

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021446Orig1s028

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type sNDA
Application Number(s) N21446/S-028
Priority or Standard Priority

Submit Date(s) December 19, 2011
Received Date(s) December 20, 2011
PDUFA Goal Date June 20, 2012
Division / Office DAAAP/ODE II

Reviewer Name(s) Joshua M. Lloyd, M.D.
Review Completion Date May 25, 2012

Established Name Pregabalin
Trade Name Lyrica
Therapeutic Class Alpha₂-Delta Ligand
Applicant Pfizer

Formulation(s) Capsule
Dosing Regimen 150-600 mg/day, divided BID
Indication(s) Management of neuropathic
pain associated with spinal
cord injury
Intended Population(s) Chronic central neuropathic
pain after spinal cord injury

Template Version: [March 6, 2009](#)

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment.....	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Tables of Currently Available Treatments for Proposed Indications	10
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues with Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	13
3	ETHICS AND GOOD CLINICAL PRACTICES.....	13
3.1	Submission Quality and Integrity	13
3.2	Compliance with Good Clinical Practices	13
3.3	Financial Disclosures.....	15
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	16
5	SOURCES OF CLINICAL DATA.....	16
5.1	Tables of Studies/Clinical Trials	16
5.2	Review Strategy	17
5.3	Discussion of Individual Studies/Clinical Trials.....	18
6	REVIEW OF EFFICACY	77
	Efficacy Summary.....	77
6.1	Indication	78
6.1.1	Methods	78
6.1.2	Demographics.....	78
6.1.3	Subject Disposition.....	79
6.1.4	Analysis of Primary Endpoint(s).....	81
6.1.5	Analysis of Secondary Endpoints(s)	82
6.1.6	Other Endpoints	84
6.1.7	Subpopulations	86
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	87
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	87
6.1.10	Additional Efficacy Issues/Analyses	87
7	REVIEW OF SAFETY.....	88
	Safety Summary	88

7.1	Methods.....	89
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	89
7.1.2	Categorization of Adverse Events	89
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	89
7.2	Adequacy of Safety Assessments	90
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	90
7.2.4	Routine Clinical Testing	91
7.3	Major Safety Results	91
7.3.1	Deaths.....	91
7.3.2	Nonfatal Serious Adverse Events	92
7.3.3	Dropouts and/or Discontinuations	99
7.3.4	Significant Adverse Events	109
7.3.5	Submission Specific Primary Safety Concerns	109
7.4	Supportive Safety Results	112
7.4.1	Common Adverse Events	112
7.4.2	Laboratory Findings	117
7.4.3	Vital Signs	121
7.4.4	Electrocardiograms (ECGs)	121
7.4.5	Special Safety Studies/Clinical Trials	121
7.5	Other Safety Explorations.....	122
7.5.2	Time Dependency for Adverse Events.....	122
7.5.3	Drug-Demographic Interactions	122
7.5.4	Drug-Disease Interactions.....	124
7.6	Additional Safety Evaluations	124
7.6.2	Human Reproduction and Pregnancy Data.....	124
7.6.3	Pediatrics and Assessment of Effects on Growth.....	124
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	125
7.7	Additional Submissions / Safety Issues	126
8	POSTMARKET EXPERIENCE.....	126
9	APPENDICES	133
9.1	Literature Review/References	133
9.2	Labeling Recommendations	133
9.3	Advisory Committee Meeting.....	137

Table of Tables

Table 1. Key Presubmission Regulatory Activity.	11
Table 2. OSI Inspected Clinical Sites.	14
Table 3. Clinical Trials Submitted in Support of this Application.	17
Table 4. Trial 125: Schedule of Activities.	26
Table 5. Trial 125: Demographic and Baseline Characteristics (Safety Population).	31
Table 6. Trial 125: History of Spinal Cord Injury (Safety Population).	32
Table 7. Trial 125: Concomitant Medications.	33
Table 8. Trial 125: Summary of Major Protocol Violations.	34
Table 9. Trial 125: Subject Evaluation Groups.	34
Table 10. Trial 125: Duration of Treatment (Safety Population).	35
Table 11. Trial 125: Maximum and Average Daily Doses (Safety Population).	36
Table 12. Trial 125: Treatment Compliance (Safety Population).	37
Table 13. Trial 125: Applicant's Primary Efficacy Analysis, Mean Pain Score at Baseline and Endpoint (ITT).	38
Table 14. Trial 125: Applicant's Analysis of Mean Pain Score at Endpoint (BOCF; ITT).	39
Table 15. Trial 125: Applicant's Analysis of Treatment Responders: 30% and 50% Reduction in Mean Pain Scores from Baseline to Endpoint (ITT).	40
Table 16. Trial 1107: Permitted Concomitant Medications.	50
Table 17. Trial 1107: Prohibited Medications.	51
Table 18. Trial 1107: Schedule of Activities.	57
Table 19. Trial 1107: Enrollment by Country.	62
Table 20. Trial 1107: Subject Disposition.	63
Table 21. Trial 1107: Demographic Characteristics of ITT Population.	64
Table 22. Trial 1107: Summary of Spinal Cord Injury History (ITT Population).	65
Table 23. Trial 1107: Summary of Major Protocol Violations Reported by the Applicant.	66
Table 24. Exploratory Analyses to Account for Potential Protocol Violations.	67
Table 25. Trial 1107: Composition of Data Sets.	68
Table 26. Trial 1107: Duration of Treatment (ITT).	69
Table 27. Trial 1107: Maximum Daily Dose and Average Daily Doses Overall and During Maintenance Phase (Safety Population Subset).	69
Table 28. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (mITT).	71
Table 29. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (PP).	71
Table 30. Study A008-1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (ITT).	71
Table 31. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of the DAAC, by Country (mITT).	72
Table 32. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of Changes from Baseline in Mean Pain Score at Endpoint (mITT; mBOCF).	73

Table 33. Trial 1107: Applicant's Statistical Analysis (Logistic Regression) of Subjects with $\geq 30\%$ Reduction from Baseline in Mean Pain Score (Responders) at Endpoint (mITT; LOCF).....	73
Table 34. Trial 1107: Applicant's Statistical Analysis (Logistic Regression) of Subjects with $\geq 50\%$ Reduction from Baseline in Mean Pain Score (Responders) at Endpoint (mITT; LOCF).....	74
Table 35. Demographic Characteristics by Study and Treatment Group: Controlled Studies 1107 and 125.	79
Table 36. Primary Efficacy Analysis for Trial 125.	81
Table 37. Primary Efficacy Analysis for Trial 1107.	82
Table 38. Proportion of Subjects with at Least a 30% Reduction in Baseline Pain at Week 16 for Trial 1107.	83
Table 39. Proportion of Subjects with at least a 30% Reduction in Pain Intensity from Baseline to Week 12 for Trial 125.	85
Table 40. Summary of Cumulative Exposure to Pregabalin in the Controlled and Uncontrolled CNP-SCI Trials: 1107, 125, and 202.	90
Table 41. Non-fatal SAEs Experienced in Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.	92
Table 42. Discontinuations Due to Adverse Events, Summarized in Decreasing Order of Frequency for Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.	100
Table 43. Discontinuations Due to Adverse Events, Summarized by Decreasing Order of Frequency for Pregabalin-Treated Subjects: Controlled and Uncontrolled Trials 1107, 125, and 202.	101
Table 44. Concomitant Medications Taken During Study by at Least 5% of Pregabalin- or Placebo-Treated Subjects: Controlled CNP-SCI Trials 1107 and 125.	111
Table 45. Common Adverse Events, Summarized by Decreasing Order of Frequency for More Than 2% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125. .	114
Table 46. Common Adverse Events, Summarized by Decreasing Order of Frequency for More Than 3% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125 and Uncontrolled Trial 202.	116
Table 47. Abnormal Postbaseline Laboratory Results in More Than 2% of Pregabalin-Treated Subjects Who Had Normal Results at Baseline: Controlled Trials 1107 and 125.	118
Table 48. Worsened Abnormal Postbaseline Laboratory Results for at Least 5 Pregabalin-Treated Subjects Who Had Abnormal Results at Baseline: Controlled Trials 1107 and 125.	118
Table 49. Median Changes in Clinical Laboratory Results From Baseline to Last Observation: Controlled Trials 1107 and 125.	120
Table 50. Adverse Events Summarized by Age Group and Decreasing Order of Frequency for More Than 5% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.	123
Table 51. Overview of Adverse Events Summarized by Gender and Race: Controlled Trials 1107 and 125.	124
Table 52. Additional Requested Clinical Submissions to NDA 21446/S-028.	126

Table 53. Characteristics of Postmarketing Cases of Pregabalin for the ISS Period: Patients with Neuropathic Pain (NP) and Central Neuropathic Pain (CNP). 128

Table 54. Characteristics of Postmarketing Cases of Pregabalin for the ISS and SU Periods: Combined Patient Population with Various Types of Neuropathic Pain. 130

Table 55. Summary of Most Commonly Reported Pregabalin Postmarketing AEs Involving Patients with Neuropathic Pain (NP; $\geq 2\%$ of Cases) and Patients with Central Neuropathic Pain (CNP; All Cases) for the ISS Period by Decreasing Frequency. 131

Table 56. Summary of Most Commonly Reported Pregabalin Postmarketing AEs in at Least 2% of Cases For the ISS and SU Periods: Combined Patient Population with Various Types of Neuropathic Pain. 132

Table of Figures

Figure 1. Trial 125: Protocol for Study Drug Administration.	24
Figure 2. Trial 125: Subject Disposition.....	30
Figure 3. Study 125: Applicant's Cumulative Responder Analysis (BOCF).....	40
Figure 4. Trial 125: Applicant's Analysis of Weekly Mean (\pm SE) Pain Scores Based on ANCOVA (ITT).	42
Figure 5. Trial 125: Applicant's Analysis of Weekly Mean (\pm SE) Pain Scores: Least-Squares Means from Repeated Measures Analysis (ITT).....	42
Figure 6. Trial 1107: Protocol for Study Drug Administration.	56
Figure 7. Trial 1107: Subject Disposition.....	63
Figure 8. Trial 1107: Applicant's Analysis of LS Mean Changes (\pm SE) from Baseline in Weekly Mean Pain Score (ITT).	75
Figure 9. Trial 1107: Applicant's Cumulative Responder Analysis (BOCF).	76
Figure 10. Subject Disposition for Controlled Trials 125 and 1107.....	80
Figure 11. Cumulative Proportion of Responders for Trial 125.	84
Figure 12. Cumulative Proportion of Responders for Trial 1107.	86

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The Applicant proposes to add the indication of management of neuropathic pain associated with spinal cord injury to pregabalin. According to review of the clinical data, I recommend approval of this supplemental NDA (sNDA) with revisions to the proposed label.

- The Applicant submitted the results of two placebo-controlled clinical trials, in patients with neuropathic pain after spinal cord injury, in support of this application. I have determined that both trials were designed and conducted in a reasonably adequate and well-controlled fashion that is sufficient to rely upon for a determination of efficacy.
- The Applicant also submitted the results of one open-label extension clinical trial, in the population of interest, in support of this application. These results, the results of the two controlled trials, and the known safety profile of pregabalin are sufficient to rely upon for a determination of safety.
- The data reviewed, in the two controlled clinical trials, in patients with chronic neuropathic pain after spinal cord injury, support the effectiveness of pregabalin for the management of neuropathic pain in this population as evidenced by the statistical significance of the preferred primary endpoints compared to placebo and the clinically meaningful benefit of this finding.
- Based on my review of the safety data submitted in support of this application, the safety profile for the intended patient population is relatively consistent with the labeling for pregabalin's use in previously approved indications.

1.2 Risk Benefit Assessment

The Applicant submitted data from two adequate and well-controlled trials that provided substantial evidence of effectiveness for the use of pregabalin in patients with central neuropathic pain associated with spinal cord injury (CNP-SCI). Safety data from clinical trials in this population are relatively consistent with what is currently labeled for pregabalin's use in previously approved indications. Further, there is extensive clinical experience worldwide with the use of this product.

Benefits:

- CNP-SCI is a difficult to treat medical condition for which there are currently no approved medications in the United States.
- Evidence of effectiveness was established in two placebo-controlled trials using the preferred primary endpoint, change in pain intensity from baseline

- to endpoint, with a conservative imputation strategy that was unlikely to assign a positive treatment effect to subjects that dropout due to adverse events.
- The primary efficacy analysis is further supported by results in favor of pregabalin on various secondary endpoints including the cumulative responder analyses.
 - Pregabalin was evaluated through flexible dose design trials, and was shown to be effective over the dose range of 150-600 mg per day, in twice daily divided doses. A similar dosing regimen is currently approved for the management of postherpetic neuralgia and partial onset seizures, while the maximum recommended dose is reduced for the treatment of fibromyalgia (i.e., 450 mg/day) and diabetic peripheral neuropathy (i.e., 300 mg/day).

Risks:

- The safety profile of pregabalin in the CNP-SCI population is relatively comparable to what is already known about pregabalin, and no unexpected or new significant safety concerns were identified during review of this application.
- The most commonly reported adverse events associated with pregabalin use, in this population, were somnolence and dizziness.
- A higher frequency of somnolence associated with pregabalin use was observed in the CNP-SCI population compared to what is reported in the labeling for previously approved indications. However, the ratio between the frequency of somnolence in the pregabalin and placebo groups observed in CNP-SCI subjects was relatively comparable to that observed for the previously approved indications.

Overall, the risk-benefit profile of pregabalin in this population is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I have identified no further safety issues in the review of this application that warrant additional postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

I do not recommend any additional postmarket requirements or commitments based on the review of this supplemental application.

2 Introduction and Regulatory Background

2.1 Product Information

Pregabalin is a gamma-aminobutyric acid analog (GABA) that exerts its activity by binding to the α_2 -delta subunit of the voltage-gated calcium channel of neurons. As a result of its ligand activity, there is a decrease in the influx of calcium at nerve terminals associated with the inhibited release of a variety of neurotransmitters (glutamate, noradrenalin, serotonin, dopamine, and substance P). The Applicant evaluated a dosage regimen of 150-600 mg/day administered as a split twice daily dose in patients with central neuropathic pain associated with spinal cord injury. A similar dose regimen for this drug is currently approved for the management of postherpetic neuralgia and partial onset seizures with a reduced maximum recommended dose of 450 mg/day for patients with fibromyalgia and 300 mg/day for patients with diabetic peripheral neuropathy.

Pregabalin is well absorbed after oral administration and is largely eliminated by renal excretion. Peak plasma concentrations occur within 1.5 hours and steady state is achieved within 24 to 48 hours. Pregabalin does not bind to plasma proteins, and the apparent volume of distribution following oral administration is approximately 0.5 L/kg. Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function.

2.2 Tables of Currently Available Treatments for Proposed Indications

Presently there are no products marketed in the United States that are approved for the management of central neuropathic pain associated with spinal cord injury.

2.3 Availability of Proposed Active Ingredient in the United States

Pregabalin is an approved drug that is already available and marketed in the United States as adjunctive therapy for adult patients with partial onset seizures, and for the management of fibromyalgia, pain associated with diabetic peripheral neuropathy, and postherpetic neuralgia.

2.4 Important Safety Issues with Consideration to Related Drugs

Serious adverse events associated with the use of pregabalin include motor (dizziness and somnolence) and visual (blurred vision) impairment, weight gain, peripheral edema, creatinine kinase elevations, thrombocytopenia, angioedema, hypersensitivity, suicidal behavior and ideation, and PR interval prolongation. Since abrupt discontinuation of

this drug can be associated with insomnia, nausea, headache, and diarrhea, pregabalin needs to be tapered slowly over one week in patients who plan to discontinue therapy.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pregabalin has previously been approved in the United States for the following indications:

- Management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia (NDA 21446; 12/2004)
- Adjunctive therapy for adult patients with partial onset seizures (NDA 21724; 6/2005)
- (b) (4)

The drug development program was conducted under IND 53763. Key regulatory activity related to this sNDA is noted in Table 1 that follows.

Table 1. Key Presubmission Regulatory Activity.

Date	Meeting/ Submission Type	Comments
4/21/2005	Type C Meeting	<ul style="list-style-type: none"> • At least two adequate, well-controlled trials would be required for a specific central pain indication such as spinal cord injury
1/26/2006	SPA for Protocol A008-1107	<ul style="list-style-type: none"> • No Agreement letter issued 3/10/2006 • Division stated that the study designs (protocols 1008-000-125 and A008-1107) appear adequate to support a finding of efficacy for the indication • The Applicant was encouraged to use a landmark analysis rather than the proposed primary efficacy parameter, duration adjusted average change (DAAC) • The Division recommended that the primary efficacy analysis include all randomized patients who receive at least one dose of study medication • The Division recommended performing a continuous responder analysis and to treat any subjects who drop out/discontinue as non-responders • The Division made additional recommendations regarding safety monitoring
4/11/2006	SPA for Protocol A008-1107	<ul style="list-style-type: none"> • No Agreement letter issued 5/23/2006 • The Division emphasized that the DAAC is unacceptable for the primary efficacy analysis and that a landmark analysis is recommended • The Division also stated that the Applicant will need to propose a plan on how to incorporate information about withdrawals in the continuous responder analysis
6/29/2006	Type A Meeting to discuss Division responses to SPA	<ul style="list-style-type: none"> • Continued disagreement over the proposed primary efficacy analysis • The Division stated that revisions incorporating additional clinical assessments adequately addressed safety concerns • The Division is in agreement regarding the proposed

Date	Meeting/ Submission Type	Comments
8/28/2006	Post Type A Meeting teleconference	<p>continuous responder analysis</p> <ul style="list-style-type: none"> Held to discuss the Division's position on acceptable primary analysis methods for demonstrating efficacy The Division stated that its policy mandates use of a conservative imputation strategy
11/2/2006	Formal Dispute Resolution Request	<ul style="list-style-type: none"> The Applicant disputed the Division's advice on the primary efficacy analysis and how missing data should be handled Formal dispute resolution request meeting was held on 3/15/2007 Conclusion to dispute resolution communicated by letter (4/13/2007): Dr. Robert Meyer, then Director, Office of Drug Evaluation II, upheld the Division's determinations with regard to the primary analyses and imputation techniques Dr. Meyer made the following comments in his letter: "At the meeting, we discussed the possibility of using the DAAC along with the landmark analysis using BOCF as a critical secondary analysis - tantamount to using two primary analyses. While this would be acceptable, having to win on two analyses presents you with a higher hurdle than simply declaring the analysis that is acceptable to the review division as the primary analysis (i.e., the landmark analysis of drug versus placebo imputing by means of baseline observation carried forward) with sensitivity analyses and the DAAC as secondary assessments."
9/30/2011	Pre-sNDA Meeting	<ul style="list-style-type: none"> Preliminary comments sent out 9/30/2011 Meeting (scheduled for 10/4/2011) was cancelled by the Applicant The Division noted that the primary efficacy endpoint for trial A008-1107 was DAAC, that the primary efficacy analysis for trial 1008-000-125 used last observation carried forward imputation, and that these methods would not support a finding of efficacy on their own The Division requested that the Applicant submit a cumulative responder analysis for each study The Division stated that the application must contain a sufficient number of patients in the safety database at the time of sNDA submission to assess the long-term safety for the intended population The Division stated that case report forms should be submitted for all serious adverse events, deaths, and discontinuations due to adverse events regardless if the clinical investigators attribute the event to be drug-related The Division stated that the Applicant will need to provide sufficient evidence that conducting pediatric studies would be impossible or highly impractical for a waiver and that the final decision will need to be made by the Pediatric Review Committee (PeRC)

Source: Derived from the presubmission regulatory history.

2.6 Other Relevant Background Information

Trial 1008-000-125 was a non-IND study conducted in Australia.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All data and documents in this application were electronically submitted following the guidances for electronic submission. The documents were organized in electronic Common Technical Document (eCTD) format. The datasets were not in Study Data Tabulation Model (SDTM) format. The overall quality of the submission was adequate. The organization and the ability to navigate the NDA were acceptable. A number of information requests were sent to the Applicant for additional information, and the responses were timely and adequate (see Section 7.7, Table 52).

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in accordance with Guidelines for Good Clinical Practice and the Declaration of Helsinki and in compliance with the United States Food and Drug Administration regulations for informed consent and protection of patient rights as described in 21 Code of Federal Regulations Parts 50, 56, and 312. The Applicant also states that the studies were approved by Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

The Office of Scientific Investigations (OSI) conducted routine inspection of four clinical investigator sites in support of this sNDA. The domestic site was selected based on the number of enrolled subjects. International sites were selected because two-thirds of the enrollment for trial A008-1107 was international, and trial 1008-000-125 was entirely conducted at international sites. Individual international sites were selected based on the number of enrolled subjects. Table 2 summarizes the OSI inspected sites.

Table 2. OSI Inspected Clinical Sites.

Clinical Site and PI	Protocol ID (Number of Subjects)	Inspection Dates	Final Classification
Site: 004 PI: Dr. Michael J. Cousins Address: Royal North Shore Hospital Dept of Anaesthesia and Pain Management Pacific Highway St. Leonards, NSW 2065 Australia	1008-000-125 (33 subjects)	May 7-10,2012	Pending Interim classification: VAI
Site: 006 PI: Dr. Guy M. Bashford Address: Port Kembla Hospital (Illawarra) Cowper Street Warrawong, NSW 2502 Australia	1008-000-125 (21 subjects)	April 30 - May 3,2012	Pending Interim classification: VAI
Site: 1072 PI: Dr. Michael Joseph Creamer Address: Rehabilitation Medical Group, P.A. 100 West Gore Street Suite 203 Orlando, FL 32806 United States	A008-1107 (13 subjects)	March 13-23, 2012	VAI
Site: 1100 PI: Alina Agafina Address: St. Petersburg State Healthcare Institution City Hospital # 40 Kurortnogo Administrativnogo Rajona Borisova ulitsa, 9, lit. B, Sestroretsk St. Petersburg 197706 Russian Federation	A008-1107 (16 subjects)	April 2-6,2012	Pending Interim classification: NAI

Abbreviations: NAI, No Action Indicated (no deviation from regulations); OAI, Official Action Indicated (significant deviations from regulations); PI, principal investigator; VAI, Voluntary Action Indicated (Deviation(s) from regulations).

Source: Adapted from Dr. Lauren Iacono-Connor's Clinical Inspection Summary Memorandum (May 16, 2012), p 4.

Site 1072 (Trial A008-1107)

According to the OSI review, inspectional findings for site 1072 revealed minor isolated observations that were not of a systemic nature and should not significantly impact the data generated by this site.

Additionally, the FDA field investigator issued a Form FDA 483 citing one inspectional observation for failure to adhere to protocol. Three subjects (10721006, 10721010, 1072012) were found to be taking concomitant pain medications during the study but not in accordance with the protocol. These concomitant medication usages were properly recorded by the site in source records and subject case report forms; however, the Sponsor failed to identify these as protocol violations in the data listings submitted to the application.

Refer to Section 5.3 under Trial 1107, Protocol Deviations (Table 24) for the exploratory analysis undertaken to determine the potential impact of unreported concomitant medication protocol violations on the primary efficacy findings.

Sites 004 and 006 (Trial 1008-000-125) and 1100 (Trial A008-1107)

According to the OSI review, preliminary inspectional findings for sites 004 and 006 revealed isolated observations that were not of a systemic nature and should not importantly impact safety or efficacy data generated by these sites. Based on preliminary inspectional findings for site 1100, there were a few minor protocol deviations noted; however, none of these should importantly impact data reliability.

OSI's Overall Assessment of Findings and Recommendations

Although regulatory violations were noted, they are unlikely to significantly impact primary safety and efficacy analyses for Study A0081107 and Study1008-000-125. Therefore, the data from these studies, submitted in support of NDA 21446 S-028, may be considered reliable based on available information.

Note: The inspectional findings at sites 004, 006, and 1100 are based on preliminary findings, and an addendum will be generated if OSI's conclusions change based on their review of the Establishment Inspection Report.

3.3 Financial Disclosures

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", attached with a list of 269 of the 272 investigators listed in the study reports, certifying that they had no financial interests or arrangements to disclose. One is listed as a Due Diligence investigator.

Of the 272 clinical investigators listed in the study reports, the remaining 2 had financial interests required to be disclosed under 21 CFR Part 54 and submitted Form FDA 3455 "Disclosure: Financial Interests and Arrangements of Clinical Investigators."

One of the clinical investigators with financial disclosures marked the checkbox classifying it as “any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.” This investigator received a total of \$70,750.00 in payments from the Sponsor between 2006 and 2011, predominantly for speaking engagements. This investigator was the principal investigator at site [REDACTED] (b) (6) which randomized [REDACTED] (b) (6) subjects.

The second clinical investigator with financial disclosures marked the checkbox classifying it as “any significant equity interest as defined in the 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.” This investigator reported ownership of stock or options valued at \$108,400.00. This investigator was the principal investigator at site [REDACTED] (b) (6) which randomized [REDACTED] (b) (6)

Given the small numbers of subjects randomized at individual clinical trial sites run by investigators with financial disclosures, the possibility of bias in the results based on financial interests is unlikely.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

No new data was submitted to or reviewed by the other review disciplines (i.e., chemistry manufacturing and controls [with the exception of an environmental assessment], clinical microbiology, preclinical pharmacology/toxicology, and clinical pharmacology). See section 2.1 (p 10) for relevant clinical pharmacology background information.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials conducted in support of this supplemental NDA for pregabalin are listed in Table 3 below).

Table 3. Clinical Trials Submitted in Support of this Application.

Clinical Trial	Population	Number of Subjects	Relevance
<i>Clinical Trials Contributing to Efficacy Review (Controlled Trials)</i>			
1008-000-125	CNP-SCI	137	Contains efficacy data in the CNP-SCI population
A008-1107	CNP-SCI	219	Contains efficacy data in the CNP-SCI population
<i>Clinical Trials Contributing to Safety Review</i>			
1008-000-125	CNP-SCI	137	Contains safety data for the CNP-SCI population
A008-1107	CNP-SCI	219	Contains safety data for the CNP-SCI population
1008-000-202	CNP-SCI	103	<ul style="list-style-type: none"> • Open-label extension of trial 1008-000-125 • Contains safety data for the CNP-SCI population
<i>Other</i>			
A008-1063	CPSP	219	Subject population is not representative of the indicated patient population
A008-1252	CNP-SCI CPSP CNP-MS	103	<ul style="list-style-type: none"> • Ongoing open-label extension of trial A008-1107 • Also enrolled CPSP and CNP-MS subjects (as requested by Japanese regulatory authority) • 63% (65/103) of subjects had either CPSP or CNP-MS • Subject population is not representative of the indicated patient population

Abbreviations: CNP-SCI, central neuropathic pain associated with spinal cord injury; CPSP, central poststroke pain; CNP-MS, central neuropathic pain associated with multiple sclerosis.

Source: Derived from Applicant's submission, sNDA 21446-028.

5.2 Review Strategy

This medical officer reviewed trials A008-1107 and 1008-000-125 (controlled trials) for efficacy and trials A008-1107, 1008-000-125, and 1008-000-202 (controlled and uncontrolled trials) for safety in the CNP-SCI. Note that these trials will be referred to as 1107, 125, and 202 throughout the remainder of this review. The design and results from the individual controlled trials submitted in support of efficacy in the indicated population are reviewed in Section 5.3, Discussion of Individual Studies/Clinical Trials. The primary and major secondary efficacy analyses of trials 125 and 1107 were confirmed by David Petullo, MS, statistical reviewer.

The Applicant submitted safety information from two additional trials as part of this submission. A008-1063 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose trial conducted in subjects with central poststroke pain. A008-1252 is an ongoing open-label extension of trial 1107 being conducted in Japan in subjects with CNP-SCI, central neuropathic pain associated with multiple sclerosis, or central poststroke pain.¹ The subject population in both of these trials is not representative of the indicated patient population. However, these trials were briefly reviewed to detect potential safety signals for pregabalin (see relevant sections in Section 7, p 89 of this review).

Deleted Sections

- Sub-sections 4.1, 4.2, 4.3, and 4.4 were deleted from Section 4 because no new data was submitted related to other review disciplines.

See Section 7, Summary of Safety (p 88), for a listing of deleted sections in the safety review.

5.3 Discussion of Individual Studies/Clinical Trials

Trial 125²

“A 12-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multicenter Study of Pregabalin for Treatment of Chronic Central Neuropathic Pain after Spinal Cord Injury”

Conducted 12 June 2002 to 29 July 2004

Eight centers enrolled subjects, all of which were located in Australia.

Protocol

Objective/Rationale

The primary objective of the clinical trial was to have evaluated the efficacy of pregabalin compared with placebo for the treatment of central neuropathic pain in spinal cord injury.

The clinical trial was also to be designed to evaluate the following secondary objectives:

- To evaluate the safety and tolerability of pregabalin in the treatment of CNP-SCI.

¹ The inclusion of subjects with central neuropathic pain associated with multiple sclerosis and central poststroke pain in addition to CNP-SCI was requested by the Japanese regulatory authority.

² Trial 125 was not conducted under an IND.

- To determine whether decreases in pain experience are associated with enhanced quality of life as measured by both general and specific measures of life satisfaction.

Overall Design

This was to be a randomized, double-blind, placebo-controlled, parallel-group, flexible dose, multicenter clinical trial with 2 phases: a 1-week baseline phase and a 12-week double-blind treatment phase. The treatment phase was to consist of a 3-week dose adjustment period followed by stable dosing for the remainder of the trial. Study medication was to be discontinued at the end of the treatment phase or eligible subjects could continue pregabalin treatment in open-label trial 202 after the termination visit. Subjects who discontinued treatment rather than continuing in the open-label trial were to have follow-up one week after stopping study medication.

Subjects were to be allowed to enter the open-label extension trial at any time after starting the double-blind treatment phase.

Treatment

Pregabalin or matched placebo capsules were to be taken orally, twice a day. Subjects randomized to the treatment arm were to receive escalating doses of pregabalin 150, 300, and 600 mg/day, titrated based on response and tolerability. Subjects randomized to the placebo arm were to be supplied study medication to mimic the dosing schedule of subjects randomized to the pregabalin arm.

All study drug supplies were to be stored in a locked area, in accordance with the manufacturer's instructions, separate from normal hospital or practice stocks.

Reviewer comment: Trial 125 was to be a flexible dose study consisting of a 3-week dose adjustment period followed by a 9-week stable dose period for a total of 12 weeks of study drug treatment. The target pregabalin dose was to be between 150 mg and 600 mg per day. Subjects were to be started at 150 mg per day at the beginning of the dose adjustment period and titrated up to a maximum dose of 600 mg per day based on efficacy and tolerability. Although this trial was conducted prior to the Agency's advice that the duration of treatment in chronic pain trials should consist of 12 weeks of fixed dosing, the study design appears acceptable as the daily dose for the entire 12-week double-blind treatment phase was to be in the final target dose range of 150-600 mg per day.

Population and Procedures

Inclusion/Exclusion Criteria

Planned enrollment was to be 132 subjects with chronic central neuropathic pain after spinal cord injury, randomized 1:1 to an active treatment arm or placebo arm.

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

General Inclusion Criteria

- At least 18 years of age, male or female
- Outpatient and inpatient subjects
- Written informed consent obtained³
- An immediate neurological investigation within the acute admission period, and a subsequent full neurological examination (including a radiographic investigation of the spine)
- Traumatic spinal cord injury of at least one year duration with a nonprogressive (chronic) stage of at least six months duration (presence of a nonprogressive spinal cord injury; a clinical diagnosis of nonprogressive spinal cord injury is acceptable)

Pain Inclusion Criteria

- A score of at least 40 mm on the visual analogue scale (VAS) of the Short-Form-McGill Pain Questionnaire (SF-MPQ) at both the screening and randomization visits
- At least four completed pain diaries with an average daily pain score of at least four during the seven days prior to randomization
- The pain is a chronic central neuropathic pain, as determined by the following definitions:
 - Definition of chronic pain: Pain symptoms are required to have persisted continuously for at least three months or with remissions and relapses for at least six months and to have started after spinal cord injury
 - Definition of central neuropathic pain: Central pain is defined by the IASP (International Association for the Study of Pain) Classification of Chronic Pain as regional pain caused by a primary lesion or dysfunction of the central nervous system

Subjects were to be excluded for the following criteria:

- Pregnant or lactating women; women of childbearing potential not using an acceptable method of contraception
- Donation of blood or blood products for transfusion during the 30 days prior to initiation of treatment with study drug, or at any time during the study
- Participation in any other studies involving investigational or marketed products, concomitantly or within 30 days prior to entry in the study
- Specific systemic diseases or other medical conditions that would interfere with the evaluation of the therapeutic response or safety of the study drug

³ In subjects physically unable to sign the informed consent (e.g., tetraplegic individuals), this could be done on behalf of the subject (e.g., by the caregiver).

- Other severe pain that may confound assessment or self-evaluation of the central pain due to spinal cord injury (if patients have central pain and musculoskeletal pain, they must be able to make a distinction between the two)
- Unable and/or unlikely to comprehend and/or follow the protocol
- Alcohol and/or any other drug abuse
- Previous participation in this trial or in any other clinical trial with the study drug
- A previous history of intolerance or hypersensitivity to the study drug(s) (including background drugs), or to drugs with similar chemical structures
- Treatment with gabapentin during the study; if patients are on gabapentin, gabapentin must be withdrawn at least seven days prior to visit V1
- Treatment with antidepressants and narcotic analgesics on an unstable dose regimen; for antidepressants and narcotic analgesics, dose must be stable within the last 30 days prior to the visit V1
- Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol
- Any other condition which, in the investigator's judgment, might increase the risk to the subject or decrease the chance of obtaining satisfactory data to achieve the objectives of the study
- Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study, and/or evidence of an uncooperative attitude
- The anticipated need for surgery during the study
- Clinically significant abnormal ECG
- Creatinine clearance <60 mL/min (estimated from serum creatinine, body weight, age, and sex using the Cockcroft and Gault equation). Subjects who have an estimated creatinine clearance ≤ 60 mL/min by this screening method may, at the investigator's discretion, have their creatinine clearance measured with a 24-hour urine collection, performed at the central laboratory. If this 24-hour urine creatinine clearance is >60 mL/min, the subject may be randomized.
- White blood cell count <2500/mm³, neutrophil count <1500/mm³, platelet count <100 x 10³/mm³

Concomitant Medications

Any medication the subject takes other than study drug was to be considered concomitant medication. Concomitant treatment with analgesics, anti-inflammatories, and antidepressants was to be allowed with the following restrictions:

- Subjects taking nonnarcotic analgesics (e.g., acetaminophen [paracetamol]), narcotic analgesics (e.g., opioids), tricyclic antidepressants (e.g., amitriptyline), selective serotonin reuptake inhibitors (e.g., sertraline), anti-

- inflammatories (e.g., acetylsalicylic acid), or nonsteroidal anti-inflammatories were to be required to be on a stable dosing regimen (for antidepressants and narcotic analgesics, stable dose within the last 30 days prior to Visit 1 was to be required), and therapy was not to be initiated during the study.
- Transcutaneous electrical nerve stimulation and concomitant treatment with antiepileptic drugs (excluding gabapentin) was also to be allowed, at stable levels/dosages.
 - If subjects were on gabapentin, gabapentin was required to be withdrawn at least 7 days prior to Visit 1.
 - Benzodiazepines or skeletal muscle relaxants were to be permitted as needed to relieve spasticity (benzodiazepines were to be taken at least six hours prior to any clinic visit)
 - Potential retinal toxic medications (hydroxychloroquine, deferoxamine, thioridazine, vigabatrin) were to be prohibited.

