while this patient was participating in the subsequent open-label study (Study 1008-074). The patient had completed Study 1008-040, receiving placebo for 58 days. On open-label Study Day 8, this patient experienced several adverse events, including deterioration in renal function and anemia. The patient stopped taking pregabalin on Study Day 19 of open-label and was withdrawn from the study. The blind was broken on open-label Study Day 32 at the request of the family.

Patient 026009

This patient had a history of ventricular extrasystoles, and experienced an AV nodal tachycardia on Study Day 59 (1 day post treatment). Treatment for the arrhythmia was dependent on the study medication that the patient had received: if the patient was on pregabalin or amitriptyline, treatment could being only 2 weeks thereafter. The patient had been taking amitriptyline.

6.5.3.1.5 Subject Disposition

Table 6.5.3.1.5 below shows that 357 patients were enrolled, and 101 were removed during the baseline phase. The reasons for the removals were: not meeting study entry criteria (84 patients), other/administrative reasons (16 patients), and an adverse event (1 patient). Of the 256 patients who were randomized, 254 received at least one dose of medication: 86 received pregabalin 600 mg/day, 81 received placebo, and 87 received amitriptyline 75 mg/day. The 2 patients who did not receive study medication were

Patient 088005 in the pregabalin group, who was lost to follow-up, and Patient 017015 in the amitriptyline group, who was withdrawn due to lack of compliance.

Table 6.5.3.1.5: Subject Disposition - Protocol 1008-040

Disposition N (%)	Placebo	Pregabalin	Amitriptyline	All Patients
Entered Baseline Phase				357
Completed Baseline Phase				256 (71.7)
Withdrawn During Baseline Phase:				101 (28.3)
Adverse Event [a]				1 (0.3)
Did not meet entry criteria				84 (23.5)
Other/administrative reasons [b]				16 (4.5)
Randomized	81	87	88	256
Intent-to-treat	81	86	87	254
Completed Titration and Fixed-Dose Phase	62 (76.5)	62 (72.1)	64 (73.6)	188 (74.0)
Withdrawn during Titration/Fixed Dose Phase:	19 (23.5)	24 (27.9)	23 (26.4)	66 (26.0)
Adverse Event [c]	4 (4.9)	11 (12.8)	16 (18.4)	31 (12.2)
Lack of compliance	2 (2.5)	4 (4.7)	2 (2.3)	8 (3.1)
Lack of Efficacy	9 (11.1)	7 (8.1)	3 (3.4)	19 (17.5)
Other [d]	4 (4.9)	2 (2.3)	2 (2.3)	8 (3.1)
V7/Follow-up, Not Done	9 (11.1)	14 (16.3)	15 (17.2)	38 (15.0)
Completed Withdrawal Phase	65 (80.2)	66 (76.7)	66 (75.9)	197 (77.6)
Withdrawn During Withdrawal Phase:	7 (8.6)	6 (7.0)	6 (6.9)	19 (7.56)
Adverse Event [e]	1 (1.2)	0 (0)	0 (0)	1 (0.4)
Lack of Compliance	1 (1.2)	2 (2.3)	0(0)	3 (1.2)
Other [f]	5 (6.2)	4 (4.7)	6 (6.9)	15 (5.9)
Entered Open Label	60 (74.1)	66 (76.7)	63 (72.4)	189 (74.4)

(Applicant's Table 8, RR 720-30054 1008-040, P. 63)

a, b Data regarding specific reasons for withdrawal during the baseline period were not provided
c Adverse events included somnolence, dizziness, and fatigue
d Other included: withdrawal of consent, loss to follow-up, protocol violation, and refusal to complete a termination visit
e One placebo patient had an AE (unspecified)
f Other includes: non-dispensing of study medication, and lack of entry into the withdrawal phase

A total of 188 subjects completed both the titration and the fixed-dose phases. That is, of the 254 patients who received study medication, 66 (26%) withdrew prior to the end of the titration/fixed-dose phase: 24 patients (28%) from the pregabalin group, 23 patients (26%) from the amitriptyline group, and 19 patients (24%) from the placebo group. Adverse events most frequently led to withdrawal from the pregabalin and amitriptyline groups [11 (13%) and 16 (18%), respectively], whereas the most frequent cause of withdrawal from the placebo group was lack of efficacy [9 (11%)]. There were 31 subjects who terminated the study early because of adverse events.

I found that there were 22 subjects who withdrew for various reasons during the titration phase: 9 subjects in the pregabalin group (10.5%), 4 placebo patients (4.9%), and 9 patients in the amitriptyline group (10.3%). Three subjects withdrew specifically due to adverse events: 2 subjects in the pregabalin group, and 1 in the amitriptyline group. During the fixed-dose phase, 22 subjects withdrew due to adverse events: 3 subjects in the placebo arm, 7 subjects in the pregabalin arm, and 12 subjects in the amitriptyline arm.

A total of 216 patients were assessed at the Follow-Up visit that occurred at the last week of the study (Week 9). Of these patients, 197 completed the withdrawal phase. This reviewer noted 4 patients who terminated the study during the withdrawal phase due to adverse events: 1 subject each in the placebo and amitriptyline groups, and 2 subjects in the pregabalin group. The Applicant included another 2 subjects (amitriptyline group) as having withdrawn during this phase as a result of AEs. However, the data show that these subjects "withdrew" from the study on Day 70 (the study ended after 63 days).

Patients who entered the open-label follow-on study, Study 1008-074, included 66 (77%) from the pregabalin group, 60 (74%) from the placebo group, and 63 (72%) from the amitriptyline group (total 189 [74% of the ITT population]).

6.5.3.1.6 Extent of exposure/Dosing information

Table 6.5.3.1.6: Drug exposure - Protocol 1008-040

Total Exposure Time*	Placebo N = 81 Number (%) patients	Pregabalin 600 mg/day N = 86 Number (%) patients	Amitriptyline 75 mg/day N = 87 Number (%) patients
≥ 1 day	81 (100)	86 (100)	87 (100)
≥ 1 week	80 (98.8)	82 (95.3)	83 (95.4)
≥ 2 weeks	78 (96.3)	77 (89.5)	79 (90.8)
≥ 3 weeks	75 (92.6)	75 (87.2)	77 (88.5)
≥ 4 weeks	73 (90.1)	74 (86.0)	73 (83.9)
≥ 5 weeks	71 (87.7)	71 (82.6)	72 (82.8)
≥ 6 weeks	63 (77.8)	67 (77.9)	68 (78.2)
≥ 7 weeks	62 (76.5)	65 (75.6)	67 (77.0)
≥ 8 weeks	61 (75.3)	54 (62.8)	59 (67.8)
≥ 9 weeks	6 (7.4)	4 (4.7)	4 (4.6)

* Zero dose days during the study are included in the summary of patient exposure to medication. The total exposure time includes titration, fixed-dose, and withdrawal phase

Table taken from Applicant's submission (see Section 9.1.34, RR 720-30054 1008-040, P. 189):

6.5.3.1.7 Demographics

There were 254 patients in the ITT population. The majority was male (57.5%) and Caucasian (92.5%). The mean age of the subjects was 60.1 (± 11.1) years, with a range of 22 to 80 years. The median age for the amitriptyline group (59 years) was 4 years less

than the median of the placebo and pregabalin groups (63 years). The median estimated creatinine clearance (CLcr) was 86.5 mL/min. The pregabalin group had a slightly lower median CLcr (83.5 mL/min) than the placebo and amitriptyline groups (87.0 and 89.0 mL/min, respectively).

Diabetes and neuropathic pain history

Most subjects had Type 2 diabetes (85.8%) and the mean duration of diabetes was 12.0 (± 8.6) years. Ninety five percent of patients reported prior (within 30 days) and/or concurrent use of antidiabetic medication. Sixty-one percent used insulin and 52% used an oral antidiabetic medication, the most frequent being metformin. The distribution of neuropathic pain was similar across treatment groups. The baseline mean pain score was 6.5 (± 1.6) for the total population. The baseline mean pain score was slightly higher in the pregabalin group (6.9) than in the placebo (6.3) or amitriptyline (6.4) groups.

Table 6.5.3.1.7.a and Table 6.5.3.1.7.b: Demographics: Protocol 1008-040
(Applicant's Tables 9 and 10, RR 720-300054 1008-040, P. 69-70)

Table 9. Summary of Patient Characteristics
(Page 1 of 2)

Characteristic		Placebo N = 87	Pregabalin 600 mg day N = 86	Amitriptyline 75 mg day N = 87	All Patients N = 254
Sex, N (%)	N	81	86	87	254
	Male	46 (56.8)	48 (55.8)	55 (63.2)	146 (57.5)
	Female	35 (43.2)	38 (44.2)	32 (36.8)	108 (42.5)
	Premenopausal	6 (17.1)	5 (13.2)	9 (28.1)	20 (18.5)
	Postmenopausal	29 (82.9)	33 (86.8)	23 (71.9)	88 (81.5)
Race, N (%)	N	81	86	87	254
	White	75 (92.6)	80 (93.0)	80 (92.0)	235 (92.5)
	Black	1 (1.2)	0 (0)	1 (1.1)	2 (0.8)
	Asian or Pacific Islander	0 (0)	3 (3.5)	2 (2.3)	5 (2.0)
	Other	5 (6.2)	3 (3.5)	4 (4.6)	12 (4.7)
Age Categories, N (%)	N	81	86	87	254
	18-64 years	45 (55.6)	50 (58.1)	61 (70.1)	156 (61.4)
	≥65 years	36 (44.4)	36 (41.9)	26 (29.9)	98 (38.6)
Age (Years)	N	81	86	87	254
	Mean (SD)	60.6 (11.5)	62.0 (9.8)	57.8 (12.0)	60.1 (11.1)
	Median	63.0	63.0	59.0	61.5
	Range	31 to 80	31 to 79	22 to 80	22 to 80
Estimated CLcr at Baseline (mL/min)	N	81	86	87	254
	Mean (SD)	96.60 (37.86)	89.31 (26.44)	95.74 (29.16)	93.84 (31.43)
	Median	87.00	83.50	89.00	86.50
	Range	48.0 to 280.0	31.0 to 192.0	47.0 to 190.0	31.0 to 280.0

SD = Standard Deviation; CLcr = Creatinine Clearance

Table 10. Summary of Diabetic and Neuropathic Pain History

	Placebo (N = 81)	Pregabalin 600 mg/day (N = 86)	Amitriptyline 75 mg/day (N = 87)	All Patients (N = 254)
Diabetes Type: N(%)				
Type 1	10 (12.3)	11 (12.8)	15 (17.2)	36 (14.2)
Type 2	71 (87.7)	75 (87.2)	72 (82.8)	218 (85.8)
Duration of Diabetes (years)				
N	81	86	87	254
Mean (SD)	12.5 (9.2)	12.7 (8.8)	11.0 (7.7)	12.0 (8.6)
Median	11	10.5	9	10
Range	0.0 to 45.0	1.0 to 36.0	0.0 to 34.0	0.0 to 45.0
Distribution of Neuropathic Pain*: N(%)				
Toe	73 (90.1)	77 (89.5)	75 (86.2)	225 (88.6)
Foot	81 (100.0)	84 (97.7)	87 (100.0)	252 (99.2)
Toe Foot	81 (100.0)	86 (100.0)	87 (100.0)	254 (100.0)
Calf	48 (59.3)	54 (62.8)	49 (56.3)	151 (59.4)
Thigh	11 (13.6)	13 (15.1)	14 (16.1)	38 (15.0)
Lower Extremities	81 (100.0)	86 (100.0)	87 (100.0)	254 (100.0)
Finger	13 (16.0)	17 (19.8)	17 (19.5)	47 (18.5)
Hand	14 (17.3)	11 (12.8)	18 (20.7)	43 (16.9)
Finger Hand	18 (22.2)	19 (22.1)	22 (25.3)	59 (23.2)
Forearm	6 (7.4)	2 (2.3)	8 (9.2)	16 (6.3)
Upper Extremities	19 (23.5)	19 (22.1)	23 (26.4)	61 (24.0)
Baseline Mean Pain Score				
N	80	86	87	253
Mean (SD)	6.3 (1.6)	6.9 (1.6)	6.4 (1.6)	6.5 (1.6)
Median	6.2	6.9	6.4	6.6
Range	3.1 to 10.0	3.7 to 10.0	3.7 to 10.0	3.1 to 10.0

SD Standard Deviation
* More than one category per patient possible

Prior and/or concurrent neuropathic pain medications were used by 106 (42%) patients. Paracetamol (acetaminophen) was used by 97 (92%) of these patients. Medications for pain taken concurrently with study medication (i.e. rescue medication) were as follows: Paracetamol, taken by 33 (41%) placebo-treated patients, 30 (35%) pregabalin-treated patients, and 28 (32%) amitriptyline-treated patients; and amitriptyline, taken by 1 (1%) placebo-treated patient.

The most frequently used other medication was aspirin, by approximately 25% of patients. Aspirin was used primarily for cardiovascular prophylaxis. Angiotensin converting enzyme inhibitors were used by approximately 24% of patients and lipid-lowering agents by approximately 19% of patients.

Other health characteristics
Two hundred and forty patients had allodynia assessments at baseline and at study termination. Of these, allodynia was present at baseline in 35 (43%) of patients randomized to pregabalin, 33 (42%) of patients randomized to placebo, and 30 (37%) of patients randomized to amitriptyline.

With respect to ECG abnormalities at screening, clinically significant abnormalities were seen in 6% of pregabalin-, 6% of placebo-, and 4% of amitriptyline-randomized patients. The most common clinically significant abnormal findings (>2% of patients in any treatment group) were abnormal rhythm-conduction and myocardial infarction.

Finally, most of the risk factors for peripheral edema were evenly distributed across the treatment groups with the exception of high cholesterol or high triglycerides (range 30% [placebo] to 39% [pregabalin] of patients) and glomerulonephritis or other kidney disease (range 2% [pregabalin] to 13% [placebo] of patients).

6.5.3.1.8 Other Evaluated Populations

In addition to conducting efficacy analyses using data from the ITT population, the Applicant conducted a supplemental analysis of the primary endpoint mean pain scores using data from the *per protocol population.* This population was defined as all patients who did not demonstrate any protocol violations.

6.5.4 Efficacy Results

Because of the blocked randomization process, any center with < 5 randomized subjects had the potential to not have all treatment groups represented in the primary analysis. Therefore, small centers (< 18 patients) were combined into clusters by geographic location after study completion, and prior to breaking of the blind, as shown in the table below. There were no significant treatment-by-cluster or treatment-by-baseline interactions for the primary analysis.

Table 6.5.3.1: Study Center Clusters - Protocol 1008-040
(Applicant's Table 7, RR 720-30054 1008-040, P. 55)

Table 7. Study Centers Grouped Into Clusters for Analysis

Cluster	Centers	Countries
1	73, 75, 76, 79	Australia
2	74, 77	Australia
3	31, 32, 81, 82, 83	Germany, Austria
4	1, 11, 12, 62, 63, 67, 69, 88	France, Belgium, UK, Switzerland
5	16, 25, 27, 29, 113	Germany
6	17, 20	Germany
7	18, 19, 23, 33, 34, 110	Germany
8	24, 28, 111	Germany
9	26, 112	Germany
10	35, 36, 38, 86	Italy, Switzerland
11	45, 46, 47, 48, 49, 50, 52	Spain
12	72	South Africa

6.5.4.1 Applicant's Primary Efficacy Analysis

6.5.4.1.1 Overview

The Applicant's analyses showed that pregabalin was not statistically different from placebo with respect to the primary efficacy endpoint. However, pregabalin did show statistically significant differences from placebo on several secondary analyses.

6.5.4.1.2 Primary Efficacy Outcome

The primary efficacy outcome was the *mean pain score at endpoint*. The endpoint mean score for the pregabalin group (4.1 (± 2.4) was not statistically different from the placebo group (4.5 (± 2.4)) (p = 0.082). There was a significant difference between endpoint mean score for the amitriptyline group compared to the placebo group. There was an apparent improvement (decrease) in mean pain scores from baseline to endpoint across all treatment groups.

Table 6.5.3.1.2.a: Endpoint Mean Pain Scores: Results of Analysis of Covariance, ITT Protocol 1008-040

		Least Squares		Treatment Comparisons (Active Drug – Placebo)		
Treatment	N	Means	SE	Difference	95% CI	p-value
Placebo	80	4.60	0.26			
Pregabalin	86	3.96	0.26	-0.64	(-1.37, 0.08)	0.0822
Amitriptyline	87	3.67	0.25	-0.93	(-1.65, -0.22)	0.0110

Table 6.5.3.1.2.b: Mean Pain Scores: Descriptive Statistics, ITT Population Protocol 1008-040

	Placebo		Pregabalin 600 mg/day		Amitriptyline 75 mg/day	
Time Point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	80	6.3 (1.6)	86	6.9 (1.6)	87	6.4 (1.6)
Endpoint	81	4.5 (2.4)	86	4.1 (2.4)	87	3.6 (2.4)
Change	80	-1.8 (2.5)	86	-2.8 (2.5)	87	-2.8 (2.6)

(Adapted from Applicant's Tables 12 and 13, RR 720-30054 1008-040, P. 74)

6.5.4.2 Supplemental Analyses of the Primary Efficacy Variable

Mean pain scores at endpoint: Per Protocol Population

These scores were similar to those for the ITT population. The endpoint mean pain score for the pregabalin group (4.1) was not statistically different from the placebo group (4.5) (p =0.069). The endpoint mean pain score for the amitriptyline group (3.6) was significantly different from placebo (p = 0.0097).

Mean pain scores: change from baseline to endpoint

In this analysis, the p-values and 95% CIs for the comparisons between pregabalin and placebo, and amitriptyline and placebo groups were the same as those for the primary analysis.

FDA Requested Efficacy Analyses:

(a) *Mean pain scores: Weekly scores and Change from Baseline*

In a comparison of the overall mean pain scores, the treatment effects for both the pregabalin and amitriptyline groups were statistically different (better) than placebo (p = 0.0015 and p = 0.0011, respectively).

Table 6.5.3.2.a: Overall mean pain scores: Results of multivariate analysis Protocol 1008-040

		Least Squares		Treatment Comparisons (Active Drug – Placebo)		
Treatment	N	Means	SE	Difference	95% CI	p-value
Placebo	80	4.91	0.20			
Pregabalin	85	4.04	0.19	-0.87	(-1.41, -0.34	0.0015
Amitriptyline	85	4.03	0.19	-0.88	(-1.41, -0.36)	0.0011

(Adapted from Applicant's Table 19, RR 720-30054 1008-040, P. 80)

Descriptive statistics for the weekly mean pain scores suggested that as the study progressed, that the pain scores decreased (i.e. pain improved) for all study groups.

Table 6.5.3.2.b: Weekly Mean Pain Scores: Descriptive Statistics – Protocol 040

	Placebo		Pregabalin 600 mg/day		Amitriptyline 75 mg/day	
Time Point	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	80	6.3 (1.6)	86	6.9 (1.6)	87	6.4 (1.6)
Week1	81	5.7 (1.8)	85	5.4 (1.9)	85	5.3 (2.0)
Week 2	79	5.2 (1.9)	77	4.9 (2.0)	83	4.5 (2.1)
Week 3	75	4.9 (2.2)	76	4.3 (2.3)	81	3.9 (2.2)
Week 4	72	4.7 (2.3)	73	3.9 (2.4)	75	3.6 (2.3)
Week 5	72	4.5 (2.2)	72	4.0 (2.5)	73	3.5 (2.3)
Week 6	65	4.3 (2.3)	68	3.8 (2.5)	69	3.4 (2.2)
Week 7	63	4.2 (2.4)	65	3.9 (2.5)	67	3.3 (2.3)
Week 8	61	4.2 (2.3)	64	3.9 (2.5)	66	3.2 (2.3)
Endpoint	81	4.5 (2.4)	86	4.1 (2.4)	87	3.6 (2.4)

(Adapted from Applicant's Table 20, RR 720-30054 1008-040, P. 80)

The Applicant states that the differences in weekly mean pain scores were better for the pregabalin group than the placebo group at Weeks 1 through 8, and the scores for the amitriptyline group were statistically significantly better than the placebo group's at all weeks except Week 1.

The difference in mean pain score between the pregabalin and amitriptyline groups was calculated for each week. The Applicant states that point estimates of the difference were < 0 (in favor of pregabalin) from Weeks 1 to 4, and > 0 from weeks 5 to 8 (in favor of amitriptyline). However these differences were not statistically significant (all confidence intervals contained zero).

(b) *Proportion of responders*

A responder was defined as a patient who had ≥ 50% decrease in mean pain score from baseline to endpoint. The table below shows that 30% of placebo-treated patients, 40% of pregabalin-treated patients, and 46% of amitriptyline-treated patients were responders. There was no statistically significant difference in the proportion of responders between the pregabalin and placebo groups ($p = 0.239$), but there was between the amitriptyline and placebo groups ($p = 0.034$).

Table 6.5.3.2.c: Analysis of Responder Status: Results of Logistic Regression – Protocol 040

			Treatment Comparisons (vs. Placebo)		
Treatment	N	No. of Responders (%)	p-value	95% CI	Odds Ratio
Placebo	80	24 (29.6)	--	--	--
Pregabalin	85	34 (39.5)	0.2390	(0.77, 2.95)	1.50
Amitriptyline	85	40 (46.0)	0.0339	(1.06, 3.97)	2.04

(Adapted from the Applicant's submission, Table 22, RR 720-30054 1008-040, P. 84)

6.5.4.3 Applicant's Secondary Efficacy Analysis

(a) SF-McGill Sensory, Affective, and Total scores, at endpoint and at Weeks 1, 2, 5, & 8

Descriptive statistics of the sensory, affective, and total scores were calculated. In general, results from the English (N = 75) and German language (N = 126) SF-MPQs showed that the sensory, affective, and total scores decreased (improved) over the course of the study. For all 3 scores, the mean change from randomization to endpoint was greater in the pregabalin group than in the placebo group. This was also observed for the amitriptyline group. There were too few subjects (N = 4 to 24) who used the other language questionnaires to draw conclusions from the data (Appendix 1, RR 720-30054 1008-040, Section 9.1.14 and 9.1.15).

(b) SF-McGill VAS, and PPI scores, at endpoint and at Weeks 1, 2, 5, and 8 (Endpoint)

1. *Endpoint (Week 8) scores*

Mean endpoint (week 8) VAS scores for the pregabalin group (39.5) and the amitriptyline group (37.4) were statistically significantly better than the placebo group's score (48.3) (p = 0.0142 and 0.0055 respectively). The point estimate of the difference between the pregabalin and amitriptyline groups' VAS scores did not reach statistical significance.

Only the amitriptyline group had significantly better PPI indices than the placebo group. For the PPI index, the point estimate of the difference between the pregabalin and amitriptyline groups was not statistically significant. (See Section 9.1.14 and 9.1.15, RR 720-30054 1008-040, P. 159-162.)

2. *Weekly scores*

Analysis of the VAS scores at Weeks 1, 2, 5, and 8, found statistically significant differences between the pregabalin and the placebo groups at each time point except Week 8 (endpoint). The amitriptyline scores were statistically significantly different from placebo at Weeks 2, 5, and 8. (See Figure 8, RR 720-30054 1008-040, P. 89)

The VAS score difference between the pregabalin and amitriptyline groups was estimated at each week. None of the results reached statistical significance. Analysis of the PPI indices at Weeks 1, 2, 5, and 8 revealed statistically significant differences only at Week 1 for the pregabalin group compared to the placebo group. The amitriptyline group was statistically significantly different from the placebo group at all 4 of these time points. The PPI index difference between the pregabalin and amitriptyline groups was estimated at each week and showed no statistically significant difference. (See Appendix E.2.1, RR 720-30054 1008-040, P. 1040.)

(c) Mean and Change in sleep interference scores, and at endpoint and at each week separately

1. *Mean endpoint scores*

Mean sleep interference scores at endpoint were statistically better for the pregabalin group (3.1) and the amitriptyline group (2.5) compared to placebo (3.8), (p = 0.0023 and 0.0003 respectively). The point estimate of the difference in scores between the pregabalin and amitriptyline groups (0.20) was not statistically significant (95% CI –0.47, 0.87).

2. *Mean weekly scores*

Both the placebo and the amitriptyline groups had statistically better mean sleep interference scores compared to the placebo group, at each week of the study. The sleep interference score difference between the pregabalin and amitriptyline groups was estimated at each week and was not statistically different. (See Figure 10 and Table 26, Appendix E.2.1; RR 720-30054 1008-040, P. 92 to 93.)

3. *Change in scores*

All of the treatment groups showed improvement in sleep scores during the study. The pregabalin and amitriptyline groups had statistically better changes sleep interference scores compared to the placebo group. (See Figure 10 and Table 26, Appendix E.2.1; RR 720-30054 1008-040, P. 92 to 93.)

(d) PGIC and CGIC

There was no statistically significant difference in the PGIC or the CGIC response of the pregabalin group when compared to the placebo group ($p = 0.130$ and $p = 0.058$). The amitriptyline group did differ significantly from the placebo group for both measures ($p = 0.020$ and 0.003). (See Appendix E.2.16; RR 720-30054 1008-040, P. 1116 to 1151.)

(e) Quality of Life and Mood Assessments

1. SF-36 Health Survey - Quality of Life

The change in each of the 8 domains of the, from randomization to termination, was statistically greater (more favorable) for the pregabalin and amitriptyline groups than for the placebo group. Both active treatment groups were statistically significantly better than placebo in the physical functioning, bodily pain, mental health, and general health perception domains. (See Table 29 P. 97 and Appendix E.2.16 P 179 to 188; RR 720-30054 1008-040.)

2. *Hospital Anxiety and Depression Scale*

There were statistically significant differences between both active groups and the placebo group with respect to anxiety only. The point estimates of the differences between the active groups for both anxiety and depression did not reach statistical significance. (See Tables 30 and 31, RR 720-30054 1008-040, P. 98)

6.5.4.4 Unplanned Analyses

1 FDA Requested Efficacy Analyses:

1. *Mean pain scores at endpoint: ITT patients without dizziness or somnolence*

The results for this population were similar to those for the entire ITT population: the endpoint mean pain score for the pregabalin group was not statistically different from that of the placebo group ($p = 0.1719$), and the score for the amitriptyline group was statistically better ($p = 0.0052$).

2. *Mean pain scores at endpoint: Baseline Carried Forward for ITT subjects who did not complete the study*

Neither the pregabalin nor the amitriptyline groups' mean pain score at endpoint was statistically different from the placebo group ($p = 0.4697$ and 0.0611, respectively).

2 *Mean pain scores at endpoint: ITT Population - Observed Cases Data*
In this analysis, the both the pregabalin and amitriptyline groups' mean endpoint scores were statistically different from the placebo group (p = 0.045 and 0.006, respectively.) The point estimate of the difference between the pregabalin and amitriptyline groups (0.27) was not statistically significant (95% CI -0.45, 0.99).

3 *Sustained Responder Patients:*
A sustained responder was defined as a patient with a reduction in mean pain score of at least 50% from baseline to a specific week and who maintained this reduction until Week 8, or until endpoint if the patient withdrew early. Since pregabalin was not statistically significantly different from placebo on the primary analysis, the analysis of time to being a sustained responder was not performed.

6.5.4.5 Reviewer's Analysis

The Applicant showed that the study failed using both the primary analysis method (LOCF) and the baseline observation carried forward (BOCF) method. Based on these findings, the Agency did not reanalyze the data.

6.5.4.6 Conclusions regarding Efficacy Data – Protocol 040

In this study, treatment with pregabalin 600 mg/day was not any more effective than placebo in the treatment of pain due to diabetic neuropathy.

6.6 Protocol 1008-131: An 8-week, double-blind, placebo-controlled trial of pregabalin (300 mg/day) for relief of pain in patients with painful diabetic peripheral neuropathy

6.6.1 Protocol

6.6.1.1 Objective/Rationale

The purpose was to assess the safety and efficacy of pregabalin (300 mg/day) compared to placebo for symptomatic relief of painful diabetic neuropathy.

6.6.1.2 Overall Design

This was a Phase 2/3, randomized, double-blind, placebo-controlled, parallel trial comparing 1 dose of pregabalin to placebo as treatment for pain due to diabetic neuropathy.

6.6.1.3 Study Population and Procedures

6.6.1.3.1 Treatment Duration: 8 weeks

6.6.1.3.2 Entry Criteria

The protocol called for enrollment of up to 140 subjects (70 per arm) at 30-35 sites in the US.

Eligibility criteria were as follows:

- Age ≥ 18 years
- Type 1 or 2 diabetes mellitus;
- Diagnosis of diabetic, distal, symmetrical, sensorimotor polyneuropathy for 1 to 5 years
- Hemoglobin A1C levels of ≤ 11%
- Normal chest x-ray prior to the baseline; or stable chest x-ray, defined as no clinically significant change from a previous exam
- At the baseline **and** randomization visits, a score of ≥ 40 mm on the VAS of the SF-MPQ;
- At randomization, completion of at least 4 daily pain diaries, and an average daily pain score of 4 over the past 7 days on the Likert-type scale

Subjects were to be excluded if they met any of the following criteria:

- Clinically significant or unstable hepatic, respiratory, or hematologic illnesses, unstable cardiovascular disease, or symptomatic peripheral vascular disease
- Creatinine clearance ≤ 60 mL/min (estimated from serum creatinine, body weight, age, and sex using the Cockcroft and Gault equation); If estimated creatinine clearance is not >60 mL/min at this visit a 24-hour urine sample could be analyzed

and if the creatinine clearance s by this measurement is ·60 mL min, the patient was eligible.

- History of pernicious anemia, untreated hypothyroidism, chronic hepatitis B, hepatitis B within the past 3 months, or HIV infection
- Neurologic disorders unrelated to diabetic neuropathy that may confound the assessment of neuropathic pain
- Skin conditions in the area affected by the neuropathy that could alter sensation
- Other severe pain that may confound assessment or self-evaluation of the pain due to diabetic neuropathy
- Failure to respond to previous treatment with gabapentin (Neurontin) at doses ≥ 1200 mg/day for treatment of pain associated with diabetic neuropathy;
- Amputations other than toes
- Abuse of illicit drugs or alcohol within the last 2 years
- Serious or unstable medical or psychological conditions
- Malignancy within the past 2 years
- WBC <2500/mm^3; neutrophil count <1500/mm^3; platelet count <100 × 10^3/mm^3;
- Abnormal ECG
- Use of prohibited medications, in the absence of appropriate washout periods

6.6.1.3.3 Study Medications

Study drug was either placebo or pregabalin (100 mg) capsules. Subjects were to be randomized to either placebo or pregabalin, and were to take 1 capsule TID. There was no titration phase, and dosage was to be fixed throughout the 8 weeks of the study.

The following medications were permissible:

- Aspirin, ≤ 325 mg daily (for myocardial infarction and stroke prophylaxis)
- Acetaminophen, ≤ 4 g daily (rescue medication for pain)
- SSRIs, for anxiety and depression only (patients had to be on a stable regiment within the last 30 days, and therapy could not be initiated during the study)

Medications prohibited by the protocol are listed in the table below:

Class of Medication	Examples[a]	Washout Period
Medications commonly used for relief of neuropathic pain and other supplements	Benzodiazepines, skeletal muscle relaxants, capsaicin, narcotics. Fatty acid supplements, evening primrose oil, myoinositol, chromium picolinate	At least 7 days prior to Visit 1
Antiepileptics for pain	Carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, vigabatrin,[b] gabapentin	At least 7 days prior to Visit 1

Class of Medication	Examples[a]	Washout Period
Potential retinotoxins	Hydroxychloroquine,[b] deferoxamine,[b] thioridazine[b]	Not applicable
Antidepressants	Tricyclic antidepressants	≥ 7 days prior to Visit 1
Analgesics	NSAIDs, Tramadol, dextromethorphan	≥ 1 day prior to Visit 1

a Not a comprehensive list

b Patients who had ever taken vigabatrin, hydroxychloroquine, deferoxamine, or thioridazine were ineligible to participate in this study.

6.6.1.3.4 Study Procedures

Visits

Patients were to be seen at 6 scheduled visits. The first visit (V1) occurred during screening, and the second (V2) 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 were assessed at 1 week (V3), and then at 2 to 3-week intervals (V 4, 5, and 6). A safety follow-up visit (V7) would occur at Study Week 9.

Baseline

Eligible subjects were defined as those who met entry criteria, were stabilized on their anti-diabetic medications, and who had undergone sufficient washout of prohibited drugs. During the baseline phase, the subjects were to provide daily pain and sleep ratings. Subjects who completed at least 4 pain diaries and had an average pain score of at least 4 were then randomized in blocks of 4to study drug at V2.

Treatment phase

Study medication was to remain at the fixed dose for all subjects. Patients unable to maintain the target dose were to be withdrawn from the study. During clinic visits, subjects were evaluated for pain, sleep, laboratory changes, physical status, as well as any adverse effects. At the final clinic visit, additional assessments regarding overall improvement and general health were to be made. A patient was to be considered as having completed the study if s/he received 8 weeks of double-blind treatment and attended the V6/Termination visit.

Table 6.6.1.3.4: Time and Events Schedule: Protocol 1008-131

APPENDIX A.1

Timetable of Visits and Procedures

Study Phase	Baseline (1 Week)		Double-Blind Treatment (8 Weeks)				
End of Study Week	Screening	Randomization	1	3	6	8	ET
Study Day	-7	1	7	21	42	63	*D
Clinic Visit	1	2	3	4	5	6 (ET or	-
Observation/Procedure							
Informed Consent	X						
Inclusion Exclusion	X						
Medical History	X						
Physical Exam	X			X	X	X	
Neurological Peripheral Sensory 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	
SF-36 QOL		X				X	
Profile of Mood States (POMS)		X				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	X	
Clinical Labs							
Hematology, Chemistry, Urinalysis	X[2]			X	X	X	X
Hemoglobin A_{1c}	X					X	
B12, folate, SPEP, T4, TSH	X						
Pregnancy Test (Serum)	X			X		X	
TSH	X					X	
Chest X-ray	X						
12-lead ECG	X					X	
Visual Examinations	X					X	

[1] 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.

[2] Clinic visit only for patients who do not enter open-label Protocol 1008-134

[3] Whenever patient withdraws from or completes the study

[4] At V1 or prior to washout if applicable

[5] Vitals only

[6] Medication will be dispensed for patients entering into open-label Protocol 1008-134

[7] Estimated creatinine clearance is calculated at V1 only

[8] Chest x-ray must be taken at baseline visit if none available in the 2 years prior to baseline

[9] Examination testing by an ophthalmologist at V1 and V6 Termination. These include dilated ophthalmoscopy (direct or indirect), 120-point Humphrey visual screening with the quantified defects routine, and best-corrected Snellen Visual Acuity

(Applicant's Appendix A.1, RR 720-04452, 1008-131, P. 134)

6.6.1.3.5 Efficacy Parameters

- Daily pain score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Daily diary of sleep interference
- Clinical Global Impression of Change (CGIC)
- Patient Global Impression of Change (PGIC)
- SF-36 Health Survey Questionnaire (SF-36 QOL)
- Profile of Mood States (POMS)

6.6.1.3.6 Pharmacokinetics

The protocol did not describe any pharmacokinetic assessments.

6.6.1.3.7 Statistical Analysis

6.6.1.3.7.1 Patient Population

The evaluable population was defined as the intent-to-treat population (all randomized patients who received at least 1 dose of study medication)

6.6.1.3.7.2 Demographics

Baseline characteristics were to be compared across treatment groups using descriptive statistics.

6.6.1.3.7.3 Primary Efficacy Outcome

The primary efficacy outcome was to be the final weekly (endpoint) mean pain score, described as the last 7 diary entries in the study while the patient was on medication.

The primary analysis would compare the final weekly mean pain score between the groups using ANCOVA, with treatment and center in the model and the baseline mean pain score as covariate.

6.6.1.3.7.4 Supplemental Analyses of the Primary Efficacy Outcome

- Mean pain score for each week separately
- Change in pain score from baseline at endpoint, and at each week separately
- Comparison of the proportion of responders between the 2 groups

(Responder = patient with ≥ 50% reduction in weekly mean pain score from baseline to endpoint.)

6.6.1.3.7.5 Secondary Efficacy Analyses

- SF-MPQ scores (sensory, affective, total, VAS, and PPI) at Weeks 1, 3, and 6, as well as at last observation
- Weekly mean sleep interference score
- CGIC and PGIC at study termination
- Change in SF-36 QOL score
- Change in POMS score

6.6.1.3.7.6 Interim Analyses

No interim analyses were included in the protocol.

6.6.1.4 Protocol Amendments

No amendments were made to the protocol.

6.6.2 Study Results

6.6.2.1 Study Conduct/Outcome

6.6.2.1.1 Subject Characteristics

The first patient was screened on December 10, 1999 and the last patient completed the double-blind treatment phase on May 9, 2000. A total of 25 centers in the US participated.

6.6.2.1.2 Enrollment by Center

The table below shows the number of patients who were randomized at each center:

No. Patients Randomized per Center	Center Number
0	116, 128
1	114, 126
2	106, 118
3	112, 130
4	104, 120
5	103, 109, 111, 117
6	102, 108, 124
7	132
8	125
10	110
11	101, 105, 122
14	131
16	113
Total = 146	Total = 25

(Adapted from Applicant's Table 1, RR 720-04452, 1008-131, P. 14)

6.6.2.1.3 Protocol Violations

The Applicant identified 21 subjects who had protocol violations, but considered only 4 patients – those who had a baseline mean pain score of < 4 – to have the potential to affect the study results. The specific types of protocol violations are detailed in the following table:

Table 6.6.2.1.3: Protocol violations, Protocol 1008-131

Violation	Total N	Pregabalin 300 mg/day	Placebo
Baseline mean pain score < 4	4	4	-
Baseline SF-MPQ < 40 mm	1	-	1
Creatinine clearance < 60 mL/min	3	-	3
Malignancy within the past 2 years	1	1	-
Prohibited medication	12	5	7
Total	20	9	11

(Adapted from Applicant's Appendix A.8, RR 720-04452, 1008-131, P. 237)

I consider the violations that would potentially impact the primary efficacy outcome to be from following subjects:

- Patients who had a baseline mean pain score < 4 (n = 4) -> if a small improvement in pain occurred with therapy, it would be difficult to detect
  - Patient 103009, Pregabalin 300 mg/day
  - Patient 111001, Pregabalin300 mg/day
  - Patient 113011, Pregabalin300 mg/day
  - Patient 131005, Pregabalin300 mg/day

- Patients who used prohibited medications that might themselves improve pain (n 12)

Placebo		Pregabalin 300 mg day	
Patient 105010	Continued venlafaxine	Patient 106003	Took Exedrin on Day 29
Patient 112004	Initiated tramadol on Day 30	Patient 109004	Continued Celecoxib
Patient 113004	Continued Exedrin	Patient 111007	Continued Celecoxib
Patient 113017	Continued venlafaxine	Patient 124006	Continued nabumetone
Patient 124004	Continued Celecoxib	Patient 120002	Took ibuprofen on Day 5
			Took panadeine on Days 48, 54
Patient 124005	Continued ibuprofen		
Patient 132006	Initiated ketorolac on Day 47		

While the use of prohibited pain medication would tend to bias the study in favor of the affected arm, the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is therefore not expected to have a significant impact on the interpretation of the results.

6.6.2.1.4 Blinding

The Applicant did not describe any instances where the study blind was broken.

6.6.2.1.5 Subject Disposition

Of the 255 subjects who were screened, only 146 were randomized to study treatment. Reasons for withdrawal of the 79 subjects during the baseline phase were as follows: failure to meet entry criteria (n = 60), withdrawal of consent (n = 10), adverse event (n = 1), loss to follow-up (n = 1), and "other/administrative" (n = 7).

All of the randomized subjects took at least one dose of study drug (ITT population). There were 70 subjects in the placebo group, and 76 in the pregabalin group. A total of 19 subjects withdrew from the study during the treatment phase. More subjects in the pregabalin group withdrew due to an adverse event (n = 8; 10%) than in the placebo group (n = 2; 3%). More subjects in the placebo group than in the active treatment group withdrew due to lack efficacy (4% versus 1%).

Table 6.6.2.1.5: Subject Disposition: Protocol 1008-131

	Placebo	Pregabalin 300 mg/day	Total
Entered baseline phase			225
Completed baseline phase			146
Withdrawn during baseline phase			79 (35.1)
Adverse event			1 (0.4)
Did not meet criteria			60 (26.7)
Lost to follow-up			1 (0.4)
Other / Administrative [1]			7 (3.1)
Patient withdrew consent			10 (4.4)
Randomized	70	76	146
Intent-to-treat	70	76	146
Completed study	62 (88.6)	65 (85.5)	127 (87.0)
Withdrawn during treatment phase	8 (11.4)	11 (14.5)	19 (13.0)
Adverse event [2]	2 (2.9)	8 (10.5)	10 (6.8)
Lack of compliance	1 (1.4)	2 (2.6)	3 (2.1)
Lack of efficacy	3 (4.3)	1 (1.3)	4 (2.7)
Lost to follow-up	1 (1.4)	0 (0.0)	1 (0.7)
Other [3]	1 (1.4)	0 (0.0)	1 (0.7)
Entered open-label study	61 (87.1)	62 (81.6)	123 (84.2)

1 Data regarding specific reasons for withdrawal during the baseline period were not provided
2 Adverse events included dizziness, somnolence, headache, confusion, paresthesia, incoordination, nausea, increased CK, ALT, and injury,
3 The subject (131-104012) discontinued the study because she was moving to another location
(Applicant's Table 10, RR 720-04452, 1008-131, P. 37)

6.6.2.1.6 Extent of Exposure/Dosing Information

The table below shows that exposure to study drug was similar between the two treatment groups. Overall, 80 randomized subjects (55%) completed at least 8 weeks of therapy. This is different from the number of 'completers' in Table 6.6.2.1.5 because the Applicant defined study completion as undergoing all of the protocol's visits and procedures. Of note, in the study protocol, study completion was defined as taking of all 8 weeks of study medication and completing the final study visit.

Table 6.6.2.1.6: Extent of Exposure, Protocol 1008-131

Total Exposure Time[a]	[Number (%) of Patients] Treatment Group	
	Placebo N = 70	Pregabalin 300 mg/day N = 76
≥1 Day	70 (100.0)	76 (100.0)
≥1 Week	70 (100.0)	73 (96.1)
≥2 Weeks	70 (100.0)	71 (93.4)
≥3 Weeks	69 (98.6)	70 (92.1)
≥4 Weeks	67 (95.7)	69 (90.8)

≥5 Weeks	66 (94.3)	68 (89.5)
≥6 Weeks	61 (87.1)	65 (85.5)
≥7 Weeks	61 (87.1)	64 (84.2)
≥8 Weeks	37 (52.9)	43 (56.6)

a Days on which patients received 0 dose are included in summary of patient exposure to study medication
(Applicant's Table 9, RR 720-04452, 1008-131, P. 36)

6.6.2.1.7 Demographics

Table 6.6.2.1.7.a shows that the demographic characteristics of sex, race, age, height, and weight for the patient populations in the 2 treatment groups were similar. The majority of patients were male (56%), White (88%) and <65 years of age (64%). The mean age of patients entering the study was 60 (± 11) years. The estimated creatinine clearance values were also comparable between the treatment groups.

Diabetes and neuropathic pain history

Most patients in the total population had Type 2 diabetes for a mean duration of 9 years. Slightly fewer patients in the pregabalin group than the placebo had Type 2 diabetes (84% versus 90%) (see Table 6.6.2.1.7.b). More subjects in the placebo group (86%) used oral antidiabetic medications than in the pregabalin group (75%). The proportion of subjects who used insulin was comparable (34% and 40%, respectively). The type of antidiabetic medication used was not expected to alter the results of the primary analysis.

The distribution of neuropathic pain was generally similar between the groups, as was the baseline mean pain score. Table 6.6.2.1.7.c shows that 9% of subjects in the pregabalin group concurrently used neuropathic pan medications, compared to 10% of the placebo group. Use acetaminophen (Paracetamol) for pain relief was also not different between the groups.

Table 6.6.2.1.7.a: Patient Characteristics, Protocol 1008-131

Table 6 Patient Characteristics (Intent-to-Treat Population)

Characteristic		Placebo N = 70	Pregabalin 300 mg d.o.v N = 76	All Patients N = 146
Sex, N (%)	N	70	76	146
	Male	40 (57.1)	42 (55.3)	82 (56.2)
	Female	30 (42.9)	34 (44.7)	64 (43.8)
	Premenopausal	5 (16.7)	4 (11.8)	9 (14.1)
	Postmenopausal	25 (83.3)	30 (88.2)	55 (85.9)
Race, N (%)	N	70	76	146
	White	64 (91.4)	64 (84.2)	128 (87.7)
	Black	3 (4.3)	6 (7.9)	9 (6.2)
	Hispanic	3 (4.3)	5 (6.6)	8 (5.5)
	American Indian or Alaskan Native	0 (0)	1 (1.3)	1 (0.7)
Age Categories, N (%)	N	70	76	146
	18-64 years	45 (64.3)	48 (63.2)	93 (63.7)
	>65 years	25 (35.7)	28 (36.8)	53 (36.3)
Age (years)	N	70	76	146
	Mean (STD)	60.3 (10.3)	59.2 (12.3)	59.7 (11.4)
	Median	61.0	60.0	61.0
	Range	37 to 79	21 to 83	21 to 83
Estimated Creatinine Clearance at Baseline (mL/min)	N	70	76	146
	Mean (STD)	122.77 (51.59)	119.79 (43.31)	121.22 (47.32)
	Median	108.55	114.00	111.00
	Range	55.0 to 313.0	60.0 to 268.0	55.0 to 313.0
Height (cm)	N	70	76	146
	Mean (STD)	171.25 (10.01)	173.22 (9.59)	172.27 (9.81)
	Median	172.70	172.60	172.70
	Range	148.6 to 190.5	148.0 to 195.6	148.0 to 195.6
Weight (kg)	N	70	76	146
	Mean (STD)	95.82 (20.80)	97.56 (19.83)	96.72 (20.25)
	Median	97.35	96.00	96.80
	Range	44.5 to 154.0	60.0 to 160.8	44.5 to 160.8

(Applicant's Table 6, RR 720-04552, 1008-131, P. 32)

Table 6.6.2.1.7.b: Patient's diabetic and neuropathic pain history

Table 7. Patient Diabetic and Neuropathic Pain History

	Placebo N = 70	Pregabalin 300 mg day N = 76	Total N = 146
Diabetes Type, N(%)			
Type I	7 (10.0)	12 (15.8)	19 (13.0)
Type II	63 (90.0)	64 (84.2)	127 (87.0)
Duration of Diabetes(years)			
N	70	76	146
Mean (STD)	9.4 (10.3)	9.3 (10.5)	9.3 (10.3)
Median	5.5	6	6
Range	0.0 to 44.0	1.0 to 62.0	0.0 to 62.0
Distribution of Neuropathic Pain, N(%)[a]			
Lower Extremities	70 (100.0)	76 (100.0)	146 (100.0)
Toe	53 (75.7)	53 (69.7)	106 (72.6)
Foot	69 (98.6)	74 (97.4)	143 (97.9)
Toe/Foot	70 (100.0)	76 (100.0)	146 (100.0)
Calf	24 (34.3)	39 (51.3)	63 (43.2)
Thigh	6 (8.6)	6 (7.9)	12 (8.2)
Upper Extremities	29 (41.4)	30 (39.5)	59 (40.4)
Finger	19 (27.1)	20 (26.3)	39 (26.7)
Hand	23 (32.9)	26 (34.2)	49 (33.6)
Finger Hand	29 (41.4)	30 (39.5)	59 (40.4)
Forearm	5 (7.1)	8 (10.5)	13 (8.9)
Baseline Mean Pain Score			
Mean (STD)	6.1 (1.5)	6.5 (1.7)	6.3 (1.6)
Median	6	6.3	6.1
Range	4.0 to 10.0	3.6 to 9.9	3.6 to 10.0

[a] More than one category per patient possible

(Applicant's Table 7, RR 720-04552, 1008-131, P. 33)

Table 6.6.2.1.7.c: Concurrent neuropathic pain mediations – Protocol 131

Medication*	Placebo (N = 70)	Pregabalin 300 mg (N =76)
NEUROPATHIC PAIN MEDICATION, N(%)	7 (10.0)	7 (9.2)
Celecoxib	1 (1 4)	0 (0.0)
Paracetamol	6 (8.6)	6 (7.9)
Tylenol PM	1 (1 4)	0 (0.0)
Venlafaxine Hydrochloride	0 (0.0)	1 (1.3)

* A patient may be taking more than one medication
(Applicant's Appendix C.2, RR 720-04452, 1008-131, P. 253)

6.6.3 Efficacy Results

6.6.3.1 Applicant's Efficacy Analysis

6.6.3.1.1 Overview

The Applicant found that the endpoint mean pain score was significantly better for the pregabalin 300 mg/day group than for the placebo group. Several secondary analyses, including the proportion of treatment responders, and the endpoint SF-MPQ VAS and PPI scores yielded similar results.

6.6.3.1.2 Primary Efficacy Analysis

The primary outcome was the mean pain score at endpoint, where endpoint was defined as the last 7 scores while the patient was receiving study medication. While both the placebo and pregabalin groups had lower scores at endpoint, a statistically significant difference was seen favoring pregabalin over placebo. These results are illustrated in the tables below:

Table 12. Mean Pain Scores: Descriptive Statistics

Time point	Placebo				Pregabalin 300 mg/day			
	N	Mean (SD)	Min	Max	N	Mean (SD)	Min	Max
Baseline[a]	70	6.1(1.5)			76	6.5(1.7)		
Endpoint[b]	69	5.3(2.4)			75	4.0(2.5)		
Change[c]	69	-0.8(1.7)			75	-2.5(2.6)		

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.

Table 13. Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance

Treatment	N	Least Squares Mean	SE	Treatment Comparisons (Pregabalin - Placebo) Difference	95% CI	p-value
Placebo	69	5.46	0.28			
Pregabalin 300 mg/day	75	3.99	0.26	-1.47	(-2.19, -0.75)	0.0001

SE = Standard error; CI = Confidence interval.
[a] Endpoint = Last 7 available scores while on study medication, up to and including day after last dose.

Table 6.6.3.1.2.a and 6.6.3.1.2.b: Primary Efficacy Analysis

6.6.3.1.3 Supplemental Analyses of the Primary Efficacy Variable

Mean pain score for each week separately

The following table shows that the mean pain scores for both groups decreased over the course of the study, however the pregabalin group had a substantial drop in mean pain score from Week 1 (the score decreased from 6.5 to 4.3). This low score varied only slightly over the remaining weeks of the study. Analysis showed that the differences between the groups' weekly mean pain scores was significant ($p = 0.001$, for every time point).

Table 6.6.3.1.3.a: Weekly mean pain scores – Protocol 131

Time point	Placebo				Pregabalin 300 mg/day			
	N	Mean (SD)	Min	Max	N	Mean (SD)	Min	Max
Baseline[a]	70	6.1(1.5)			76	6.5(1.7)		
Week 1[b]	68	5.9(1.7)			75	4.3(2.3)		
Week 2	69	5.8(1.8)			73	4.2(2.5)		
Week 3	68	5.7(2.0)			72	4.1(2.4)		
Week 4	68	5.6(2.0)			71	4.4(2.4)		
Week 5	67	5.7(2.1)			69	4.2(2.3)		
Week 6	62	5.6(2.3)			68	4.1(2.3)		
Week 7	60	5.4(2.3)			64	4.2(2.4)		
Week 8	59	5.3(2.5)			62	4.1(2.4)		
Endpoint[c]	69	5.3(2.4)			75	4.0(2.5)		

SD = Standard deviation.

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

b Week 1, 2, etc. All data for all patients who entered the week of interest were used in the analysis.

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

(Applicant's Table 14, RR 720-04452, 1008-131, P. 41)

Change in pain score from baseline

Neither of the treatment groups' mean pain scores returned to baseline during the study. Analysis of the weekly mean score change from baseline showed a statistically significant difference, favoring pregabalin over placebo ($p < 0.01$).

Comparison of the proportion of responders

Patients with ≥ 50% reduction in weekly mean pain score from baseline to endpoint were considered responders to treatment. Among the patients receiving pregabalin, 40% were responders, whereas 14.5% of patients in the placebo group were responders. The difference in the proportion of responders between the 2 treatment groups was statistically significant ($p = 0.001$).

6.6.3.2 Secondary Efficacy Analysis

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

Although the protocol specified a comparison of patients' mean SF-MPQ scores at endpoint and Weeks 1, 3, and 6, the Applicant presented data for Weeks 1, 3, 5, and 8.

The endpoint and weekly mean VAS and PPI scores were consistently lower for the pregabalin group than for the placebo group. Analysis of the differences in weekly VAS scores found statistically significant differences at all time-points. The PPI scores for the pregabalin group were significantly different from placebo at all weeks except Week 8.

When the percentage of patients that chose a particular pain descriptor at baseline was compared to the percentage at endpoint, a greater reduction was noted in the pregabalin group than in the placebo group for all descriptors in the questionnaire. There were statistically significant differences between the treatment groups in all 3 categories and time-points, except for the Week 8 affective score. This comparison failed normality testing and the apparent significant finding was not confirmed by rank ANCOVA.