Procedures

General

Subjects were to score pain and sleep interference on 11-point scales every day upon awakening, and record the results in a diary. The number of study medication capsules taken during the previous 24 hours were also to be recorded in the daily diary.

Study drug compliance was to be defined as the ingestion of between 80 and 125% of the theoretically assigned dose. If subjects were found to be non-compliant during one of the interim visits, the importance of compliance with study procedures was to be reinforced. These subjects were to be withdrawn if they were to be found non-compliant on the next visit.

The visit schedules are outlined in the following paragraphs according to clinical trial phase along with the procedures that were to be performed at those times. Also, refer to Table 4, the schedule of activities.

Baseline Phase (1 week)

The baseline phase was to start with the screening visit (Visit 1) and was to last one week. No study medication was to be dispensed during this phase. If a subject was taking medications required to be withdrawn for eligibility into the trial, written informed consent was to be obtained before the prohibited medications were to be withdrawn.

Screening for inclusion into the clinical trial was to occur at Visit 1. A screen failure was to be any subject who signs an informed consent, but is found ineligible for randomization into the double-blind phase of the trial. Demographic information, reason for not entering the double-blind treatment phase, and withdrawals due to adverse events were to be monitored and collected on screen failure subjects.

Visit 1 (screening visit):

- Collect spinal cord injury history including information on the accident, neurological and radiological lesion level, completeness or incompleteness of the injury, type of injury (paraplegia or tetraplegia), and zone of partial preservation.
- Instruct subjects on the proper completion of daily diaries for pain and sleep assessments.
- Perform additional procedures as detailed in the schedule of activities (Table 4)

Double-Blind Treatment Phase (12 weeks)

The double-blind treatment phase was to consist of a 3-week dose adjustment period followed by 9 weeks of stable dosing. Subjects were to be randomized 1:1 to the treatment arm or the placebo arm at the baseline visit (Visit 2). Subjects were to take the first dose of study medication on the morning of the day after Visit 2.

Dose Adjustment:

Study medication dose was to be adjusted according to Figure 1 below. Beginning at Visit 3 (end of week 1), subjects whose pain has been reduced by a minimum of 50% during the preceding week were to be allowed to continue on the current dose for the remainder of the study or were to be allowed to be titrated to achieve further pain reduction as directed by the investigator. After the initial dose increase, doses were to be reduced for tolerability. Doses were to be required to be stable no later than Visit 5 (end of week 3).

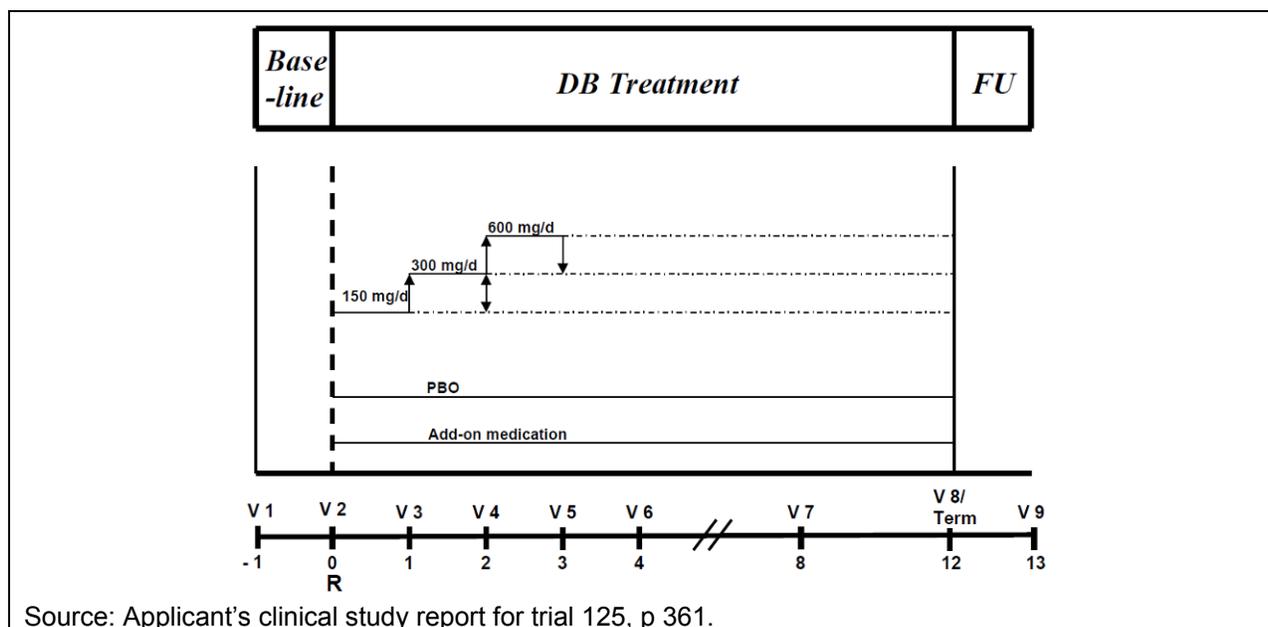
Visit 2 (baseline visit; Week 0, Day 0):

- Collect and review daily diaries.
 - In order to be randomized, subjects were to have completed at least four pain diaries within the last seven days with an average pain score of four or higher.
- Review all laboratory and ECG results.
- Dispense diaries for pain and sleep interference.
- Perform additional procedures as detailed in the schedule of activities ().

Visits 3 (Week 1, Day 7), 4 (Week 2, Day 14), and 5 (Week 3, Day 21):

- Dispense daily diaries for pain and sleep interference.
- Record dosing changes.
- Perform additional procedures as detailed in the schedule of activities (Table 4).

Figure 1. Trial 125: Protocol for Study Drug Administration.



Stable Dosing:

At the end of the dose adjustment period, subjects were to remain on a stable dosing regimen for the remaining nine weeks of the clinical trial.

Visits 6 (Week 4, Day 28) and 7 (Week 8, Day 56):

- Dispense daily diaries for pain and sleep interference.
- Perform additional procedures as detailed in the schedule of activities (Table 4).

Visit 8 (termination visit; Week 12, Day 84):

- Assess Patient Global Impression of Change.
- Perform additional procedures as detailed in the schedule of activities (Table 4).

The procedures performed at Visit 8 were to be completed when a subject finishes the double-blind treatment phase or when a subject withdraws prematurely.

For subjects entering the open-label extension trial (202), Visit 8 was to correspond with Visit 1 of the open-label trial.

Follow-up Period (1 week)

A 1-week follow-up period was to occur at the end of the trial.

Visit 9 (follow-up/final visit; Week 13, Day 91):

This visit was to pertain only to those subjects who do not enter the open-label extension trial. The procedures that were to be performed at this visit are detailed in the schedule of activities (Table 4).

Extra Visit (any time during the study)

The extra visit was to assess and record adverse events, review study medication dosing, review concurrent medications, and perform clinical labs (optional). This visit was to take place as needed.

Table 4. Trial 125: Schedule of Activities.

Study Periods and Follow-Up	Double-Blind Treatment (12 Weeks)								Follow-Up
Clinic Visit Number	V1 Screening	V2 Baseline	V3	V4	V5	V6 ^f	V7 ^f	V8/Term	V9
End of Weeks in Study	-1	0	1	2	3	4	8	12	13
Study Day	-7	0	7	14	21	28	56	84	91
Informed Consent	X								
Inclusion/Exclusion Criteria, Patient Demographics	X								
Medical/Surgical/SCI History	X								
Physical Exam Incl Peripheral Edema Assessment	X ^g			X ^d		X ^d	X ^d	X	
Abbreviated Neurological Exam (ASIA score)	X							X	
12-Lead ECG	X							X	
SF-McGill Pain Questionnaire	X	X	X	X	X	X	X	X	X
Daily Diaries (Pain, Sleep)	X	X	X	X	X	X	X	X	X
Patient Global Impression of Change								X	
MOS Sleep-Scale		X						X	
HADS; SWLS; Q-LES-Q/General activities; BSI-18		X						X	
Adverse Events		X	X	X	X	X	X	X	X
Clinical Laboratories (Hematology/Chemistry/Urinalysis)	X ^b			X		X		X	
FOR SELECTED SITES ONLY: <i>VEGF/PDGF, Urine bFGF, and Platelet Ultrastructure^h</i>	X					X		X	
Pregnancy Test ^c	X			X		X	X	X	
Prior and Concurrent Medications	X	X	X	X	X	X	X	X	X
Study Medication Dispensing/Dosing		X	X	X	X	X	X		
Patient Status :—End of Baseline		X							
Patient Status :—End of Double-Blind Treatment								X	

a Whenever patient withdraws from or completes the study
 b Estimated creatinine clearance is calculated at V1. Fasting lipid profiles are measured at V1 and V8/Termination only.
 c Serum pregnancy test at V1. All other pregnancy tests will be urine pregnancy tests unless positive, which would then be confirmed with a serum pregnancy test.
 d Vital signs, weight, and edema assessment only
 e V9/Follow-up is only performed for patients not entering open-label Study 1008-202.
 f Telephone contact has to be made with the patient between V6 and V7 (after 6 weeks in study) and between V7 and V8 (after 10 weeks in study) to ensure performance of the self-assessed VAS (VAS section of SF-MPQ), and to ensure compliance with study procedures and assess adverse events.
 g New York Heart Association classification will be done at V1.
FOR SELECTED SITES ONLY:
 h Sites may perform either: 1) platelet associated vascular endothelial growth factor (VEGF)/platelet-derived growth factor (PDGF), urine basic fibroblast growth factor (bFGF), and platelet ultrastructure, or 2) only platelet associated VEGF/PDGF and urine bFGF.⁴

Abbreviations: ASIA, American Spinal Injury Association; SF-McGill Pain Questionnaire, short form McGill Pain Questionnaire; MOS, Medical Outcomes Study; HADS, Hospital Anxiety and Depression Scale; SWLS, Satisfaction With Life Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire; BSI, Brief Symptom Inventory.

Source: Applicant's Clinical Study Report for trial 125, p 404-5.

Subject Withdrawal

Subjects were to be discontinued from the study at any time, in the best interest of the subject, at the discretion of the investigator.

Subjects could also be withdrawn from the study for the following reasons:

- Study drug noncompliance
- Adverse events

⁴ **Rationale:** To determine the effect of pregabalin on platelet associated Vascular endothelial growth factor (VEGF)/platelet-derived growth factor (PDGF), platelet ultrastructure, and urine basic fibroblast growth factor (bFGF) in humans. Platelet ultrastructure was to be performed at sites only with adequate and available laboratory resources.

- Medical follow-up of any adverse event or significantly abnormal laboratory value was to continue until the abnormality resolves or an adequate medical explanation is apparent.

Evaluations/Endpoints

Subjects were to complete daily pain rating and sleep scales upon awakening and record the results in a diary. The daily pain scale was to be rated on an 11-point numerical scale ranging from 0 (no pain) to 10 (worst possible pain). Pain-related daily sleep interference was to be rated on an 11-point scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep).

The prespecified primary efficacy variable was to be the weekly mean pain score at endpoint, defined as the mean of the last seven post-randomization entries of the daily pain diary while on study drug. This was to include the day after the last day of dosing. If less than seven diary entries are present, the mean of the available post-randomization entries was to be used.

Key secondary efficacy variables identified in the protocol included:

- Weekly mean sleep interference score at endpoint
- Medical Outcome Study (MOS) optimal sleep score at endpoint
- SF-MPQ VAS score at endpoint
- Hospital Anxiety and Depression Scale (HADS) anxiety subscale score at endpoint
- Patient global impression of change (PGIC) at endpoint

Additional Secondary Variable

- Weekly mean pain score⁵

Safety Assessments

- Adverse events (regardless of treatment group or suspected causal relationship to study drug)
- Physical examination (any negative changes from the entry examination were to be recorded as adverse events)
- Abbreviated neurologic examination (based on the ASIA impairment scale)
- Laboratory tests
 - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count
 - Chemistry: amylase, AST, ALT, albumin, alkaline phosphatase, B-12/folate (visit 1), blood urea nitrogen, creatine phosphokinase, creatinine, estimated creatinine clearance (visit 1), c-reactive protein (visit 1),

⁵ The weekly mean pain score was to be calculated each week during the double-blind treatment phase as the mean of the seven entries of the daily pain diary from that week (or fewer if seven entries were not available).

- electrolytes (sodium, potassium, chloride, calcium), glucose, serum protein electrophoresis (visit 1), serum pregnancy test, total protein, total bilirubin, uric acid
- Urinalysis: colorimetric urine protein, pH, specific gravity, glucose, microscopic sediment examination
- All clinically important abnormal laboratory tests occurring during the study were to be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable, or until an explanatory diagnosis is made.
- ECG
- Prior and concomitant medications
 - Prior medications taken up to 30 days before Visit 1 were to be recorded.

Refer to Table 4 for the frequency at which the safety assessments were to be performed (unless otherwise noted in the above list).

Exploratory Assessments

- VEGF, PDGF, and platelet morphology for selected sites only
- Urine bFGF for selected sites only

Statistical Plan

The primary efficacy variable was to be the weekly mean pain score at endpoint, defined as the mean of the last seven post-randomization entries of the daily pain diary while on study drug. This was to include the day after the last day of dosing. The primary efficacy analysis was to be performed on the intent-to-treat (ITT) population, defined as all randomized subjects who take at least one dose of study medication and have at least one post-randomization efficacy assessment on any efficacy scale.⁶ The endpoint mean pain score (last observation carried forward; LOCF) was to be analyzed using an analysis of covariance (ANCOVA) model with treatment and center as fixed effects and baseline mean pain score as a covariate.

Supplemental analyses of the primary efficacy variable were to include:

- ANCOVA model with tests for the interaction terms, treatment by baseline and treatment by center
- ANCOVA model with baseline observation carried forward (BOCF) imputation method – endpoint mean score was to be used for the completers and the mean pain score at baseline was to be used for the noncompleters
- Responders – the proportion of subjects with at least 30% and at least 50% reduction in mean pain score from baseline to endpoint using logistic regression

⁶ One subject in the pregabalin group discontinued due to an adverse event after three days of double-blind treatment and had no post-baseline efficacy data. This was the only subject the Applicant excluded from the ITT population. This subject was included in the statistical reviewer's primary efficacy analysis.

- Percentages of subjects with reductions in pain, including all possible values from 0 to 100%, at week 12 and at endpoint⁷

The secondary analyses were to be performed using the ITT population. Weekly mean pain score at each week during the double-blind treatment phase was to be analyzed using an ANCOVA model with treatment and center as factors, and the baseline value as a covariate. Repeated measures analysis was also to be performed on the weekly mean pain diary scores. No adjustments were to be made to control for multiplicity.

Based on previous pregabalin studies in pain and a review of literature on gabapentin and other antiepileptic drug's use in central pain, the Applicant determined a difference of 1.3 points in the weekly mean pain diary score at the last post-baseline visit could be detected between the pregabalin and placebo groups at 90% power with 57 subjects randomized per group. Because some subjects are expected to discontinue before their post randomization pain score is obtained, the number randomized per treatment arm was to be increased by 15% to 66.

The safety population was to be defined as all subjects in the randomized population who took at least one dose of study medication. Safety parameters; including rates of treatment-emergent adverse events, median changes in laboratory variables, rates of treatment-emergent clinically significant abnormal laboratory values, changes in vital signs and weights, rates of concurrent medication use, physical examination findings, ECG findings, and rates of discontinuation; were to be summarized.

Results

Subject Overview

Of the 165 subjects screened, 70 were assigned to the pregabalin group and 67 to the placebo group. All 67 subjects in the placebo group and 69 of the 70 (98.6%) subjects in the pregabalin group were included in the ITT population.⁸ All randomized and treated subjects were evaluated for adverse events.

Subject Disposition

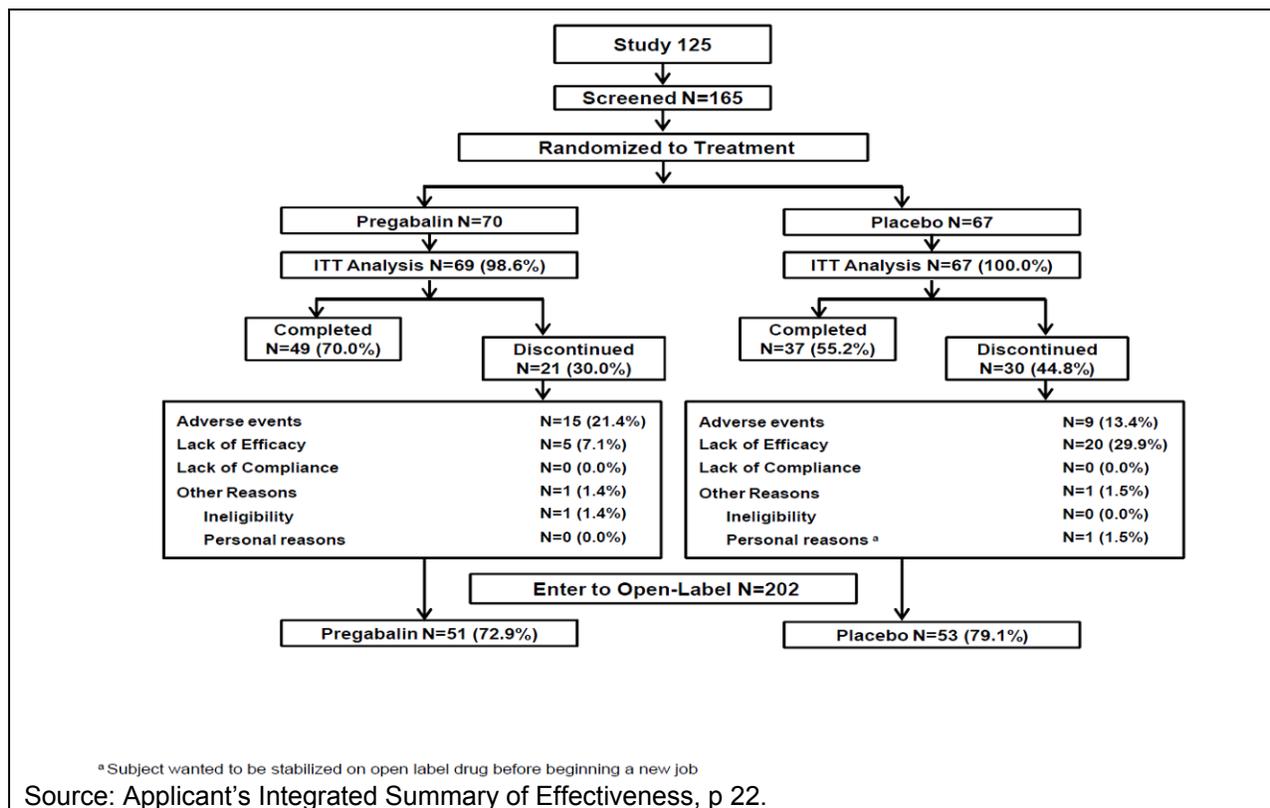
Among screened subjects, 137 were randomized to study treatment, including 67 subjects in the placebo group and 70 subjects in the pregabalin group. A greater percentage of subjects in the pregabalin group (70%) completed the study as compared to the placebo group (55.2%). The most frequent reason for discontinuation in the pregabalin group was adverse events (21.4%), whereas the most frequent reason for discontinuation in the placebo group was lack of efficacy (29.9%). Overall, most

⁷ Added with Applicant's Statistical Analysis Plan Amendment 2, dated 23 September 2004

⁸ Subject 6020, in the pregabalin group, discontinued after 3 days of double-blind treatment and had no post-baseline efficacy data.

subjects entered the open-label extension trial. Subject disposition for trial 125 is summarized in Figure 2.

Figure 2. Trial 125: Subject Disposition.



Demographics

The demographic information for trial 125 (safety population) is summarized in Table 5 below.⁹ Most subjects were male (83.2%), almost all were white (97.1%), and the mean age was 50.1 years (range 21-80 years).

Reviewer comment: The treatment groups were comparable with respect to demographic data. The predominance of male subjects is reflective of and consistent with the epidemiology of the underlying disease process, spinal cord injury. The racial make-up of the study groups is reflective of the racial make-up of Australia.¹⁰

⁹ Only one subject in the safety population (from the pregabalin group) was not in the ITT population.

¹⁰ Trial 125 was entirely conducted in Australia. The ethnic make-up of Australia is 92% white, 7% Asian, and 1% aboriginal and other, according to the Central Intelligence Agency (CIA) World Fact Book (accessed online 5/17/2012).

Table 5. Trial 125: Demographic and Baseline Characteristics (Safety Population).

	Placebo (N=67)	Pregabalin (N=70)	Total (N=137)
Age (years), n (%)			
18 - 64	58 (86.6)	59 (84.3)	117 (85.4)
65 - 74	7 (10.4)	8 (11.4)	15 (10.9)
75 - 84	2 (3.0)	3 (4.3)	5 (3.6)
N	67	70	137
Mean	49.8	50.3	50.1
SD	14.2	14.3	14.2
Median	52	51	51
Range	21 - 80	23 - 78	21 - 80
Sex, n (%)			
Male	54 (80.6)	60 (85.7)	114 (83.2)
Female	13 (19.4)	10 (14.3)	23 (16.8)
Race n (%)			
White	66 (98.5)	67 (95.7)	133 (97.1)
Asian or Pacific Islander	1 (1.5)	2 (2.9)	3 (2.2)
Other	0	1 (1.4)	1 (0.7)
Weight (kg)			
N	67	70	137
Mean	77.2	79.4	78.3
SD	17.6	17.2	17.4
Median	77	78.3	77.6
Range	41 - 140	50 - 126	41 - 140
Height (cm)			
N	67	70	137
Mean	172.5	173.6	173.0
SD	10.5	9.5	10.0
Median	173	174.6	173.0
Range	145 - 199	153 - 193	145 - 199
Hospitalized n (%)			
Yes	3 (4.5)	1 (1.4)	4 (2.9)
No	64 (95.5)	69 (98.6)	133 (97.1)

Source data: [Table 9.1.2.1](#)

Source: Applicant's clinical study report for trial 125, p 38.

Screening/Baseline Disease Characteristics

The pregabalin and placebo groups were comparable with regard to spinal cord injury history, and this information is summarized in the table below (Table 6).

Table 6. Trial 125: History of Spinal Cord Injury (Safety Population).

	Placebo (N=67)	Pregabalin (N=70)	Total (N=137)
SCI Type - n (%)			
Paraplegia	38 (56.7)	41 (58.6)	79 (57.7)
Tetraplegia	29 (43.3)	29 (41.4)	58 (42.3)
Cause of SCI - n (%)			
Gun Shot	0	1 (1.4)	1 (0.7)
Accident	59 (88.1)	57 (81.4)	116 (84.7)
Other	8 (11.9)	12 (17.1)	20 (14.6)
Neurologic Lesion Level - n (%)			
Complete	34 (50.7)	34 (48.6)	68 (49.6)
Incomplete	33 (49.3)	36 (51.4)	69 (50.4)
Classification of Central Neuropathic Pain - N (%)			
Continuous and persistent pain	59 (88.1)	62 (88.6)	121 (88.3)
Persistent pain with remissions and relapses	8 (11.9)	8 (11.4)	16 (11.7)
Primary Symptom Descriptor - n (%)			
Allodynia	2 (3.0)	8 (11.4)	10 (7.3)
Burning Pain	39 (58.2)	41 (58.6)	80 (58.4)
Shooting Pain	18 (26.9)	11 (15.7)	29 (21.2)
Other pain	8 (11.9)	10 (14.3)	18 (13.1)
Duration of Pain (months)			
N	67	70	137
Mean (SD)	125.2 (118.0)	119.8 (91.8)	122.4 (105.1)
Median	84	97	90
Range	14 - 552	4 - 480	4 - 552

Source data: [Table 9.1.2.3.1](#)

Source: Applicant's clinical study report for trial 125, p 41.

Prior and Concomitant Drug Treatments

Nearly all subjects in the safety population took at least 1 concomitant medication during the study (94.0% and 97.1% in the placebo and pregabalin groups, respectively). The most common classes of medications taken in both groups were central nervous system acting agents, including baclofen (37.3%-placebo; 54.3%-pregabalin), benzodiazepines (37.3%-placebo; 40%-pregabalin; e.g., diazepam, clonazepam, and temazepam), and tricyclic antidepressants (17.9%-placebo; 34.3%-pregabalin).

68.7% of subjects in the placebo group and 75.7% of subjects in the pregabalin group were taking concomitant analgesics, anti-inflammatories, and antidepressants for pain during the study. The most commonly taken ($\geq 10\%$ of subjects in either treatment group) analgesics, anti-inflammatories, and antidepressants for pain were acetaminophen (32.8%-placebo; 30.0% pregabalin), acetaminophen with codeine (10.4%-placebo; 4.3%-pregabalin), morphine (11.9%-placebo; 8.6%-pregabalin), oxycodone (13.4%-placebo; 5.7%-pregabalin), amitriptyline (6.0%-placebo; 17%-pregabalin), and tramadol (10.4%-placebo; 10.0%-pregabalin).

Reviewer comment: A higher frequency of placebo subjects were on opioids, and a higher frequency of pregabalin subjects were on tricyclic antidepressants. The differences between treatment groups were relatively minor and subjects requiring treatment with these concomitant medications were required to be on a stable dosing regimen 30 days prior to Visit 1. Therefore, the differences between treatment groups are not anticipated to have a big impact on efficacy or safety outcomes.

Table 7 below summarizes concomitant medications taken by ≥10% of subjects for any indication.

Table 7. Trial 125: Concomitant Medications.

	Placebo N=67 n (%)	Pregabalin N=70 n (%)
Number (%) of Subjects with Medications	63 (94.0)	68 (97.1)
Baclofen	25 (37.3)	38 (54.3)
Oxybutynin	18 (26.9)	28 (40.0)
Acetaminophen (paracetamol)	22 (32.8)	21 (30.0)
Methenamine	15 (22.4)	16 (22.9)
Diazepam	13 (19.4)	17 (24.3)
Amitriptyline	7 (10.4)	16 (22.9)
Docusate sodium and sennaside (Coloxyl with Senna)	10 (14.9)	13 (18.6)
General nutrients	9 (13.4)	10 (14.3)
Bisacodyl	8 (11.9)	10 (14.3)
Sennaside (Senna)	11 (16.4)	6 (8.6)
Cephalexin	6 (9.0)	10 (14.3)
Tramadol	7 (10.4)	7 (10.0)
Morphine	8 (11.9)	6 (8.6)
Oxycodone	9 (13.4)	4 (5.7)
Laxatives	3 (4.5)	9 (12.9)
Temazepam	7 (10.4)	5 (7.1)
Docusate	9 (13.4)	3 (4.3)
Acetaminophen with codeine (Panadeine Co)	8 (11.9)	3 (4.3)

Source data: [Table 9.1.3.2](#)

Source: Applicant's Clinical Study Report for trial 125, p 42.

Protocol Violations

The Applicant reported protocol violations for subjects who entered the study even though they did not meet all of the entrance criteria and subjects who deviated from the protocol during the trial. The Applicant considered most protocol violations to be minor, and did not exclude any subjects from the efficacy analysis due to a protocol violation. The major protocol violations are summarized in the table below (Table 8).

Table 8. Trial 125: Summary of Major Protocol Violations.

Protocol Violation	Trial 125	
	Placebo (N=67)	Pregabalin (N=70)
Did not satisfy entry or randomization criteria	3 (4.5%)	3 (4.3%)
Used prohibited medications during study	5 (7.5%)	4 (5.7%)
Not compliant with study medication (i.e., more than 4 consecutive days without study medication)	2 (3%)	2 (2.9%)

Source: Clinical reviewer

Reviewer comment: The frequency of major protocol violations (Table 8) is low and relatively comparable across treatment groups; therefore, it is unlikely that these protocol violations biased the primary efficacy analysis.

Subject Evaluation Groups

The composition of the evaluation groups is summarized in Table 9 below.

Reviewer comment: The Applicant excluded one subject from the ITT population; however, this subject was included in the statistical reviewer's primary efficacy analysis.

Table 9. Trial 125: Subject Evaluation Groups.

	Placebo	Pregabalin	Total
Screened (N=165)			
Randomized and Treated, N	67	70	137
Completed, n (%)	37 (55.2)	49 (70.0)	86 (62.8)
Discontinued, n (%)	30 (44.8)	21 (30.0)	51 (37.2)
Analyzed for Safety			
Adverse Events, n (%)	67 (100.0)	70 (100.0)	137 (100.0)
Laboratory Data ^a , n (%)	66 (98.5)	69 (98.6)	135 (98.5)
Analyzed for Efficacy			
Intent-to-treat ^b , n (%)	67 (100.0)	69 ^c (98.6)	136 (99.3)
Entered Open-Label Extension Study, n (%)	53 (79.1)	51 (72.9)	104 (75.9)

Note: Percentages are based on the total number of randomized (treated) subjects in each treatment group.

^a All randomized subjects who took at least 1 dose of study medication and had at least 1 post-baseline laboratory measurement available.

^b All randomized subjects who took at least 1 dose of study medication and had at least 1 post-baseline efficacy measurement available.

^c Subject 6020, who was randomized to pregabalin, took study medication for 3 days (Listing 9.2.3) but did not have any efficacy evaluations. Listing 9.2.1 shows that this subject only had Visit 1 and 2 data. No pain diaries were collected (Listing 9.2.13) and no other efficacy data was collected (Listings 9.2.14-9.2.23).

Source data: Table 9.1.1.1

Source: Applicant's Clinical Study Report for trial 125, p 37.

Dosing Information

The planned duration of double-blind treatment was 12 weeks (84 days). The median duration of exposure was 82 days (range 5-98 days) in the placebo group and 83 days (range 2-103 days) in the pregabalin group. The tables below summarize duration of exposure (Table 10), dosing (Table 11), and compliance with study medication (Table 12) by treatment group.

Table 10. Trial 125: Duration of Treatment (Safety Population).

Cumulative duration (Days)	Placebo (N=67) n (%)	Pregabalin (N=70) n (%)
> 1	67 (100.0)	70 (100.0)
> 7	65 (97.0)	67 (95.7)
> 14	63 (94.0)	65 (92.9)
> 21	54 (80.6)	62 (88.6)
> 28	47 (70.1)	56 (80.0)
> 35	47 (70.1)	56 (80.0)
> 42	46 (68.7)	56 (80.0)
> 49	45 (67.2)	55 (78.6)
> 56	42 (62.7)	53 (75.7)
> 63	38 (56.7)	51 (72.9)
> 70	37 (55.2)	49 (70.0)
> 77	36 (53.7)	48 (68.6)
> 84	18 (26.9)	19 (27.1)
> 91	5 (7.5)	3 (4.3)
> 98	0	1 (1.4)
Median Duration	82	83
Range (Days)	5 - 98	2 - 103
Source data: Table 9.1.3.1.1		

Source: Applicant's Clinical Study Report for trial 125, p 44.

Table 11. Trial 125: Maximum and Average Daily Doses (Safety Population).

	Placebo ^a (N=67)	Pregabalin (N=70)
Maximum Daily Dose (mg/day), n (%)		
150	3 (4.5)	5 (7.1)
300	5 (7.5)	11 (15.7)
600	59 (88.1)	54 (77.1)
Overall Average Daily Dose (mg/day)		
N	67	70
Mean	438.2	387.6
SD	122.2	144.2
Median	511	388
Range	150.0 - 555.6	112.5 - 546.7
Average Daily Dose (Days 1-7)(mg/day)		
N	67	70
Mean	151.6	152.2
SD	14.5	10.7
Median	150	150
Range	75.0 - 192.9	112.5 - 192.9
Average Daily Dose (Days 8-14)(mg/day)		
N	65	67
Mean	293.9	279.5
SD	40.6	51.9
Median	300	300
Range	139.3 - 385.7	107.1 - 385.7
Average Daily Dose (Days 15-21)(mg/day)		
N	63	65
Mean	539.8	480
SD	111.3	146.6
Median	600	557
Range	150.0 - 600.0	150.0 - 600.0
Average Daily Dose (Days 22-84)(mg/day)		
N	54	62
Mean	564.5	460.1
SD	91.4	169.8
Median	600	582
Range	264.5 - 600.0	37.5 - 600.0

^a The placebo dosage is based on the number of capsules taken and the algorithm used to calculate the pregabalin dosage.

Source data: [Table 9.1.3.1.2](#)

Source: Applicant's Clinical Study Report for trial 125, p 46.

Table 12. Trial 125: Treatment Compliance (Safety Population).

	Placebo (N=67)	Pregabalin (N=70)
Dose Compliance^a		
N	67	70
Mean (%)	98.2	97.7
SD	6.9	6.5
Median (%)	100	100
Range	48.2 - 101.5	63.4 - 106.7
Study Day Compliance^b		
N	67	70
Mean (%)	95.1	94.2
SD	14.2	14.9
Median (%)	100	100
Range	0.0 - 100.0	19.3 - 100.0
Protocol Compliance,^c n (%)		
No	2 ^d (3.0)	2 ^e (2.9)
Yes	65 (97.0)	68 (97.1)
^a Dose Compliance = (number of capsules actually taken)/(number of capsules should have taken)*100 ^b Day Compliance = (number of days took correct number of capsules)/(number of days from first day of dosing to and including last day of dosing)*100 ^c Protocol Compliance = 'No' if subject had any stretch of 4 consecutive study days (up to visit 8) when he/she took no study medication, else 'Yes' ^d Subject 4018 had 13 consecutive days with no study medication; Subject 8011 had 6 consecutive days with no study medication. ^e Subject 7025 had 7 consecutive days with no study medication; Subject 4033 had 4 consecutive days with no study medication.		
Source data: Table 9.1.3.1.3, Listing 9.2.10		
Source: Applicant's clinical study report for trial 125, p 47.		

Reviewer comment: Treatment compliance was high and similar between treatment groups, and therefore does not appear to be a concern in interpreting the study results.

Efficacy Results

Primary Efficacy Analysis

The primary efficacy variable was the endpoint mean pain score based on an 11-point (0-10) numerical scale. The endpoint mean pain score was calculated based on the pain scale results from the previous seven days (or fewer if seven post-baseline entries were not available) of treatment regardless of when the subject exited the study (equivalent to LOCF imputation strategy). Table 13 below summarizes the results of the Applicant's primary efficacy analysis for the placebo and pregabalin groups.

Table 13. Trial 125: Applicant's Primary Efficacy Analysis, Mean Pain Score at Baseline and Endpoint (ITT).

	Placebo	Pregabalin	Treatment Difference (Placebo - Pregabalin) ^a		
			Estimate (S.E.)	95% CI	p-value
Baseline					
N	67	69			
Mean (SD)	6.727 (1.446)	6.540 (1.253)			
LS Mean (S.E.)	6.615 (0.174)	6.430 (0.170)	0.185 (0.230)	-0.27, 0.641	0.423
Endpoint					
N	67	69			
Mean Change	-0.454	-1.917			
LS Mean (S.E.)	6.199 (0.235)	4.665 (0.231)			
LS Mean Change	-0.433	-1.967	1.533 (0.312)	0.916, 2.150	<0.001

LS Mean = Least squares mean; S.E. = Standard error; LS Mean Change = Least squares mean of change from baseline; SD = Standard deviation; Mean Change = Mean change from baseline, 95% CI = 95% Confidence Interval.

^a Placebo - Pregabalin difference in LS Means from the ANCOVA Model with Treatment, Center, and Baseline (Baseline not included at baseline time point) as factors.

Source data: [Table 9.1.5.1.1](#)

Source: Applicant's Clinical Study Report for trial 125, p 53.

Reviewer comment: The results of the Applicant's analysis on the primary efficacy variable are statistically significant in favor of pregabalin; however, the Applicant's definition of endpoint is analogous to using an LOCF imputation strategy. This is not acceptable for a chronic pain trial in that this approach may impute a good score for a subject with a bad outcome (i.e., adverse dropout).

Supplemental Analyses

The endpoint mean pain score was analyzed, as a supplemental analysis of the primary efficacy variable, using BOCF for subjects who did not complete the trial and the endpoint scores for subjects who completed the trial (Table 14).

Table 14. Trial 125: Applicant's Analysis of Mean Pain Score at Endpoint (BOCF; ITT).

	Placebo	Pregabalin	Treatment Difference (Placebo - Pregabalin)		
			Estimate (S.E.)	95% CI	p-value
Endpoint (BOCF)					
N	67	69			
Baseline Mean	6.727	6.540			
Mean	6.389	5.225			
SD	1.914	2.012			
Median	6.571	5.571			
Range	1.286 -10.000	1.000 - 9.571			
Mean Change	-0.338	-1.315			
LS Mean	6.252	5.250			
S.E. of LS Mean	0.207	0.204			
LS Mean Change	-0.380	-1.382	1.003 (0.276)	0.457, 1.548	<0.001
Endpoint, test for treatment by center interaction ^a			0.613		
Endpoint, test for treatment by baseline interaction ^b			0.013		

LS Mean = Least squares mean; S.E. = Standard error; LS Mean Change = Least squares mean of change from baseline; SD = Standard deviation; Mean Change = Mean change from baseline, 95% CI = 95% Confidence Interval. Placebo - Pregabalin difference in LS Means from the ANCOVA Model with Treatment, Center, and Baseline (except at baseline time period).
 Summary statistics for baseline visit are based on subjects with both baseline and endpoint data.
 Endpoint (BOCF) = The mean pain score at endpoint for the completers and the mean pain score at baseline for noncompleters. A listing of subjects who did not complete the study, reason for discontinuation, and percent change from baseline to endpoint in weekly mean pain score is provided in [Appendix E.2.3](#).

^a Test for Treatment by Center Interaction based on the ANCOVA Model with Center, Baseline, Treatment, and Treatment*Center.
^b Test for Treatment by Baseline Interaction based on the ANCOVA Model with Center, Baseline, Treatment, and Treatment*Baseline.

Source data: [Table 9.1.5.1.1](#)

Source: Applicant's Clinical Study Report for trial 125, p 54.

The Applicant's analysis for treatment by center interaction was not statistically significant (p=0.613).

The Applicant conducted a responder analysis for subjects with a $\geq 30\%$ or $\geq 50\%$ decrease in mean pain score from baseline to endpoint. The results of that analysis are summarized in Table 15 below.

Table 15. Trial 125: Applicant's Analysis of Treatment Responders: 30% and 50% Reduction in Mean Pain Scores from Baseline to Endpoint (ITT).

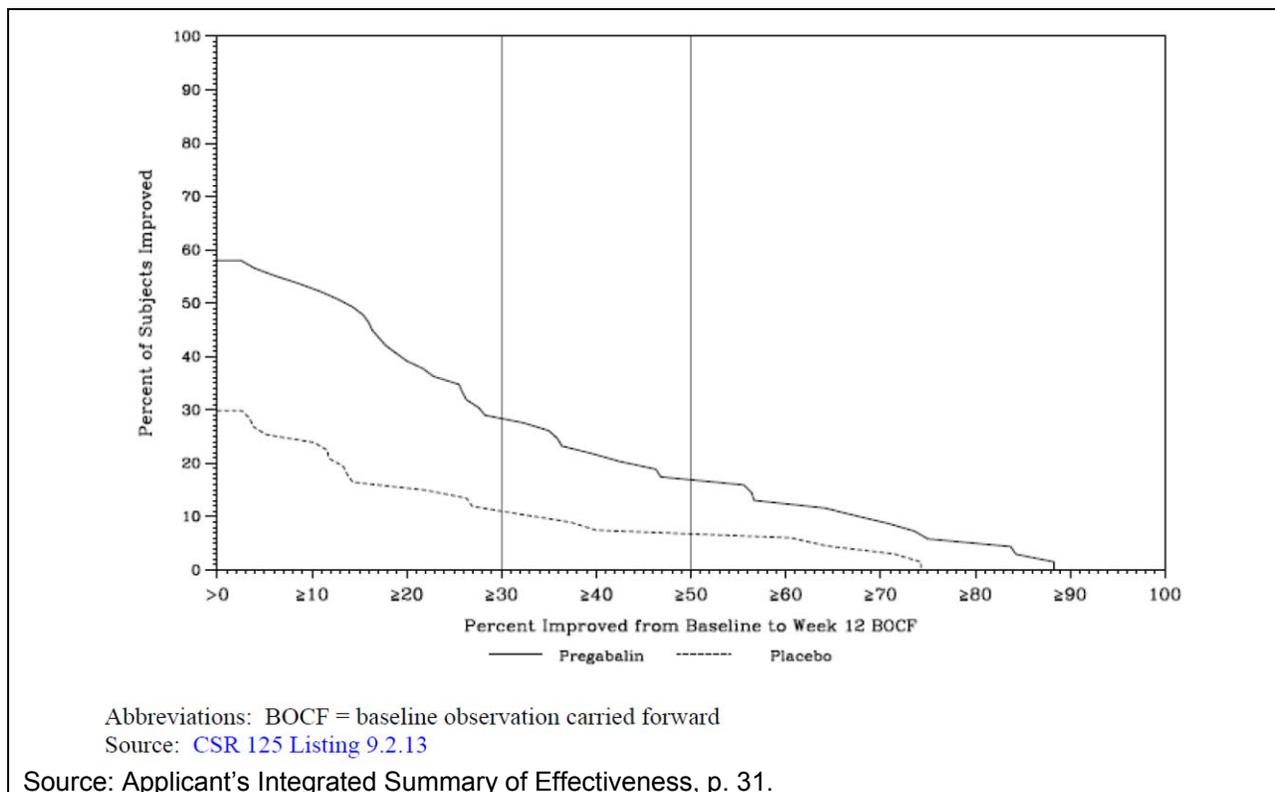
Reduction Statistic	Placebo (N=67)	Pregabalin (N=69)	Treatment Difference (Placebo/Pregabalin)		
	n (%)	n (%)	Odds Ratio	95% CI	p-value ^a
≥30%	11 (16.4)	29 (42.0)	0.235	(0.098, 0.563)	0.001
≥50%	5 (7.5)	15 (21.7)	0.285	(0.094, 0.865)	0.027

^a P-value was based on the odds ratio and its 95% CI (calculated by exponentiating the log odds ratio and 95% CI that correspond to the treatment contrast in the logistic regression model with treatment and center in the model and mean pain score at baseline included as the covariate).

Source data: [Table 9.1.5.1.2](#)
 Source: Applicant's clinical study report for trial 125.

The results of the Applicant's cumulative responder analysis are presented in the figure below (Figure 3). Subjects who did not complete the study were assigned 0% improvement.

Figure 3. Study 125: Applicant's Cumulative Responder Analysis (BOCF).



Reviewer comment: While the results of the Applicant's supplemental analyses are supportive of a treatment effect in favor of pregabalin, no adjustments were made to control for multiplicity.

Key Secondary Endpoints

The Applicant's analysis of other secondary efficacy variables, including weekly mean pain-related sleep interference scores, SF-MPQ VAS at endpoint, HADS anxiety subscale score at endpoint,¹¹ and PGIC at endpoint, showed statistical significance in favor of pregabalin.

Reviewer comment: While the results of the Applicant's secondary analyses are supportive of a treatment effect in favor of pregabalin, no adjustments were made to control for multiplicity.

The Applicant's analysis of the secondary endpoint, MOS optimal sleep score at Week 12 or endpoint, did not demonstrate a statistically significant difference between treatment groups.

Additional Secondary Analyses

The Applicant performed a secondary analysis comparing the placebo group to the pregabalin group with respect to the mean pain score at baseline and at each week during the treatment phase. The Applicant noted that a statistically significant treatment difference was maintained at each week through week 12 in favor of pregabalin. Those results are summarized in Figure 4 below.

¹¹ Although the HADS anxiety subscale score showed statistical significance in favor of pregabalin at endpoint, it did not demonstrate a statistically significant difference between treatment groups at Week 12, according to the Applicant's analysis.

Figure 4. Trial 125: Applicant's Analysis of Weekly Mean (\pm SE) Pain Scores Based on ANCOVA (ITT).

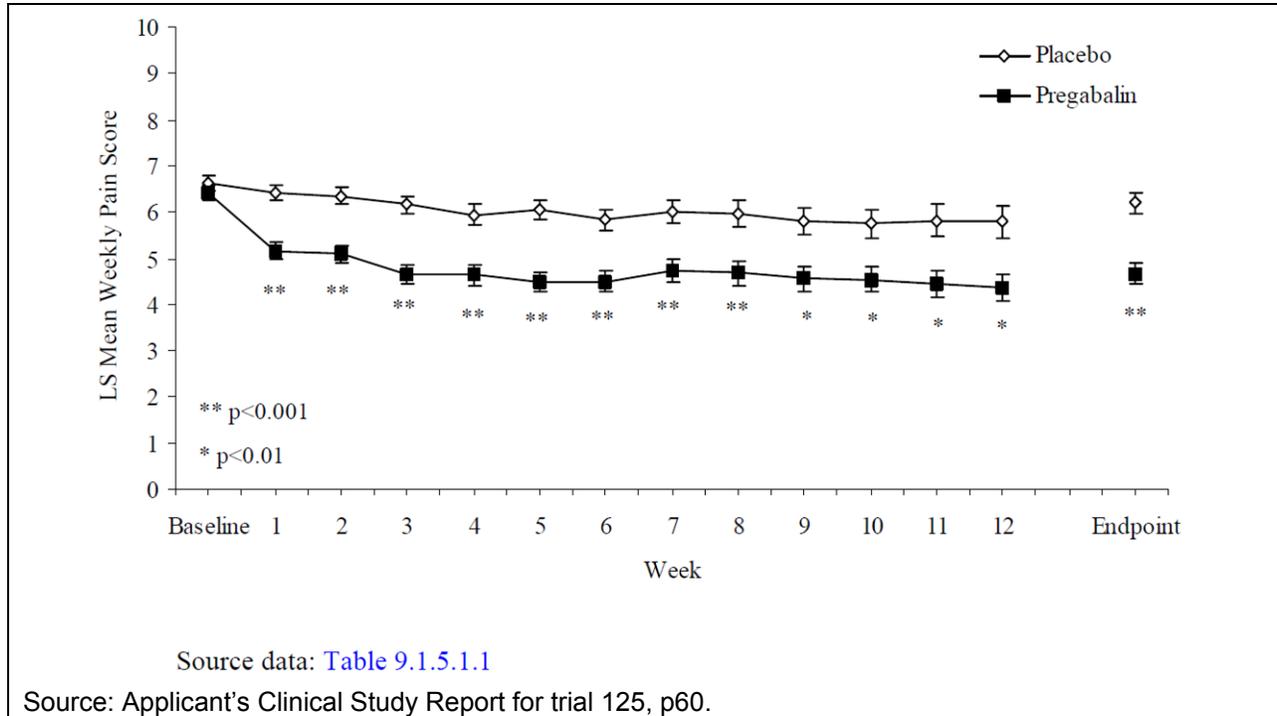
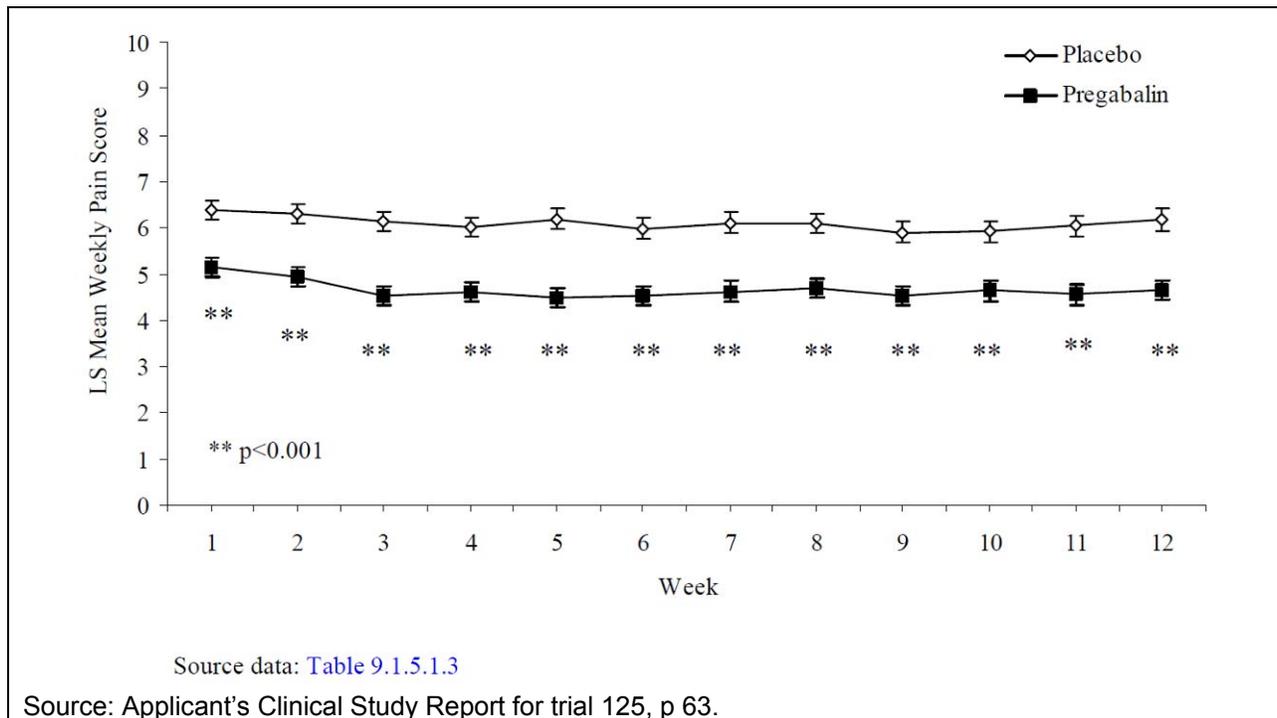


Figure 5. Trial 125: Applicant's Analysis of Weekly Mean (\pm SE) Pain Scores: Least-Squares Means from Repeated Measures Analysis (ITT).



Reviewer comment: While the results of the Applicant's additional secondary analyses are supportive of a treatment effect in favor of pregabalin, no adjustments were made to control for multiplicity.

The statistical reviewer, David Petullo, MS, conducted a statistical analysis, and his findings will be discussed in Section 6.

Safety Findings

A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7 (p 88).

Deaths

No subjects died during the study.

Serious Adverse Events (SAEs)

Three subjects in the placebo group and five subjects in the pregabalin group experienced non-fatal SAEs. The SAEs in the placebo group included urinary tract infection (one subject), constipation (one subject), and subarachnoid hemorrhage (one subject). The SAEs in the pregabalin group included cellulitis (one subject); fecal impaction (one subject); hypervolemia (hemodilution), edema, and thrombocytopenia (one subject); urinary tract infection (one subject); and withdrawal syndrome (withdrawal reaction) and increased muscle spasticity (one subject).

Discontinuations Due to Adverse Events

Nine (13.4%) subjects in the placebo group and 15 (21.4%) subjects in the pregabalin group discontinued due to treatment-emergent adverse events (TEAEs). The most common AEs leading to discontinuation in the pregabalin group were somnolence, edema, and asthenia.

Common Adverse Events

Among the safety population, 50 out of 67 (74.6%) subjects in the placebo group and 67 out of 70 (95.7%) subjects in the pregabalin group experienced at least one TEAE. The most frequently reported TEAEs in the pregabalin group, occurring more frequently in the pregabalin group compared to the placebo group with at least a 5% difference, were somnolence (41.4%), dizziness (24.3%), asthenia (15.7%), dry mouth (15.7%), constipation (12.9%), edema (12.9%), amnesia (10.0%), amblyopia (8.6%), and thinking abnormal (8.6%).

Trial 1107

“A 17-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin for the Treatment of Chronic Central Neuropathic Pain after Spinal Cord Injury”

Conducted 23 January 2007 to 28 February 2011

Sixty clinical trial sites in nine countries enrolled subjects including Japan (22 centers), the United States (18 centers), India (6 centers), China (4 centers, one of which is in Hong Kong), Czech Republic (3 centers), the Philippines (3 centers), the Russian Federation (2 centers), Chile (1 center), and Colombia (1 center). Seventy-six out of two-hundred-twenty subjects (35%) were enrolled in the United States.

Protocol

Objective/Rationale

The primary objective of the clinical trial was to evaluate the efficacy of pregabalin dosed 150 to 600 mg per day, divided twice daily, compared with placebo for the treatment of chronic central neuropathic pain after spinal cord injury.

The clinical trial was also designed to evaluate the following secondary objectives:

- To evaluate the safety and tolerability of pregabalin in the treatment of chronic central neuropathic pain after spinal cord injury.
- To evaluate the effect of pregabalin on the following parameters in subjects with chronic central neuropathic pain after spinal cord injury:
 - Pain-related sleep interference and overall sleep disturbance
 - Self-reported symptoms of depression and anxiety
 - PGIC and quality of life
 - Functional limitations due to pain interference
 - Neuropathic pain symptoms
 - Quantitative assessment of neuropathic pain

Overall Design

This was to be a randomized, double-blind, placebo-controlled, two-arm, parallel-group, flexible dose, multicenter clinical trial. Treatment was to consist of a 4-week dose adjustment phase, a 12-week maintenance phase, and a 1-week taper phase with pregabalin or placebo. Additionally, there was to be a 1-week off treatment phase at the end of the trial.

Treatment

Pregabalin or matched placebo capsules were to be taken orally. The target final doses were to be 150 mg/day, 300 mg/day, 450 mg/day, or 600 mg/day, divided twice daily.

All study medication was to be dispensed from locked, room temperature storage that was separate from normal hospital or practice stocks.

Population and Procedures

Inclusion/Exclusion Criteria

Planned enrollment was to be 200 subjects with chronic central neuropathic pain after spinal cord injury randomized 1:1 to an active treatment arm (i.e., pregabalin) or placebo arm. Separate sets of inclusion and exclusion criteria were to be applied at screening and randomization.

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

General Inclusion Criteria

- Subjects who are able and willing to provide informed consent
- Male and non-pregnant, non-lactating, postmenopausal, or surgically sterilized female subjects at least 18 years of age, of any ethnic origin; males and females of childbearing potential must use contraception; all females must have a confirmed negative serum pregnancy test prior to randomization
- Subjects deemed to comply with study schedule, procedures, and medications as specified by the protocol
- Subjects with a documented diagnosis of spinal cord injury (SCI) including all of the following:
 - Outpatient or inpatient subjects
 - SCI resulting from accident (examples include motor vehicle, fall, gunshot, electric shock)
 - SCI from diving
 - SCI due to spinal cord ischemia
 - Post-surgical SCI after benign tumor (except meningiomas and fibromas) has been removed and the level of injury has been stable for at least six months
- Complete or incomplete SCI of at least 12 months duration:
 - Complete SCI: Grade A on the American Spinal Injury Association (ASIA) Impairment Scale - No sensory or motor function is preserved in the sacral segments S4-S5
 - Incomplete SCI: Grade B - Sensory but no motor function is preserved below the neurological level and includes the sacral segments S4-S5
 - Incomplete SCI: Grade C - Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3 (0 to 2)
 - Incomplete SCI: Grade D - Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade greater than or equal to 3 (3 to 5)

- Neurological examination findings consistent with SCI and/or appropriate radiographic/imaging studies (such as X-ray, CT, myelogram, MRI) demonstrating a corresponding anatomical lesion documented by present or past medical records
- The Neurological Level of Injury (NLI) must be from C2-T12 inclusive (the NLI is defined as the most caudal segment of the spinal cord with normal sensory and motor function). C2 and C3 lesions are permitted as long as the subject is able to breathe without assistance. Low thoracic NLI (T11-T12) are allowed as long as the subject does not have radicular pain
- Subjects may also be included if they have the following conditions as long as all other entry criteria are met:
 - Central cord syndrome, Brown-Sequard syndrome, and anterior cord syndrome

Pain Inclusion Criteria

- For the purpose of this study, the pain is chronic central neuropathic pain, defined as:
 - Pain can be experienced unilaterally or bilaterally, and must have started after the spinal cord injury and persisted continuously for at least 3 months or with remissions and relapses for at least 6 months
 - Below-level neuropathic pain according to the Bryce-Ragnarsson SCI pain taxonomy type 14 or 15:
 - Type 14 – SCI below level central pain is neuropathic pain which occurs caudal to the two dermatomal levels below the neurological level of injury. Its distribution is generally not dermatomal but regional, enveloping large areas such as the anal region, the bladder, the genitals, the legs, or commonly the entire body below the neurologic level. The character is often described as “burning” or “aching,” although other descriptors have included “pressure,” “heaviness,” “cold,” “numbness,” and “pins and needles.” It is usually continuous in presence, although the intensity of the pain can fluctuate in response to a number of factors including psychological stress, anxiety, fatigue, smoking, noxious stimuli below the level of injury, and weather changes.
 - Type 15 – SCI below level neuropathic—other pain occurs only in persons with a neurologically incomplete SCI or complete SCI with a zone of partial preservation extending to the level of the pain. It includes all the neuropathic types of pain which are not specifically known to be more common after SCI, and which occur in areas innervated by segments more than two levels below the neurological level of injury.
 - Subject must have “below-level” pain
 - At-level or above-level pain can be present as long as the subject also has below-level pain.

Subjects were to be excluded for the following criteria at **screening**:

- Pregnant or lactating females or females of childbearing potential not practicing an effective method of contraception
- Neurologic disorders unrelated to spinal cord injury that may confound the assessment of the central neuropathic pain due to spinal cord injury (including but not limited to pain due to hereditary neuropathies; compression-related neuropathies, i.e., leprosy; diabetic peripheral neuropathy; traumatic neuropathy; metabolic abnormalities such as hypothyroidism; and vascular, inflammatory, malignancy-mediated, and immune-mediated neuropathies)
- Preexisting myelopathy due to other causes
- Congenital canal stenosis with trauma-induced spinal cord injury
- Presence of severe pain associated with conditions other than spinal cord injury that could confound the assessment or self-evaluation of pain due to spinal cord injury
- Specific systemic diseases or other medical conditions that would interfere with the evaluation of the therapeutic response or safety of the study drug
- Abuse or dependence of drugs or alcohol within the past 12 months according to the Diagnostic and Statistical Manual of mental disorders criteria (DSM-IV)
- Previous or current participation in another clinical study of pregabalin; intolerance to doses of pregabalin (150 to 600mg/day); pregabalin use within 60 days prior to screening
- Concurrent or previous participation in another clinical trial within 30 days prior to screening
- A previous history of intolerance or hypersensitivity to gabapentin or drugs with similar chemical structures
- Anticipated need for surgery during the course of the study
- Malignancy within the past year, with the exception of basal cell carcinoma, which is not exclusionary
- Clinically significant or unstable medical condition that, in the opinion of the investigator, would compromise participation in the study
- Mental or psychological condition rendering the subject unable to understand the requirements of participation in the study and risks/benefits thereof, and/or evidence of an uncooperative attitude in the judgment of the investigator
- Significant psychiatric disorder, recurrent episodes of severe depression (any pharmacologic treatment or hospitalization for the illness within one year prior to screening), or subjects with serious suicidal risk per criteria. A risk assessment should be done by a qualified mental health professional (MHP) to assess whether it is safe for the subject to participate in the trial if at least one of the following three conditions are met:
 - Subject's responses on the Sheehan-Suicidality Tracking Scale (Sheehan-STS, Lifetime Assessment version) items 1a, 1b, 3 and 4, 5, 6, or 8 is positive (score ≥ 1)

- Subject's total Patient Health Questionnaire-8 (PHQ-8) ≥ 15
- Presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria
 - Subjects with mild, chronic depression without recent hospitalization who are being maintained on a stable dose of a single antidepressant are acceptable
- Pending civil litigation or disability claims pertinent to the subjects spinal cord injury, current involvement in out-of-court settlements for claims pertinent to the subjects spinal cord injury, or other legal complications related to the spinal cord injury that could confound assessments
- Likelihood of requiring treatment during the study period with drugs prohibited by the study protocol
- A history of retinal abnormalities or treatment with retinotoxic agents
- Use of prohibited medications in the absence of appropriate washout periods

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

- Completed at least 4 daily pain diary entries during the 7 days prior to randomization with an average score of ≥ 4 on the 11-point rating scale for pain

Subjects were to be excluded for the following criteria at **randomization**:

- Creatinine clearance < 60 mL/min (estimated from serum creatinine). Subjects who have an estimated creatinine clearance < 60 mL/min may, at the investigator's discretion, may have their creatinine clearance measured with a serum sample and a 24-hour urine collection obtained at an unplanned visit and analyzed at the central laboratory. If the 24-hour urine creatinine clearance is ≥ 60 mL/min, the subject may be randomized provided that all other inclusion/exclusion criteria have been satisfied.
- White blood cell count $< 2500/\text{mm}^3$, neutrophil count $< 1500/\text{mm}^3$, platelet count $< 100 \times 10^3/\text{mm}^3$
- Clinically significant abnormal electrocardiogram (ECG)

Concomitant Medications

All concomitant medications were to be recorded. Concomitant medications were to be defined as any medication that a subject takes other than study drug. This was to include the following prescription and nonprescription treatments:

- Contraceptives
- Vitamins
- Topical preparations
- Herbal preparations
- Pharmacological therapies

Any non-drug therapy that a subject receives or uses was to be considered concomitant non-drug therapy, and was to include the following treatments:

- Transcutaneous electrical nerve stimulation (TENS)
- Acupuncture
- Spinal cord stimulation

Rescue Medications

Subjects were to be allowed to start acetaminophen (up to 1.5 g per day) and nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors, at any point during the trial as rescue therapy. The use of these medications was to be recorded as concomitant treatment.

Permitted Treatments

Permitted treatments were to be required to be administered on a stable dosage regimen and meet the criteria outlined in Table 16 below. Permitted treatments were not to be initiated during the study, unless where indicated as rescue medications.

Table 16. Trial 1107: Permitted Concomitant Medications.

Class of Medication	Examples^a	Criteria
Medication Commonly Used for Relief of Neuropathic Pain and Miscellaneous Supplements	Skeletal muscle relaxants (including baclofen (oral or pump) and Dantrolene, capsaicin, α -lipoic acid, local anaesthetics, opioids, tramadol, memantine, fatty acid supplements, evening primrose oil, myoinositol, chromium picolinate	Permitted if on a stable dose regimen or level within the last 30 days prior to Visit 1 and throughout study participation
Anti-inflammatories	Acetylsalicylic acid (Aspirin)	Permitted if on a stable dose regimen within the last 30 days prior to Visit 1 and throughout study participation
Narcotic Analgesics	Opioids, morphine, codeine, hydrocodone, oxycodone	Permitted if on a stable dose regimen within the last 30 days prior to Visit 1 and throughout study participation
Nonnarcotic Analgesics	Acetaminophen	Permitted; maximum dose should not exceed 1.5g/day
Anti-inflammatories	NSAIDS, COX-2 inhibitors	Permitted
Antidepressants	SNRIs (venlafaxine and duloxetine); SSRIs (sertraline and fluoxetine); TCAs (amitriptyline)	Permitted if on a stable dose regimen within the last 30 days prior to Visit 1 and throughout study participation
Antiepileptics	Carbamazepine, phenytoin, valproic acid, lamotrigine, topiramate, levetiracetam	Permitted if on a stable dose regimen within the last 30 days prior to Visit 1 and throughout study participation
Benzodiazepines or non-benzodiazepine hypnotics	Ativan (lorazepam) Ambien (zolpidem), Restoril (temazepam), Sonata (zaleplon), clonazepam	Permitted if on a stable dose regimen within the last 30 days prior to Visit 1 and throughout study participation
Nonpharmacologic Treatments	TENS, spinal cord stimulator, acupuncture, physical therapy	Rehabilitation and nonpharmacological treatments are allowed as long as they have started 30 days or more prior to Visit 2 and are anticipated to remain stable in their use throughout the trial.

^a Not a comprehensive list.

Source: Applicant's protocol for trial 1107, p 35.

Prohibited Medications

Prohibited medications are summarized in the table below.

Table 17. Trial 1107: Prohibited Medications.

Class of Medication	Comment/Example(s)
Potential Retinal Toxins	Hydroxychloroquine, deferoxamine, thioridazine, vigabatrin ^a
Pregabalin	Subject is excluded from study if there was previous or current participation in a another clinical study with pregabalin, or history of intolerance to doses of pregabalin (150 to 600 mg/day), or pregabalin use within 60 days prior to screening
Gabapentin	Must be completely discontinued for at least 7 days prior to screening (Visit 1)
Cannabinoids	Must be completely discontinued for at least 7 days prior to screening (Visit 1)

^a Not a comprehensive list

Source: Applicant's protocol for trial 1107, p 34.

Subjects who have ever taken retinal toxins were not to be eligible for the trial.

Lifestyle Guidelines

Subjects were to be advised that pregabalin may cause dizziness and somnolence, and that they should not drive a car or operate other complex machinery until they have gained sufficient experience. Subjects were to be prohibited from initiating or altering an exercise regimen during their participation in the trial to minimize potential influence on the efficacy results based on pain scale scores.

Procedures

General

Subjects were to score pain and sleep interference on 11-point scales every day upon awakening, and record the results in a diary.

Study drug compliance was to be assessed at each clinic visit following randomization (Visit 2). Subjects were to be considered noncompliant with dosing if the percent compliance meets the following criteria:

- Less than 80% or greater than 120% for more than two visits through Visit 5
- Less than 80% or greater than 120% between study visits after Visit 5

Subjects were to complete at least four out of every seven daily diaries. Subjects were expected to attend all required study visits.

The visit schedules and planned telephone contacts are outlined in the following paragraphs according to clinical trial phase along with the procedures that were to be performed at those times. Also, refer to Table 18, the schedule of activities.

Screening Phase

Informed consent was to be obtained from the subject prior to performing any study assessments. If a subject was currently taking pregabalin, gabapentin, or cannabinoids, informed consent was to be obtained and the subject was to start a taper of the drug. Gabapentin or cannabinoids were to be discontinued for at least 7 days and pregabalin for at least 60 days before returning to the clinic for screening procedures. Subjects who met eligibility criteria were to have up to two weeks to complete daily pain and sleep diaries to establish baseline values.

Visit 1: screening visit

- Collect spinal cord history and review radiology data
- Review of deep vein thrombosis history
- Collect laboratory tests including serum hematology and chemistry panels, urinalysis, serum creatinine clearance, fasting lipid profile, and serum pregnancy test (all females)
- Train subjects in completion of daily pain and sleep diaries
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Dose Adjustment Phase (4 weeks)

All randomized subjects were to have entered a 4-week, double-blind dose adjustment phase, and were to have been assessed weekly to adjust pregabalin and matched placebo doses in a blinded manner. Dose adjustment was to be based on a balance between pain relief and tolerability and was to occur according to Figure 6 below. Subjects randomized to the treatment group were to begin treatment at 150 mg/day. By the end of the dose adjustment phase, possible dose levels were to be 150 mg/day, 300 mg/day, 450 mg/day, or 600 mg/day.

Visit 2 (Week 0, Day 1):

- Evaluate continued eligibility based on randomization inclusion and exclusion criteria
- Review laboratory and ECG evaluations collected at Visit 1
 - Any clinically significant laboratory findings outside of the reference range were to be commented on prior to randomization.
- Randomize subjects 1:1 to pregabalin 150-600 mg/day (starting at 150 mg/day) or matched placebo
- Instruct subjects to start taking study medication on the evening of Day 1
- Collect and distribute daily diary booklets

- Perform additional procedures as detailed in the schedule of activities (Table 18)

Day 7:

- Contact subjects by telephone to assess the dose, and maintain or titrate up study treatment according to Figure 6 below; No dose reduction was to be allowed at this point
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Visit 3 (Week 2, Day 15):

- Evaluate dose, and maintain or titrate up or down study treatment according to Figure 6 below
- Assess compliance with the daily diary completion and study drug regimen
- Collect and distribute daily diary booklets
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Day 21:

- Contact subjects by telephone to assess the dose, and maintain or titrate up or down study treatment according to Figure 6 below
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Visit 4 (Week 4, Day 29):

- Evaluate dose, and maintain or titrate up or down study treatment according to Figure 6 below
- Assess compliance with the daily diary completion and study drug regimen.
- Collect and distribute daily diary booklets
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Visit 4 was to be the last time subjects could have their dose increased as it was to be the end of the dose adjustment phase and the beginning of the maintenance phase.

Maintenance Phase (12 weeks)

At the end of the dose adjustment phase, subjects were to be at their optimized dose of pregabalin or matched placebo. Subjects were to remain on their optimized dose for the duration of the maintenance phase. However, if a subject were to experience an intolerable adverse event during the maintenance phase, their dose may be reduced by one level, on one occasion only. This was to be accomplished during the next scheduled visit or during an unplanned visit requested by the subject. No dose increases were to be allowed.

Day 43:

- Contact subjects by telephone to assess their response and tolerability to the study treatment
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Visit 5 (Week 8, Day 57):

- Assess subjects' response and tolerability to the study treatment
- Assess compliance with the daily diary completion and study drug regimen
- Collect and distribute daily diary booklets
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Day 71:

- Contact subjects by telephone to assess their response and tolerability to the study treatment
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Visit 6 (Week 12, Day 85):

- Assess subjects' response and tolerability to the study treatment
- Assess compliance with the daily diary completion and study drug regimen
- Collect and distribute daily diary booklets
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Day 99:

- Contact subjects by telephone to assess their response and tolerability to the study treatment
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Visit 7 (Week 16, Day 113)

- Assess subjects' response and tolerability to the study treatment
- Perform laboratory collection for serum hematology and chemistry panels, urinalysis, serum creatinine clearance, fasting lipid profile, and serum pregnancy test (all females)
- Assess compliance with the daily diary completion and study drug regimen
- Collect daily diary booklets
- Perform additional procedures as detailed in the schedule of activities (Table 18)

Visit 7 was to be the end of the maintenance phase and the beginning of the taper phase, and subjects were to be given three bottles of study medication containing sequentially decreasing doses of study medication for the taper. Subjects were to begin taking study medication from the first bottle that evening.