Weekly mean sleep interference score
The pregabalin treatment group had an immediate drop in mean sleep interference score from baseline (5.6) to Week 1 (3.2), and the score remained low for the rest the study. The weekly sleep interference score for the placebo group decreased slightly during the course of the study (from 5.0 at baseline, to 4.7 at Week 1, and 4.1 at endpoint). Analysis of sleep interference scores between the treatment groups showed statistically significant differences that favored pregabalin over placebo at every weekly time point

CGIC and PGIC at study termination
In the pregabalin group, 67% of patients reported improvement (very much improved, much improved, or minimally improved), compared to 39% of the placebo patients. Similarly, clinicians reported that 67% of pregabalin-treated patients were improved, compared to 39% of placebo patients. These differences were statistically significant.

Change in SF-36 QOL and POMS scores
The only difference between the two groups with respect to the SF-36 QOL questionnaire was seen for the bodily pain domain. The pregabalin group also had significantly more favorable tension/anxiety and total mood disturbance scores on the POMS than did the placebo group.

6.6.3.3 Unplanned 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.

BOCF Analysis
In this analysis of the primary outcome, the Applicant used the baseline mean pain score instead of the endpoint score for 17 patients who did not complete the study (as determined by the investigator on the Patient Status case report form). Of note, this number is different from the 19 subjects who prematurely withdrew from the study during the treatment phase (see Table 6.6.2.1.5). Table 6.6.3.3 shows that the results of this analysis were similar to those of the primary analysis (i.e. patients treated pregabalin had significantly greater pain relief than those treated with placebo).

Table 6.6.3.3: BOCF analysis of the primary outcome (see below)

Primary analysis removing patients with dizziness/somnolence
The Applicant identified 44 patients (35 receiving pregabalin and 9 receiving placebo) who reported TESS AEs of dizziness and/or somnolence. The primary analysis was

repeated after removing these patients and showed that the pregabalin group had a significantly greater improvement in pain compared to the placebo group (p 0.009)

Table 6.6.3.3: BOCF analysis of the primary outcome

Table 1 Endpoint[1] Mean Pain Scores Results of Analysis of Covariance with BOCF

				Treatment Comparisons (Pregabalin Placebo)		
Treatment	N	Least Squares Means	SE	Difference	95% CI	p-Value
Placebo	69	5.45	0.27			
Pregabalin 300	75	4.28	0.26	-1.16	(-1.87, -0.46)	0.0014

SE Standard error; CI Confidence interval
[1] Endpoint Last 7 available scores while on study medication, up to and including day after last dose.

(Applicant's Table 1, Appendix D.3, RR 720-04452)

Longitudinal analysis
A longitudinal analysis was performed on the observed values of the weekly mean pain score, using ANCOVA with treatment, center, 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 no evidence of a treatment by week interaction (p=0.1833). The results of the main effects ANCOVA model yielded a significant difference for pregabalin 300 mg/day compared to placebo (p=0.0001).

Analysis of allodynia and hyperalgesia
Neither allodynia nor hyperalgesia was significantly associated with treatment (p=0.3479, p=0.0599, respectively).

Use of rescue medication
Up to 4g per day of acetaminophen was permitted during the study. In the pregabalin 300 mg/day group 9 (11.8%) patients took acetaminophen compared to 7 (10.0%) in the placebo group. Since the proportion of patients taking acetaminophen was nearly the same in both treatment groups, the Applicant did not believe that acetaminophen usage would affect the results.

6.6.3.4 Reviewer's Analysis

This trial had the same deficiencies in its analysis plan as were described for Protocols 1008-014 and 1008-029 (see Sections 6.3.3.5 and 6.4.3.6 above). The data were reanalyzed using the preferred BOCF method and descriptive statistics showed that both the pregabalin and the placebo group had a decrease in pain score by the last week of the treatment period:

Reviewer's Analysis: Endpoint mean pain scores – Protocol 131

	Placebo		Pregabalin 300 mg/day	
Time Point	N	Mean (SD)	N	Mean (SD)
Baseline	70	6.12 (1.48)	76	6.53 (1.66)
Endpoint	70	5.53 (2.16)	76	4.74 (2.45)
Change		-0.59 (1.47)		-1.79 (2.46)*

Baseline = the last 7 days prior to randomization; Endpoint = the last 7 days of the treatment period
* P value = 0.0005

The BOCF analysis of the primary outcome, mean pain score during the last week of the study, found that the pregabalin 300 mg/day group had significantly improved pain compared to the placebo group (p = 0.0005)

Approximately 13% of both the pregabalin and placebo groups used rescue medication during the final treatment week. Repeat BOCF analysis of the primary outcome after factoring in the use of rescue medication showed that there was no significance difference in pain score between the two groups (p = 0.0308, 1-sided alpha = 0.0250).

The results of a responder analysis based on the BOCF analysis, with and without imputation for use of rescue medication are depicted in the table below:

Reviewer's analysis: Percentage change in endpoint mean pain score by dose: BOCF analysis - Protocol 1008-131

Total N	70	76
Pain Score	Placebo N (%)	Pregabalin 300 mg/day N (%)
Any increase	26 (37.14)	9 (11.84)
No change	7 (10.00)	9 (11.84)
> 0% decrease	37 (52.86)	58 (76.32)
≥ 10 % decrease	27 (38.57)	52 (68.42)
≥ 20 % decrease	22 (31.43)	40 (52.63)
≥ 30 % decrease	18 (25.71)	34 (44.74)
≥ 40 % decrease	8 (11.43)	28 (36.84)
≥ 50 % decrease	***5 (7.14)***	***25 (32.89)***
≥ 60 % decrease	1 (1.43)	18 (23.68)
≥ 70 % decrease	0 (0.00)	12 (15.79)
≥ 80 % decrease	0 (0.00)	6 (7.89)
≥ 90 % decrease	0 (0.00)	4 (5.26)
= 100% decrease	0 (0.00)	4 (5.26)

Ten to 12% percent of the patients in each group reported no change in their pain following 8 weeks of treatment with study drug. More patients in the placebo group (37%) reported an increase in their pain by the end of the study compared to the pregabalin group (13%). There was a greater proportion of treatment responders in the pregabalin group (33%) than in the placebo group (7%).

The responder analysis was repeated, using the BOCF method and imputation for use of rescue medication. The results are shown in the table below:

Reviewer's Analysis: Percentage change in endpoint mean pain score by dose: BOCF analysis and maximum baseline score imputation for rescue medication - Protocol 1008-131

Total N Pain Score	70 Placebo N (%)	76 Pregabalin 300 mg/day N (%)
Any increase	22 (31.43)	10 (13.16)
No change	17 (24.29)	19 (25.00)
> 0% decrease	31 (44.29)	47 (61.84)
≥ 10 % decrease	23 (32.86)	42 (55.26)
≥ 20 % decrease	18 (25.71)	32 (42.11)
≥ 30 % decrease	15 (21.43)	26 (34.21)
≥ 40 % decrease	8 (11.43)	20 (26.32)
≥ 50 % decrease	***5 (7.14)***	***17 (22.37)***
≥ 60 % decrease	1 (1.43)	11 (14.47)
≥ 70 % decrease	0 (0.00)	8 (10.53)
≥ 80 % decrease	0 (0.00)	5 (6.58)
≥ 90 % decrease	0 (0.00)	4 (5.26)
= 100% decrease	0 (0.00)	4 (5.26)

Consideration of the use of rescue medication during the last week of the study resulted in lower decreases in pain across both groups. One quarter of patients in each group reported no change in their pain, and more patients in the placebo group (31%) reported an increase in their pain by the end of the study compared to the pregabalin group (13%). There were more treatment responders in the pregabalin 300 mg/day group than in the placebo group.

6.6.4 Conclusions Regarding Efficacy Data in Study – Protocol 131

Similar to the Applicant, the Agency found that treatment with pregabalin 300 mg/day resulted in a decrease in pain that was statistically significantly different from treatment with placebo. Although consideration of the use of rescue medication made the difference in endpoint mean pain scores statistically insignificant, a considerable difference in responder rates was observed between the two groups, regardless of the use of rescue medication.

6.7 Protocol 1008- 149: A 12-week, randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) for relief of pain associated with Diabetic Peripheral Neuropathy

6.7.1 Protocol

6.7.1.1 Objective/Rationale

The purpose of this study was evaluate the efficacy and safety of pregabalin (150, 300, or 300/600 mg/day) given in two divided doses compared to placebo for relief of pain in patients with diabetic neuropathy.

6.7.1.2 Overall Design

The study was to be a randomized, double-blind, multicenter, multi-national, placebo-controlled study in 352 subjects with painful diabetic neuropathy. The study was to be conducted in parallel to an identical study (Protocol 1008-173) in the United States. The data from these two studies would be pooled for analysis.

6.7.1.3 Study Population and Procedures

6.7.1.3.1 Treatment Duration: 12 weeks (1-week titration, 11 weeks fixed dose phase)

6.7.1.3.2 Entry Criteria

A total enrollment of 100 subjects was planned. These subjects were to be added to the patients enrolling in the parallel US study (Protocol 1008-173), for a total population of at least 352 subjects. In the combined population, there were to be approximately 88 subjects in each treatment arm.

Eligible subjects were required to meet all of the following criteria:

- Age ≥18 years
- Type 1 or 2 diabetes mellitus for at least 1 year
- Hemoglobin A1C ≤ 11%
- Diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy, which is due to diabetes, for at least 1 year
- Score of ≥40 mm on the VAS of the SF-MPQ at baseline (V1)
- Completion of at least 4 daily pain diaries at randomization (V2)
- Score of at least 40 mm on the VAS of the SF-MPQ, *and* average daily pain score of ≥4 over the last 7 days (based on the daily pain diary entries) at randomization (V2)
- Normal or stable chest x-ray at/prior to baseline
- Normal ophthalmologic exam (dilated ophthalmoscopy, visual field testing, visual acuity testing) prior to randomization (V2), or explainable abnormality on eye exam
- Women at risk of pregnancy: appropriate contraception and a negative serum pregnancy test (at screening and randomization)

Subjects were to be excluded for:

- Clinically significant or unstable hepatic, respiratory, hematologic, cardiovascular disease
- Creatinine clearance ≤ 30 mL/min (as estimated from the Cockcroft and Gault equation), or <30 mL/min based on a 24-hour urine collection
- Symptomatic peripheral vascular disease
- History of pernicious anemia, untreated hypothyroidism, chronic hepatitis B or C, hepatitis B or C within the past 3 months, or HIV infection
- WBC < 2500/mm3, neutrophil count < 1500/mm^3, platelet count < 100 x 10^3/ mm^3
- Abnormal ECG
- Neurologic disorders unrelated to diabetic neuropathy that may confuse the assessment of neuropathic pain
- Any pain that may confound assessment or self-evaluation of the pain due to diabetic neuropathy
- Skin conditions in the area affected by the neuropathy that could alter sensation
- Amputations other than toes
- Malignancy within the past 2 years, with the exception of basal cell carcinoma
- Failure to respond to previous treatment with gabapentin (Neurontin) at doses ≥1200 mg/day for treatment of pain associated with diabetic neuropathy
- Use of prohibited medications, in the absence of appropriate washout phases
- Serious or unstable psychological conditions, including substance abuse, that would compromise participation in the study

6.7.1.3.3 Study Medications

Study drug was either placebo or pregabalin capsules (75-, 150-, 200-, and 300-mg). Subjects were randomized to placebo, pregabalin 150 mg/day, pregabalin 300 mg/day, or pregabalin 300/600 mg/day. Study medication was to be administered in two divided doses (BID).

All patients randomized to active drug were to begin study drug at 150 mg/day (75 mg bid). Subjects randomized to the 300- and 300/600 mg/day treatment groups were to have their medication progressively increased to the full dose over a 1-week titration period. Patients in the 300/600 mg/day arm and who had a creatinine clearance > 60 mL/min were to receive the maximal dose of 600 mg/day. Those patients in the arm who had a creatinine clearance between 30 and 60 mL/min were to receive 300 mg/day.

Patients unable to attain the target (fixed) dose were to be withdrawn from the study. No dose adjustment was to occur during the 11-week fixed-dose period.

Titration Schedule :

Milligrams (mg) pregabalin, morning evening

Final Target Dose	Day 1*	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
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

* On Day 1 (randomization), patients were to take 1 capsule in the evening only

(Applicant's Table 3, RR 720-30080 1008-149, P. 46)

Permitted Medications:

The following concomitant medications were permitted by the protocol:

- Aspirin (≤ 325 mg/day) for stroke and myocardial infarction prophylaxis
- Antidepressants (as long as the regimen was stable for at least 30 days, and was not started during the study) – for depression and anxiety only
- Acetaminophen, ≤ 4 g daily
- Benzodiazepines (as long as the regimen was stable for at least 30 days, and was not started during the study) for sleep only

Prohibited Medications:

Patients were not to use the following medications during the study (in the absence of a pre-defined washout period):

Class of Medication	Examples [a]	Washout Period
Medications commonly used for relief of neuropathic pain and miscellaneous supplements	Benzodiazepines (if not given at a stable bedtime dose for sleep), skeletal muscle relaxants, capsaicin, α-lipoic acid, local anesthetics, opioids, tramadol, memantine, fatty acid supplements, chromium picolinate, evening primrose oil, or myoinositol	At least 7 days prior to V1
Antiepileptics	Carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, gabapentin	At least 7 days prior to V1
Potential retinotoxins	Vigabatrin, hydroxychloroquine, deferoxamine, thioridazine [b]	Not applicable [b]
Antidepressants	TCAs including amitriptyline, venlafaxine. SSRIs allowable if given at a stable dose > 30 days for anxiety or depression only	At least 7 days prior to V1
Analgesics	NSAIDS (including COX-2 inhibitors), dextromethorphan	At least 1 day prior to V1

[a] Not a comprehensive list

[b] Patients who have ever taken these medications were ineligible for the study

6.7.1.3.4 Study Procedures

Study visits:

Subjects were to be seen at 6 scheduled visits, plus 1 follow-up visit. The first visit (V1) would occur during screening, and the second visit (V2) at the end of the baseline phase. Visit 2 was also to be the day of randomization and initiation of study medication. Thereafter, subjects were to be evaluated 1 week after beginning study drug (V3), and then at weeks 4, 8, and 12 of the study (Visit 4, 5, and 6 respectively). A safety follow-up visit (V7) would occur for subjects not entering the open-label study, Protocol 1008-165.

Screening phase (V1):

Subjects were to undergo physical and neurological exams, edema and visual acuity assessments, laboratory testing, a chest x-ray, and a 12-lead ECG. In addition to meeting the criteria above, eligible subjects needed to be stabilized on their anti-diabetic medication before initiating study drug. The antidiabetic medication was to remain unchanged for the duration of the study.

Baseline phase (V2):

Screened subjects were to undergo a 1-week baseline phase during which they would enter pain and sleep ratings for the previous day into diaries. Entries were to be made each morning upon awakening. Subjects who completed at least 4 daily pain diaries, who had an average daily pain score of ≥ 4 over the previous seven days, and who had a score at least 40 mm on the VAS of the SF-MPQ were to be randomized to study drug.

Patients were to be randomized to placebo, 150, 300, or 300/600 mg/day pregabalin, where the maximal pregabalin dose was dependent on creatinine clearance. Randomization was to be blocked in 2 strata, based on the patient's creatinine clearance: patients with a creatinine clearance of > 30 to 60 mL/min were to be randomized to placebo, 150, or 300 mg/day pregabalin. Patients with a creatinine clearance of > 60 mL/min were to be randomized to placebo, 150, 300, or 600 mg/day pregabalin. Therefore, patients in the 300/600 mg/day treatment group would receive 300 mg/day if their creatinine clearance was between 30 and 60 mL/min, or 600 mg/day if their creatinine clearance was > 60 mL/min.

Randomized subjects were also to complete questionnaires on sleep, quality of life, and general health.

Treatment phase:

Titration (Week 1)

The placebo and pregabalin 150 mg/day treatment groups were to begin at their fixed doses on the evening of randomization (V2). Study medication was to be increased over 1 week for subjects in the pregabalin 300- and 300/600 mg/day treatment groups, as per the titration schedule. Patients unable to attain or maintain the target (fixed) dose were to be withdrawn from the study. Subjects were to be evaluated in the clinic at the end of the 1-week titration period for continued eligibility (V3).

Fixed-Dose (Weeks 2-12)

From the end of the 1-week titration period onward, study medication was to remain at the fixed dose for all subjects. Subjects were to be evaluated at monthly intervals (V4, 5, 6) for pain, sleep, and laboratory changes, as well as any adverse effects. At Week 12 (V6/Termination), subjects were to repeat the assessments of the screening phase. They were also to have the option of entering the open-label extension study (Protocol 1008-165). Subjects who did not enter the extension study were to return for a follow-up visit in another week (V7).

Table 6.7.1.3.4: Time and Events Schedule, Protocol 1008-149

Table 7 Timetable of Study Procedures Evaluations

End of Study Week	Baseline (1 Week)	Double-Blind Treatment (12 Weeks)					FU (1 Week)
		Titration		Fixed dose			
	Screening	Random	1	4	8	12	13
Study Day,	-7	1	8	29	57	85	92
Clinic Visit,[1]	1	2	3	4	5	6 Term[6]	7 FU
Informed Consent	X						
Inclusion Exclusion	X						
Medical History	X						
Physical Exam Incl Peripheral Edema Assessment	X		X[7]	X[7]	X[7]	X	
Abbreviated Neurological and Peripheral Sensory Exam	X					X	
SF-McGill Pain Questionnaire	X	X	X	X	X	X	
Daily Diaries (Pain, Sleep)	X	X	X	X	X	X	
Global Impression of Change (Clinician & Patient)						X	
MOS Sleep Scale		X				X	
SF-36		X				X	
EQ-5D		X	X	X[7]	X	X	
Adverse Events		X	X	X	X	X	X
Prior and Concurrent Medications	X	X	X	X	X	X	X
Prior and Concurrent Neuropathic Pain Medications	X	X	X	X	X	X	X
Study Medication Dosing Dispensing		X	X	X	X		
Clinical Labs							
Hematology Chemistry Urinalysis	X		X	X	X	X[7]	
Pregnancy Test (Serum)	X		X	X	X	X	
12-Lead ECG	X					X	
Ophthalmologic Assessment	X					X	
Patient Status End of Baseline		X					
Patient Status End of Double-Blind Treatment Phase						X	
Chest X-Ray	X						

[1] Telephone contact was 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

[2] Whenever a patient withdrew from or completed the study

[3] V7 Follow-up was only performed for patients not entering open-label Study 1008-165

[4] At V1 or prior to washout of previous analgesics if applicable

[5] Vitals, weight, and edema assessments only

[6] VAS section only

[7] Estimated creatinine clearance was calculated at V1. Fasting lipid profiles were measured at V1 and V6 termination only.

[8] Examination/testing by an ophthalmologist including, peripheral visual screening, best-corrected Snellen visual acuity, and dilated ophthalmoscopy (direct or indirect). See Section 3.2 for removal of formal ophthalmological testing for all sites.

[9] Chest X-ray was taken at baseline visit if none available in the 1 year prior to baseline

(Applicant's Table 7, RR 720-30800, 1008-149, P. 51)

6.7.1.3.5 Efficacy Parameters

The following measures of patient pain and function were to be utilized:

- Daily pain score
- Short Form McGill Pain Questionnaire (SF-MPQ)
- Daily diary of sleep interference
- Medical Outcomes Study – Sleep Scale
- Clinical Global Impression of Change (CGIC)
- Patient Global Impression of Change (PGIC)
- SF-36 Health Survey Questionnaire (SF-36 QOL)
- EuroQol

Pharmacokinetics:
No pharmacokinetic assessments of study drug were to be conducted during this study.

6.7.1.3.6 Statistical Analysis

6.7.1.3.6.1 Patient Population

The *intent-to-treat (ITT)* and the *safety* populations was defined as all randomized subjects (from both the US and International trials) who received at least one dose of study medication. The primary population to be analyzed was the ITT population.

6.7.1.3.6.2 Primary Efficacy Outcome

The primary efficacy parameter was to be the weekly mean pain score based on the pain scores from the daily patient diary. The primary efficacy outcome was to be the *final (endpoint) weekly mean pain score*, defined as the mean of the last available 7 pain diary entries while the patient was on medication.

The primary efficacy analysis was to be performed on the ITT population. The analysis was to compare the endpoint mean pain scores of the 3 treatment groups using ANCOVA, with treatment, cluster, and creatinine clearance stratum as main factors of the model, and the baseline mean pain score as covariate. The comparisons of 300/600 mg pregabalin versus placebo, 300 mg pregabalin versus placebo, and 150 mg pregabalin versus placebo were to be considered primary. Using Hochberg's approach to protect the Type I error rate at the 0.05 level, 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 was <0.05 then all comparisons were to be declared significant at the overall Type I level of 0.05. Otherwise, if the next largest p-value were $<(0.05)/2 = 0.025$, then the remaining 2 comparisons were to be declared significant. Failing that, the final comparison was to be considered significant if the smallest p-value was $<(0.05)/3 = 0.0167$.

6.7.1.3.6.3 Supplemental Analyses of the Primary Efficacy Outcome

a) Responder analysis
   A patient with at least 50% reduction in weekly mean pain score from baseline to endpoint was defined as a "responder." The proportion of responders was to be analyzed for each pregabalin group versus placebo.

b) A comparison was to be made of patients with expected similar plasma concentrations of pregabalin versus patients who received placebo:
   - Patients with a low CLcr (30-60 mL/min) who received pregabalin 150 mg/day were to be pooled with patients with CLcr > 60 mL/min who received pregabalin 300 mg/day to form the *"300 mg/day 'adjusted dose' group."*
   - Patients with a low CLcr who received pregabalin 300 mg/day and patients with a CLcr > 60 ml/min who received pregabalin 600 mg/day were to be pooled to form the *"600 mg/day 'adjusted dose' group."*

The analysis was to compare 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 CLcr > 60 mL/min who received 150 mg/day would not be included in the analysis.

c) The Week 8 endpoint mean pain scores were also to be analyzed using the main ANCOVA model. This endpoint was defined as the mea of the last 7 available diary entries while on study medication by Week 8.

d) A mixed model repeated measures analysis was to be performed using all available weekly mean pain scores (post-baseline) as the response, with site, week, and the baseline score as covariates. If the treatment by time interaction was suggestive, a pair-wise comparison of each pregabalin dose versus placebo was to be performed at each time point.

6.7.1.3.6.4 Secondary Efficacy Outcomes

- SF-MPQ sensory, affective, total, VAS and PPI scores at Visits 3, 4, 5, and 6/Termination
- The mean sleep interference scores were for each week and at endpoint
- CGIC and PGIC at V6/Termination
- Changes in MOS sleep sub-scale scores
- Change in SF-36 Health Survey scores
- The VAS area under the curve (AUC) score and the single index value score were to be calculated from the EuroQol Health State Profile (EQ-5D)

No adjustment was to be made for testing multiple parameters with the secondary and supplemental analyses. However, due to the large number of secondary and supplemental analyses being performed, some significant results were expected to occur by chance alone. Undue consideration would not be given to any particular significant difference; rather, interpretation of the results was to be based on patterns of significant differences.

6.7.1.3.6.5 Interim Analyses

No interim analyses were planned.

6.7.1.3.7 Protocol Amendments

The Applicant identified 3 protocol amendments, and 5 protocol addenda.

Amendment 1
October 31, 2000
At the request of the study investigators during the Investigator's Meeting, a visual exam was added to the procedures of the V6/Termination clinic visit. The visual exam comprised dilated ophthalmoscopy (direct or indirect), best-corrected Snellen visual acuity, and peripheral visual screening.

Various clarifications in the statistical section were also made. Notably, several analyses would include adjustment for creatinine clearance, in addition to cluster.

Amendment 2
March 28, 2001
Since the parallel US study 1008-173, was terminated early due to imposition of a partial clinical hold, Protocol 1008-149 was changed to a stand-alone study, and the statistical section was revised to reflect this.

- The number of subjects to be enrolled at the international sites was changed from 100 to 352 subjects, and the number of participating sites was increased from a maximum of 30 to a maximum of 80.
- The study was to be considered positive if at least 1 of the 3 pregabalin doses was declared to be significantly better than placebo

Other relevant changes to the protocol were as follows:

- Deletion of "failure to respond to previous treatment with gabapentin (Neurontin)" from the exclusion criteria. Under the partial hold, patients who were 'refractory' to other available therapies, including gabapentin, could be enrolled into clinical trials.
- Collection of data on previous medication for neuropathic pain for all patients. Data was to be collected retrospectively, as indicated.

Amendment 3
November 12, 2001

- Consequent to findings of hemangiomas/hemangiosarcomas in preclinical studies, the Australian Ministry of Health and the Ethics Committees of various European countries (MoH/EC) decided to place neuropathic pain trial on partial clinical hold. As a result of this regulatory decision, 11 patients were prematurely discontinued from the study. These patients did not complete 12 weeks of treatment, and therefore could not contribute to the primary efficacy analysis. Therefore, these patients were replaced to reach the desired sample size of 352 subjects.
- The primary population to be analyzed was the *modified intent-to-treat (MITT)*, defined as all randomized patients who took at least one dose of study drug and who were not withdrawn following the MoH/EC decisions.
- Supportive analyses of the primary efficacy parameter were carried out using the ITT and a *per protocol* population (defined as the MITT patients without major protocol violations).
- The Applicant believed that ophthalmologic safety assessments showed no evidence of toxic effects of pregabalin on the retina or optic nerve. Therefore, formal ophthalmologic testing (at baseline and V6/Termination) was eliminated from the protocol.

Addendum A - October 12, 200
The German ethics committee expressed concern regarding the requirement for a baseline chest x-ray. The protocol was changed to reflect that if a patient did not have an x-ray within the previous 1 year, none was needed. If an x-ray was available, it had to be normal. The addendum applied to only the German study sites.

Addendum B - December 18, 2000
In response to a request from the Hungarian ethics committee, a gamma-glutamyl-transferease (GGT) test was added to all study visits for all Hungarian study sites.

Three additional addenda were made to the protocol, but were not implemented prior to study completion:
Addendum C -August 22, 2001
Addition of nerve conduction studies at baseline and V6/Termination.
Addendum D - October 19, 2001
Addition of the Neuropathic-Specific Quality of Life Questionnaire (NeuroQol) at one British study site, #455.
Addendum E - January 25, 2002
Addition of measurements of vascular endothelial cell growth factor (VEGF), platelet derived growth factor (PDGF), and basic fibroblast growth factor (bFGF) at selected sites.

6.7.2 Study Results

6.7.2.1 Study Conduct/Outcome

6.7.2.1.1 Subject Characteristics

The study was conducted between November 30, 2000 and May 23, 2003. A total of 58 centers in Europe, Australia, and South Africa participated in the study.

6.7.2.1.2 Enrollment by Center

Of the 384 patients in the MITT population, 162 (42%) came from 14 sites in Poland. Patients from Australia and Germany comprised 18% and 17% of the population, respectively.

Table 6.7.2.1.2: Enrollment by Center, Protocol 1008-149

Total No. of patients	Country	Sites
21	UK	396, 430, 451, 456, 490
32	South Africa	386, 387, 388, 389, 390, 391
34	Hungary	371, 372, 373, 374, 375
66	Germany	360, 361, 362, 363, 365, 366, 368, 369, 405. 406, 408, 409, 460, 463, 464, 466, 470, 471
69	Australia	350, 353, 354, 355, 356, 357, 400, 401
162	Poland	378, 379, 381, 382, 383, 415, 416, 417, 418, 419, 480, 483, 484

6.7.2.1.3 Protocol Violations

The Applicant identified 35 patients in the MITT population who had protocol violations that could potentially impact the primary efficacy outcome. Six patients were randomized to placebo (n = 93), 9 patients to pregabalin 150 mg/day (n = 97), 7 patients

to pregabalin 300 mg day (n = 96), and 13 patients to pregabalin 300/600 mg/day (n = 98). Violations were reported at 21 of the 56 sites, with 1 to 5 violations reported per site. The specific types of protocol violations are detailed in Table 6.7.2.1.4.a below:

Table 6.7.2.1.4.a: Protocol violations, Protocol 1008-149

Violation	Total N	Pregabalin 150 mg/day	Pregabalin 300 mg/day	Pregabalin 300/600 mg/day	Placebo
Incorrect diagnosis	7	1	1	3	2
Diabetic neuropathic pain < 1 yr	3	1	1	-	1
< 4 baseline diary scores	1	-	-	-	1
Baseline mean pain score < 4	10	4	1	4	1
Baseline SF-MPQ VAS < 40 mm	2	-	1	1	-
Prohibited medication	8	2	2	3	1
Study medication noncompliance	3	-	1	2	-
Hemoglobin A1c > 11% (11.5%)	1	1	-	-	-
Total	35	9	7	13	6

(Source: Section 9.3.2, RR 720-30800, 1008-149, P. 400)

The protocol violations that would potentially impact the primary efficacy outcome were from the following subjects:

- Patients who at baseline had a pain score < 4 (n = 10), or a VAS score < 40 mm (n = 2): if a small improvement in pain occurred with therapy, it would be difficult to detect

  Pain score < 4
  - Patient 356022 (pregabalin 300/600)
  - Patient 379009 (pregabalin 150)
  - Patient 400002 (pregabalin 150)
  - Patient 406013 (pregabalin 300)
  - Patient 408002 (placebo)
  - Patient 416002 (pregabalin 300/600)
  - Patient 417003 (pregabalin 150)
  - Patient 417004 (pregabalin 300/600)
  - Patient 456002 (pregabalin 150)
  - Patient 480005 (pregabalin 300/600)

  VAS < 40
  - Patient 379011 (pregabalin 300/600)
  - Patient 408006 (pregabalin 300)

- Patients who used prohibited medications during the study that might themselves improve pain (n = 8)
  - Patient 361003 (placebo)
  - Patient 388004 (pregabalin 300/600)
  - Patient 396005 (pregabalin 300/600)
  - Patient 406003 (pregabalin 150)
  - Patient 406005 (pregabalin 300/600)
  - Patient 406010 (pregabalin 300)
  - Patient 430001 (pregabalin 300)
  - Patient 430005 (pregabalin 150)
- Subjects who were non-compliant with their assigned study drug (n = 3)
  - Patient 430002 (pregabalin 300/600)
  - Patient 356007 (pregabalin 300/600)
  - Patient 365001 (pregabalin 300)

The Applicant also identified 9 subjects who had "eligibility exceptions" related to the study's entry criteria (see Table 6.7.2.1.4.b). Although these subjects did not strictly

meet certain entry criteria, they were considered sufficiently eligible for participation based on other documented evidence. In addition to these 9 subjects, I found 2 other subjects who apparently were "eligibility exceptions." However, reasons for their admission into the study were not provided.

Table 6.7.2.1.4.b: Eligibility exceptions – Protocol 131

Entry criterion not met	Patient ID	Rx Group	Reason for admission
Normal/stable chest x-ray within the last 12 months (1 year)	354002	PGB 300/600	Patient had a normal chest x-ray 13 months prior to V1
Diagnosis of distal, painful, symmetrical polyneuropathy	354008	PGB 150	Symmetrical pain was supported by EMG dates
	354019	PGB 300/600	Only electrophysiological evidence of symmetrical polyneuropathy
	354020	PGB 300/600	Only electrophysiological evidence of symmetrical polyneuropathy
	354021	Placebo	Only electrophysiological evidence of symmetrical polyneuropathy
Diabetic polyneuropathy with decreased or absent ankle reflexes	396002	PGB 300	Patient had normal reflexes, but had symmetrical pain and supporting EMG/NCV data
Missing neutrophil count at V1	418014	PGB 300	"Neutrophils should have been normal"
Platelet count < 100 x $10^3/mm^3$	419006	PGB 300/600	Patient had a known history of thrombocytopenia (of unknown etiology)
Ophthalmologic exam must be done prior to V2/randomization	456001	Placebo	A partial ophthalmologic exam was done. The patient was "randomized on advice."
Not stated	356011	PGB 300	Not stated
	369001	PGB 300	Not stated

(Source: Section 9.3.4, RR 720-30800, 1008-149, P. 416)

While the use of prohibited pain medication would tend to bias the study in favor of the affected arm, the lack of stable dose during the fixed-dose phase might be expected to bias the study against the affected arm. The overall effect of this pattern of violations is not expected to have a significant impact on the interpretation of the results.

6.7.2.1.4 Blinding

The Applicant states that the study blind was broken for Patient 388011 who was randomized to pregabalin 150 mg/day. This patient completed Protocol 1008-149 and had entered into the open-label extension study, Protocol 1008-165. The patient reportedly had visual field deterioration at the end of Protocol 1008-149, and treatment was stopped temporarily while the patient was in the extension study. After the visual field returned to normal, the patient continued treatment in the extension trial.

6.7.2.1.5 Subject Disposition

The disposition of the enrolled patients is detailed in Table 6.7.2.1.6 below. A total of 512 patients were screened, and 116 were removed during the baseline phase. Subjects were removed due to not meeting inclusion criteria (n=74), experiencing an adverse event (n = 2), and other/administrative reasons (n = 40).

Of the 396 patients who were randomized to treatment, 395 received at least one dose of study medication (ITT population). The one patient who did not take study drug was Patient 355002 who was randomized to placebo. This patient apparently was dispensed study medication, but had not taken any when he was later found to not have met study criteria. Ninety-six patients received placebo, 99 patients received pregabalin 150 mg/day, 99 patients received pregabalin 300 mg/day, and 101 patients received pregabalin 300 or 600 mg/day, depending on their creatinine clearance. In the pregabalin 300/600 mg/day group, there were 13 subjects with a CLcr < 60 mL min, therefore 85 subjects received 600 mg/day.

Of the 395 patients in the ITT population, 77 (20%) were withdrawn from the study. Seventeen patients (17%) were withdrawn from the pregabalin 150 mg/day group, 20 patients (20%) from the pregabalin 300 mg/day group, 23 patients (23%) from the pregabalin 300/600 mg/day group, and 17 patients (18%) from the placebo group. Reasons for withdrawal were as follows: adverse effects (n = 32; 8%), lack of efficacy (n = 27; 7%), EC/MoH's regulatory decision (n = 11; 3%), lack of compliance (n = 1; 0.3%), and other/administrative reasons (n = 6; 2%). Adverse events most frequently led to withdrawal from the pregabalin 300 mg/day and 300/600 mg/day groups [11 (11%) and 13 (13%), respectively]. The most frequent cause of withdrawal from the placebo and pregabalin 150 mg/day groups was lack of efficacy [11 (12%) and 8 (8%), respectively]. A total of 330 patients (83.5%) entered the open-label extension study, Protocol 1008-165.

As noted above, 11 patients were removed from the study due to regulatory decisions of the MoH/EC. Consequently, there were 384 subjects in the MITT population: 98 in the 300/600 mg/day pregabalin group, 96 patients in the 300 mg/day pregabalin group, 97 patients in the 150 mg/day pregabalin group, and 93 patients in the placebo group.

Table 6.7.2.1.6: Subject Disposition, Protocol 1008-149

	Placebo	Pregabalin (mg/day), N (%)			All Patients
	N (%)	150	300	300/600	N (%)
Entered baseline					512
Withdrawn during baseline [a]					116 (22.7)
Did not meet entry criteria					74 (14.5)
Adverse event [b]					2 (0.4)
Other/Administrative [b]					40 (7.8)
Entered double-blind (randomized) phase	97	99	99	101	396
Intent-to-treat population	96	99	99	101	395
Withdrawn during the Treatment phase	17 (17.7)	17 (17.2)	20 (20 2)	23 (22.8)	77 (19.5)
Lack of compliance	0 (0.00)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Lack of efficacy	11 (11.5)	8 (8.1)	5 (5.1)	3(3.0)	27 (6.8)
Adverse event [c]	3 (3.1)	5 (5.1)	11 (11.1)	13 (12.9)	32 (8.1)
Withdrawn after MoH/EC decision	3 (3.1)	2 (2.0)	3 (3.0)	3(3.0)	11 (2.8)
Other/Administrative [d]	0 (0.0)	2 (2.0)	1 (1.0)	3 (3.0)	6 (1.5)
Completed the study	79 (82.3)	82 (82.8)	79 (79.8)	78 (77.2)	318 (80.5)
Entered open-label study	85 (88.5)	85 (85.9)	78 (78.8)	82 (81.2)	330 (83.5)

MoH = Ministry of Health; EC = Ethics Committee

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

b Information regarding specific reasons for withdrawal during the baseline phase were not provided

c Adverse events included dizziness, vertigo, peripheral edema, face edema, somnolence, paresthesia, abnormal thinking, and incoordination,

d Other included hospitalization for non-treatment related reason (2), withdrawal of consent (4)

(Applicant's Table 9, RR 720-30080, 1008-149, P. 69)

6.7.2.1.6 Extent of Exposure/Dosing Information

The table below shows the exposure duration across treatment groups. Drug exposure was similar across the groups, over the duration of the study.

Table 6.7.2.1.7: Patient Drug Exposure, ITT Population – Protocol 149

Total Exposure Time, N(%)	Placebo (N = 96)		Pregabalin 150 mg/day (N = 99)		Pregabalin 300 mg/day (N = 99)		Pregabalin 300/600 mg/day (N = 101)		Pregabalin Any (N = 299)	
Greater or Equal to										
1 Day	96	(100)	99 (100)		99 (100)		101	(100)	299	(100)
1 Week	95	(99.0)	98 (99.0)		96 (97.0)		101	(100)	295	(98.7)
2 Weeks	94	(97.9)	97 (98.0)		95 (96.0)		95	(94.1)	287	(96.0)
3 Weeks	94	(97.9)	97 (98.0)		95 (96.0)		94	(93.1)	286	(95 7)
4 Weeks	91	(94.8)	97 (98.0)		90 (90.9)		92	(91.1)	279	(93.3)
5 Weeks	89	(92.7)	91 (91.9)		88 (88 9)		89	(88.1)	268	(89.6)
6 Weeks	87	(90.6)	90 (90.9)		86 (86.9)		87	(86.1)	263	(88.0)
7 Weeks	84	(87.5)	87 (87.9)		85 (85.9)		84	(83 2)	256	(85.6)
8 Weeks	83	(86.5)	86 (86.9)		85 (85.9)		82	(81.2)	253	(84.6)
9 Weeks	80	(83.3)	83 (83.8)		80 (80.8)		81	(80.2)	244	(81.6)
10 Weeks	79	(82.3)	82 (82.8)		79 (79.8)		79	(78.2)	240	(80.3)
11 Weeks	77	(80.2)	79 (79.8)		77 (77.8)		77	(76.2)	233	(77.9)
12 Weeks	66	(68.8)	66 (66.7)		69 (69.7)		61	(60.4)	196	(65.6)

[a] Zero dose days during study are summarized as pregabalin days.
(Applicant's Table 54, RR 720-30800, 1008-149, P. 139)

6.7.2.1.7 Demographics

The tables below illustrate the demographic and baseline characteristics of the ITT and MITT populations. Patient characteristics of the MITT population were similar to the patient characteristics of the ITT population.

With respect to the MITT population, most patients were male (54.7%) and Caucasian (96.1%). The mean age was 58.6 (± 11.6) years, with a range of 21 to 85 years. The median age was similar across treatment groups (59-60 years). The median estimated creatinine clearance (CLcr) was 92 mL/min. The pregabalin 150 mg/day had the largest CLcr (95 mL/min), and the pregabalin 300 and 300/600 mg/day groups had the lowest Clcr (90.5 mL/min). The proportion of subjects with a normal CLcr (> 60 mL/min) in each treatment group was as follows: 87% of the placebo group, 88% of the pregabalin 150 mg/day group, 90% of the pregabalin 300 mg/day group, and 87% of the pregabalin 300/600 mg/day group.

Table 6.7.2.1.8.a: Patient Characteristics, ITT, Protocol 1008-149

Table 10. Summary of Patient Characteristics: ITT

		Placebo N = 96	Pregabalin 150 mg day N = 99	Pregabalin 300 mg day N = 99	Pregabalin 300/600 mg day N = 101	Pregabalin Any N = 299	All Patients N = 395
Gender							
Male	n (%)	51 (53.1)	54 (54.5)	53 (53.5)	61 (60.4)	168 (56.2)	219 (55.4)
Female	n (%)	45 (46.9)	45 (45.5)	46 (46.5)	40 (39.6)	131 (43.8)	176 (44.6)
Premenopausal	n (%)	3 (6.7)	4 (8.9)	6 (13.0)	6 (15.0)	16 (12.2)	19 (10.8)
Postmenopausal	n (%)	42 (93.3)	41 (91.1)	40 (87.0)	34 (85.0)	115 (87.8)	157 (89.2)
Race							
White	n (%)	95 (99.0)	95 (96.0)	95 (96.0)	95 (94.1)	285 (95.3)	380 (96.2)
Black	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (0.7)	2 (0.5)
Asian or Pacific Islander	n (%)	0 (0.0)	2 (2.0)	2 (2.0)	3 (3.0)	7 (2.3)	7 (1.8)
Other	n (%)	1 (1.0)	2 (2.0)	2 (2.0)	1 (1.0)	5 (1.7)	6 (1.5)
Age (Years)	n	96	99	99	101	299	395
	Mean	58.93	58.51	57.28	59.70	58.51	58.61
	(SD)	11.670	12.435	10.504	11.302	11.444	11.486
	Median	59.5	59	59	61	59	59
	Min, Max	26, 81	23, 85	25, 78	21, 83	21, 85	21, 85
Age Categories							
18 to 64 Years	n (%)	63 (65.6)	68 (68.7)	73 (73.7)	71 (70.3)	212 (70.9)	275 (69.6)
≥65	n (%)	33 (34.4)	31 (31.3)	26 (26.3)	30 (29.7)	87 (29.1)	120 (30.4)
Weight (kg)	n	96	99	99	101	299	395
	Mean	82.96	85.44	87.66	86.83	86.65	85.75
	(SD)	12.898	15.365	16.654	15.658	15.873	15.271
	Median	82	85	87	86	85.8	85
	Min, Max	58, 125	54, 127.5	55.8, 131.7	55, 148.6	54, 148.6	54, 148.6
Height (cm)	n	96	99	99	101	299	395
	Mean	169.73	169.66	169.39	169.83	169.63	169.65
	(SD)	8.648	9.889	10.287	9.316	9.804	9.526
	Median	168.75	170	169	171	170	170
	Min, Max	150, 190	152, 194	149, 196	148, 190	148, 196	148, 196
Estimated Baseline CLcr (mL/mm)	n	96	99	99	101	299	395
	Mean	91.72	95.34	95.07	91.75	94.04	93.48
	(SD)	27.132	31.592	28.941	28.438	29.627	29.023
	Median	91	95	92	91	93	92
	Min, Max	[redacted]					
CLcr Status							
Normal (>60mL/mm)	n (%)	84 (87.5)	87 (87.9)	89 (89.9)	88 (87.1)	264 (88.3)	348 (88.1)
Low (30-60 mL/mm)	n (%)	12 (12.5)	12 (12.1)	10 (10.1)	13 (12.9)	35 (11.7)	47 (11.9)

Table 6.7.2.1.8.b: Baseline Estimated Creatinine Clearance, ITT, Protocol 1008-149

Table 11 Summary of Baseline Estimated Creatinine Clearance by Creatinine Clearance Strata, Intent-to-Treat Population

Estimated Creatinine Clearance at Baseline (ml/min)	Placebo (N=96)		Pregabalin 150 mg/day (N=99)		Pregabalin 300 mg/day (N=99)		Pregabalin 600 mg/day (N=103)	
	Low	Normal	Low	Normal	Low	Normal	Low	Normal
N	12	84	12	87	10	89	15	88
Mean (SD)	48.3 (7.3)	97.9 (22.9)	48.8 (12.1)	102.4 (27.8)	51.4 (5.2)	100.1 (26.2)	50.4 (8.8)	97.9 (25)
Median	48	91.5	55	98	52.5	97	53	96
Range	[redacted]							

Creatinine clearance (Cl cr) Stratum is Normal for patients with Cl cr more than 60 ml/min and is Low for patients with Cl cr 60 ml/min

(Applicant's Tables 10 and 11, RR 720-30800, 1008-149, P. 71- 72)

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Table 6.7.2.1.8.c: Patient Characteristics, MITT, Protocol 1008-149

Table 12. Summary of Patient Characteristics: MITT

		Placebo	Pregabalin				All Patients
		N 93	150 mg/day N 97	300 mg day N 96	300-600 mg day N 98	Any N = 291	N 384
Gender							
Male	n (%)	48 (51.6)	53 (54.6)	51 (53.1)	58 (59.2)	162 (55.7)	210 (54.7)
Female	n (%)	45 (48.4)	44 (45.4)	45 (46.9)	40 (40.8)	129 (44.3)	174 (45.3)
Premenopausal	n (%)	3 (6.7)	4 (9.1)	6 (13.3)	6 (15.0)	16 (12.4)	19 (10.9)
Postmenopausal	n (%)	42 (93.3)	40 (90.9)	39 (86.7)	34 (85.0)	113 (87.6)	155 (89.1)
Race							
White	n (%)	92 (98.9)	93 (95.9)	92 (95.8)	92 (93.9)	277 (95.2)	369 (96.1)
Black	n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (0.7)	2 (0.5)
Asian or Pacific Islander	n (%)	0 (0.0)	2 (2.1)	2 (2.1)	3 (3.1)	7 (2.4)	7 (1.8)
Other	n (%)	1 (1.1)	2 (2.1)	2 (2.1)	1 (1.0)	5 (1.7)	6 (1.6)
Age (Years)	n	93	97	96	98	291	384
	Mean	58.84	58.54	57.56	59.49	58.54	58.61
	(SD)	11.785	12.554	10.519	11.389	11.508	11.561
	Median	60	59	59	60	59	59.5
	Min, Max	26, 84	23, 85	25, 78	21, 83	21, 85	21, 85
Age Categories							
18 to 64 years	n (%)	61 (65.6)	66 (68.0)	70 (72.9)	70 (71.4)	206 (70.8)	267 (69.5)
≥65	n (%)	32 (34.4)	31 (32.0)	26 (27.1)	28 (28.6)	85 (29.2)	117 (30.5)
Weight (kg)	n	93	97	96	98	291	384
	Mean	82.65	85.48	87.13	86.48	86.36	85.46
	(SD)	12.976	15.336	16.006	15.447	15.558	15.042
	Median	81.5	85	86.75	86	85.5	85
	Min, Max	58, 125	54, 127.5	55.8, 130	55, 148.6	54, 148.6	54, 148.6
Height (cm)	n	93	97	96	98	291	384
	Mean	169.46	169.66	169.41	169.69	169.59	169.56
	(SD)	8.577	9.944	10.365	9.412	9.878	9.568
	Median	168	170	169.5	170.75	170	170
	Min, Max	150, 190	152, 194	149, 196	148, 190	148, 196	148, 196
Estimated Baseline CLcr (mL/mm)	n	93	97	96	98	291	384
	Mean	91.48	95.34	93.91	91.84	93.69	93.15
	(SD)	27.466	31.807	28.337	28.748	29.605	29.081
	Median	91	95	90.5	90.5	92	92
	Min, Max	[redacted]					
CLcr Status							
Normal (>60mL/mm)	n (%)	81 (87.1)	85 (87.6)	86 (89.6)	85 (86.7)	256 (88.0)	337 (87.8)
Low (30-60 mL/mm)	n (%)	12 (12.9)	12 (12.4)	10 (10.4)	13 (13.3)	35 (12.0)	47 (12.2)

Table 6.7.2.1.8.a: Baseline Estimated Creatinine Clearance, MITT, Protocol 1008-149

Table 13. Summary of Baseline Estimated Creatinine Clearance by Creatinine Clearance Strata: Modified Intent-to-Treat Population

Estimated Creatinine Clearance at Baseline (mL/min)	Placebo (N = 93)		Pregabalin 150 mg/day (N = 97)		Pregabalin 300 mg/day (N = 96)		Pregabalin 300/600 mg/day (N = 98)	
	Low	Normal	Low	Normal	Low	Normal	Low	Normal
Baseline								
N	12	81	12	85	10	86	13	85
Mean (SD)	48.3 (7.3)	97.9 (23.2)	48.8 (12.1)	102 (28)	51.4 (8.7)	98.8 (25.5)	50.4 (8.8)	98.2 (25.2)
Median	48	94	55	98	52.5	94.5	53	96
Range	[							]

Creatinine clearance (CLCr) Stratum is Normal for patients with CLCr more than 60 mL/min and is Low for patients with CLCr less or equal to 60 mL/min.

(Applicant's Tables 12 and 13, RR-720-30080, 1008-149, P. 74-75)

Diabetes and Neuropathic Pain History

The majority of subjects (85%) in the MITT population had Type 2 diabetes. The proportion of subjects with Type 2 diabetes was similar across treatment groups. The mean duration of diabetes in was also similar across treatment groups (13 years). Subjects had been diagnosed with diabetic neuropathy for an average of 4 years. The distribution of neuropathic pain was similar across the groups. The baseline mean pain score was slightly higher in the pregabalin 300/600 mg/day group (6.6, ± 1.4) compared to the scores of the pregabalin 150 and 300 mg/day groups and the placebo group (6.2, 6.4, and 6.4 respectively)

Two hundred and seventy-four (71%) of the patients reported prior (within 30 days) and/or concurrent use of insulin. More subjects in the pregabalin 150 mg/day group used insulin (74.2%) than subjects in the pregabalin 300 and 300/600 groups, and the placebo groups respectively (70.8%, 71.4%, and 68.8%, respectively). There were 237 subjects (62%) who reported prior (within 30 days) and/or concurrent use of an oral antidiabetic medication. More subjects in the pregabalin 300/600 mg/day group used an oral antidiabetic drug (64.3%) than subjects in the pregabalin 150 and 300 groups, and the placebo groups respectively (58.8%, 62.5%, and 61.3%, respectively).

Other health characteristics

a) *Peripheral Edema Risk Factors*

Patients were assessed for their medical history relevant to peripheral edema. Sixty-eight percent of patients had high blood pressure, 50% of the patients had high cholesterol or high triglycerides, 32% had swelling of the feet, ankles, or legs, and 32% had used diuretics in the past 6 months. Other risk factors such as glomerulonephritis or other kidney disease were noted for up to 14% of the patients; thyroid disorder and congestive heart failure were present for up to 12% of the

patients; and cirrhosis, hepatitis, or other liver diseases were noted for 3% of the patients. Most risk factors assessed were evenly distributed across the treatment groups with the exception of congestive heart failure, which was higher in the 300 and 300/600 mg/day pregabalin treatment groups. Patients with a medical history of cardiac disease were classified according to the NYHA system. There were no patients in the MITT population with Class III or IV cardiac disease.

b) Prior Neuropathic Pain Medications

(1) Tricyclic antidepressants (TCAs)

Forty (10%) of the patients in the MITT population reported prior (within 30 days) and/or concurrent use of TCAs. Amytriptyline was most commonly used in each of the treatment groups. More subjects in the placebo and pregabalin 300 mg/day groups used TCAs (11.8 and 11.4%, respectively) than subjects in the pregabalin 150 and 300/600 mg/day groups (10.3 and 8.1%, respectively)

(2) Anticonvulsants

Seventy (18%) of the MITT patients reported prior and/or concurrent use of anticonvulsants. Carbamazepine was most commonly used. More subjects in the pregabalin 300 mg/day group used an anticonvulsant (21.9%) compared to the pregabalin 150 and 300/600 mg/day groups and the placebo group (17.5%, 15.3%, and 19.4% respectively).

(3) Opiates

There were 44 patients (11%) who reported recent or concurrent use of an opiate. Use of opiate medications was higher in the pregabalin 300 mg/day group (14.6%) than in the pregabalin 150 and 300/600 mg/day groups and the placebo group (8.2, 12.2, and 10.8 % respectively).

(4) Other medications, including NSAIDs

A total of 152 subjects recently or concurrently used another pain medication such as an NSAID. Paracetamol (acetaminophen) was most commonly used. Again, more subjects in the pregabalin 300 mg/day group used another type of pain medication (42.7%) compared to the pregabalin 150 and 300/600 mg/day groups and the placebo group (39.2, 36.7, and 39.8 % respectively).

6.7.3 Efficacy Results

As centers with < 20 MITT patients were expected and could decrease the power for the treatment-by-center interaction, clustering of centers was performed. A cluster was defined as a single center of at least 20 MITT patients, or an aggregation of centers located in the same region. For logistic regression, patients were pooled into large clusters called 'countries.'

Table 8. Study Centers Grouped for Analysis

Clusters	Sites	Total Number of Patients	Country (for Information)	Country Variable (for Logistic Regression)
1	355, 356	20	Australia	1
2	354	27	Australia	1
3	350, 353, 357, 400, 401	22	Australia	1
4	386, 387, 388, 389, 390, 391	32	South Africa	2
5	396, 430, 451, 456, 490	21	UK	2
6	366, 408, 409, 460, 464, 470	20	Germany	3
7	360, 363, 369, 405, 406, 471	24	Germany	3
8	361, 362, 365, 368, 463, 466	22	Germany	3
9	371, 372, 373, 374, 375	34	Hungary	4
10	382, 416, 417, 419	26	Poland	5
11	415, 484	24	Poland	5
12	379, 483	21	Poland	5
13	378, 383, 480	37	Poland	6
14	418	33	Poland	6
15	381, 482	21	Poland	6

(Applicant's Table 8, RR 720-30080, 1008-149, P. 62)

6.7.3.1 Applicant's Primary Efficacy Analysis

6.7.3.1.1 Overview

Under the proposed statistical analysis plan, Protocol 1008-149 would be considered positive if any of the active treatment groups (pregabalin 150, 300, or 300/600 mg/day) showed a significantly better result compared to placebo with respect to the primary efficacy outcome (see Section 6.7.2.1.1, Amendment 2).

The Applicant's analyses showed that compared to the placebo group, the pregabalin 300/600 mg BID treatment arm showed a statistically significant improvement with respect to the primary efficacy outcome, the endpoint mean pain score. The Applicant's analysis using the ITT and Per Protocol populations yielded similar results to those of the MITT population.

The Applicant's analyses also showed that the weekly mean pain scores of the 300/600 mg/day pregabalin group were statistically different from placebo from Weeks 2 through 12, and that there were more 'responders' in this pregabalin group compared to the placebo group. Additionally, there was a statistically significant difference in the comparison of endpoint mean pain scores based on plasma concentrations, favoring the adjusted 600 mg/day pregabalin over placebo. Finally, the 300/600 mg/day pregabalin group was statistically better than placebo with respect to the majority of the secondary efficacy measures.

6.7.3.1.2 Primary Efficacy Outcome: Mean Pain Score at Endpoint

The tables below show that there was a statistically significant difference in the endpoint mean pain score for the pregabalin 300/600 mg/day group [3.7 (± 2.2)] compared to the

placebo group [4.4 (± 2.3)] (p = 0.0054). The other active treatment groups were not significantly better than placebo.

Table 6.7.3.1.2.a: Endpoint Mean Pain Scores: Descriptive Statistics, MITT -Protocol 149

Time Point	Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 300/600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline	93	6.4 (1.5)	97	6.2 (1.4)	96	6.4 (1.3)	98	6.6 (1.5)
Endpoint	93	4.5 (2.3)	96	4.1 (2.3)	96	4.4 (2.2)	98	3.7 (2.2)
Change	93	-1.9 (2.1)	96	-2.1 (2.4)	96	-2.1 (2.1)	98	-3.0 (2.4)

(Adapted from Applicant's Table 18, RR 720-30080, 1008-149, P. 84)

Table 6.7.3.1.2.b: Endpoint Mean Pain Scores: ANCOVA, MITT - Protocol 149

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug – Placebo) Difference	95% CI	p-value
Placebo	93	4.66	0.26			
Pregabalin 150	96	4.33	0.26	-0.33	(-0.94, 0.28)	0.5580
Pregabalin 300	96	4.48	0.26	-0.18	(-0.79, 0.43)	0.5580
Pregabalin 300/600	98	3.69	0.25	-0.97	(-1.58, -0.36)	0.0054

(Adapted from Applicant's Table 17, RR 720-30080, 1008-149, P. 83)

6.7.3.2 Supplemental Analyses of the Primary Efficacy Variable

a) Mean Pain Scores at Endpoint: ITT population.

There were 395 subjects in the ITT population: 96 in the placebo group, 99 in the pregabalin 150 mg/day group, 99 in the pregabalin 300 mg/day group, and 101 in the pregabalin 300/600 mg/day group. The endpoint mean pain score for the pregabalin 300/600 mg/day group [3.7 (± 2.2)] was statistically better compared to the placebo group [4.5 (± 2.3)] (p = 0.0093). The other active treatment groups were not significantly better than placebo.

b) Mean Pain Scores at Endpoint: Per Protocol population

There were 349 subjects in the Per Protocol population: 87 in the placebo group, 88 in the pregabalin 150 mg/day group, 89 in the pregabalin 300 mg/day group, and 85 in the pregabalin 300/600 mg/day group. [NOTE: The Applicant incorrectly identified only 87 subjects in the pregabalin 150 mg/day group.] The endpoint mean pain score for the pregabalin 300/600 mg/day group [3.7 (± 2.2)] was statistically better compared to the placebo group [4.5 (± 2.3)] (p = 0.0060). The other active treatment groups were not significantly better than placebo.

c) Responder analysis

Patients with a ≥ 50% decrease in mean pain score from baseline to endpoint were considered to be responders. The percent of responders in the MITT population was 46% in the 300/600 mg/day pregabalin group, 33% in the 300 mg/day pregabalin group, and 34% in the 150 mg/day pregabalin group, compared with 30% in the placebo group. There was a statistically significantly greater proportion of responders

for the 300/600 mg/day pregabalin group when compared with the placebo group (p = 0.036).

d) Comparison of patients with expected similar plasma concentrations of pregabalin versus patients who received placebo

Patients with a low CLcr (30-60 mL/min) who received pregabalin 150 mg/day were pooled with patients with CLcr > 60 mL/min who received pregabalin 300 mg/day to form the *"300 mg/day 'adjusted dose' group."* Similarly, patients with a low CLcr who received pregabalin 300 mg/day and patients with a CLcr > 60 ml/min who received pregabalin 600 mg/day were pooled to form the *"600 mg/day 'adjusted dose' group."* The analysis compared the endpoint mean pain scores of the 2 adjusted dose groups with those of the placebo group. Patients with CLcr > 60 mL/min who received 150 mg/day were not included.

A statistically significant difference was seen in the comparison of the endpoint mean pain scores based on expected plasma concentrations for the adjusted 600 mg/day group [3.8 (± 2.2)] compared to placebo [4.5 (± 2.3)] (p = 0.0060). The adjusted 300 mg/day group did not show a significant difference.

e) Week 8 mean pain scores

A statistically significant difference was seen in the comparison of Week 8 endpoint mean pain scores, favoring the 300/600 mg/day pregabalin treatment group over placebo (p = 0.0015). The 300/600 mg/day pregabalin treatment group showed greater improvements in mean pain scores for baseline to endpoint and baseline to Week 8 endpoint than the placebo treatment group.

f) Weekly mean pain scores

Repeated measures analysis was performed using all available weekly mean pain scores (post-baseline) as the response. A pair-wise comparison of each pregabalin dose versus placebo was performed at each time point. The 300/600 mg/day pregabalin treatment group was statistically significantly different from placebo starting at Week 2 and the difference was maintained through Week 12.

6.7.3.3 Applicant's Secondary Efficacy Analysis

SF-MPQ sensory, affective, total, VAS and PPI scores:

There was a statistically greater change from baseline to study endpoint with respect to the VAS score for the 300/600 mg/day pregabalin group compared to the placebo group.

Table 6.7.3.3.a: Endpoint SF-MPQ VAS: Descriptive statistics, MITT, Protocol 1008-149

Time Point	Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 300/600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Endpoint	93	46.7 (25.5)	96	40.7 (24.4)	95	45.3 (22.6)	98	34.9 (22.7)

(From Appendix E.2.10, RR 720-30080, 1008-149, P. 1737)

Table 6.7.3.3.b: Endpoint SF-MPQ VAS: ANCOVA, MITT, Protocol 1008-149

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug – Placebo) Difference	95% CI	p-value*
Placebo	93	46.91	2.79			
Pregabalin 150	96	40.59	2.78	-6.32	(-12.95, 0.32)	0.1238
Pregabalin 300	95	45.35	2.81	-0.55	(-8.20, 5.09)	0.6458
Pregabalin 300/600	98	34.36	2.72	-12.55	(-19.16, -5.94)	0.0006

* Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo
(Adapted from Applicant's Table 33, RR 720-30080, 1008-149, P. 103)

Analysis of the SF-MPQ VAS scores at Weeks 1, 4, and 8 showed a statistically significant difference from placebo for the 300/600 mg/day pregabalin group. The pregabalin 300 mg/day group showed a significant difference at Week 1 only placebo.

A statistically significant decrease was seen for the endpoint PPI when all pregabalin treatment groups were compared to placebo. A comparison of the PPI scores at Weeks 1, 4, and 8 was also significantly different from placebo with respect to the 300/600 mg/day pregabalin group.

The SF-MPQ sensory, affective, and total scores at endpoint were analyzed only for English-speaking patients (n = not stated). Comparisons favored the 300/600 mg/day pregabalin treatment group over placebo for these endpoint SF-MPQ scores (p = 0.008 and 0.013, respectively). With respect to the weekly SF-MPQ sensory, affective, and total scores, there were statistically significant differences from placebo for the 300/600 and 300 mg/day pregabalin treatment groups at Week 1 only.

Mean sleep interference scores
The mean sleep interference scores for the 300/600 mg/day pregabalin group was significantly different from placebo from Week 1 through Week 12. Neither of the other pregabalin treatment groups was statistically different from the placebo group.

Clinical and Patient Global Impression of Change
The results were very similar for the two types of ratings. More than 50% of subjects and investigators provided ratings of "very much" and "much" improvement for the pregabalin 300/600 mg/day compared to the placebo group (33% and 34% of subjects and investigators, respectively). The differences in these ratings reached statistical significance.

Medical Outcomes Study – Sleep Scale Scores
The optimal sleep subscale was analyzed using logistic regression. The other subscales and the overall sleep index were analyzed using ANCOVA. No significant difference from placebo was seen for any pregabalin treatment group for the optimal sleep subscale. However, all 3 pregabalin treatment groups had a more favorable mean score for sleep disturbance, quantity of sleep, and overall sleep problem index when compared with placebo. In addition, the 300/600 mg/day pregabalin treatment group was statistically significantly more favorable than placebo for sleep adequacy.

SF-36 Health Survey
While there were positive differences (improvements) for each of the pregabalin groups with respect to bodily pain, social functioning, and (with the exception of the pregabalin 300 mg/day group) general health perception, none of these differences reached statistical significance.

VAS area under the curve (AUC) score and the EQ-5D utility score
EQ-5D utility scores for all pregabalin treatment groups were statistically significantly better when compared with the placebo treatment group. Statistical significance was not reached for the EQ-5D VAS and VAS AUC for any dose of pregabalin.

6.7.3.4 Unplanned Analyses

The following analyses were not specified in the protocol. The NDA does not describe whether they were conducted prior to breaking the study blind.

a) *Endpoint Mean Pain Score: Baseline Observation Carried Forward (BOCF) Analysis*
In this analysis of the primary outcome, the baseline score was carried forward for any patient who did not complete the study. None of the pregabalin treatment groups was statistically significantly different from placebo.

Table 6.7.3.4.a: Endpoint Mean Pain Scores, BOCF: Descriptive Statistics, MITT - Protocol149

Time Point	Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 300/600 mg/day	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Endpoint	93	4.6 (2.4)	96	4.3 (2.4)	96	4.6 (2.2)	98	4.0 (2.3)

(From Appendix E.2.8, RR 720-30080, 1008-149, P. 1649)

Table 6.7.3.4.b: Endpoint Mean Pain Scores, BOCF: ANCOVA, MITT - Protocol 149

Treatment	N	Least Squares Means	SE	Treatment Comparisons (Active Drug – Placebo) Difference	95% CI	p-value*
Placebo	93	4.76	0.26			
Pregabalin 150	96	4.57	0.26	-0.19	(-0.81, 0.43)	0.9156
Pregabalin 300	96	4.72	0.26	-0.03	(-0.65, 0.58)	0.9156
Pregabalin 300/600	98	4.07	0.25	-0.68	(-1.30 –0.06)	0.0912

* Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo
(Adapted from Applicant's Table 31, RR 720-30080, 1008-149, P. 101)

I noted that, per this analysis, only 383 (and not 384) subjects are included in the MITT population. Also, the Applicant does not identify which or how many subjects were considered "non-completers."

b) *Endpoint mean pain scores: MITT patients without dizziness and/or somnolence*
None of the pregabalin treatment groups was statistically significantly different from placebo in this analysis.

c) Endpoint mean pain score by cluster and country, MITT

The Applicant also conducted an exploratory analysis of the endpoint mean pain scores for the MITT population using ANCOVA by cluster. Again, the endpoint mean pain scores were calculated from the last 7 available pain scores of each patient. A clinically relevant treatment effect was evident in the 300/600 pregabalin treatment group for a majority of the non-Polish sites. However, all Polish sites, except the two in cluster 12, did not show any benefit from any pregabalin treatment group over placebo.

Table 6.7.3.4.c: Endpoint mean pain scores, results of ANCOVA by cluster, Protocol 1008-149

Table 1. Endpoint [a] Mean Pain Scores: Results of Analysis of Covariance by Cluster Modified Intent-To-Treat Population

Cluster		N	Treatment Comparisons (Pregabalin – Placebo) Difference –(95% CI) [a]		
			PGB 150 mg/day	PGB 300 mg/day	PGB 300/600 mg/day
1	Australia	20	0.89 (-1.51, 3.28)	-1.79 (-4.48, 0.90)	-0.44 (-2.84, 1.97)
2	Australia	27	0.08 (-2.15, 2.31)	-0.32 (-2.64, 1.99)	-2.24 (-4.74, 0.26)
3	Australia	22	-0.65 (-3.84, 2.54)	-3.26 (-6.81, 0.29)	-1.12 (-4.16, 1.93)
4	South Africa	32	-2.21 (-4.81, 0.39)	-1.67 (-4.25, 0.90)	**-2.78 (-5.36, -0.20)***
5	UK	21	-2.42 (-5.51, 0.68)	-0.96 (-4.27, 2.35)	-2.12 (-4.99, 0.75)
6	Germany	20	0.13 (-2.60, 2.87)	0.86 (-1.57, 3.30)	-0.54 (-2.90, 1.81)
7	Germany	24	-0.66 (-2.89, 1.56)	-0.03 (-2.23, 2.16)	-2.10 (-4.70, 0.51)
8	Germany	22	-0.68 (-3.74, 2.38)	-1.05 (-3.79, 1.69)	-2.59 (-5.24, 0.06)
9	Hungary	34	-2.30 (-4.64, 0.04)	-0.07 (-2.45, 2.30)	-2.17 (-4.44, 0.09)
10	Poland	26	1.49 (-1.02, 4.01)	0.78 (-1.38, 2.94)	0.86 (-1.43, 3.15)
11	Poland	23	1.28 (-1.36, 3.91)	1.71 (-0.81, 4.23)	0.11 (-2.46, 2.69)
12	Poland	21	-0.85 (-3.46, 1.76)	-1.44 (-3.80, 0.91)	-1.92 (-4.55, 0.71)
13	Poland	37	0.46 (-1.54, 2.46)	0.57 (-1.34, 2.48)	-0.27 (-2.32, 1.79)
14	Poland	33	0.70 (-1.16, 2.56)	0.27 (-1.53, 2.07)	0.97 (-0.89, 2.83)
15	Poland	21	-2.66 (-4.87, -0.44)	0.85 (-1.54, 3.24)	-0.59 (-2.70, 1.52)

SE = Standard error; CI = Confidence interval

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

(*) Significance of the difference, based on Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

(Applicant's Table 1, RR 720-30080, 1008-149, P. 3454)

The endpoint mean pain scores for the MITT population were then analyzed using ANCOVA by country. The treatment effect in Poland was smaller than the other 4 countries. When combining the non-Polish countries, a statistically significant treatment effect was seen in the 300/600mg/day pregabalin treatment group whereas in Poland there was no difference from placebo seen for any pregabalin treatment group.

Table 6.7.3.4.c: Endpoint mean pain scores, results of ANCOVA by country, Protocol 1008-149

Table 2. Endpoint [a] Mean Pain Scores: Results of Analysis of Covariance by Country: Modified Intent-To-Treat Population

		Treatment Comparisons (Pregabalin – Placebo) Difference – (95% CI) [a]		
Country	N	PGB 150 mg/day	PGB 300 mg/day	PGB 300/600 mg/day
Australia	69	0.05 (-1.44, 1.55)	-1.48 (-3.11, 0.14)	-1.11 (-2.64, 0.42)
SA & UK	53	-1.68 (-3.65, 0.30)	-1.04 (-3.09, 1.01)	**-2.67 (-4.62, -0.72)***
Germany	66	-0.57 (-1.87, 0.72)	-0.18 (-1.44, 1.09)	**-1.74 (-3.03, -0.45)***
Hungary	34	-2.30 (-4.64, 0.04)	-0.07 (-2.45, 2.30)	-2.17 (-4.44, 0.09)
Poland NE	70	0.98 (-0.39, 2.35)	0.54 (-0.73, 1.81)	-0.03 (-1.37, 1.31)
Poland SW	91	-0.17 (-1.31, 0.98)	0.46 (-0.67, 1.58)	0.10 (-1.04, 1.25)
Poland	161	0.30 (-0.58, 1.18)	0.47 (-0.36, 1.31)	0.05 (-0.81, 0.92)
Not Poland	222	-0.92 (-1.75, -0.08)	-0.77 (-1.62, 0.09)	**-1.85 (-2.69, -1.01)***

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).
(*) Significance of the difference, based on Adjusted p-value based on Hochberg's procedure for the 3 pairwise comparisons versus placebo.

(Applicant's Table 2, RR 720-30080, 1008-149, P. 3455)

As stated above, 40% of the subjects in this study were from Polish sites. The data were reviewed to evaluate for differences in demographic or medical characteristics of Polish vs. non-Polish subjects. No sizeable differences in age, treatment assignment, pain at baseline, or creatinine clearance were noted. The fact that the pregabalin 300/600 treatment arm at the non-Polish sites demonstrated superior effect compared to placebo is reassuring since it is supportive of drug efficacy in a heterogeneous population.

d) Signs and symptoms of allodynia and hyperalgesia at baseline and termination
While allodynia and hyperalgesia appeared to be decreased in all treatment groups by the end of the study, the difference in occurrence of these signs was not statistically different from placebo for any of the pregabalin group.

e) Mean pain scores by CLcr strata
The Applicant calculated descriptive statistics of the mean pain scores by CLcr for each of the treatment groups. Since there were fewer patients in the low CLcr strata than in the normal CLcr strata, comparisons between the two could not be made.

Table 6.7.3.4.d: Mean pain scores by creatinine clearance, Protocol 1008-149

Table 19. Summary of Mean Pain Scores by Creatinine Clearance Strata[a]: Modified Intent-to-Treat Population

	Placebo (N = 93)		Pregabalin 150 mg/day (N = 97)		Pregabalin 300 mg/day (N = 96)		Pregabalin 300/600 mg/day (N = 98)	
	Low	Normal	Low	Normal	Low	Normal	Low	Normal
Baseline[b]								
N	12	81	12	85	10	86	13	85
Mean (SD)	6.4 (1.7)	6.4 (1.4)	6.2 (1.4)	6.2 (1.5)	6.1 (1.8)	6.5 (1.3)	6.7 (1.4)	6.6 (1.5)
Median	5.5	6.6	6	6.1	5.6	6.4	6.8	6.6
Range	[							]
Endpoint[b]								
N	12	81	11	85	10	86	13	85
Mean (SD)	4.5 (2.8)	4.5 (2.3)	3.9 (2.3)	4.2 (2.3)	4.4 (2.4)	4.4 (2.2)	4.6 (2.1)	3.6 (2.2)
Median	3.8	4.4	3.6	4	4	4.3	4.6	3.1
Range	[							]
Change From Baseline to Endpoint								
N	12	81	11	85	10	86	13	85
Mean (SD)	-1.9 (2)	-1.9 (2.1)	-2.2 (2)	-2.1 (2.4)	-1.7 (1.7)	-2.1 (2.1)	-2.2 (2.4)	-3.1 (2.4)
Median	-2.1	-1.9	-1.9	-1.6	-1.7	-2	-1.1	-3.1
Range	[							]

SD = Standard Deviation. For each timepoint Mean Score, if less than 7 diary entries, then mean of available entries.

[a] Creatinine clearance (CLcr) Stratum is Normal for patients with CLcr more than 60 mL/min and is Low for patients with CLcr less or equal to 60 mL/min and greater than 30 mL/min.

[b] Baseline/Endpoint Mean Pain Score: mean of the last 7 entries of the daily pain diary up to and including day 1/while on study drug.

(Applicant's Table 19, RR 720-30080, 1008-149, P. 85)

f) Weekly Mean Pain Scores – As Observed Cases

Results were similar to those obtained using the repeated measures model, except that the scores for the 300 and 300/600 mg/day pregabalin treatment groups were also statistically significant at Week 1.

6.7.3.5 Reviewer's Analysis

Similar to the analysis plans for the other efficacy studies, this protocol had three major weaknesses:

- Computation of the endpoint mean pain score
- Handling of missing data
- Insufficient consideration of the effect of use of rescue medication for pain

Additionally, the Applicant's interpretation of treatment efficacy for all subjects in the pregabalin 300/600 mg/day group is incorrect. The Applicant concluded that because the 300/600 mg/day treatment arm showed greater improvement in pain from placebo, then treatment with either 300 or 600 mg/day (where dosing is dependent on creatinine

clearance) is effective. This conclusion is incorrect because it fails to take into account that the 13 subjects in the 300/600 treatment arm who had a creatinine clearance ≤ 60 mL/min and received 300 mg/day of drug, were exactly the same as the 10 subjects with low creatinine clearance who were randomized to the pregabalin 300mg/day arm (see Table 6.7.3.4.d). Data analysis showed that treatment for all subjects in this latter arm was not significantly different from placebo.

Consequently, Dr. Chen reanalyzed the data after reassigning the aforementioned 13 subjects to the 300 mg/day treatment arm, and grouping them with the 10 subjects who also had a low creatinine clearance. The data were analyzed separately for subjects with a creatinine clearance > 60 mL/min, and for subjects with a creatinine clearance ≤ 60 mL/min but ≥ 30 mL/min.

BOCF analysis of the data for subjects with a creatinine clearance > 60 mL/min showed that none of the pregabalin treatment groups had a significantly different mean pain score at study endpoint compared to placebo. The p-values for the difference in median percentage changes for the pregabalin 150, 300, and 600 mg/day groups were 0.54, 0.39, and 0.08 respectively (1-sided alpha = 0.0083). The BOCF analysis was repeated after factoring the use of rescue medications during the final week of the study, and yielded similar results.

BOCF analysis of the data for subjects with a creatinine clearance ≤ 60 mL/min but ≥ 30 mL/min also showed an insignificant difference between pregabalin 150 and 300 mg/day compared to placebo (p = 0.53 and 0.78 respectively, with 1-sided alpha = 0.0125). BOCF analysis after factoring in the use of rescue medication was even more statistically insignificant.

Responder rates based on creatinine clearance were calculated and are summarized below:

Reviewer's analysis: Proportion of Responders based on creatinine clearance, BOCF analysis – Protocol 149

	Proportion of Responders (%)			
		Pregabalin		
Creatinine clearance	Placebo	150 mg/day	300 mg/day	600 mg/day
> 60 mL/ min	25	30	28	36
≤ 60 mL/min	33	25	22	-

Reviewer's analysis: Proportion of Responders based on creatinine clearance, with imputation of pain scores due to use of rescue medication, BOCF analysis – Protocol 149

	Proportion of Responders (%)			
		Pregabalin		
Creatinine clearance	Placebo	150 mg/day	300 mg/day	600 mg/day
> 60 mL/ min	21	29	24	35
≤ 60 mL/min	33	17	18	-

The tables show that a considerable proportion (25-33%) of subjects in the placebo group responded to treatment. This proportion is considerably larger than what was observed in

other studies. On the other hand, the proportion of responders in the pregabalin group was similar to other studies. The large placebo response could therefore explain why the treatment effect of pregabalin in this study sample was small and not statistically significant. The tables also show that the greatest difference in responder rates was for the pregabalin 600 mg/day group. Again, imputation for use of rescue medication lowered the proportion of treatment responders in all groups.

6.7.3.6 Conclusions Regarding Efficacy Data in Study

Based on the Agency's reanalysis of the data, treatment with pregabalin (150, 300, or 600 mg/day, in two divided doses) does not result in pain relief that is statistically different from treatment with placebo. However, the responder analysis suggests that treatment with 600 mg/day is effective.

6.8 Protocol 1008-173: A 12-week, randomized, double-blind, multicenter, placebo-controlled study of pregabalin twice a day (BID) for relief of pain associated with diabetic peripheral neuropathy

As described above (Section 5.1), this study was prematurely terminated due to imposition of a partial clinical hold by the Agency. Only 7 of the enrolled subjects completed the full 12 weeks of therapy, therefore this study was considerably under-powered to show a difference between active treatment and placebo. Therefore, this study was not considered contributory to the efficacy database.

6.9 Analysis of the correlation between baseline pain score and percent change in pain score among treatment responders and non-responders

The data show that more patients treated with pregabalin had a 50% decline in their baseline pain score than did patients treated with placebo. That is, there were more 'responders' in the pregabalin group than in the placebo group. It is possible that responders were different from non-responders in that responders had less pain at baseline, and therefore more easily achieved a benefit from treatment benefit. To explore this possibility, Dr. Celia Winchell, (Team Leader, HFD 170) analyzed data from the 3 positive efficacy trials (014, 029, and 131) with respect to distribution of baseline pain scores within responders and non-responders (as identified by the Division's BOCF analysis). Dr. Winchell also determined the correlation between baseline pain score and percent change in pain score.

There were 562 non-responders and 167 responders in the 3 trials. The mean baseline pain score among treatment responders was 6.3 (median 6.0), and ranged from 3.75 to 10.0. The mean baseline pain score for non-responders was 6.5 (median 6.5), and ranged

from 2.0 to 10.0. There was no consdierable difference between the groups with regards to mean baseline pain score, however non-responders had a slightly higher median baseline pain score.

Per each of the protocols, subjects with a baseline pain score < 4 were considered ineligible. A total of 15 patients (2 responders, 13 non-responders) were therefore excluded from the analysis and the mean pain score for the groupswas re-calculated. The mean baseline score was subsequently 6.3 for responders (median 6.1) and 6.6 for non-responders (median 6.1). These scores are not appreciably different.

Data from pain scores was then analyzed to determine whether there was an association between baseline pain score and percent change from baseline. A correlation was not found for neither the responder nor the non-responder group.

Figure 6.9.a: All subjects, studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF

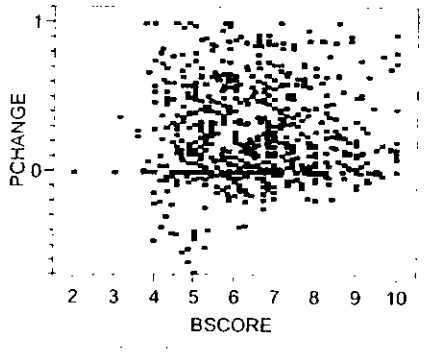


Figure 6.9.b: Responders, Studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF

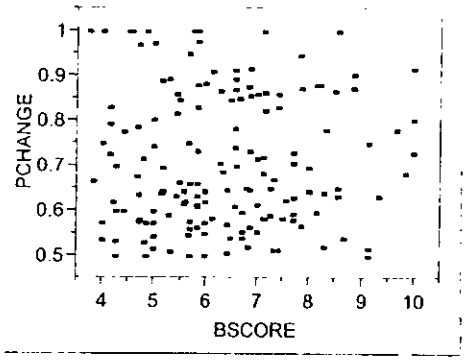
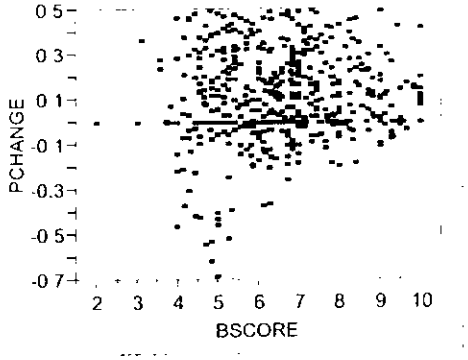


Figure 6.9.c: Non-responders, Studies 131, 014, and 029, average pain scores during baseline week vs. percent change from baseline at endpoint, BOCF



7 INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

Exposure
In total, 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 [ ] pain, [ ] fibromyalgia, acute mania, panic disorder, and social anxiety disorder. With respect to patients with pain due to peripheral diabetic neuropathy, a total of 1413 patients have received at least one dose of pregabalin. To date, 289 subjects with pain due to diabetic neuropathy (DPN) have been treated with pregabalin 600 mg/day (the highest proposed marketed dose) for at least 6 months, and 201 for at least 1 year. Therefore, as regards this indication, the company has met 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 (SAEs)
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 similar pattern was seen when only the DPN population was considered. In this population, however, treatment with pregabalin appeared to convey a slightly greater risk of these AEs, as well as infection, dyspnea, and hypoglycemia

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) AEs
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.

AEs of interest
Data from brief controlled trials across indications, as well as from controlled DPN trials alone, indicate that treatment with pregabalin does not convey a greater risk of skin related AEs, including skin ulcers. The open-label, long-term data from DPN studies also do not suggest an association between pregabalin and skin ulcers. However, in the absence of a comparison group exposed for a similar duration, it is not possible to rule out a real effect with long term use.

Compared to placebo patients, patients treated with pregabalin more frequently reported blurred vision, diplopia and "abnormal vision". Additionally, slightly more pregabalin-treated patients reported visual field defects than placebo patients. Similar results were seen when data from only the DPN population were examined. Blurred vision appeared to be dose dependent.

Also in the DPN population, information from controlled trials suggested that pregabalin treatment is associated with a greater risk of glucose abnormalities compared to treatment with placebo.

Finally, the incidence of peripheral edema 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, and 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 exlpain all of the weight gain. Pregabalin did not appear to have a clinically significant effect on ECG parameters.

7.2 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 pain due to diabetic peripheral neuropathy

(DPN). 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. Instead, the population considered most vulnerable to adverse drug effects, the DPN population, was used to explore certain drug effects, such as the incidence of common adverse events (AEs) or the frequency of select AEs of interest.

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, and counted patients who were enrolled in more than one study only once for all AE summaries.

To evaluate the accuracy of adverse event (AE) coding procedures, I compared investigator verbatim terms with the corresponding preferred terms assigned by the Applicant for a select sample of patients in all trials. For selected events (e.g. edema, skin ulcers, amblyopia, neoplasms, ECG abnormalities), I reviewed the coding of a sample of those events in more detail by examining the CRF, electronic data, narrative summaries, and study report listings to determine if 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 at the time of this review.

7.3 Materials Utilized in the Review

The Summary of Clinical Safety (SCS) includes data from studies completed as of February 14, 2003, the SCS cut-off date, as well as all data entered into the Oracle Clinical database for 12 ongoing, long-term, open-label (uncontrolled) studies. The 120-day safety update included additional data from two open-label pain trials, a psychiatric relapse prevention trial, and entered into the Oracle Clinical database between Feb 14 and October 10, 2003. Finally, in response to specific requests by the Agency, additional data

sets from the controlled and/or open-label studies, as well as results of various data analyses were also submitted.

There were 53 trials submitted for safety analyses in the NDA and the safety update, an they explored the following indications: epilepsy, [ ] fibromyalgia, [ ] generalized anxiety disorder (GAD) [ ] postherpetic neuralgia (PHN), pain due to diabetic neuropathy (PDN), and [ ]

Pfizer presented the pregabalin safety data using 2 major groupings. "Group 1" data comprises 30 Phase 2/3 double-blind, placebo-controlled studies in the indications listed above. "Group 2" data includes all controlled and uncontrolled studies. 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.

These trials are depicted in the table below:

Table 7.3.a: Trials contributing to the safety data

		Trial type	Protocol number
Group 2	Group 1	All placebo controlled trials	DPN: 014, 029, 040, 131, 149, 173 PHN: 030, 045, 127, 132, 196 EPI: 009, 011, 034 GAD: 021, 025, 026, 083, 085, 087 [ ] 031, 032, 104, 105 Other psychiatry: 017, 022, 080, 081/153 [a], 092 [b], 094 [b]
		Placebo-controlled studies not integrated with the 30 controlled trials because of differences in study design or because they were terminated early with minimal enrollment	Epilepsy: 007, 145 GAD: 088, 181 Other psychiatry: 082 Other neuropathic pain: 060, 160
		All open-label extension trials	[ ] 015, 033, 061, 074, 134, 165, 174, 197 [c], 198 Other neuropathic pain: 183 Epilepsy: 008, 010, 012, 035 Psychiatry: 084, 100

a Studies 081 (Europe/South Africa) and 153 (USA) were twin studies summarized in one research report and were counted as 1 study

b Studies 092 and 094 were summarized in 1 report but were originally planned as separate studies and were therefore counted as 2 studies

c Patients who completed Study 015 or who were ongoing in studies 015, 033, 132, 134, 173, and 174 at the time they were closed by Pfizer were eligible to enroll in Study 197

7.3.1 Primary Source Data

7.3.2 Group 1 studies

Group 1 studies comprised 30 of the Applicant's controlled Phase 2/3 studies. These studies are considered the primary source for safety because they were placebo-controlled, conducted in patients with the respective indications, and have the largest

exposure to the pregabalin doses that are proposed for marketing. Twenty-three of the 30 trials were conducted in the US.

Table 7.3.2: Group 1 studies

Protocol	Location	Indication	No. of subjects [a]	Duration	PGG Dose [b]
Pain due to diabetic peripheral neuropathy (DPN)					
014	USA Canada	DPN	PGB: 161 Placebo: 85	Titration: 2 wks Fixed dose: 6 wks	150 mg/day 600 mg/day
029	USA	DPN	PGB: 240 Placebo: 97	Titration: 1 wk Fixed dose: 4 wks	75 mg/day 300 mg/day 600 mg/day
040	Europe Australia South Africa	DPN	PGB: 86 Placebo: 81 Amitriptyline: 87	Titration: 2 wks Fixed dose: 6 wks Withdrawal: 1 wk	600 mg/day
131	USA	DPN	PGB: 76 Placebo: 70	Fixed dose: 8 wks	300 mg/day
149	Europe Australia South Africa	DPN	PGB: 299 Placebo: 96	Titration: 1 wk Fixed dose: 11 wks	150 mg/day * 300 mg/day * 600 mg/day *
173 [d]	USA	DPN	PGB: 117 Placebo: 30	Titration: 1 wk Fixed dose: 11 wks	150 mg/day * 300 mg/day * 600 mg/day *
Epilepsy					
009	USA Canada	EPI	PGB: 103 Placebo: 98	Fixed dose: 12 wks Withdrawal: 1 wk	600 mg/day [c]
011	Europe	EPI	PGB: 191 Placebo: 96	Titration: 1 wk Fixed dose: 11 wks Withdrawal: 1 wk	150 mg/day 600 mg/day
034	USA	EPI	PGB: 353 Placebo: 100	Fixed dose: 12 wks Withdrawal: 6 days	50 mg/day* 150 mg/day* 300 mg/day* 600 mg/day*
Generalized Anxiety disorder					
021	USA	GAD	PGB: 139 Placebo: 69 Lorazepam: 68	Fixed dose: 4 wks Withdrawal: 1 wk	150 mg/day 600 mg/day
025	USA	GAD	PGB: 142 Placebo: 70 Lorazepam: 70	Titration: 1 wk Fixed dose: 4 wks Withdrawal: 1 wk	150 mg/day 600 mg/day
026	USA	GAD	PGB: 142 Placebo: 70 Lorazepam: 70	Titration: 6 days Fixed dose: 4 wks Withdrawal: 1 wk	150 mg/day 600 mg/day
083	USA	GAD	PGB: 271 Placebo: 91 Alprazolam: 93	Titration: 1 wk Fixed dose: 4 wks Withdrawal: 2 wks	300 mg/day 450 mg/day 600 mg/day
085	USA Canada	GAD	PGB: 253 Placebo: 86	Titration: 1 wk Fixed dose: 4 wks Withdrawal: 1 wk	200 mg/day* 400 mg/day* 450 mg/day
087	Europe	GAD	PGB: 206 Placebo: 101 Venlafaxine: 113	Titration: 1 wk Fixed dose: 5 wks Withdrawal: 1 wk	400 mg/day* 600 mg/day*

Table 7.3.2: Group 1 studies (continued)

Protocol	Location	Indication	No. of subjects [a]	Duration	PGG Dose [b]
Postherpetic neuralgia					
030	USA	PHN	PGB: 167 Placebo: 88	Fixed dose: 5 wks	75 mg/day 150 mg/day
045	Europe Australia	PHN	PGB: 157 Placebo: 81	Titration: 1 wk Fixed dose: 7 wks	150 mg/day 300 mg/day
127	USA	PHN	PGB: 89 Placebo: 84	Titration: 1 week Fixed dose: 7 wks	300 mg/day 600 mg/day
132	USA	PHN	PGB: 164 Placebo: 52	Titration: 1 wk Fixed dose: 11 wks	150 mg/day * 300 mg/day * 600 mg/day *
196	Europe Australia	PHN	PGB: 275 Placebo: 93	Titration: 1 week Fixed dose: 12 wks	150 mg/day * 300 mg/day * 600 mg/day *
Other pain					
032	USA	—	PGB: 163 Placebo: 90	Fixed dose: 7 wks	150 mg/day 600 mg/day
104	US	—	PGB: 303 PBO: 103	Titration: 1 wk Fixed dose: 7 wks	300 mg/day 450 mg/day 600 mg/day
Other psych (continued)					
105	US	—	PGB: 408 Placebo: 131	Titration: 4 days Fixed dose: 8 wks	150 mg/day 300 mg/day 450 mg/day
031	USA Canada	—	PGB: 204 Placebo: 92	Titration: 1 week Fixed dose: 11 wks	300 mg/day 600 mg/day
Other psych					
017	US	—	PGB: 89 Placebo: 46	Titration: 1 wk Fixed dose: 9 wks Taper: 1 wk	150 mg/day 600 mg/day
080	USA	—	PGB: 246 Placebo: 82	Titration: 1 wk Fixed dose: 9 wks Withdrawal: 1 wk	300 mg/day 450 mg/day 600 mg/day
081/153 [d]	Europe Israel South Africa	—	PGB: 181 Placebo: 95 PAR:	Titration: 6 days Fixed dose: 9 wks Withdrawal: 1 wk	200 mg/day 400 mg/day
022	USA	—	PGB: 28 Placebo: 31	Fixed dose: 3 wks	600 mg/day
092/094 [d]	US	Panic disorder	PGB: 158 Placebo: 79 PAR: 77	Titration: 2 wks Fixed dose: 6 wks	200 mg/day* 400 mg/day* 600 mg/day*

CLBP: chronic low back pain; DPN: pain due to diabetic peripheral neuropathy; EPI: Epilepsy; GAD: Generalized anxiety disorder;

a Subjects who received at least 1 dose of study medication
b All dosing was TID dosing unless otherwise indicated
c Subjects were randomized to either 200 mg TID or 300 mg BID
d Study was prematurely terminated
* BID dosing

7.3.3 Group 2 studies

As stated above, "Group 2" data include information from the Group 1 studies, all uncontrolled studies, and additional controlled studies. The last category of trials is listed below:

Safety Database: Group 2 studies, Additional controlled studies

Protocol	Location	Indication	No. of subjects [a]	Duration	PGG Dose [b]
060	US		OL PGB: 19 DB PGB: 2 DP PBO: 3	3 wks open label, followed by 5 wks double-blind	300 mg/day 600 mg/day
007	US, Germany	Epilepsy	PGB: 42 GBP: 51 PBO	Fixed dose: 8 days	600 mg/day
145	US	Epilepsy	PGB: 3 PBO: 1	Fixed dose: 12 wks	600 mg/day (fixed) 150-600 mg/day (flexible)
181	US	GAD	PGB: 4 PBO: 2	Titration: 1 wk Flexible dosing: 5 wks	PGB 200 to 600 mg/day
88	US	GAD	OL PGB: 624 DB PGB: 339	Open label: 8 wks Double blind: 24 wks Withdrawal: 2 wks	PGB 450 mg/day
160	US	Neuropathic pain patients	PGB: 6 PBO: 6 ALP: 7	Titration: 1 wk Fixed dose: 4 wks Single blind: 1-wk	300 mg/day
82	US		OL PGB: 348 DB PGB: 153	Open label: 10 wks Double blind: 26 wks Withdrawal: 2 wks	PGB 450 mg/day

DB: double blind; GAD: generalized anxiety disorder; OL: open label; PBO: placebo; PGB: pregabalin

a Subjects who received at least 1 dose of study medication

b All dosing was TID dosing unless otherwise indicated

7.3.4 Integrated clinical pharmacology database

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 14 February 2003 data cutoff date. The source and number of subjects in the integrated clinical pharmacology database are listed below:

Table 7.3.5: Trials in the integrated clinical pharmacology database

Study Type	Study Number	Treatment			
		Placebo	Other[a]	Pregabalin	Total
Absorption, Distribution, Metabolism, and Excretion	001	29	0	29	29
	002	12	0	45	57
	005	0	0	6	6
	023	3	0	13	16
Bioequivalence and Bioavailability	003	0	0	12	12
	128	0	0	14	14
	190	0	0	16	16
Drug Interaction Studies in Patients	018	0	11	11	11
	019	0	14	14	14
	020	0	12	12	12
	120	0	2	2	2
	126	0	5	5	5
	140	0	11	11	11
Drug Interaction Studies in Healthy Volunteers	075	0	16	15	16
	076	12	12	12	12
	077	0	12	12	12
	078	12	12	12	12
	079	11	12	13	13
	144	0	21	21	21
Special Populations	049	0	0	26	26
	121	0	0	12	12
Other	004	0	0	7	7
	036	0	0	16	16
	047	0	0	18	18
	048	0	0	14	14
	072	16	0	30	46
	097	23	0	23	23
	098	16	0	19	19
Total		*134*	*140*	*440*	*472*

[a] Drug co-administered in drug interaction studies
[b] Two complementary studies reported in a single research report
[c] Six subjects in this study were healthy volunteers and 20 were patients with renal impairment

Of the 28 Phase 1 studies, 20 used an immediate release formulation, 1 used a modified release formulation, and 4 used a combination of immediate and modified release formulations, and 3 were special safety studies.

Finally, 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 integreated safety database.

7.3.5 Secondary Data Sources

There were no secondary sources for safety data since all of the Applicant's safety data were derived from studies conducted under the IND.

7.4 Safety findings from clinical studies

7.4.1 Description of Patient Exposure

7.4.1.1 Numbers 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 7.4.1.1.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

Subject exposure to pregabalin in controlled and uncontrolled trials, for DPN as well as all indications, was as follows

Table 7.4.1.1.a: Exposure to pregabalin, uncontrolled and controlled studies

Indication	Controlled Trials		Uncontrolled trials
	Placebo	Pregabalin	Pregabalin
All Indications	2 384	5 508	8 666
DPN	459	979	1 164

7.4.1.2 Duration of exposure to pregabalin

Pfizer also 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 28% of subjects in both controlled and uncontrolled studies were exposed to pregabalin for at least 1 year, and 11% for at least 2 years.

Table 7.4.1.2.a: 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 Daily Dose of Pregabalin in mg/day (Regimen)									
Total Exposure Time[a]	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 7.4.1.2.b: 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:

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Table 7.4.1.2.c: 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.

I also reanalyzed the data to determine how many subjects in the DPN trials were exposed to the proposed marketed doses (300- and 600 mg/day) for at least 1 year (Table 7.4.3.2.c). I found that, for the DPN population, there was adequate drug exposure, with 1 413 subjects exposed in total, and greater than 300 and 100 subjects exposed to the proposed marketed doses for more than 6 months and one year, respectively.

Table 7.4.3.2.c: Exposure to pregabalin by dose and duration, Controlled and Uncontrolled studies, DPN vs. All Indications

	Pregabalin dose			
	300 mg/day (N = 6969) N(%)		600 mg/day (N = 3333) N(%)	
Duration	DPN [N=1413]	ALL* [N=8666]	DPN [N=1413]	ALL* [N=8666]
≥4 wks	657	2 423	571	2 514
≥ 8 wks	467	1 537	458	1 999
≥ 12 wks	339	1 041	370	1 550
≥ 26 wks	215	526	289	1106
≥ 52 wks (1 year)	102	193	201	664
≥ 78 wks (1.5 years)	52	83	149	484
≥ 104 wks (2 years)	22	32	49	263

* ALL: All subjects exposed to pregabalin

7.4.1.3 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 — 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).

7.4.2 Deaths

7.4.2.1 Deaths in the overall integrated database

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:

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). Ageny 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 pregablin 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 7.4.2.1: Number of cause-specific deaths in the safety population

Cause of death	No patients		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.

7.4.2.2 Deaths by Indication

Pfizer provided the following table that summarizes the deaths by indication for the integrated safety database.

Table 7.4.4.2. 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.

As noted above, I counted 20 deaths in the PHN population. Therefore, the percent of deaths was 1.8%, and the mortality rate was 30.8/1000 PY (20/649 PY).

7.4.2.3 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 Appendix. None of the deaths appeared attributable to study medication.

7.4.2.4 Deaths in Epilepsy Trials

Pfizer reported that no deaths occurred during epilepsy controlled trials. Fourteen pregabalin-treated subjects died during epilepsy uncontrolled trials (0.9%, 14/1613). The mortality rate for these trials was 5.6/1000PY (14/2461PY).

Four of the epilepsy trial deaths were not witnessed, and the subjects were found dead. These deaths were coded to the preferred terms heart arrest, sudden death, apnea, and cardiomyopathy. Three deaths were associated with seizure activity, with two of these events involving aspiration (preferred terms respiratory disorder, lung disorder). Two deaths were cerebrovascular accidents (intracranial hemorrhage, cerebral hemorrhage), and the remaining deaths were attributed to cardiovascular disorder (possible MI), carcinoma, pulmonary embolism, accidental injury, and septicemia. Using the patient narratives, CRFs, datasets, and patient profiles, Dr. Gerard Boehm (Medical Reviewer, Division of Neuropharmacological Drug Products) constructed summaries of the clinical details for the epilepsy study deaths. Those summaries are provided in the Appendix, and are listed in the table below.

Table 7.4.4.4: Deaths in Epilepsy Trials

Body System	Cause of Death	No. Patients
Body as a whole	Sudden death	1
	Fall	1
	Septicemia	1
Pulmonary	Respiratory failure	1
	Respiratory disorder	1
	Lung disorder	1
	Pulmonary embolus	1
Neurological	Convulsion	1
	Sudden death in epilepsy	1
Cerebrovascular	Intracranial hemorrhage	2
Cardiovascular	Myocardial infarction	2
Neoplasm	Adenocarcinoma (unspecified)	1

7.4.2.5 Deaths in Generalized Anxiety Disorder Trials

The Applicant reported one death that occurred during or after participation in one of the six controlled GAD studies. One death occurred in a pregabalin-treated patient (patient 181_002003) whereas no deaths occurred in patients who were receiving or had received placebo or a comparator as of the termination date for data collection (February 14, 2003). Based on that information, Dr. Boehm calculated that the proportion of deaths observed in pregabalin-treated patients in controlled studies was .087% (1/1149) compared with 0% (0/484) in placebo-treated patients and 0% (0/412) in patients treated with an active comparator. Dr. Boehm also estimated that the death rate in controlled studies in patients treated with pregabalin was .90/100 patient-years (1 death in 110.5 patient-years) compared with 0/100 patient-years (0 deaths in 46.3 patient-years) in patients treated with placebo.

The death that occurred after pregabalin exposure in a controlled study was a result of suicide (self-inflicted gunshot wound) committed 42 days after Patient 181_002003, a 54 year old man with GAD and a history of major depression as well as hypertension and type 2 diabetes mellitus, had received his last dose of pregabalin. The patient had received just two days of treatment at 400 mg/day before study 1008-181, a double-blind placebo-controlled flexible-dose study, was terminated early by the Applicant. Concomitant medications included venlafaxine, gabapentin, glibenclamide, and diltiazem.

No deaths occurred in GAD open-label extension studies. Among the 1962 patients with GAD exposed to pregabalin in the ten controlled and uncontrolled studies[1], the proportion of deaths observed and reported by the Applicant was 0.05% (1/1962); this indication had the lowest proportion of deaths observed compared with the other indications for which the Applicant is seeking approval. The rate of death observed in this population was also the lowest compared with the other populations -1.6 deaths/1000 patient-years (calculated by the Applicant based on one death observed in 626 patient-years exposure to pregabalin).

7.4.2.6 Deaths in Trials of Pain due to Diabetic Peripheral Neuropathy (DPN)

As indicated in Table 7.4.4.2, there were 17 deaths in patients with DPN, making the total mortality for subjects in DPN studies 1.2% (17/1413). The mortality rate for these trials was 11.9/1000 PY (17/1421PY). Pfizer reported that one subjected died during participation in a controlled trial, and 3 subjects died following participation in a controlled trial. Furthermore, 13 subjects died during DPN uncontrolled trials,.

Using the patient narratives, CRFs, datasets, and patient profiles, I constructed summaries of the clinical details for the DPN study deaths. I found that of the all of the 17 patients who died had been treated pregabalin. Three subjects died while taking medication during controlled trials, while 1 subject died after prematurely discontinuing medication during the controlled trial. Thirteen subjects died while participating in uncontrolled studies. The majority of deaths were cardiac related (arrhythmia, cardiac arrest heart failure, and myocardial infarction; n = 2 each). Four deaths were due to unknown causes. The remaining deaths were from respiratory failure (n = 3), cancer (n = 1) and sudden death (n = 1). Deaths in DPN trials are listed below, and the associated narratives are provided in the Appendix. None of the deaths suggested a causal relationship with pregabalin.

[1]These ten studies include six double-blind placebo-controlled studies, two open-label extension studies, and one relapse prevention study; see attached table 1 for a summary of all ten studies provided by the Applicant.

Table 7.4.4.6: Deaths in DPN Trials

Body System	Cause of Death	No. Patients
Controlled Trials		
Body as a whole	Sudden death	1
Cardiovascular	Myocardial infarction	1
	Heart failure	1
Pulmonary	Pulmonary congestion	1
Uncontrolled Trials		
Body as a whole	Unknown	3
	Sudden death	1
Cardiovascular	Cardiopulmonary arrest	2
	Myocardial infarction	1
	Dilated cardiomyopathy	1
	Arrhythmia	1
	Heart failure	1
Pulmonary	Respiratory failure	2
Neoplasm	Hepatic adenocarcinoma	1

7.4.2.7 Deaths in Trials of Postherpetic Neuralgia (PHN)

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, datasets, and patient profiles and are in the Appendix. None of the deaths is indicative of a clear association with pregabalin treatment.

Table 7.4.4.7: 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

7.4.3 Assessment of Dropouts

7.4.3.1 Overall pattern of dropouts

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" CRF. Tables 7.4.3.1.a and 7.4.3.1.b 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 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 studies is shown in Table 4.4.5.1. 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 controlled trials than patients treated with pregabalin. Placebo patients dropped out more frequently for lack of efficacy than did pregabalin patients. Conversely, more pregabalin patients dropped out due to adverse events.

Table 7.4.3.1: Patient disposition – Controlled trials, All indications

	Placebo [N = 2384]*		Pregabalin [N = 5508]*	
Patient Status	**N**	**%**	**N**	**%**
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)

Table 7.4.3.1.b shows my results regarding subject disposition of subjects in all uncontrolled trials. Using the stat.xpt dataset, 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 CRFs. 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 the 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 most recent study CRF, and not just the Termination Visit CRF.

Table 7.4.3.1.b: 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 dataset: 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

7.4.3.2 Dropouts in DPN trials

I also assessed dropout rates in DPN trials (controlled and uncontrolled) alone. Disposition data for DPN controlled trials show that 1525 subjects completed Termination Visit CRFs (placebo = 459; amitriptyline = 87, pregabalin = (979).

Controlled trials

As illustrated in Table 7.4.3.2.a, more pregabalin-treated subjects withdrew due to adverse events (9%) compared to placebo patients (4%). Almost twice as many placebo patients (6%) withdrew because of lack of efficacy compared to pregabalin patients (3%). Slightly fewer pregabalin patients completed DPN controlled studies than placebo patients did.

Table 7.4.3.2.a: Patient disposition, DPN controlled trials

Patient status	Placebo N	[N = 459]* %	All Pregabalin N	[N = 979]* %
Completed	365	79 52	732	74.77
Reason for discontinuation				
Adverse Event	17	3 70	86	8.78
Lack of Efficacy	27	5 88	33	3.37
Lack of Compliance	4	0.87	10	1.02
Lost to Follow-Up	1	0.22	0	0.00
Other [1]	45	9.80	118	12.05

* N = number of subjects exposed to pregabalin
1 "Other" includes withdrawal of consent, loss to follow-up, and early termination of the study per the FDA, or failure to meet requalification criteria

Uncontrolled trials

Table 7.4.3.2.b lists the patient disposition for subjects in DPN uncontrolled trials. Of the 1164 subjects who participated in these trials, only 841 have disposition data for the Termination Visit. The table shows that a greater proportion of subjects dropped out of controlled trials due to adverse events (13%) than for lack of efficacy (6%).

Table 7.4.3.2.b: Patient disposition – DPN Uncontrolled trials

Patient Status	Pregabalin [N = 1164]* N (%)
Ongoing at data cutoff	295
Completed	171
Reasons for discontinuation	
Adverse event	150 (12.8)
Lack of efficacy	67 (5.8)
Lack of compliance	52 (4.5)
Withdrew consent	44 (3.8)
Experienced pain relief	4 (0.3)
Other **	381 (32.7)

* N = number of subjects exposed to pregabalin in DPN uncontrolled trials
** Other includes, but is not limited to, early termination of the study per the FDA, or failure to meet requalification criteria; patient request (n = 23); protocol violation (n=2), loss to follow up (43)

7.4.3.3 Adverse events associated with dropout - DPN Controlled trials

The table below lists adverse events that led to premature discontinuation of treatment at an incidence of at least 0.3% among subjects treated with pregabalin during DPN controlled trials. Dizziness, somnolence, and headache occurred with a frequency of more than 1%, and were the 3 most common reasons for study withdrawal among pregabalin-treated subjects.