Taper Phase (1 week)

All subjects who complete the trial or terminate it at any time were to have been tapered off study medication over a one week period. Subjects who discontinue at any time during the trial, were to be requested to complete Visit 7 termination procedures. Subjects were to be encouraged not to take any new pain medications during the treatment taper or at any time before the follow-up visit. If a subject were to require a new pain medication, it was to be recorded.

Day 115:

- Contact subjects by telephone as a reminder to switch to the next study medication bottle on days 116 and 117 for the taper
- Record adverse events and record any new concomitant medications, including non-drug treatments

Day 117:

- Contact subjects by telephone as a reminder to switch to the final study medication bottle on days 118 and 119 for the taper
- Assess compliance with daily diary completion, record adverse events, and record any new concomitant medications, including non-drug treatments

Study medication was to be stopped on day 119.

Day 120:

- Contact subjects by telephone to confirm that the subject has stopped dosing
- Record AEs and record any new concomitant medications, including non-drug treatments

Off-Treatment Phase (1 week)

Visit 8 (Week 18, Day 127):

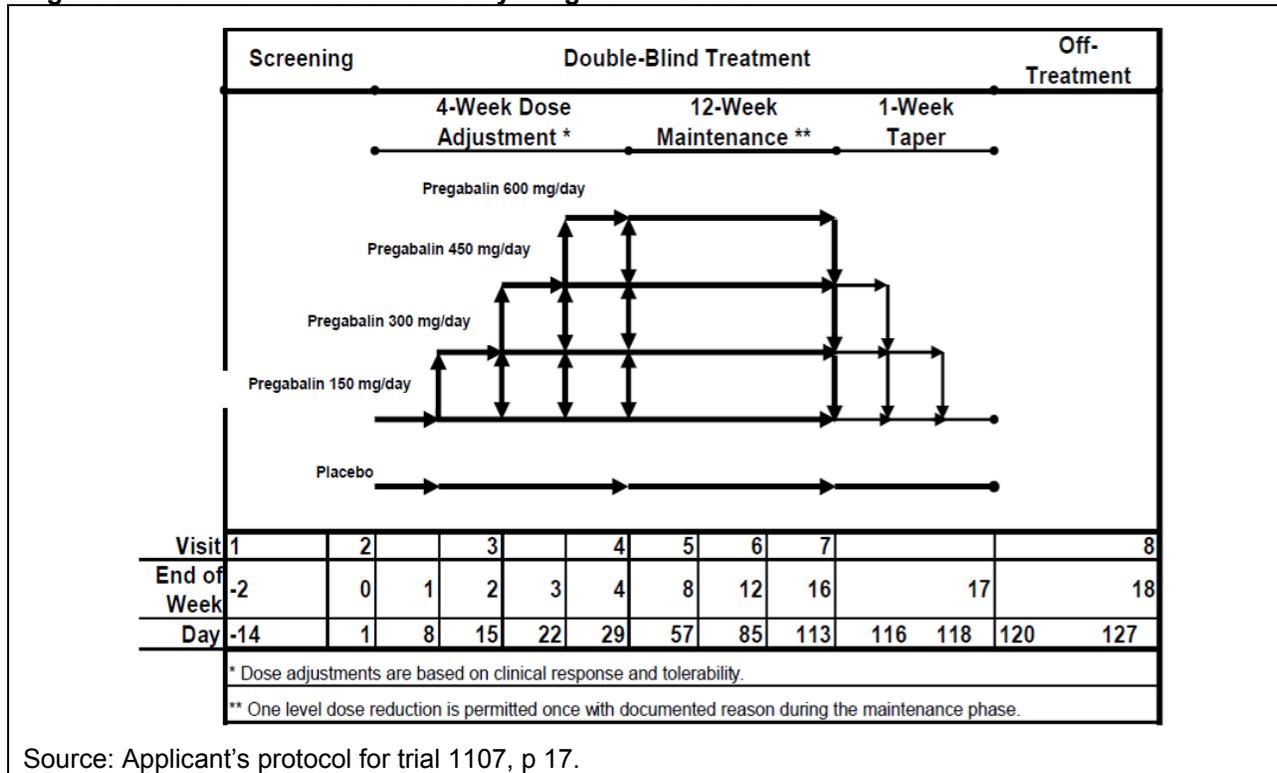
- Perform follow-up procedures as detailed in the schedule of activities (Table 18)

Subjects who discontinued at any time during the study were to be requested to attend the follow-up visit one week after the taper phase.

Unplanned Visit

If a subject were to require assessment between study visits (i.e., for dose reduction, laboratory testing, physical exams, or adverse events), the subject was to return to the clinic for an unplanned visit.

Figure 6. Trial 1107: Protocol for Study Drug Administration.



Source: Applicant's protocol for trial 1107, p 17.

Table 18 details the activities that were to be performed during the trial.

Table 18. Trial 1107: Schedule of Activities.

Trial Period	Screening	Double Blind Treatment Phase					Follow-Up	
	V1 to V2: Up to 2 Weeks	V2 to V4: 4-Week Dose Adjustment		V4 to V7: 12-Week Maintenance			V7 to one-week after V7: 1-Week Taper	1-Week Off-Treatment
Clinic Visit	V1	V2	V3	V4	V5	V6	V7	V8
Week in Trial	Screening	Randomization					Termination ^b	Follow-Up ^b
Trial Day ^a	-2	0	2	4	8	12	16	18
	-14	1	15	29	57	85	113	127
Telephone Contact			X ^c	X ^c	X ^d	X ^d	X ^d	X ^e X ^f X ^g
Informed Consent	X							
Inclusion/Exclusion Criteria, Subject Demographics	X							
Medical/Spinal Cord Injury History	X							
Physical Examination	X ^h			X		X	X	
Full Neurological Examination	X						X	
Abbreviated Neurological Examination		X	X	X	X	X		X
American Spinal Injury Association Scale (ASIA)	X						X	
Vital Signs/Weight/Edema/DVT Assessment ^l	X	X	X	X	X	X	X	X
12-Lead Electrocardiogram (ECG)	X						X	
Quantitative Assessment of Neuropathic Pain		X					X	
Clinical Laboratories ^l	X						X	
Pregnancy Test	X ^l						X ^l	
Adverse Events		X	X	X	X	X	X	X
Prior/Concurrent Medications/Non-drug Treatments	X	X	X	X	X	X	X	X
Trial Treatment Dispensing/Dosing		X	X	X	X	X	X	
Subject-Completed Assessments/Questionnaires								
Neuropathic Pain Screening Tool (ID Pain)	X							
Daily Pain/Sleep Interference Rating Scale ^k	X	X	X	X	X	X	X	
Modified Brief Pain Inventory (10-item) (mBPI-10)		X					X	
Medical Outcomes Study (MOS) Sleep Scale		X					X	
Hospital Anxiety and Depression Scale (HADS)		X					X	
Neuropathic Pain Symptom Inventory (NPSI)		X					X	
Pain Catastrophizing Scale (PCS)		X						
Patient Global Impression of Change (PGIC)							X	
Patient Health Questionnaire-8 (PHQ-8)	X							
Sheehan-Suicidality Tracking Scale (Sheehan-STSS) ^m	X	X	X	X	X	X	X	X

Schedule of Activities Footnotes

- a. All study visits should occur within \pm 3 calendar days of the scheduled Trial Day.
- b. Whenever subject discontinues at any time from trial, or completes the maintenance phase, subject should return for a termination visit and enter the 1-week taper phase, followed by a follow-up visit, as applicable.
- c. On Day 7 and Day 21, all subjects are contacted by telephone for dose adjustment assessment.
- d. Telephone contact should be initiated with the subject 2 weeks after Visits 4, 5 and 6 to ensure compliance with daily diaries, and study drug regimen, and to record any AEs, concomitant medications, and non-drug treatments. Also an unplanned visit may be scheduled for dose reduction if necessary.
- e. On Day 115, subjects are to be contacted by telephone to switch to taper Bottle B on Days 116 and 117.
- f. On Day 117, subjects are to be contacted by telephone to switch to taper Bottle C on Days 118 and 119.
- g. On Day 120, the day after the last dose of taper treatment, all subjects are contacted by telephone to confirm and to record final dates of treatment.
- h. New York Heart Association classification is done at Visit 1 as part of the Physical Examination.
- i. Fasting status for labs. CRP and estimated creatinine clearance are measured at Visit 1 only. If estimated serum creatinine clearance is <60 mL/min, at the investigator's discretion, a serum sample and a 24-hour urine collection may be obtained at an unplanned visit.
- j. Serum pregnancy test is to be done on all females at Visits 1 and 7.
- k. Daily diaries are dispensed to subjects at Visit 1 to complete at home throughout treatment period. Additional daily diaries are dispensed to subjects as needed. All other questionnaires are to be completed during clinic visits.
- l. If the subject's disability does not allow the subject to be weighed safely it is permissible to indicate an estimated weight on the Case Report Form (CRF), and this should be also noted in source documents.
- m. The Sheehan-Suicidality Tracking Scale (Sheehan-STS) has two versions. The "Lifetime Assessment" version is administered at screening and the "Since Last Visit" version is used for all other visits. This scale can be administered either by a clinician or patient through self-report.

Source: Applicant's protocol for trial 1107, p 6-7.

Subject Withdrawal

Subjects were to be withdrawn from the study, at any time, at their own request or at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In all circumstances, every effort was to be made to document subject outcome. If a subject discontinues from the study, every effort was to be made to request that the subject attend the termination visit (Visit 7) to taper off study drug, and return for the follow-up visit (Visit 8).

Subjects were to be withdrawn from the study for the following reasons:

- Noncompliance with study drug dosing
- Noncompliance with daily diary completion
- Missing required study visits
- Starting prohibited medication
- Emergence of any condition that will confound assessment of the subject's neuropathic pain associated with spinal cord injury
- Serious violations of the protocol (eligibility or on-study)
- Subject's decision to withdraw or withdrawal of consent

Evaluations/Endpoints

Subjects were to complete a daily pain rating and daily sleep interference scale upon awakening and record the results in a diary. The daily pain scale was to be rated on an 11-point numerical scale ranging from 0 (no pain) to 10 (worst possible pain). A rating of 1-3 was to be considered mild pain; 4-6, moderate pain; and 7-10, severe pain. Pain-related daily sleep interference was to be rated on an 11-point numerical scale ranging from 0 (did not interfere with sleep) to 10 (completely interfered with sleep [unable to sleep due to pain]).

The prespecified primary endpoint was to be the Duration Adjusted Average Change (DAAC). The DAAC is the mean of all post-baseline pain scores, derived from the daily pain diary, minus the baseline score then multiplied by the proportion of the planned study duration completed by the subject.

Key secondary endpoints identified in the protocol included:

- Change from baseline to endpoint in the mean pain score from subject diary (modified intent-to-treat [mITT] population, modified baseline observation carried forward [mBOCF] imputation)
 - mBOCF imputation was to be defined as the baseline mean pain score for subjects who discontinued double-blind treatment due to an adverse event or who have no post baseline observations and last observation carried forward (LOCF) mean pain score for all other subjects.
- Proportion of subjects with $\geq 30\%$ reduction in weekly mean pain score from baseline to endpoint (mITT population, LOCF imputation)
- PGIC at endpoint (mITT population, LOCF)

- Change from baseline to endpoint in mean sleep interference score from subject diary (mITT population, LOCF)

Additional Secondary Endpoints

- Proportion of subjects with $\geq 30\%$ reduction from baseline in mean pain score at weekly assessment
- Proportion of subjects with $\geq 50\%$ reduction from baseline in mean pain score at weekly assessment and at endpoint
- Weekly change from baseline in mean pain score (repeated measures model)

Supplemental Analysis

- Cumulative responder analysis

Safety Assessments

The following safety assessments were to be performed:

- Adverse events
- Physical examination (any clinically significant negative changes from the screening examination were to be recorded as adverse events)
- Neurologic examination
- Sheehan-Suicidality Tracking Scale
- Patient Health Questionnaire-8
- ASIA Impairment Scale
- Laboratory tests
 - Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, platelet count
 - Chemistry: amylase, AST, ALT, albumin, alkaline phosphatase, BUN, creatinine, creatine phosphokinase, electrolytes (sodium, potassium, chloride, calcium), glucose, total protein, total bilirubin, uric acid, LDH
 - Urinalysis: colorimetric urine protein, pH, specific gravity, glucose, nitrate, ketones, occult blood, leukocyte esterase, microscopic sediment examination
 - Serum pregnancy test (all females)
 - C-reactive protein
 - Fasting lipid profile: total cholesterol, HDL, LDL, LDL/HDL ratio, triglycerides
 - Creatinine clearance: estimated from serum creatinine
 - ECG
- Previous and concomitant medications (including non-drug treatments)

Refer to Table 18 for the frequency at which the safety assessments were to be performed.

Statistical Plan

The primary efficacy analysis was to compare the DAAC between pregabalin and placebo groups using an ANCOVA model that includes baseline severity (pain) as a covariate and investigational center as a fixed (class) cofactor. The mITT population was to be used for primary and secondary efficacy analyses, unless otherwise specified. The mITT population was to include all ITT subjects (all randomized subjects who take at least one dose of study drug and have at least one post-randomization efficacy assessment) except for eight subjects who were randomized before the protocol was amended for flexible dosing.¹² For the primary analysis, any subject who took randomized treatment and did not have any post-randomization pain diary scores, the DAAC was to be assigned a value of zero. Analysis of key secondary endpoints was to be adjusted for multiplicity using a sequential step down procedure.

Based on previous results, the Applicant determined a difference of 1 point in the DAAC could be detected between the pregabalin and placebo groups at 90% or greater power with 56 subjects randomized per group. However, the trial was powered at 82% (based on planned enrollment of 200 subjects) to detect a 0.9 point treatment difference in change from baseline to endpoint in mean pain score in the modified baseline observation carried forward (mBOCF) analysis.

The Per Protocol population (PP) was to be defined as all mITT subjects who completed the full double blind treatment phase, had total medication compliance within 80-120% during double-blind treatment, and had no other significant protocol violations.

The safety population was to include all randomized subjects who took at least one dose of study drug. The primary safety parameter was to be discontinuation due to adverse event. The proportion of subjects who discontinue from the study due to an adverse event will be calculated for each treatment group and relative risk and risk difference with 95% confidence intervals was to be calculated between each pregabalin regimen and placebo. All other safety parameters were to be reported in summary tables and listings.

Results

Subject Overview

Of 280 potential subjects with neuropathic pain secondary to spinal cord injury screened, 112 were assigned to the pregabalin group and 107 were assigned to the placebo group.¹³ Sixty centers in nine countries randomized subjects (refer to Table 19 below). Seventy-six (34.5%) subjects were enrolled in the United States in a total of 18 centers.

¹² Amendment 2, 3/25/2008

¹³ One additional subject was assigned to the placebo group; however, this subject did not return after the baseline visit despite multiple attempts to contact the subject. There are no post-baseline measurements for this subject, and it is uncertain if this subject took any study medication.

Table 19. Trial 1107: Enrollment by Country.

Country	Number of Centers	Number Enrolled
Chile	1	2 (0.9%)
China	3	15 (6.8%)
Colombia	1	4 (1.8%)
Czech Republic	3	11 (5%)
Hong Kong	1	7 (3.2%)
India	6	18 (8.1%)
Japan	22	59 (26.8%)
Philippines	3	11 (5%)
Russian Federation	2	17 (7.7%)
United States	18	76 (34.5%)
Total	60	220 (100%)

Source: Derived from Applicant's List of Investigators for trial 1107, p 32-57.

Subject Disposition

Among subjects assigned to study treatment, 112 were in the pregabalin group and 107 were in the placebo group. One additional subject was randomized to the placebo group; however, that subject did not return to the study site after the baseline visit despite multiple contact efforts.

Study completion rates were similar between the pregabalin and placebo groups. Ninety-three (83%) subjects in the pregabalin group and 91 (85%) subjects in the placebo group completed the study. Nineteen (17%) subjects in the pregabalin group and 16 (15%) subjects in the placebo group discontinued from the study. The most frequent reason for discontinuation in both groups was adverse event (8 [7.1%] and 8 [7.5%] subjects in the pregabalin and placebo groups, respectively). The table and figure below summarize subject disposition in the trial.

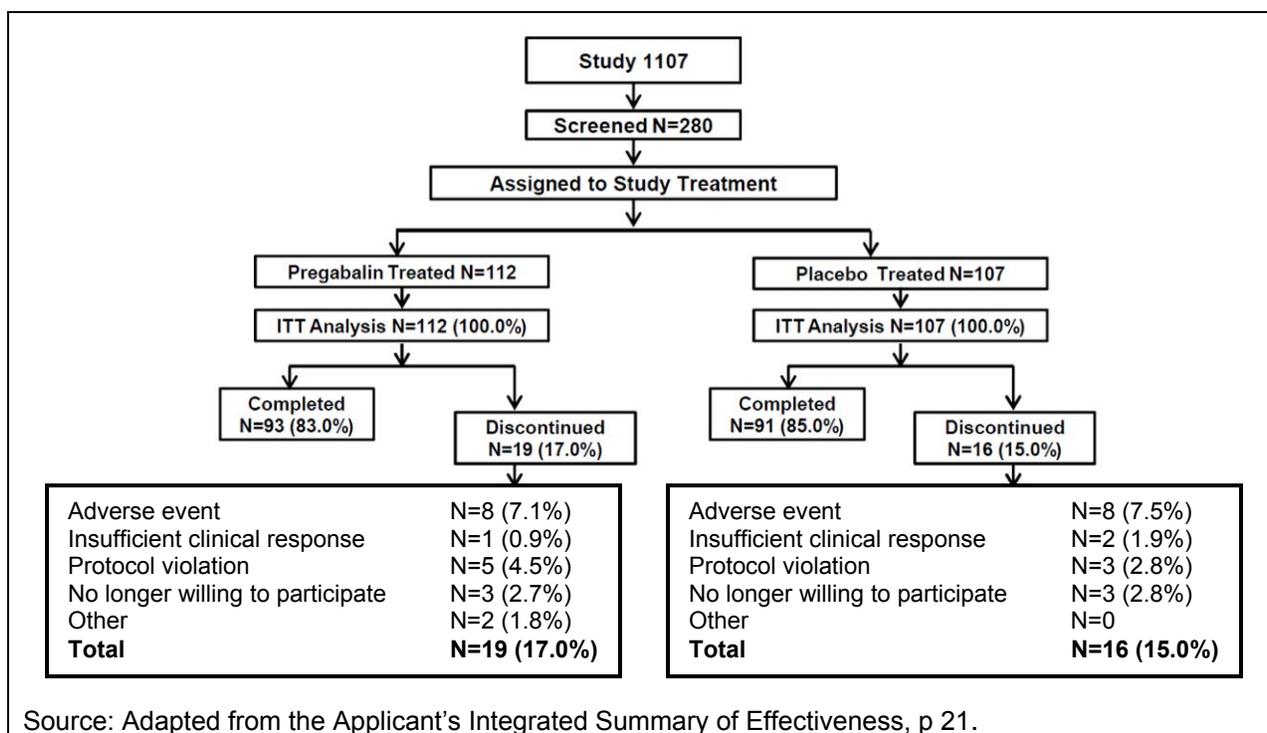
Table 20. Trial 1107: Subject Disposition.

No. (%) of Subjects	Pregabalin	Placebo
Screened	280	
Assigned to study treatment	220	
Treated	112	107 ^a
Completed	93 (83.0)	91 (85.0)
Discontinued	19 (17.0)	16 (15.0)
Relation to study drug not defined	11 (9.8)	8 (7.5)
Insufficient clinical response	1 (0.9)	2 (1.9)
No longer willing to participate in study	3 (2.7)	3 (2.8)
Other	2 (1.8)	0
Protocol violation	5 (4.5)	3 (2.8)
Related to study drug	6 (5.4)	5 (4.7)
Adverse event	6 (5.4)	5 (4.7)
Not related to study drug	2 (1.8)	3 (2.8)
Adverse event	2 (1.8)	3 (2.8)

Source: Tables 13.1.1 and 13.1.3
 Abbreviation: No.=number
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.
^aThe number of randomized subjects was different from the number of treated subjects due to Subject 11051003. The subject did not receive any study medication (Appendices B4.1 and B12).

Source: Applicant's Clinical Study Report for trial A008-1107, p 68.

Figure 7. Trial 1107: Subject Disposition.



Demographics

Most subjects were male (176/219, 80.4%), and the most frequent race was Asian (110/219, 50.2%). The mean age was comparable between treatment groups (46.1 years [range 22-72] in the pregabalin group and 45.6 years [range 19-81] in the placebo group). The table below summarizes the demographic information for the ITT population.

Table 21. Trial 1107: Demographic Characteristics of ITT Population

Parameter	Pregabalin N=111	Placebo N=108
Gender, n (%):		
Male	84 (75.7)	92 (85.2)
Female	27 (24.3)	16 (14.8)
Premenopausal	14	8
Postmenopausal	13	8
Age (years):		
Mean (SD)	46.1 (12.7)	45.6 (13.8)
Range	22 – 72	19 – 81
Race, n (%):		
White	42 (37.8)	43 (39.8)
Black	6 (5.4)	8 (7.4)
Asian	57 (51.4)	53 (49.1)
Other	6 (5.4)	4 (3.7)
Ethnicity, n (%):		
Hispanic/Latino	13 (11.7)	7 (6.5)
Not Hispanic/Latino	98 (88.3)	101 (93.5)
Weight (kg):		
Mean (SD)	69.9 (16.0)	73.5 (17.8)
Range	40.0 – 117.9	38.6 – 134.0
BMI (kg/m²):		
Mean (SD)	23.9 (4.5)	24.8 (5.1)
Range	13.5 – 38.9	14.0 – 44.8
Height (cm):		
Mean (SD)	170.6 (10.1)	171.7 (9.6)
Range	142.8 – 193.0	143.8 – 203.0

Source: Tables 13.2.1.1 and 13.2.1.2
 Abbreviations: SD=standard deviation; BMI=body mass index; N=number of subjects; n=number of subjects in category; ITT=intent to treat
 Body mass index was calculated as weight/(height×0.01)².
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 74.

Reviewer comment: The treatment groups were comparable with respect to demographic data. The predominance of male subjects is reflective of and consistent with the epidemiology of the underlying disease process, spinal cord injury. The racial make-up of the study groups is reflective of the distribution of countries in which the trial took place.

Screening/Baseline Disease Characteristics

Spinal cord injury history (summarized in Table 22) was relatively comparable between groups, with one exception. Compared to the placebo group, subjects in the pregabalin group who reported pain with remissions and relapses had a longer mean spinal cord

injury duration (121.8 months-pregabalin; 99.4 months-placebo) and a shorter duration of pain (65.2 months-pregabalin; 76.4 months-placebo).

Reviewer comment: The variability in this subset of subjects can at least partially be explained by the relatively small numbers of subjects with remissions and relapses (35 subjects) compared to subjects with continuous persistent pain (184 subjects). Regardless, these differences are relatively minor, and are not anticipated to bias the results.

Table 22. Trial 1107: Summary of Spinal Cord Injury History (ITT Population)

Parameter	Pregabalin N=111	Placebo N=108
Combined classification of pain:		
Duration of SCI (months)		
N	111	108
Mean	126.0	128.8
Range	1.1-557.4	0.6-609.9
Duration of pain (months)		
N	111	108
Mean	97.8	97.5
Range	5.0-396.0	3.0-497.0
Pain has continuously persisted:		
Duration of SCI (months)		
N	92	92
Mean	126.8	133.9
Range	1.1-557.4	0.6-609.9
Duration of pain (months)		
N	92	92
Mean	104.6	101.1
Range	5.0-396.0	10.0-497.0
Pain has persisted with remissions and relapses:		
Duration of SCI (months)		
N	19	16
Mean	121.8	99.4
Range	14.3-358.2	3.5-282.9
Duration of pain (months)		
N	19	16
Mean	65.2	76.4
Range	14.0-263.0	3.0-192.0

Source: [Table 13.2.2.2](#)
 Abbreviations: N=number of subjects; ITT=intent to treat
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 76.

Prior and Concomitant Drug Treatments

Most subjects received at least one concomitant drug treatment during the study. The most frequently used drug was baclofen (received by 37.5% of subjects in the pregabalin group and 27.1% of subjects in the placebo group). The most common prior

drug treatment was also baclofen, which was received by 36.9% of subjects in the pregabalin group and 26.9% of subjects in the placebo group.

Reviewer comment: Within each group, baclofen use rates are consistent prior to and during the trial, suggesting the difference in baclofen use between the pregabalin and placebo groups was an inherent characteristic of the populations rather than a consequence of the treatment received. Regardless, these differences are relatively minor between treatment groups and are not anticipated to bias the results.

Protocol Violations

The Applicant reported protocol violations for subjects who entered the trial even though they did not strictly meet inclusion and exclusion criteria, subjects who deviated from the conduct of the trial after starting study drug, and subjects who did not participate in study assessments as required by the protocol. The major protocol violations are summarized below (Table 23).

Table 23. Trial 1107: Summary of Major Protocol Violations Reported by the Applicant.

Protocol Violation	Trial 1107	
	Placebo (N=107)	Pregabalin (N=112)
Inclusion/exclusion criteria	6 (5.6%)	5 (4.5%)
Concomitant medications	5 (4.7%)	0 (0%)
Not compliant with study medication (i.e., did not meet the total medication compliance within 80-120% condition)	6 (5.6%)	5 (4.5%)

Source: Derived from Applicant's submission, sNDA 21446-028.

Reviewer Comment: The treatment groups were comparable with regard to inclusion/exclusion criteria and study medication compliance protocol violations, and the frequency of these violations was relatively low. Therefore, it is unlikely that these protocol violations biased the primary efficacy analysis. However, according to the Applicant, five subjects in the placebo group and none in the pregabalin group were in violation of the protocol with respect to concomitant medication use.

Concomitant medication protocol violations, in three subjects, were identified through OSI's inspection of clinical site 1072 that were not reported as protocol violations by the Applicant (see Section 3.2, p 13, Compliance with Good Clinical Practices for the inspectional findings). Based on these findings, we requested the Applicant to provide a table containing all concomitant medication changes that occurred 30 days prior to Visit 1 and throughout the conduct of trial 1107. Review of the requested materials, showed that 26 subjects in the pregabalin

group and 33 subjects in the placebo group¹⁴ (inclusive of the 3 subjects identified through OSI’s inspection of site 1072) used concomitant medications that may have influenced their pain scores and were potentially in violation of the protocol. These only represent potential violations as dosing was not captured on case report forms and the specific pain indication for which the concomitant medication was used is unknown (e.g., neuropathic pain versus musculoskeletal pain). This information would be required to further determine if these potential concomitant medication violations represent true violations; however, a conservative approach was used for the purposes of an exploratory analysis (i.e., the assumption that all of the potential violations represent true violations).

The statistical reviewer used two separate approaches to explore the influence of these subjects on the primary efficacy analysis. The first approach was to exclude them from the analysis. The second approach was to include them, but consider them as treatment failures (i.e., BOCF). Regardless of the approach, there was still a statistically significant treatment effect in favor of pregabalin (Table 24).

Table 24. Exploratory Analyses to Account for Potential Protocol Violations.

	Treatment	N	Change	Diff	p-value
Excluded	Placebo	75	0.9 (0.2)	-	-
	Lyrica	87	1.8 (0.2)	0.9	0.004
Considered as BOCF	Placebo	108	0.7 (0.2)	-	-
	Lyrica	111	1.5 (0.2)	0.8	< 0.001

Source: David Petullo, Statistical Review, Table 19, p 21.

Subject Evaluation Groups

The composition of the data sets analyzed is summarized below (Table 25).

¹⁴ **Pregabalin-treated subjects** with potential concomitant medication-related protocol violations include subjects 10261002, 10261005, 10721006, 10721012, 10781001, 10791001, 11001001, 11001012, 11091001, 11111007, 11411001, 11581002, 11631004, 11701001, 10121002, 10381001, 10691007, 10981001, 10981005, 10981007, 11121002, 11551007, 11621001, 11641003, 11761001, and 11771002.

Placebo-treated subjects with potential concomitant medication-related protocol violations include subjects 10261008, 10551001, 10691004, 10691005, 10691008, 10721008, 10721010, 10721014, 10921002, 11001005, 11061004, 11071009, 11091006, 11091007, 11111004, 11111005, 11111006, 11491007, 11551001, 11551004, 10251001, 10721003, 10721011, 10981006, 11001007, 11071008, 11091010, 11111003, 11121001, 11301002, 11561003, 11701003, 11701008.

Table 25. Trial 1107: Composition of Data Sets.

No. (%) of Subjects	Pregabalin	Placebo
Assigned to study treatment	220	
Treated	112 ^a	107 ^b
Analyzed for efficacy		
Intent to treat (ITT)	112 (100.0)	107 (100.0)
Subjects excluded from ITT	0	1
Did not receive study medication	0	1
Modified intent to treat (MITT)	106 (94.6)	105 (98.1)
Subjects excluded from MITT	6	3
Excluded from ITT	0	1
Randomized before Protocol Amendment 1 ^b	6	2
Per protocol (PP)	77 (68.8)	80 (74.8)
Subjects excluded from PP	34	29
Excluded from MITT	6	3
Did not complete double blind phase	18	16
Not ≥80 - ≤120% compliant	5	6
Had significant protocol deviation(s)	5	4
Analyzed for safety		
Adverse events	112 (100.0)	107 (100.0)
Laboratory data ^c	106 (94.6)	100 (93.5)
Safety population	112 (100.0)	107 (100.0)

Source: Tables 13.1.1 and 13.4

Abbreviations: No.=number; ITT=intent to treat; MITT=modified intent to treat; PP=per protocol

Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group (see Table 13.1.1).

^aThe number of randomized subjects (assigned to study treatment) was different from the number of treated subjects due to Subject 11051003 who had missing information about doses taken. This subject was randomized to placebo. The subject decided not to come back to the site after Visit 2 despite the multiple efforts of the site to contact the subject; therefore, no information after Visit 2 (including the medication bottles for accountability) was collected.

^bChange from fixed dosing to flexible dosing; see Section 5.11.1.1.

^cSubjects who were not included in the laboratory data analysis set did not have any on-treatment laboratory assessments.

Source: Applicant's Clinical Study Report for trial 1107, p 73.

Dosing Information

The median treatment duration in both groups was 119 days (range 2-128 days). Overall, the majority of subjects received 91-120 days of study drug (150/219, 68.5%). The tables below summarize duration of exposure and dosing, by treatment group.

Table 26. Trial 1107: Duration of Treatment (ITT).

Duration of Treatment (days) No. of Subjects	Pregabalin N=112	Placebo N=107
≤1	0	0
2-14	3	2
15-28	3	2
29-59	7 ^a	8
60-90	4	4
91-120	79	71
121-150	16	20
≥151	0	0
Median	119.0	119.0
Range	6-128	2-128

Source: [Table 13.3.1.1](#)
 Abbreviations: No.=number; N=number of subjects; ITT=intent to treat
 Duration is the total number of dosing days from the first to last day of each study treatment, inclusive.
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.
^aSubject 10791001 (pregabalin) took 7 capsules over a 2-week period but on unknown dates within ([Appendix B3.1](#)). Table programming cannot encapsulate such a dosing pattern; due to this reason number of capsules was set up to 0 for Days 26-39 following the team decision. This subject's total duration in the study was 48 days.

Source: Applicant's Clinical Study Report for trial 1107, p 78.

Table 27. Trial 1107: Maximum Daily Dose and Average Daily Doses Overall and During Maintenance Phase (Safety Population Subset).

	Pregabalin N=106	Placebo N=105
Maximum Daily Dose (mg/day), n (%)		
150	12 (11.3)	3 (2.9)
300	23 (21.7)	19 (18.1)
450	30 (28.3)	22 (21.0)
600	41 (38.7)	61 (58.1)
Average Daily Dose During Maintenance Phase, Days 29-112 (mg/day)		
N	101	102
Mean (SD)	409.7 (160.37)	469.1 (153.82)
Median	446.4	575.0
Range	75.0 – 600.0	147.6 – 600.0
Overall Average Daily Dose (mg/day)		
N	106	105
Mean (SD)	357.0 (131.01)	411.3 (125.98)
Median	378.6	473.9
Range	140.2 – 537.7	148.8 – 533.3

Source: [Table 13.3.1.2](#)
 Abbreviations: N=number of subjects; SD=standard deviation; n=number of subjects in category
 Safety Population Subset: All treated subjects except the 8 subjects who were randomized before the protocol was amended on 12 February 2008 ([Amendment 1](#)). Placebo dosage is indicated in mg/day to match the Pregabalin dosage for treatment blinding in this study.
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.

Source: Applicant's Clinical Study Report for trial 1107, p 79.

Efficacy Results

Overview

The Applicant's analysis demonstrated the superiority of pregabalin with respect to placebo for the primary endpoint and all key secondary endpoints with statistical significance.

Primary endpoint results:

- Treatment with pregabalin resulted in improved DAAC over the 16-week double-blind period compared to placebo (p-value=0.0032).

Key secondary endpoint results:

- Treatment with pregabalin resulted in a greater reduction in mean pain score from baseline (utilizing an mBOCF imputation strategy for missing data) compared to placebo at endpoint (p-value=0.0066)
- The proportion of subjects who had a $\geq 30\%$ reduction in mean pain score from baseline to endpoint was higher in the pregabalin group compared to placebo (p-value=0.0390).
- Subjects in the pregabalin group had greater improvement in PGIC at endpoint compared to placebo (p-value=0.0006).
- Treatment with pregabalin resulted in a greater reduction in pain-related sleep interference score from baseline compared to placebo at endpoint (p-value<0.0001).

Other secondary endpoint results:

- The proportion of subjects who had a $\geq 50\%$ reduction in mean pain score from baseline to endpoint was higher in the pregabalin group compared to placebo (p-value=0.0256).

Primary Efficacy Results

The primary efficacy analysis was based on the primary endpoint, DAAC, in the mITT population, and the Applicant's results are presented in Table 28 below.

Table 28. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (mITT).

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.64 (1.465)	-5.9, 1.5	-1.66 (0.157)	-0.59 (0.198)	(-0.98, -0.20)	0.0032
Placebo	106	106	-1.05 (1.446)	-4.7, 3.1	-1.07 (0.149)	NA	NA	NA

Source: Table 13.4.2.1.1
 Abbreviations: DAAC=Duration Adjusted Average Change; N=number of subjects in MITT Population; n=number of subjects analyzed for this endpoint; LS=least squares; CI=confidence interval; Diff=difference; SE=standard error; NA=not applicable; MITT=modified intent to treat; ANCOVA=analysis of covariance; SD=standard deviation; Min=minimum; Max=maximum; DPRS=Daily Pain Rating Scale
 $DAAC = (Weighted\ Postbaseline\ Mean - Baseline) \times ([Total\ Postbaseline\ Days] / Planned\ Study\ Duration)$ based on the DPRS.
 If $(Total\ Postbaseline\ Days) \geq 112$ then $DAAC = (Weighted\ Postbaseline\ Mean - Baseline)$.
 LS means from ANCOVA model with terms of Baseline severity of pain and Baseline Pain Catastrophizing Scale (PCS) Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 81.

The results from the Applicant's analysis of DAAC, in the PP (Table 29) and ITT (Table 30) populations, are summarized in the tables below. They are consistent with the Applicant's analysis of DAAC in the mITT population.

Table 29. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (PP).