Table 7.4.3.3: Adverse events reported as reason for discontinuation, by decreasing frequency - DPN controlled trials

Preferred term	Placebo N	[N=459] %	All pregabalin N	[N=979] %
Dizziness	3	0 65	34	3 47
Somnolence	0	0 00	27	2 76
Headache	4	0.87	11	1.12
Asthenia	1	0.22	8	0 82
Amblyopia	1	0.22	8	0.82
Dry mouth	0	0.00	7	0.72
Nausea	3	0.65	7	0.72
Confusion	1	0.22	7	0.72
Peripheral edema	1	0.22	6	0.61
Accidental injury	0	0.00	4	0.41
Infection	0	0.00	4	0.41
Ataxia	0	0.00	4	0.41
Neuropathy	1	0.22	4	0.41
Tremor	0	0.00	4	0.41
Constipation	1	0.22	3	0.31
Diarrhea	1	0.22	3	0.31
Incoordination	1	0.22	3	0.31
Thinking abnormal	0	0.00	3	0.31

7.4.4 Serious Adverse Events

Pfizer pooled the safety data from the Phase 2/3 clinical trials in the following ways:
Across Indications: (1) all controlled studies alone and (2) all controlled and open-label extension studies combined
By *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.

7.4.4.1 Overview of Serious Adverse Events

Pfizer reports that there have been 726 (8.4%, 726/8666) pregabalin subjects with one or more serious adverse events in the integrated safety database (Summary of Clinical Safety, p.40). The rate of experiencing on or more SAEs in the integrated safety database is 113/1000PY (726/6393PY).

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 7.4.5.1.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 nonneuropathic pain studies and other psychiatry studies.

(Adapted from Applicant's Table 16, RR-REG 720-30199, P. 40)

There was no serious adverse event that was clearly related to pregabalin treatment. However, the cases of myopathy/rhabdomyolysis require further investigation, and information regarding these cases has been requested. Investigation into the potential for pregabalin to cause rhabdomyolysis is important given the evidence that pregabalin causes increases in creatinine phosphokinase. Also, patients with diabetes, already vulnerable due to their pre-existing renal disease, might be at additional risk of further kidney damage as a consequence of pregabalin treatment.

SAEs in Controlled Studies

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) (Table 7.4.5.1.b below).

SAEs in uncontrolled studies

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 in Table 7.4.5.1.c).

Table 7.4.5.1.b: 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.

Table 7.4.5.1.c: 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

7.4.4.2 SAEs of Interest – All indications

Pfizer provided a listing of all SAEs experienced by pregabalin treated subjects in any of their safety databases (Appendix ALL.62), and Dr. Boehm reviewed this list to identify subjects with SAEs coded to preferred terms of potential importance. Dr. Boehm identified subjects with the following SAEs:

Body system	Preferred term (No. subjects)
Body as a whole	Anaphylactoid reaction (2)
	Allergic reaction (2)
	Face edema (1)
Urogenital system	Kidney function abnormal (5)
	Acute kidney failure (4)
	Kidney failure (1)
	Nephrosis (1)
	Nephritis (1)
	Glomerulitis (1)
Digestive system	Pancreatitis (4)
	Necrotizing pancreatitis (1)
	Cholestatic jaundice (2)

	Jaundice (1)
	Abnormal LFT (3)
Cardiovascular system	Cardiomyopathy (3)
Metabolic and nutritional disorders	CPK increased (3)
	Creatinine increased (1)
	Acidosis (1)
Respiratory system	Lung fibrosis (3)
	Pulmonary hypertension (1)
Skin and appendages	Rash (2)
	Stevens Johnson Syndrome (1)
Musculoskeletal system	myopathy/rhabdomyolysis (2)
Hematological system	Leukopenia (1)
	Pancytopenia (1)

Dr. Boehm read the narratives for these events and in some cases there were plausible explanations for the events. Events relevant to DPN and PHN are summarized below, in the sections that review safety by indication. Those events deemed possibly related are described in greater detail in the relevant sections.

7.4.4.3 SAEs by Indication

7.4.4.3.1 Pain due to diabetic peripheral neuropathy

DPN controlled trials

The Applicant reported that 3.9% (38/979) of pregabalin-treated patients and 2.4% (11/459) placebo subjects experienced at least one SAE. There was no SAE that was reported by more than 1% of pregabalin-treated subjects in DPN controlled trials. As shown in the table below, chest pain was the most common SAE (pregabalin 0.5%, placebo 0.2%), followed by accidental injury (pregabalin 0.4%, placebo 0%). Congestive heart failure, myocardial infarction, infection, and pneumonia each occurred with a frequency of 0.3% in pregabalin-treated subjects, and these frequencies were not considerably different from the placebo group. The table below shows the SAEs that occurred in at least 0.2% of pregabalin-treated patients. A complete listing of SAEs in this sample can be found in the Appendix.

Table 7.4.4.3.1.a: SAEs, by decreasing frequency - Controlled DPN trials

Body system	Preferred term	Placebo [N=459]		All PGB [N=979]	
		N	%	N	%
Body as a whole	Chest pain	1	0.22	5	0.51
	Accidental injury	0	0.00	4	0.41
	Infection	1	0.22	3	0.31
Respiratory system	Pneumonia	1	0.22	3	0.31
Cardiovascular system	Congestive heart failure	1	0.22	3	0.31
	Myocardial infarct	0	0.00	3	0.31
	Angina pectoris	0	0.00	2	0.20
	Cerebrovascular accident	0	0.00	2	0.20
Respiratory system	Dyspnea	0	0.00	2	0.20
Metabolic and nutritional disorders	Hypoglycemia	0	0.00	2	0.20
Digestive system	Vomiting	0	0.00	2	0.20

SAEs in DPN controlled trials that coded to preferred terms of interest in pregabalin subjects were acute kidney failure, kidney function abnormal, jaundice, macrocytic anemia, myopathy, and skin ulcer (n = 1, each). The narrative for the event suggestive of a relationship to study drug pregabalin treatment is provided below. The remaining SAEs appear to have alternate explanations for the events.

Acute kidney failure, myopathy

149 430001 This 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

DPN combined controlled and uncontrolled trials

Among the pregabalin-treated subjects in combined controlled and uncontrolled DPN studies, 17.3% (245/1413) experienced at least one SAE. Congestive heart failure, myocardial infarct, and chest pain were the most commonly reported SAEs. SAEs reported by at least 1% of subjects in DPN are listed in Table 7.4.4.3.1.b:

Table 7.4.4.3.1.b: SAEs, by decreasing frequency - Controlled and uncontrolled DPN trials

Body system	Preferred term	Patients [N = 1413]*	
		N	%
Body as a whole	Chest pain	14	0.99
	Infection	13	0.92
	Cellulitis	12	0.85
	Accidental injury	9	0.64
	Abscess	4	0.28
Cardiovascular system	Congestive heart failure	17	1.20
	Myocardial infarct	16	1.13
	Angina pectoris	13	0.92
	Coronary artery disorder	12	0.85
	Cerebrovascular accident	10	0.71
	Peripheral vascular disorder	7	0.50
	Syncope	6	0.42
	Atrial fibrillation	5	0.35
	Cerebral infarct	5	0.35
	Heart failure	5	0.35
	Bradycardia	4	0.28
Digestive system	Gastrointestinal disorder	6	0.42
	Cholecystitis	4	0.28
	Cholelithiasis	4	0.28
	Vomiting	4	0.28
Endocrine system	Diabetes mellitus	5	0.35
Metabolic and nutritional disorders	Hypoglycemia	6	0.42
Musculoskeletal system	Arthritis	4	0.28
Nervous system	Depression	4	0.28
Respiratory system	Pneumonia	12	0.85
Respiratory system	Dyspnea	6	0.42
Skin and appendages	Skin ulcer	7	0.50

* Number of patients exposed to pregabalin in combined controlled and uncontrolled trials

Data from combined DPN trials were queried for SAEs coding to preferred terms of interest, excluding dermatological SAEs (dermatological SAEs are discussed below). The table that follows lists the non-dermatological SAEs of interest:

Table 7.4.4.3.1.c: SAEs in DPN combined trials that coded to preferred terms of interest

SAE	Any Dose Pregabalin [N = 1413] N (%)	SAE	Any Dose Pregabalin [N = 1413] N (%)
Acute kidney failure	3 (0.2)	Edema	1 (0.1)
Kidney function abnormal	3 (0.2)	Generalized edema	1 (0.1)
Kidney failure	1 (0.1)	Leukemoid reaction	1 (0.1)
Nephrosis	1 (0.1)	Macrocytic anemia	1 (0.1)
Lung disorder	2 (0.1)	Megaloblastic anemia	1 (0.1)
Lung edema	1 (0.1)	Pancytopenia	1 (0.1)
Lung fibrosis	1 (0.1)	Allergic reaction	1 (0.1)
Pancreatitis	2 (0.1)	Anaphylactoid reaction	1 (0.1)
Liver function tests abnormal	1 (0.1)	Myopathy	1 (0.1)
Cholestatic jaundice	1 (0.1)		
Jaundice	1 (0.1)		

Of these SAEs, only 1 occurred during double-blind trials, but was considered unrelated to study medication. There were 7 SAEs that were possibly related to pregabalin treatment, or for which an alternate explanation was not apparent. The summaries of these events are provided below:

Acute kidney failure:

014 017006 This 71 year old male with diabetes mellitus, neuropathy, renal insufficiency, left renal artery stenosis, atrophic right kidney, and gout developed acute renal failure. The subject was hospitalized on study day 8 (open label pregabalin) following a fall (possible syncope), inability to rise due to weakness, and shoulder pain. His creatinine was 4.2mg/dL, BUN was 78mg/dL and potassium was 5.1. During a preceding RCT where he received placebo, his creatinine was 1.6 mg/dL and during a preceding open label pregabalin trial his creatinine ranged from 1.6-2.1mg/dL. He was considered recovered by study day 12. He continued in this open label trial and his creatinine ranged from 1.9-2.2mg/dL.

029 043036 This 62 year old female with diabetes mellitus, neuropathy, thyroid carcinoma, hypertension, and congestive heart failure was hospitalized for acute renal failure on open label study day 301. The narrative noted that she visited her cardiologist on open label study day 287 with worsening symptoms of congestive heart failure and that changes to her medication regimen were made. She visited her doctor on study day 297 and changes were made to her diuretic and potassium medications (not specified). On study day 302, she collapsed and her BUN was 205 , creatinine 5.4, sodium 124 and potassium 7.9 (no units provided in the narrative). She was treated with kayexalate, calcium gluconate, bicarbonate, saline, a diuretic, an ace inhibitor and her insulin was switched to pioglitazone. On open label study day 306, her BUN was 25, creatinine 1.3, and potassium 4.2. Renal ultrasound was reportedly unremarkable. The subject recovered and continued in the study.

149 430001 This 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

Lung fibrosis:

Patient 013006 (Study 1008-015)

A 71-year-old white man with painful diabetic neuropathy, was presented to the ER on Study Day 181, was ruled out for heart failure, then hospitalized for pulmonary fibrosis on Study Day 184. History included gastroesophageal reflux, Raynaud's disease, and asthma. The patient had received pregabalin 500 mg/day for 73 days when he decided to discontinue the study medication. He had participated in previous Study 1008-014 five months earlier, receiving placebo. At last follow-up, he had not yet recovered.

Leukemoid reaction

Patient 015001 (Study 1008-033)

Patient 015001, Study 1008-033, a 72-year-old white woman with painful diabetic neuropathy and a family history of leukemia was hospitalized for cognitive changes on Study Day 386 (3 days post treatment) of open-label pregabalin. Study medication consisted of pregabalin 600 mg/day for 375 days. The patient participated in a previous Study 1008-029 and received pregabalin 600 mg/day for 37 days. The patient was diagnosed with a low platelet count on Study Day 320, and medication was temporarily discontinued until Study Day 335. On study day 856 she developed pancytopenia, and myelodysplasia (leukemoid reaction), and on Day 383, the pregabalin was interrupted due to a low platelet count. On Day 867 she was diagnosed with myelodysplastic syndrome. She died on Study Day 941 (519 days post-treatment). Total exposure to the study medication was 420 days.

Edema

Patient 029-024003

A 52 year old man with diabetes received pregabalin 75 mg/day for 35 days in he double blind trial 10089-029, and open label treatment with 600 mg/day for 492 days when he was hospitalized for edema in both lower extremities.

Macrocytic anemia

Patient 356021 (Study 1008-149)

Patient 356021, Study 1008-149, a 62-year-old white man with diabetic neuropathy, was hospitalized with macrocytic anemia, shortness of breath and pitting edema in the lower extremities on Study Day 63 of pregabalin 300 mg/day. On study Day 64, a peripheral blood smear showed marked macrocytic anemia, occasional target cells, slight polychromasia, and eosinophylia. Core liver biopsies showed established cirrhosis with mild activity.

As stated earlier, the AE database was queried to identify DPN subjects who reported select dermatologically-related AEs that would suggest a wound or infections origin. This search was conducted due to the findings of dermatopathy in animal studies. The query identified several preferred terms of interest, listed in the table that follows. Additionally, subjects who had allergic, anaphylactoid, or unevaluable reactions were identified. A total of 34 patients had one or more of these dermatologically-relevant SAEs, and their frequency is shown below.

Table 7.4.4.3.1.c: Dermatologically-related SAEs of interest – DPN combined trials

SAE	Any Dose Pregabalin [N = 1413] N (%)	SAE	Any Dose Pregabalin [N = 1413] N (%)
Cellulitis	12 (0.8)	Healing abnormal	1 (0.1)
Skin ulcer	7 (0.5)	Joint disorder	1 (0.1)
Abscess	4 (0.3)	Osteomyelitis	1 (0.1)
Anaphylactoid reaction	1 (0.1)	Pyogenic arthritis	1 (0.1)
Peripheral gangrene	3 (0.2)	Rash	1 (0.1)
Allergic reaction	2 (0.1)	Sepsis	1 (0.1)

All of the corresponding CRFs were reviewed to ascertain whether there was a relationship to study drug. Specific narratives suggestive of a relationship to pregabalin are described below:

Abscess

Patient 035008, a 53-year-old white man with diabetic peripheral neuropathy was hospitalized for groin abscess on Study Day 1139 of open-label pregabalin. History includes penile implant. Study medication consisted of pregabalin 300-500 mg/day (exact dose at the time of hospitalization is unknown) for 1139 days. The patient participated in a previous double blind study and received pregabalin 75 mg/day for 33 days. Total exposure to study medication was 1172 days.

Cellulitis

Patient 036013, Study 1008-033, a 69-year-old white female with painful diabetic neuropathy was hospitalized for bilateral lower extremity cellulitis, bilateral urticaria of arms, and bilateral lower extremity swelling (peripheral edema) on Study Day 58. History includes hypertension, hypothyroidism, hyperlipidemia, and post-operative streptococcal infection. Open label treatment consisted of varying pregabalin doses (300- to 450 mg/day). She had previously participated in a double blind trial and received pregabalin 75 mg/day for 36 days. Total pregabalin exposure was 92 days . Study medication was discontinued upon hospitalization. The patient's edema had begun on Study Day 15 of the double blind treatment and progressed. It was believed that the bilateral lower extremity cellulitis was due to streptococcus. However, blood cultures were not reported.

Patient 015009, a 46-year-old white woman with painful diabetic neuropathy, was hospitalized for cellulitis of the left leg on Study Day 50 and again on Study Day 177 of open-label treatment with pregabalin 600 mg/day. . History included morbid obesity, atrial flutter, non-pitting edema, and hypertension. The patient participated in previous double blind trial and received pregabalin 600 mg/day for 40 days. Total exposure to study medication was 88 days at the time of the first hospitalization, and 217 days at the second hospitalization. The etiology of the cellulitis was not described (e.g. accidental injury to the skin).

Patient 015016 a 69-year-old white man with painful diabetic neuropathy, was hospitalized for cellulitis of the right leg on Study Day 42 of open-label treatment with pregabalin 600 mg/day. The patient developed an ulcer on his right great toe with red streaks spreading upward from the lesion. History included hypertension and obesity. The patient had previously received placebo in a double blind trial. Total exposure to pregabalin was therefore 42 days. It is not clear if the ulcer developed spontaneously or not.

7.4.4.3.2 Postherpetic neuralgia - SAEs

PHN Controlled Trials - SAEs

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 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. Unlike the DPN patients, the most common SAE was cerebral ischemia (pregabalin 0.35%, placebo 0.25%).

Table 7.4.4.3.2.a: SAEs, by decreasing frequency - Controlled PHN trials

Body system	Preferred term	Placebo [N=398] N	Placebo [N=398] %	All PGB [N=852] N	All PGB [N=852] %
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 only SAE in that is suggestive of a relationship with pregabalin is the anaphylactoid reaction:

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.

PHN Combined Controlled and Uncontrolled Trials - SAEs

The Applicant reported that 13% (145/1111) of pregabalin-treated patients in PHN combined controlled and uncontrolled studies had at least one SAE. Accidental injury was the most common SAE and the only one reported by more than 1% of the patients. The other more frequently experienced SAEs were pneumonia, myocardial infarction, syncope, and urinary tract infection.

Table 7.4.4.3.2.b: SAEs, by decreasing frequency – Controlled and uncontrolled PHN trials

Body system	Preferred term	No. pts	%
Body as a whole	**Accidental injury**	**15**	**1.35**
	Carcinoma	5	0.45
	Chest pain	4	0.36
Cardiovascular system	Myocardial infarct	7	0.63
	Syncope	6	0.54
	Congestive heart failure	5	0.45
	Angina pectoris	4	0.36
	Atrial fibrillation	4	0.36
	Cerebral ischemia	4	0.36
	Heart failure	4	0.36
	Ventricular extrasystoles	4	0.36
	Cerebrovascular accident	3	0.27
	Coronary artery disorder	3	0.27

Table 7.4.4.3.2.b: SAEs, by decreasing frequency – Controlled and uncontrolled PHN trials

Body system	Preferred term	No. pts	%
Cardiovascular system	Heart arrest	3	0.27
Digestive system	Gastroenteritis	4	0.36
	Gastrointestinal hemorrhage	4	0.36
	Colitis	3	0.27
Metabolic and nutritional disorders	Dehydration	5	0.45
Respiratory system	**Pneumonia**	**10**	**0.90**
	Lung disorder	3	0.27
Urogenital system	Urinary tract infection	6	0.54

SAEs in combined PHN trials that coded to preferred terms of interest (and that are not listed above) are provided in the table that follows. There were no SAEs of acute hepatic failure, rhabdomyolysis, or aplastic anemia.

Table 7.4.4.3.2.b: SAEs of interest in PHN combined trials

SAE	Any Dose Pregabalin [N = 1111] N (%)
Lung disorder	3 (0.3)
Retinal edema	2 (0.2)
Retinal disorder	1 (0.1)
Visual field defect	1 (0.1)
Necrotizing pancreatitis	1 (0.1)
Pancreatitis	1 (0.1)
Acute kidney failure	1 (0.1)
Creatinine increased	1 (0.1)
Generalized edema	1 (0.1)
Peripheral edema	1 (0.1)
Lung edema	1 (0.1)
Lung fibrosis	1 (0.1)
Myalgia	1 (0.1)
Abscess	1 (0.1)

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 reported no gall bladder inflammation and that abdominal CT and MRI were negative. She recovered without sequelae.

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.

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.

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.

7.4.4.3.3 SAEs in Epilepsy

Epilepsy Controlled trials

Pfizer summarized serious adverse event risk for the controlled epilepsy trials included in the integrated database in Appendix Epilepsy .048. Pfizer reported that 3.8% (29/758) of pregabalin subjects and 4.4% (13/298) placebo subjects reported one or more SAEs. Accidental injury was the only SAE reported by more than 1% of pregabalin subjects (pregabalin 1.2%, 9/758, placebo 0.3%, 1/294). There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, rhabdomyolysis or aplastic anemia in the epilepsy controlled trials.

Since there was an increased risk for accidental injury SAEs among pregabalin subjects compared to placebo subjects in the epilepsy controlled trials, Dr. Boehm read the narrative summaries for these events. Of the nine pregabalin subjects who experienced accidental injury SAEs during controlled trials, two (009-035008, 011-002001) had their events during the baseline phase, prior to study drug administration. One subject

experienced a burn from a cooking accident (034-003001). Two of the accidental injury SAEs were falls that occurred following a seizure (009-002006, 011-060001) and two were falls that appeared to have explanations (009-029003 lost footing and fell from ladder, 011-083007 fell from an icy roof). The two remaining accidental injury SAEs were both falls without obvious explanation for the events, but also without evidence to suggest a relationship to study drug. Those events are summarized below:

009-004012, This 63 year old male with a history of osteoporosis and static encephalopathy (cerebral palsy) fell on study day 44 while taking pregabalin 600mg/day BID. He was hospitalized for a leg fracture and withdrew from the study. He subsequently re-enrolled in the open label extension.

011-073012, This 37 year old male was hospitalized for a painful swollen leg that developed one day after a fall at work. The event occurred on study day 34 and the subject was taking pregabalin 600mg/day at the time. The circumstances surrounding the fall were not described. The subjects did have an AE of "drowsy" at a visit prior to the fall. Concomitant medications included lamotrigine, carbamazepine, and clobazam.

Epilepsy Combined Controlled and Uncontrolled Trials - SAEs

Pfizer reported that 13% (210/1613) of subjects exposed to pregabalin in combined controlled and uncontrolled epilepsy studies experienced one or more SAEs. Dr. Boehm reviewed Pfizer's table 2.74 Appendix Epilepsy.053 to examine the types of serious AEs reported during the epilepsy studies. Pregabalin subjects most frequently experienced SAEs from the Body as a Whole body system (5.6%, 90/1613). Accidental Injury was the only SAE reported by more than 1% of pregabalin subjects in the combined controlled and uncontrolled trials (2.9%, 46/1613). There were no SAEs of acute hepatic failure, acute renal failure, rhabdomyolysis or aplastic anemia in the epilepsy combined controlled and uncontrolled trials. There were several SAEs coded to preferred terms of interest including ventricular tachycardia (1), LFT abnormal (2), cholestatic jaundice (1), pancreatitis (1), CPK increased (3), psychosis (6), psychotic depression (2) hallucinations (1), schizophrenic reaction (1), Stevens Johnson syndrome (1), maculopapular rash (1), and kidney calculus (5). I reviewed the narrative for the patients with LFT abnormalities and cholestatic jaundiced, and found that the following two events did not have an alternate explanation, and suggested a relationship to pregabalin treatment:

Abnormal LFT

009-033005 This 44 year old male with partial seizures had elevated liver function tests. His baseline LFTs included AST 55U/L, ALT 92U/L, a total bilirubin of 0.3mg/dL and ALP 303U/L. On study day 14 his labs included AST 61U/L, ALT 121U/L, total bilirubin 0.3mg/dL and ALP 304U/L. His liver function tests results were similar on study day 28. On study day 56 his AST was 585U/L, ALT 840 U/L, total bilirubin 0.5mg/dL and ALP was 440U/L. A RUQ ultrasound showed a dilated common bile duct and intrahepatic ducts. Hepatitis A,B,C, and CMV serologies were negative and EBV serology showed evidence of a potential infection. Concomitant medications included phenytoin, topiramate, ibuprofen, folic acid, alendronate, hydroxyzine, famotidine, detrol, and paracetamol/oxycodone. The subject was withdrawn from the study on study day 59. Termination labs on day 112 included AST 30U/L, ALT 52U/L, total bilirubin 0.3mg/dL and ALP 172U/L. He later entered the open label extension. On study day 28 of the OL phase, his ALT was 71U/L, AST 39U/L, ALP 293U/L, and total bilirubin was 0.4mg/dL.
On study day 38, his ALT was 466U/L, AST 148U/L, ALP 291U/L and total bilirubin was 0.3mg/dL. On study day 48, his ALT was 143 U/L, AST 44U/L, ALP 275U/L and total bilirubin was 0.3mg/dL. Between study days 57 and 245, ALT fluctuated between 98 and 120U/L, AST between 41 and 64U/L, ALP 272 and 342U/L, and total bilirubin 0.2 and 0.3mg/dL. On study days 36-243 his pregabalin dose was 600mg/day, TID. At the last visit, ALT was 57U/L, AST 28U/L, ALP 292U/L and total bilirubin 0.4mg/dL.

Cholestatic jaundice

009-011006 This 64 year old male with intractable epilepsy, was hospitalized on study day 13 for increasing confusion. He was taking pregabalin 600mg/d BID at the time of the event. On study days 1-4 he developed ataxia and tremors and on study day 5 he developed headache. He was instructed to hold the evening doses of the study medication. The symptoms abated and he was told to resume his previous study medication dose. Subsequently, his symptoms recurred and on study day 12 he had moments of myoclonus, confusion, diplopia, and visual hallucinations. He was instructed to taper the study medication and withdraw from the study but investigators determined he was unable to follow instructions due to confusion and therefore he was admitted to a hospital on study day 13. On study day 14 he was withdrawn from the study. Last pre-study labs (study day -4) included an ALT of 26U/L, an AST of 27U/L and a total bilirubin of 0.4mg/dL. He was diagnosed with cholestatic jaundice but the narrative included no hospital lab results. He was discharged from the hospital on study day 21. Concomitant medications included carbamazepine, valproic acid, folic acid, glipizide, propranolol, furosemide, amitriptyline, lansoprazole, and prednisone

7.4.4.3.4 SAEs in GAD Trials

GAD Controlled Trials

The Applicant lists SAEs experienced by patients in controlled GAD studies in Appendix GAD.048 (SCS, p. 14245). SAEs are listed by body system, and the SAE risk is calculated for placebo patients, all pregabalin-treated patients, and patients assigned to each dose of pregabalin individually. The SAE risk among patients assigned to any dose of pregabalin during controlled GAD studies was 0.6% (7/1149), which was half of the risk of SAEs among patients assigned to placebo(1.2%, [6/484]). The SAE rate in the pregabalin group of 6.3/100 person-years (7/110.5 person-years) was also about half the SAE rate in the placebo group (13.0/100 person-years; [6/46.3 person-years]).

The Applicant presents SAE risks by indication and in all studies in table 16 (SCS, p. 40). The overall risk of SAEs in the pregabalin treated GAD population was considerably lower than the risk for pregabalin treated subjects in all controlled studies combined (2.3%; 129/5508), as well as the risk for pregabalin treated subjects in controlled studies for any of the other indications individually (SAE risk in DPN studies was 3.9% [38/979]; SAE risk in PHN studies was 3.3% [28/852]; SAE risk in epilepsy studies was 3.8% [29/758]).

The seven pregabalin-treated patients who experienced SAEs in controlled GAD studies experienced a total of eight SAEs (one patient experienced two concomitant events both coded as SAEs to the preferred terms dizziness and accidental injury). The only SAE that occurred in more than one patient was "accidental injury," which occurred in two patients (0.2%; 2/1149 patients). One out of 484 patients (0.2%) assigned to placebo experienced an SAE of accidental injury.

Of the SAEs coded as accidental injuries that were experienced by pregabalin-treated patients, one was a fall leading to a right wrist fracture that occurred in the setting of dizziness, and one was an injury of a finger with an axe that occurred while the patient was chopping wood. Patient 087_015013, a 71 year old female, developed dizziness and sustained a fall and right wrist fracture on study day five while in the dose titration phase; she was on pregabalin 300 mg/day at the time of the event. Concomitant medications taken by the patient at the time of the event were fluticasone, ipratropium, salbutamol,

nystatin, domperidone, ranitidine, and mebeverine. Pregabalin was discontinued on study day 6. Patient 087_032009, a 34 year old male, sustained an injury to his finger with an axe on study day 31, the last day of his taper; he had been taking pregabalin 400 mg/day but was on 300 mg/day at the time of the finger injury, which required surgery. Prior to the finger injury, the patient had developed difficulty concentrating (which was coded as "thinking abnormal") on study day 13.

Other SAEs reported by the Applicant that were experienced by one pregabalin-treated patient each were cardiomyopathy, myocardial infarction, appendicitis (coded to the preferred term "gastrointestinal disorder"), left iliac fossa pain (coded to the preferred term "bone pain")[2], and worsening of underlying GAD. No pregabalin-treated patient in a controlled GAD study had an SAE due to hepatic failure, renal failure, rhabdomyolysis, serious skin reaction, blood dyscrasia, or pancreatitis.

Dr. Boehm reviewed the patient narratives and case report forms for all the patients with SAEs. He considered the following SAEs to be possibly attributable to pregabalin treatment:

Patient 025_004031, a 39 year old male with a history of GERD and major depressive disorder as well as GAD, was diagnosed with cardiomyopathy on study day 9 after presenting with chest pain and shortness of breath while being treated with pregabalin 600 mg/day. Medications at the time of the event included only omeprazole. Of note, the patient had had a viral syndrome beginning 12 days and ending five days before the event. He underwent angioplasty and was treated with furosemide, lisinopril, and digoxin. As of study termination, he had not recovered from the SAE. No information is provided regarding the etiology of the cardiomyopathy.

Patient 085_401004, a 30 year old female with no significant past medical history other than GAD and on no medication other than pregabalin, was diagnosed with a myocardial infarction based on a routine EKG on study day 45 while receiving pregabalin 450 mg/day. This event was later considered by the Applicant to have been misreported, although it was not reclassified within the database. The patient, who had gained 8 kg since the study's inception (initially 98.0 kg, her weight had increased to 106 kg at the time of the SAE), had a routine EKG on study day 45 which was machine-read as being consistent with a recent anterior myocardial infarction. Upon questioning, she reported that she had experienced recent chest pain. She was sent to the Emergency Room and was seen by a cardiologist, who considered her chest pain to be atypical and her EKG to be "within normal limits." The case report form mentions that cardiac enzymes were ordered but the Applicant provides no results. The Applicant states that the cardiologist's opinion was not obtained until the database had been closed and locked, and therefore the event remains classified as an SAE.

GAD Combined Controlled and Uncontrolled Trials

The overall risk of serious SAEs in the controlled and uncontrolled studies combined was 1.9% (38 /1962). According to the Applicant, no individual SAEs were experienced by more than two patients. Accidental injury, bone pain, dizziness, gastrointestinal disorder

[2] Patient 087_017004 was a 37 year old woman hospitalized for four days beginning on study day 36 of pregabalin treatment; she was receiving 600 mg/day at the time of her SAE. She was treated with hydration and analgesics and discharged with a diagnosis of abdominal pain. Three months later, the patient was diagnosed with diverticulitis of the sigmoid colon. This information was obtained by the Applicant after follow-up with the investigative site on 2/2/04.

(appendicitis in both instances), myocardial infarction, neoplasm, and overdose were each experienced by two patients (0.1%; 2/1962).

There were no cases of serious skin rashes, blood dyscrasias, renal failure[3], hepatic failure, renal calculi, or rhabdomyolysis. Of note, there was one SAE each of pancreatitis, syncope, grand mal convulsion, and urinary tract disorder (verbatim term was "urinary obstruction"). Some subjects experienced concurrent SAEs: one patient had gastrointestinal hemorrhage and myocardial infarction; another patient experienced concurrent SAEs of cholelithiasis and cholecystitis. Dr. Boehm noted that one subject had a convulsion (the investigator had termed this SAE "acute possible seizure"), and three (non-cardiac) vascular SAEs --one left leg thrombosis (coded to the preferred term thrombosis), one cerebrovascular accident, and one pulmonary embolism. The CRF and narrative for the patient who had pancreatitis was reviewed and were not suggestive of a relationship to pregabalin.

7.4.4.4 Summary: SAEs

Data from controlled trials show that chest pain was the most common SAE in the DPN population, followed by accidental injury. In comparison, accidental injury was the most common SAE in the GAD and epilepsy controlled trials. Subjects in PHN controlled trials reported cerebral ischemia as the most common SAE. Notable SAEs in controlled trials that could be related to pregabalin treatment were acute renal failure and anaphylactoid reaction (n = 1, each).

Data from combined controlled and uncontrolled trials showed that again, chest pain was the most commonly reported SAE in the DPN population. On the other hand, accidental injury was the most frequent SAE in GAD, PHN, and epilepsy trials. SAEs that coded to preferred terms of interest, and for which an alternate possible cause was not clearly evident, included acute renal failure (n = 3), cellulitis (n = 3), lung fibrosis (n = 2), edema (n = 2), fall/accidental injury (n = 2), as well as pancreatitis, LFT abnormalities, jaundice, cardiomyopathy, myocardial infarction/EKG abnormality, visual field defect, retinal disorder, leukemoid reaction, and macrocytic anemia (n = 1, each).

7.4.4.5 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

[3] Patient 083_305017 had an SAE of renal infarction after 37 days of exposure to placebo in study 83. The patient was enrolled in the subsequent open-label study 84 and received pregabalin 300 mg/day for 22 days in that study. The patient's renal function remained stable while receiving pregabalin. Serum creatinine, which was 2.6 on the day of the SAE, was 2.5 after 22 days of pregabalin treatment.

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.

7.4.5 Select AEs of Interest:

As noted in the Pharmacology section above (Section 2), non-clinical studies in mice, rats, and monkeys showed spontaneous development of tail lesions (dermatopathy) which caused ulceration and loss of tails in some animals. Since patients with DPN are at significant risk of foot ulcers, I queried the AE database to identify diabetic patients who reported AEs that were suggestive of skin and/or healing abnormalities to determine if there was an increased risk of these events in patients treated with pregabalin.

Although the Clinical Pharmacology data did not indicate a possible effect of pregabalin on glucose control, or interaction with commonly used anti-diabetic medications, I queried the data to identify subjects who experienced either hyper or hypoglycemia. Rates in pregabalin-treated patients were compared to those who did not take pregabalin.

Additionally, due to reports of peripheral edema and vision abnormalities in early clinical studies, I queried the integrated safety database for AEs related to the eye, and metabolic/nutritional AEs. I carefully 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.

Finally, even though it was not expect that the data would show any remarkable findings with respect to neoplasms, the frequency of neoplasms in all pregabalin-exposed subjects was calculated. This was because the dataset was relatively large (8, 666 subjects), and at least 200 patients had been exposed to the highest proposed dose (600 mg/day) for upwards of 2 years. The types of cancers reported were reviewed for similarities to hemangiomas.

7.4.5.1 Dermatological AEs

All Controlled trials - All Indications

A total of 514 patients reported a skin or appendage AE – 6.9% (165/2384) of placebo patients, and 5.6% (312/5508) – during controlled trials. A list of these AEs is found below:

Table 7.4.5.1.a: Frequency of skin/appendage AEs – Controlled trials, All indications

Skin AE	Total No. Pts	Placebo N	N=2384 %	All PGB N	N=5508 %
Rash	**164**	**55**	**2.31**	**100**	**1.82**
Pruritus	74	32	1.34	40	0.73
Sweating	71	20	0.84	32	0.58
Acne	39	16	0.67	22	0.40
Dry skin	31	8	0.34	23	0.42
Herpes simplex	26	9	0.38	17	0.31
Alopecia	18	10	0.42	8	0.15
Skin disorder	17	3	0.13	14	0.25
Eczema	14	2	0.08	11	0.20
Herpes zoster	14	2	0.08	11	0.20
Contact dermatitis	13	3	0.13	10	0.18
Maculopapular rash	10	2	0.08	5	0.09
Urticaria	9	0	0.00	8	0.15
Furunculosis	8	3	0.13	5	0.09
Fungal dermatitis	7	2	0.08	4	0.07
Skin ulcer	**6**	**2**	**0.08**	**3**	**0.05**
Vesiculobullous rash	6	1	0.04	4	0.07
Nail disorder	5	3	0.13	2	0.04
Skin discoloration	5	1	0.04	4	0.07
Exfoliative dermatitis	3	1	0.04	2	0.04
Ichthyosis	2	1	0.04	1	0.02
Pustular rash	2	0	0.00	2	0.04
Skin nodule	2	1	0.04	1	0.02
Subcutaneous nodule	2	1	0.04	1	0.02
Angioedema	1	0	0.00	0	0.00
Cutaneous moniliasis	1	0	0.00	1	0.02
Hair disorder	1	0	0.00	1	0.02
Hirsutism	1	0	0.00	1	0.02
Seborrhea	1	0	0.00	1	0.02
Skin atrophy	1	0	0.00	1	0.02
Skin carcinoma	1	0	0.00	1	0.02
Skin hypertrophy	1	0	0.00	1	0.02

Rash was the most commonly reported AE in both treatment groups, but did not occur with greater frequency among pregabalin treated patients. Skin ulcer occurred in 0.05% of pregabalin-treated patients, and was also not suggestive of a relationship to drug treatment.

DPN Controlled trials

Data from DPN controlled trials was searched for all repots of skin- or appendage AEs. In addition, since the preferred term "cellulitis" was occasionally coded under "body as a whole", this was used as a separate search term. The frequency of these events was compared across treatment groups and is shown in Table 7.4.5.1.b. Again, rash was the most common skin-related AE, occurring with greater frequency in the placebo group. Otherwise, there was essentially no difference in the frequency of skin-related AEs between the placebo and pregabalin treatment groups.

Table 7.4.5.1.b: Frequency of skin/appendage AEs – DPN Controlled trials

	Number of Patients (%)									
	Total pregabalin daily dose (mg/day)									
	Placebo	N=459	150	N=212	300	N=321	600	N=369	All PGB	N=979
Preferred term	N	%	N	%	N	%	N	%	N	%
Rash	8	1.74	1	0.47	2	0.62	7	1.9	10	1.02
Pruritus	6	1.31	0	0	3	0.93	0	0	5	0.51
Cellulitis	0	0	1	0.47	2	0.62	1	0.27	4	0.41
Eczema	0	0	2	0.94	1	0.31	1	0.27	4	0.41
Skin disorder	0	0	0	0	1	0.31	3	0.81	4	0.41
Vesiculobullous rash	0	0	0	0	2	0.62	2	0.54	4	0.41
Dry skin	2	0.44	0	0	1	0.31	1	0.27	3	0.31
Fungal dermatitis	0	0	1	0.47	1	0.31	0	0	3	0.31
Skin ulcer	2	0.44	1	0.47	1	0.31	1	0.27	3	0.31
Urticaria	0	0	1	0.47	1	0.31	1	0.27	3	0.31
Furunculosis	0	0	0	0	1	0.31	1	0.27	2	0.2
Herpes zoster	0	0	0	0	0	0	2	0.54	2	0.2
Skin discoloration	0	0	1	0.47	0	0	1	0.27	2	0.2
Sweating	2	0.44	0	0	1	0.31	0	0	2	0.2
Acne	3	0.65	0	0	0	0	1	0.27	1	0.1
Contact dermatitis	1	0.22	0	0	0	0	1	0.27	1	0.1
Hirsutism	0	0	0	0	1	0.31	0	0	1	0.1
Ichthyosis	1	0.22	0	0	1	0.31	0	0	1	0.1
Pustular rash	0	0	1	0.47	0	0	0	0	1	0.1
Skin carcinoma	0	0	0	0	0	0	0	0	1	0.1
Alopecia	1	0.22	0	0	0	0	0	0	0	0
Exfoliative dermatitis	1	0.22	0	0	0	0	0	0	0	0
Herpes simplex	1	0.22	0	0	0	0	0	0	0	0
Maculopapular rash	1	0.22	0	0	0	0	0	0	0	0
Nail disorder	1	0.22	0	0	0	0	0	0	0	0

Skin abnormalities are of greatest concern amongst patients with diabetes, due to their unique vulnerabilities to ulceration and their increased risk of amputation. Therefore, the specific data regarding skin ulceration reports were reviewed. There were 6 subjects (6/1438; 0.4%) in controlled trials that experienced a skin ulcer:

Table 7.4.5.1.c: Patients with skin ulcers – DPN Controlled trials

Subject Number	Treatment assignment/ Dose (mg/day)at AE onset	Serious AE?	Study Day of AE onset
029-030009	Placebo/200 mg*	No	37
040-073-005	Amitriptyline/ 75 mg	No	43
040-112016	Pregabalin/600 mg	No	48
173-336010	Pregabalin / 300 mg	No	4
149-356024	Pregabalin /150 mg	Yes	36
149-391010	Placebo/ 0.0 mg	No	10

* It is unclear why the reported dose at onset is 200 mg, given that the patient was in the placebo arm

The incidence of skin ulcer by treatment group was 0.4% (2/459) for the placebo group, and 0.3% (3/979) for the pregabalin group. This suggests that treatment with pregabalin is not associated with a greater risk of skin ulceration. However, since exposure to

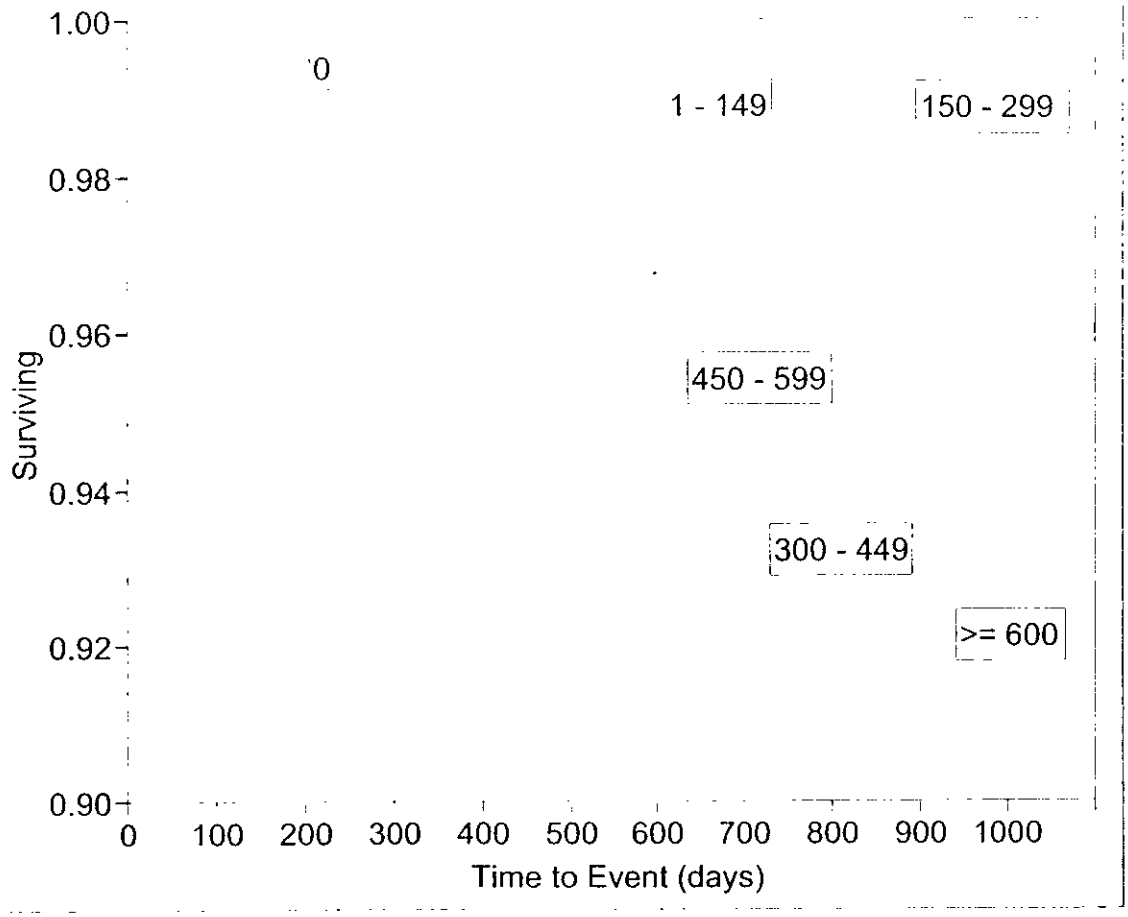
pregabalin in DPN controlled trials was relatively short (≤ 12 weeks), these findings may not accurately capture the incidence of skin ulceration in DPN patients treated with pregabalin. Therefore the data were reanalyzed after combining both controlled and uncontrolled DPN trials.

DPN - combined controlled and uncontrolled trials

In the combined DPN trials, there were 271 subjects who reported a skin-related AE. Rash was the most commonly reported dermatological AE, and occurred with greater frequency among patients taking pregabalin. Skin ulcer was the next most common skin-related AE (n = 45) (see the Appendix). The majority of skin ulcers were located on the foot, ankle, or lower extremity. Additional locations of ulcers were the groin, scrotum and abdomen (n = 1, each). Only 7 ulcers were categorized as 'serious.' Each of these SAEs has an alternate possible cause for the development and/or worsening of the skin ulcer.

I attempted to ascertain whether there was a difference in the proportion of skin ulcers between patients taking no pregabalin and pregabalin-exposed patients, and whether there was a dose-response effect. Unfortunately, unlike the controlled trials, the uncontrolled (open-label) studies did not incorporate a fixed dose. Instead, the uncontrolled trials used a titration design and allowed dose adjustments throughout the period of participation. Most people were titrated to target doses of 300 mg/day or 600 mg/d, but various intermediate doses were used at different times. Therefore to explore for dose dependency in the development of skin ulcers, dose at onset was used, even though that is, to some degree, especially at the lower doses, a reflection of time in study. When the number of people who reported skin ulcers, by dose at onset, was examined, there was suggestion that the frequency was highest among patients who were taking 600 mg/d or higher, and that some dose-dependence was apparent.

Dr. Thomas Permutt, the Statistics Team Leader, conducted a Kaplan-Meier plot of ulcer-free "survival" for DPN patients (all DPN trials). This type of analysis took duration of drug exposure into account, and showed no considerable difference in the frequency of skin ulcers across dose groups (refer to the review by Dr. Permutt).



Consequently, the data do not establish an association between pregabalin treatment and skin ulcers in the DPN population. However, in the absence of a comparator group exposed for a similar duration as the pregabalin group, the possibility of a real effect cannot be ruled out.

7.4.5.2 Eye-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 7.4.5.2.b: 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
Amblyopia	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)
Amblyopia coded to verbatim terms of "blurry vision"

DPN controlled trials

The analysis was repeated using data from DPN controlled trials only. A total of 76 patients reported decreased visual acuity (n = 43), visual field defects (n = 11), diplopia (n = 9), or vision abnormalities (n = 13). The frequency of these events by treatment group is shown in Table 7.4.5.2.b. Blurred vision (amblyopia) and vision abnormalities were more frequent in DPN pregabalin-treated patients, and appeared to be dose-dependent. There did not appear to be a considerable difference between pregabalin and placebo groups with respect to visual field defects.

Table 7.4.5.2.b: Select vision AEs – DPN Controlled trials

	Number of Patients (%)									
					Total pregabalin daily dose (mg/d)					
Preferred term	Placebo N=459		All PGB N=979		150 N=212		300 N=321		600 N=369	
	N	%	N	%	N	%	N	%	N	%
Abnormal vision	1	0.22	11	1.12	1	0.47	4	1.24	5	1.36
Amblyopia	7	1.53	35	3.58	3	1.42	9	2.80	21	5.69
Diplopia	0	0.00	8	0.82	2	0.94	4	1.24	1	0.27
Visual field defect	5	1.09	6	0.61	3	1.42	1	0.31	2	0.54

All PGB includes 75 mg/day
Amblyopia coded to verbatim terms of "blurry vision"

All Indications, All trials

There were 2005 patients who reported an eye-related AE. There were 289 reports of eye-related AEs when patients were taking either placebo or no study drug at all, and 2125 reports when subjects were taking pregabalin.

Amblyopia (verbatim term, "blurry vision") was the most commonly reported eye-disorder (10%, 865 patients), followed by diplopia (3.7%, 320 patients), abnormal vision (3.1%, 267 patients), and visual field defects (2.4%, 212 patients).

7.4.5.3 Metabolic AEs: Hyperglycemia and Hypoglycemia

DPN Controlled trials

I queried data from DPN trials only using the term "metabolic" and then selecting for all reports of hyperglycemia. There were 17 patients in DPN controlled trials who reported hyperglycemia, 1 of whom (patient 149_371008, pregabalin 600 mg/d) had a serious episode of hyperglycemia which was unlikely to be drug-related. With respect to hypoglycemia, 22 patients experienced 36 episodes of this AE. Two patients had hypoglycemia SAEs (Patient 149_400002, pregabalin 150 mg/d and Patient 149_430002, pregabalin 300 mg/d). These episodes were also considered not likely to be drug related. A comparison of the frequency of hyperglycemia and hypoglycemia by treatment group is shown in the table.

Table 7.4.5.3: Frequency of hyper- and hypoglycemia AEs – DPN controlled trials

	Number of Patients (%)									
					Total pregabalin daily dose (mg/d)					
Preferred term	Placebo N=459		All PGB N=979		150 N=212		300 N=321		600 N=369	
	N	%	N	%	N	%	N	%	N	%
Hyperglycemia	3	0.65	14	1.4	4	1.9	5	1.6	5	1.4
Hypoglycemia	5	1.1	17	1.7	7	3.3	5	1.6	4	1.1

All PGB includes 75 mg/day

Overall, treatment with pregabalin appears to be associated with a greater risk of glucose abnormalities compared to placebo. The risk of hyperglycemia seems to be greater than that of hyperglycemia. These findings, however, are not supported by the clinical pharmacology data which show that pregabalin did not alter the pharmacokinetics of the anti-diabetic medications that were used by patients in the study, and vice versa.

7.4.5.4 Metabolic AEs: Peripheral 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 7.4.5.4: Peripheral edema by indication – 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
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)

Combined controlled and uncontrolled studies – All indications
Overall, 9.9% of patients in the combined controlled and uncontrolled studies had an adverse event of peripheral edema during pregabalin treatment. Relative to the controlled studies, the overall incidence of peripheral edema in patients with DPN, PHN, and epilepsy generally increased with long-term exposure. Similar results were obtained when the terms "generalized edema" and "edema" were included. Although the adverse events of hypertension and dyspnea had higher incidences in patients with peripheral edema than in patients without, these events were not associated with other complications that were considered related to pregabalin

Eight pregabalin-treated patients had serious adverse events of peripheral edema (Patients 010_008101, 011_073012, 011_093002, 029_036013 in Study 033, and 196_206001) or edema/generalized edema (014_017002, 029_024003 and 030_131024) One placebo-treated patient had a serious event of edema (Patient 045_068006). Of the pregabalin-treated patients, 1 DPN patient (Patient 029_024003 in Study 033) and 1 PHN

patient (Patient 196 206001) had a serious, treatment-related event of edema/peripheral edema.

Reviewer comment: Similar to the preclinical findings of dermatopathy, the clinical events of edema especially conderning with regards to the DPN population. Edema can disrupt skin integrity, and may have serious consequences in the diabetic population that is already at risk for skin ulceration.

7.4.5.5 Neoplasms

Of the total exposed population, 70 subjects (0.8%) developed at least one neoplasm. Most tumors were described as "polyps" and were considered "non-serious." Eight neoplasms were described as serious, and included 1 case each of an eye mass, a corpus polyp, nasal polyps, ethmoid polyps, as well as 4 cases of renal tumors (including 1 case of a bleeding angioleiomyoma). Additionally, 1 patient reported cherry angiomas and another developed "angiomas." Neither case was considered serious. There were 4 unspecified and non-serious face/scalp tumors, and no hepatic tumors.

7.4.5.6 Male fertility

As described in Section 2.3.5, animal studies showed that treatment with high doses of pregabalin was associated with changes in male fertility and sperm motility. To evaluate any effects of pregabalin on sperm and semen in human males, Pfizer conducted a brief study of pregabalin 600 mg/d in 46 healthy male volunteers. The men were randomized to placebo (n=16) or pregabalin 200 mg TID (n = 30) for 4 weeks.

Dr. Olivia Johnson (HFD 580reviewed the data from this clinical study and foundthat although the study did not show clinically meaningful changes in seminal fluid parameters, the study was not powered to detect a signficant effect in sperm concentration. Also, although a similar number of placebo and pregabalin patients had > 15% decrease in sperm motility, the small sample size and the study design limit definite conclusions about the reproductive safety of pregabalin in men.

Reproductive AEs – All controlled trials, all indications

In an effort to determine whether treatment with pregabalin affected male sexual and/or reproductive funciton, I evaluated the frequency of reporting of abnormalities in factors related to male fertility in all controlled trials. I identified 317 males (47 placebo, 218 pregabalin, 52 "other") who reported AEs coded under the "endocrine" and "urogenital," body systems. There were 148 patients who experienced AEs consistent with reproductive abnormalities, none which was considered "serious.":

Table 7.4.5.6: Reproductive AEs - All controlled trials, all indications

AE	PBO N = 2384		All PGB N = 5508	
	N	%	N	%
Abnormal ejaculation	1	0.04	36	0.65
Anorgasmia	0	0.00	21	0.38
Breast pain	2	0.08	1	0.02
Gonadotropic follicle stim hormone increase	1	0.04	2	0.04
Hypogonadism male	1	0.04	0	0.00
Impotence	8	0.34	74	1.34
Penis disorder	0	0.00	5	0.09
Prostatic carcinoma	1	0.04	0	0.00
Prostatic disorder	3	0.13	3	0.05

The mean age of the patients with the AEs listed above was 46.5 years (range 20-79 years), and the median age of subjects with impotence was 48 years (range 22-75). The majority of patients were enrolled in trials of GAD or other psychiatric disorders. There were 4 patients in DPN controlled trials who reported impotence, all of whom were treated with pregabalin (150 mg/d (1 patient) and 600 mg/d).

Adverse event data from controlled trials suggest that, in the short term, treatment with pregabalin is not associated with negative effects on male reproductive function.

7.4.6 Common Adverse Events

To examine the common adverse event profile for pregabalin, only the controlled studies of patients with pain due to diabetic peripheral neuropathy (controlled DPN 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 diabetes 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 DPN controlled studies was felt to be otherwise reasonable because they were placebo-controlled and of similar design.