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment vs Placebo		
								Difference (SE)	95% CI	p-value
Pregabalin	77	77	-5.3	-1.68	0.6	-1.86 (1.352)	-1.95 (0.173)	-0.69 (0.219)	(-1.12, -0.26)	0.0020
Placebo	80	80	-4.7	-1.03	1.5	-1.22 (1.412)	-1.25 (0.163)			

N is the number of subjects in the PP population for the given treatment group.
 n is the number of subjects that can be analyzed for the given endpoint.
 DAAC - Duration Adjusted Average Change.
 $DAAC = (Weighted\ Post-Baseline\ Mean - Baseline) \times (Total\ Post-Baseline\ Days) / Planned\ Study\ Duration$.
 If $(Total\ Post-Baseline\ Days) \geq 112$ then $DAAC = (Weighted\ Post-Baseline\ Mean - Baseline)$.
 PP - Per Protocol.
 SD - Standard Deviation, SE - Standard Error, CI - Confidence Interval.
 LS Means from ANCOVA model with terms of baseline severity of pain and Baseline Pain Catastrophizing Scale Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
 PFIZER CONFIDENTIAL Source Data: A10.2.1.2 Date of Reporting Dataset Creation: 16MAY2011 Date of Table Generation: 27JUN2011 (10:19)

Source: Applicant's Clinical Study Report for trial 1107, p 251.

Table 30. Study A008-1107: Applicant's Statistical Analysis (ANCOVA) and Summary of DAAC (ITT).

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment vs Placebo		
								Difference (SE)	95% CI	p-value
Pregabalin	111	111	-5.9	-1.56	1.5	-1.63 (1.459)	-1.66 (0.157)	-0.59 (0.198)	(-0.98, -0.20)	0.0032
Placebo	108	108	-4.7	-0.81	3.1	-1.06 (1.448)	-1.07 (0.149)			

N is the number of subjects in the ITT population for the given treatment group.
 n is the number of subjects that can be analyzed for the given endpoint.
 DAAC - Duration Adjusted Average Change.
 $DAAC = (Weighted\ Post-Baseline\ Mean - Baseline) \times (Total\ Post-Baseline\ Days) / Planned\ Study\ Duration$.
 If $(Total\ Post-Baseline\ Days) \geq 112$ then $DAAC = (Weighted\ Post-Baseline\ Mean - Baseline)$.
 ITT - Intent to Treat.
 SD - Standard Deviation, SE - Standard Error, CI - Confidence Interval.
 LS Means from ANCOVA model with terms of baseline severity of pain and Baseline Pain Catastrophizing Scale Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
 PFIZER CONFIDENTIAL Source Data: A10.2.1.3 Date of Reporting Dataset Creation: 16MAY2011 Date of Table Generation: 27JUN2011 (10:18)

Source: Applicant's Clinical Study Report for trial 1107, p 252.

Reviewer comment: The results of the Applicant's primary efficacy analysis are supportive of a treatment effect in favor of pregabalin. However, the primary

endpoint is not acceptable for a chronic pain trial as this approach may assign good scores to subjects with bad outcomes (i.e., adverse dropouts).

The Applicant's analysis of DAAC, by country (mITT population), is summarized in the table below.

Table 31. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of the DAAC, by Country (mITT).

Country	Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment vs Placebo		
									Difference (SE)	95% CI	p-value
Chile	Pregabalin	105	1	-0.8	-0.80	-0.8	-0.80				
	Placebo	106	1	-4.4	-4.45	-4.4	-4.45				
China	Pregabalin	105	7	-2.6	-0.64	0.0	-1.04 (0.945)	-0.92 (0.451)	-0.08 (0.642)	(-1.50, 1.33)	0.8995
	Placebo	106	8	-2.8	-0.65	0.9	-0.72 (1.289)	-0.83 (0.419)			
Colombia	Pregabalin	105	2	-2.0	-1.05	-0.1	-1.05 (1.406)				
	Placebo	106	1	-4.0	-4.02	-4.0	-4.02				
Czech Republic	Pregabalin	105	4	-1.7	-1.37	-0.9	-1.32 (0.377)	-1.32 (0.365)	-0.86 (0.459)	(-1.95, 0.23)	0.1030
	Placebo	106	7	-1.8	-0.14	0.1	-0.46 (0.744)	-0.46 (0.275)			
Hong Kong	Pregabalin	105	3	-2.6	-1.97	-0.5	-1.69 (1.085)	-1.96 (0.708)	-0.59 (1.013)	(-3.81, 2.64)	0.6040
	Placebo	106	4	-2.6	-1.42	-0.8	-1.57 (0.787)	-1.37 (0.595)			
India	Pregabalin	105	9	-5.1	-2.32	-0.9	-2.44 (1.293)	-2.59 (0.463)	-1.13 (0.664)	(-2.55, 0.29)	0.1105
	Placebo	106	9	-4.0	-1.54	1.0	-1.60 (1.558)	-1.46 (0.463)			
Japan	Pregabalin	105	32	-4.2	-1.13	0.6	-1.24 (1.193)	-1.23 (0.232)	-0.95 (0.343)	(-1.64, -0.26)	0.0078
	Placebo	106	27	-4.2	-0.01	3.1	-0.28 (1.424)	-0.28 (0.253)			
Philippines	Pregabalin	105	6	-4.6	-2.44	-0.7	-2.60 (1.706)	-2.32 (0.386)	-0.45 (0.590)	(-1.85, 0.94)	0.4690
	Placebo	106	5	-3.6	-1.13	0.0	-1.53 (1.428)	-1.86 (0.425)			
Russian Federation	Pregabalin	105	8	-4.8	-1.19	1.5	-1.41 (1.827)	-1.34 (0.610)	-0.05 (0.830)	(-1.86, 1.76)	0.9505
	Placebo	106	9	-3.2	-0.99	0.4	-1.15 (1.260)	-1.29 (0.534)			
United States	Pregabalin	105	33	-5.9	-1.72	0.3	-1.92 (1.714)	-1.89 (0.279)	-0.48 (0.385)	(-1.25, 0.29)	0.2215
	Placebo	106	35	-4.7	-1.29	0.9	-1.35 (1.346)	-1.41 (0.258)			

N is the number of subjects in the MITT population for the given treatment group.
 n is the number of subjects that can be analyzed for the given endpoint.
 DAAC - Duration Adjusted Average Change.
 DAAC = (Weighted Post-Baseline Mean - Baseline)*(Total Post-Baseline Days) / Planned Study Duration).
 If (Total Post-Baseline Days) >= 112 then DAAC = (Weighted Post-Baseline Mean - Baseline).
 MITT - Modified Intent to Treat.
 SD - Standard Deviation, SE - Standard Error, CI - Confidence Interval.
 LS Means from ANCOVA model with terms of baseline severity of pain and Baseline Pain Catastrophizing Scale Total Score as covariates and treatment as a fixed (class) cofactor.
 PFIZER CONFIDENTIAL Source Data: A10.2.1.7 Date of Reporting Dataset Creation: 16MAY2011 Date of Table Generation: 27JUN2011 (12:02)

Source: Applicant's Clinical Study Report for trial 1107, p 256.

Reviewer comment: Although the trial was not powered to detect differences within individual countries, the treatment effect in the United States, as measured by the DAAC, was in a similar direction compared to other countries.

Key Secondary Efficacy Results

- Change from baseline in the mean pain score at endpoint
 - The baseline mean pain scores (SD) for the pregabalin and placebo groups (mITT population) were 6.5 (1.45) and 6.5 (1.41), respectively. The mean pain scores (SD) at endpoint (mBOCF) were 4.6 (2.37) and 5.3 (2.13), respectively.
 - The Applicant's results for the change from baseline in the weekly mean pain score at endpoint in the mITT (mBOCF) are summarized in Table 32 below. The Applicant's results in the PP (LOCF) and the ITT (LOCF) populations were consistent with those in the mITT population.

Table 32. Trial 1107: Applicant's Statistical Analysis (ANCOVA) and Summary of Changes from Baseline in Mean Pain Score at Endpoint (mITT; mBOCF).

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.90 (1.906)	-7.0, 2.6	-1.92 (0.203)	-0.70 (0.255)	(-1.20, -0.20)	0.0066
Placebo	106	106	-1.18 (1.778)	-6.4, 4.0	-1.22 (0.192)	NA	NA	NA

Source: Table 13.4.3.8.1
 Abbreviations: N=number of subjects in MITT Population; n=number of subjects analyzed for this endpoint; LS=least squares; CI=confidence interval; Diff=difference; SE=standard error; NA=not applicable; mBOCF=modified Baseline observation carried forward; MITT=modified intent to treat; ANCOVA=analysis of covariance; SD=standard deviation; Min=minimum; Max=maximum; LOCF=last observation carried forward
 On the Daily Pain Rating Scale (DPRS), 0=no pain and 10=worst possible pain.
 Endpoint (mBOCF) was implemented for subjects who discontinued due to an adverse event or had no postbaseline observation, otherwise, Endpoint (LOCF) applied. Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applied if the Week 16 assessment was missing.
 LS means from ANCOVA model with terms of Baseline severity of pain and Baseline Pain Catastrophizing Scale (PCS) Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 83.

- ≥30% reduction from baseline in mean pain score at endpoint
 - The Applicant's results are presented Table 33 below.

Table 33. Trial 1107: Applicant's Statistical Analysis (Logistic Regression) of Subjects with ≥30% Reduction from Baseline in Mean Pain Score (Responders) at Endpoint (mITT; LOCF).

	No.	Evaluable N	Responders n (%)	Difference From Placebo		
				Odds Ratio	95% CI for OR	p-value
Pregabalin	105	105	48 (45.7)	1.85	(1.032, 3.328)	0.0390
Placebo	106	105	33 (31.4)	NA	NA	NA

Source: Table 13.4.4.1.1
 Abbreviations: No. or N=number of subjects; n=number of responders; NA=not applicable; CI=confidence interval; OR=odds ratio; LOCF=last observation carried forward; MITT=modified intent to treat
 Summary statistics based on subjects with both Baseline and endpoint data.
 Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applied if the Week 16 assessment was missing.
 Odds ratio and its 95% CI calculated by exponentiating the log odds ratio and 95% CI that correspond to the treatment contrast in the Logistic Regression Model with pooled center and treatment as the categorical factors, and Mean Pain Score at Baseline and Baseline Pain Catastrophizing Scale (PCS) Total Score as the covariates.
 Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 84.

The Applicant's analysis of subjects with ≥30% reduction from baseline in mean pain score at endpoint (responders) in the mITT population using an mBOCF imputation strategy showed that 47/105 (44.8%) subjects in the pregabalin group were classified as responders based on this criterion compared to 32/106 (30.2%) subjects in the placebo group (p-value=0.0356). The Applicant's analysis in the PP (LOCF) and ITT (LOCF) populations were consistent with the above results.

Reviewer comment: The Applicant's analysis on the key secondary endpoints are supportive of a treatment effect in favor of pregabalin. The Applicant used a

sequential step down procedure to control for multiplicity when analyzing the key secondary endpoints.

Other Secondary Endpoints

- ≥50% reduction from baseline in mean pain score at endpoint
 - The Applicant’s results for the mITT population (LOCF) are summarized in Table 34 below. The Applicant’s analysis in the PP (LOCF) and ITT (LOCF) populations were consistent with the results in the mITT population.

Table 34. Trial 1107: Applicant's Statistical Analysis (Logistic Regression) of Subjects with ≥50% Reduction from Baseline in Mean Pain Score (Responders) at Endpoint (mITT; LOCF).

	No.	Evaluable N	Responders n (%)	Difference From Placebo		
				Odds Ratio	95% CI for OR	p-value
Pregabalin	105	105	31 (29.5)	2.24	(1.103, 4.546)	0.0256
Placebo	106	105	16 (15.2)	NA	NA	NA

Source: Table 13.4.4.2.1

Abbreviations: No. or N=number of subjects; n=number of responders; NA=not applicable; CI=confidence interval; OR=odds ratio; LOCF=last observation carried forward; MITT=modified intent to treat

Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applies if the Week 16 assessment was missing.

Odds ratio and its 95% CI calculated by exponentiating the log odds ratio and 95% CI that correspond to the treatment contrast in the Logistic Regression Model with pooled center and Treatment as the categorical factors, and Mean Pain Score at Baseline and Baseline Pain Catastrophizing Scale (PCS) Total Score as the covariates.

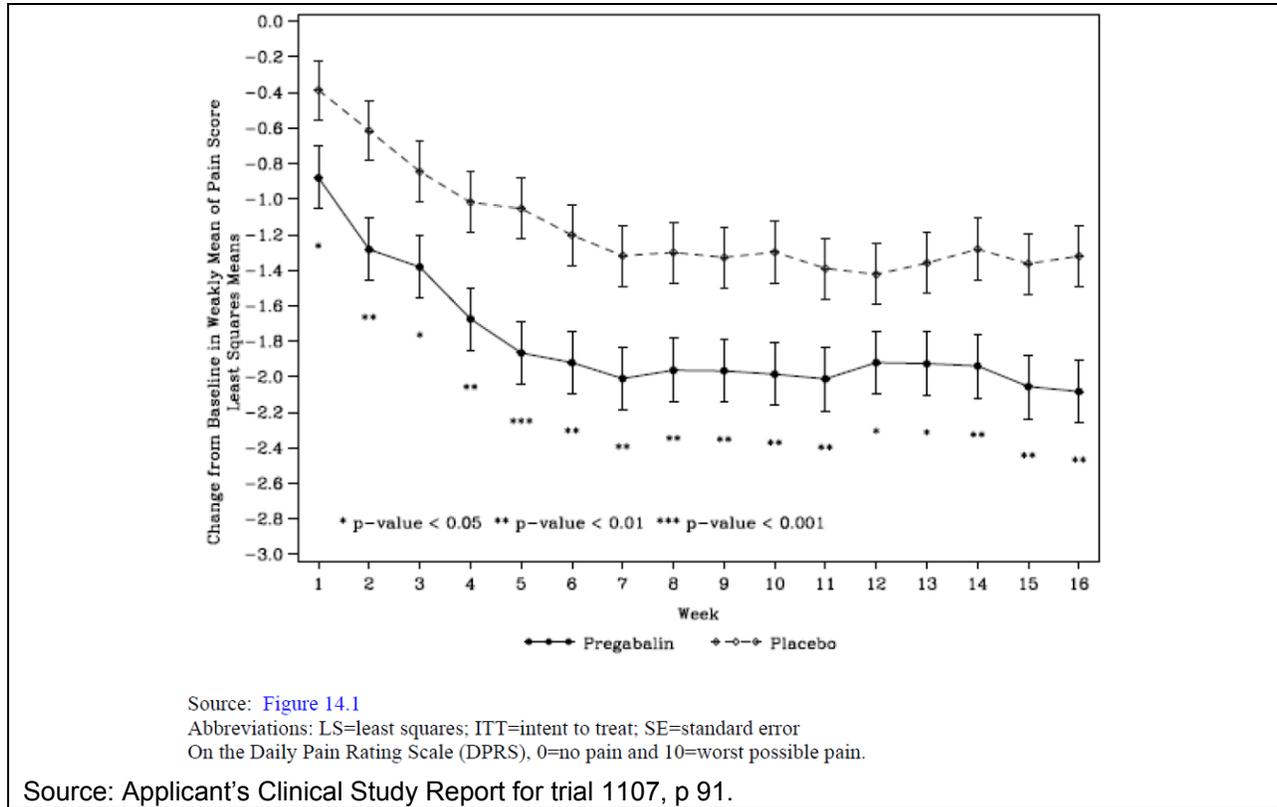
Summary statistics based on subjects with both Baseline and endpoint data.

Subject 11081001 was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.

Source: Applicant's Clinical Study Report for trial 1107, p 92.

- Weekly change from baseline in mean pain score
 - The Applicant’s results showed that treatment with pregabalin resulted in statistically significant improvements in mean pain scores from baseline compared to placebo for weeks 1 through 16 in the ITT population. The Applicant’s results are summarized in Figure 8 below.

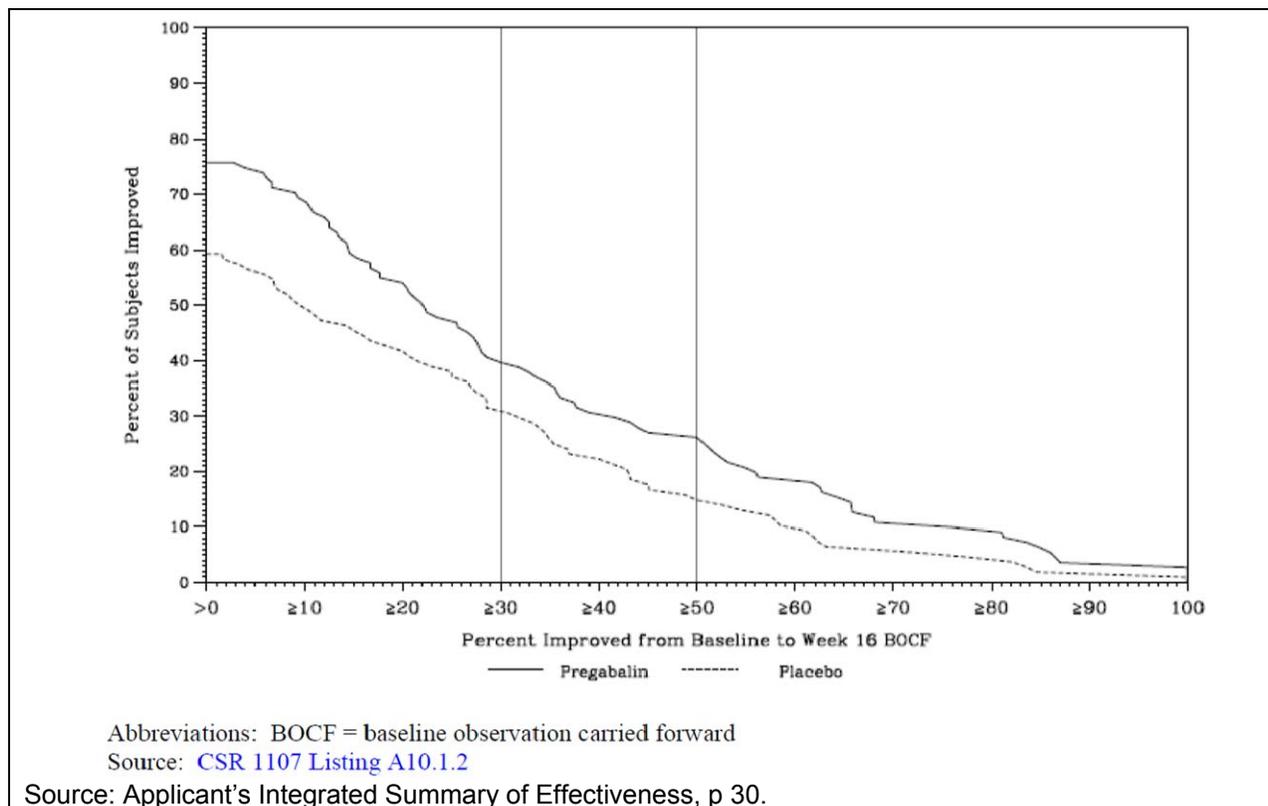
Figure 8. Trial 1107: Applicant's Analysis of LS Mean Changes (\pm SE) from Baseline in Weekly Mean Pain Score (ITT).



Supplemental Analysis

- The results of the Applicant's cumulative responder analysis are presented in the figure below (Figure 9). Subjects who did not complete the study were assigned 0% improvement.

Figure 9. Trial 1107: Applicant's Cumulative Responder Analysis (BOCF).



Reviewer comment: While the results of the Applicant's supplemental analyses and analyses on other secondary endpoints are supportive of a treatment effect in favor of pregabalin, no adjustments were made to control for multiplicity on these endpoints.

The statistical reviewer conducted a statistical analysis, and his findings will be discussed in detail in Section 6 (p 77).

Safety Findings

A brief summary of the safety findings for this clinical trial is provided herein. A complete discussion of safety can be found in Section 7 (p 88).

Deaths

No subjects died during the trial.

Serious Adverse Events (SAEs)

Nine (8%) subjects experienced SAEs in the pregabalin group, and 10 (9.3%) subjects experienced SAEs in the placebo group. There were 12 SAEs in each treatment group, and 9 of the 12, in each group, were severe in intensity. SAEs in the pregabalin group included three reports of pneumonia and one report each of bradycardia, cholelithiasis,

dysuria, hypoglycemia, hypotension, muscle spasms, pain in extremity, Prinzmetal angina, and ulnar fracture.

Discontinuations Due to Adverse Events

Eight (7.1%) subjects discontinued the study due to AEs in the pregabalin group, and 8 (7.5%) subjects discontinued due to AEs in the placebo group. Three of the eight AEs resulting in discontinuation in the pregabalin group were SAEs (pneumonia, hypoglycemia, and hypotension).

Common Adverse Events

In the pregabalin group, 95 (84.8%) subjects experienced at least 1 TEAE with a total of 381 AEs reported. The most frequently reported TEAEs in the pregabalin group were somnolence (33%), dizziness (19.6%), and peripheral edema (13.4%).

6 Review of Efficacy

Efficacy Summary

Based on the review of two phase 3, randomized, double-blind, placebo-controlled clinical trials evaluating 150-600 mg per day of pregabalin, in twice daily divided doses, there was evidence of efficacy for pregabalin in the treatment of central neuropathic pain associated with spinal cord injury. For both trials, the analyses of the acceptable primary endpoints were statistically significant in favor of pregabalin.

The prespecified primary endpoints for the clinical trials, 1107 and 125, were the DAAC and the weekly mean pain score at endpoint, respectively. In trial 125, endpoint was defined as the mean of the last seven post-randomization entries of the daily pain diary while on study drug. That is, endpoint could occur at any time in the post-randomization period and not necessarily at the end of the planned treatment phase.

The Applicant's primary endpoints and analyses are of limited utility in a chronic pain trial, where symptomatic relief is the primary potential clinical benefit, in that subjects with bad outcomes could potentially contribute to findings of effectiveness (see Section 6.1.4, p 81). The design for trial 125 was chosen without the Agency's input as the trial was conducted entirely outside of the United States and not under an IND. Additionally, the primary endpoint for trial 1107, DAAC, was used despite advice provided at several milestone meetings and formal dispute resolution (see Section 2.5).

The Applicant proposes to use the proportion of subjects with at least 30% and at least 50% reduction in mean pain score from baseline to endpoint, cumulative responder analyses, and weekly change from baseline in the mean pain score in the label, which were performed as secondary analyses. For trial 125, the Applicant's analyses on the above endpoints did not involve an adjustment to control for multiplicity. While the 30%

responder analysis included an adjustment to control for multiplicity in trial 1107, the remainder of analyses on the above endpoints for that trial did not.

Although the Applicant's prespecified primary endpoints were not the Agency's preferred primary endpoints as they could potentially assign a treatment benefit to subjects with bad outcomes (i.e., discontinuation due to AEs), they demonstrated a treatment effect in favor of pregabalin that was statistically significant. The statistical reviewer evaluated the studies using the Agency's accepted primary efficacy analysis, a landmark analysis with a conservative imputation strategy, and a statistically significant treatment effect in favor of pregabalin was confirmed. This analysis also showed that the results on the abovementioned secondary endpoints support a treatment effect, with statistical significance, in favor of pregabalin with one exception. Although treatment with pregabalin increased the proportion of subjects with at least a 30% reduction in baseline pain intensity at endpoint in trial 1107, this finding did not reach statistical significance.

6.1 Indication

The proposed indication is for the management of neuropathic pain associated with spinal cord injury.

6.1.1 Methods

See Section 5.3, p 18.

6.1.2 Demographics

The demographics were generally comparable across treatment groups in each study. Basic demographic data, by study and treatment group, is presented below (Table 35). The most notable difference between studies with regard to demography was race. The most common race in trial 1107 was Asian, which represented approximately half of all subjects (49.1%-placebo; 51.4%-pregabalin). In contrast, the vast majority of subjects in trial 125 were white (98.5%-placebo; 95.7%-pregabalin). This difference reflects the locations where each trial took place. Trial 125 was entirely conducted in Australia, whereas trial 1107 was conducted in numerous countries, including several research centers in Asia (Table 19 details enrollment by country for trial 1107). For trial 1107, the Applicant analyzed their primary endpoint, DAAC, by country (refer to Table 31), and this showed that the treatment effect was in a similar direction for the United States population compared to subjects in other countries.

Table 35. Demographic Characteristics by Study and Treatment Group: Controlled Studies 1107 and 125.

Characteristic	Study 1107		Study 125	
	Pregabalin N = 111 n (%)	Placebo N = 108 n (%)	Pregabalin N = 70 n (%)	Placebo N = 67 n (%)
Sex				
Male	84 (75.7)	92 (85.2)	60 (85.7)	54 (80.6)
Female	27 (24.3)	16 (14.8)	10 (14.3)	13 (19.4)
Age (years)				
18-44	52 (46.8)	53 (49.1)	59 (84.3) ^a	58 (86.6) ^a
45-64	50 (45.0)	45 (41.7)		
≥65	9 (8.1)	10 (9.3)	11 (15.7) ^b	9 (13.4) ^b
Mean	46.1	45.6	50.3	49.8
Range	22 - 72	19 - 81	23 - 78	21 - 80
Race				
White	42 (37.8)	43 (39.8)	67 (95.7)	66 (98.5)
Black ^c	6 (5.4)	8 (7.4)	NA	NA
Asian ^d	57 (51.4)	53 (49.1)	2 (2.9)	1 (1.5)
Other	6 (5.4)	4 (3.7)	1 (1.4)	0 (0.0)
Hospitalized				
Yes	NA	NA	1 (1.4)	3 (4.5)
No	NA	NA	69 (98.6)	64 (95.5)

^aAge category in Study 125 was from 18 to 64 years.
^bAge categories in Study 125 of 65 to 74 and 75 to 84 were combined for this table.
^cClassification not included in Study 125.
^dClassified as Asian or Pacific Islander in Study 125.
 Abbreviations: n = sample population, N = total population, NA = not applicable
 Sources: CSR 1107 Tables 13.2.1.1 and 13.2.1.2; CSR 125 Table 9.1.2.1

Source: Applicant's Integrated Summary of Effectiveness, p 18.

Demographics, for trials 1107 and 125, are described in Section 5.3, p 18.

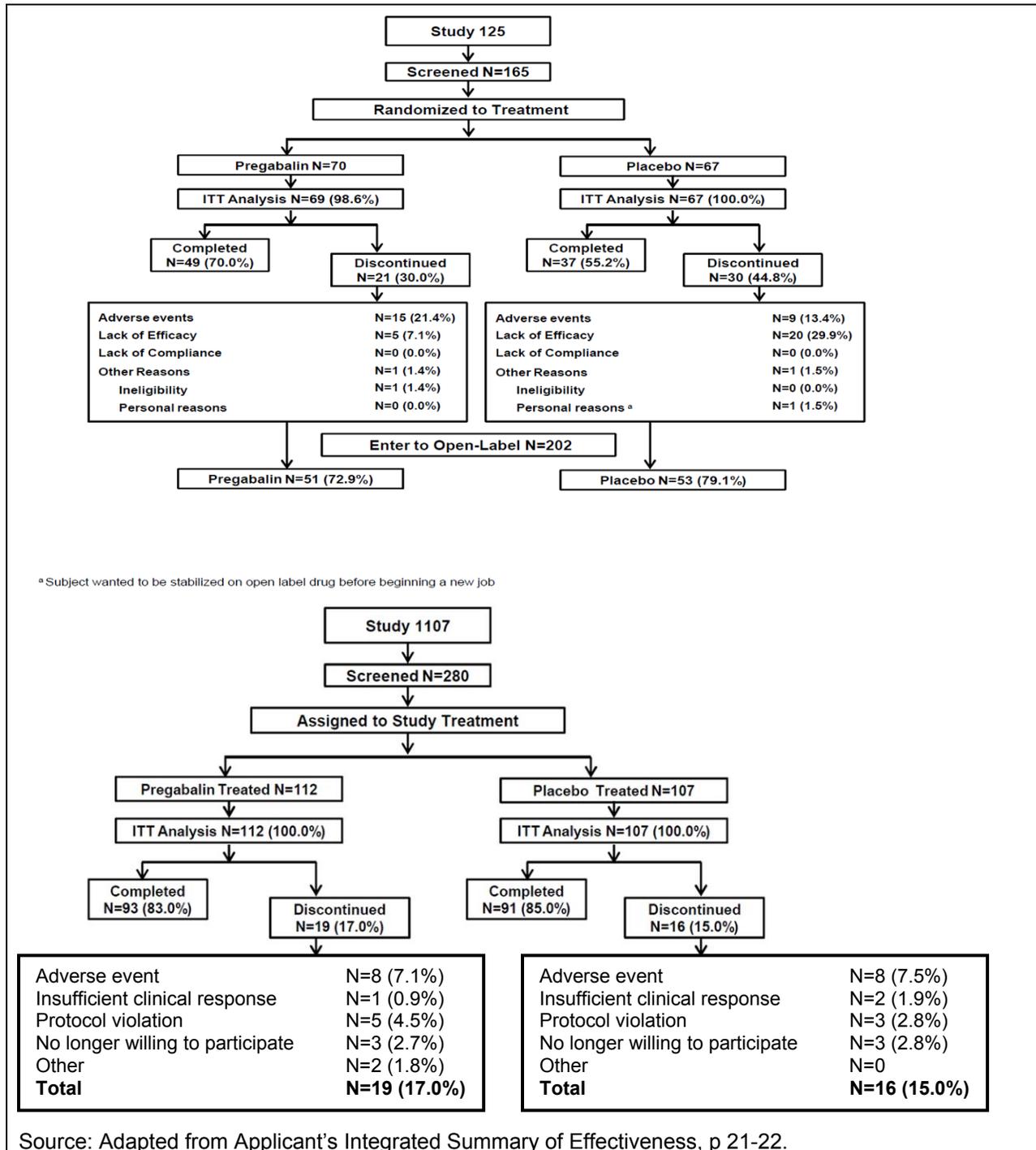
6.1.3 Subject Disposition

Refer to the figure below (Figure 10) for subject disposition in the controlled trials.

Discontinuation was higher for pregabalin- and placebo-treated subjects in trial 125 compared to trial 1107. Among pregabalin-treated subjects, this difference (30% and 17%, respectively) can be potentially explained by the frequency of discontinuation due to AEs in each trial. In trial 125, 21.4% of subjects discontinued due to AEs compared to 7.1% in trial 1107. This difference may be partly attributed to study design. Trial 125 had a shorter titration period (3 weeks compared to 4 weeks in trial 1107) and less flexibility during the dose maintenance phase. In trial 1107, subjects were allowed to decrease their dose by one level on one occasion only for intolerable AEs during the maintenance phase, whereas this flexibility was not outlined in the protocol for trial 125. As a result, more pregabalin-treated subjects reached a maximum daily dose of 600 mg

for trial 125 as compared to trial 1107 (77.1% and 38.7%, respectively; see Table 11 and Table 27).

Figure 10. Subject Disposition for Controlled Trials 125 and 1107.



Subject disposition, for trials 1107 and 125, is described in Section 5.3, p 18.

6.1.4 Analysis of Primary Endpoint(s)

Trial 125

The Applicant's primary endpoint for trial 125 was the weekly mean pain score at endpoint, defined as the mean of the last seven post-randomization entries of the daily pain diary while on study drug. Since endpoint could occur at any time during the post-randomization phase rather than at the end of the treatment period (Week 12), subjects with bad outcomes (i.e., adverse dropouts) could potentially contribute good pain scores to the efficacy analysis. The endpoint mean pain score, as defined, is equivalent to using LOCF for Week 12 pain scores. The only benefit of analgesic drugs to patients is symptomatic improvement, therefore, evidence of efficacy based, in part, on subjects with bad outcomes is of questionable value for informing patient use. Therefore, the statistical reviewer, considered the primary endpoint to be the change from baseline in pain intensity (PI) at Week 12. This trial was entirely conducted in Australia and not under an IND; therefore its design was chosen without the Agency's input.

See Section 5.3 for a discussion of the Applicant's analysis on the prespecified primary endpoints.

Mr. Petullo performed an analysis on the change from baseline to Week 12 in PI using BOCF and modified BOCF (mBOCF; BOCF for missing data due to AEs and LOCF for all other missing data) to handle missing data. Subjects needed at least 4 pain scores during Week 12, otherwise the data was considered missing. The Applicant excluded any subject that lacked post-treatment efficacy assessments from the ITT population. With this criterion, only one subject was excluded from the Applicant's ITT population. However, Mr. Petullo included this subject in his primary efficacy analysis. There was a statistically significant treatment effect observed in favor of pregabalin regardless of how missing data was handled (Table 36).

Table 36. Primary Efficacy Analysis for Trial 125.

Imputation	Treatment	N	Mean Pain Intensity (SE)			
			Baseline	WK12	Change	p-value
BOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.1)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.2 (0.2)	< 0.001
mBOCF	Placebo	67	6.7 (0.2)	6.4 (0.2)	0.3 (0.2)	
	Lyrica	70	6.5 (0.2)	5.3 (0.3)	1.3 (0.2)	< 0.001

Source: David Petullo, MS, Statistical Review, Table 4, p 9.

Trial 1107

The Applicant’s primary endpoint for trial 1107, the DAAC, also potentially assigns good scores for subjects with bad outcomes. The DAAC is the difference between the baseline pain score and the mean of all post-baseline pain scores, adjusted by the proportion of the planned study duration completed by the subject. The Applicant submitted the primary efficacy analysis based on the DAAC despite advice provided at several milestone meetings and formal dispute resolution (see Section 2.5, p 11).

See Section 5.3 (p 18) for a discussion of the Applicant’s analysis on the prespecified primary endpoints.

Mr. Petullo considered the primary endpoint to be the change in baseline PI at Week 16, and he performed his analysis on the ITT population. One subject, 11081001, was randomized to placebo, however, this subject received pregabalin. Mr. Petullo considered this subject to be in the placebo group for his primary efficacy analysis. The results of his analysis using BOCF and mBOCF imputation strategies are summarized in the table below (Table 37). Regardless of the imputation method, there was a statistically significant treatment effect in favor of pregabalin.

Table 37. Primary Efficacy Analysis for Trial 1107.

Imputation	Treatment	N	Mean Pain Intensity (SE)				
			baseline	Wk16	Change	Diff	p-value
BOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.014
mBOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.015

Source: David Petullo, MS, Statistical Review, Table 13, p 15.

Summary Comment

The statistical reviewer’s analysis on the Agency’s accepted primary endpoints are supportive of a treatment effect in favor of pregabalin. See his review for additional details.

6.1.5 Analysis of Secondary Endpoints(s)

Trial 125

The Applicant assessed the following key secondary endpoints for trial 125¹⁵:

- Weekly mean sleep interference score at endpoint
- MOS optimal sleep score at endpoint

¹⁵ The Applicant did not make any adjustments to control for multiplicity for the analyses on these endpoints.

- SF-MPQ VAS score at endpoint
- HADS anxiety subscale score at endpoint
- PGIC at endpoint

See Section 5.3 for a discussion of the Applicant’s analysis on the aforementioned prespecified key secondary endpoints.