Table 7.4.6. lists, by body system, the non-serious adverse events reported by more than 1% of pregabalin-treated patients in the controlled DPN studies. Overall, nervous system abnormalities were the most common AEs. Specifically, dizziness (21.4%) and somnolence (12.2%) were the most frequent (relative risks of 4.7 each). Other CNS AEs included changes in mental status (confusion, abnormal thinking, euphoria), motor effects (gait abnormalities, incoordination, tremor, ataxia), and vertigo. Another notable common AE was edema, which occurred in 13.5% of pregabalin-treated patients. Also, amblyopia and vision abnormalities occurred with greater frequency than in placebo

patients. Finally, there were gastrointestinal effects of dry mouth, constipation, and dyspepsia.

Table 7.4.6 Non-serious AEs in DPN controlled trials

Body system	Preferred term	Pregabalin dose at which AE occurred (mg/d)											
		Placebo	[N=459]	75	[N=77]	150	[N=221]	300	[N=321]	600	[N=369]	All PGB	[N=979]
		N	%	N	%	N	%	N	%	N	%	N	%
Body as a whole	Headache	41	8.93	5.00	6.49	13	5.88	23	7.17	29	7.86	70	7.15
	Infection	33	7.19	5.00	6.49	18	8.14	29	9.03	16	4.34	68	6.95
	Asthenia	12	2.61	3.00	3.90	4	1.81	14	4.36	27	7.32	48	4.90
	Pain	20	4.36	4.00	5.19	9	4.07	10	3.12	19	5.15	42	4.29
	Accidental injury	16	3.49	4.00	5.19	6	2.71	7	2.18	18	4.88	35	3.58
	Back pain	3	0.65	0.00	0.00	5	2.26	4	1.25	8	2.17	17	1.74
	Chest pain	5	1.09	2.00	2.60	3	1.36	4	1.25	4	1.08	13	1.33
	Face edema	2	0.44	0.00	0.00	2	0.90	3	0.93	8	2.17	13	1.33
	Flu syndrome	11	2.40	1.00	1.30	1	0.45	3	0.93	7	1.90	12	1.23
Digestive system	Dry mouth	5	1.09	2.00	2.60	4	1.81	15	4.67	24	6.50	45	4.60
	Constipation	6	1.31	0.00	0.00	5	2.26	13	4.05	22	5.96	40	4.09
	Diarrhea	23	5.01	4.00	5.19	6	2.71	6	1.87	13	3.52	29	2.96
	Nausea	26	5.66	1.00	1.30	5	2.26	12	3.74	9	2.44	27	2.76
	Flatulence	6	1.31	2.00	2.60	0	0.00	7	2.18	10	2.71	19	1.94
	Vomiting	7	1.53	1.00	1.30	3	1.36	7	2.18	4	1.08	15	1.53
	Dyspepsia	4	0.87	0.00	0.00	3	1.36	5	1.56	6	1.63	14	1.43
Metabolic and nutritional disorders	Peripheral edema	12	2.61	3.00	3.90	13	5.88	31	9.66	48	13.01	95	9.70
	Weight gain	2	0.44	0.00	0.00	9	4.07	12	3.74	23	6.23	44	4.49
	Edema	0	0.00	0.00	0.00	4	1.81	13	4.05	7	1.90	24	2.45
	Hypoglycemia	5	1.09	1.00	1.30	6	2.71	5	1.56	4	1.08	16	1.63
	Hyperglycemia	3	0.65	1.00	1.30	2	0.90	5	1.56	4	1.08	12	1.23
Musculoskeletal system	Leg cramps	8	1.74	1.00	1.30	0	0.00	4	1.25	5	1.36	10	1.02
Nervous system	Dizziness	21	4.58	6.00	7.79	19	8.60	77	23.99	108	29.27	210	21.45
	Somnolence	12	2.61	3.00	3.90	13	5.88	42	13.08	61	16.53	119	12.16
	Neuropathy	16	3.49	7.00	9.09	4	1.81	7	2.18	20	5.42	38	3.88

Table 7.4.6 Non-serious AEs in DPN controlled trials (continued)

		Pregabalin dose at which AE occurred (mg/d)											
Body system	**Preferred term**	**Placebo**	**[N=459]**	**75**	**[N=77]**	**150**	**[N=221]**	**300**	**[N=321]**	**600**	**[N=369]**	**All PGB**	**[N=979]**
		N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Nervous system	Ataxia	6	1.31	5.00	6.49	2	0.90	7	2.18	17	4.61	31	3.17
	Vertigo	5	1.09	1.00	1.30	4	1.81	8	2.49	13	3.52	26	2.66
	Confusion	3	0.65	0.00	0.00	3	1.36	7	2.18	12	3.25	22	2.25
	Euphoria	1	0.22	0.00	0.00	1	0.45	11	3.43	6	1.63	18	1.84
	Incoordination	2	0.44	1.00	1.30	1	0.45	6	1.87	7	1.90	15	1.53
	Thinking abnormal	0	0.00	1.00	1.30	0	0.00	3	0.93	11	2.98	15	1.53
	Tremor	0	0.00	1.00	1.30	3	1.36	4	1.25	6	1.63	14	1.43
	Abnormal gait	0	0.00	1.00	1.30	0	0.00	2	0.62	10	2.71	13	1.33
	Insomnia	4	0.87	1.00	1.30	3	1.36	3	0.93	6	1.63	13	1.33
	Reflexes decreased	8	1.74	3.00	3.90	1	0.45	4	1.25	5	1.36	13	1.33
	Amnesia	1	0.22	2.00	2.60	2	0.90	0	0.00	8	2.17	12	1.23
	Nervousness	1	0.22	0.00	0.00	2	0.90	3	0.93	5	1.36	10	1.02
Respiratory system	Bronchitis	6	1.31	2.00	2.60	3	1.36	2	0.62	7	1.90	14	1.43
	Dyspnea	3	0.65	2.00	2.60	0	0.00	6	1.87	6	1.63	14	1.43
	Pharyngitis	5	1.09	0.00	0.00	2	0.90	5	1.56	4	1.08	11	1.12
Skin and appendages	Rash	8	1.74	0.00	0.00	1	0.45	2	0.62	7	1.90	10	1.02
Special senses	Amblyopia	7	1.53	2.00	2.60	3	1.36	9	2.80	21	5.69	35	3.58
	Abnormal vision	1	0.22	1.00	1.30	1	0.45	4	1.25	5	1.36	11	1.12
Urogenital system	Urinary tract infection	6	1.31	0.00	0.00	2	0.90	4	1.25	6	1.63	12	1.23

This list of all non-serious adverse events was reviewed to identify AEs that coded to preferred terms of potential importance, but occurred in less than 1% of pregabalin-treated patients. The following select AEs were identified:

AE of interest	% Pregabalin	% Placebo
Creatinine clearance decreased*	0.41	0.22
Creatinine increased	0.1	0.0
Kidney function abnormal	0.1	0.0
Liver function tests abnormal	0.2	0.0
Pancreatitis	0.1	0.0
Cellulitis	0.41	0.0
Mouth ulceration	0.31	0.0

* Relative risk = 1.9

While the table shows suggests there was an apparent increased risk of a decrease in creatinine clearance, the small numbers of patients involved makes this conclusion unlikely. There was no apparent greater risk of skin ulcer, wounds, rash, visual field defects, myopathy/rhabdomyolysis, jaundice, renal or hepatic abnormalities, pancytopenia, leukopenia, or lung disorders in controlled DPN trials.

7.4.6.1 DPN controlled trials: Trials with titration vs. trials without titration

The safety data for controlled DPN trials were evaluated to see if there were differential rates of dropouts, non-serious adverse events, and dropouts due to these non-serious adverse events. All protocols except for 1008-131 incorporated a titration phase.

Dropout rates

Non-titrated DPN controlled trial (Protocol 1008-131)

All 146 subjects (70 placebo, 76 pregabalin) in Protocol 131, completed study termination visits. A total of 127 subjects completed double-blind treatment, and 19 subjects withdrew prematurely. The dropout rate for this non-titrated trial was therefore 13% (19/146). Dropout rates by treatment group were 11% (8/70) in the placebo group and 14.5% (11/76) in the pregabalin group.

Titrated DPN controlled trials

There were 1034 subjects who completed titrated DPN controlled trials. A total of 345 subjects withdrew, including 118 subjects in Protocol 1008-173 who were withdrawn due to the FDA's imposition of a partial clinical hold. Therefore, dropout rates in DPN controlled trials were analyzed after removing subjects enrolled in Protocol 1008-173 (n = 147). Consequently, out of 1232 subjects in titrated DPN controlled trials, 1027 subjects completed treatment, and 205 subjects (16.6%) dropped out. Dropout rates among the placebo- and pregabalin-treated subjects were 15.9% (57/359) and 17% (148/873), respectively.

Comparison of the overall dropout rates for titrated trials (15.9%) vs. non-titrated trials (13%) suggests that titration is associated with a higher rate of dropout. The data also

suggest that treatment with pregabalin is associated with a greater rate of dropout than placebo.

Non-serious (common) AEs – titrated DPN trials
A total of 884 subjects reported a non-serious AE (211 placebo, 59 amitriptyline, and 614 pregabalin subjects). Table 7.4.6.1.a. lists, by body system, the non-serious adverse events reported by patients in titrated studies compared to patients in the single non-titrated study.

The table illustrates that dizziness and somnolence were the most common AEs for both titrated and non-titrated controlled DPN studies. However the non-titrated trial was associated with almost twice the rate of dizziness and somnolence (36% and 20%) than the non-titrated trials (19% and 10%, respectively). Lack of drug titration was also associated with a greater frequency of euphoria (5% vs. 0%). Otherwise, rates of non-serious AEs was similar between titrated and non-titrated controlled DPN studies.

Rates of dropout due to common AEs
There were 10 subjects in the non-titrated trial and 121 subjects in the titrated trials who withdrew due to AEs (13 in Study 014, 18 in Study 029, 33 in Study 040, 32 in Study 149, and 15 in study 173). The rates of dropout due to AEs were therefore 6.8% (10/146) in non-titrated trials, and 11.7% in titrated trials. Table 7.4.8.1.b shows all of the non-serious AEs that led to subject withdrawal in the titrated DPN trial. It also lists the non-serious AEs that occurred in more than 0.3% of subjects who discontinued titrated DPN controlled studies.

The table shows that non-serious CNS-related AEs were the most common reasons for withdrawal from DPN controlled trials in which drug titration was incorporated. Also, dizziness and somnolence were the leading causes of study withdrawal for both titrated and non-titrated DPN controlled trials.

Table 7.4.6.1.a: Non-serious (common) AEs in DPN controlled trials – Titrated trials vs. Non-titrated trials

		Titrated trials*				Non-titrated Trials**			
Body System	**Preferred term**	Placebo	[N=389]	All PGB	[N=903]	Placebo	[N=70]	All PGB	[N=76]
		N	%	N	%	N	%	N	%
Body as a whole	Infection	28	6.10	57	5.82	5	7.14	11	14.47
	Asthenia	10	2.18	45	4.60	2	2.86	3	3.95
	Accidental injury	12	2.61	32	3.27	4	5.71	3	3.95
	Cellulitis	-	-	-	-	0	0.00	2	2.63
	Back pain	3	0.65	16	1.63	0	0 00	1	1.32
	Face edema	2	0.44	12	1.23				
Nervous system	Dizziness	13	2.83	183	18.69	8	11.43	27	35.53
	Somnolence	10	2.18	104	10.62	2	2.86	15	19.74
	Ataxia	5	1.09	30	3.06	1	1.43	1	1.32
	Vertigo	5	1.09	26	2.66	-	-	-	-
	Confusion	2	0.44	22	2.25	-	-	-	-
	Thinking abnormal	0	0.00	15	1.53				
	Euphoria	-	-	-	-	0	0 00	4	5 26
	Incoordination	1	0.22	14	1.43	-	-	-	-
	Tremor	0	0.00	14	1.43	-	-	-	-
	Reflexes decreased	8	1.74	13	1.33	-	-	-	-
	Insomnia	3	0.65	12	1.23	-	-	-	-
	Amnesia	1	0.22	12	1.23	-	-	-	-
	Abnormal gait	0	0.00	12	1.23	-	-	-	-
	Depersonalization	-	-	-	-	0	0.00	2	2.63
	Depression	-	-	-	-	0	0 00	2	2 63
	Nervousness	-	-	-	-	0	0.00	2	2.63
Special senses	Amblyopia	6	1.31	31	3.17	1	1.43	4	5.26
	Diplopia	-	-	-	-	0	0.00	2	2 63
	Abnormal vision	1	0.22	10	1.02				
Metabolic and nutritional disorders	Peripheral edema	10	2.18	87	8.89	2	2.86	8	10.53
	Weight gain	2	0.44	43	4.39	-	-	-	-
	Edema	0	0.00	24	2.45	-	-	-	-
	Hypoglycemia	5	1.09	16	1.63	-	-	-	-
	Hyperglycemia	-	-	-	-	0	0.00	3	3.95

Body System	Preferred term	Titrated trials* Placebo N	[N=389] %	All PGB N	[N=90.3] %	Non-titrated Trials** Placebo N	[N=70] %	All PGB N	[N=76] %
Digestive system	Dry mouth	4	0.87	44	4.49	-	-	-	-
	Constipation	6	1.31	36	3.68	0	0.00	4	5.26
	Diarrhea	21	4.58	26	2.66	2	2.86	3	3.95
	Flatulence	5	1.09	16	1.63	1	1.43	3	3.95
	Vomiting	6	1.31	12	1.23	1	1.43	3	3.95
	Dyspepsia	4	0.87	12	1.23	0	0.00	2	2.63
Respiratory system	Dyspnea	2	0.44	14	1.43	-	-	-	-
	Lung disorder	-	-	-	-	1	1.43	2	2.63
	Sinusitis	-	-	-	-	1	1.43	2	2.63
Skin and appendages	Vesiculobullous rash	-	-	-	-	0	0.00	2	2.63
Urogenital system	Urinary tract infection	3	0.65	11	1.12	-	-	-	

* Only AEs occurring in ≥ 1% of pregabalin-treated patients are listed

** Only AEs occurring in N ≥ 1 of pregabalin-treated patients are listed

Table 7.4.6.1.b: AEs reported as reason for discontinuation from DPN controlled trials – Titrated vs. non-titrated trials

		Titrated trials				Non-titrated Trials			
Body System	**Preferred term**	Placebo	[N=389]	All PGB	[N=90.3]	Placebo	[N=70]	All PGB	[N=76]
		N	%	N	%	N	%	N	%
Nervous system	***Dizziness***	1	0.26	28	3.10	1	1.43	2	2.63
	Somnolence	0	0.00	18	1.99	0	0.00	2	2.63
	Confusion	0	0.00	7	0.78	1	1.43	0	0.00
	Ataxia	0	0.00	4	0.44	-	-	-	-
	Incoordination	0	0.00	4	0.44	1	1.43	0	0.00
	Thinking abnormal	0	0.00	3	0.33	-	-	-	-
	Tremor	0	0.00	3	0.33	-	-	-	-
	Paresthesia					1	1.43	0	0.00
	Vertigo	1	0.26	6	0.66				
Body as a whole	Asthenia	1	0.26	7	0.78	0	0.00	1	1.32
	Headache	4	1.03	6	0.66	1	1.43	0	0.00
	Accidental injury	-	-	-	-	0	0.00	1	1.32
Metabolic and nutritional disorders	Peripheral edema	1	0.26	5	0.55	-	-	-	-
	Creatinine phosphokinase increased	-	-	-	-	0	0.00	1	1.32
	SPGT increased					0	0.00	1	1.32
Digestive system	Dry mouth	0	0.00	3	0.33	-	-	-	-
	Nausea	-	-	-	-	0	0.00	1	1.32
Respiratory system	Dyspnea	2	0.51	3	0.33	-	-	-	-
Musculoskeletal system	Tendon rupture					0	0.00	1	1.32

7.4.6.2 Common AEs in DPN controlled trials: Patients with CLcr 30-60 mL/min vs. CLcr > 60 mL/min

Protocols 1008149 and -173 were reviewed to assess the effects of creatinine clearance on incidence of common (non-serious) AEs.

Protocol 149

In this study, 47 patients had a CLcr ≤ 60 mL/min (12 placebo subjects, and 35 pregabalin subjects), and 348 patients had a CLcr > 60 mL/min (85 placebo subjects and 267 pregabalin subjects). AEs occurring in at least 1 pregabalin-treated patient with a CLcr ≤ 60 mL/min are listed below. CNS-related AEs were most common, with dizziness occurring with the greatest frequency (11% in pregabalin subjects, compared to 0% in placebo patients).

Protocol 1008-149: Non-serious AEs occurring in patients with CLcr ≤ 60 mL

Body system	Preferred term	Placebo N	[N=12] %	All PGB N	[N=35] %
Nervous system	**Dizziness**	0	0.00	4	11.43
	Vertigo	1	8.33	2	5.71
	Ataxia	0	0.00	2	5.71
	Somnolence	0	0.00	2	5.71
	Tremor	0	0.00	2	5.71
Metabolic and nutritional disorders	Peripheral edema	1	8.33	3	8.57
	Weight gain	0	0.00	2	5.71
Digestive system	**Dry mouth**	0	0.00	3	8.57
Body as a whole	Headache	1	8.33	2	5.71
Cardiovascular system	Myocardial infarct	0	0.00	2	5.71
Hemic and lymphatic system	Anemia	0	0.00	2	5.71
Special senses	Amblyopia	0	0.00	2	5.71

The non-serious AEs occurring in ≥ 3 pregabalin-treated patients with a creatinine clearance > 60 mL/min are shown in the table below. In this group of subjects, peripheral edema was the most frequent AE. CNS-related AEs were also very common, particularly dizziness and somnolence

Protocol 1008-149: Non-serious AEs occurring in patients with CLcr > 60 mL/min

Body system	Preferred term	Placebo [N= 85]		All PGB [N=267]	
		N	%	N	%
Metabolic and nutritional disorders	**Peripheral edema**	2	2.35	28	10.49
	Weight gain	0	0.00	23	8.61
	Edema	0	0.00	21	7.87
	Hypoglycemia	3	3.53	12	4.49
	Hyperlipemia	0	0.00	6	2.25
	Hyperglycemia	1	1.18	5	1.87
Body as a whole	Infection	4	4.71	15	5.62
	Headache	5	5.88	11	4.12
	Pain	2	2.35	10	3.75
	Asthenia	0	0.00	10	3.75
	Accidental injury	3	3.53	8	3.00
	Face edema	1	1.18	7	2.62
	Abdominal pain	3	3.53	4	1.50
	Back pain	0	0.00	4	1.50
Nervous system	**Dizziness**	2	2.35	27	10.11
	Somnolence	1	1.18	15	5.62
	Vertigo	1	1.18	14	5.24
	Incoordination	0	0.00	4	1.50
	Insomnia	0	0.00	4	1.50
Digestive system	**Dry mouth**	0	0.00	13	4.87
	Diarrhea	4	4.71	4	1.50
	Flatulence	2	2.35	7	2.62
	Constipation	2	2.35	6	2.25
	Gastritis	0	0.00	4	1.50
	Vomiting	0	0.00	4	1.50
	Nausea	3	3.53	4	1.50
Respiratory system	Bronchitis	0	0.00	8	3.00
Cardiovascular system	Hypertension	2	2.35	6	2.25
Respiratory system	Pharyngitis	1	1.18	6	2.25
Urogenital system	Urinary tract infection	0	0.00	4	1.50

Protocol 173:

There were 27 patients with a CLcr ≤ 60 mL/min and 121 patients with a CLcr > 60 mL/min. CNS-related AEs, specifically dizziness and somnolence, were the most common AEs both groups of patients. Again, a CLcr > 60 appeared to be associated with more AEs, however this finding is likely due to the fact that there were more patients in this CLcr group. AEs occurring in at least 1 pregabalin-treated patient are listed below, according to CLcr.

Protocol 1008-173: Non-serious AEs occurring in patients with CLcr ≤ 60 mL [1]

Body system	Preferred Term	Placebo [N=5]		All PGB [N=22]	
		N	%	N	%
Nervous system	Dizziness	1	20.00	7	31.82
	Somnolence	0	0.00	2	9.09
Body as a whole	Infection	0	0.00	4	18.18
Cardiovascular system	Congestive heart failure	0	0.00	2	9.09
Metabolic and nutritional disorders	Peripheral edema	0	0.00	2	9.09

Protocol 1008-173: Non-serious AEs occurring in patients with CLcr > 60 mL/min [2]

Body system	Preferred term	Placebo [N=25]		All PGB [N=96]	
		N	%	N	%
Nervous system	Dizziness	3	12.00	11	11.46
	Somnolence	1	4.00	3	3.13
	Vertigo	0	0.00	3	3.13
	Ataxia	0	0.00	2	2.08
	Convulsion	0	0.00	2	2.08
Body as a whole	Infection	0	0.00	6	6.25
	Accidental injury	0	0.00	3	3.13
	Pain	1	4.00	2	2.08
	Face edema	0	0.00	2	2.08
	Asthenia	0	0.00	2	2.08
Metabolic and nutritional disorders	Peripheral edema	2	8.00	4	4.17
	Hypoglycemia	1	4.00	3	3.13
	Amylase increased	0	0.00	2	2.08
Digestive system	Constipation	0	0.00	2	2.08
Respiratory system	Dyspnea	0	0.00	2	2.08

1 AEs in > 1 pregabalin-treated patient
2 AEs in ≥ 2 pregabalin-treated patients

7.4.7 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).

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7.4.7.1 Laboratory mean changes - All indications, All controlled trials

The most notable differences between treatment groups from Pfizer's analysis of the mean changes from baseline to study endpoint, and from baseline to maximium value, werean increase in creatinine kinase (CK) and a decrease in platelets among pregabalin treated patients compared to placebo patients. 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. Also, 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 (Table 7.4.7.1.a)

A comparison of the mean change in CK from baseline to maximum value showed similar findings: subjects in the pregabalin group had a mean increase in CK of 60.1 U/L, compared to 27.9 for the placebo group. However, with respect to mean change from baseline to maximum value for platelets, the pregabalin group had an increase of 1.7 x $10^3/\mu L$ compared to 10.3 x $10^3/\mu L$ for the placebo group (Table 7.4.7.1.b)

While decreased platelet counts were also observed in animal studies, the animal studies did not predict the increase in creatinine kinase. This finding of an elevated CK associated with pregabalin treatment is of concern considering the potential for renal injury in the DPN population, a group that already has a high prevalence of renal impairment.

It is possible that the observed mean increase in creatinine kinase in the overall population is due to CK release during seizure episodes among the epilepsy patients. Data from controlled epilepsy trials show that the mean change in CK from baseline to study endpoint in pregabalin-treated patients was 62.7 U/L, compared to –1.2 U/L in the placebo group. The GAD population is the healthiest of all the four treatment populations, and Pfizer used the mean change in CK from baseline to endpoint for that group to compare against the epilepsy population. Mean laboratory values for the GAD population showed an increase in pregabalin-treated patients of 10.3 U/L at study endpoint, which Pfizer did not believe was considerably different from placebo (16.0 U/L). Therefore, it is possible that mean increase in CK seen in the overall safety database was driven by changes in the epilepsy population.

Table 7.4.7.1a.: Mean change at endpoint compared to baseline – All controlled trials

Test Name	Units	Placebo	150 mg/day	200 mg/day	300 mg/day	400 mg/day	450 mg/day	600 mg/day	All PGB
Hemoglobin	g/dL	-0.127	-0.173	**-0.266**	**-0.202**	**-0.224**	**-0.207**	**-0.189**	**-0.193**
Hematocrit	%	-0.411	-0.48	-0.453	**-0.517**	-0.343	**-0.745**	-0.503	**-0.504**
RBC	$\times^{106}/\mu^{L}$	-0.047	-0.049	-0.075	**-0.058**	-0.069	-0.06	-0.055	-0.056
WBC	$\times^{103}/\mu^{L}$	-0.102	-0.177	-0.318	**-0.281**	-0.266	**-0.376**	-0.185	**-0.231**
Differential-Neutrophils	%	-0.482	-0.976	**-1.95**	**-1.145**	-1.35	**-2.317**	**-1.317**	**-1.308**
Absolute-Neutrophils	$\times^{103}/\mu^{L}$	-0.078	-0.126	**-0.311**	**-0.251**	-0.257	**-0.383**	**-0.178**	**-0.22**
Differential-Lymphocytes	%	0.3525	0.7589	**1.642**	**1.0714**	1.0384	**1.6317**	**0.9817**	**1.0332**
Differential-Monocytes	%	0.1049	0.2031	0.1334	0.0091	0.1815	**0.4436**	0.1781	0.1605
Absolute-Monocytes	$\times^{103}/\mu^{L}$	0.0023	0.0138	0.0123	**-0.016**	-0.002	0.002	-0.01	-0.005
Differential-Eosinophils	%	0.0372	**0.1279**	0.0985	**0.1368**	0.1397	**0.2457**	**0.1771**	**0.1581**
Absolute -Eosinophils	$\times^{103}/\mu^{L}$	0.0009	**0.0056**	**0.0038**	0.0014	**0.0104**	0.0046	0.0018	**0.0032**
Platelets	$\times^{103}/\mu^{L}$	-0.333	**-5.348**	**-5.538**	**-11.6**	**-12.08**	**-12.3**	**-11.49**	**-9.542**
Glycosylated Hemoglobin	%	-0.043	0.0914	NC	**0.0919**	NC	NC	0.0189	0.0484
Glucose-Nonfasting	mg/dL	10.178	0.9337	0.1318	**-3.358**	-1.178	NC	3.1049	**-0.282**
CK-Creatine Kinase	U/L	4.8228	**26.341**	**21.588**	**9.6167**	**2.7786**	**-9.516**	**10.085**	**9.6638**
Creatinine	mg/dL	0.0035	0.0093	**0.018**	0.0112	0.0125	0.0056	0.0088	0.0093
Uric Acid	mg/dL	0.0205	**0.1083**	0.0216	**0.1602**	**0.1063**	**0.163**	**0.1433**	**0.1303**
BUN	mg/dL	0.1358	0.3432	0.3325	**0.7382**	0.3573	0.4454	**0.7276**	**0.5383**
Bilirubin-Total	mg/dL	-0.01	0.0033	**-0.045**	**-0.022**	**-0.042**	-0.015	-0.014	-0.015
Albumin	g/dL	-0.041	**-0.057**	**-0.129**	**-0.086**	**-0.115**	**-0.128**	**-0.102**	**-0.091**
Total Protein	g/dL	-0.052	-0.082	-0.111	**-0.101**	**-0.165**	**-0.13**	**-0.103**	**-0.104**
Alkaline Phosphatase	U/L	-1.185	**2.6064**	-0.529	**2.7793**	0.3292	-0.343	**3.1229**	**2.1067**
AST	U/L	-0.016	**0.6673**	0.2874	**0.7177**	**0.6409**	**1.3362**	**1.3913**	**0.9414**
ALT	U/L	-0.023	0.4201	-0.333	0.4876	0.4582	**2.3276**	**1.6442**	**0.9569**
HDL Cholesterol	mg/dL	0.3883	**-0.832**	NC	**-1.131**	NC	NC	**-1.854**	**-1.218**
Sodium	mEq/L	-0.237	-0.1	-0.414	**0.0932**	**0.1115**	**0.1456**	**0.1773**	**0.0459**
Calcium	mg/dL	-0.06	-0.082	-0.106	**-0.101**	**-0.14**	**-0.111**	**-0.111**	**-0.103**
Amylase	U/L	-1.258	-0.853	-1.333	**-1.306**	-1.594	**-1.576**	**-1.967**	**-1.384**
Chloride	mEq/L	0.1823	0.3949	0.3793	**0.8195**	0.2857	0.2634	**0.7203**	**0.5772**
Urine Protein	mg/dL	-1.833	-2.082	-2.307	0.1413	0.6214	-0.096	**-1.092**	**-0.725**
Urine WBC	/HPF	1.1212	0.5259	NC	**-0.427**	NC	NC	0.2841	0.1859

Values in **bold** = Statistically significantly different ($p < 0.05$) from placebo by Wilcoxon Rank-Sum test; NC = Not collected.
(Applicant's Table 25, Summary of Clinical Safety, P. 65)

Table 7.4.7.1.b.: Mean change in creatinine kinase from baseline to maximum value – All controlled trials

Test Name	Units	Placebo	150 mg/day	200 mg/day	300 mg/day	400 mg/day	450 mg/day	600 mg/day	All PGB
Creatinine kinase	U/L	27.896	44.642	39.672	31.194	8.4924	182.86	52.027	60.129

(Adapted from Applicant's Table 1.MAX.ALL (submitted March 16, 2004)

Table 7.4.7.1.c.: Mean change in platelets from baseline to minimum value – All controlled trials

Test Name	Units	Placebo	150 mg/day	200 mg/day	300 mg/day	400 mg/day	450 mg/day	600 mg/day	All PGB
Platelests	$10^3/\mu L$	-11.26	-16.79	-11.37	-22.6	-15.51	-19.7	-22.34	-19.91

(Adapted from Applicant's Table 1.MIN.ALL (submitted March 16, 2004)

7.4.7.1.1 Platelets and related hematological parameters

Controlled trials All indications

Pfizer found that a comparison of the mean decrease in platelet values from baseline to endpoint between pregabalin and placebo patients showed a considerable difference across all treatment groups. The mean decrease was not dose-related, and ranged from -5.348 x $10^3/\mu L$ in the pregabalin 150 mg/day group to –12.3 x $10^3/\mu L$ in the pregabalin 450 mg/day group (compared to –0.33 x $10^3/\mu L$ for patients who received placebo) (Table 7.4.7.1.a). Evaluation of the mean change in platelet value from baseline to lowst (minimum) value also found that the pregabalin group had a greatrer decrease in platelets (-19.91 x $10^3/\mu L$) than the placebo group (-11.26 x $10^3/\mu L$)(Table 7.4.7.1.c, 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). Patients were also divided according to whether they had 'low' (≤ 100 x10 3/mm^3) or 'very low' (count ≤ 10 x $10^3/mm^3$) platelet counts at endpoint. Low platelet counts occurred in 0.4% of placebo-treated patients and 0.9% of pregabalin-treated patients. Pfizer did not identify any patients in controlled trials who had a very low platelet count (Applicant's Appendix ALL.092).

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).

Combined controlled and uncontrolled studies – All indications

Pfizer reports that in these 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 initially identified 114 patients who had a post-baseline platelet count ≤ 100 x $10^3/mm^3$, and reveiwed these patients' data for the pattern of change over time, for accompanying adverse events of bleeding or bruising, and for concomitant decreases in other hematologic parameters. There was one pregabalin-treated patient with thrombocytopenic purpura (Patient 030_131014) and 1 pregabalin-treated patient with epistaxis (Patient 029_015001). 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.

Additionally, all patients with adverse events of thrombocytopenia, thrombocytopenic purpura, purpura, petechia were reviewed for any bleeding adverse events. One patient (Patient 010_008125) withdrew due to concurrent thrombocytopenia and rectal hemorrhage Another patient (Patient 034_026008) had concurrent petechia and intermittent rectal bleeding/rectal hemorrhage (platelet count of 122,000/mm^3), but neither event was considered serious nor led to withdrawal.

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, and categorized them by their lowest on-treatment platelet count.

Table 7.4.7.1.1.1: Pregabalin Treated Subjects with Low Platelet Counts Classified by their Lowest on Treatment Platelet Counts

Lowest Platelet Count	Number of Subjects
None ≤100,000 on treatment*	7
100,000	6
90-99,000	36
80-89,000	21
70-79,000	14
60-69,000	9
50-59,000	8
40-49,000	6
30-39,000	4
20-29,000	2
10-19,000	4
0-9,000	3

*pts either had baseline or post-treatment values < 100,000

Sixteen of the 120 subjects had a baseline platelet count <100,000. For these 16 subjects, 8 had platelet count declines on treatment, 7 had their lowest platelet count at baseline, and 1 had no on-treatment platelet counts.

Seven of 120 subjects had their only platelet count ≤100,000 either at baseline or post pregabalin treatment (i.e. no on-treatment platelet count <100,000). Of the 113 remaining patients with an on-treatment platelet count ≤100,000, 94 did not have a platelet count below 50,000. For the nine subjects with on-treatment platelet counts below 30,000, one had a baseline platelet count of 17,000. For the remaining eight subjects with on-treatment platelet counts below 30,000, this was a solitary event and none of these subjects had an additional on-treatment platelet count below 100,000. Three of these subjects had repeat normal platelet counts within days of their very low platelet counts.

To look for evidence of a treatment emergent persistent decline in platelet counts, Dr. Bohem identified subjects with a baseline platelet count ≥100,000 who had more than one on treatment platelet count <100,000 or had their last on treatment platelet count <100,000. Thirty-one subjects met these criteria (See Appendix 12) and were noted to have had baseline platelet counts that were below the lower limit of normal (140,000 or 150,000) for the study laboratories that performed the analyses (Applicant's Appendix ALL.82-85).

In addition to the platelet count information, the Agency requested a listing of all AEs for the 120 subjects with a platelet count <100,000 to determine if the low platelet counts were associated with bleeding events. Eleven of the subjects had one or more AE terms suggestive of bleeding. Dr. Boehm attempted to identify the platelet count near the time

of the AE to assess the temporal relationship. 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. Subject 030-131014 had a strong temporal relationship between AE (bruising) and a treatment emergent very low platelet count (13,000). A summary of this patient's history and treatment course is provided below:

030-131014 This 81 year old male with post herpetic neuralgia, questionable mild idiopathic thrombocytopenia (stable platelet count around 110,000), discontinued pregabalin treatment for worsening thrombocytopenia and PVCs.

Study Day	Event	Platelet count
Double blind study	PGB dose	
Baseline		123 000
End of study		87 000
Open label study	PGB dose	
Day 14		58 000
Day 25	PGB discontinued	121 000
Day 36	Pt self-administered quinine	-
Day 38	Bruising of the arm	13 000 (study site), 8000 (local ER)
Day 39	Multiple bruises	

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.

Effects of pregabalin on platelet function

As described in Section 2.3, the Applicant theorized that abnormalities in platelet function were involved in the developemnt of hemangiomas in mice. In addition to pre-clinical experiments, Pfizer conducted a clinical pharmacology study to assess the effects of pregabalin on human platelet activation. A report of the study was included in the NDA, however data from the study were not included in the integrated clinical pharmacology database because it was completed after the February 14 2003 cutoff date. This study is summarized below:

Study A0081022

"An Investigation Into the Effects of Pregabalin on Platelet Activation and Aggregation: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Single-Center Study in Healthy Volunteers"

This was a randomized, double-blind, placebo controlled 4-week study in healthy volunteers. Subjects were randomized to pregabalin 300 mg BID (n=20) or placebo (n=22) and blood samples were collected on Study Days 15 and 29. The primary endpoint was platelet activation, as assessed by expression of platelet p-selectin. The secondary endpoints were platelet aggregation and endothelial cell activation. Platelet aggregation was measured using 2 different methods: ADP-[redacted] methods; as well as the PFA-100 method [redacted] Results from Study Days 15 and 29 were compared to values from predose Day 1.

Pfizer found no evidence of platelet activation in humans, and the level of maximum platelet aggregation was not affected. Changes in ADP aggregation threshold (a measure of platelet aggregation) appeared consistent with a minor and clinically insignificant effect on circulating platelets. Pregabalin also appeared to have no clinically relevant effect on PFA closure time with ADP or epinephrine, consistent with a lack of an effect on platelet aggregation. Finally, the absence of an effect on soluble thrombomodulin suggested the absence of endothelial cell activation.

These finding led Pfizer to conclude that the effects of pregabalin on platelet parameters that were observed in mice are not evident in humans. I will add that these findings also do not explain why pregabalin-treated patients experience decreases in platelet count.

7.4.7.1.2 Creatinine kinase

Controlled trials All indications

Pfizer found that, for 5 of the 6 dose groups, the mean change from baseline to study endpoint in creatine kinase among pregabalin-treated patients was significantly increased compared with placebo (mean increases ranged from 9.6 to 26.3 U/L). There did not appear to be a dose-response relationship, and the creatine kinase value declined, (mean of -9.5 U/L), rather than increased, for the pregabalin 450 mg/day group.

Dr. Boehm noted that the mean increase from baseline to end of study for pregabalin subjects was not consistent across the different study indication databases. The epilepsy and pain controlled studies, but not the GAD controlled studies, found higher mean increases in CK for pregabalin subjects compared to placebo subjects. The mean CK increase among pregabalin subjects in the GAD studies was similar to the mean increase in pregabalin subjects in other studies, but the placebo subjects in the GAD studies experienced a mean CK increase that was inconsistent (higher) with the placebo groups in other studies. Dr. Boehm's summary of the CK results by indication is shown below.

Table 7.7.4.1.2.a: Mean Change in CK from Baseline to End of Study, Controlled Trials

Indication/Database	**Placebo** (U/L)	**Pregabalin** (U/L)
Overall	4.82	9.66
Diabetic Peripheral Neuropathy	-3.10	11.91
Post Herpetic Neuralgia	2.11	7.78
Epilepsy	-1.23	62.73
GAD	16.01	10.33

A similar evaluation was done using the mean change in CK from baseline to maximum on-treatment value and yielded the following results:

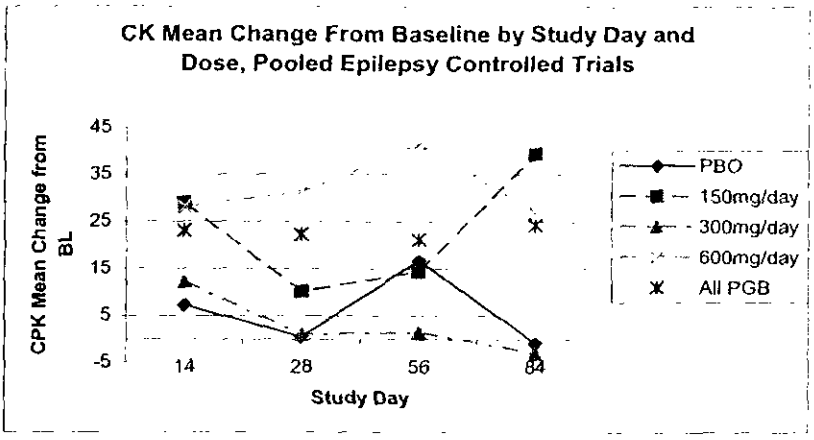
Table 7.7.4.1.2.b: CK Mean Change from Baseline to Maximum Value, Controlled Trials

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

Table 7.7.4.1.2.b above shows that the mean change in CK was greater for pregabalin subjects compared to placebo patients. Again, the largest difference is seen in the epilepsy population, which suggests that the increase may be seizure-related. Nevertheless, there are considerable differences between treatment groups across all populations, and this could be representative of a real drug effect. However, interpretation of these results is difficult since the trials were of varying duration, and some groups may have had more post-baseline laboratory assessments per patient.

Changes in CK over time

To assess when the CK changes were occurring, the Agency requested analyses of mean CK change by study visit for the epilepsy, DPN, and PHN controlled trials. Changes in CK were evaluated by indication because the trial durations and testing intervals varied considerably and made it difficult to interpret the results. Trial durations and testing intervals were identical for all the epilepsy trials, therefore this population was selected for display of CK changes over time. Dr. Boehm plotted the CK mean changes by study visit for the pooled epilepsy controlled trials. The graph shows that the mean CK increases from baseline relative to placebo were present early, varied over the course of the study, and did not suggest dose response for the studied doses.



Analysis of Outliers

In the initial NDA submission, Pfizer stratified the highest creatine kinase values during the study by multiples of the ULN, and found that 0.8% (12/1529) placebo-treated patients and 1.7% (62/3742) pregabalin-treated patients had increases >3 times the ULN.

"High" creatine kinase levels (340 U/L in males; ≥ 180 U/L in females) were observed in 8.1% (125/2384) of placebo-treated patients and 10.5% (397/5508) of pregabalin-treated patients. "Very high" creatine kinase levels (1000 U/L) were observed in 0.3% (5/2384) of placebo-treated patients and 0.7% (28/5508) of pregabalin-treated patients. Pfizer did not find a monotonic relationship between dose and percentage of patients with "high" or "very high" values, or with values that were potentially clinically important. Creatine phosphokinase increased was reported as an adverse event in 0.3% of placebo-treated patients and 0.7% of pregabalin-treated patients.

Since Pfizer's initial NDA analyses could have included subjects with abnormal results at baseline, Dr. Bohem requested an outlier analyses that included only subjects with normal CK results at baseline. Dr. Boehm summarized both the NDA analyses (all subjects) and the updated analyses (only those normal at baseline) in the following table.

Table 7.7.4.1.2.c: Summary of CK Outlier Analyses Results - Pregabalin Controlled Trials, Overall population and by Indication, *

	NDA Analysis (All Subjects)		Updated Analysis (Subjects with Normal Baseline CK)	
Outlier Criterion	Pregabalin	Placebo	Pregabalin	Placebo
Overall Pooled Controlled Trials				
>3x ULN	1.7% (62/3742)	0.8% (12/1529)	0.9 (27/2944)	0.4% (5/1223)
>340 U/L males, ≥180 U/L females	10.5% (397/3781)	8.1% (125/1544)	6.7% (200/2969)	5.6% (69/1234)
>1000 U/L	0.7% (28/3781)	0.3% (5/1544)	0.5% (16/2969)	0.2% (2/1234)
Diabetic Peripheral Neuropathy Pooled Controlled Trials				
>3x ULN	0.8% (5/595)	(0/289)	0.6% (3/517)	(0/252)
≥340 U/L males, ≥180 U/L females	7% (45/647)	5.9% (18/307)	3.6% (19/524)	4% (10/253)
≥1000 U/L	0.3% (2/647)	0.3% (1/307)	0.2% (1/524)	(0/253)
Post Herpetic Neuralgia Controlled Trials				
>3x ULN	0.4% (2/562)	0.4% (1/259)	0.4% (2/500)	0.4% (1/240)
≥340 U/L males, ≥180 U/L females	9.5% (57/598)	7% (19/273)	5.6% (28/503)	4.6% (11/241)
≥1000 U/L	(0/598)	(0/273)	(0/503)	(0/241)
Epilepsy Controlled Trials				
>3x ULN	2.3% (5/222)	(0/64)	2.4% (5/205)	(0/58)
≥340 U/L males, ≥180 U/L females	12.4% (54/421)	9.5% (12/126)	13.9% (29/208)	6.9% (4/58)
≥1000 U/L	1.2% (5/421)	0.8% (1/126)	1.9% (4/208)	(0/58)
GAD Controlled Trials				
>3x ULN	0.8% (6/756)	0.7% (2/295)	0.4 (3/686)	0.4% (1/274)
≥340 U/L males, ≥180 U/L females	7.1% (57/808)	7.3% (23/316)	2.9% (20/685)	5.8% (16/276)
≥1000 U/L	0.9% (7/808)	0.3% (1/316)	0.3% (2/685)	(0/276)

* Pfizer included some subjects with post treatment results in this analysis. Corrected tables that only include on-treatment results were still pending at the time of this review.

The table shows that the initial NDA analysis (in which data from all subjects was included) suggested that for the overall population, treatment with pregabalin was associated in an increase in CK to > 3x ULN (1.7% vs. 0.8% in the placebo group). This association was not seen when data from only patients with normal CK at baseline were considered. With respect to the epilepsy population, both analyses found that more pregabalin-treated patients had an increase in CK compared to the placebo patients.

At the Agency's request, Pfizer prepared shift tables of CK from baseline to maximum value for the overall pouplation, and for each indication. These data are summarized in the table that follows:

* In this analysis Pfizer classified subjects to a single category based on their most extreme result, so that the High (≥340U/L males, ≥180U/L females) and Very High (≥1000U/L) categories are mutually exclusive. In other words, subjects in the Very High category are not also included in the High category.

Table 7.7.4.1.2.d: Shift tables from baseline to maximum value for creatinine kinase

Creatinine kinase	Placebo (N = 2384) Maximum [N (%)]			All PGB (N = 5508) Maximum [N (%)]		
	Overall Population					
Baseline [n (%)]	< 2x ULN	2 to ≤ 3x ULN	> 3x ULN	< 2x ULN	2 to ≤ 3x ULN	> 3x ULN
< 2x ULN	1308 (97.4)	10 (0.7)	6 (0.6)	3155 (95.5)	61 (1.8)	38 (1.2)
2 to ≤ 3x ULN	5 (0.4)	5 (0.4)	1 (0.1)	16 (0.5)	9 (0.3)	9 (0.3)
> 3x ULN	0 (0.0)	3 (0.2)	3 (0.2)	6 (0.2)	0 (0.0)	9 (0.3)
	Epilepsy Population					
< 2x ULN	63 (98.4)	0 (0.0)	1 (1.6)	216 (96.0)	3 (1.3)	5 (2.2)
2 to ≤ 3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
> 3x ULN	-	-	-	-	-	-
	DPN Population					
< 2x ULN	275 (94.8)	3 (1.0)	1 (0.3)	557 (92.2)	25 (4.1)	8 (1.3)
2 to ≤ 3x ULN	2 (0.7)	4 (1.4)	0 (0.0)	3 (0.5)	3 (0.5)	4 (0.7)
> 3x ULN	0 (0.0)	3 (1.0)	1 (0.3)	1 (0.2)	0 (0.0)	3 (0.5)
	GAD Population					
< 2x ULN	292 (98.3)	2 (0.7)	1 (0.3)	730 (96.7)	10 (1.3)	6 (0.8)
2 to ≤ 3x ULN	1 (0.3)	0 (0.0)	0 (0.0)	5 (0.7)	1 (0.1)	2 (0.3)
> 3x ULN	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
	PHN Population					
< 2x ULN	255 (98.1)	3 (1.2)	1 (0.4)	554 (97.7)	3 (0.5)	4 (0.7)
2 to ≤ 3x ULN	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.4)
> 3x ULN	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)	1 (0.2)

(Source: Applicant's tables Appendix ALL_sft.03, Appendix phn_sft.03, Appendix epi_sft.03, Appendix dpn_sft.03, Appendix gad_sft.03)

The table allows for comparison of results from the DPN studies with the overall population, the epilepsy population (considered to be the 'high risk' population) and the GAD population (the most 'healthy' population). 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).

Creatinine Kinase: Combined controlled and uncontrolled studies – All indications
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.

Pfizer provided tabulated the number and percentage of patients with CK increases, stratified by increase over the ULN:

Table 7.7.4.1.2.c: Summary of Creatine Kinase Levels Stratified by Increase Over Upper Limit of Normal Combined Controlled and Uncontrolled Studies - All Indications

	All Pregabalin Patients
<=1X ULN	5243 (77.4)
>1 to 2X ULN	1110 (16.4)
>2 to 3X ULN	232 (3.4)
>3 to 4X ULN	79 (1.2)
>4 to 5X ULN	31 (0.5)
>5 to 10X ULN	44 (0.6)
> 10X ULN	37 (0.5)

(Applicant's Table: Appendix FDA2004.APR07)

There were 81 patients who had a CK >5 x ULN. Dr. Boehm requested that Pfizer determine which of these subjects also had recorded AEs that were suggestive of myopathy (e.g. muscle weakness, muscle pain, etc.). Pfizer identified 12 such subjects. The narratives of these patients are summarized in Table 7.7.4.1.2.f.

In total, 6 patients had CK abnormalities that were suggestive of a relationship to pregabalin treament. 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 rhabdomylosis 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.

Dr. Bohem noted that Pfizer did not include Subject 149-430001 in its analysis of patients with CK elevations and symptoms of myopathy. This subject's narrative is provided below:

Patient 149_430001, a 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

Table 7.7.4.1.2.f: Narratives of patients with CK > 5x ULN and AE suggestive of myopathy

Patient	Event	CK value (U/L)	Days between event and CK ↑
010-026100 / EPI PGB 75-600 mg/d	Day 149 OL study: Partial seizure, right leg weakness	BL: 413 , Day 57: 180 , Day 288: 1700 , Day 384: 91 , Day 566: 73 , Day 589: 302	139
014-015007 DPN PGB 300 – 600 mg/d	Day 107 OL study: Leg cramps/pain	Day 253: 163 , Day 602: 1684, Day 680: 327	495
029-030008 / DPN	Day 14 DB study (300 mg/d): Leg cramps Pt entered OL study (300 mg/d)	OL Day 57: 68 , OL Day 84: 1403 , OL Day 176: 89	104
030-108005 / PHN	Day 530 of OL study: Calf pain	BL: 62, Day 455: 951, Day 476: 146 (Day 476, serum creatinine = 2.1 mg/dl) Day 546: 60 Day 587: 118 (this was 18d post-treatment)	- 75 (CK ↑ occurred before calf pain)
032-306004 / chronic pain 150 – 600 mg/d	*Event 1:*Day 160 of OL study Leg cramps, hypertonia *Event 2:*Day 191 of OL study: Leg and stomach cramps (PGB discontinued)	Day 167: "elevated CK"; AST and ALT > 2 x ULN Day 169: 1893 Day 206: 287	8 days (between 1st event and 1st CK elevation)
032-322019 / chronic pain	Day 22 of DB study (600 mg/d): Fibromyalgia (myalgia) (PGB discontinued)	Day 21of DB study: 1139 Day 29: 108	1
035-021112 / EPI 100 – 600 mg/d	Day 41 of OL study: muscle aches Day 98: partial seizure	BL: 86; Day 99: 5391; Day 190: 123	1
040-073005 / DPN DB study: amitriptyline OL study: 600 mg/d	Day 65 of OL study: Myasthenia	Double blind study: BL: 120; Study end: 84 OL study: Day 65: 130; Day 358 : 486; Day 449: 38	0

Table 7.7.4.1.2.f: Narratives of patients with CK > 5x ULN and AE suggestive of myopathy

Patient	Event	CK value (U/L)	Days between event and CK ↑
040-074010 / DPN DB study: amitriptyline OL study: 200-600 mg/d	History of lower leg cramps and spamsm DB study: Day 29: leg cramps OL Day 482: Surgery; leg pain	Double blind study: BL – 273; Study end – 306 OL study: Day 9 - 541; Day 544 – 1123; Day 635 – "CK resolved"	Temporal relationship uncertain
080-112001 / SAD Double blind: 300 mg/d	DB study, Day 16: rhabdomylosis Day 17: muscle soreness, in the setting of recent weight-lifting (PGB discontinued on Day 19)	Double blind study: BL – 94; Day 16 – 30700; Day 17 – 44700; Day 19 – 39743 (Pt had concomitant increases in AST (up to 762) and ALT (up to 142)	3
085-416002 / GAD Double blind: 450 mg/d OL : 300 – 600 mg/d	DB study, Day 40: muslce ache (in the setting of exercise) Patient subsequently entered OL study	Double blind study: Day 43 – 12310; Day 45 – 2642; Day 49 – 340 OL study:Day 22 – 816; Day 30 – 154; Day 100 - 5146	3
127-031003 / PHN Double blind: 600 mg/d OL: 300 – 450 mg/d	OL study Day 261: Fibromyalgia	Double blind study: BL - 130; Study end – 285 OL study: Day 35 – 268; Day 93 – 2019; Day 128 – 249; Day 142 – 427; Day 178 – 181; Day 272 – 169; Day 331 - 474	Temporal relationship uncertain
010-008124 / EPI 400 mg/d	OL Day 330: cellulitis, rhabdomyolosis Patient continued on medication	OL Day 330 (local lab): 4672; Day 337 – 614; Day 344: "within normal limits"	1

Key:
BL – baseline DB – double blind DPN: pain due to diabetic peripheral neuropathy GAD - Generalized anxiety disorder
EPI – Epilepsy PHN - postherpetic neuralgia OL: open label Pt- patient SAD - Social anxiety disorder

To further examine instances of extreme CK elevation, Dr. Bohem 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 and cases of rhabdomyolysis that resulted in limiting of the maximum recommended dose (80mg dose was not approved). In the rosuvastatin NDA, the risk for CK elevations >5x the ULN in the combined controlled and uncontrolled data lower dose groups (5-40mg) was 0.5% (30/5544) compared to 2.4% (32/1314) in the 80mg group. The risk for CK elevations >10x the ULN in the combined controlled and uncontrolled data lower dose groups (5-40mg) was 0.2% (11/5544) compared to 1.3% (17/1314) in the 80mg group. The reviewer reported that 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. There were no cases of rhabdomyolysis in the lower dose groups while the risk for rhabdomyolysis in the 80mg group was 0.5% (6/1314)

As shown in Table above, the frequency of CK > 5x ULN in pregabalin combined controlled uncontrolled trials was 1.1% (all doses). 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 elevation, 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.

Elevated CK and serum creatinine

Pfizer evaluated data for all patients who had evidence of CK elevation for evidence of renal dysfunction (defined as an increase in creatinine of > 0.2 mg/dL). With 4 exceptions, none of these patients had evidence of renal dysfunction associated with increases in creatine kinase. Two patients had renal impairment, with elevated creatinine values, at baseline; their creatinine values subsequently increased further, either transiently with a transient rise of creatine kinase (Patient 149_375009), or in association with pneumonia, dehydration, and elevated creatine kinase levels (Patient 149_430001,

serious adverse event of myopathy). A third patient (Patient 014_017005) also had renal impairment at baseline was withdrawn due to CPK increase. The fourth patient (Patient 131_104008) had an elevated creatine kinase level at baseline and withdrawn due to CPK increase. Both creatinine and creatine kinase returned to normal when the patient was withdrawn from pregabalin. While useful, this information is not reassuring of the absence of a relationship between CK elevation and renal dysfunction.

One additional patient (Patient 010_008124) had a non-serious adverse event of rhabdomyolysis (with elevation of creatine kinase above 3 times upper limit of normal). This occurred in the setting of cellulitis with fever, anemia, electrolyte abnormalities, and evidence of renal dysfunction as indicated by an increase in creatinine. Creatinine returned to normal, and creatine kinase returned toward normal within 2 weeks after initial discovery, while the patient continued on pregabalin. Since the laboratory data associated with these conditions were taken at a local laboratory, they are not in the clinical database.

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 rhabdomyolosis or renal failure associated with increased CK.

7.4.7.2 Analyses of Liver Function Tests -- Controlled trials, All indications

As seen in Table 7.4.7.1a, 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 blirubin

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:

- 2 cases were likely related to cholelithiasis
- 1 case occurred in a subject with a history of alcohol abuse and hospitalizations for pancreatitis;

- 1 subject was rechallenged following the event without recurrence of LFT abnormalities;
- 1 case was noted eight days after a subject had discontinued from a trial, following a GI bleed (on day 6);
- 1 case occurred in a subject who had slightly elevated AST and total bilirubin at baseline.

7.4.7.3 Laboratory mean changes -- DPN trials

DPN controlled trials

Table 7.7.4.2.a and b display 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.

Table 7.4.7.3.a: Mean change from baseline for laboratory parameters with a statistically significant difference between placebo and pregabalin – DPN controlled trials

Test Name	Units	Placebo	PGB 150 mg/day	PGB 300 mg/day	PGB 600 mg/day	All PGB[a]
Hemoglobin	g/dL	-0.056	-0.126	**-0.176**	**-0.281**	**-0.2**
Hematocrit	%	-0.162	-0.019	-0.178	**-0.626**	-0.315
RBC	$\times^{10^6}/\mu^L$	-0.038	-0.041	-0.055	**-0.094**	-0.064
WBC	$\times^{10^3}/\mu^L$	0.0844	-0.016	**-0.209**	**-0.049**	**-0.099**
Absolute Neutrophils	$\times^{10^3}/\mu^L$	0.0574	-0.031	**-0.178**	**-0.07**	**-0.099**
Platelets	$\times^{10^3}/\mu^L$	0.5915	**-4.324**	**-11.33**	**-11.91**	**-9.546**
Glycosylated Hemoglobin	%	-0.043	0.0914	**0.0919**	0.0189	0.0484
Glucose-Non fasting	mg/dL	24.021	**-44.5**	**-4.066**	13.672	**1.9622**
CK-Creatine Kinase	U/L	-3.104	10.417	**11.717**	**13.579**	**11.914**
Creatinine	mg/dL	0.0088	0.0035	0.0137	**0.0258**	0.0157
Uric Acid	mg/dL	0.0669	-0.013	0.1747	**0.1836**	0.1257
BUN	mg/dL	0.2453	**0.6856**	0.762	**1.5676**	**0.9952**
Bilirubin-Total	mg/dL	-0.023	**-0.049**	**-0.056**	-0.031	**-0.041**
Albumin	g/dL	-0.044	-0.06	-0.067	**-0.121**	**-0.088**
Total Protein	g/dL	-0.025	-0.079	-0.015	**-0.113**	**-0.073**
Alkaline Phosphatase	U/L	0.1305	8.9621	**4.0547**	**5.7967**	**5.2183**
AST	U/L	-0.763	0.7251	**1.2508**	**0.3654**	**0.5894**
HDL Cholesterol	mg/dL	1.8753	**-0.297**	0.1736	**-1.814**	**-0.55**
Sodium	mEq/L	-0.175	-0.36	**0.5434**	0	0.0593
Calcium	mg/dL	-0.039	-0.051	-0.073	**-0.109**	**-0.083**
Chloride	mEq/L	-0.004	-0.019	**0.9453**	0.1813	0.3472
Urine Protein	mg/dL	-7.046	-2.433	1.544	**-3.265**	**-1.533**
Urine WBC	/HPF	0.8854	-0.184	**-0.505**	0.375	**-0.136**

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 81, Summary of Clinical Safety, P. 157)

There is no page 210 in this review

Per the reviewer, the blank page was just an error in pagination due to a shift in a section break

Table 7.4.7.3.b: No. and % of patients with changes in specific lab values – DPN controlled trials

Test Name	Direction of Change	Placebo			150			300			600			All PGB		
		%	No.	Total	%	No.	Total	%	No.	Total	%	No.	Total	%	No.	Total
Platelets	Decrease	2.5	11	448	1.9	4	210	5.2	16	309	7.5	27	361	5.7	54	954
	Increase	0.4	2	448	0.5	1	210	0.0	0	309	0.3	1	361	0.2	2	954
Glucose-Fasting	Decrease	3.2	10	314	0.5	1	197	1.3	3	224	1.4	4	293	1.3	10	790
	Increase	72.9	229	314	66.0	130	197	56.3	126	224	65.9	193	293	63 5	502	790
CK-Creatine Kinase	Increase	0.0	0	289	1.5	2	132	0.4	1	240	0.9	2	216	0.8	5	595
Creatinine	Increase	2.0	9	452	1.4	3	211	3.5	11	311	3.8	14	364	2.9	28	962
Uric Acid	Increase	1.8	8	452	0.0	0	211	0.3	1	311	2.2	8	364	0.9	9	962
BUN	Increase	5.5	25	452	2.4	5	211	10.0	31	311	7.1	26	364	6.7	64	962
Bilirubin-Total	Increase	2.4	11	451	1.9	4	211	0.6	2	311	1.4	5	364	1 2	12	962
Albumin	Decrease	0.2	1	452	0.0	0	211	0.0	0	311	0 3	1	364	0 1	1	962
Total Protein	Decrease	0.7	3	452	0.9	2	211	0.3	1	311	0.5	2	364	0.6	6	962
	Increase	0.4	2	452	0.0	0	211	0.6	2	311	0.3	1	364	0.3	3	962
Alkaline Phosphatase	Increase	1.1	5	452	2.4	5	211	1.6	5	311	2.2	8	364	1.9	18	962

The tables 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 (-9.546 x $10^3/\mu L$) compared to mild increase in the placebo group (0.5195 x $10^3/\mu L$). In addition, the pregabalin group showed an increase in creatine kinase (11.9 U/L), compared to a slight decrease in the placebo group (-3.104 U/L). When the mean change in platelets from baseline to maximum value was analyzed, there was no considerable difference between placebo (15.891 x $10^3/\mu L$) and pregabalin (8.7474 x $10^3/\mu L$) (Applicant's Table1.MAX.DPN, submitted March 16 2004).

Creatinine kinase DPN controlled trials
As discussed in Section 7.4.7.1.2, an evaluation of the mean change in CK from baseline to maximum on-treatment value also showed a greater increase in CK for the pregabalin group (32.41 U/L) than for the placebo group (13.17 U/L).

An analysis of change in mean CK by study week showed that treatment with the higher pregabalin doses (300 and 600 mg/d) was associated with a CK inrease, and that a difference from placebo was apparent by Week 2. Continued treatment with pregabalin resulted in slightly greater increases in CK.

Table 7.4.7.3.c: Mean change in CK from baseline to each study visit

	Placebo N=459		150 mg/day PGB N=212		300 mg/day PGB N=321		600 mg/day N=369		All PGB N=979	
Visit	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Wk 1-2 (Day 2-17)	218	-3.4 (45.7)	129	8.6 (40.1)	168	6.9 (33.7)	213	12.5 (54.7)	517	9.5 (45.0)
Wk 3-4 (Day 18-31)	195	-4.7 (59.8)	107	6.2 (25.7)	186	9.6 (40.6)	105	6.2 (52.7)	404	7.4 (40.9)
Wk 5-6 (Day 32-45)	163	-4.2 (62.3)	14	4.6 (22.4)	97	13.9 (66.8)	100	15.4 (53.2)	217	13.5 (58.0)
Wk 8 (Days 46-70)	212	-3.3 (46.3)	97	22.7 (127.9)	169	16.0 (51.4)	146	11.2 (48.5)	412	15.9 (75.8)
Wk 12-13 (>=Day 71)	79	3.4 (26.6)	85	4.1 (18.6)	91	13.3 (34.9)	73	13.4 (81.9)	249	10.2 (50.3)

(Applicant's Appendix dpn-ckmean)

DPN Uncontrolled trials
In the DPN open-label extension studies, the magnitude of mean changes for creatine kinase, ALT, AST, and albumin were small and similar to those observed in the controlled DPN studies. The mean changes from baseline to study endpoint were 6.8 U/L, -0.4 U/L, 0.7 U/L, and –0.1 g/dL, respectively (Appendix DPN.087). Seventeen (3.0%) patients had a potentially clinically significant increase in creatine kinase during open-label treatment. For platelets, the mean change was small in the uncontrolled DPN studies (-1.1 x 10 3 /μL). Ninety-five (9.4%) patients had potentially clinically significant decreases in platelet values, and 5 (0.5%) had potentially clinically significant increases. Based on changes in serum creatinine, there was no indication of deterioration in renal function associated with long-term pregabalin treatment, which is similar to the 1.1% observed in the placebo group for controlled studies. High (2.0 mg/dL) serum creatinine values were observed in 3.2% of the controlled and uncontrolled DPN population, and no DPN patients had a very high (6 mg/dL) creatinine value. There was no pattern of clinically meaningful change in glucose control based on mean change in glycosylated hemoglobin (mean change of 0.266%) (SCS, P. 157-58).

7.4.7.4 Glycemic control – DPN trials

Pfizer did not detect consistent changes in glycosylated hemoglobin during the controlled studies. However, the duration of most controlled studies was not long enough for drug-induced changes in glycosylated hemoglobin to occur. Table 7.4.7.3 shows the number of subjects in controlled trials that experienced a change (increase or decrease) in glucose and glycosylated hemoglobin during the trial. A similar proportion of patients in the placebo and pregabalin groups had increases in non-fasting glucose, suggesting that pregabalin has no effect on glucose levels. However, as mentioned above, although some glucose measurements were labeled as 'fasting' or 'non-fasting', all glucose measurements should be considered 'non fasting.' This is because only protocols 1008-149 and 173 specified fasting samples at some visits. There was no indication that pregabalin-treated patients were at greater risk for potentially clinically significant increases in glucose compared with placebo-treated patients (Tables 7.7.4.2.a, 7.7.4.2.b [above; Table 7.4.7.3)

Table 7.4.7.3: Percent of patients with laboratory values changing to low or high at study endpoint – DPN controlled trials

		Placebo			150			300			600			All PGB		
Test Name	High or Low	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%
Glycosylated Hemoglobin	H	20	70	28.6	11	30	36.7	10	31	32.3	9	57	15.8	32	133	24.1
	L	0	421	0.0	0	198	0.0	0	284	0.0	1	338	0.3	1	893	0.1
Glucose-Fasting	H	30	48	62.5	11	19	57.9	15	24	62.5	21	36	58.3	54	90	60.0
	L	7	310	2.3	0	196	0.0	2	221	0.9	5	286	1.7	8	778	1.0
Glucose-Non fasting	H	16	50	32.0	0	0	0.0	9	34	26.5	8	10	80.0	17	44	38.6
	L	1	117	0.9	0	4	0.0	3	75	4.0	0	55	0.0	3	134	2.2

N at Risk for "L" or "H" is the # of pts with low, high or normal values at the beginning of the study.
Dose (e.g., 150 mg) is the total daily dose in mg/day, given with a BID or TID regimen.
All PGB Includes all other doses of Pregabalin

7.4.7.5 Renal function – DPN trials

Table 7.4.7.5.a and b show that the proportion of patients with a decrease in estimated creatinine clearance of at least 15% was similar between pregabalin (10.9%) and placebo (11.3%). Further, compared with 1.1% of placebo-treated patients, no pregabalin-treated patients had a doubling of serum creatinine. There were statistically significant changes in albumin and urine protein compared to placebo (Table 7.4.7.2), but these changes were small mean decreases from baseline, leading Pfizer to suggest that pregabalin is not associated with renal impairment in this population. Similarly, the small magnitude of mean increase in AST was not believed to be of clinical importance.

Table 7.7.7.5.a: Change in Clcr from baseline to any time during the study – DPN controlled trials

	Total Daily Dose of Pregabalin in mg/day, Combined BID/TID Regimens					
	Placebo	75	150	300	600	ALL PGB
	N=459	N=77	N=212	N=321	N=369	N=979
Change in Serum Creatinine	N*=442	N*=74	N*=207	N*=311	N*=356	N*=948
Creatinine Clearance (mL/min)						
N (%) with >= 15 % Decrease	50(11.3)	9(12.2)	13(6.3)	37(11.9)	44(12.4)	103(10.9)
N (%) with >= 15 % Increase	115(26.0)	8(10.8)	102(49.3)	122(39.2)	113(31.7)	345(36.4)
Change in Serum Creatinine (mg/dL)						
N (%) with > 100 % Increase	N*=454	N*=76	N*=211	N*=318	N*=366	N*=971
	5(1.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Number of Patients with data at both baseline and during the study
(Applicant's Appendix DPN.079, Summary of Clinical Safety, P. 8769)

Table 7.4.7.5.b shows the number (and percent) of patients in DPN controlled trials who had an increase or decrease in creatinine or creatinine clearance. Although more patients the pregabalin group had higher creatinine, and BUN values at endpoint than those in the placebo group, there was no real difference between groups with respect to change in creatinine clearance and urine protein. Changes in creatinine and BUN are early indicators of changes in renal function, while creatinine clearance and urine protein are markers of long-term and/or severe renal injury. The results from the DPN controlled studies therefore suggest that acute changes in renal function occurred with pregabalin treated, but were not severe.

Table 7.4.7.5.b: % of patients with changes in renal lab values – controlled DPN studies

		Placebo			150			300			600			All PGB		
Test Name	High or Low	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%	N	N at Risk	%
Creatinine	H	18	362	5.0	8	170	4.7	14	249	5.6	29	297	9.8	60	768	7.8
	L	0	449	0.0	2	210	1.0	1	309	0.3	0	362	0.0	3	957	0.3
Serum Creatinine for Calculated Creat	H	0	0	0.0	0	1	0.0	0	0	0.0	0	0	0.0	0	1	0.0
	L	0	0	0.0	0	1	0.0	0	0	0.0	0	0	0.0	0	1	0.0
Creatinine Clearance Estimated	H	5	149	3.4	0	0	0.0	5	62	8.1	2	139	1.4	9	255	3.5
	L	7	99	7.1	0	0	0.0	4	66	6.1	10	81	12.3	21	195	10.8
Uric Acid	H	27	371	7.3	10	168	6.0	20	242	8.3	26	292	8.9	62	763	8.1
	L	5	426	1.2	7	197	3.6	2	301	0.7	12	332	3.6	23	895	2.6
BUN	H	21	397	5.3	14	190	7.4	21	260	8.1	34	325	10.5	75	844	8.9
	L	2	452	0.4	0	211	0.0	1	310	0.3	1	364	0.3	2	961	0.2
Urine protein	H	13	146	8.9	4	75	5.3	8	91	8.8	7	146	4.8	22	366	6.0
	L	0	197	0.0	0	104	0.0	0	125	0.0	0	185	0.0	0	490	0.0

N at Risk for "L" or "H" is the # of pts with low, high or normal values at the beginning of the study.
Dose (e.g., 150 mg) is the total daily dose in mg/day, given with a BID or TID regimen.
All PGB Includes all other doses of Pregabalin

To evaluate the effect of pregabalin on renal function during long-term treatment, Pfizer compared the proportion of patients in combined (controlled and uncontrolled) DPN studies who had increases in serum creatinine values to the proportion in the placebo group for controlled trials. The Applicant reports that there no difference between the treated patients and the placebo patients (1.3% vs. 1.1%,

respectively) (Table 7.4.7.5.c). The limitation of this analysis is that it compares effects of pregabalin exposure of long duration to that of no more than 12 weeks. High (2.0 mg/dL) serum creatinine values were observed in 3.2% of the controlled and uncontrolled DPN population, and no DPN patients had a very high (6 mg/dL) creatinine value (SCS, Appendix DPN.090).

Table 7.7.7.5.c: Change in renal function from baseline to any time during the study – DPN combined controlled and uncontrolled studies

	All PGB N=1413
Change in Estimated Serum Creatinine Clearance (mL/min)	N*=1366
N (%) with >= 15 % Decrease	387(28.3)
N (%) with >= 15 % Increase	634(46.4)
Change in Serum Creatinine (mg/dL)	N*=1387
N (%) with > 100 % Increase	18 (1.3)

*Number of Patients with data at both baseline and during the study

7.4.8 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, Prizer also provided ummaries of mean changes in vital signs from baseline to maximum and minimum value, as well as shift tables to identify extreme outliers. Criteria for clinically significant changes in vital signs are provided in the Appendix.

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 resepcet 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).

7.4.9 Weight

All clinical trials included an assessment of patients' weight. Simlar outlier analyses and shifts from baseline to maximum and minimum value were conducted as for the vital signs data.

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 7.4.9.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=267	--	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 (Table 7.4.9.b). 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 7.4.9.b: Cumulative distribution of weight gain by dose – All controlled studies

[Number of Patients (%)]

		Pregabalin Dose, mg/day (BID and/or TID)						
	Placebo	150	200	300	400	450	600	Any Dose[a]
% Increase	N=2384	N=1164	N=208	N=1224	N=360	N=501	N=1802	N=5508
N at Risk[b]	2233	1122	175	1158	320	470	1701	5181

≥7	38 (1.7)	53 (4.7)	4 (2.3)	81 (7.0)	22 (6.9)	33 (7.0)	198 (11.6)	401 (7.7)
≥10	13 (0.6)	21 (1.9)	2 (1.1)	21 (1.8)	6 (1.9)	8 (1.7)	72 (4.2)	134 (2.6)
≥15	2 (0.1)	8 (0.7)	0 (0.0)	3 (0.3)	2 (0.6)	3 (0.6)	16 (0.9)	33 (0.6)
≥20	1 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.6)	2 (0.4)	5 (0.3)	11 (0.2)
≥25	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.0)
≥30	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)
≥35	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.0)

[a] Includes all other doses of pregabalin (i.e., 50 and 75 mg/day).
[b] N at risk = the number of patients with both baseline and termination/LOCF weight recorded.
(Applicant's Table 31, Summary of Clinical Safety, P. 82)

DPN controlled studies

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 (Applicant's Appendices DPN_sft.01 and DPN_chg.01).

The cumulative distribution of weight gain in controlled DPN trials is shown in the table below. Treatment with pregabalin conferred a greater risk of weight gain, but a dose dependent association was not clearly evident. Subjects taking the highest dose of pregabalin (600 mg/day) appeared to suffer the greatest risk of weight increases > 7%.

Table 7.4.9.c: Cumulative distribution of weight gain by dose – DPN controlled studies

		Pregabalin Dose, mg/day (BID and/or TID)				
	Placebo	75	150	300	600	Any Dose
Percent Change	N=459	N=77	N=212	N=321	N=369	N=979
N at Risk*	444	73	207	309	358	947
Increase						
>=7	6 (1.4)	3 (4.1)	7 (3.4)	12 (3.9)	27 (7.5)	49 (5.2)
>=10	2 (0.5)	1 (1.4)	2 (1.0)	3 (1.0)	4 (1.1)	10 (1.1)
>=15	0 (0.0)	1 (1.4)	0 (0.0)	1 (0.3)	1 (0.3)	3 (0.3)
>=20	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.135, Summary of Clinical Safety, P. 7366)

Risk factors for weight gain

There were no apparent risk factors for weight gain, other than treatment with pregabalin

Correlation between weight gain and peripheral edema – All controlled trials

Pfizer assessed all controlled trials for the incidence of edema (including peripheral edema, generalized edema, or edema) in patients with ≥ 7% weight gain. Approximately 13% (51 of 401) of pregabalin-treated patients with weight gain had a concurrent adverse event of edema. None of the 38 (0.0%) of placebo-treated patients with ≥7% weight gain had concurrent edema. DPN and PHN patients with ≥ 7% weight gain had the highest incidence of concurrent edema (30.6% and 26.8%, respectively). The epilepsy population had a lower incidence of edema and ≥ 7% weight gain (8.3%), whereas the GAD population had no overlap between weight gain and peripheral edema.

Table 7.4.9.c: Edema[a] in pregabalin patients with ≥ 7% weight gain: All controlled studies – All indications51*11

Grouping	Any Dose Pregabalin N With ≥7% Weight Gain	N (%) With Concurrent Edema
All Studies[b]	N=401	51 (12.7)
NeP	N=105	30 (28.6))
DPN	N=49	15 (30.6)
PHN	N=56	15 (26.8)
Epilepsy	N=133	11 (8.3)
GAD	N=42	0 (0.0)

[a] Includes TESS peripheral edema, generalized edema, or edema.
[b] Includes other non-neuropathic pain studies and other psychiatry studies.

To examine whether edema alone accounts for the observed ≥ 7% weight gain, Pfizer calculated the expected rate of co-occurrence in the same patient (assuming independence) by multiplying the incidence of edema (peripheral, generalized or 'edema') (7.8%, all pregabalin) by the incidence of ≥ 7% weight gain (7.7%, all pregabalin). The expected rate was then compared to the observed number and percent of patients who experienced both AEs (n = 51, 1.0%). Pfizer concluded that although the observed rate was higher than the expected rate, the analysis showed that edema alone did not account for weight gain.

7.4.10 ECG

ECG data were collected in 28 clinical trials. Both placebo and pregabalin patients, were included in the analysis, as long as they had an ECG at baseline and during the treatment period which were analyzed by a central reader. Pfizer created two summary reports of the data. The first presented ECG analysis according to the following treatment indications: epilepsy; "pain" (DPN, PHN, chronic [ ] pain, [ ] fibromyalgia); and 'psychiatry' (GAD, [ ] (RR-Memo-720-04340). The second report summarized ECG data from other 'psychiatry' studies. A summary report for all combined ECG data from all studies was not provided. The results described below were obtained from the first summary report.

At the Division's request, Pfizer calculated the percentage of patients who had shifts from baseline to maximum value in ventricular rate, as well as PR, QRS, and QTc intervals. Of note, Pfizer has not conducted any formal studies to evaluate the effects of pregabalin on cardiac function.

7.4.10.1 ECG data in all clinical trials

Overview

The first summary report contained data from 2876 pain patients, 850 epileptic patients, and 1019 psychiatric patients. The report found that 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. Overall, pregabalin treatment was not associated with significant cardiac-associated sequelae (SCS, P. 69)

PR interval - All indications

On average, the maximum increases from baseline in PR interval were statistically significantly higher in doses of pregabalin ≥ 300 mg/day compared to placebo. This effect appeared to be dose-related. Pregabalin 600 mg/day showed a significant effect on mean PR interval across all 3 indications, and in the diabetic neuropathy sub-population. Pregabalin 450 mg/day had a significant effect on mean PR interval in the only indication (pain) in which it was studied. The mean effect on PR interval was small (3-6 msec) and is not clinically relevant.

Table 7.4.10.a: Maximum change from baseline in PR interval (msec)

Treatment Comparison (vs. Placebo)	Estimated Difference (95% CI)		Statistical Interpretation
Pooled Pain Studies			
PGB 75 mg/day TID	2.01	(-0.72, 4.74)	Not Significant
PGB 150 mg/day TID	1.89	(-0.10, 3.87)	Not Significant
PGB 300 mg/day TID	3.03	(1.20, 4.85)	Significant
PGB 450 mg/day TID	3.26	(0.70, 5.82)	Significant
PGB 600 mg/day TID	3.40	(1.76, 5.03)	Significant
Pooled Diabetic Neuropathic Pain Studies			
PGB 75 mg/day TID	1.64	(-2.20, 5.48)	Not Significant
PGB 150 mg/day TID	-0.06	(-4.11, 4.00)	Not Significant
PGB 300 mg/day TID	1.08	(-2.06, 4.21)	Not Significant
PGB 600 mg/day TID	3.56	(1.05, 6.07)	Significant
Pooled Epilepsy Studies			
PGB 50 mg/day BID	0.30	(-3.24, 3.84)	Not Significant
PGB 150 mg/day BID	2.13	(-1.39, 5.65)	Not Significant
PGB 300 mg/day BID	0.06	(-3.49, 3.62)	Not Significant
PGB 600 mg/day BID	5.14	(2.48, 7.80)	Significant
PGB 600 mg/day TID	3.81	(0.42, 7.20)	Significant
Pooled Psychiatry Studies			
PGB 150 mg/day TID	0.90	(-1.64, 3.44)	Not Significant
PGB 600 mg/day TID	3.06	(0.54, 5.58)	Significant

CI = Confidence Interval, PGB = Pregabalin.

[a] Difference between Least-Squares Means

[b] Based on ANCOVA; not significant $p > 0.05$, significant $p \leq 0.05$

Based on the data from the shift tables, slightly more patients (2.8%) in the pregabalin group had a shift in the PR interval from normal to 'high' compared to 2.1% in the placebo group. The change was greatest in the pregabalin 600 mg/d group (3.4%) but was not dose related.

The percentage of patients with an absolute post-baseline PR =220 msec and a maximum increase in PR ≥ 40 msec (0.005%) was the same for the pregabalin 600 mg/day group (5/966) as the placebo group (6/1160). The percentage of any pregabalin-treated patients meeting these PR criteria was 0.002%.

To examine the possible clinical significance of pregabalin's effect on PR interval, the incidence of AV block was compared between placebo and pregabalin in 19 controlled trials. The frequency of AV block first degree was the same (0.1%) in placebo- treated and pregabalin-treated patients (RR-Memo 720-04340, P. 17-18). There were 2 pregabalin-treated patients had a report of 2nd degree AV block. *Patient 011_083004*, a 26 year old man treated with 600 mg/day pregabalin, had AV block first degree at baseline (Study Day Œ56) that progressed to 2nd degree AV block on Study Day 15. Medication was continued and an ECG on Study Day 29 showed returned AV block. The cardiology consultant did not review this patient's data. *Patient 014 024013*, a 69 year old man treated with pregabalin 600 mg/day, had a history of rare premature atrial contractions and prolonged PR interval. The cardiology consultant considered this patient to have AV block second degree at baseline (Study Day 9), Study Days 15 and 29, and AV block first degree on Study Day 45. Neither event was considered an SAE nor led to premature termination of the study.

QT interval – All trials

Data from shift tables show that there was no difference between pregabalin and placebo patients with respect to increases in the QTc ingerval. Also, on average, the maximum increases from baseline in linear-corrected QT interval (QTs) were not statistically significantly different during pregabalin treatment compared to placebo treatment. In 2 cases, pregabalin statistically significantly decreased mean QTs intervals compared to placebo (pooled epilepsy 300 mg/day and pooled psychiatry 600 mg/day). The observed differences did not appear dose-related.

Table 7.4.10.b: Maximum change (increase) from baseline in QTs interval (msec)

Treatment Comparison (vs. Placebo)	Estimated Difference (95% CI)	Statistical Interpretation
Pooled Pain Studies		
PGB 75 mg/day TID	0.55 (-2.06, 3.17)	Not Significant
PGB 150 mg/day TID	1.45 (-0.45, 3.34)	Not Significant
PGB 300 mg/day TID	-0.53 (-2.29, 1.23)	Not Significant
PGB 450 mg/day TID	0.07 (-2.39, 2.53)	Not Significant
PGB 600 mg/day TID	-1.07 (-2.64, 0.49)	Not Significant
Pooled Diabetic Neuropathic Pain Studies		
PGB 75 mg/day TID	0.14 (-3.60, 3.88)	Not Significant
PGB 150 mg/day TID	1.98 (-1.91, 5.87)	Not Significant
PGB 300 mg/day TID	0.85 (-2.20, 3.90)	Not Significant
PGB 600 mg/day TID	-0.75 (-3.15, 1.65)	Not Significant
Pooled Epilepsy Studies		
PGB 50 mg/day BID	-3.05 (-6.69, 0.59)	Not Significant
PGB 150 mg/day BID	-2.45 (-6.06, 1.16)	Not Significant
PGB 300 mg/day BID	-4.56 (-8.20, -0.92)	Significant
PGB 600 mg/day BID	-1.56 (-4.29, 1.17)	Not Significant
PGB 600 mg/day TID	-1.36 (-4.83, 2.12)	Not Significant
Pooled Psychiatry Studies		
PGB 150 mg/day TID	-0.57 (-3.39, 2.24)	Not Significant
PGB 600 mg/day TID	-3.38 (-6.17, -0.59)	Significant

CI = Confidence Interval, PGB = Pregabalin.
[a] Difference between Least-Squares Means
[b] Based on ANCOVA; not significant $p > 0.05$, significant $p \leq 0.05$

QRS duration, Ventricular rate, -- All trials
On average, the maximum increases from baseline in QRS duration or ventricular rate were not consistently different between the pregabalin and placebo treatment groups. Data from shift tables also show no difference between treatment groups with regards to the percentage of patients who had increases in QRS duration from baseline.

Premature ventricular contractions
PVCs did not occur more commonly in pregabalin-treated than placebo-treated patients in the combined pain trials, epilepsy trials, or psychiatry trials. In the diabetic neuropathic pain sub-population, PVCs occurred more commonly in pregabalin-treated than placebo- treated patients, but no clear dose relationship was seen. Cardiovascular-related adverse events, as reported by the site investigators, occurred at similar frequencies in pregabalin- treated and placebo-treated patients.

7.4.10.2 ECG data in DPN patients

In the initial NDA, Pfizer pooled data from DPN studies 1008-014, -029, -040, and –131 to analyze changes from baseline to study endpoint in PR, QRS, QTs, and VR intervals. At the Division's request, Pfizer calculated mean changes from baseline of these parameters from baseline to maximum value. Changes in ECG parameters were presented by assigned treatment dose, and comparisons made to placebo.

Statistical analyses of ECGs from the diabetic neuropathy population gave similar results to the overall pain population. Among diabetic patients, statistically significant differences from placebo were limited to the pregabalin 600 mg/day group. The greatest mean differences from placebo in PR, QRS, and QTs were 3.56, -1.21, and -1.98 msec, respectively. Patients in the pregabalin group had a mean change in PR from baseline to maximum value of 6.62 msec, compared to 4.82 msec in the placebo group. This increase was not dose-related.

None of the changes in PR appear to be clinically meaningful average differences.

QTs interval

Patients with QTc prolongation at baseline were to be excluded from a study as specified in the protocol. The proportions of patients with abnormal or possibly significant changes in QTc were similar across treatment groups. A summary of maximum QT changes from baseline by dose group is provided below:

	Placebo (N 332)		75 (N = 77)		150 (N = 79)		300 (N = 157)	600 (N = 247)		All Pregabalin (N = 560)	
ıge in QTc (msec)											
Risk (%)[a]	291	(87.7%)	70	(90.9%)	74	(93.7%)	123 (78.3%)	216	(87.4%)	483	(86.3%)
Max Change <60	16	(5.5%)	4	(5.7%)	7	(9.5%)	6 (4.9%)	17	(7.9%)	34	(7.0%)
Max Change <90	0	(0.0%)	0	(0.0%)	0	(0.0%)	0 (0.0%)	0	(0.0%)	0	(0.0%)
Change ≥90	0	(0.0%)	0	(0.0%)	0	(0.0%)	0 (0.0%)	1	(0.5%)	1	(0.2%)
(msec) During Double-Blind											
Risk (%)b	295	(88.9%)	72	(93.5%)	75	(94.9%)	130 (82.8%)	227	(91.9%)	504	(90.0%)
	1	(0.3%)	0	(0.0%)	0	(0.0%)	0 (0.0%)	0	(0.0%)	0	(0.0%)

er of ITT patients.
Risk = Number of patients with a baseline QTc and QTc while on double-blind treatment.
Risk = Number of patients with a QTc while on double-blind treatment.
(Applicant's table 16, RR-MEMO 720-04340, P. 43)

The 150 mg/d group had a mean increase from baseline to maximum value of 10.01 msec, compared to 3.6, 7, and 8.53 msec increases for the placebo, 300- and 600 mg/d grups respectively. However, the mean increase for all pregabalin patients was 3.78 msec, suggesting that there was no considerable difference from placebo.

7.5 Miscellaneous Studies

The Applicant submitted reports for the following pain studies that were not considered as supportive of efficacy in DPN, but did contribute to the safety data for pregabalin:

Protocol number	Indication/treatment population
031	[redacted]
032	Chronic [redacted] pain
060	[redacted]
104	Chronic [redacted] pain
105	Fibromyalgia
183	[redacted]

7.6 Literature Review for Safety

The Applicant did not support any published literature in support of drug safety.

7.7 Postmarketing Surveillance

Since pregabalin is not marketed in any country, there are no post-marketing data for review.

7.8 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	Pregablin (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.

7.8.1 Exposure

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 numer of patients exposed to pregablin during controlled trials was therefore 5781 (compared to 5508 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 7.8.1 showes the source and number of patients who were exposed to study drug, using both the initial NDA data and the new exposure data:

	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
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)

7.8.2 Deaths

Pfizer originally reported 55 deaths among pregabalin-treated patients. Thirteen additional deaths are reported in the Safety Update, 8 of which occurred during trials that are now complete, and 5 that occurred in trials that are ongoing. 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). It is

not stated whether the fall occurred in the setting of somnolence or dizziness related to pregabalin treatament. 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 treatement).

7.8.3 Serious Adverse Events

The Safety update includes information on SAEs occurring in 54 additional patients. Of the 54 patients, there were 19 patients (2 placebo, 17 pregabalin) who who experienced a SAE during a completed controlled trial or its open label extension. Among these 19 patients, notable SAEs were acute renal failure and symptoms of pregabalin drug withdrawal, both of which occured in the same individual:

Pregabalin drug withdrawal, Acute renal failure

Patient 354-28, Protocol 1008-165

This 83 yo male with a history of DPN initially received double-blind treatment with pregablin (150 mg/d) for 28 days, and then entered into the open-label study (Protocol 1008-165) during which he was treated with pregabalin 150-450 mg.d. Son Study Day 82 of open-label treatment, the patient attempted a drug holiday from pregabalin 450 mg/d. Two days later, he experienced nausea, vomiting, confusion, and flushing which were considered to be a withdrawal syndrome. The patient recovered with resumption of pregabalin treatment. A second drug holiday was attempted on Study Day 169, and the subject experienced vomiting for 2 days. Pregabalin was resumed on Study Day 172. The following day, the subject was admitted to the ICU with bronchopneumonia, hyperglycemia, and acute renal failure. The patient recovered with treatment, and pregabalin was continued.

Pfizer considered that among the 35 patients who had an SAE during ongoing trials, 6 patients had SAEs that were related to study drug:

Patient Identification	Protocol Number	SAE
005-1	1008-112	Soft tissue swelling of fingers
147-7	1008-114	Seizure exacerbation
004-10	1008-202	Exacerbation of bipolar disorder
132-6	1008-112	Status epilepticus
001-6	1008-125	Haemodilution, Marked pitting oedema
112-23	1008-164	Worsening of depression

Source Data: Appendix ALL.33.2
(Applicant's Table 17, Safety Update, P. 29)

With respect to the information regarding patient exposure, deaths, and SAEs, the Safety Update provided little additional insight into the safety of the medication.

7.9 Drug Withdrawal, Abuse, and Overdose Experience

Drug Withdrawal:

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)

In the clinical pharmacology studies, 58 healthy volunteers were treated with as much as 900 mg/day of pregabalin for up to 28 days. Medication was discontinued without tapering, and effects were recorded.

DESS were defined post hoc as adverse events occurring after the last dose of study medication. A total of 14 of the 58 pregabalin-treated subjects (24%) experienced DESS, the most common being headache, nausea, and diarrhea. This was in comparison to 27% (4/15) of placebo patients who experienced accidental injury, infection, skin disorder, and ventricular extra-systole. In other clinical pharmacology studies, subjects reported anxiety and nervousness following discontinuation of pregabalin (up to 600 mg/day) for as many as 14 weeks.

In Phase 2/3 psychiatry studies (, DESS adverse events were defined per protocol as treatment-emergent adverse events that either started during the taper or withdrawal phase or continued from the treatment phase but increased in intensity during the taper or withdrawal phase. Pfizer reviewed DESS events that occurred within 10 days after the last full dose of study medication. Studies varied with respect to duration of dose taper (3-6 days). In short term psychiatry studies, 15.7% of pregabalin patients had at least one DESS AE compared to 11/1% of placebo patients. The common DESS AEs in pregabalin patients were insomnia, headache, and nausea. In long-term psychiatry studies, common DESS events also occurred with greater frequency among pregabalin-treated patients, with the most common being insomnia, headache, infection, and nausea.

DESS AEs were prospectively collected in one DPN study, Protocol 1008-040. In this study, subjects were treated with placebo, amitriptyline (75 mg/d) or pregabalin (600 mg/d) for 8 weeks, and then underwent a drug taper over 1 week. Th incidence of DESS adverse events in the pregabalin-treated patients (10.5%) was slightly lower than the incidence observed with placebo (16.0%) and amitriptyline (13.8%). Similarly, DESS events considered associated with study drug occurred in 3.5% of pregabalin treated patients, 6.2% of placebo-treated patients, and 4.6% of amitriptyline- treated patients. DESS events experienced by more than 1 pregabalin-treated patient were weight gain (2 patients) and reflexes decreased (2 patients), and the DESS events experienced by more than 1 amitriptyline-treated patient were creatinine clearance decreased (2 patients) and vomiting (2 patients).

Pfizer stated that one limitation of the DESS analysis is the potential confounding by re-emergence of the somatic and psychic symptoms of anxiety. Therefore the Physician Withdrawal Checklist (PWC), a physician-rated interview was also used. The PWC measures the presence of signs and symptoms potentially related to benzodiazepine-like withdrawal. In both short- and long-term studies, the least squares mean PWC change scores for pregabalin-treated patients were generally small, and lower than those of lorazepam.

In summary, therefore, 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. Dr. Katherine Bonson, the CSS Pharmacology Reviewer, tabulated the incidence of "euphoria" in GAD and epilepsy trials:

	% Patients		
Pregabalin dose	GAD	Epilepsy	NeP*
150	0.5	0	1 0
200	10.3	-	-
300	3.3	2 2	2 4
400	4.8	-	-
450	11.8	-	-
600	2.5	1 0	1.5
All doses	4.5	0.8	1 4
Placebo	1.2	0.3	0

*Neuropathic pain

Pfizer found that the median time to onset of euphoria was 1 day and the median duration was 7 days. Among all patients with euphoria in the controlled studies (205 patients), a concurrent episode of a CNS adverse event (e.g., somnolence, dizziness, confusion) was reported in 65.4% (134 of 205 patients) (SCS P. 102)

Pfizer conducted a clinical abuse potential study with sedative/alcohol abusers, and a study of self-administration in animals. While Pfizer considered these studies showed that pregabalin lacks abuse potential, CSS considered the subjective responses to pregabalin (200 mg and 450 mg) to be similar to or greater than the responses to 15 and 30 mg of diazepam. Furthermore, animal studies showed that pregabalin produces a reinforcing effect.

Therefore, based on the high proportion of subjects reporting euphoria (up to 11.8%) relative to placebo (1.2%), as well as the results of the clinical abuse potential study and animal study, CSS recommends that pregabalin be a controlled substance (Schedule IV).

Overdose

In Phase 1 trials, 600 mg/day was associated with fewer CNS-related AEs and was chosen as the maximum dose for the Phase 2/3 trials. Consequently, when considering the frequency and severity of overdoses, any dose > 600 mg/day was considered an 'overdose'. Also, any doses taken that were not in the dosing records or doses that were intended for a suicide attempt were recorded as 'overdoses'.

Pfizer found that, based on the dosing records, 91 patients took pregabalin total daily dosages >600 mg/day during the clinical trials. Based on exposure data, I found that there were 97 patients who took pregabalin doses exceeding 600 mg. The overdoses ranged from 625 to 2400 mg/day, with durations of 1 day to a maximum of 464 days. The 10 most commonly reported AEs are listed below:

Most commonly reported AEs in patients who took > 600 mg of pregabalin

		Total N = 97	
Body system	**Preferred term**	N	%
Body as a whole	Infection	38	39.2
	Accidental injury	30	31.0
	Headache	25	25.8
	Asthenia	17	17.5
	Pain	15	15.5
Metabolic and nutritional disorders	Weight gain	23	23.7
Nervous system	Dizziness	33	34.0
	Somnolence	32	33.0
	Ataxia	17	17.5
Special senses	Amblyopia	16	16.5

Other notable AEs were confusion (13%), peripheral edema (11%), diplopia (10%), and abnormal vision (9%). The majority of the adverse events reported during overdoses between >600 mg were comparable to events observed with the patients' regularly scheduled doses.

There were 20 patients who reported taking >900 mg/d. Two of these patients had serious adverse events of suicide attempt or overdose (Patient 009_008019 in Study 010 and Patient 087_069008 in Study 100). The maximum reported overdose, 15000 mg in Patient 087_069008 (from ARISg database), reportedly revealed no additional safety consequences; however, this overdose was not substantiated by blood levels or the dosing information recorded in the clinical study database (1700 mg was recorded).

Eleven of the 18 patients who did not have serious adverse events associated with overdoses >900 mg/d reported at least 1 nonserious adverse event during the overdose period or within 1 week after the dosage was corrected. AEs included somnolence, agitation, paresthesia, liver function tests abnormal, myasthenia, asthenia, ataxia, amblyopia, euphoria, nausea, dizziness, hallucination, headache, and edema. The abnormal liver function tests (Patient 034_021004) occurred the day after the patient was in a motor vehicle accident. No clinically significant abnormalities in physical examinations, vital signs, ECG, or clinical laboratory examinations were found after Pfizer reviewed all safety data collected from these patients.

With regards to overdoses not recorded in the dosing record, there were 6 patients who took overdoses that ranged from 1500 mg to 8000 mg. Five overdoses were intentional and occurred in patients with epilepsy or GAD: Patients 012_055106, 012_084117, 081_127007, 081_129002, and 087_015011. Additionally, Patient 011_016012 in Study 012 was hospitalized for ataxia and nystagmus after she had unintentionally doubled her randomized dose of 450 mg/day during open-label treatment. One other case of pregabalin overdose involved the son of a patient who experienced slight drowsiness after taking 6000 mg (from the ARISg database).

There were no deaths associated with pregabalin overdose. All patients who experienced serious adverse events involving overdoses of pregabalin recovered.

The data show therefore 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.

7.10 Adequacy of Safety Testing

As per the Safety Update, 9278 pateints have had at least 1 dose of pregabalin, 1650 of whom were enrolled in DPN 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.

7.11 Labeling Safety Issues and Postmarketing Commitments

At the End of Phase 2 meeting in June 1999, the Applicant was informed that, with respect to efficacy of pregabalin in patients with DPN, evidence was necessary that drug effectiveness was not due to a toxic effect on the nerves. The Applicant had intended to incorporate studies of nerve function into long-term (≥ 12 weeks) DPN studies. However, with the imposition of the partial hold in February 2001, Pfizer was unable to initiate such studies. Prior to submission of the NDA it was agreed that a 12-week, adequate and well-controlled study demonstrating that efficacy in DPN does not correlate with accelerated nerve damage could be completed as a Phase 4 commitment.

8 Dosing, Regimen, and Administration Issues

The proposed marketing dose for the treatment of DPN is 150 mg — (300 mg/d) and 200 mg — (600 mg/d). However, review of the data show that these doses are effecacious only with a TID dosing regimen. Lower doses were studied in the submitted efficacy trials, however these doses were either not replicated or were found to be ineffective. Additionally, the data do not suggest any benefit of treatment with 600 mg/d over 300 mg/d, with respect to either the endpoint mean pain score, change in mean pain score, or proportion of responders to therapy. The pharmacokinetic data show that pregabalin can be administered with or without meals.

9 Use in Special Populations

9.1 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 DPN population, the overwhelming majority of subjects were Caucasian (91.5%). Therefore it is not possible to draw conclusions about the effect of race on the efficacy of pregabalin for this indication. There were more male patients than female (58% vs. 41%); nevertheless, pregabalin

appears to be effective in both men and women. Approximately one third of subjects studied were ≥ 65 years, with a median age of 60 years. Exposure in this age group was therefore appropriate.

9.2 Pediatric Program (e.g. pediatric waivers, deferrals, written requests)

Pediatric data has not been submitted regarding use in patients with pain due to peripheral diabetic neuropathy (DPN). Pfizer has requested a full waiver of the requirement for pediatric studies, noting the incidence of pain due to DPN is too low in that population to conduct appropriate studies, or to assess a meaningful therapeutic benefit. Also, pregabalin is not likely to be used in a substantial number of pediatric patients for neuropathic pain. [redacted] This rationale and strategy is acceptable.

9.3 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).

10 CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1 Conclusions Regarding Safety and Efficacy

The data provided in this application show that pregabalin, at doses of 300 mg/d and 600 mg/d, administered in three divided doses, is efficacious in reducing pain associated with diabetic peripheral neuropathy.

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 occuring 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. The vision-related effects of pregabalin are of concern, especially for the diabetic population. Patients with diabetes are already at considerable risk of retinopathy and vision loss. The combined effects of long-standing disease and possible drug-induced vision changes 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 diabetes is also of of concern, given that edema can lead to diminished skin integrity, a serious occurence in patients already at risk for skin ulceration.

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.
The non-clinical finding of dermatopathy raises the concern of possible skin breakdown in humans, a particularly worrisome event for patients with diabetes who are already at risk for skin ulceration, poor wound healing, and subsequent amputation. While the available data did not establish an association between pregabalin treatment and skin ulcers in the DPN population, the absence of a comparator group exposed for a similar duration as the pregabalin group, does not rule out the possibility of a real effect. Furthermore, the mechanism and risk factors for skin changes have not been fully characterized.

Finally, because pregabalin is cleared via the kidneys and because patients with diabetes experience decline in renal function over time, diabetic patients will progressively be exposed to higher systemic levels of pregabalin and will be more likely to experience adverse effects.

10.2 Recommendations on Approvability

The risks of dermatological and ophthalmologic effects of pregabalin are currently of uncertain clinical significance, yet of considerable concern, particularly with regard to patients with diabetes. Consequently, it does not appear that the benefits of the drug in patients with DPN outweigh the risks. I therefore do not recommend approval of this application. I recommend further studies to characterize the effects of pregabalin on the skin and 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.

10.3 Labeling

In anticipation of possible future approval pregablin 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 review will need to be revised.

CLINICAL STUDIES

Neuropathic pain associated with diabetic peripheral neuropathy

In this section, the number of studies contributing to the finding of efficacy will need to be changed from 4 to 3. Consequently, values related to the number of patients enrolled in the efficacy studies, their

mean baseline pain score, and the completion rate will need to be revised. Additionally, it should be stated that efficacy was shown with TID dosing, and not both BID and TID dosing as Pfizer has proposed.

Diabetic peripheral neuropathy 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-values for the comparisons of the difference from placebo will need to be revised. P-values based on a BOCF analysis of responder rates will also need to be changed. The section describing the 12-week trial of BID dosing should be deleted, since this study did not contribute to the efficacy findings.

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 efficacy trials, and data based on the Agency's BOCF analyses of the percentage of patients with reduction in pain.

Pfizer provides information regarding changes in scores using the Pateint 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.

WARNINGS

The Sponsor has not proposed any language for this section.

I recommend that the risk of vision changes (including blurry vision and visual field defects) should be included in this section.

PRECAUTIONS

Dizziness and Somnolence

[

]

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, ~~some patients reported~~ [ ] symptoms [ ] including insomnia, nausea, headache, and diarrhea.

The PRECAUTIONS section should also mention the risks of edema, weight gain, and changes in vision. Description of pregabalin's effects on platelets should also be included

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. Also, 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 diabetic peripheral neuropathy

Table 1 should be replaced with the table generated upon the Agency's review of these data (Table 7.4.6 of this Review)

11 APPENDIX

APPENDIX 1: DEATHS IN ONGOING STUDIES, OR NOT INCLUDED IN THE INTEGRATED SAFETY DATABASE

Pfizer identified nine additional pregabalin deaths that are not included in the integrated safety database (from ongoing blinded studies or reported to the sponsor's serious adverse event database but not entered into the clinical trial safety database-Summary of Clinical Safety p.39). Dr. Boehm summarized the reported causes of death for these nine patients:

1008-155 074-20 52 year old male, cause of death: cardiac arrest, decompensation of diabetes mellitus, third degree heart block, metabolic acidosis, hypovolemic shock.
1008-155 106-8 81 year old male, cause of death: worsening of COPD.
1008-166 033-4 67 year old female, cause of death: myocardial infarction.
1008-166 038-3 74 year old male, cause of death: apoplexia cerebri.
1008-166 132-2 67 year old male, cause of death: myocardial infarction.
009-003004 Impaired gait, personality disorder, thinking abnormal, cerebral hemorrhage, brain herniation (120 days post-treatment)
009-045013 accidental injury, confusion, abnormal gait, hostility, depression, convulsion, cardiac arrest
198-008002 Aortic aneurysm, myocardial infarction
029-015001 pancytopenia (bone marrow biopsy diagnosis-myelodysplastic syndrome), thinking abnormal, cholecystitis, diarrhea, malaise, leukemoid reaction.
(Source: Summary of Clinical Safety, Appendix ALL.289 p. 7674)

APPENDIX 2: 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 the open label study on day 170 and died 21 days later.

APPENDIX 2: NARRAITIVES OF DEATHS IN EPILEPSY TRIALS (CONTINUED)

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.

APPENDIX 3: 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.

APPENDIX 3: NARRITIVES 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.

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

APPENDIX 3: NARRITIVES OF DEATHS IN DPN TRIALS (CONTINUED)

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.

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.

APPENDIX 3: NARRITIVES OF DEATHS IN DPN TRIALS (CONTINUED)

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.

APPENDIX 4: DEATHS IN POSTHERPETIC NEURALGIA (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 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

APPENDIX 4: DEATHS IN PHN TRIALS (CONTINUED)

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 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

APPENDIX 4: DEATHS IN PHN TRIALS (CONTINUED)

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.