Trial 1107

The Applicant assessed the following key secondary endpoints for trial 1107¹⁶:

- Change from baseline to endpoint in the mean pain score from subject diary (mITT population, mBOCF imputation)
- Proportion of subjects with ≥30% reduction in weekly mean pain score from baseline to endpoint (mITT population, LOCF imputation)
- PGIC at endpoint (mITT population, LOCF imputation)
- Change from baseline to endpoint in mean sleep interference score from subject diary (mITT population, LOCF imputation)

See Section 5.3 (p 18) for a discussion of the Applicant’s analysis on the aforementioned prespecified key secondary endpoints.

The results of the statistical reviewer’s analysis on the proportion of subjects with at least a 30% response rate was tested using the ITT population. Mr. Petullo considered subjects who withdrew prior to Week 16 or had missing PI scores for Week 16 as non-responders in his analysis. The Applicant performed the analysis on the mITT population and used LOCF for subjects with missing Week 16 data. Mr. Petullo’s results are presented in the table below (Table 38) alongside the Applicant’s results. Treatment with pregabalin increased the proportion of subjects with at least a 30% reduction in baseline PI at Week 16, although this finding did not reach statistical significance.

Table 38. Proportion of Subjects with at Least a 30% Reduction in Baseline Pain at Week 16 for Trial 1107.

Analysis	Proportion of responders (%)		p-value
	placebo	Lyrica	
Applicant	33/105 (31)	48/105 (46)	0.04
FDA	32/108 (30)	43/111 (39)	0.16

Source: David Petullo, MS, Statistical Review, Table 16, p 17.

¹⁶ The Applicant used a sequential step down procedure in the analysis of key secondary endpoints to adjust for multiplicity.

Summary Comment

Although not statistically significant, the statistical reviewer's analysis showed that pregabalin increased the proportion of subjects with at least a 30% reduction in baseline pain at Week 16 for trial 1107. This finding is supportive of the results from the primary efficacy analysis.

6.1.6 Other Endpoints

Trial 125

The Applicant assessed the following additional secondary endpoint for trial 125:

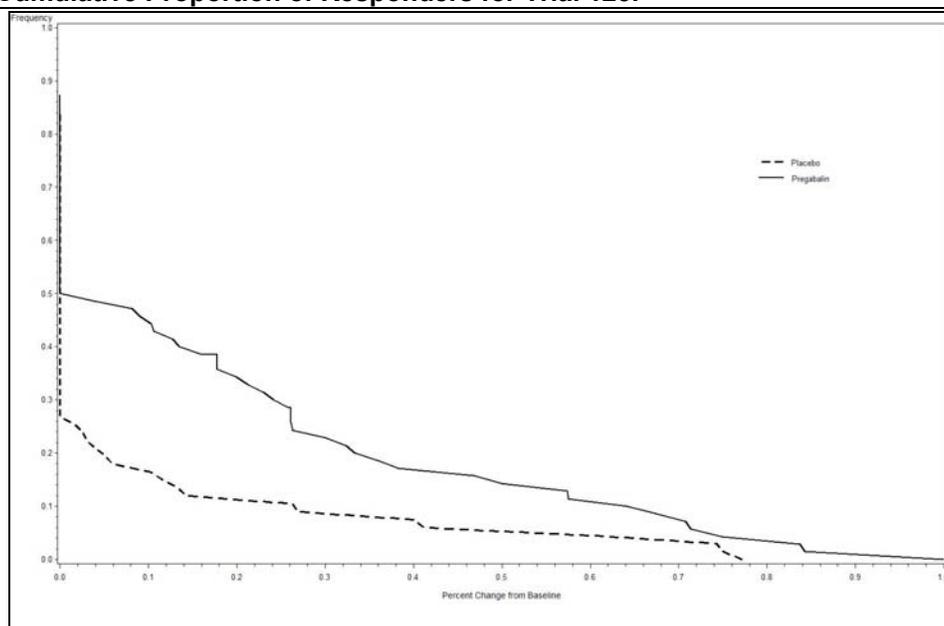
- Weekly mean pain score

The Applicant performed supplemental analyses on the proportion of subjects with at least 30% and at least 50% reduction in mean pain score from baseline to endpoint. The Applicant also performed a cumulative responder analysis at endpoint.

See Section 5.3 (p 18) for a discussion of the Applicant's analysis on the aforementioned endpoints.

The statistical reviewer performed a cumulative responder analysis. If subjects were missing the Week 12 assessment, they were considered to be non-responders. The analysis is presented in Figure 11 below. There is clear separation between the two curves, with pregabalin having a better response profile compared to placebo. This difference was reported as statistically significant.

Figure 11. Cumulative Proportion of Responders for Trial 125.



Source: David Petullo's analysis.

Mr. Petullo also looked at the proportion of subjects who achieved at least a 30% reduction in PI from baseline to Week 12 using a BOCF approach for missing data (Table 39). Note, in the Applicant's analyses, study endpoint was not Week 12 for all subjects. There are more responders in the pregabalin arm than the placebo arm, and the difference is statistically significant.

Table 39. Proportion of Subjects with at least a 30% Reduction in Pain Intensity from Baseline to Week 12 for Trial 125.

Imputation	Proportion of responders (%)		p-value
	placebo	Lyrica	
Applicant	11/67 (16)	29/69 (42)	0.001
Reviewer	6/67 (9)	18/70 (26)	0.02

Source: David Petullo, MS, Statistical Review, Table 7, p 11.

Trial 1107

The Applicant assessed the following additional endpoints for trial 1107:

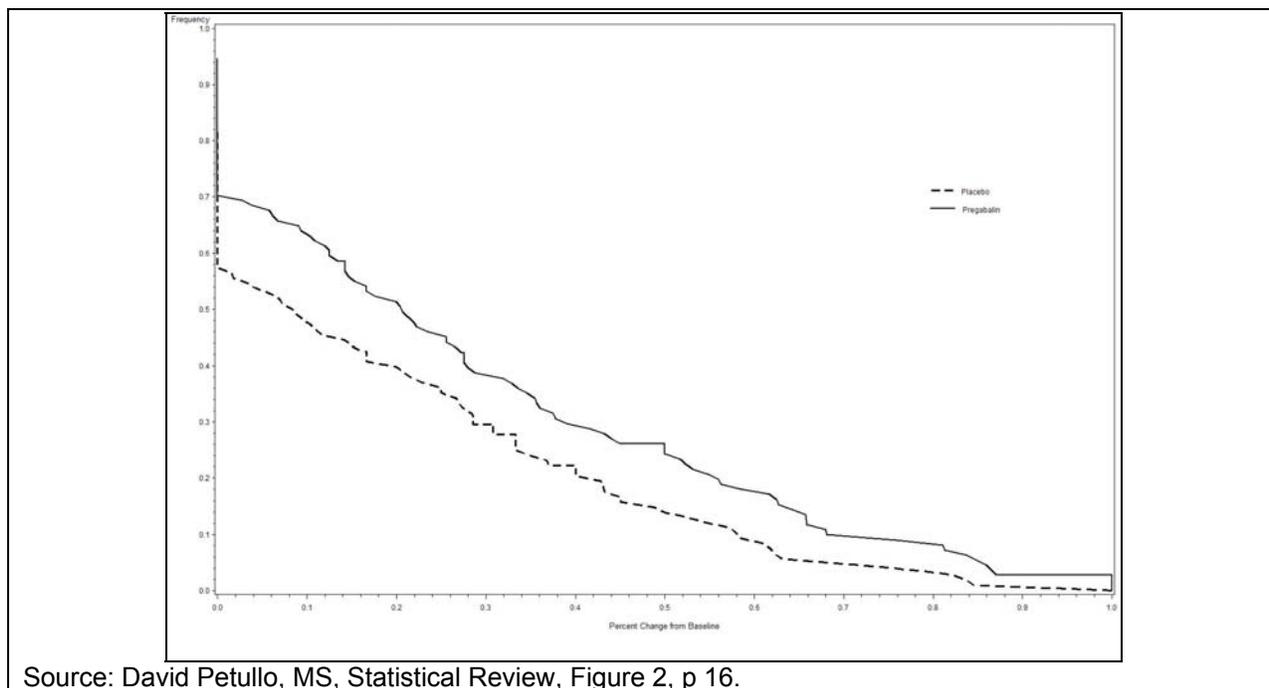
- Proportion of subjects with $\geq 30\%$ reduction from baseline in mean pain score at weekly assessment
- Proportion of subjects with $\geq 50\%$ reduction from baseline in mean pain score at weekly assessment and at endpoint
- Weekly change from baseline in mean pain score (repeated measures model)

The Applicant performed a cumulative responder analysis as a supplemental analysis.

See Section 5.3 (p 18) for a discussion of the Applicant's analysis on the aforementioned endpoints.

The results of Mr. Petullo's cumulative responder analysis are presented in Figure 12 below. There is clear separation between the two curves with pregabalin having a better response profile compared to placebo. This difference was statistically significant.

Figure 12. Cumulative Proportion of Responders for Trial 1107.



Summary Comment

The results of Mr. Petullo's cumulative responder analyses for trials 125 and 1107 and his analysis on the proportion subjects who achieved at least a 30% reduction in PI from baseline to Week 12 for trial 1107 are supportive of a treatment effect in favor of pregabalin. The Applicant's analysis of the proportion of subjects with at least 50% reduction in mean pain score from baseline to endpoint for trials 125 and 1107 was indicative of a treatment effect in favor of pregabalin, and this result was statistically significant (confirmed by Mr. Petullo; see his review for more details). However, the Applicant did not make any adjustments to control for multiplicity on these endpoints, and LOCF was used for missing data.

6.1.7 Subpopulations

Mr. Petullo evaluated the primary efficacy results with respect to gender, race, age (≤ 55 years old or > 55 years old), study site (trial 125), and country (trial 1107). For trial 125, the vast majority of subjects were reported as being Caucasian (95.7-98.5%), therefore racial subgroups were not summarized. There were no significant interactions by gender, age, or study site. The subgroup analyses, by age and gender, show a treatment difference that favors pregabalin. While there was an overall treatment effect noted by study site, the effect for individual sites was not significant as the trial was not powered to detect a difference at individual sites. For trial 1107, there were no significant interactions for age, racial subgroups (Caucasian, Asian, Black, Other), and gender. Mr. Petullo also performed a subgroup analysis by country, and he found that,

while not statistically significant, the treatment effect in the United States trended toward favoring pregabalin. The study was not powered to detect a treatment effect in individual countries. See Mr. Petullo's review for more details.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Pregabalin was evaluated at a dose of 150-600 mg per day, given in twice daily divided doses, in two adequate and well-controlled clinical trials. Evaluation of dose-response is limited by the flexible-dose design used in both trials. A similar dose regimen for this drug is currently approved for the management of postherpetic neuralgia and partial onset seizures with a reduced maximum recommended dose of 450 mg/day for patients with fibromyalgia and 300 mg/day for patients with painful diabetic peripheral neuropathy.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The Applicant performed analyses on the weekly mean pain score (trial 125) and weekly change from baseline in mean pain score (trial 1107). The results of the Applicant's analysis suggest that subjects had a decrease in pain score in week 1, which persisted throughout the treatment phase (Week 12 for trial 125; Week 16 for trial 1107), in favor of pregabalin. These results were confirmed by Mr. Petullo (see his review for more details). However, the Applicant did not make any adjustments to control for multiplicity on these endpoints. See Section 5.3 for more details regarding the Applicant's results.

6.1.10 Additional Efficacy Issues/Analyses

Exploratory Responder Analysis

Mr. Petullo performed an exploratory responder analysis to evaluate the significance of the primary efficacy results of both clinical trials. If a subject had a moderate pain score (PI between 4 and 7) at baseline reduced to a mild pain score (PI between 1 and 3) at endpoint (Week 12 for trial 125 and Week 16 for trial 1107), they were considered a responder. For trial 125, there were more responders in the pregabalin group than in the placebo group, and the difference was statistically significant. A similar analysis was performed for trial 1107. While there was not a statistically significant difference between study groups, the treatment effect was in the direction favoring pregabalin. Refer to Mr. Petullo's review for more details regarding this analysis. These findings are supportive of the primary efficacy analyses.

Exploratory Concomitant Medication Analysis

In trial 1107, a subset of subjects used concomitant medications that possibly could have influenced their pain scores and were potentially in violation of the protocol. Mr. Petullo performed an analysis to explore the influence of these subjects on his primary efficacy analysis using two approaches. The first approach was to exclude these

subjects. The second approach was to include them in the analysis, but to consider them as treatment failures (i.e., no change in pain intensity). Based on this exploratory analysis, there was still a significant treatment effect in favor of pregabalin. See Section 3.2 (p 13) for details regarding OSI's inspectional findings that prompted this analysis and Section 5.3 (p 18) Protocol Violations, under Trial 1107 for more details. Also, see Mr. Petullo's review.

7 Review of Safety

Safety Summary

The safety profile of pregabalin in the central neuropathic pain associated with spinal cord injury (CNP-SCI) population was assessed in 235 subjects who received at least 1 dose of pregabalin. Pregabalin was dosed 150 to 600 mg per day, divided twice daily, and was evaluated through flexible dose design trials. Of the 235 subjects, 84 (35.7%) received pregabalin at any dose for at least 24 weeks, and 68 (28.9%) received pregabalin at any dose for at least 52 weeks.

Pregabalin- and placebo-treated CNP-SCI subjects experienced a higher frequency of somnolence (see Section 7.3.5 for a discussion) compared to populations for previously approved indications. Otherwise, the safety profile is relatively consistent with what is currently contained in the approved labeling. No new significant safety concerns were identified that were unique to the CNP-SCI population.

The information available within this application appears adequate to assess the safety of pregabalin in the CNP-SCI population.

Deleted Sections

- No data was submitted to inform a discussion of Sub-sections 7.2.3 Special Animal and/or In Vitro Testing and 7.2.5 Metabolic, Clearance and Interaction Workup, and these sections were deleted.
- Sub-sections 7.2.2 Exploration for Dose Response and 7.5.1 Dose Dependency for Adverse Events were deleted. These sections were not relevant to this application because of study design (flexible dosing schedule).
- Sub-section 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class was not relevant to the review of this application and was deleted.
- Sub-section 7.4.6 was deleted because there are no immunogenicity concerns to discuss.
- No data was submitted to inform a discussion of Sub-section 7.5.5 Drug-Drug Interactions, and this section was deleted.
- Sub-section 7.6.1 was deleted because there were no data submitted on human carcinogenicity.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Two controlled trials and one uncontrolled, open-label trial conducted in the CNP-SCI population were submitted in support of this supplemental NDA. Refer to Section 5.1 (p 16) for a brief listing and Section 5.3 (p 18) for a detailed description of the controlled trials (1107 and 125).

Trial 202 was an open-label extension of trial 125 conducted in Australia. A total of 103 subjects (50 from the pregabalin group and 53 from the placebo group) were treated with pregabalin 150-600 mg/day, in twice daily divided doses. Subjects were started on pregabalin 150 mg/day and titrated up to 600 mg/day as needed through a flexible dose design. The planned duration was nine months of open-label treatment with mandatory drug holidays every three months.

The Applicant submitted safety information from two additional trials as part of this submission. A008-1063 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose trial conducted at 32 centers in the Asia Pacific region to evaluate the efficacy of pregabalin in subjects with central poststroke pain. A008-1252 is an ongoing open-label extension of trial 1107 being conducted in Japan in subjects with CNP-SCI, central neuropathic pain associated with multiple sclerosis, or poststroke central neuropathic pain. This trial included a broader range of central neuropathic pain subjects as requested by the Japanese regulatory authority. Well over half (63%, 65/103) of subjects in this trial have either central neuropathic pain associated with multiple sclerosis or poststroke pain. The subject population in both of these trials is not representative of the indicated patient population.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA) Version 14.0 terminology. The Applicant's approach to safety coding appears to be adequate.

The term, adverse event, as it appears in this review, refers to all-causality, TEAEs.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant pooled safety data for the two controlled trials (1107 and 125) and for the combined controlled and uncontrolled trials (1107, 125, and 202). The controlled trials were of similar design. They included 356 subjects; 182 received at least 1 dose of pregabalin and 174 received at least 1 dose of placebo. The combined controlled and uncontrolled trials included 235 subjects who received at least 1 dose of pregabalin.

The combined population consisted of 182 pregabalin-treated subjects from the controlled trials and 53 subjects who previously received placebo in controlled trial 125, and subsequently received pregabalin in open-label extension trial 202.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

In the controlled trials (1107 and 125), there do not appear to be any significant differences between pregabalin and placebo with respect to treatment exposure. Table 40 summarizes treatment exposure for the pooled controlled and uncontrolled CNP-SCI population. Eighty-four (35.7%) subjects received pregabalin at any dose for at least 24 weeks, and 68 (28.9%) subjects received pregabalin at any dose for at least 52 weeks.

Table 40. Summary of Cumulative Exposure to Pregabalin in the Controlled and Uncontrolled CNP-SCI Trials: 1107, 125, and 202.

	Number of Subjects ^a						Any Dose#
	Total Daily Dose of Pregabalin (mg/day)						
	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	>=600	
<24 weeks	0	137	211	187	119	97	151
>=24 weeks, <36 weeks	0	0	6	8	2	3	8
>=36 weeks, <52 weeks	0	0	4	5	3	0	8
>=52 weeks, <104 weeks	0	0	10	9	6	11	27
>=104 weeks, <156 weeks	0	0	3	4	4	15	34
>=156 weeks	0	0	1	0	0	0	7
Total Subject-Days	0	228	16132	18838	11451	25316	71965
Total Subject-Weeks	0	32.57	2304.57	2691.14	1635.86	3616.57	10280.71
Total Subject-Years	0	0.62	44.17	51.58	31.35	69.31	197.03

^a Each subject is counted only once within a column. Subjects who received more than one dose level of pregabalin will appear in multiple columns.
[#] Indicates days on all specified pregabalin doses. Does not include days off drug and days when dose was unknown.
 PFIZER CONFIDENTIAL Date of Table Generation: 24FEB2012 (09:49)

Source: Applicant's response to information requested in the Filing Letter (dated 3/9/2012), p 2.

Reviewer comment: Treatment exposure appears adequate for the CNP-SCI population to support the safety findings in this supplemental NDA.

Demographics

Among the controlled trials, the pregabalin and placebo groups appear to be comparable with respect to baseline demographic and other subject characteristics and

commonly reported underlying diseases. Demographic information is reviewed in more detail in Section 5.3 (p 18) under each individual trial.

7.2.4 Routine Clinical Testing

The safety monitoring plan is outlined for each of the controlled CNP-SCI trials in Section 5.3 (p 18), and it appears adequate for this population.

7.3 Major Safety Results

7.3.1 Deaths

One subject with CNP-SCI died during clinical investigation, and this death occurred in the open-label trial (202). No other deaths, in any of the trials submitted, were reported.

Subject 004-2 was a 63-year-old Caucasian male with a history of paraplegia, osteoporosis/osteopenia, and esophageal adenocarcinoma arising in the background of Barrett's esophagus who died of metastatic carcinoma during the open-label extension trial (202). He received daily treatment with pregabalin dosed at 150-600 mg per day from study day 1 through study day 938. His history is also significant for two left femur fractures while on study drug (study days 172 and 492); his pregabalin dosing remained unchanged during those events. The second femur fracture was complicated by a postoperative MRSA wound infection. On study day 549, a gastroscopy and sigmoidoscopy were performed for poor appetite and weight loss. The sigmoidoscopy was normal; however, esophageal examination and biopsy revealed infiltrating adenocarcinoma in the background of Barrett's esophagus with high-grade dysplasia. On study day 587, the subject underwent esophagectomy. His pregabalin treatment remained unchanged. On study day 925, the subject fell and experienced exacerbated pain. X-ray revealed a fractured right rib. On study day (b) (6), the subject was admitted to the hospital for assessment of his pain, and he was diagnosed with metastatic cancer. His pregabalin treatment was permanently discontinued on study day (b) (6). The subject died on study day (b) (6) with the cause of death reported as metastatic cancer. No autopsy was performed.

The fractured femur x2, wound infection, esophageal adenocarcinoma, exacerbated pain, and death reported as secondary to metastatic cancer were unlikely related to pregabalin treatment.

7.3.2 Nonfatal Serious Adverse Events

Similar incidences of non-fatal serious adverse events (SAEs) were observed in the pregabalin and placebo groups (controlled trials 1107 and 125); 14 (7.7%) subjects in the pregabalin group and 13 (7.5%) subjects in the placebo group experienced at least one non-fatal SAE. Table 41 summarizes the non-fatal SAEs among the pregabalin group.

Table 41. Non-fatal SAEs Experienced in Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.

Study No./ Subject ID	Sex/ Age (Years)	Dose (mg/day)	MedDRA PT	Action Taken	Clinical Outcome ^a
Study 1107					
10551002	Male/23	75	Pneumonia	Drug previously discontinued	Recovered
10721012	Male/24	75	Cholelithiasis	Drug previously discontinued	Recovered
10791001	Female/44	300	Pneumonia	No action taken	Recovered
		150	Muscle spasms	No action taken	Recovered
10981001	Female/58	600	Pneumonia	Discontinued	Recovered
10981005	Female/46	225	Hypoglycaemia	Discontinued	Recovered
10981007	Male/45	300	Hypotension ^b	Discontinued	Recovered
11111007	Male/44	75	Pain in extremity	No action taken	Recovered
		75	Dysuria	No action taken	Recovered
11761001	Male/52	450	Bradycardia	No action taken	Recovered
		450	Prinzmetal angina	No action taken	Recovered
11771002	Male/50	300	Ulna fracture	No action taken	Not recovered
Study 125					
001-1	Male/31	300	Muscle spasticity	Drug previously discontinued	Recovered
		300	Withdrawal syndrome	Drug previously discontinued	Recovered
001-6	Male/41	600	Haemodilution	Discontinued	Recovered
		600	Oedema	Discontinued	Recovered
		600	Platelet count decreased	Discontinued	Recovered
007-8	Male/30	600	Cellulitis	No action taken	Recovered
007-12	Male/62	300	Faecaloma	No action taken	Recovered
007-19	Male/26	600	Urinary tract infection	No action taken	Recovered

Data source: [Appendix Table SD4](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, ID=identification, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term.
^a At the time of reporting
^b Subject also took amlodipine, and hypotension was assessed as related to amlodipine treatment.

Source: Adapted from Applicant's Integrated Summary of Safety, p 59.

All SAEs in the pregabalin group resolved with the exception of one subject with an ulna fracture, whose outcome was “not recovered” at the time of reporting.

The SAEs experienced by the 13 subjects in the placebo group included urinary tract infection, constipation, subarachnoid hemorrhage, chronic osteomyelitis, pyelonephritis,

cholecystitis, urinary calculus, peri-arthritis, hematuria, head injury, ear hemorrhage, fall, and back pain.

Representative SAEs were selected from the controlled trial population. The case narratives for these subjects are summarized below.

Trial 125:

Subject 001-1 is a 31-year-old white male with a history of C4-5 fracture with incomplete spinal cord injury, bradycardia, and severe muscle spasticity. The subject was titrated up to 600 mg/day of pregabalin; however, he became unable to do a standing transfer and he experienced incontinence. Therefore, the dose was reduced back down to 300 mg/day for the remainder of the study. The subject's muscle spasticity significantly improved while on pregabalin therapy. One day after completing the treatment phase, he developed worsening muscle spasticity beyond his baseline. He also developed impaired coordination resulting in him requiring assistance from his wife. On post-therapy day 5, after being treated with gabapentin, the subject's spasticity returned to pre-study levels, and he was considered recovered from the withdrawal reaction (impaired coordination) and increased muscle spasticity. Creatine phosphokinase levels remained within normal limits during the episode. Concomitant therapy taken within two weeks prior to the onset of the above events included docusate sodium, baclofen, oxybutynin, bisacodyl, ginkgo biloba, ascorbic acid, and citalopram hydrobromide. The clinical outcome was reported as resolved.

The SAEs, withdrawal reaction and increased muscle spasticity, could possibly be related to discontinuation of pregabalin treatment. This trial did not include a taper phase at the end of treatment in the study design. Currently approved labeling includes directions for a gradual drug taper over a minimum of one week upon discontinuation.

Subject 001-6 is a 41-year-old white male with a history of spinal cord injury, recurrent urinary tract infection, autonomic dysreflexia, MRSA infection, and pressure sore of the left ischial tuberosity. The subject's pregabalin dose was titrated up to 600 mg/day, according to the study protocol. On study day 28 (the same day his dose was decreased to 300 mg/day), the subject came to the study site and was noted to have increased drowsiness to the point of falling asleep, weight gain of 11 kg since baseline, increased hip and calf girths, and 3+ pitting edema. Laboratory examination revealed mildly decreased hemoglobin and white blood cell count from baseline consistent with hemodilution and a markedly decreased platelet count from baseline ($117 \times 10^9/L$ at baseline to $23 \times 10^9/L$ on study day 28). Pregabalin was permanently discontinued in response to these findings, and he was switched to gabapentin for the prevention of rebound pain and spasticity. The subject was found to have a concurrent urinary tract infection for which he was treated with norfloxacin, and he was referred to cardiology. The cardiologist felt that the subject was fluid overloaded. One week following withdrawal from the study, the subject's weight decreased by 5 kg and his pitting edema

improved to 2+; however, he remained drowsy, had slurred speech, responded slowly to interview questions, and had a persistently low platelet count. The subject's course was further complicated by multi-drug resistant *Pseudomonas aeruginosa* in the urine. He was treated with intravenous ceftriaxone for three days followed by oral cephalexin. The subject's condition gradually improved. On study day 48 (post-therapy day 20), the subject was considered recovered from hemodilution; however, his platelet count remained low. Carbamazepine was suspected as a potential cause, and it was discontinued that day. On study day 49 (post-therapy day 21), the subject's weight returned to baseline, and the pitting edema resolved. On study day 50 (post-therapy day 22), he was considered to be recovered from the decreased platelet count. Concomitant therapy taken within two weeks prior to the onset of hemodilution, marked pitting edema, and decreased platelet count included dantrolene, baclofen, cephalexin monohydrate, zinc sulfate, ascorbic acid, betamethasone valerate, vaccinium macrocarpon, senna fruit, diazepam, carbamazepine, oxybutynin, gabapentin, prazosin, norfloxacin, sennoside a+b/docusate sodium, and bisacodyl. The clinical outcome was reported as resolved.

The SAE, marked pitting edema, was probably related to pregabalin treatment as there is an established association between the two. The SAE, hemodilution, was likely secondary to fluid overload, and therefore, was possibly related to pregabalin treatment. While the subject was taking several concomitant medications that could contribute to thrombocytopenia, and improvement in the platelet count was temporally associated with discontinuation of carbamazepine, a contribution by pregabalin therapy cannot be excluded. As such, the SAE, decreased platelet count, was possibly related to pregabalin therapy. The adverse event, somnolence, was probably related to pregabalin therapy with concurrent urinary tract infection as an exacerbating factor.

Subject 007-12 is a 62-year-old white male with a history of spinal cord injury, psoriasis, bladder dysfunction, and urinary tract infection who developed fecal impaction, on study day 45, while on 300 mg/day of pregabalin. Four days later he was admitted to the hospital for persistent fecal impaction, and management consisted of senna fruit, paraffin/phenolphthalein, and glycerin enema. The subject recovered from the incident, and his pregabalin treatment remained unchanged in response to this event. Concomitant therapy taken within two weeks before the onset of fecal impaction included baclofen, bisacodyl, docusate sodium, temazepam, and clonazepam. The clinical outcome was reported as resolved.

The SAE, fecal impaction, was unlikely related to pregabalin treatment.

Subject 007-19 is a 26-year-old white male with a history of spinal cord injury and left buttock pressure sore. On study day 22, while being dosed 600 mg/day of pregabalin, the subject developed high fever and was admitted to the hospital. The diagnostic work-up was significant for positive urine cultures for *Pseudomonas aeruginosa*, and a diagnosis of urinary tract infection was made. He was treated with intravenous

antibiotics, and pregabalin continued unchanged in response to the event. On study day 27, the subject was discharged from the hospital on oral antibiotics (norfloxacin). On study day 30, he developed urinary tract infection again, and was readmitted to the hospital. Urine culture was positive for *Acinetobacter calcoaceticus*. Pregabalin remained unchanged, and he was treated with intravenous antibiotics and suprapubic catheter replacement. On study day 42, the subject was discharged on oral antibiotics (flucloxacillin). Concomitant therapy taken within two weeks before the onset of urinary tract infection included diazepam, ranitidine, phenoxybenzamine, baclofen, propantheline bromide, and amitriptyline. The clinical outcome was reported as resolved.

The SAEs, urinary tract infection x 2, were unlikely related to pregabalin treatment.

Subject 007-8 is a 30-year-old white male with a history of spinal cord injury, Darier's disease, T4 to T12 posterior instrumented fusion, spinal abscess, and osteomyelitis. On study day 55, while being dosed 600 mg/day of pregabalin, the subject came in to the study site for Visit 7, and routine laboratory assessment performed at that visit revealed an ALT of 46 U/L, an AST of 46 U/L, and a CPK of 1592 U/L. The subject became febrile and developed a rash over his left leg that evening. On study day 56, the subject was diagnosed with left lower leg cellulitis, and he was admitted to the hospital for management with intravenous antibiotics. Pregabalin therapy continued unchanged in response to this event. On study day 69, the subject was discharged from the hospital on oral antibiotics. Follow-up testing one week after hospital discharge revealed a CPK of 120 U/L. Concomitant therapy taken within two weeks before the onset of left lower leg cellulitis included acitretin, oxybutynin, dantrolene, diazepam, and baclofen. The clinical outcome was reported as resolved.

The SAE, left lower leg cellulitis, was unlikely related to pregabalin treatment.

Trial 1107:

Subject 10981005 is a 46-year-old white female with a history of spinal cord injury, chronic bowel and bladder spasm, and urinary tract infection. On study day 72, while being dosed 225 mg/day of pregabalin, the subject was admitted to the hospital with severe hypoglycemia. She had presented to the emergency department with confusion, disorientation, and a blood sugar of 31 after not eating breakfast or much of her lunch. It was also noted that the subject had lost weight. The subject has no reported history of hypoglycemia or any other history relevant to this event. She was treated with intravenous glucose and inpatient monitoring. Pregabalin was permanently discontinued in response to the event. Concomitant therapy taken within two weeks before the onset of hypoglycemia included baclofen, oxybutynin, citric acid/gluconic acid via urinary bladder catheter, sodium chloride 9% via urinary bladder catheter, calcium carbonate, fish oil, multivitamin, super concentrated cranberry with vitamin C, odorless

garlic, and azithromycin. The event was considered recovered one day after presentation.

Given the lack of relevant medical history and resolution of the event after discontinuation of pregabalin, the SAE, hypoglycemia, was possibly related to pregabalin treatment.¹⁷

Subject 10981007 is a 45-year-old white male with a history of spinal cord injury and hypertension. On study day 36, while being dosed 300 mg/day of pregabalin, the subject was hospitalized for hypotension that was characterized as severe; however, vital sign information was not reported. The subject began taking amlodipine 5 mg daily prior to starting the trial. His amlodipine dose was reduced to 2 mg daily, and the subject recovered from the event. Pregabalin was permanently discontinued in response to this event. Concomitant therapy taken within two weeks before the onset of hypotension included baclofen, tizanidine, oxybutynin, and amlodipine.

The SAE, hypotension, was unlikely related to pregabalin treatment and was more likely related to the subject's amlodipine therapy.

Subject 10981001 is a 58-year-old black female with a history of spinal cord injury with quadriplegia, type 2 diabetes mellitus, urinary and fecal incontinence, spasticity, neurogenic bowel, constipation, bladder spasm, urinary tract infection, and heartburn. On study day 71, while being dosed 600 mg/day of pregabalin, the subject was admitted to the hospital with fever, malaise, fatigue, shortness of breath, and an elevated white blood cell count. Chest x-ray revealed right upper and left lower lobe pneumonia. The subject was treated with intravenous antibiotics, and she required ventilatory support. Pregabalin therapy was permanently discontinued in response to this event. Concomitant therapy taken within two weeks prior to the onset of pneumonia included dantrolene, tizanidine, baclofen, oxybutynin, diazepam, amitriptyline, macrogol, and botox type A. The clinical outcome was reported as recovered approximately one month after the onset of the event.

The SAE, pneumonia, was unlikely related to pregabalin treatment.

Subject 10721012 is a 24-year-old Hispanic male with a history of spinal cord injury. The subject was administered 75 mg/day of pregabalin from study day 1 through 119. On study day 134 (during the follow-up period), the subject presented to the emergency department with abdominal pain, nausea, and vomiting. The subject had an elevated serum amylase, and CT scan of the abdomen and pelvis demonstrated cholelithiasis

¹⁷ According to the currently approved labeling for pregabalin, 2% of subjects treated with pregabalin for neuropathic pain associated with diabetic peripheral neuropathy experienced hypoglycemia compared to 1% of placebo treated subjects. It should be emphasized that patients with diabetes are at risk of developing hypoglycemia, and that a history of diabetes or any other metabolic disturbance was not reported for this subject.

without evidence of acute cholecystitis. Ultrasound demonstrated cholelithiasis with mild dilation of the common bile duct. Cholecystectomy was recommended; however, the subject initially refused surgery. Subsequently, a laparoscopic cholecystectomy was performed (four days after the initial presentation). Concomitant therapy taken within two weeks before the onset of cholelithiasis included cyclobenzaprine and oxycodone/paracetamol. The clinical outcome was reported as recovered seven days after the initial presentation.

The SAE, cholelithiasis, was possibly related to pregabalin therapy.

Subject 10791001 is a 44-year-old white female with a history of spinal cord injury (paraplegia) and asthma. On study day 10, while being dosed 300 mg/day of pregabalin, the subject developed pneumonia requiring hospitalization. Antibiotic therapy was initiated, and the clinical outcome was reported as recovered three days later. Pregabalin was continued unchanged in response to this event. On study day 43, while being dosed 300 mg/day of pregabalin, the subject developed an increase in muscle spasms in a new location (stomach area). Abdominal x-ray showed no significant findings. Pregabalin treatment was discontinued on study day 46 because the subject completed the termination taper in response to this event. Subsequent treatment consisted of intrathecal catheter replacement and intrathecal baclofen and hydromorphenol. This resulted in improvement in the muscle spasms, and the clinical outcome was reported as recovered approximately 11 weeks after the event began. Concomitant medications taken with two weeks before the onset of pneumonia and two weeks before the onset of increased muscle spasms included hydrocodone/paracetamol and diazepam.

The SAE, pneumonia, was unlikely related to pregabalin treatment. The SAE, increased muscle spasms, was possibly related to pregabalin treatment.¹⁸

Subject 1111007 is 44-year-old male with a history of L2 spinal cord injury (paraplegia) secondary to motor vehicle accident, pain syndrome, neuropathy, cholecystectomy, and multiple abdominal and spine surgeries. On study day 16, while being dosed 75 mg/day of pregabalin, the subject experienced right leg pain and dysuria. The subject stated that he developed sharp and burning right lower extremity pain after a fall at a board and care facility. He also reported a four day history of dysuria. X-ray of the right femur, pelvis, and chest were negative for any acute abnormality. Laboratory work-up was significant for bacteruria and hyponatremia (sodium=132). The subject was admitted to the hospital with hyponatremia, bacteruria, and acute on chronic right leg pain. The subject received intravenous antibiotics, intravenous normal saline, and intravenous hydromorphone. Pregabalin therapy remained unchanged in response to this event. Concomitant therapy taken within two weeks before the onset of right leg

¹⁸ According to the currently approved labeling for pregabalin, muscle spasm is reported in 4% of patients receiving pregabalin therapy in clinical trials compared with 2% of patients on placebo.

pain and dysuria included transdermal baclofen, oral ibuprofen, and oral hydrocodone/paracetamol as needed. The clinical outcome for right leg pain and dysuria was reported as recovered 11 days after the onset of the event.

The SAEs, right leg pain and dysuria, were unlikely related to pregabalin treatment.

Subject 11761001 is a 52-year-old Asian male with a history of spinal cord injury and orthostatic hypotension. On study day 100, while being dosed 450 mg/day of pregabalin, the subject experienced a feeling of breathlessness and malaise. He went to the hospital and underwent examination and Holter monitoring. Two days later the subject was diagnosed with bradycardia, and he was admitted to the hospital. Cilostazol 100 mg once daily in the morning was started for the symptomatic bradycardia, and the subject was subsequently discharged from the hospital. On study day 115, the subject followed up at the study site where the investigator commented that the echocardiogram revealed no abnormality. The subject continued unchanged on pregabalin treatment until study day 121 (end of the treatment phase). On study day 123, the subject developed angina pectoris consisting of dyspnea and a “chest strangled” feeling. He was admitted to the hospital. ECG showed inverted T wave at leads V1 to V3. Coronary CT scan showed no stenosis, and the subject was diagnosed with suspected coronary arteriospasm (Prinzmetal angina). The clinical team at the hospital suspected the recently started medication, cilostazol, to have played a role in the development of coronary arteriospasm. Nicorandil, a vasodilatory agent used to treat angina, was started. The subject was discharged from the hospital one week after admission for angina pectoris secondary to coronary arteriospasm. Concomitant medications taken within two weeks before the onset of bradycardia and suspected coronary arteriospasm included loxoprofen, baclofen, sofalcone, glycerol, mecobalamin, famotidine, zolpidem, propiverine, dimeticone, and imidafenacin. The clinical outcome was reported as recovered for bradycardia and Prinzmetal angina.

The SAEs, bradycardia and Prinzmetal angina, were unlikely related to pregabalin treatment.

Subject 11771002 is a 50-year-old Asian male with a history of spinal cord injury. On study day 101, while being dosed 300 mg/day of pregabalin, the subject fell and injured his left arm. On study day 102, the subject went to an emergency outpatient unit where he was diagnosed with a left arm fracture. The subject followed up the next day with orthopedics, and the diagnosis was clarified as a left olecranon fracture. The subject was admitted to the hospital, and on study day 104, he underwent osteosynthesis of the left olecranon. He was discharged from the hospital approximately two weeks later. Pregabalin therapy remained unchanged in response to the event. Concomitant medications taken within two weeks before the onset of the fractured left olecranon included senna, etizolam, imipramine, diazepam, brotizolam, sofalcone, sodium bicarbonate, sodium phosphate monobasic, magnesium oxide, glycyrrhiza extract, rheum palmatum, tandospirone, clostridium butyricum, sennoside a plus b, zopiclone,

zolpidem, flunitrazepam, losartan, amlodipine, furosemide, insulin, isophane, loxoprofen, ketoprofen, baclofen, and organ lysate standardized. The clinical outcome was reported as not yet recovered at the time of the report.

The SAE, ulna fracture, was unlikely related to pregabalin treatment.

Summary Comment

Review of the non-fatal SAEs that occurred in controlled trials 125 and 1107 revealed no new significant safety information for pregabalin.

Cursory review of the non-fatal SAEs that occurred in open-label trial 202 revealed no unexpected or new significant safety information for pregabalin. Cursory review of the trials conducted in different patient populations that were submitted as part of this application (A008-1063 and ongoing study A008-1252) also revealed no new significant safety information for pregabalin.

7.3.3 Dropouts and/or Discontinuations

Discontinuations Secondary to Adverse Events

In the controlled trials (1107 and 125), the frequency of discontinuation due to adverse events (AEs) was 12.6% (23/182) for the pregabalin group and 9.8% (17/174) for the placebo group. The combined controlled and uncontrolled population (trials 1107, 125, and 202) had a discontinuation frequency of 15.7% (37/235) for pregabalin-treated subjects. Among the 23 subjects in the pregabalin group who were discontinued from the controlled trials secondary to AEs, 3 were receiving 75 mg/day, 9 were receiving 150 mg/day, 1 was receiving 225 mg/day, 5 were receiving 300 mg/day, and 5 were receiving 600 mg/day, at the time of discontinuation. The overall median time from receiving the first dose of treatment to discontinuation due to any AE was four weeks for the pregabalin group and three weeks for the placebo group. The AEs leading to discontinuation in the controlled and controlled/uncontrolled populations are summarized in Table 42 and Table 43 below.

Table 42. Discontinuations Due to Adverse Events, Summarized in Decreasing Order of Frequency for Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.

MedDRA PT	No. (%) of Subjects	
	Pregabalin (N=182)	Placebo (N=174)
Any AE	23 (12.6)	17 (9.8)
Somnolence	6 (3.3)	0 (0)
Oedema	4 (2.2)	0 (0)
Fatigue	3 (1.6)	1 (0.6)
Balance disorder	2 (1.1)	1 (0.6)
Amnesia	1 (0.5)	0 (0)
Choking sensation	1 (0.5)	0 (0)
Circulatory collapse	1 (0.5)	0 (0)
Diarrhoea	1 (0.5)	1 (0.6)
Euphoric mood	1 (0.5)	0 (0)
Haemodilution	1 (0.5)	0 (0)
Hypoglycaemia	1 (0.5)	0 (0)
Hypotension	1 (0.5)	0 (0)
Muscular weakness	1 (0.5)	1 (0.6)
Nausea	1 (0.5)	0 (0)
Neck pain	1 (0.5)	0 (0)
Oedema peripheral	1 (0.5)	2 (1.1)
Platelet count decreased	1 (0.5)	0 (0)
Pneumonia	1 (0.5)	0 (0)
Urinary incontinence	1 (0.5)	0 (0)
Vision blurred	1 (0.5)	1 (0.6)

Source data: [Appendix Table 5.1.1.a](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term, N=total number of subjects who received at least 1 dose of study drug, AE=adverse event.

Source: Applicant's Integrated Summary of Safety, p 64.

Table 43. Discontinuations Due to Adverse Events, Summarized by Decreasing Order of Frequency for Pregabalin-Treated Subjects: Controlled and Uncontrolled Trials 1107, 125, and 202.

MedDRA PT	No. (%) of Subjects (N=235)
Any AE	37 (15.7) ^{a,b}
Somnolence	7 (3.0)
Fatigue	4 (1.7)
Oedema	4 (1.7)
Balance disorder	2 (0.9)
Disturbance in attention	2 (0.9)
Muscular weakness	2 (0.9)
Oedema peripheral	2 (0.9)
Vision blurred	2 (0.9)
Amnesia	1 (0.4)
Asthenia	1 (0.4)
Bipolar disorder	1 (0.4)
Cellulitis	1 (0.4)
Choking sensation	1 (0.4)
Circulatory collapse	1 (0.4)
Decubitus ulcer	1 (0.4)
Depression	1 (0.4)
Diarrhoea	1 (0.4)
Eczema	1 (0.4)
Euphoric mood	1 (0.4)
Haemodilution	1 (0.4)
Hypoglycaemia	1 (0.4)
Hypotension	1 (0.4)
Injury	1 (0.4)
Metastasis	1 (0.4)
Nausea	1 (0.4)
Neck pain	1 (0.4)
Pain	1 (0.4)
Photosensitivity reaction	1 (0.4)
Platelet count decreased	1 (0.4)
Pneumonia	1 (0.4)
Urinary incontinence	1 (0.4)
Weight increased	1 (0.4)

Source data: [Appendix Table 5.1.1.b](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term, N=total number of subjects who received at least 1 dose of study drug (pregabalin), AE=adverse event.
^a Includes Subjects 004-22, 004-37 and 006-06 who had been discontinued from Study 125 due to AEs but then were enrolled in Study 202 from which they were not discontinued.
^b Subject 004-20 had been discontinued from Study 125 due to edema, then participated in Study 202, and subsequently was discontinued again due to edema. Since both Studies 125 and 202 are included in the controlled and uncontrolled study grouping, Subject 004-20 was counted only once among all subjects (n=37) who were discontinued from the controlled and uncontrolled studies due to AEs.

Source: Applicant's Integrated Summary of Safety, p 67.

Adverse dropouts that were or were partly secondary to AEs less commonly associated with pregabalin or not typical of the known pregabalin AE profile or the underlying disease process (i.e., spinal cord injury) are discussed below.

Trial 125:

Subject 3007 is a 57-year-old white male with a history of spinal cord injury, cardiac disease, hypertension, indigestion, edema, and recurrent urinary tract infection. On study day 20, while being dosed 150-600 mg/day of pregabalin, the subject physically collapsed. The event was characterized as moderate, and it was not classified as serious. Other adverse events reported at that same time included confused state, hypotension (characterized as moderate), and severe diarrhea. All of the aforementioned AEs except for the severe diarrhea started and ended on study day 20. The severe diarrhea had been going on since study day 17. Pregabalin was permanently discontinued in response to the AE physical collapse with the last dose taken on study day 24. Concomitant medications included pantoprazole, amoxicillin/clavulanic acid, and trimethoprim. The clinical outcome for all of the aforementioned AEs were reported as recovered.

The AE resulting in discontinuation, physical collapse, was possibly related to pregabalin treatment with hypotension likely secondary to dehydration/severe diarrhea as a contributing factor.

Subject 4013 is a 62-year-old white male with a history of spinal cord injury, chronic constipation, discectomy, lumbar radiculopathy, olecranon bursitis, pneumonia with right-sided pleural effusion, reflux esophagitis, and sacral pressure sore. On study day 1, while being dosed 150 mg/day of pregabalin, the subject developed nausea, fatigue, and dry mouth. The nausea and fatigue were characterized as severe and the dry mouth was characterized as moderate in severity. Pregabalin was discontinued in response to the nausea and fatigue, and the last dose was taken on study day 2. Concomitant medications included senna, methenamine, celecoxib, paracetamol, diazepam, and laxatives. The clinical outcome was reported as recovered on post-therapy day 1.

The AEs resulting in discontinuation, nausea, fatigue, and dry mouth, were probably related to pregabalin treatment.

Subject 4037 is a 62-year-old white male with a history of spinal cord injury, bladder calculi, headaches, hypercholesterolemia, neurogenic bladder and bowel, septicemia, and T12/L1 spinal fixation. On study day 2, while being dosed 300 mg/day of pregabalin, the subject developed euphoria that was considered moderate in severity. Other AEs reported at the same time included nausea (mild), posterior head pain (mild), irritability (mild), anxiety (mild), and photophobia (moderate). Pregabalin was discontinued in response to the euphoria, and the last dose of pregabalin was taken on study day 12. Concomitant medications included paracetamol. The clinical outcome for the subject's euphoria was reported as resolved on post-therapy day 20.

The AE that resulted in discontinuation, euphoria, was probably related to pregabalin treatment. The additional AEs, nausea, posterior head pain, irritability, anxiety, and photophobia, were probably related to pregabalin treatment.

Subject 6018 is a 59-year-old white male with a history of spinal cord injury, left calf deep venous thrombosis, right femur fracture, frequent urinary tract infections, hypertension, muscle spasm, and swollen feet. The subject was dosed 150 mg/day of pregabalin on study days 1-8 and 300 mg/day of pregabalin on study days 9-15. On study day 10, the subject experienced drowsiness and blurred vision followed by memory loss on study day 11. These AEs were considered moderate in severity. Pregabalin was permanently discontinued on study day 15 in response to these events. Concomitant medications included diazepam, methenamine, baclofen, codeine, and norfloxacin. The clinical outcome was reported as resolved on study day 15.

The AEs resulting in discontinuation, blurred vision, memory loss, and drowsiness, were probably related to pregabalin treatment.

Subject 6020 is a 38-year-old white male with a history of spinal cord injury, neck injury, T9-L1 Harrington rod fixation, hypertension, deep vein thrombosis, constipation, perianal abscess, perineal pain, rectal prolapse, swollen feet, and urinary tract infections. On study day 3, while being dosed 150 mg/day of pregabalin, the subject experienced neck pain (severe). Pregabalin was permanently discontinued in response to the event with the last dose taken on study day 3. Concomitant medications included paracetamol, baclofen, bisacodyl, oxycodone, and dosulepin. The clinical outcome was reported as resolved on post-therapy day 188.

The AE resulting in discontinuation, neck pain, was unlikely related to pregabalin treatment given the subject's history of neck injury and lack of a temporal relationship between stopping study medication and resolution of symptoms.

Subject 8005 is a 49-year-old white male with a history of spinal cord injury, cholecystectomy, type 2 diabetes mellitus, gastroesophageal reflux, recurrent urinary tract infections, transient elevation in liver function tests, and renal scarring. On study day 5, while being dosed 150 mg/day of pregabalin, the subject developed mildly increased blood sugar level. The pregabalin dose was decreased in response to this event.¹⁹ On study day 19, while being dosed 150 mg/day of pregabalin, the subject developed diarrhea (moderate in severity). Pregabalin was permanently discontinued in response to the diarrhea with the last dose taken on study day 25. The subject also experienced headache behind the eyes associated with computer usage on study day 6, which resolved on the same day after taking paracetamol. The subject additionally

¹⁹ The subject reported the event during a study visit on study day 14. His pregabalin dose had been titrated up to 300 mg/day by the time of the visit. The dose was reduced back down to 150 mg/day in response to elevated blood sugars.

developed constipation on study days 9-11 that was associated with titration of study medication to 300 mg/day. Concomitant medications included diazepam, coloxyl with senna, baclofen, metformin, cranberry, multivitamin, nitrazepam, glimepiride, pantoprazole, pain relief patches, and norfloxacin. The clinical outcomes for increased blood sugar level and diarrhea were reported as resolved on post-therapy days 120 and 143, respectively.

The AE leading to discontinuation, diarrhea, was unlikely associated with pregabalin treatment given the lack of temporal relationship between discontinuation of study drug and resolution of symptoms. The AE, increased blood sugar level, was also unlikely related to pregabalin treatment for the same reason above and given the subject's medical history. The AEs, constipation and headache, were possibly related to pregabalin treatment with contributing factors of underlying illness (spinal cord injury) for constipation and computer usage for headache.

Trial 1107:

Subject 11671001 is a 63-year-old Asian female with a history of spinal cord injury, constipation, type 2 diabetes mellitus, hyperlipidemia, insomnia, and neurogenic bladder. On study day 8, the subject experienced a choking sensation (strangled feeling), which the investigator characterized as moderate in severity. The subject experienced nausea and vomiting at the same time. The subject's screening physical examination was significant for anorexia. The minimum dose of pregabalin taken was 75 mg/day and the maximum dose was 150 mg/day. Pregabalin was permanently discontinued on study day 12 in response to the event of choking sensation, and the subject withdrew from the study 4 days later. Concomitant medications included famotidine, carbocisteine, dimethicone, mosapride citrate, baclofen, atorvastatin, zolpidem tartrate, herbal preparation (tokakujokito), sitagliptin, normosol, glycerin (enema), and vitamin B-complex. The clinical outcome for nausea and vomiting was reported as resolved after a one day duration, and the outcome for choking sensation was ongoing at the time of study withdraw. No further follow-up information was provided.

The AE resulting in discontinuation, choking sensation (strangled feeling), and the AEs, nausea and vomiting, were possibly related to pregabalin therapy.

Trial 202:

Subject 4010 is a 39-year-old white male with a history of spinal cord injury, bipolar disorder, and surgical detethering of the spinal cord who was previously on the placebo arm of trial 125. The subject received 150 mg/day of pregabalin for a total of 19 days. On study day 8, the subject underwent surgical detethering of the spinal cord. His postoperative course was complicated by a CSF leak, hypotension, decreased hemoglobin (required blood transfusion), and hypoxia (required supplemental oxygen

via nasal cannula). At the time of admission, the subject was noted to have a depressed mood, and he was feeling fearful. Just prior to this, the subject experienced an increased energy level, an elevated mood, and talkativeness. On study day 14, the subject experienced insomnia, and a psychiatry consult was ordered. The psychiatrist felt the history and findings were consistent with an unstable mood/mood disorder, which had been present for several years, and that he was currently experiencing a hypomanic syndrome. The subject did not experience any delusions, paranoia, or suicidal ideation. The subject was started on a psychiatric drug regimen and pregabalin was discontinued (study day 19). Concomitant medications taken within two weeks before the onset of the event included oxybutynin, baclofen, methenamine, hippurate, diazepam, amitriptyline, and cephalexin. The clinical outcome was reported as resolved on post-therapy day 21.

The SAE leading to discontinuation, exacerbation of bipolar disorder, was possibly related to pregabalin treatment; however, the cause was likely multifactorial in nature.

Subject 5002 is 55-year-old Asian male with a history of hyperlipidemia and spinal cord injury with T4 paraplegia who was previously on the placebo arm of trial 125. Four days prior to starting study medication, the subject developed an isolated rash (mild). The location and character of the rash were not reported; however, the rash was noted to have worsened one day prior to starting study medication. Hydrocortisone cream was started, which did not improve the rash. The subject started study medication and was titrated up to 450 mg/day. On study day 28, the subject developed worsening of the rash (moderate), and pregabalin was discontinued the same day. Concomitant medications included coloxyl with senna, general nutrients, baclofen, oxybutynin, hydrocortisone, betamethasone, methylprednisolone, permethrin, triamcinolone, prednisolone, and tramadol. The clinical outcome was reported as resolved on post-therapy day 108.

While the AE resulting in discontinuation, rash, was unlikely related to pregabalin treatment as it started prior to initiation of therapy, worsening of the rash was possibly related to study drug treatment.

Subject 5008 is a 55-year-old white male with a history of spinal cord injury, left hip and knee arthritis, hyperlipidemia, hypertension, kidney cysts, lower limb weakness, neurogenic bladder weakness, neurogenic bowel, obesity, peripheral vascular disease, peptic ulcers, and swollen feet who was previously on the placebo arm of trial 125. On post-therapy day 2 (study day 89), the subject developed a photosensitivity rash (moderate). Pregabalin treatment was permanently discontinued in response to this event with the last dose taken on study day 87. Other significant AEs reported around the time of the event included painful calves while walking up hill (moderate, study day 56), bilateral lower extremity blood clots (mild, study day 60), and first degree AV block (mild, post-therapy day 11). The location of the bilateral lower extremity blood clots is not specified (i.e., deep or superficial; proximal or distal); however, the event was

characterized as mild and not serious. Concomitant medications included celecoxib, atorvastatin, irbesartan, acetylsalicylic acid, urea, and betamethasone. The clinical outcome for the photosensitivity rash was reported as resolved on post-therapy day 85.

The AE resulting in discontinuation, photosensitivity rash, was possibly related to pregabalin treatment. The AEs, painful calves while walking up hill, bilateral lower extremity blood clots, and first degree AV block, were unlikely related to pregabalin treatment given the subject's medical history and thrombotic/cardiovascular disease risk factors. The adjudication of the bilateral lower extremity blood clot event to deep or superficial and proximal or distal will not affect the interpretation of the safety data from this individual clinical trial.

Discontinuations Secondary to Other Reasons

Among the controlled trials (125 and 1107), 3.3% (6/182) of pregabalin-treated subjects discontinued secondary to "other" reasons or "no longer willing to participate." Taking the controlled trials and the open-label extension trial (202) together, 6.8% (16/235) of pregabalin treated subjects discontinued secondary to "other" reasons or "no longer willing to participate." Selected cases were reviewed to confirm that potential safety issues were not underlying these reasons.

Trial 202:

Subject 2012 is 57-year-old white female with a history of spinal cord injury, ileal conduit urinary diversion, deep vein thrombosis, scoliosis, left thyroidectomy, intermittent urinary tract infections, acute delirium associated with urinary tract infection²⁰, depression, and psychosis who was previously treated on the pregabalin arm of trial 125 for 85 days. On study day 217, while being dosed 300 mg/day of pregabalin, the subject began a down-titration of pregabalin in anticipation of a mandatory drug holiday. The last dose of pregabalin was taken on study day 226. On post-therapy day 1, the subject became confused while at home. On post-therapy day 8, the subject was admitted to the hospital for acute psychosis, and she was noted to have thought disorder and flight of ideas on admission. This event was classified as an SAE. Laboratory work-up revealed a urinary tract infection. The clinical outcome was reported as recovered 15 days later. The subject subsequently withdrew from the study at the advice of the investigator. Concomitant therapy taken within two weeks before the onset of the event, acute psychosis, included clonazepam, metaclopramide, omeprazole, ramipril, ascorbic acid, levothyroxine, diazepam, medroxyprogesterone acetate, docusate, senna, and sorbitol.

²⁰ The event of acute delirium associated with urinary tract infection occurred during the course of trial 202 (study day 9). The clinical outcome was reported as resolved on study day 16. Pregabalin therapy was temporarily stopped in response to this event, and it was restarted on study day 51.

Although this subject was reported, in the submission, to have discontinued secondary to “other” reasons, it seems more reasonable to deduce that this subject discontinued secondary to the SAE, acute psychosis. The SAE, acute psychosis, is probably related to the subject’s underlying illness (urinary tract infection) and relevant medical history (psychosis and acute delirium associated with urinary tract infection). However, a contributing or exacerbating role of pregabalin therapy cannot be excluded.

Subject 2013 is a 55-year-old white male who was treated with up to 150 mg/day of pregabalin for 302 days. On study day 302, the subject was withdrawn from the study as he was no longer willing to participate. Adverse events reported for this subject included decrease in alertness, drowsiness, euphoria, emotional flatness, right shoulder pain, internatal pressure sore, and urinary tract infection.

The reason the subject was no longer willing to participate is not reported; however, a significant safety reason is not identified.

Subject 4001 is a 71-year-old white female who was treated with up to 600 mg/day of pregabalin for 876 days (inclusive of trials 125 and 202). The subject had been previously treated on the pregabalin arm of trial 125 for 85 days (600 mg/day). On study day 787, while being dosed 300 mg/day of pregabalin, the subject’s husband found her delirious and confused. On admission to the hospital, the subject’s sodium was 123 mmol/L (range 136-146 mmol/L). This event was classified as serious. CT scan of the brain showed no cortical infarct and EEG showed no focal abnormalities or epileptical activities. On study day 791, the subject was withdrawn from study treatment for the management of chronic organic brain syndrome (secondary to hyponatremia). Concomitant therapy taken within two weeks before the onset of the events included oxybutynin, baclofen, coloxyl with senna, amitriptyline, temazepam, psyllium hydrophilic mucilloid, general nutrients, and estropipate. The clinical outcome was reported as resolved. Other AEs reported for this subject included drowsiness, dry mouth, speech disturbance, amblyopia, diplopia, constipation, flatulence, asthenia, increased appetite, amnesia, dizziness, euphoria, abnormal thinking, urinary tract infection, anxiety, increased spasticity, word recall difficulty, swelling in hands, depression, right leg swelling, raised creatine phosphokinase blood levels, increased intraocular pressure, and oral thrush.

The SAE, confusion, was probably secondary to hyponatremia, and the SAE, hyponatremia, was probably related to an intercurrent illness. However, additional information or documentation of potential causes and the subject’s clinical diagnostic work-up were not provided. A contributing role by pregabalin cannot be excluded.

Subject 8006 is a 50-year-old white male who was treated with up to 600 mg/day of pregabalin for 235 days. The subject discontinued the study due to “withdrew consent.” Adverse events reported for this subject included increased urinary incontinence, reduced grip strength in hands, increased leg weakness, blurred vision, constipation,

nausea, headache, dry mouth, influenza, insomnia, fecal incontinence, urinary tract infection, ingrown toenail, elevated blood glucose, fall, autonomic dysreflexia, increased blurred vision, lethargy, and basal cell carcinoma right arm.

The reason the subject withdrew consent is not reported; however, a significant safety reason is not identified.

Trial 1107:

Subject 10781001 is a 38-year-old female who was treated with up to 600 mg/day of pregabalin for 91 days. On post-therapy day 8, the subject was withdrawn from the study as she was no longer willing to participate. Adverse events reported for this subject included mild dizziness, mild preprandial disorientation, increased edema to bilateral lower extremities, mild rash appearing as small red bumps on bilateral lower extremities, and insomnia.

The reason the subject was no longer willing to participate is not reported; however, a significant safety reason is not identified.

Subject 11611002 is a 41-year-old Asian female with a history of spinal cord injury, gastritis, irritable bowel syndrome, left facial nerve paresis, peritonitis, and sleep disorder who was treated with up to 600 mg/day of pregabalin for 63 days. The subject was discontinued from study treatment, on post-therapy day 8, by the investigator because of the subject's response on the Sheehan-Suicidality Tracking Scale (Sheehan STS) at Visit 4.²¹ While the subject's responses on the Sheehan-STS indicated increased suicidal ideation from the previous two visits, they represented an improvement from the screening visit.²² However, the investigator considered the subject at increased risk for suicidal ideation or behavior, and felt that it would be in the subject's best interest to be withdrawn from the study. Concomitant medications taken

²¹ The Sheehan-STS is a self-administered questionnaire, and it does not appear in English on this subject's case report form. This subject's questionnaire was compared to the English version, as it appears in the sample case report form. The forms have the same format and numbering scheme, therefore, the results of the Sheehan-STS for this subject were deduced by comparing the two versions.

²² The subject's responses >0 on the Sheehan-STS were:

Screening:

- "Extremely" (4) for "think that you would be better off dead or wish you were dead?" (item 2)
- "Moderately" (2) for "think about suicide?" (item 4)

Visit 2:

- "A little" (1) for "think that you would be better off dead or wish you were dead?" (item 2)

Visit 3:

- "A little" (1) for "think that you would be better off dead or wish you were dead?" (item 2)

Visit 4:

- "A little" (1) for "think that you would be better off dead or wish you were dead?" (item 2)
- "A little" (1) for "think about suicide?" (item 4)

by the subject during the course of the study included famotidine, flurbiprofen, triazolam, lornoxicam, etizolam, felbinac, syakuyakukanzoto, brotizolam, and urea. This subject also experienced the AE of dizziness.

This subject was listed as discontinuing due to other reasons; however, further examination revealed that the subject was discontinued, by the investigator, for reasons relating to suicidal ideation. Suicidality, as measured by the Sheehan-STS, actually overall improved for this subject from baseline while taking pregabalin. Therefore, a significant safety concern is not identified.

Subject 11481002 is a 54-year-old Asian female who was treated with up to 300 mg/day of pregabalin for 14 days. The subject was no longer willing to participate in the study.

The reason the subject was no longer willing to participate is not reported; however, a significant safety reason is not identified.

Summary Comment

Review of the discontinuations secondary to adverse events and other/no longer willing to participate revealed no new significant safety information for pregabalin.

7.3.4 Significant Adverse Events

All relevant adverse events are discussed in Sections 7.3(p 91) and 7.4 (p 112).

In the controlled trials (1107 and 125), 12.6% (23/182) of pregabalin subjects experienced adverse events (AEs) reported as severe compared to 10.9% (19/174) in the placebo group. The most common severe AEs (experienced by more than one subject) among the pregabalin group included fatigue (three subjects), muscular weakness (three subjects), edema (three subjects), disturbance in attention (two subjects), muscle spasms (two subjects), and somnolence (two subjects). The aforementioned AEs were reported at higher frequencies than in the placebo group. Despite these trends, no new significant safety information is identified for pregabalin.

7.3.5 Submission Specific Primary Safety Concerns

Somnolence

A higher frequency of somnolence associated with pregabalin use was observed in clinical trials for CNP-SCI (35.7% for pregabalin-treated subjects and 11.5% for placebo-treated subjects; see Section 7.4.1, p 112) compared to reported rates in the approved labeling for the neuropathic pain in diabetic peripheral neuropathy, postherpetic neuralgia, adult partial onset seizure, and fibromyalgia populations. The frequency of somnolence in pregabalin-treated subjects (all doses) in these other populations is summarized below:

- Neuropathic pain associated with diabetic peripheral neuropathy – 12% (16% for 600 mg dose)
- Postherpetic neuralgia – 16% (25% for 600 mg dose)
- Adult partial onset seizure – 22% (28% for 600 mg dose)
- Fibromyalgia – 20% (22% for 600 mg dose)

The Applicant analyzed the frequency of somnolence in the controlled CNP-SCI population with respect to concomitant benzodiazepines. Among pregabalin-treated subjects, the frequency of somnolence was 46.6% in subjects who took concomitant benzodiazepines compared to 30.6% in subjects who did not take these medications. Similarly, the frequency of somnolence among placebo-treated subjects who took concomitant benzodiazepines was 15.4% compared to 9.2% in those who did not take these medications. The ratio between the frequency of CNP-SCI subjects in the pregabalin group and placebo groups with somnolence was 3.1, which was comparable to the diabetic peripheral neuropathy/postherpetic neuralgia population (3.6). This ratio was 2 in the adult partial onset seizure population and 5 in the fibromyalgia population.

Concomitant benzodiazepine use only partly explains the higher frequency of somnolence seen in the CNP-SCI population as its frequency among pregabalin treated subjects *not* taking concomitant benzodiazepines is higher than its frequency among pregabalin treated subjects for other approved indications. However, the comparable ratios between populations suggests that the phenomenon is attributable to some aspect of the population rather than study drug alone.

Other potentially sedating concomitant medications, particularly when taken in combination, and factors related to the underlying disease process could also contribute to the higher frequency of somnolence in the CNP-SCI population. Potentially sedating concomitant medications (e.g., baclofen, opioids, amitriptyline, and oxybutynin), in addition to benzodiazepines, were commonly used by subjects in the pregabalin and placebo groups. The most common concomitant medications used by subjects in the controlled trials are summarized in Table 44 below.

Table 44. Concomitant Medications Taken During Study by at Least 5% of Pregabalin- or Placebo-Treated Subjects: Controlled CNP-SCI Trials 1107 and 125.

Concomitant Medication ^a	No. (%) of Subjects	
	Pregabalin (N=182)	Placebo(N=174)
Any concomitant medication	170 (93.4)	160 (92.0)
Baclofen	80 (44.0)	54 (31.0)
Oxybutynin	36 (19.8)	25 (14.4)
Paracetamol	33 (18.1)	34 (19.5)
Diazepam	25 (13.7)	23 (13.2)
Amitriptyline	21 (11.5)	11 (6.3)
Bisacodyl	21 (11.5)	18 (10.3)
Methenamide	17 (9.3)	15 (8.6)
Coloxyl with senna	14 (7.7)	10 (5.7)
Carbamazepine	13 (7.1)	4 (2.3)
Clonazepam	11 (6.0)	13 (7.5)
Omega-3 marine triglyceride	11 (6.0)	7 (4.0)
Omeprazole	11 (6.0)	7 (4.0)
Senna	11 (6.0)	15 (8.6)
Cefalexin	10 (5.5)	6 (3.4)
Ciprofloxacin	10 (5.5)	7 (4.0)
Ketoprofen	10 (5.5)	6 (3.4)
Laxoprofen	10 (5.5)	7 (4.0)
Vicodin	10 (5.5)	6 (3.4)
Acetylsalicylic acid	9 (4.9)	12 (6.9)
Ascorbic acid	9 (4.9)	12 (6.9)
Tramadol	8 (4.4)	14 (8.0)
Mecobalamin	6 (3.3)	10 (5.7)
Morphine	6 (3.3)	11 (6.3)
Famotidine	5 (2.7)	9 (5.2)
Ibuprofen	5 (2.7)	13 (7.5)
Levofloxacin	5 (2.7)	10 (5.7)
Docusate	4 (2.2)	11 (6.3)

Source data: [Appendix Table 2.3.a](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, N=total number of subjects who received at least 1 dose of study drug.
^a Started before or during the study.

Source: Applicant's Integrated Summary of Safety, p. 25.

Currently approved labeling cautions about the potential additive effects on cognitive and gross motor functioning with co-administration of pregabalin and certain other centrally-acting drugs (e.g., oxycodone, lorazepam, ethanol).

Venous Embolic and Thrombotic Disorders

Patients with spinal cord injury are at risk for DVT and pulmonary embolism, particularly in the first several months following injury. Although the population studied in clinical trials for CNP-SCI only included subjects with stable disease (i.e., not acute), the Applicant provided an analysis of venous embolic and thrombotic disorders for this population. The Applicant reported that no subjects in the controlled CNP-SCI trials experienced an AE related to venous embolic or thrombotic disorders. One subject in the controlled and uncontrolled CNP-SCI population experienced pulmonary embolism, which was classified as serious. The subject, a 60-year-old white male, was enrolled in open-label Trial 202, and he developed pulmonary embolism 24 weeks after starting pregabalin treatment (600 mg/day). Pregabalin treatment remained unchanged, and the subject recovered.

Review of the application revealed one additional subject with a venous thrombotic disorder. Subject 5008, in Trial 202, was noted to have bilateral lower extremity blood clots while taking pregabalin (see Section 7.3.3 Dropouts and/or Discontinuations under “Discontinuations Secondary to Adverse Events” for more detailed case information). This event was classified as mild and the location of the blood clots was not specified (i.e., superficial or deep; proximal or distal).

With only two events reported in the open-label extension trial and none in the controlled CNP-SCI trials, there is insufficient evidence to conclude that pregabalin use is associated with increased venous embolic and thrombotic disorders in the CNP-SCI population.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant defined the safety population as all subjects who received at least one dose of study drug. TEAEs were defined as any AE not observed during screening or at baseline and not recorded as continuing on the case report form, or any AE that worsened relative to screening, baseline, or the time when it was recorded on the case report form. The overall AE frequency for subjects in the controlled trials (1107 and 125) was 89% (162/182) for the pregabalin group and 77% (134/174) for the placebo group. For the controlled and uncontrolled trials in CNP-SCI, 91.9% (216/235) of pregabalin treated subjects experienced at least 1 AE and 27.2% (64/235) experienced severe AEs.

TEAEs, reported by system organ class (SOC), occurred most commonly in the Nervous system disorders SOC. The percentage of subjects experiencing an AE within the Nervous system disorders SOC was higher for the pregabalin group (61%) compared to the placebo group (31.6%).

A summary of the most common TEAEs, by preferred term and in decreasing order of frequency, for more than 2% of pregabalin-treated subjects in the controlled trials, is presented in Table 45. I performed a spot check on the Applicant's dataset and found no substantial differences that would affect my perception of the adverse event profile.

Table 45. Common Adverse Events, Summarized by Decreasing Order of Frequency for More Than 2% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.