APPENDIX 5: SAEs IN DPN TRIALS

Body system	Preferred term	Placebo N	N=459 %	All PGB N	N=979 %
Body as a whole	Chest pain	1	0.22	5	0.51
	Accidental injury	0	0.00	4	0.41
	Infection	1	0.22	3	0.31
	Abdominal pain	0	0.00	1	0.10
	Back pain	0	0.00	1	0.10
	Fever	0	0.00	1	0.10
	Generalized edema	0	0.00	1	0.10
	Malaise	0	0.00	1	0.10
	Neoplasm	0	0.00	1	0.10
	Sudden death	0	0.00	1	0.10
	Allergic reaction	1	0.22	0	0.00
	Suicide attempt	0	0.00	0	0.00
Cardiovascular system	Congestive heart failure	1	0.22	3	0.31
	Myocardial infarct	0	0.00	3	0.31
	Angina pectoris	0	0.00	2	0.20
	Cerebrovascular accident	0	0.00	2	0.20
	Coronary artery disorder	1	0.22	1	0.10
	Bradycardia	0	0.00	1	0.10
	Cerebral infarct	0	0.00	1	0.10
	Heart failure	0	0.00	1	0.10
	Migraine	0	0.00	1	0.10
	Sinus bradycardia	0	0.00	1	0.10
	Supraventricular extrasystoles	0	0.00	1	0.10
	Syncope	0	0.00	1	0.10
	Coronary occlusion	1	0.22	0	0.00
	Nodal tachycardia	0	0.00	0	0.00
Digestive system	Vomiting	0	0.00	2	0.20
	Gastrointestinal disorder	0	0.00	1	0.10
	Cholecystitis	0	0.00	1	0.10
	Colitis	0	0.00	1	0.10
	Gastrointestinal hemorrhage	0	0.00	1	0.10
	Jaundice	0	0.00	1	0.10
	Constipation	1	0.22	0	0.00
	Rectal hemorrhage	1	0.22	0	0.00
Endocrine system	Diabetes mellitus	0	0.00	1	0.10
Hemic and lymphatic system	Macrocytic anemia	0	0.00	1	0.10
	Rupture of spleen	0	0.00	1	0.10
Metabolic and nutritional disorders	Hypoglycemia	0	0.00	2	0.20
	Hyperglycemia	0	0.00	1	0.10
	Ketosis	0	0.00	1	0.10
	Dehydration	1	0.22	0	0.00
Musculoskeletal system	Myasthenia	0	0.00	1	0.10
	Myopathy	0	0.00	1	0.10
Nervous system	CNS neoplasia	1	0.22	0	0.00
	Convulsion	1	0.22	0	0.00
	Vestibular disorder	1	0.22	0	0.00
Respiratory system	Pneumonia	1	0.22	3	0.31
Respiratory system	Dyspnea	0	0.00	2	0.20

APPENDIX 5: SAEs IN DPN TRIALS (CONTINUED)

Body system	Preferred term	Placebo N	N=459 %	All PGB N	N=979 %
Respiratory system	Bronchitis	0	0.00	1	0.10
	Epistaxis	0	0.00	1	0.10
Skin and appendages	Skin ulcer	0	0.00	1	0.10
Special senses	Ophthalmoplegia	0	0.00	1	0.10
	Retinal edema	0	0.00	1	0.10
	Retinal disorder	1	0.22	0	0.00
Urogenital system	Acute kidney failure	0	0.00	1	0.10
	Kidney function abnormal	0	0.00	1	0.10
	Urinary tract infection	0	0.00	1	0.10
	Endometrial carcinoma	0	0.00	0	0.00

APPENDIX 6: SAEs IN PHN TRIALS

Body system	Preferred term	Placebo N	N = 398 %	All PGB N	N = 852 %
Body as a whole	Chest pain	0	0.00	2	0.23
	Pain	0	0.00	2	0.23
	Accidental injury	0	0.00	1	0.12
	Anaphylactoid reaction	0	0.00	1	0.12
	Cellulitis	0	0.00	1	0.12
	Face edema	0	0.00	1	0.12
	Abscess	1	0.25	0	0.00
	Infection	1	0.25	0	0.00
	Overdose	1	0.25	0	0.00
Cardiovascular system	Cerebral ischemia	1	0.25	3	0.35
	Ventricular extrasystoles	1	0.25	2	0.23
	AV block	0	0.00	1	0.12
	Atrial arrhythmia	0	0.00	1	0.12
	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
	Occlusion	0	0.00	1	0.12
	Syncope	0	0.00	1	0.12
	Thrombophlebitis	0	0.00	1	0.12
	Ventricular tachycardia	0	0.00	1	0.12
	Angina pectoris	1	0.25	0	0.00
	Myocardial ischemia	1	0.25	0	0.00
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	Hypokalemia	0	0.00	1	0.12
	Peripheral edema	0	0.00	1	0.12
	Edema	1	0.25	0	0.00
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	Pneumonia	0	0.00	2	0.23
	Asthma	0	0.00	1	0.12
	Dyspnea	0	0.00	1	0.12
	Lung fibrosis	0	0.00	1	0.12
Special senses	Glaucoma	0	0.00	1	0.12
Urogenital system	Urinary tract infection	0	0.00	2	0.23
Urogenital system	Uterine hemorrhage	1	0.25	0	0.00

APPENDIX 7: SAEs 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[4] 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)

[4] 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 [redacted] and study 093/192 for [redacted]

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

APPENDIX 8: SKIN-RELATED AEs – DPN COMBINED TRIALS

	Total N = 1413	
Preferred term	**No. Pts**	**%**
Rash	76	5.38
Skin ulcer	**45**	**3.18**
Pruritus	31	2.19
Skin disorder	28	1.98
Nail disorder	20	1.42
Dry skin	18	1.27
Eczema	16	1.13
Sweating	14	0.99
Vesiculobullous rash	13	0.92
Fungal dermatitis	11	0.78
Acne	10	0.71
Urticaria	9	0.64
Skin benign neoplasm	8	0.57
Alopecia	7	0.50
Skin carcinoma	7	0.50
Contact dermatitis	6	0.42
Herpes zoster	6	0.42
Maculopapular rash	6	0.42
Herpes simplex	5	0.35
Seborrhea	4	0.28
Skin hypertrophy	4	0.28
Skin discoloration	3	0.21
Cutaneous moniliasis	2	0.14
Furunculosis	2	0.14
Hirsutism	2	0.14
Ichthyosis	2	0.14
Psoriasis	2	0.14
Pustular rash	2	0.14
Skin atrophy	2	0.14
Skin nodule	2	0.14
Angioedema	1	0.07
Exfoliative dermatitis	1	0.07
Melanosis	1	0.07
Purpuric rash	1	0.07
Skin melanoma	1	0.07
Subcutaneous nodule	1	0.07

APPENDIX 9: GUIDELINES FOR CLINICALLY IMPORTATN CHANGES IN VITAL SIGNS

Criteria for the General Patient Population
Vital sign values were considered to constitute clinically important changes from baseline if they met the following criteria:

Weight
Increase: if ratio to baseline is ε 1.07 (equivalent to a ε7% increase)
Decrease: if ratio to baseline is δ 0.93 (equivalent to a ε7% decrease)

Systolic Blood Pressure
Increase: if >180 and increase from baseline of ε 40 mm Hg
Decrease: if <90 and decrease from baseline of ε 30 mm Hg

Diastolic Blood Pressure
Increase: if >105 and increase from baseline of ε30 mm Hg
Decrease: if <50 and decrease from baseline of ε 20 mm Hg

Heart Rate
Increase: if >120 and increase from baseline of ε30 beats per minute
Decrease: if <50 and decrease from baseline of ε30 beats per minute

Respiratory Rate
Increase: if >30 resp/min OR increase from baseline of ε10 resp/min
Decrease: if <10 resp/min OR decrease from baseline of ε10 resp/min.

Criteria for Patients in Studies of Diabetic Neuropathy
Due to the more frequent occurrence of comorbidities in patients with longstanding diabetes, more stringent criteria for clinically important changes in vital signs were applied for systolic blood pressure, diastolic blood pressure, and heart rate in additional summaries of data for patients in studies of diabetic neuropathy. In these summaries, vital sign values were considered to constitute clinically important changes from baseline if they met the following criteria:

Systolic Blood Pressure
Increase: if > 160 and increase from baseline of ε 30 mm Hg;
Decrease: if < 90 and decrease from baseline of ε 30 mm Hg;

Diastolic Blood Pressure
Increase: if > 100 and increase from baseline of ε 20 mm Hg
Decrease: if < 60 and decrease from baseline of ε 20 mm Hg

Heart Rate
Increase: if > 120 and increase from baseline of ε 30 bpm;
Decrease: if < 60 and decrease from baseline of ε 20 bpm;

APPENDIX 10: CLINICALLY IMPORTANT CHANGES IN VITAL SIGNS (BASELINE TO TERMINATION): CONTROLLED STUDIES, ALL INDCATIONS

				Total Daily Dose of Pregabalin in mg/day, Combined BID/TID Regimens					
		Placebo N=2384		150 N=1164		200 N=208		300 N=1224	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Weight	Decrease	33 (1.5)	2233	12 (1.1)	1122	1 (0.6)	175	13 (1.1)	1158
	Increase	38 (1.7)	2233	53 (4.7)	1122	4 (2.3)	175	81 (7.0)	1158
Heart Rate (Supine)	Decrease	1 (0.1)	1160	0 (0.0)	722	0 (0.0)	0	0 (0.0)	849
	Increase	1 (0.1)	1160	0 (0.0)	722	0 (0.0)	0	0 (0.0)	849
Systolic Blood Pressure (Supine)	Decrease	0 (0.0)	1153	0 (0.0)	723	0 (0.0)	0	1 (0.1)	847
	Increase	3 (0.3)	1153	2 (0.3)	723	0 (0.0)	0	0 (0.0)	847
Diastolic Blood Pressure (Supine)	Decrease	1 (0.1)	1153	2 (0.3)	723	0 (0.0)	0	1 (0.1)	847
	Increase	1 (0.1)	1153	0 (0.0)	723	0 (0.0)	0	1 (0.1)	847
Systolic Blood Pressure (Standing)	Decrease	0 (0.0)	1280	0 (0.0)	713	0 (0.0)	0	0 (0.0)	844
	Increase	8 (0.6)	1280	2 (0.3)	713	0 (0.0)	0	1 (0.1)	844
Diastolic Blood Pressure (Standing)	Decrease	1 (0.1)	1280	2 (0.3)	713	0 (0.0)	0	0 (0.0)	844
	Increase	2 (0.2)	1280	2 (0.3)	713	0 (0.0)	0	1 (0.1)	844

				Total Daily Dose of Pregabalin in mg/day, Combined BID/TID Regimens					
		Placebo N=2384		150 N=1164		200 N=208		300 N=1224	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Heart Rate (Sitting)	Decrease	0 (0.0)	1175	0 (0.0)	429	0 (0.0)	202	0 (0.0)	352
	Increase	0 (0.0)	1175	0 (0.0)	429	0 (0.0)	202	0 (0.0)	352
Systolic Blood Pressure (Sitting)	Decrease	1 (0.1)	1175	0 (0.0)	429	0 (0.0)	202	0 (0.0)	352
	Increase	1 (0.1)	1175	0 (0.0)	429	0 (0.0)	202	0 (0.0)	352
Diastolic Blood Pressure (Sitting)	Decrease	2 (0.2)	1175	0 (0.0)	429	1 (0.5)	202	0 (0.0)	352
	Increase	0 (0.0)	1175	0 (0.0)	429	0 (0.0)	202	0 (0.0)	352

				Total Daily Dose of Pregabalin in mg/day, Combined BID/TID Regimens					
		Placebo N=2384		150 N=1164		200 N=208		300 N=1224	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Respiratory Rate	Decrease	10 (1.1)	950	7 (1.6)	428	1 (0.5)	202	1 (0.4)	255
	Increase	5 (0.5)	950	3 (0.7)	428	1 (0.5)	202	2 (0.8)	255

†Clinically significant decreases are defined as follows:
Weight - if ratio to baseline of ≤ 0.93; Heart Rate - if < 50 and decrease from baseline of ≥30 bpm;
Systolic Blood Pressure - if < 90 and decrease from baseline of ≥ 30 mm Hg;
Diastolic Blood Pressure - if < 50 and decrease from baseline of ≥20 mm Hg;
Respiratory Rate - if <10 resp/min OR decrease from baseline of ≥10 resp/min.
Clinically significant increases are defined as follows:
Weight - if ratio to baseline of ≥ 1.07; Heart Rate - if > 120 and increase from baseline of ≥30 bpm
Systolic Blood Pressure - if > 180 and increase from baseline of ≥ 40 mm Hg;
Diastolic Blood Pressure - if > 105 and increase from baseline of ≥30 mm Hg;
Respiratory Rate - if >30 resp/mm OR increase from baseline of ≥10 resp/min
*Number of patients with data at both baseline and termination
‡Dose (eg, 150 mg) is the total daily dose in mg/day, combined BID/TID regimen

		Pregabalin Dose mg day#							
		400 N=360		450 N=501		600 N=1802		ALL PGB N=5508	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Weight	Decrease	2 (0.6)	320	3 (0.6)	470	13 (0.8)	1701	46 (0.9)	5181
	Increase	22 (6.9)	320	33 (7.0)	470	198 (11.6)	1701	401 (7.7)	5181
Heart Rate (Supine)	Decrease	0 (0.0)	0	0 (0.0)	229	1 (0.1)	685	1 (0.0)	2645
	Increase	0 (0.0)	0	0 (0.0)	229	0 (0.0)	685	0 (0.0)	2645
Systolic Blood Pressure (Supine)	Decrease	0 (0.0)	0	0 (0.0)	228	2 (0.3)	683	3 (0.1)	2641
	Increase	0 (0.0)	0	0 (0.0)	228	3 (0.4)	683	5 (0.2)	2641
Diastolic Blood Pressure (Supine)	Decrease	0 (0.0)	0	1 (0.4)	228	0 (0.0)	683	4 (0.2)	2641
	Increase	0 (0.0)	0	0 (0.0)	228	0 (0.0)	683	2 (0.1)	2641
Systolic Blood Pressure (Standing)	Decrease	0 (0.0)	94	0 (0.0)	228	2 (0.2)	810	2 (0.1)	2845
	Increase	1 (1.1)	94	1 (0.4)	228	3 (0.4)	810	8 (0.3)	2845
Diastolic Blood Pressure (Standing)	Decrease	0 (0.0)	94	0 (0.0)	228	1 (0.1)	809	3 (0.1)	2844
	Increase	0 (0.0)	94	0 (0.0)	228	0 (0.0)	809	3 (0.1)	2844

		Pregabalin Dose mg day#							
		400 N=360		450 N=501		600 N=1802		ALL PGB N=5508	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Heart Rate (Sitting)	Decrease	1 (0.3)	348	0 (0.0)	259	0 (0.0)	1071	2 (0.1)	2748
	Increase	0 (0.0)	348	0 (0.0)	259	0 (0.0)	1071	0 (0.0)	2748
Systolic Blood Pressure (Sitting)	Decrease	0 (0.0)	348	0 (0.0)	259	3 (0.3)	1071	3 (0.1)	2748
	Increase	1 (0.3)	348	0 (0.0)	259	0 (0.0)	1071	1 (0.0)	2748
Diastolic Blood Pressure (Sitting)	Decrease	0 (0.0)	348	0 (0.0)	259	0 (0.0)	1071	1 (0.0)	2748
	Increase	0 (0.0)	348	0 (0.0)	259	0 (0.0)	1071	0 (0.0)	2748

		Pregabalin Dose mg day#							
		400 N=360		450 N=501		600 N=1802		ALL PGB N=5508	
Parameter Summarized	Direction	n %	Total*	n %	Total*	n %	Total*	n %	Total*
Respiratory Rate	Decrease	2 (0.8)	254	2 (0.8)	259	10 (1.2)	834	23 (1.0)	2319
	Increase	2 (0.8)	254	0 (0.0)	259	1 (0.1)	834	9 (0.4)	2319

+Clinically significant decreases are defined as follows:
Weight - if ratio to baseline of <= 0.93; Heart Rate - if < 50 and decrease from baseline of >=30 bpm;
Systolic Blood Pressure - if < 90 and decrease from baseline of >= 30 mm Hg;
Diastolic Blood Pressure - if < 50 and decrease from baseline of >=20 mm Hg.;
Respiratory Rate - if <10 resp/min OR decrease from baseline of >10 resp/min

Clinically significant increases are defined as follows:
Weight - if ratio to baseline of >= 1.07; Heart Rate - if > 120 and increase from baseline of >=30 bpm
Systolic Blood Pressure - if > 180 and increase from baseline of >= 40 mm Hg.
Diastolic Blood Pressure - if >= 105 and increase from baseline of >=30 mm Hg.
Respiratory Rate - if >30 resp/min OR increase from baseline of ≥10 resp/min

*Number of patients with data at both baseline and termination

#Dose (eg, 150 mg) is the total daily dose in mg/day, combined BID/TID regimen.

APPENDIX 11: CLINICALLY IMPORTANT CHANGES IN VITAL SIGNS (BASELINE TO ANY TIME): CONTROLLED STUDIES, ALL INDCATIONS

				Pregabalin Dose mg/day#					
		Placebo N=2384		150 N=1164		200 N=208		300 N=1224	
		n(%)	Total*	n(%)	Total*	n(%)	Total*	n(%)	Total*
Weight	Decrease	6(0.9)	673	3(0.8)	369	0(0.0)	78	3(1.0)	310
	Increase	16(2.4)	673	34(9.2)	369	2(2.6)	78	41(13.2)	310
Heart Rate (Supine)	Decrease	1(0.1)	1070	0(0.0)	680	0(0.0)	0	2(0.3)	781
	Increase	1(0.1)	1070	0(0.0)	680	0(0.0)	0	0(0.0)	781
Systolic Blood Pressure (Supine)	Decrease	2(0.3)	644	0(0.0)	418	0(0.0)	0	2(0.4)	449
	Increase	3(0.5)	644	1(0.2)	418	0(0.0)	0	0(0.0)	449
Diastolic Blood Pressure (Supine)	Decrease	1(0.1)	916	3(0.5)	575	0(0.0)	0	1(0.2)	655
	Increase	2(0.2)	916	1(0.2)	575	0(0.0)	0	1(0.2)	655
Systolic Blood Pressure (Standing)	Decrease	0(0.0)	766	2(0.5)	436	0(0.0)	0	3(0.6)	468
	Increase	2(0.3)	766	0(0.0)	436	0(0.0)	0	2(0.4)	468
Diastolic Blood Pressure (Standing)	Decrease	1(0.1)	967	2(0.4)	547	0(0.0)	0	1(0.2)	629
	Increase	5(0.5)	967	3(0.5)	547	0(0.0)	0	2(0.3)	629
Heart Rate (Sitting)	Decrease	0(0.0)	1112	2(0.5)	411	0(0.0)	190	0(0.0)	337
	Increase	0(0.0)	1112	0(0.0)	411	1(0.5)	190	0(0.0)	337
Systolic Blood Pressure (Sitting)	Decrease	2(0.2)	983	0(0.0)	394	0(0.0)	181	0(0.0)	286
	Increase	1(0.1)	983	0(0.0)	394	0(0.0)	181	0(0.0)	286
Diastolic Blood Pressure (Sitting)	Decrease	3(0.3)	1029	1(0.3)	378	1(0.6)	173	0(0.0)	317
	Increase	2(0.2)	1029	0(0.0)	378	0(0.0)	173	1(0.3)	317
Respiratory Rate	Decrease	5(0.6)	876	2(0.5)	383	3(1.6)	182	1(0.4)	244
	Increase	3(0.3)	876	7(1.8)	383	2(1.1)	182	4(1.6)	244

		Pregabalin Dose mg/day#							
		400 N=360 n(%)	Total*	450 N=501 n(%)	Total*	600 N=1802 n(%)	Total*	All PGB N=5508 n(%)	Total*
Weight	Decrease	0(0.0)	141	1(0.7)	147	5(1.0)	483	12(0.8)	1588
	Increase	14(9.9)	141	14(9.5)	147	90(18.6)	483	200(12.6)	1588
Heart Rate (Supine)	Decrease	0(0.0)	0	0(0.0)	216	1(0.2)	628	3(0.1)	2457
	Increase	0(0.0)	0	0(0.0)	216	0(0.0)	628	0(0.0)	2457
Systolic Blood Pressure (Supine)	Decrease	0(0.0)	0	0(0.0)	174	2(0.5)	372	5(0.3)	1494
	Increase	0(0.0)	0	0(0.0)	174	0(0.0)	372	1(0.1)	1494
Diastolic Blood Pressure (Supine)	Decrease	0(0.0)	0	1(0.5)	193	3(0.6)	525	8(0.4)	2078
	Increase	0(0.0)	0	0(0.0)	193	0(0.0)	525	3(0.1)	2078
Systolic Blood Pressure (Standing)	Decrease	0(0.0)	64	0(0.0)	176	2(0.4)	480	7(0.4)	1712
	Increase	1(1.6)	64	0(0.0)	176	1(0.2)	480	4(0.2)	1712
Diastolic Blood Pressure (Standing)	Decrease	0(0.0)	70	0(0.0)	183	1(0.2)	605	4(0.2)	2164
	Increase	0(0.0)	70	0(0.0)	183	2(0.3)	605	7(0.3)	2164
Heart Rate (Sitting)	Decrease	1(0.3)	330	0(0.0)	250	0(0.0)	1028	4(0.2)	2629
	Increase	0(0.0)	330	0(0.0)	250	0(0.0)	1028	1(0.0)	2629
Systolic Blood Pressure (Sitting)	Decrease	0(0.0)	301	0(0.0)	242	5(0.6)	902	5(0.2)	2380
	Increase	0(0.0)	301	0(0.0)	242	1(0.1)	902	1(0.0)	2380
Diastolic Blood Pressure (Sitting)	Decrease	1(0.3)	296	0(0.0)	229	1(0.1)	932	4(0.2)	2402
	Increase	1(0.3)	296	0(0.0)	229	2(0.2)	932	4(0.2)	2402
Respiratory Rate	Decrease	5(2.2)	228	2(0.8)	249	2(0.3)	773	16(0.7)	2141
	Increase	1(0.4)	228	0(0.0)	249	4(0.5)	773	18(0.8)	2141

(Source: Applicant's Appendix ALL_chg.01)
+Clinically significant decreases are defined as follows: Weight - if ratio to baseline of <= 0.93; Heart Rate - if < 50 and decrease from, , , , , , , , baseline of >=30 bpm; Systolic Blood Pressure - if < 90 and decrease from baseline of >= 30 mm Hg; Diastolic Blood Pressure -, , , , , , , , , if < 50 and decrease from baseline of >=20 mm Hg.; Respiratory Rate - if <10 resp/min OR decrease from baseline of >=10 resp/min., , , , , , , , , Clinically significant increases are defined as follows: Weight - if ratio to baseline of >= 1.07; Heart Rate - if > 120 and increase, , , , , , , , ,

from baseline of >=30 bpm; Systolic Blood Pressure - if > 180 and increase from baseline of >= 40 mm Hg; Diastolic Blood Pressure - if > 105 and increase from baseline of >=30 mm Hg. Respiratory Rate - if >30 resp/min OR increase from baseline of >=10 resp/min *Number of patients with data at both baseline and anytime during treatment #Dose (eg, 150 mg) is the total daily dose in mg/day, combined BID/TID regimen.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 12: PATIENTS WITH PLATELET COUNT ≥ 100, 000 AT BASELINE, BUT AT LEAST ONE ON-TREATMENT COUNT OF < 100, 000 - COMBINED CONTROLLE D AND UNCONTROLLED TRIALS, ALL INDICATIONS

Subject	Age	Sex	Baseline PLT*	Lowest on Treatment PLT	Baseline PLT - Lowest PLT
007-001003	26	Female	176,000	77,000	99,000
009-008015	26	Male	101,000	84,000	17,000
010-003106	58	Female	102,000	38,000	64,000
011-033004	48	Male	154,000	100,000	54,000
014-015013	61	Female	109,000	89,000	20,000
029-001013	56	Male	114,000	73,000	41,000
029-009005	61	Female	146,000	88,000	58,000
029-012010	68	Male	110,000	91,000	19,000
029-015001	70	Female	184,000	82,000	102,000
029-031012	52	Female	255,000	33,000	222,000
029-043014	72	Male	108,000	70,000	38,000
030-118014	73	Male	158,000	96,000	62,000
030-127030	81	Male	194,000	62,000	132,000
030-131014	81	Male	104,000	58,000	46,000
030-217007	76	Male	105,000	87,000	18,000
032-324002	31	Male	142,000	52,000	90,000
032-331005	65	Male	100,000	72,000	28,000
034-003001	28	Female	158,000	87,000	71,000
034-077003	58	Male	108,000	95,000	13,000
035-073108	42	Female	104,000	86,000	18,000
040-023001	67	Male	119,000	59,000	60,000
040-072021	64	Male	101,000	64,000	37,000
045-003003	65	Male	154,000	43,000	111,000
083-303012	35	Male	184,000	95,000	89,000
088-504035	46	Male	151,000	92,000	59,000
104-432005	35	Male	110,000	99,000	11,000
127-002007	75	Male	100,000	70,000	30,000
132-106014	64	Male	125,000	95,000	30,000
149-379002	45	Male	110,000	86,000	24,000
149-483009	66	Male	116,000	70,000	46,000
196-501002	69	Female	131,000	88,000	43,000

* The lowest platelet count prior to starting pregabalin treatment

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

/s/

Mwango Kashoki
5/20/04 11:10:04 AM
MEDICAL OFFICER

Celia Winchell
5/20/04 05:24:47 PM
MEDICAL OFFICER
I concur with Dr. Kashoki's review overall; see my memo for additional comments and recommendations.

DRUDP (HFD-580)
Consult response
5-6-04

Memorandum of Consultation

To: Robert Rappaport, MD
Director, HFD-170
(Lisa Malandro, Project Manager)

From:
Olivia Johnson, MD, Medical Officer DRUDP (HFD-580)
George S. Benson, MD, Team Leader DRUDP (HFD-580)
Daniel Shames, MD, Division Director DRUDP (HFD-580)

Re: Consultation concerning male reproductive effects of pregabalin

Date received:
April 20, 2004

Date of consultation:
May 3, 2004

Background:

Pregabalin is a GABA analogue which is the subject of NDA's 21-446 (neuropathic pain associated with diabetic peripheral neuropathy), 21-723 (neuropathic pain associated with herpes zoster), 21-724 (epilepsy), and — (general anxiety disorder). In preclinical studies, pregabalin was found to have adverse effects on male reproductive parameters. Because of the pre-clinical findings, the sponsor conducted a clinical study of the effects of pregabalin on semen analyses in 30 men (plus 16 placebo subjects).

The consultation from HFD-170 requests the following:

"As noted in the pharm/tox review, pregabalin has been shown to have reproductive toxicity in animals. Pfizer has submitted a study, #072, in humans, which purports to demonstrate lack of detrimental effect on reproductive function in humans. Please evaluate the adequacy of the design of study #072 to support the claim that "pregabalin did not exhibit significant detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, when compared with placebo." If study 072 is not adequate, please provide input on the design of a study to evaluate the reproductive effects of pregabalin in human males."

Materials reviewed:

1. Pharmacology/toxicology review

2. Protocol for Trial 072 (" A Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Effects of Pregabalin on Reproductive Function in Healthy Male Subjects")
3. Study report of Trial 072
4. Proposed reproductive labeling

Medical Officer Review:

1. Pre-clinical reproductive data:

   a. Rat

   Study RR 745-02359 "Oral Fertility and Early Embryonic Development Study in Male Rats with CI-1008": Male rats received 0, 250 (low-dose, or LD), 1250 (mid-dose, MD) or 2500 mg/kg (high dose, HD) orally for 11 weeks prior to mating, throughout mating and for up to 6 weeks after mating. Statistically significant decreases in epididymal weights (15 and 24% below control), epididymal sperm counts (28 and 36% below control), vas deferens sperm motility (43 and 94% below control) and the percent sperm with normal morphology (8 and 59% below control) were seen in MD and HD males after 15 weeks of treatment. There was also a statistically significant decrease (6%) in sperm motility in the low-dose group.
   No effect on testicular weights was observed.
   No female rat mated to a HD male became pregnant.
   The effects on male reproduction appeared to be reversible. All reproductive parameters were comparable to control five weeks after the drug was discontinued.

   Study RR 745-02829 "Oral Fertility and Early Embryonic Development Study in Male Rats with Lower Doses of CI-1008": A follow-up study of the effect of pregabalin on male rat fertility was performed with lower doses of the drug. Male rats were treated with 0, 50, 100, or 250 mg/kg for 11 weeks prior to mating, throughout mating and until necropsy after 15 weeks. There were no treatment-related effects on fertility and copulation indices, number of days to mating or male reproductive parameters. The decreased sperm motility effect observed in the previous study at 250 mg/kg was not reproduced. There were no treatment-related gross or microscopic pathological findings.

   Reviewer's comment: A dose of 100mg/kg/day in rats is approximately four times the maximum human dose of pregabalin.

   Study RR 745-02809 (2500mg/kg/d for up to 6 weeks in rats): Decreased sperm motility in the cauda epididymis and vas deferens, decreased caudal epididymal sperm count, and abnormal sperm morphology within 2 to 3 weeks of treatment were seen. The effects on sperm were reversed within 4 to 6 weeks after treatment was discontinued.

The pharmacology/toxicology reviewer notes that "the time course of these effects was thought to indicate an effect on epididymal sperm maturation. However, the additional observation of decreased sperm count and increased sperm abnormalities in the caput epididymis after 4 weeks of treatment also suggested a testicular effect."

Study RR 745-02994 (2500mg/kg/d for 1 to 6 weeks in rats): Ultrastructural changes in sperm and luminal contents in the cauda and caput epididymis were seen on electron microscopic evaluation, but no ultrastructural effects in the testis were demonstrated. Epididymal changes included multiple mitochondrial defects in the sperm, frayed sperm tails/midpieces, and tailless sperm heads. It was concluded that the nature and location of the sperm abnormalities were consistent with an effect primarily involving sperm maturation in the epididymis.

The pharmacology/toxicology reviewer noted, however, that the presence of "cytoplasmic lobes" in the epididymal lumen suggested a possible testicular effect, since these lobes are thought to only come from the testis.

2-year rat study (50, 150, and 450 mg/kg): Gross findings of small testes and seminal vesicles and increased incidences of atrophy of the seminiferous tubules and aspermatogenesis in the testes and aspermia in the epididymis were seen at all doses.

In a second study with the same doses, increased atrophy and degeneration of the testicular germinal epithelium was observed at all doses.

Other rat studies: Epididymal enlargement, epididymal tubular hypospermia and fibrosis and mononuclear cell infiltrates in the interstitium were observed in rats treated with $\geq$ 500 mg/kg/d for 4 weeks.

Spermatogenic epithelial degeneration of the testis was observed after 13 weeks of 1250 mg/kg/d.

No treatment-related effects on spermatogenic epithelia or other reproductive tissues were observed in rats after 52 weeks at doses < 500mg/kg (500mg/kg in rats is approximately equal to 20 times the maximum human dose).

Reviewer's comment: Although the rat data appear to be inconsistent across studies, two 2-year studies reported "increased incidences of atrophy of the seminiferous tubules and aspermatogenesis."

b. Monkey

1-year study: No reported effects on sperm parameters or reproductive organ histopathology was observed at doses up to 500mg/kg.

4-week study: hypospermia of the testis and epididymis associated with small testes and low testicular weights in 1 monkey at 100mg/kg/d and 2 monkeys at 500mg/kg bid.

Reviewer's comment: No further information about this 4-week monkey study was provided. The findings in the 4-week and 1-year monkey studies are inconsistent.

Reviewer's comment: According to the pharmacology/toxicology reviewer, NOELs for the most sensitive endpoints on rat sperm were 100mg/kg which correlates with an AUC value of 408 ug.h/ml. The dose of 500mg/kg in monkeys is associated with an AUC of 1040 ug.h/ml. The expected maximum exposure in humans of 600mg/day of pregabalin would yield an AUC of 122 ug.hr/ml.

2. Clinical data from Trial 072:

Study design: This was a 14-week, double-blind, placebo-controlled, parallel-group study to assess the effects of pregabalin on reproductive function in healthy men, aged 18-55 years. Forty-six subjects (n=16 placebo, n=30 pregabalin) were randomized to treatment – pregabalin 200mg tid or placebo tid. The study included a 14-day blinded titration to study medication, followed by an active treatment phase of 12 weeks. An 8-week washout phase concluded the study.

The primary endpoint was the percent of sperm with normal motility [WHO Class "a+b+c" (%)] at the end of the double-blind treatment period. The median of measurements taken from the semen samples from the last 3 double-blind visits (V9, V10, and V11) was used to determine the endpoint.

Secondary outcome measures were:

- Computer aided sperm analysis (CASA) results
- The percent of sperm with normal WHO Class "a" motility
- The percent of sperm with normal morphology
- Sperm concentration
- Semen volume
- Results from testicular and breast examination
- The percent of sperm with normal motility at the end of the washout phase.

Key **inclusion criteria** were a negative urine drug screen, agreeable to using a condom during intercourse throughout the study, and ability to comply with medication dosing schedule. Subjects with <65% compliance during the titration phase were discontinued from the trial.

Exclusion criteria were leukopenia (WBC<2500/mm^3), neutropenia (<1500/mm^3), thrombocytopenia (<100,000/mm^3); renal dysfunction; abnormal vision screen; use of medications that could interfere with the evaluation of the test medication (i.e. psychotropics, antipsychotics); treatment with gabapentin;

history of substance abuse within last 2 years; evidence of hypogonadism or gynecomastia; testes measuring <12 cc; evidence of varicocele or spermatocele; median screening sperm concentration <20 x10^6/mL; median screening sperm motility <50% motile (WHO criteria "a+b+c") or <25% Class "a" motile (using WHO criteria), or median screening sperm morphology <10% normal (using the WHO "strict criteria").

Reviewer's comment: The World Health Organization (1999)[1] defines the following reference values for semen analysis:

Volume: 2.0 ml or more
pH 7.2 or more
Sperm concentration: 20 x 10^6 or more sperm/ml
Total sperm number: 40 x 10^6 or more spermatozoa per ejaculate
Motility: 50% or more with grade A + B motility or 25% or more with grade A motility (A= rapid progressive motility; B= slow or sluggish progressive motility; C= non-progressive motility)
Morphology: 15% or more by strict criteria
Viability: 75% or more of sperm viable
White blood cells: less than 1 million/ml

The finding of parameters below these levels is suggestive of infertility.

The sample size was chosen based on the primary outcome measure, sperm motility. At least 13 subjects per treatment group were to be randomized to provide 80% power to determine whether pregabalin causes a decrease of at least 13 percentage points compared to placebo. The criterion of 13 percentage points was chosen for the following reasons:

- The expected mean WHO "a+b+c" sperm motility in healthy males is 66% based on the US population
- The level at which male fertility problems begin is 40%.
- The 13% reduction is halfway between these 2 points.

A 97.5% confidence interval of the difference in sperm motility between placebo and pregabalin was estimated. If the upper limit of the confidence interval were <13%, that would indicate that pregabalin had no significant effect on sperm motility.

Study results:
All subjects completed the study and had at least 13 weeks of drug exposure. Compliance with drug was similar between pregabalin (mean 85.3%) and placebo (85.2%).

[1] Walsh: Campbell's Urology, 8th ed. 2002.

Protocol violations: One subject with gynecomastia at visit 1 was enrolled in the trial. One subject had a median sperm concentration of 19.5 x 10^6/mL at screening. Seven subjects were enrolled who had a varicocele on physical examination. One subject had a screening motility (a+b+c) of 49%. One subject had a screening "a" motility of 25%. Three subjects had sperm morphology < 10% normal (two with 8% and one 9%). The sponsor concluded that these violations would not compromise the study results.

Primary outcome assessment:
There was no significant difference detected in sperm motility WHO "a+b+c" % at the end of treatment between placebo and pregabalin (mean 64.4% and 60.5%, respectively, p = 0.21). Neither group demonstrated any substantial change from baseline in WHO "a+b+c" sperm motility (mean change +1.68% in placebo, -1.97% in pregabalin).

Reviewer's comment: Line listings for the sperm motility values throughout the study and after treatment were not provided.

Analysis of the motility values at the end of the washout phase also indicated no difference between placebo (mean 62.5%) and pregabalin (mean 63.7%).

Three pregabalin subjects and 2 placebo subjects had reductions in sperm motility of >15% from baseline (Table 1).

Table 1 Subjects with Reductions in Sperm Motility WHO "a+b+c"(%)>15% from Baseline

	Baseline	End of Double-Blind	Change from Baseline
Prebagalin Subjects			
2001	52.0	35.0	-17.0
2018	53.5	37.0	-16.5
2022	63.0	35.0	-28.0
Placebo Subjects			
1007	78.0	54.0	-24.0
1031	78.0	62.0	-16.0

Reviewer's comment: Though nearly equal numbers of placebo and pregabalin subjects had >15% reductions in sperm motility, only the pregabalin subjects decreased to a level that would be considered below the fertile reference range by WHO criteria.

A blinded review of the data from the 5 subjects with a decrease in sperm motility of ≥15% at the end of treatment was conducted by two andrology experts. Expert 1 felt that two pregabalin subjects (#2022, 2001) and one placebo subject (1007) had a clinically significant decrease in motility and of these, only subject (2022) was believed to have his sperm motility return to baseline after the washout phase. This same expert also believed that 2 placebo subjects (#1007 and 1031) and 2 pregabalin subjects (#2001 and 2022) had a significant decrease in sperm count.

Reviewer's comment: The protocol required withdrawal of any subject whose sperm count fell below 10 x 10^6/mL during the trial. As no subject was withdrawn early, presumably no subject fell below this level. However, actual sperm counts were not included in the study report. It is not known if sperm counts in subjects 2001 and 2022 returned to baseline after the drug was discontinued.

Expert 2 determined that there were no changes that could be attributable to pregabalin treatment. In that reviewer's estimate, the lowest motility for subject 2022 (pregabalin) was seen at visit 4 (day 1 of treatment) and motility at visit 11 (final observation during treatment) was normal. For subject 2001 (pregabalin), the observed decrease in motility was not progressive and returned towards baseline with continued treatment.

Reviewer's comments: Case report forms were not included in the study report. One of the andrology experts consulted by the sponsor was an investigator in this trial.

Secondary outcome measures:

No difference was detected between placebo and pregabalin in changes from baseline in sperm concentration, percent of sperm with normal WHO Class "a" motility, percent of sperm with normal morphology or most parameters of CASA. There were also no differences in breast examination in the two groups – "normal" in 94% of placebo and 97% of pregabalin subjects. Mean sperm concentration increased in both groups (Table 2).

Table 2. Baseline Sperm Concentration and Post-Treatment Change

	Placebo	Pregabalin
Mean (SE) sperm concentration (x 10^6/mL) at baseline	111.81 (20.401)	91.46 (9.348)
Mean change (SE) in concentration (x10^6/mL) from baseline at end of double-blind	5.5 (15.5)	10.8 (10.2)

Reviewer's comment: The standard deviation for baseline sperm concentration was large in both groups (81.602 in the placebo group and 51.199 in the pregabalin group). Subjects with sperm counts as low as 19.6 x 10^6/mL and 23.6 x 10^6/mL were included in the placebo and pregabalin groups, respectively. Standard deviation of change in sperm concentration from baseline is not

provided. No outlier analysis or individual sperm concentration data are provided.

Semen volume was decreased by 0.2 mL compared to baseline in the pregabalin group, and increased by 0.2 mL in the placebo group, a significant difference between placebo and pregabalin (>1 standard error of zero).

Significant differences between placebo and pregabalin were seen in mean CASA rapid motility (+5.2% in placebo vs. +0.3% in pregabalin) and mean right testicular volume (+1.3 cc in placebo, +0.3 cc in pregabalin). In both cases though, the change from baseline for pregabalin was also positive, indicating no detrimental effects, according to the sponsor.

Significant Laboratory Measurements:
Five pregabalin-treated subjects and one placebo-treated subject had FSH values that shifted from the normal range at baseline (FSH 0.9-15 mIU/mL) to below the normal range (0.3-0.5 mIU/mL) at end of treatment. These pregabalin subjects whose FSH levels decreased also had reductions in WHO "a+b+c" sperm motility (between -1 to -11% from baseline). The sponsor notes that no decreases in CASA motility, or changes in sperm morphology were noted in the semen analyses of these subjects. The sponsor concluded that the changes in FSH were not clinically significant.

Reviewer's comment: Testosterone levels were not provided. The clinical significance of these changes in FSH is not clear. One would expect increases (not decreases) in FSH if pregabalin has a direct toxic effect on the testis. If pregabalin causes a decrease in FSH levels, one would have to speculate on a direct effect of the drug on the hypothalamic-pituitary axis.

3. Summary and Conclusions:

The data from rat studies demonstrate male reproductive toxicity of pregabalin at doses 4 times the expected maximum human dose. Adverse effects were seen on both sperm parameters and reproductive organ histopathology. In the 2 year rat study, there were aspermatogenesis in the testes and aspermia in the epididymis at all doses.

The results of two studies in monkeys are disparate. While "hypospermia" of the testis and epididymis associated with small testes and low testicular weights were reported in monkeys in a short-term (4-week study) of pregabalin, data from the long-term trial do not support this adverse effect. No effects on sperm parameters or reproductive organ histopathology were demonstrated in the 1-year study.

No other animal species were used in preclinical testing of male reproductive toxicity.

Study 072 in healthy men does not provide reasonable reassurance that pregabalin has no adverse effect on human sperm. The clinical study was powered to detect a 13% decrease in WHO "a+b+c" sperm motility compared to placebo. This trial did not demonstrate any clinical meaningful changes in seminal fluid parameters, but was not powered to detect a significant effect in sperm concentration (e.g. percentage of patients with a 50% change in sperm concentration or percentage of patients with lower than "normal" concentration of $20x10^6$/ml). While similar numbers of subjects had >15% reduction in sperm motility, the small sample size and study design limit any definite conclusions about the reproductive safety of pregabalin in men.

4. Recommendations:

A decision concerning the clinical implications of the preclinical findings of the effect of pregabalin on male reproductive function and the need for additional studies depend on the risk/benefit ratio of this drug. The current preclinical and clinical data could simply be described in the label, but, if a portion of the target population is younger men of reproductive age and potential, DRUDP believes that an additional clinical trial should be performed. This could be performed as a Phase 4 commitment. The clinical study which was performed (Trial 072) examined sperm motility (WHO "a+b+c" motility) and was not powered to examine effects of pregabalin on sperm concentration.

If a Phase 4 trial is required of the sponsor, this study should be a parallel group, placebo-controlled trial. The primary endpoint should be either percentage of patients with a 50% reduction from baseline in sperm concentration or percentage of patients with lower than normal (20×10^6/ml) sperm concentration compared to a placebo group. Drug or placebo should be given for 3 months and semen analyses (at least 2 and preferably 3) should be obtained at baseline, month 3, and month 6. Because of the effects on FSH seen in pregabalin subjects in study 072, the sponsor should also measure FSH and testosterone levels at baseline, month 3, and month 6. Depending upon the non-inferiority margin, these studies usually require approximately 100 patients per group.

Suggested Label comments:

DRUDP was also asked to comment on the "adequacy of the design of study #072 to support the claim [redacted]

Although Study 072 showed no changes in semen parameters, the trial was designed and powered to detect only a significant difference in motility (WHO "a+b+c") between pregabalin and placebo. Although an effect on sperm concentration was not seen, the trial was not adequately designed and powered to demonstrate a difference (if one exists). In DRUDP's opinion, insufficient data

are submitted to conclude that pregabalin has no effect on sperm concentration or on male reproductive function and the data do not support the proposed labeling

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/s/

Olivia Johnson
5/5/04 08:05:20 AM
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George Benson
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Daniel A. Shames
5/6/04 01:41:26 PM
MEDICAL OFFICER

April 2, 2004

Medical Officer's Review of NDA 21-446, 21-723, 21-724, 21-725
Ophthalmology Consultation

Ophthalmology Consult #1

Submission date: 10/30/03
Review date: 3/31/03

Sponsor: Pfizer Global Research and Development
2800 Plymouth Road
Ann Arbor, MI 48105
734-622-5377

Contact: Jonathan M. Parker, R.Ph., M.S.
Associate Director, Worldwide Regulatory Affairs

Drug Name: Lyrica (pregabalin capsules)

Pharmacologic Category: alpha2-delta protein binder

Proposed Indications: Neuropathic Pain,

Background: Following concerns related to visual field constriction in Vigabatrin, a GABA-transaminase inhibitor, a visual acuity and visual field monitoring program for pregabalin was initiated.

Reviewed: Electronic Submission
Report RR-Memo 720-04341
Report RR-Memo 720-30218
Report RR-Memo 720-30219
Visual Fields
Proposed package insert labeling
Integrated Summary of Safety

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling identifies the potential of pregabalin to cause decreased visual acuity and decreased fields of view (i.e., visual fields). Specific changes to the labeling have been identified in this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

Additional adequate and well-controlled studies are recommended to better quantitate the effect of pregabalin on visual function The following studies should be conducted: best corrected distance visual acuity, threshold perimetry of the periphery (visual fields), color vision (Farnsworth-Munsell 100 hue) and retinal physiology (as measured by ERG testing). Testing should include both short term, two-six months and long term (six months or more) repeated dosing.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Changes in visual fields, visual acuity, and fundoscopy were monitored using screening tests at baseline and termination in the controlled studies and periodically throughout the long-term open-label extension studies. The methodology used to assess visual fields consisted of a basic screening test using a suprathreshold target in which no defects would have been expected. The visual acuity measurements used Snellen charts and did not use visual acuity charts with equal numbers of letters per line or equal spacing between lines. Only screening level signals could be obtained using this methodology. While this would might have been sufficient if no differences had been detected between the pregabalin and placebo groups, visual function deficits (both visual acuity and visual field) were observed in the pregabalin group more frequently than in the placebo group. The differences persisted even when the visual field cases were re-reviewed by the external panel and when a higher visual acuity threshold was used.

There were numerous problems with the presentation of the visual information. These included incorrect interpretations of logMAR visual acuity changes, incorrect assumptions of clinically significant changes, questionable selection of the date used for baseline (Day 14 instead of Day 1), incorrect methodology to assess color vision (Ishihara), use of incorrect ocular terminology for adverse events (Amblyopia) and the reporting of ocular adverse events as "unknown."

B. Efficacy

Not evaluated in this review.

C. Safety

Visual acuity and visual field changes were more commonly seen in the Pregabalin group than the placebo group. This was particularly true for visual field changes at the 300 mg dose and visual acuity changes at the 600 mg dose.

It was not possible to identify a specific pattern of visual acuity or visual field defects. The changes were relatively small and in most cases only affected the visual function reserve of an individual. Relatively few of the changes would significantly affect typical activities of daily living.

No significant changes between groups were observed with respect to fundoscopic changes.

Review of Ophthalmic Evaluations

Ophthalmologists monitored changes in visual fields/peripheral vision, visual acuity, and fundoscopy at baseline and termination of the controlled studies, and periodically throughout the long-term open-label extension studies. In addition, independent ophthalmologic experts experienced in the assessment of visual field defects reviewed the visual field data and provided an opinion of the validity of each case. A description of the methods used to collect and evaluate ophthalmologic data in the pregabalin clinical program and the results of these evaluations was provided in RR-MEMO 720-04341 with updated open-label information in RR-MEMO 720-30218 and long-term data from the psychiatry studies in RR-MEMO 720-30219.

The following ophthalmic safety data were used to define clinical cases:

- Spontaneous reports of visual adverse events obtained from case report forms (CRFs), including serious visual adverse events and withdrawals due to visual adverse events;
- Examining ophthalmologist assessment of visual acuity, visual fields, and fundoscopy as recorded on ophthalmology worksheets;
- Visual field (obtained from Humphrey Field Analyzer source documents) and visual acuity (obtained from ophthalmology worksheets) test results; and
- External ophthalmologic expert review of cases meeting criteria for visual field loss.

Results of the assessments performed by the ophthalmologists (recorded as normal, abnormal, not done) for visual fields (usually the Humphrey 120-point examination), best-corrected Snellen visual acuity, and dilated fundoscopy (direct or indirect) were collected on CRFs at specified visits and entered into the sponsor's clinical database for each study. These assessments were based on worksheets that recorded more detailed results of the Humphrey 120-point suprathreshold examination, Snellen visual acuity test, and dilated fundoscopic examination.

To investigate the magnitude of change in visual acuity among patients who had baseline and termination Snellen visual acuity examinations, patients were categorized by change in logMAR score. A logMAR change of 0.15 was used in the outlier analysis, which corresponds to approximately a 2-line deterioration in Snellen visual acuity (e.g., a change from 20/20 to 20/30 or from 20/100 to 20/400). At least 85% of patients in each treatment group had a logMAR change of -0.0999 to 0.0999, which was interpreted as no change from baseline. Similar to the analysis of all visual acuity cases in the database, where the incidence of cases in the pregabalin 600 mg/day group was significantly higher than placebo, the difference between placebo and pregabalin 600 mg/day was also significant in this analysis ($p = 0.018$).

Reviewer's Comments:

1. *The example given of a 20/100 to 20/400 visual acuity change is a 0.6 logMAR change, not a 0.15 change.*
2. *Snellen visual acuity testing is acceptable as a screening test, but has a higher variability than other standardized visual acuity test methodologies. Reproducibility could likely be improved by using best corrected distance visual acuity with a chart that has an equal number of letters per line and equal spacing between lines. The Early Treatment for Diabetic Retinopathy Study (ETDRS) protocols is one example of this type of better testing methodology.*

Data Evaluated in Placebo-Controlled Studies By Indication

Indication for Pooling	Specific Patient Population	Formal Visual Fields	Visual Acuity	Fundoscopy	Adverse Events	Ophthalmologic Examination Schedule	Doses Studied (mg/day)
Epilepsy							
1008-00719	Epilepsy	--[a,b]	x[b]	x[b]	x	BL, Term (1 wk), FU	PGB 600, GBP 300
1008-00920	Epilepsy	--[d]	x	x	x	BL, Term (12 wk)	PGB 600
1008-01121,c	Epilepsy	--	--	--	x	Noned	PGB 150, 600
1008-03422	Epilepsy	x	x	x	x	BL, Term (12 wk)	PGB 50, 150, 300, 600
Neuropathic Pain							
1008-01423	Diabetic Neuropathy	x	x	x	x	BL, 6wk, Term (8 wk)	PGB 150, 600
1008-02924	Diabetic Neuropathy	x	x	x	x	BL, Term (7 wk)	PGB 75, 300, 600
1008-03025	Postherpetic Neuralgia	x	x	x	x	BL, Term (7 wk)	PGB 75, 150
1008-04026,c	Diabetic Neuropathy	--	--	--	x	None	PGB 600, AMI 75
1008-04527,c	Postherpetic Neuralgia	--	--	--	x	None	PGB 150, 300
1008-12728	Postherpetic Neuralgia	x	x	x	x	BL, Term (8 wk)	PGB 150, 600
1008-13129	Diabetic Neuropathy	x	x	x	x	BL, Term (8 wk)	PGB 300
Other Chronic Pain							
1008-03130	—	x	x	x	x	BL, Term (12 wk)	PGB 300, 600
1008-03231	—	x	x	x	x	BL, Term (9 wk)	PGB 150, 600
1008-10432	—	x	x	x	x	BL, Term (8 wk), FU	PGB 300, 450, 600
1008-10533	—	x	x	x	x	BL, Term (8 wk)	PGB 150, 300, 450
Anxiety Disorders							
1008-01734	—	x	x	x	x	BL, Term (12 wk)	PGB 150, 600
1008-02135	GAD	x	x	x	x	BL, Term (5 wk)	PGB 150, 600, LOR 6
1008-02236	—	--	--	--	x	None	PBG 600
1008-02537	GAD	x	x	x	x	BL, Term (5 wk)	PGB 150, 600, LOR 6
1008-02638	GAD	x	x	x	x	BL, Term (5 wk)	PGB 150, 600, LOR 6

"—"= Not Planned; BL = Baseline Visit; Term = Termination Visit; FU = After Completion of Study Treatment; wk = Week; GAD = Generalized Anxiety Disorder; PGB = Pregabalin; GBP = Gabapentin; AMI = Amitriptyline; LOR = Lorazepam. a Ophthalmologic examinations consisted of confrontation field testing, no formal visual field testing was performed. b Due to the short duration of the study, visual fields, visual acuity, and funduscopy data were not summarized. Data are pooled with data from other studies only in combination with data from Study 1008-008,its open-label extension. c International study d Ophthalmologic testing (funduscopy, vision assessment, confrontational field test, and Ishihara Score) was discontinued after approximately one-third of the study patients had both baseline and termination ophthalmologic testing performed.

Table 5. Data Evaluated in Uncontrolled Studies — By Indication

Indication for Pooling[a]	Population	Formal Visual Fields	Visual Acuity	Funduscopy	Adverse Events	Ophthalmologic Examination Schedule	Doses Studied (mg/day)
Epilepsy							
1008-00839	OL Safety Extension of 1008-007	--[b]	x	X	X	2, 4, 12, 16 Weeks, 3-Month Intervals, FU	PGB 450 (max 600)
1008-01039	OL Safety Extension of 1008-009	--[b]	x	X	X	6-Month Intervals, FU	PGB 450 (225-600)
1008-01239,[c]	OL Safety Extension of 1008-011	--[d]	--[d]	--[d]	X	None	PGB 450 (75-600)
1008-03539	OL Safety Extension of 1008-034	x	x	X	X	6-Month Intervals, FU	PGB 400 (100-600)
Chronic Pain							
1008-01540	OL Safety Extension of 1008-014	x	x	X	X	3-Month Intervals, FU	PGB 300 (max 600)
1008-03341	OL Safety Extension of 1008-029, -030, -031, 032, 104, and 105	x	x	X	X	6-Month Intervals, FU	PGB 300 or 75 (max 600)
1008-06142,[c]	OL Safety Extension of 1008-045	--[d]	--[d]	--[d]	X	None	PGB 150 (75-600)
1008-07443,[c]	OL Safety Extension of 1008-040	--[d]	--[d]	--[d]	X	None	PGB 600 (150-600)
1008-13444	Pain OL Safety for 1008-127 and 131	x	x	X	X	6-Month Intervals	PGB 300 (75-600)

"—"= Not Planned; OL = Open-Label; BL = Baseline Visit; Term = Termination Visit; FU = After Completion of Study Treatment. a All studies listed were pooled by indication for each applicable parameter (eg, Visual Fields, Visual Acuity, Funduscopy, Adverse Events). b These studies included ophthalmologic examinations, which consisted of confrontation field testing, but no formal visual field testing was performed. c International study d No formal ophthalmologic testing was performed

Visual Field and Visual Acuity Outliers

The sponsor established criteria to define visual field and visual acuity outliers, resulting in the identification of additional patients with potentially clinically significant change in visual test results. The definition of these outliers was based on the number of points missed on Humphrey 120-point supra-threshold testing of 60 degrees of the visual field and the quantitative visual acuity data in the ophthalmologic database. The criteria used in the outlier definitions are consistent with reports of normal variability in the population and were discussed at the August 3, 2000, meeting with the FDA. These definitions were formally presented to the agency in a revised analysis plan.

Visual field outlier criterion was defined as an increase of $\geq$10 points missed (post baseline minus baseline) on any post baseline visual field exam. Patients who met the visual field outlier criterion at any visit in the double-blind studies and at the last available visit in open-label studies were listed and further examined. Patients meeting criterion at any visit in open-label were also identified.

For visual acuity, outliers were defined as any deterioration in visual acuity of $\geq$0.15 logMAR. The numerical values (Snellen denominators) for visual acuity were transformed to the logarithm of the minimum angle of resolution (logMAR) in order to approximate a normal distribution of the data. Patients who met the visual acuity outlier criterion at any post baseline visit in double-blind or open-label were identified.

The number of patients with outlying visual field and visual acuity deterioration from baseline was summarized by treatment group for the controlled studies and for combined controlled/uncontrolled pregabalin exposure.

Blinded Review of Visual Field Data by Ophthalmologic Experts

Ophthalmologic experts performed a blinded review of each identified case and completed a worksheet for each patient. On the worksheet, each expert first evaluated whether test results represented a change from baseline. If a change was judged to be a worsening of visual field status, the expert characterized: the nature of the defect, whether the worsening was due to damage or dysfunction to the sensory visual system, and whether the damage or dysfunction was attributable to a known medical cause.

Valid cases were defined as all cases in which there was a worsening that was not solely due to artifact. In judging whether a change was due to dysfunction in the primary sensory pathway, the experts were to base this decision on the likelihood that the worsening could be caused by something other than dysfunction/damage to the primary visual pathway (e.g., lid artifact, lens rim artifact, poor cooperation, technical error). For combined controlled/uncontrolled pregabalin exposure cases, the experts also were to judge whether the deterioration could be attributed to known preexisting disease or was unexpected and unexplained. Any other comments regarding the expert's impression of the case were also recorded.

Three external ophthalmologic experts reviewed the visual field data [redacted] In the controlled studies, at least 2 of these 3 experts reviewed each case. If at least 2 of the experts considered a case to be valid, then the sponsor

considered the case as valid and summarized it as such. For split decisions among 2 experts, the third expert adjudicated the case. All cases identified in uncontrolled studies were also reviewed by at least one expert and were summarized as valid if considered valid in the opinion of at least one expert. After reviewing all of the individual visual field cases and other results, Dr [ ] provided a written assessment of his overall interpretation of the pregabalin ophthalmologic data.

Reviewer's Comments: *Re-interpretation of the visual field data by this group of external experts decreased the number of positive cases but did not alter the signal or the significance level of the findings.*

Case Definitions for Post-Hoc Review of Visual Acuity Cases

Although a review of the visual acuity cases was not specified in the analysis plan, the sponsor performed such a review to distinguish medically relevant cases from those with obvious data errors. Only medically relevant cases were included in the post-hoc analysis, thus providing a more accurate characterization of the visual acuity data. Several objective criteria were used to identify cases of medically relevant deterioration of visual acuity. If at least one of the criteria was met, the case was not considered medically relevant.

- Deterioration of <0.15 logMAR (<2 lines of Snellen acuity) in cases categorized as clinically significant change by the ophthalmologist: These cases were considered to be within normal test/retest variation.
- Evidence that the patient was not properly refracted: This information was obtained from comments in the ophthalmologic database, such as "forgot glasses" or "pinhole acuity 20/20."
- Final visual acuity of 20/25 or better: These cases were excluded because the final visual acuity was consistent with normal acuity values.
- Return of visual acuity to <0.15 logMAR change from baseline at last observation: For example, a patient who had 20/20 acuity at baseline, 20/40 acuity at termination of double-blind, and 20/25 acuity at last observation in open-label was not considered a case.

Reviewer's Comments:

1. *"Forgot glasses" is not a valid reason to exclude the case as medically relevant. The ophthalmologist could have provided a proper refraction or used a pinhole vision to evaluate whether the vision was impaired.*
2. *Most individuals have 20/15 vision. 20/25 is not considered normal vision and is not a reason to exclude visual loss as medically relevant.*

Data Evaluability

Day 1 was defined as the first day of treatment with double-blind study medication. Days prior to Day 1 were assigned consecutive negative numbers starting with Day -1. In all instances, the pregabalin dose labels in the tables for controlled studies refer to the randomly assigned treatment groups.

For evaluation of controlled studies, double-blind baseline was defined as the last ophthalmologic examination with non-missing data on or before double-blind Study Day 14 (allowing up to a 14-day window of treatment exposure). The same baseline definition was used for pregabalin-treated patients in the evaluation of combined controlled/uncontrolled studies, while baseline for patients treated with placebo during double-blind was defined as the last observation with nonmissing data no more than 14 days after the double-blind termination visit. For patients treated in (a 1-week controlled trial) who continued in the open-label extension, baseline was the first visit in (scheduled at Week 2). For double-blind studies, termination was defined as the last ophthalmologic examination no more than 14 days after the last dose of study medication. Last observation refers to the last examination performed during the open-label study period, including examinations that occurred when the patient was no longer receiving study medication.

Reviewer's Comments: *Disagree with using the last visit on or before Day 14 as the baseline visit. The baseline visit should have been the closest visit to Day 1.*

Quantitative Visual Acuity Data
Visual acuity change score was defined as the change in logMAR from baseline to termination/last observation (logMAR at termination minus logMAR at baseline). These scores were summarized by magnitude of change from baseline acuity using a 7-point ordinal scale. Summaries were provided for the worst eye, defined as the eye with the greatest deterioration from baseline.

Spontaneously Reported Vision-Related Adverse Events
For summarization, the investigator's terms for individual vision-related adverse events were mapped to preferred terms using the COSTART IV dictionary.

Frequencies of patients experiencing at least one adverse event were displayed by COSTART preferred term. Only treatment-emergent signs and symptoms (TESS) events were summarized. Treatment-emergent adverse events were defined as those that were not present at baseline or that increased in intensity or frequency from baseline. Adverse events were summarized by treatment group for the controlled studies and for combined controlled/uncontrolled pregabalin exposure. Patients with serious vision-related adverse events or vision-related adverse events that led to withdrawal were also listed.

In addition, the COSTART adverse event term "amblyopia" was summarized according to an algorithm to identify patients who had nontransient blurred vision without other potentially confounding central nervous system (CNS) side effects. Since most investigator terms for adverse events of amblyopia used the terms "blurred" or "blurry" vision and all implied a blurring of vision, the term "blurred vision" was used instead of the COSTART term amblyopia to describe such events in the remaining sections of this report.

Reviewer's Comments: *The term "amblyopia" should not be used to identify patients who develop blurred vision after the age of 9.*

APPEARS THIS WAY
ON ORIGINAL

Statistical Methods

Statistical testing was done using SAS procedures. All testing used a 2-sided criterion of ≤0.05 for significance. Odds ratios and 95% confidence intervals were used to compare the percentage of visual field, visual acuity, and fundoscopic abnormalities, while Fisher's exact test was used to make inferential statistical comparisons.

Visual Acuity Results

Controlled Studies	All Indications (Studies 9, 14, 17, 21, 25, 26, 29, 30, 31, 32, 34, 104, 105, 127, 131)						
	[Number and (%) of Patients]						
logMAR Change (Termination-Baseline)	Placebo	Pregabalin <300 mg/day	Pregabalin 300 mg/day	Pregabalin 450 mg/day	Pregabalin 600 mg/day	All Pregabalin	Lorazepam 6 mg/day
	N = 1064	N = 784	N = 518	N = 194	N = 778	N = 2274	N = 106
≤-0.3	1 (0.1%)	3 (0.4%)	1 (0.2%)	0 (0%)	2 (0.3%)	6 (0.3%)	0 (0%)
-0.2 to - 0.2999	3 (0.3%)	1 (0.1%)	1 (0.2%)	0 (0%)	2 (0.3%)	4 (0.2%)	0 (0%)
-0.1 to -0.1999	22 (2.1%)	17 (2.2%)	10 (1.9%)	7 (3.6%)	15 (1.9%)	49 (2.2%)	0 (0%)
-0.0999 to 0.0999	940 (88.3%)	688 (87.8%)	452 (87.3%)	167 (86.1%)	661 (85.0%)	1968 (86.5%)	100 (94.3%)
0.1 to 0.1999	70 (6.6%)	50 (6.4%)	35 (6.8%)	11 (5.7%)	66 (8.5%)	162 (7.1%)	4 (3.8%)
0.2 to 0.2999	10 (0.9%)	10 (1.3%)	10 (1.9%)	4 (2.1%)	17 (2.2%)	41 (1.8%)	0 (0%)
≥0.3	18 (1.7%)	15 (1.9%)	9 (1.7%)	5 (2.6%)	15 (1.9%)	44 (1.9%)	2 (1.9%)
p-value	--	0.957	0.241	0.321	**0.018**	0.487	0.717

Reviewer's Comments: *Visual acuity is significantly decreased in the Pregabalin 600 mg/day group compared to placebo.*

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Category	Visual Field	Acuity	Fundus	Any
All Indications				
Number of Patients	3432	3621	3397	3621
All Clinically Significant Abnormality[b]	519 (15.1%)	385 (10.6%)	468 (13.8%)	956 (26.4%)
Outliers[c]	825 (24.0%)	763 (21.1%)	NA	1439 (39.7%)
Patients With Any Visual Abnormality	990 (28.8%)	819 (22.6%)	468 (13.8%)	1805 (49.8%)
Neuropathic Pain				
Number of Patients	1067	1101	1059	1101
All Clinically Significant Abnormality[b]	206 (19.3%)	198 (18.0%)	232 (21.9%)	420 (38.1%)
Outliers[c]	330 (30.9%)	390 (35.4%)	NA	630 (57.2%)
Patients With Any Visual Abnormality	381 (35.7%)	413 (37.5%)	232 (21.9%)	775 (70.4%)
Diabetic Neuropathy				
Number of Patients	670	695	666	695
All Clinically Significant Abnormality[b]	116 (17.3%)	101 (14.5%)	171 (25.7%)	262 (37.7%)
Outliers[c]	186 (27.8%)	205 (29.5%)	NA	341 (49.1%)
Patients With Any Visual Abnormality	225 (33.6%)	216 (31.1%)	171 (25.7%)	462 (66.5%)
Postherpetic Neuralgia				
Number of Patients	397	406	393	406
All Clinically Significant Abnormality[b]	90 (22.7%)	97 (23.9%)	61 (15.5%)	158 (38.9%)
Outliers[c]	144 (36.3%)	185 (45.6%)	NA	289 (71.2%)
Patients With An Visual Abnormality				
Pain				
Number of Patients	1259	1314	1237	1314
All Clinically Significant Abnormality[b]	183 (14.5%)	105 (8.0%)	145 (11.7%)	317 (24.1%)
Outliers[c]	300 (23.8%)	196 (14.9%)	NA	460 (35.0%)
Patients With Any Visual Abnormality	351 (27.9%)	220 (16.7%)	145 (11.7%)	587 (44.7%)
Epilepsy				
Number of Patients	520	589	535	589
All Clinically Significant Abnormality[b]	102 (19.6%)	58 (9.8%)	59 (11.0%)	156 (26.5%)
Outliers[c]	112 (21.5%)	121 (20.5%)	NA	220 (37.4%)
Patients With Any Visual Abnormality	161 (31.0%)	126 (21.4%)	59 (11.0%)	280 (47.5%)
Psychiatry				
Number of Patients	586	617	566	617
All Clinically Significant Abnormality[b]	28 (4.8%)	24 (3.9%)	32 (5.7%)	63 (10.2%)
Outliers[c]	83 (14.2%)	56 (9.1%)	NA	129 (20.9%)
Patients With An Visual Abnormality				

[a] For each indication, the MITT Population was defined as all intent-to-treat patients who had baseline and post baseline ophthalmology examinations or assessments and received at least one dose of pregabalin.

[b] As determined by the ophthalmologist

[c] As determined by sponsor. Visual field outliers were defined as ≥10 points missed in either eye on the baseline examination. Visual acuity outliers were defined as >20/25 in either eye on the baseline examination.

Pooled Subset	Placebo	Pregabalin	Pregabalin	Pregabalin	Pregabalin	Pregabalin	Lorazepam
MITT Population		<300	300	450	600	All	6 mg/day
Any Visual Field Abnormality							
All Indications	11.7%	11.0%	**16.4%***	9.1%	12.0%	12.4%	7.3%
Neuropathic Pain	14.3%	13.9%	13.6%	--	16.2%	14.5%	--
Diabetic Neuropathy	13.1%	12.8%	11.8%	--	16.2%	13.6%	--
Postherpectic Neuralgia	16.0%	15.0%	24.0%	--	16.1%	16.2%	--
Pain	10.7%	8.5%	**18.4%***	9.1%	14.4%	13.3%	--
Epilepsy	9.9%	13.1%	15.2%	--	8.4%	11.1%	--
Anxiety Disorders	8.9%	7.1%	--	--	7.2%	7.2%	7.3%
Validated Visual Field Abnormality							
All Indications	4.8%	4.4%	**7.3%***	3.0%	5.3%	5.3%	3.7%
Neuropathic Pain	7.0%	5.4%	6.5%	--	6.9%	6.1%	--
Diabetic Neuropathy	5.9%	5.0%	5.6%	--	6.8%	5.8%	--
Postherpectic Neuralgia	8.6%	5.9%	12.0%	--	7.1%	6.8%	--
Pain	4.1%	4.3%	**8.0%***	3.0%	5.9%	5.6%	--
Epilepsy	2.1%	6.6%	6.1%	--	3.7%	5.0%	--
Anxiety Disorders	3.2%	1.2%	--	--	4.6%	2.8%	3.7%
Any Visual Acuity Abnormality							
All Indications	4.8%	6.0%	6.4%	5.5%	**7.4%***	**6.5%***	2.5%
Neuropathic Pain	6.9%	8.8%	9.9%	--	**12.1%***	10.1%	--
Diabetic Neuropathy	5.8%	8.1%	6.2%	--	12.7%*	9.1%	--
Postherpectic Neuralgia	8.4%	9.5%	**30.8%***	--	10.7%	12.1%	--
Pain	2.9%	3.6%	5.4%	5.5%	6.1%	5.2%	--
Epilepsy	3.8%	8.6%	2.7%	--	7.8%	7.2%	--
Anxiety Disorders	4.9%	1.7%	--	--	2.5%	2.1%	2.5%
Post-Hoc Review of Visual Acuity Abnormality							
All Indications	3.3%	3.2%	5.3%	4.0%	4.2%	4.1%	0%*
Neuropathic Pain	4.9%	4.2%	8.7%	--	6.5%	6.1%	--
Diabetic Neuropathy	3.3%	3.4%	4.8%	--	5.1%	4.4%	--
Postherpectic Neuralgia	7.2%	5.1%	**30.8%***	--	10.7%	9.2%	--
Pain	2.1%	2.1%	4.3%	4.0%	3.6%	3.6%	--
Epilepsy	1.9%	4.3%	1.3%	--	4.1%	3.7%	--
Anxiety Disorders	3.1%	1.7%	--	--	1.9%	1.8%	0%
Any Funduscopic Abnormality							
All Indications	2.1%	1.6%	1.2%	2.1%	2.1%	1.7%	0.9%
Neuropathic Pain	2.5%	2.4%	1.8%	--	4.0%	2.7%	--
Diabetic Neuropathy	3.4%	2.8%	2.1%	--	4.8%	3.2%	--
Postherpectic Neuralgia	1.2%	2.0%	0%	--	1.8%	1.7%	--
Pain	2.2%	0.5%	1.1%	2.1%	1.4%	1.3%	--
Epilepsy	2.7%	1.6%	0%	--	2.6%	1.8%	--
Anxiety Disorders	0%	1.2%	--	--	0%	0.6%	0.9%

* Statistically different from placebo ($p<0.05$)

Reviewer's Comments: Visual acuity and visual field changes were not more commonly with Pregabalin than placebo. This is particularly true for visual field changes at the 300 mg dose and visual acuity changes at the 600 mg dose.

Overview of Results for Combined Controlled/Uncontrolled Pregabalin Exposure by Parameter – MITT Population			
Pooled Subset Parameter	Total Pregabalin Exposure[a]	All Pregabalin-Controlled Studies	Placebo-Controlled Studies
Any Visual Field Abnormality			
All Indications	16.8%	12.4%	11.7%
Neuropathic Pain	24.1%	14.5%	14.3%
Diabetic Neuropathy	23.9%	13.6%	13.1%
Postherpectic Neuralgia	24.5%	16.2%	16.0%
/ Pain	15.6%	13.3%	10.7%
Epilepsy	15.1%	11.1%	9.9%
Anxiety Disorders	NA	7.2%	8.9%
Validated Visual Field Abnormality			
All Indications	5.4%	5.3%	4.8%
Neuropathic Pain	8.8%	6.1%	7.0%
Diabetic Neuropathy	8.9%	5.8%	5.9%
Postherpectic Neuralgia	8.8%	6.8%	8.6%
/ Pain	5.0%	5.6%	4.1%
Epilepsy	3.7%	5.0%	2.1%
Anxiety Disorders	NA	2.8%	3.2%
Any Visual Acuity Abnormality			
All Indications	9.4%	6.5%	4.8%
Neuropathic Pain	16.7%	10.1%	6.9%
Diabetic Neuropathy	15.8%	9.1%	5.8%
Postherpectic Neuralgia	18.3%	12.1%	8.4%
/ Pain	7.5%	5.2%	2.9%
Epilepsy	7.5%	7.2%	3.8%
Anxiety Disorders	NA	2.1%	4.9%
Post-Hoc Review of Visual Acuity			
Abnormality			
All Indications	7.8%	4.1%	3.3%
Neuropathic Pain	14.0%	6.1%	4.9%
Diabetic Neuropathy	13.3%	4.4%	3.3%
Postherpectic Neuralgia	15.4%	9.2%	7.2%
/ Pain	6.0%	3.6%	2.1%
Epilepsy	6.2%	3.7%	1.9%
Anxiety Disorders	NA	1.8%	3.1%
Any Funduscopic Abnormality			
All Indications	5.9%	1.7%	2.1%
Neuropathic Pain	14.0%	2.7%	2.5%
Diabetic Neuropathy	17.9%	3.2%	3.4%
Postherpectic Neuralgia	6.7%	1.7%	1.2%
/ Pain	2.9%	1.3%	2.2%
Epilepsy	3.6%	1.8%	2.7%
Anxiety Disorders	NA	0.6%	0%
NA = Not applicable; anxiety disorder studies did not have open-label extensions.			
[a] Combined controlled/uncontrolled pregabalin exposure			

Adverse Events Related to Vision

Spontaneous reports of visual adverse events obtained from CRFs, including serious visual adverse events and withdrawals due to visual adverse events, were collected and entered in the clinical database during the conduct of each study. Additionally, any clinically significant changes identified by the study ophthalmologist were reported as adverse events and recorded on CRFs.

Vision-related adverse events included any sign or symptom reported by the patient or noted by the investigator and any clinically significant deterioration in visual examination reported to the investigator by the ophthalmologist.

Reported Adverse Events from Ophthalmologic Findings

007_000701	Small Retinal Hemorrhage Of Right Eye
007_000706	Superficial Intraretinal Hemorrhage
007_001301	OD: Epiretinal Membrane Reticular Pigment Degeneration, OS: Reticular Pigment Degeneration
007_001505	Epithelial Pigment Deposits OS
007_001804	Cataract
007_002103	R Drusen Near Fovea
007_002107	Bilateral Retinal Pigment Epithelial Disturbance OD: Spot Of Hyperpigmentation Inferotemporally, OS
009_007001	Normal: C/D 0.65 With Healthy Rim
009_008011	Peripheral Retinal Tear-O.D.
009_012001	Drusen
009_029007	Peripheral Lattice Degeneration In Both Eyes
009_031003	Posterior Pole Drusen OS; Peripheral Pigmented Scar OS In Periphery Infero Temporally
009_033002	Probably very old Scar may have been missed before.
009_037006	Retinal Wrinkling
009_037007	Pseudopapilledema
009_044005	**Unknown**
009_045004	Cataract
009_045006	Faint Epiretinal Membrane OD Abnormal:
009_045020	Increased C/D Ratio 0.7 Large Cups, OS: Increased C/D 0.6 Ratio Large Cups
010_006118	Subretinal Fluid-Left Eye
034_010001	Macular Cyst R Eye
034_014001	**Unknown**
034_019004	**Unknown**
034_024002	Cataract OD
034_025004	Sickle Cell Retinopathy
034_025005	Bilateral Lattice Degeneration
034_026004	Operculosis Retinal Hole Right Eye
034_027017	OD Unspecified

034_035004	Choroidal Nevus
034_059003	Cataract Worsened
034_069011	Macular RPE Detachment OD
034_069013	Drusen OS
034_077001	Left Eye Retinal Holes
034_079003	Retinal Pigment Epithelium Changes
035_056104	Age Related Macular Degeneration
035_069109	OD; Macular Drusen, OS; Macular Hemorrhage
035_072103	Left Cataract
014_002002	Attenuated Perivessels With Peripheral Ischemia OU
014_002010	Advanced BDR, OU. Has Required Focal Laser For Maculopathy OS And OD.
014_002014	Early Age Related Macular Degeneration OU; Pre-Proloferative Retinopathy OU; Me
014_002015	Serous Detachment Temporal To Fovea OS
014_004009	Background Retinopathy Changes Right Eye
014_004010	Left Eye Background Retinopathy;Rt Eye Extensive Background Retinopathy; PRP
014_004011	Background Retinopathy
014_005002	OS, OD, Abnormal; Tortuos Bv's; BDR; Me OD
014_005006	Broken Blood Vessel L Eye; BDR; Me OS
014_007005	Clinically Significant Macular Edema L Eye & Right Eye; NPDR
014_009002	Vitreous Hemorrhage L Eye
014_009004	Beginning Cataract, Left Eye
014_010002	BDR OU; ME + Laser TX OS
014_011005	Diabetic Retinopathy; ME
014_011010	Retinal Hole Right Eye
014_011012	OS, OD; Rare Dot/Blot Hemorrhage; CWS
014_012008	Diffuse Macular Edema
014_012019	OS, OD; Cotton Wool Spots Related To Htn.
014_012030	CWS Related To Hypertension; BDR
014_013005	Non Prolific Diabetic Retinopathy
014_013012	Diabetic Retinopathy Both Eyes
014_014001	Microaneurysms
014_014007	Cotton Wool Spots
014_014015	NPDR; Retinal Thickening OS
014_016014	Early Peripheral Diabetic Retinopathy
014_016019	Background Diabetic Retinopathy OD
014_016020	Cataract OS
014_017004	Bilateral Proliferative Diabetic Retinopathy
014_017005	Laser Tx For ME OD.
014_017009	NPDR, Me OU
014_017018	Retinal Tear R Eye
014_017020	Diabetic Retinopathy With Macular Edema OD>OS
014_018002	Background Retinopathy; Cotton Wool Spots Left Eye

014_018003	Early (L) Cataract
014_019001	Diabetic Retinopathy OU; Laser Tx OD
014_019018	**Unknown**
014_019024	BDR OU
014_020005	Macular Edema Left Eye
014_020006	Hypertensive Retinopathy
014_023001	Scleral Hemorrhage
014_024009	Early Cataracts
014_026018	Mild Increase In BDR OD
014_026022	Diabetic Retinopathy OU; Ma, Dot/Blot Heme, Laser Tx OS.
014_026030	Increased Diabetic Macular Changes; Worsening Cataract OD
029_001009	Macular Edema L Eye
029_002003	Cataracts
029_002013	OD; BDR + PRP
029_003005	Few Microaneurisms Per Ophth Exam
029_003011	CWS OD
029_006001	Worsening R Cataract
029_007002	Ischemic Optic Neuropathy OS
029_007012	Cataract, Left Eye
029_009001	Mild Diabetic Retinal Changes L Eye
029_009005	Dot Hemorrhages From Diabetes OD
029_009026	Worsening Of Cataract OD
029_012005	BDR Change OS
029_012010	Worsening Background Diabetic Retinopathy
029_015002	BDR OU
029_017002	Background Diabetic Retinopathy
029_017004	Early Cataracts; OS Diabetic Retinopathy
029_017016	Mild Cataracts
029_017027	Bilateral Cataracts; Diabetic Retinopathy
029_019001	Diabetic Macular Edema; Retinal Hemorrhage
029_020002	Exacerbation Of Diabetic Retinopathy
029_021014	Diabetic Retinopathy
029_024002	Eye Infection; Worsening Of Cataracts OU
029_025003	Beginning Cataract, Left Eye
029_027001	Increased Retinopathy OD; Nuclear Sclerosis OU
029_027004	Macular Degeneration OU
029_027006	Worsening Cataracts OU
029_027007	NPDR Change
029_027008	Retinopathy Improved
029_027010	Diabetic Maculopathy OU
029_028004	Macular Drusen
029_028005	Bilateral Microaneurysms
029_028006	Mild Background Retinopathy
029_028010	Cataract Left Eye
029_028012	Left Eye Cataract

029_028022	Progressive BDR
029_029001	Hemorrhages Near Fovea
029_029003	Mild Diabetic Retinopathy
029_030002	Few Dot Blot Hem's OD
029_030008	**Unknown**
029_032004	Immature Bilateral Cataracts
029_033006	Cataracts
029_033007	Mild Cataracts
029_035010	Bilateral Cataracts; Early Macular Degeneration
029_035015	BDR
029_036004	Cataract Left Eye; Recurrent Cataract Of Right Eye
029_036007	Background Retinopathy
029_037004	Improvement Of Me
029_037006	Right Eye Proliferative Diabetic Retinopathy
029_037020	Cataract L Eye
029_039005	Microaneurysms; Retinal Neovascularization
029_043001	Improvement Of Venous Congestion
029_043005	BDR Change OS
029_043008	ME Related To Diabetic & Vascular Drusen
029_043014	Background Retinopathy; Cataract Changes
029_043019	BDR Changes
029_043025	Background Retinopathy
029_043028	Improved BDR
029_043034	Macular Edema L Eye; Retinopathy (Background)
029_043035	Lens Fibrosis
131_109001	Macular Degeneration O.S.
131_122013	Microaneurysm OD
030_103004	Retinopathy
030_107004	OS Cataract
030_111004	Early Macular Degeneration OS
030_111006	Retinopathy R Eye
030_111007	Small Cataract L Eye
030_115004	Pale Optic Disc R/O Optic Neuropathy
030_117001	Diabetic Retinopathy
030_118011	Para Macular Drusen
030_122004	R Cataract Worsening
030_125001	Cup/Disc Assymetry .7/.3 Dx: Glaucoma Suspect Unrelated To Drug.
030_126023	Increased Cataract O.S.
030_131008	Macular Edema OD; Worsened Cataract OD
030_132003	Cataract OU OS>OD
030_132006	Cataracts OU
030_132014	Abnormal Epiretinal Membrane
127_002004	Cataract
127_004005	Increasing Cataract OD
127_010001	Cataract OD

127_018001	Cataract
127_021002	OS; Wet ARMD + Laser Tx;
031_208010	?? Keratitis Sicca
031_213014	Retinal Detachment R Eye
031_220009	OS; Macular Drusen, OD; Cataract, Proptosis
031_228012	Progression Of Senile Cataract Left Eye
031_235009	Early Cataract Bilateral
031_238009	Fine Macular Drusen OU
032_308012	Lens Haze R Eye
032_312027	Retinal Detachment Right Eye
032_320012	Cataract
032_323007	Age Related Macular Degeneration; Cataracts OU
032_323008	Retinal Epithelial Defect OD
104_405008	Cataracts OU
104_405012	Cataracts OU
104_411008	Retinal Edema Both Eyes
104_411017	Background Diabetic Retinopathy
104_419031	Cataracts OU
104_428006	Cataracts OU
104_436015	Early Cataract Changes
104_436016	Small Cataract, Left Eye
104_437018	Increasing Cloudiness In Vision Sec To Cataracts B Eyes
104_439035	Cataracts Bilateral Eyes
105_508001	Cataracts
105_513016	Bilateral Cataract
105_516003	Macular Hole Rt Eye
105_517005	Increased C/D Ratio OS
105_530020	Retinal Hemorrhage-OD
105_535013	Blurred Vision Secondary To Cataract
105_541007	Increasing Cataract Formation OS

Reviewer's Comments:

1. *The development of diabetic retinopathy cases is reported as an adverse event, but only in patients treated for diabetic indications. The frequency of these cases is within the rate that would be expected to develop for any population with this indication, regardless of the treatment.*

2. *Cases should not be listed as" unknown". If the abnormality cannot be identified, a description of the change should be listed.*

Listing of Vision-Related Adverse Event Terms Sorted by Body System and Preferred Term: TESS Events Only

Adverse Event Term	Verbatim	FDA Reviewer Comment
Photosensitivity reaction	Fair sundamaged complexion	
	Increased intensity of lights at night	Should be with photophobia
	Increased sun sensitivity	Should be with photophobia
	Increased sun sensitivity (skin)	
	Light sensitivity	Should be with photophobia
	Photosensitivity	Should be with photophobia
	Photosensitivity on left arm	
	Photosensitivity, r eye	Should be with photophobia
	Sensitivity to bright light	Should be with photophobia
	Skin more sensitive to sun	
	Sun burn	
	Sunburn	
Retinal vascular disorder	Attenuated perivessels with peripheral ischemia OU	
	Bilateral microaneurysms	
	Few microaneurisms per ophth exam	
	Microaneurysm	
	Microaneurysm left eye	
	Microaneurysm OD	
	Microaneurysms	
	Microaneurysms left eye	
	Retinal neovascularization	
Nystagmus	Bil sustained horizontal nystagmus	
	Bilateral end gaze nystagmus	
	Bilateral nystagmus on lateral gaze	
	Bilateral sustained horizontal gaze evoked nystagmus	
	Bilateral unsustained endpoint nystagmus	
	Bilateral-lateral gaze nystagmus	
	Down-beat-nystagmus	
	Downbeat nystagmus	
	End gaze nystagmus	
	Fixation losses high OD	Should be with visual field
	Fixation losses left eye	Should be with visual field
	Fixation losses-OS	Should be with visual field
	High fixation losses	Should be with visual field
	Horizontal nystagmus	
	Horizontal saccadic eye movement	
	Horizontal sustained nystagmus	
	Horizontal unsustained end point nystagmus	
	Increased nystagmus	
	Increased vertical nystagmus	
	Intermittent nystagmus	
	Involuntary eye movements	
	Lateral gaze nystagmus on exam	
	Lateral gaze nystagmus-unsustained	

	Lateral nystagmus	
	Lateral nystagmus on exam	
	Lateral nystagmus upon exam	
	Min. Unsustained lateral nystagmus	
	Nystagmus	
	Nystagmus (horizontal)	
	Nystagmus both eyes	
	Nystagmus jumpy eye	
	Nystagmus on l end gaze	
	Nystagmus on sustained gaze (l)	
	Nystagmus r eye	
	Nystagmus-end point	
	Nystagmus-left eye	
	Nystagmus-unsustained end point	
	Nystagmus-unsustained endpoint	
	Rotary nystagmus	
	Saccadic eye movement	
	Unsustained endpoint nystagmus	
	Unsustained horizontal endpoint nystagmus on l gaze	
	Unsustained horizontal nystagmus	
	Unsustained nystagmus	
	Vertical nystagmus	
	Worsening nystagmus	
Abnormal vision	blackspots in peripheral vision	should be with vitreous disorder
	bugs in peripheral vision	should be with vitreous disorder
	2 line acuity decrease OU	
	Abnormal vision in right eye	
	After image both eyes	
	Alteration in vision l eye	
	Altered focus-vision	
	Altered vision r eye	
	Bidirectional oscillopsia	
	Black spots in vision	should be with vitreous disorder
	Brow shadow OU	
	Decrease in visual acuity	
	Decrease in visual acuity (left eye)	
	Decrease in visual acuity (right eye)	
	Decrease in visual acuity from baseline of 20/25	
	Decrease visual acuity	
	Decreased best correction-OD	
	Decreased l eye acuity	
	Decreased VA OD (visual acuity right eye)	
	Decreased vision	
	Decreased vision left eye	
	Decreased vision OS>OD	
	Decreased vision right eye	

Decreased visual activity
Decreased visual activity l
Decreased visual acuity
Decreased visual acuity OD
Decreased visual acuity OS
Decreased visual acuity OU
Decreased visual acuity right eye
Decreased visual acuity-r eye
Decreased visual sensitivity
Depth perception difficulty
Depth perception impaired
Depth perception off
Deteriorating vision
Deterioration of visual acuity
Difference in visual acuity (OD)
Difficulty focusing
Difficulty focusing eyes
Difficulty focusing vision
Difficulty focusing-vision
Difficulty in focusing when reading
Difficulty seeing
Difficulty visualizing objects
Difficulty with vision focusing
Diminished vision left eye
Distorted vision
Episode of sudden blindness
Episodic disruption of binocular vision
Eye filminess/cloudiness
Flash of white light for sec
Flashes of lights in eyes
Flashing in peripheral area
Flashing lights as 11.9.99
Flashing streaks of light-l eye
Focusing difficulties of eyes
Focusing difficulty - abnormal vision
Focusing difficulty of the eyes
Frequent visual after images
Halo noted around all objects
Impaired vision
Impaired vision, trouble focusing
Inability to focus
Inability to focus eyes
Increased vision disturbances
Increased vividness of color
Intermittent blindness l eye
Intermittent difficulty focusing (eyesight)
Intermittent difficulty focusing-eyesight
Intermittent vision disturbance
Intermittent visual phenomena in right lower visual field

Interrupted vision
L eye visual acuity reduced
Mild vision disturbances
Nonspecific visual changes right eye
Not focusing left eye
Oscillopsia
Out of focus right eye
Peripheral field constriction inferior
Peripheral light flashes-left eye
Poor vision
Poor vision focus
Reduced visual acuity
Rolling vision
Scintillating scotoma
Seeing spots
Sees spots & light streaks l eye
Sharper vision
Slightly reduced visual acuity from screening
Spot r peripheral vision intermittent
Trouble focusing
Trouble focusing (eyes)
Trouble vision
Unable to focus
Unable to focus correctly (eyes)
Unclear vision
Unfocused vision
Variable focus of eyes
Vision disturbance
Vision in l eye decreased
Vision in right eye seems weak
Vision out of focus
Vision problems
Vision worsening
Visual acuity change
Visual acuity decreased
Visual acuity drop l eye
Visual changes
Visual difficulties (depth perception off)
Visual distortion
Visual disturbance
Visual disturbance (related to implants for glaucoma)
Visual disturbance seeing prisms
Visual disturbance, wavy lines
Visual disturbances
Visual field flashes
Visual flashing lights
Visual impairment in left frontotemporal region
Visual jumpiness

	Visual problems	
	Visual trailer	
	Visual trailing phenomena	
	Visualizes orange and yellow colors	should be color vision change
	Visus impairment 8/10 to 4.5/10	
	White spots (vision)	
	Worsened oscillopsia	
	Worsening of sight deterioration	
	Worsening visual acuity	
Amblyopia	Bilateral blurred vision	
	Blurred vision	
	Blurred vision (peripheral)	
	Blurred vision after taking meds	
	Blurred vision in both eyes	
	Blurred vision in r eye	
	Blurred vision intermittent	
	Blurred vision l eye	
	Blurred vision O.U.	
	Blurred vision OD	
	Blurred vision OU	
	Blurred vision r eye	
	Blurred vision right eye	
	Blurred vision when looking up	
	Blurred vision with black wavy lines	
	Blurred vision with reading	
	Blurred vision, worsened	
	Blurred vision-bilaterally	
	Blurred vision-intermittent	
	Blurred vision-left eye	
	Blurring of vision	
	Blurring vision	
	Blurry eyes	
	Blurry eyes when wakes up	
	Blurry vision	
	Blurry vision both eyes	
	Blurry vision r eye	
	Blurry vision right eye	
	Blurry vision-intermittent	
	Brief period of blurred vision	
	Cloud over eyes	
	Cloudy vision in right eye	
	Dimmed vision	
	Episodes of blurred vision	
	Eye blurriness (left)	
	Fuzziness-visual disturbances	
	Fuzzy "blurred" vision l eye	
	Hazy eyes - can't quite focus	
	Hazy vision	

	Increased blurred vision
	Increased frequency blurred vision
	Increased visual blurring
	Intermittent blurred vision
	Intermittent blurry vision
	Left eye blurred vision
	Mild intermittent blurred vision
	Occasional blurred vision
	Occasional blurred vision r eye
	Probable amblyopia
	R eye blurred vision
	Slightly blurred vision
	Slt blurred vision
	Transient blurring vision
	Vision blurry
	Vision fuzzy
	Visual blurriness
	Visual blurring
	Worsened blurred vision (periphery)
	Worsening of blurred vision
Cataract NOS	Blurry vision right eye secondary to cataract
	Exacerbation of cataracts b eyes
Cataract specified	Beginning cataract, left eye
	Bilateral cataract
	Bilateral cataracts
	Blurred vision secondary to cataract
	Cataract
Cataract changes	Cataract changes
	Cataract l eye
	Cataract left eye
	Cataract OD
	Cataract OS
	Cataract OU OS>OD
	Cataract worsened
	Cataract, left eye
	Cataract-r eye
	Cataracts
	Cataracts bilateral eyes
	Cataracts both eyes
	Cataracts l eye > r eye
	Cataracts OU
	Decreasing central acuity OS secondary to cataract
	Early (l) cataract
	Early cataract bilateral
	Early cataract changes
	Early cataracts
	Immature bilateral cataracts
	Increased cataract o.s.

	Increasing cataract formation OS
	Increasing cloudiness in vision sec to cataracts b eyes
	Left cataract
	Left eye cataract
	Left eye worsening of cataracts
	Lens haze r eye
	Mild cataracts
	Nuclear sclerosis OU
	OD cataract
	OS cataract
	Progression of cataracts
	Progression of senile cataract left eye
	R cataract worsening
	Recurrent cataract of right eye
	Right eye worsening of cataracts
	Small cataract l eye
	Small cataract, left eye
	Worsened cataract OD
	Worsening cataract OD
	Worsening cataracts OU
	Worsening cataracts per exam
	Worsening of cataract OD
	Worsening r cataract
Color blindness	Abnormal ishihara score
	Impaired color vision
Diplopia	Abnormal vision "seeing double"
	Diplopia
	Diplopia (worse than baseline)
	Diplopia increase
	Diplopia intermittent
	Diplopia on looking to left
	Double vision
	Double vision (not previously reported)
	Double vision - 2 episodes: 1 hr and 1/4 hr
	Double vision - right eye
	Double vision l eye
	Double vision left eye
	Double vision worsened
	Double vision, intermittent
	Double vision-intermittent
	Double-vision
	Increase in double vision
	Increased diplopia
	Increased double vision
	Intermittent diplopia
	Intermittent double vision
	L eye-double vision
	Left eye diplopia
	Occasional double vision

	Worsened double vision	
	Worsening diplopia	
	Worsening of double vision	
Dry eyes	Dry eye	
	Dry eye OU	
	Dry eye syndrome	
	Dry eyes	
	Dry eyes (bilateral)	
	Dry eyes/intermittent	
	Dry scratchy left eye	
	Dryness of eyes	
	Eye dryness	
	Increased dry eyes	
	Inferior corneal drying	
	R eye dryness	
Eye disorder	heavy eyes	should be ptosis
	Abnormal dilated fundoscopic exam - probable old scar	
	Abnormal dilated funduscopic exam	
	Active evolutive graves ophtalmopathy	
	Asymmetrical optical cups OD	
	Bilateral (OU) non specific constriction	
	Bilateral eye infection	
	Bilateral itchy eyes	
	Bilateral nervous eye movement	
	Blisters in both eyes	
	Chalazion	
	Chalázion left eye	
	Chalazion rt. Eyelid	
	Crossed eyes	
	Discoloration l eye sclera	
	Drooping eyelids	should be ptosis
	Drooping right eye	should be ptosis
	Epithelial sloughing l eye	
	Eye drainage	
	Eye fatigue	
	Eye infection	
	Eye infection OU	
	Eye infection/OD	
	Eye irritation zoster side	
	Eye strain	
	Eyelashes falling out	
	Eyes burning	
	Eyes crossed	
	Eyes feel heavy after study med dosage	
	Eyes itching	
	Fine drusen both eyes	should be retinal disorder
	Glassy eyes	
	Glossy eyes	
	Heavy eyelids	should be ptosis

	Heavy eyelids-bilat	should be ptosis
	Heavy eyelids-bilat.	should be ptosis
	Heavy eyes	should be ptosis
	Infected l eye	
	Infection left eye	
	Inferior temporal depression left eye	
	Involuntary left eye closing	
	Itching eye	
	Itching eyes	
	Jumpy eyes	
	L exophthalmos secondary to retrobulbar fat	
	L eye infection	
	L eyelid retraction	
	L horner's syndrome	should be ptosis
	Left eye droopy	should be ptosis
	Left eye infection	
	Left superior defect due to lesion on eyelid	
	Lesion lt. Eyelid	
	Lesion rt eyelid	
	Misty film over eyes every morning	
	Pulling sensation left eye	
	R & l ocular infection	
	R eye infection	
	R eye itchy	
	R eye lid won't open in am after sleep	
	R eye stye	
	Right eye infection	
	Rt eye infection bacterial	
	Sand feeling under upper eye lids	
	Serous detachment temporal to fovea OS	
	Slight inferior nasal stye l eye	
	Small paracentral defect left eye	
	Sty right eye	
	Stye left eye	
	Stye on left eyelid	
	Stye r eye	
	Tired eyes	
	Tiredness in eyes	
	Visual difficulties (eyelids heavy)	
	Weak, tired eyes	
	Worsening left eye droop	should be ptosis
	Worsening of graves' ophthalmopathy	
Eye hemorrhage	Bilateral hyperemia-nasal edge of optic disc	
	Bilateral one dot hemorrhage	
	Bilateral subconjunctival hemorrhage	
	Broken blood vessel l eye	
	Broken blood vessel lt eye	
	Broken blood vessels l eye	
	Dot hemorrhage lt. Eye	

	Dot hemorrhage/microaneurysm left eye-eye hemorrhage	
	Eyes-flame hemorrhages	
	Few dot blot hemorrhages in peripheral field on eye exam	
	Hemorrhage r eye	
	Hemorrhages near fovea	
	L eye blood vessel burst	
	Left conjunctival hemorrhage	
	Left vitreous hemorrhage	
	Lt eye broken blood vessel	
	OS.-isolated extramacular dot and blot hemorrhage	
	On eye exam few dot blot hemorrhages in peripheral field	
	OS blood shot outside corner between iris and corner of eye	
	OS-isolated ventricular dot and blot hemorrhage	
	Scleral hemorrhage	
	Scleral hemorrhage OD	
	Second hemorrhage right eye	
	Single dot hemorrhage left eye	
	Small hemorrhage right upper eye	
	Subconjunctival hemorrhage	
	Vitreous hemorrhage l eye	
Eye pain	Achy eyes	
	Bilateral eye pain	
	Burning eyes	
	Burning eyes OU	
	Burning in eyes	
	Burning sensation bilateral eyes	
	Burning sensation eyes	
	Elevated pressure right eye pain	
	Eye ache	
	Eye pain	
	Eye pain - bilateral	
	Eye pressure	
	Eyes aching	
	Eyes hurt watching tv or when wearing contact lenses	
	Increased eye pressure	should be glaucoma
	Increased pressure in l eye	should be glaucoma
	Increased pressure right eye (eye pain)	should be glaucoma
	Intermittent discomfort behind eyes	
	L eye pain	
	Left eye pain	
	Mild ache behind eyes	
	Pain behind eyes	
	Pain behind l eye	
	Pain in eye rt	
	Pain in l eye increasing	
	Pain in OD	
	Pain in r eye	
	Pain right eye	

	Pain to (r) eye
	Painful eyes
	Pressure & burning in eyes
	Pressure behind eye
	Pressure behind eyes
	Pressure behind l eye
	R eye pain
	Retro orbital pain
	Retro-orbital pain
	Right eye pain
	Rt eye pain
	Shooting pain in l eye
	Shooting pain over left eye
	Sore eye
	Sore eyes
	Sore lower eye lid l
	Sore right eye
	Stabbing pain l eye
	Stinging eyes
Glaucoma	Early glaucoma
	Exacerbate glaucoma
	Glaucoma
	Glaucoma (r) eye
	Glaucoma both eyes
	Glaucoma l eye
	Glaucoma r eye
	Increase of intraocular pressure
	Increased intraocular pressure
	Increased pressure OD dx glaucoma
	Intraocular pressure increased
	Possible glaucomatous loss
Night blindness	Difficulty focusing at night
Optic atrophy	Pale optic disc r/o optic neuropathy
Papilledema	Fullness to optic nerve head bilat
Photophobia	Eyes more sensitive to light
	Eyes sensitive to light
	Increased light sensitivity (photophobia)
	Increased sensitivity to bright light
	Increased sensitivity to bright lights at night
	Photophobia
	Photophobia to bright sunlight
	Photosensitivity (visual)
	Photosensitivity of eyes
	Sensitivity of eyes to light
Ptosis	Lt. Ptosis
	Ptosis
	Ptosis o.d.
	Ptosis of eyelids, intermittent
	Ptosis os

Retinal degeneration	Bilateral lattice degeneration	
	Peripheral lattice degeneration in both eyes	
Retinal depigmentation	Epiretinal membrane peripheral pigment degeneration	
	Tiny macular serous pigment epithelial detachment OD	
Retinal detachment	Retinal detachment	
	Retinal detachment r eye	
	Retinal detachment right eye	
Retinal disorder	Abnormal epiretinal membrane	
	Age related macular degeneration	
	Background diabetic retinopathy	
	Background diabetic retinopathy OD	
	Background retinopathy	
	Background retinopathy changes right eye	
	Background retinopathy OS	
	Bg retinopathy	
	Bilateral macular degeneration	
	Bilateral proliferative diabetic retinopathy	
	Bilateral retinal pigment epithelial disturbance	
	Cotton wool spot	
	Cotton wool spot on retina left eye	
	Cotton wool spots	
	Cotton wool spots left eye	
	Diabetic maculopathy OD	
	Diabetic maculopathy OS	
	Diabetic retinopathy	
	Diabetic retinopathy both eyes	
	Diabetic retinopathy OD	
	Drusen	
	Early age related macular degeneration OU	
	Early macular degeneration	should be retinal degeneration
	Early macular degeneration OS	should be retinal degeneration
	Early peripheral diabetic retinopathy	
	Exacerbation of diabetic retinopathy	
	Faint epiretinal membrane	
	Fine macular drusen OU	
	Hypertensive retinopathy	
	Increased diabetic macular changes	
	Increased retinopathy OD	
	Left eye background retinopathy	
	Left eye retinal holes	
	Macular cyst r eye	
	Macular degeneration	should be retinal degeneration
	Macular degeneration o.s.	should be retinal degeneration
	Macular drusen l eye	
	Macular hole rt eye	

	Mild background retinopathy	
	Mild diabetic retinal changes l eye	
	Mild diabetic retinopathy	
	Mild diabetic retinopathy OD	
	Mild nonproliferative diabetic retinopathy	
	Non prolific diabetic retinopathy	
	Nonproliferative diabetic retinopathy	
	Operculosis retinal hole right eye	
	OS diabetic retinopathy	
	Peripheral retinal tear-o.d.	
	Pre-proloferative retinopathy OU	
	Progression of macular degeneration	should be retinal degeneration
	Pseudopapilledema	
	R drusen near fovea	
	Redness of eyeground	
	Retinal changes-OU	
	Retinal epithelial defect OD	
	Retinal hole right eye	
	Retinal pigment epithelium changes	
	Retinal tear	
	Retinal tear r eye	
	Retinal wrinkling	
	Retinopathy	
	Retinopathy (background)	
	Retinopathy r eye	
	Right eye proliferative diabetic retinopathy	
	Rt eye extensive background retinopathy	
	Sickle cell retinopathy	
	Subretinal fluid-left eye	
	Worsening background diabetic retinopathy	
	Worsening of retinopathy	
Retinal edema	Clinically significant macular edema l eye	
	Clinically significant macular edema r eye	
	Diabetic macular edema	
	Diabetic retinopathy with macular edema OD>OS	
	Diffuse macular edema	
	Macular edema	
	Macular edema l eye	
	Macular edema left eye	
	Macular edema OD	
	Retinal edema both eyes	
Retinal hemorrhage	Rare diabetic hemorrhage o.s.	
	Retinal hemorrhage	
	Retinal hemorrhage-OD	
	Small retinal hemorrhage of right eye	
Retinal pigmentation	OD retinal pigment epithelium	
Visual field defect	(l) upper quadrant visual defect	
	Abnormal peripheral vision	

Abnormal peripheral vision exam
Abnormal vision (peripheral)
Abnormal visual field.
Abnormal visual field OD
Abnormal visual field right eye inferior arcuate changes
Altitudinal defect OU
Arcuate defects left eye
Bi-nasal scotoma
Bilateral constricted peripheral vision
Bilateral missed points nasally
Bilateral nasal field defect
Bilateral visual defect
Bilateral visual field defect
Binasal hemianopia
Blurred peripheral vision
Bright spots in r superior visual field
Central scotoma
Change in peripheral vision
Change in peripheral vision assessment
Change in peripheral visual assessment
Changes in visual field
Concentric constriction of peripheral vision
Concentric constriction of peripheral vision worsened
Concentric peripheral depression OS
Concentric visual field constriction
Constricted peripheral vision x360 degrees OS
Constriction of peripheral vision
Constriction of peripheral vision OU
Contraction of field left eye
Decline in peripheral vision
Decreased l peripheral vision
Decreased peripheral vision
Decreased peripheral vision OU
Decreased r visual field
Decreased sensitivity-peripheral vision O.U..
Decreased visual fields, OU
Dense nasal loss with peripheral constriction both eyes
Dots on upper & lower fields l & r eye - visual field defect
Elevated peripheral vision
Far peripheral defect OU
Fixation losses peripheral vision
Generalized constriction of visual field
Homonymous hemianopia
Increase in visual field constriction
Increased peripheral constriction visual field
Increased peripheral deficit O. U.
Increased peripheral deficit O.U.
Increased scotomatous encroaching axis
Increased visual field loss right eye

Inferior changes OD
Inferior nasal peripheral constriction
Inferior nasal visual field defect
Inferior peripheral constriction-both eyes
Inferior peripheral depression (visual)
Inferior visual field defect OU
Infero nasal peripheral vision defect left eye
L eye nasal defects (inferior & superior)
L eye peripheral defect
L homonymous superior visual field depression
L superior quadrantanopia
L visual field flashes
Left eye central scotoma on visual field exam
Left eye nasal depression in periphery
Left eye non-specific scotomas on exam
Left eye peripheral visual disturbance
Left eye visual field worsening of
Lt. Arcuate changes
Mild bilateral visual field abnormality
Mild far peripheral field changes
Narrowing of visual field
Nasal arcuate scotoma
Nasal concentric arcuate scotomas
Nasal field loss-both eyes
Nasal step (visual field deficit)
New missed points nasally left eye
New missed points superiotemporal periphery-left eye
New peripheral defect OU
Non specific peripheral defect OS > OD
OD central scotoma
OD: change in peripheral visual field
OU superior field depression
Perimeter peripheral changes OD
Peripheral constriction of visual fields
Peripheral defect OD
Peripheral defect, OU, increased
Peripheral defects c/w ischemia OU
Peripheral points missed, OU, on peripheral vision testing
Peripheral restriction (ophthalmic)
Peripheral vision change - nasal depression OS
Peripheral vision change from baseline
Peripheral vision change since baseline
Peripheral vision changes
Peripheral vision constricted
Peripheral vision constricted bilaterally
Peripheral vision defect
Peripheral vision deficit
Peripheral vision fixed loss
Peripheral vision loss

	Peripheral vision loss (left eye)
	Peripheral vision loss (right eye)
	Peripheral vision loss-r homonymous hemianopsia
	Peripheral vision: missed pts nasally (both eyes)
	Peripheral visual field constriction
	Peripheral visual field constriction-o.d.
	Peripheral visual increased superior defect OU
	Peripheral visual restriction
	Progressive visual field loss-left eye
	R eye reduced central sensitivity
	R eye-reduced central sensitivity
	R homonymous hemianopia
	R quadrantanopia
	R temporal p point loss between 40-50 degree field of vision
	Reduced visual field
	Relative scotomata-both eyes
	Right eye peripheral nasal and inferior depression changes
	Right small scotomas in 0 degree to 15 degree field on exam
	Right visual field deficit
	Scattered peripheral defects (visual field)
	Scattered scotomata OD & OS
	Scotoma
	Slight increase in far peripheral field points not seen OU
	Slight nasal arcuate scotoma
	Slight peripheral vision constriction left eye
	Small inferior paracentral scotoma OD
	Small peripheral vision defect
	Superior defect r eye
	Temporal defect OU
	Temporal field worsening vision
	Tunnel vision
	Visual disturbance (visual field restriction)
	Visual field change
	Visual field changes
	Visual field constriction OU
	Visual field defect
	Visual field defect both eyes
	Visual field defect right eye
	Visual field defects
	Visual field disturbance
	Worsened rt. Homonymous hemianopia
	Worsening of peripheral vision
	Worsening of peripheral vision left eye
	Worsening OS peripheral vision
	Worsening peripheral vision
	Worsening visual field
Vitreous disorder	Asteroid hyalosis
	Bilateral floater
	Change in floater OD

Floaters
Floaters in eyes
Floaters in vision field
Increased floaters in eyes
Inferior peripheral vitreous opacity left eye
L eye floaters
Ocular floater
Posterior vitreous detachment
Seeing floaters White floaters on left eye

Reviewer's Comments:

1. *There are a relatively large number of visual field disorders. The actual visual fields were reviewed by this medical officer. There is no consistent pattern of visual field change, but the majority of the defects are located in the peripheral visual field.*

2. *There are a number of misclassifications in the Vision-Related Adverse Event Terms table. These should be corrected.*

6 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Regulatory Recommendations:

Recommendation on Approvability

From an ophthalmologic prospective, there is no objection to the approval of this NDA provided that the labeling identifies the potential of pregabalin to cause decreased visual acuity and decreased fields of view (i.e., visual fields). Specific changes to the labeling have been identified in the review.

Recommendation on Phase 4 Studies and Risk Management Steps

Additional adequate and well-controlled studies are recommended to better quantitate the effect of pregabalin on visual function The following studies should be conducted: best corrected distance visual acuity, threshold perimetry of the periphery (visual fields), color vision (Farnsworth-Munsell 100 hue) and retinal physiology (as measured by ERG testing). Testing should include both short term, two-six months and long term (six months or more) repeated dosing.

/S/

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

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/s/

Wiley Chambers
4/2/04 02:32:15 PM
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