MedDRA PT	No. (%) of Subjects	
	Pregabalin (N=182)	Placebo (N=174)
Any AE	162 (89.0)	134 (77.0)
Somnolence	65 (35.7)	20 (11.5)
Dizziness	38 (20.9)	12 (6.9)
Dry mouth	20 (11.0)	5 (2.9)
Fatigue	20 (11.0)	7 (4.0)
Oedema peripheral	19 (10.4)	9 (5.2)
Urinary tract infection	16 (8.8)	23 (13.2)
Constipation	15 (8.2)	10 (5.7)
Nasopharyngitis	15 (8.2)	8 (4.6)
Oedema	15 (8.2)	2 (1.1)
Headache	14 (7.7)	17 (9.8)
Vision blurred	12 (6.6)	2 (1.1)
Diarrhoea	10 (5.5)	11 (6.3)
Muscular weakness	9 (4.9)	3 (1.7)
Nausea	9 (4.9)	7 (4.0)
Disturbance in attention	7 (3.8)	0 (0)
Insomnia	7 (3.8)	5 (2.9)
Memory impairment	6 (3.3)	2 (1.1)
Pain	6 (3.3)	2 (1.1)
Pain in extremity	6 (3.3)	4 (2.3)
Upper respiratory tract infection	6 (3.3)	6 (3.4)
Weight increased	6 (3.3)	2 (1.1)
Blood creatine phosphokinase increased	5 (2.7)	0 (0)
Decubitus ulcer	5 (2.7)	2 (1.1)
Fall	5 (2.7)	8 (4.6)
Neck pain	5 (2.7)	2 (1.1)
Urinary incontinence	5 (2.7)	2 (1.1)
Vertigo	5 (2.7)	2 (1.1)
Vomiting	5 (2.7)	2 (1.1)
Back pain	4 (2.2)	3 (1.7)
Euphoric mood	4 (2.2)	1 (0.6)
Hypertension	4 (2.2)	2 (1.1)
Hypotension	4 (2.2)	0 (0)
Joint swelling	4 (2.2)	0 (0)
Muscle spasms	4 (2.2)	6 (3.4)
Paraesthesia	4 (2.2)	1 (0.6)
Pyrexia	4 (2.2)	4 (2.3)

Source data: [Appendix Table 6.2.a](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term, N=total number of subjects who received at least 1 dose of study drug, AE=adverse event.

Source: Applicant's Integrated Summary of Safety, p 36.

The most common TEAEs, by preferred term and in decreasing order of frequency, for more than 3% of pregabalin-treated subjects in the controlled and uncontrolled trials, is presented in Table 46. The AE profile seen in the combined population is consistent with the AE profile of the controlled population with many of the most common AEs including somnolence, dizziness, dry mouth, peripheral edema, and fatigue. Notable

exceptions include urinary tract infection and constipation. Urinary tract infection was experienced by 8.8% of subjects in the controlled trials compared to 21.3% of subjects in the combined controlled and uncontrolled trials. Similarly, constipation was experienced by 8.2% of subjects in the controlled trials compared to 15.3% of subjects in the combined population. This observation can, in part, be explained by the fact that urinary tract infection and constipation are often complications associated with the underlying disease process, spinal cord injury. Therefore, the longer duration of the uncontrolled trial (202) likely presented a greater opportunity for subjects to experience these complications.

Table 46. Common Adverse Events, Summarized by Decreasing Order of Frequency for More Than 3% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125 and Uncontrolled Trial 202.

MedDRA PT	No. (%) of Subjects (N=235)
Any AE	216 (91.9)
Somnolence	79 (33.6)
Dizziness	56 (23.8)
Urinary tract infection	50 (21.3)
Constipation	36 (15.3)
Fatigue	32 (13.6)
Dry mouth	28 (11.9)
Nausea	28 (11.9)
Oedema peripheral	26 (11.1)
Headache	24 (10.2)
Oedema	21 (8.9)
Diarrhoea	20 (8.5)
Insomnia	19 (8.1)
Vision blurred	19 (8.1)
Decubitus ulcer	18 (7.7)
Muscle spasms	17 (7.2)
Nasopharyngitis	17 (7.2)
Upper respiratory tract infection	15 (6.4)
Blood creatine phosphokinase increased	14 (6.0)
Fall	14 (6.0)
Anxiety	13 (5.5)
Muscle spasticity	13 (5.5)
Muscular weakness	13 (5.5)
Disturbance in attention	12 (5.1)
Weight increased	11 (4.7)
Chest pain	10 (4.3)
Hypotension	10 (4.3)
Thermal burn	10 (4.3)
Abdominal distension	9 (3.8)
Abdominal pain	9 (3.8)
Cellulitis	9 (3.8)
Joint swelling	9 (3.8)
Pain in extremity	9 (3.8)
Rash	9 (3.8)
Vomiting	9 (3.8)
Arthralgia	8 (3.4)
Hypertension	8 (3.4)
Musculoskeletal pain	8 (3.4)

Source data: [Appendix Table 6.2.b](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term, N=total number of subjects who received at least 1 dose of study drug (pregabalin), AE=adverse event.

Source: Applicant's Integrated Summary of Safety, p 39.

Summary Comment

CNP-SCI subjects experienced a higher frequency of somnolence compared to subjects studied for previously approved indications (diabetic peripheral neuropathy, postherpetic neuralgia, adult patients with partial onset seizures, and fibromyalgia), as documented in the currently approved labeling for pregabalin (see Section 7.3.5, p 8 for a detailed discussion). Otherwise, review of the most common AEs that occurred in the controlled trials (125 and 1107) and the uncontrolled open-label trial (202) revealed no new significant safety information for pregabalin.

Cursory review of the trials conducted in different patient populations that were submitted as part of this application (A008-1063 and ongoing study A008-1252) also revealed no new significant safety information for pregabalin.

7.4.2 Laboratory Findings

Among subjects with normal baseline laboratory results in the controlled CNP-SCI trials (1107 and 125), 54.3% (95/175) of pregabalin-treated subjects and 47% (78/166) of placebo treated subjects were found to have abnormal postbaseline results. Among subjects with abnormal baseline laboratory results in the controlled CNP-SCI trials, 47.9% (81/169) of pregabalin-treated subjects and 37.9% (58/153) were found to have worsened abnormal postbaseline results.

The most common abnormal postbaseline laboratory results reported for subjects in the controlled trials with *normal* baseline values are summarized in Table 47. It should be noted that urinary tract infection was a common AE among these subjects and that some of the abnormal urine laboratory results may be attributed to this finding. Also, although there was a greater incidence of increased creatine kinase reported for the pregabalin group compared to the placebo group, no rhabdomyolysis AEs were reported in any of the trials.

Table 47. Abnormal Postbaseline Laboratory Results in More Than 2% of Pregabalin-Treated Subjects Who Had Normal Results at Baseline: Controlled Trials 1107 and 125.

Laboratory Test Group	Laboratory Test	Unit	Criteria for Abnormal Test Results	No. of Subjects With Abnormal Postbaseline Test Results, n/N (%)	
				Pregabalin	Placebo
Hematology	Basophils (%)	%	>1.2 × ULN	16/156 (10.3)	8/151 (5.3)
	Monocytes (%)	%	>1.2 × ULN	11/151 (7.3)	14/145 (9.7)
	Eosinophils (%)	%	>1.2 × ULN	4/166 (2.4)	4/153 (2.6)
Lipids	Triglycerides	mg/dL	>1.3 × ULN	6/117 (5.1)	9/111 (8.1)
Clinical chemistry (other)	Creatine kinase	U/L	>2.0 × ULN	4/155 (2.6)	1/151 (0.7)
Urinalysis (dipstick)	Urine protein (qual)	--	≥1	13/152 (8.6)	11/146 (7.5)
	Urine pH	--	>8	7/166 (4.2)	4/159 (2.5)
	Urine glucose (qual)	--	≥1	4/164 (2.4)	1/161 (0.6)
	Urine specific gravity	--	>1.050	4/170 (2.4)	1/159 (0.6)
Urinalysis (microscopy)	Urine white blood cells	/HPF	>5	30/80 (37.5)	27/89 (30.3)
	Urine red blood cells	/HPF	>3	22/91 (24.2)	15/92 (16.3)
	Urine bacteria	/HPF	>20	18/94 (19.1)	9/91 (9.9)

Source data: [Appendix Table 7.1.a](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, n=number of subjects with abnormal postbaseline laboratory test results meeting specified criteria while on study treatment or during follow-up period and who had normal or missing baseline laboratory test results, N=total number of subjects with normal or missing baseline laboratory test results who had at least 1 result of the given laboratory test while on study treatment or during lag time, LLN=lower limit of normal, ULN=upper limit of normal, qual=qualitative, HPF=High Power Field.

Source: Applicant's Integrated Summary of Safety, p 90.

The most common abnormal postbaseline laboratory results reported for subjects in the controlled trials with **abnormal** baseline values are summarized in Table 48.

Table 48. Worsened Abnormal Postbaseline Laboratory Results for at Least 5 Pregabalin-Treated Subjects Who Had Abnormal Results at Baseline: Controlled Trials 1107 and 125.

Laboratory Test Group	Laboratory Test	Unit	Secondary Criteria for Worsened Abnormal Test Results ^a	No. of Subjects With Worsened Postbaseline Test Results, n/N (%)	
				Pregabalin	Placebo
Hematology	Monocytes (%)	%	>1.2 × baseline	5/22 (22.7)	2/15 (13.3)
Lipids	LDL Cholesterol	mg/dL	>1.2 × baseline	13/85 (15.3)	3/76 (3.9)
Clinical chemistry (other)	Glucose	mg/dL	>1.25 × baseline	7/28 (25.0)	1/12 (8.3)
Urinalysis (dipstick)	Urine protein (qual)	--	≥1	11/22 (55.0)	7/17 (42.2)
	Urine glucose (qual)	--	≥1	5/10 (50.0)	1/2 (50.0)
Urinalysis (microscopy)	Urine white blood cells	/HPF	>5	43/56 (76.8)	33/42 (78.6)
	Urine red blood cells	/HPF	>3	14/28 (50.0)	6/14 (42.9)
	Urine bacteria	/HPF	>20	10/23 (43.5)	10/13 (76.9)

Source data: [Appendix Table 7.2.a](#).
 CNP-SCI=central neuropathic pain associated with spinal cord injury, n=number of subjects with worsened abnormal postbaseline laboratory test results meeting both specified criteria while on study treatment or during follow-up period and who had abnormal test results at baseline, N=total number of subjects with abnormal baseline laboratory test results who had at least 1 result of the given laboratory test while on study treatment or during follow-up period,
 LDL=low-density lipoprotein, qual=qualitative, HPF=High Power Field.
^a Primary criteria for abnormal postbaseline test results are shown in [Appendix Table 7.1.a](#).

Source: Applicant's Integrated Summary of Safety, p 91.

The median change in laboratory results for subjects in the controlled trials are summarized in Table 49. The most prominent changes reported were a decrease in platelets (by -8 and $-2 \times 10^3/\text{mm}^3$ for pregabalin and placebo, respectively), increased creatine kinase (by 15 and -8 U/L for pregabalin and placebo, respectively), and increased triglyceride levels (by 6 and 1 mg/dL for pregabalin and placebo, respectively). Increased creatine kinase levels and decreased platelets appear in currently approved labeling for pregabalin as warnings and precautions.

Table 49. Median Changes in Clinical Laboratory Results From Baseline to Last Observation: Controlled Trials 1107 and 125.

Laboratory Test	Median Change in Laboratory Test Results From Baseline to Last Observation ^a	
	Pregabalin	Placebo
Hemoglobin (g/dL)	-0.1	0
Hematocrit (%)	-0.3	-0.7
RBC count (10 ⁹ /mm ³)	-0.01	-0.03
Platelets (10 ³ /mm ³)	-8	-2
WBC count (10 ³ /mm ³)	-0.3	0.1
Lymphocytes (10 ³ /mm ³)	0	0.03
Lymphocytes (%)	2.0	0
Total neutrophils (10 ³ /mm ³)	-0.25	0
Neutrophils (%)	-2.0	-0.6
Basophils (10 ³ /mm ³)	0	0
Basophils (%)	0	0
Eosinophils (10 ³ /mm ³)	0	0
Eosinophils (%)	0	0.1
Monocytes (10 ³ /mm ³)	0	0
Monocytes (%)	0	0
Total bilirubin (mg/dL)	0	0
AST (IU/L)	1	0
ALT (IU/L)	2	0
AP (IU/L)	1	-1
Total protein (g/dL)	0	0
Albumin (g/dL)	-0.1	0
BUN (mg/dL)	0.9	0
Uric acid (mg/dL)	0.2	0
Cholesterol (mg/dL)	0	0
HDL cholesterol (mg/dL)	0	0
LDL cholesterol (mg/dL)	-1	-4
Triglycerides (mg/dL)	6	1
Sodium (meq/L)	0	0
Potassium (meq/L)	0	0
Chloride (meq/L)	1	0
Calcium (mg/dL)	0	0
Glucose (mg/dL)	0	-1
Creatine kinase (U/L)	15	-8
Urine specific gravity	0	0
Urine pH	0	0

Source data: [Appendix Table 7.4.a](#).
 RBC=red blood cell, WBC=white blood cell, AST=aspartate aminotransferase, IU=international unit, ALT=alanine aminotransferase, AP=alkaline phosphatase, BUN=blood urea nitrogen, HDL=high-density lipoprotein, LDL=low-density lipoprotein, meq=milliequivalent.
^a Defined as last observation while receiving study drug or during a follow-up period.

Source: Applicant's Integrated Summary of Safety, p 92.

Abnormal laboratory findings reported as AEs, for more than one pregabalin-treated subject in the controlled trials, included increased blood creatine phosphokinase (5 subjects [2.7%]), increased blood glucose (2 subjects [1.1%]), abnormal liver function test (2 subjects [1.1%]). Abnormal laboratory findings reported as AEs for one pregabalin-treated subject each included increased ALT and blood amylase; increased

white blood cell count; decreased hemoglobin; and decreased neutrophil, platelet, and white blood cell counts.

Although abnormal or worsening postbaseline laboratory results were reported for pregabalin in CNP-SCI controlled studies, the most prominent findings are consistent with the already approved labeling for pregabalin. No new significant safety information relative to laboratory findings is identified.

7.4.3 Vital Signs

There were no notable differences in vital sign parameters between the pregabalin group and the placebo group.

7.4.4 Electrocardiograms (ECGs)

Among the controlled CNP-SCI trials (1107 and 125), pregabalin-treated subjects had a lower incidence of abnormal ECG findings at termination (30.8%) compared to placebo (39.1%). One (0.5%) subject in the pregabalin group had an abnormal ECG finding at termination that was assessed as clinically significant by the investigator compared to two (1.1%) subjects in the placebo group. The clinically significant ECG finding at termination for the pregabalin-treated subject was ST-T changes or abnormal Q wave (≥ 30 msec) compatible with ischemia. This finding was present at screening and is consistent with the subject's past medical history of myocardial infarction.

At screening, two pregabalin-treated subjects were noted to have first degree AV block compared to none in the placebo group. At the termination visit, 4 (2.2%) pregabalin-treated subjects were noted to have first degree AV block compared to 1 (0.6%) in the placebo group. PR interval changes for subjects or other indicators of PR prolongation were not reported. Mild prolongation of the PR interval is reported in the approved labeling for pregabalin.

Otherwise, there were no notable differences in ECG parameters between treatment groups.

7.4.5 Special Safety Studies/Clinical Trials

No special safety trials were included in this application.

7.5 Other Safety Explorations

7.5.2 Time Dependency for Adverse Events

The Applicant analyzed the controlled CNP-SCI and the combined controlled and uncontrolled CNP-SCI populations for median time to onset and median duration of the most common AEs. In comparing pregabalin and placebo in the controlled population, a longer median duration of somnolence (73 days and 14 days, respectively) and edema (101 days and 22 days, respectively) was observed. Otherwise, no obvious significant trends are observed in comparing pregabalin to placebo with respect to AE time to onset and duration.

7.5.3 Drug-Demographic Interactions

The Applicant analyzed adverse events (AEs) by age, gender, and race.

Age

The Applicant summarized AEs experienced by more than 5% of pregabalin-treated subjects in the controlled CNP-SCI studies, by age group (Table 50).

Table 50. Adverse Events Summarized by Age Group and Decreasing Order of Frequency for More Than 5% of Pregabalin-Treated Subjects: Controlled Trials 1107 and 125.

MedDRA PT	No. (%) of Subjects: 18-44 Years of Age	
	Pregabalin (N=78)	Placebo (N=75)
Any AE	69 (88.5)	60 (80.0)
Somnolence	21 (26.9)	14 (18.7)
Dizziness	14 (17.9)	5 (6.7)
Fatigue	14 (17.9)	3 (4.0)
Oedema peripheral	11 (14.1)	4 (5.3)
Oedema	8 (10.3)	0 (0)
Urinary tract infection	8 (10.3)	13 (17.3)
Dry mouth	7 (9.0)	1 (1.3)
Nasopharyngitis	7 (9.0)	5 (6.7)
Headache	5 (6.4)	6 (8.0)
Blood creatine phosphokinase increased	4 (5.1)	0 (0)
Diarrhoea	4 (5.1)	3 (4.0)
Disturbance in attention	4 (5.1)	0 (0)
Insomnia	4 (5.1)	3 (4.0)
Neck pain	4 (5.1)	1 (1.3)
Pain in extremity	4 (5.1)	3 (4.0)
Vision blurred	4 (5.1)	0 (0)
	No. (%) of Subjects: 45-64 Years of Age	
	Pregabalin (N=84)	Placebo (N=80)
Any AE	75 (89.3)	61 (76.3)
Somnolence	34 (40.5)	6 (7.5)
Dizziness	18 (21.4)	7 (8.8)
Dry mouth	11 (13.1)	2 (2.5)
Constipation	9 (10.7)	7 (8.8)
Headache	8 (9.5)	8 (10.0)
Oedema peripheral	8 (9.5)	3 (3.8)
Vision blurred	8 (9.5)	1 (1.3)
Urinary tract infection	7 (8.3)	9 (11.3)
Fatigue	6 (7.1)	3 (3.8)
Nasopharyngitis	6 (7.1)	3 (3.8)
Diarrhoea	5 (6.0)	6 (7.5)
Nausea	5 (6.0)	2 (2.5)
Oedema	5 (6.0)	1 (1.3)
	No. (%) of Subjects: ≥65 Years of Age	
	Pregabalin (N=20)	Placebo (N=19)
Any AE	18 (90.0)	13 (68.4)
Somnolence	10 (50.0)	0 (0)
Dizziness	6 (30.0)	0 (0)
Constipation	4 (20.0)	1 (5.3)
Muscular weakness	4 (20.0)	0 (0)
Dry mouth	2 (10.0)	2 (10.5)
Nasopharyngitis	2 (10.0)	0 (0)
Oedema	2 (10.0)	1 (5.3)
Source data: Appendix Table 6.7.1.a		
CNP-SCI=central neuropathic pain associated with spinal cord injury, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term, N=total number of subjects within age group who received at least 1 dose of study drug, AE=adverse event.		

Source: Applicant's Integrated Summary of Safety, p. 101.

The overall frequency of AEs was relatively consistent across the pregabalin age groups; however, AEs decreased in frequency with increasing age in the placebo group. The most common AE for all age ranges in the pregabalin group was somnolence, and the frequency of somnolence increased as age increased. The opposite trend was observed for the placebo group. Dizziness was the second most common AE among all pregabalin age groups, and a similar trend of increasing frequency with increased age was observed.

Gender and Race

The Applicant summarized an overview of AEs by gender and race (Table 51).

Table 51. Overview of Adverse Events Summarized by Gender and Race: Controlled Trials 1107 and 125.

Demographic Category	No. (%) of Subjects							
	Pregabalin				Placebo			
Sex	Men (N=145)		Women (N=37)		Men (N=145)		Women (N=29)	
	130 (89.7)		32 (86.5)		108 (74.5)		26 (89.7)	
Race	White (N=110)	Black (N=6)	Asian (N=59)	Other (N=7)	White (N=108)	Black (N=8)	Asian (N=54)	Other (N=4)
	102 (92.7)	5 (83.3)	51 (86.4)	4 (57.1)	84 (77.8)	6 (75.0)	42 (77.8)	2 (50.0)

Source data: Appendix Table 6.7.2.a and Table 6.7.3.a.
 CNP-SCI=central neuropathic pain associated with spinal cord injury, N=total number of subjects within a demographic group who received at least 1 dose of study drug.

Source: Applicant's Integrated Summary of Safety, p 103.

The majority of subjects were men (290/356, 81.5%), and over half were white (218/356, 61.2%). The frequency of AEs was similar between male and female pregabalin-treated subjects. The AE frequency was relatively comparable between white and Asian pregabalin-treated subjects. There were too few black or "other" subjects to draw meaningful conclusions with respect to AE frequencies among those groups.

7.5.4 Drug-Disease Interactions

The CNP-SCI population has a similar adverse event profile with pregabalin as other studied populations for previously approved indications. The only notable exception is an increased frequency of somnolence compared to the other populations as discussed in Section 7.3.5 (p 109).

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

The Applicant included a section in the ISS summarizing information to inform the use of pregabalin in pregnancy and lactation. No AEs related to exposure in utero or nursing were reported in the clinical trials reviewed in the Applicant's ISS. Relevant information pertaining to these subpopulations currently appears in the approved labeling for pregabalin.

7.6.3 Pediatrics and Assessment of Effects on Growth

No studies have been carried out in pediatric patients. The Applicant requested a full waiver of the requirement to conduct pediatric studies of pregabalin for the management

of neuropathic pain associated with spinal cord injury relative to this sNDA. The Applicant cited the reason of conducting necessary studies in patients in this age range are impossible or highly impractical because the number of patients is so small and the patients are geographically dispersed. The Applicant provided references supporting that pediatric spinal cord injury is relatively rare compared to its adult counterpart and that neuropathic pain is a less common complication of spinal cord injury in younger patients compared to older patients. This application was discussed at a meeting of the Pediatric Review Committee (PeRC) on April 11, 2012. The PeRC concurred with the request for a full waiver of the requirement to conduct pediatric studies of pregabalin for the management of neuropathic pain associated with spinal cord injury.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant included sections in the ISS summarizing information on overdose, drug abuse potential, and withdrawal and rebound.

Overdose

Four pregabalin-treated subjects with CNP-SCI received a pregabalin dose varying from 750 to 1200 mg/day. These doses exceeded the maximum recommended daily dose of 600 mg. None of these subjects experienced an AE onset around the time of the overdose. Information on overdose appears in the currently approved labeling for pregabalin.

Drug Abuse

Pregabalin is a Schedule V controlled substance. The abuse potential has been previously reviewed in the original NDA 21446.

In the controlled CNP-SCI trials, the AE of euphoric mood was experienced by four pregabalin-treated subjects (2.2%) compared to one placebo-treated subject (0.6%). All of these AEs were mild or moderate in severity, none were classified as serious, and none resulted in discontinuation. Median time to onset for euphoric mood was 5 days and the median duration was 57 days, for pregabalin-treated subjects. No additional subjects experienced euphoria-related AEs in open-label trial 202.

No new significant safety concerns relating to abuse potential have been identified.

Withdrawal and Rebound

The currently approved labeling for pregabalin calls for the medication to be gradually tapered over a minimum one week period when discontinuing. In the controlled CNP-SCI trials, an AE of withdrawal syndrome was experienced by three (1.6%) pregabalin-treated subjects. One of these AEs was characterized as severe and serious.²³ All three of these AEs were experienced by subjects in trial 125, which did not have a drug

²³ This subject (001-1) was reviewed in Section 7.3.2 Nonfatal Serious Adverse Events.

taper specified by the protocol. In contrast, no pregabalin-treated subject in trial 1107 experienced an AE of withdrawal syndrome. The study protocol for 1107 outlined a drug taper at the end of the study.

Three additional pregabalin-treated subjects experienced the AE of withdrawal syndrome in open-label trial 202. All three of these additional AEs were characterized as severe, but none were classified as serious.

Review of these AEs emphasizes that the abrupt cessation of pregabalin may be associated with a withdrawal syndrome. Currently approved labeling addresses these concerns, therefore, no new safety concerns have been identified.

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 90-day safety update on March 20, 2012. No new information was provided for the controlled trials, 1107 and 125, or the open-label extension trial, 202. Additional information was provided in the safety update for open-label extension trial A008-1252; however, this study was conducted in a different patient population than the indicated population for this submission.²⁴ Based on cursory review of the available information for this trial, no new significant safety concerns for pregabalin are identified.

Table 52. Additional Requested Clinical Submissions to NDA 21446/S-028.

Submission Date	Information Submitted
3/9/2012 & 3/30/2012	Responses to information requested in the filing letter
4/17/2012	Response to three separate information requests made by the Division on the 3rd, 4th, and 6 th of April 2012
4/24/2012	Response to an information request made by the Division on April, 13, 2012
5/23/2012	Response to a labeling information request and clarification of that request by the Division on May 10, 2012 and May 15, 2012, respectively

Source: Derived from Applicant's submission, sNDA 21446-028.

8 Postmarket Experience

The Applicant provided an analysis of postmarketing safety data in the Integrated Summary of Safety (ISS) and the Safety Update (SU).

²⁴ Trial A008-1252 is an open-label extension trial of trial 1107; however, the subject population includes central neuropathic pain in poststroke (58.3% of enrolled subjects, 60/103), spinal cord injury (36.9% of enrolled subjects, 38/103), and multiple sclerosis (4.9% of enrolled subjects, 5/103) patients, as requested by the Japanese regulatory authority.

Pregabalin was first approved in the United States in December 2004 for the treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Pregabalin was subsequently approved as adjunctive therapy in adult patients with partial onset seizures (June 2005) and for the management of fibromyalgia (June 2007). Pregabalin was approved for marketing in the European Union in July 2004 where it is approved for neuropathic pain (peripheral and central), add-on therapy for partial onset seizures, and generalized anxiety disorder. Overall, pregabalin is marketed in over 110 countries worldwide. The estimated worldwide exposure (excluding clinical trials) to pregabalin for the period of the third quarter of 2004 through the second quarter of 2011 was $(b)(4) \times 10^3$ patient-years.²⁵ The country with the highest estimated cumulative exposure to pregabalin was the United States, followed by France, Spain, United Kingdom, Italy, and Canada.

The Applicant's safety database contains postmarketing AE reports and includes cases reported spontaneously to the sponsor, cases reported from health authorities, cases published in the medical literature, and cases reported from the Applicant's sponsored marketing programs regardless of causal association with the drug. Cases were retrieved for the combined neuropathic pain (including central neuropathic pain) and central neuropathic pain populations. In the ISS, the Applicant's postmarket safety analysis included cases confirmed by a health care professional (HCP) received from the day pregabalin was launched (July 6, 2004) through August 1, 2011. In the SU, the analysis included HCP-confirmed cases received from August 2, 2011 through February 1, 2011.

AEs included in the System Organ Class of Nervous system disorders were reported most frequently for pregabalin during both the ISS and SU periods.

During the ISS period (summarized in Table 53 below), 14,276 HCP-confirmed cases (containing 35,829 AEs) were reported that involved patients taking pregabalin for various types of neuropathic pain. Over the same time period, 13 HCP-confirmed cases (containing 29 AEs) were reported that involved patients taking pregabalin for central neuropathic pain.

Neuropathic Pain (ISS Period)

When gender was reported, the proportion of women (60.7%) involved in these cases was higher than that of men (33.9%). The most commonly reported outcome was recovered or recovering (53.1%). Cases were reported as serious 44.8% of the time, and 1.7% (249) of cases were reported as fatal. No additional information was included by the Applicant with regards to these deaths.

²⁵ The worldwide cumulative exposure estimate was based on the audited pharmacy and/or wholesaler sales data received from the International Marketing Services Health Midas Database.

Central Neuropathic Pain (ISS Period)

When gender was reported, the proportion of women (38.5%) and men (46.2%) involved in these cases was relatively comparable. Cases were reported as serious 69.2% of the time. The outcome was reported as recovered or recovering 46.2% of the time; however, the most commonly reported outcome was unknown (53.8%). No fatal outcomes were reported.

Table 53. Characteristics of Postmarketing Cases of Pregabalin for the ISS Period: Patients with Neuropathic Pain (NP) and Central Neuropathic Pain (CNP).

Case Characteristics		No. of Cases (%)	
		NP (N=14,276) ^a	CNP (N=13)
Sex	Female	8665 (60.7)	5 (38.5)
	Male	4840 (33.9)	6 (46.2)
	Unknown	771 (5.4)	2 (15.4)
Age (years)	<17	53 (0.4)	0 (0)
	18-30	318 (2.2)	1 (7.7)
	31-50	2549 (17.9)	1 (7.7)
	51-64	2973 (20.8)	3 (23.1)
	65-74	2632 (18.4)	1 (7.7)
NP: Mean (±SD)=61.9 (±16.3)	≥75	2933 (20.5)	3 (23.1)
	Unknown	2818 (19.7)	4 (30.8)
	CNP: Mean (±SD)=63.6 (±19.3)		
Daily dose (mg) ^b	≤50	973 (6.8)	0 (0)
	>50 - 100	2298 (16.1)	1 (7.7)
	>100 - 300	7651 (53.6)	5 (38.5)
	>300 - 600	1023 (7.2)	4 (30.8)
	>600	133 (0.9)	0 (0)
	Other	38 (0.3)	0 (0)
	Unknown	2163 (15.2)	3 (23.1)
Case outcome	Fatal	249 (1.7)	0 (0)
	Not recovered	2497 (17.5)	0 (0)
	Recovered or recovering	7574 (53.1)	6 (46.2)
	Recovered with sequelae	72 (0.5)	0 (0)
	Unknown	3884 (27.2)	7 (53.8)
Case seriousness ^c	Serious	6398 (44.8)	9 (69.2)
	Nonserious	7875 (55.2)	4 (30.8)
	Unknown	3 (0.02)	0 (0)
Concomitant medications/ products	Present	8215 (57.5)	5 (38.5)
	None	600 (4.2)	1 (7.7)
	Unknown	5461 (38.3)	7 (53.8)
Cosuspect medications	Present	1835 (12.9)	2 (15.4)
	None	12441 (87.1)	11 (84.6)
Countries where cases most commonly originated	US – 2842 (19.9)	Germany – 4 (30.8)	
	Japan – 2153 (15.1)	US – 4 (30.8)	
	France – 1979 (13.9)	Japan – 2 (15.4)	
	UK – 1405 (9.8)	Brazil – 1 (7.7)	
	Germany – 1254 (8.8)	France – 1 (7.7)	
	Australia – 472 (3.3)	Thailand – 1 (7.7)	
	Canada – 464 (3.3)		
	Finland – 346 (2.4)		
	Netherlands – 306 (2.1)		
Spain – 258 (1.8)			
Source data: Appendix SA3.1 and SA3.2 .			
NP=neuropathic pain, CNP=central neuropathic pain, N=total number of reported cases, US=United States, UK=United Kingdom.			
^a Most common NP indications included neuralgia, postherpetic neuralgia, pain, peripheral neuropathy, and diabetic neuropathy.			
^b Dose at first event reported (several doses may have been reported in duplicate).			
^c Case was classified as serious if at least 1 of the reported AEs was assessed as serious.			

Source: Applicant's Integrated Summary of Safety, p 114.

During the SU period (summarized in Table 54 below), 1,257 additional cases were entered into the safety database that involved patients taking pregabalin for various types of neuropathic pain. No new postmarketing HCP-confirmed cases of pregabalin involving patients with central neuropathic pain (including central neuropathic pain associated with spinal cord injury) were entered in the safety database for the period covered by the SU. The characteristics of cases in neuropathic pain patients for this period were generally comparable to the ISS period.

Table 54. Characteristics of Postmarketing Cases of Pregabalin for the ISS and SU Periods: Combined Patient Population with Various Types of Neuropathic Pain.

Case Characteristics		No. of Cases (%)	
		ISS Period (N=14,276) ^a	SU Period (N=1257) ^a
Sex	Female	8665 (60.7)	744 (59.2)
	Male	4840 (33.9)	461 (36.7)
	Unknown	771 (5.4)	52 (4.1)
Age (years)	≤17	53 (0.4)	10 (0.8)
	18-30	318 (2.2)	35 (2.8)
	31-50	2549 (17.9)	213 (16.9)
	51-64	2973 (20.8)	258 (20.5)
	65-74	2632 (18.4)	253 (20.1)
	≥75	2933 (20.5)	315 (25.1)
	Unknown	2818 (19.7)	173 (13.8)
		Mean(±SD)=61.9 (±16.3), n=11,150	Mean(±SD)=62.9 (±16.6), n=1075
Daily dose (mg) ^b	≤50	973 (6.8)	159 (12.6)
	>50 - 100	2298 (16.1)	255 (20.3)
	>100 - 300	7651 (53.6)	560 (44.6)
	>300 - 600	1023 (7.2)	59 (4.7)
	>600	133 (0.9)	7 (0.6)
	Other	38 (0.3)	10 (0.8)
	Unknown	2163 (15.2)	207 (16.5)
Case outcome	Fatal	249 (1.7)	17 (1.4)
	Not recovered	2497 (17.5)	171 (13.6)
	Recovered or recovering	7574 (53.1)	680 (54.1)
	Recovered with sequelae	72 (0.5)	5 (0.4)
	Unknown	3884 (27.2)	384 (30.5)
Case seriousness ^c	Serious	6398 (44.8)	612 (48.7)
	Nonserious	7875 (55.2)	645 (51.3)
	Unknown	3 (0.02)	0 (0)
Concomitant medications/ products	Present	8215 (57.5)	685 (54.5)
	None	600 (4.2)	48 (3.8)
	Unknown	5461 (38.3)	524 (41.7)
Cosuspect medications	Present	1835 (12.9)	174 (13.8)
	None	12441 (87.1)	1083 (86.2)
Most commonly originated cases by country		US – 2842 (19.9)	Japan – 475 (37.8)
		Japan – 2153 (15.1)	US – 176 (14.0)
		France – 1979 (13.9)	South Africa – 109 (8.7)
		UK – 1405 (9.8)	France – 85 (6.8)
		Germany – 1254 (8.8)	Germany – 71 (5.6)
		Australia – 472 (3.3)	Canada – 47 (3.7)
		Canada – 464 (3.3)	Australia – 45 (3.6)
		Finland – 346 (2.4)	UK – 42 (3.3)
		Netherlands – 306 (2.1)	Netherlands – 24 (1.9)
		Spain – 258 (1.8)	Switzerland – 17 (1.4)
Source data: ISS Table 69 and SU Appendix SU_SA3.1. HCP=health care professional, IBD=International Birth Date, ISS=Integrated Summary of Safety, SU=Safety Update, NP=neuropathic pain, N=total number of reported cases, SD=standard deviation, n=number of cases, US=United States, UK=United Kingdom. ^a Most commonly reported NP indications included neuralgia, postherpetic neuralgia, pain, peripheral neuropathy, and diabetic neuropathy. ^b Dose at first AE reported (several doses may have been reported in duplicate). ^c Case was classified as serious if at least 1 of the reported AEs was assessed as serious.			

Source: Applicant's Safety Update, p. 12.

Table 55 and Table 56 summarize the common AEs reported during the postmarketing period for pregabalin in the relevant populations. The postmarketing data are relatively consistent with the known safety profile for pregabalin.

Table 55. Summary of Most Commonly Reported Pregabalin Postmarketing AEs Involving Patients with Neuropathic Pain (NP; ≥2% of Cases) and Patients with Central Neuropathic Pain (CNP; All Cases) for the ISS Period by Decreasing Frequency.

Patients With NP (N=14,276)		Patients With CNP (N=13)	
MedDRA PT	No. (%) of Patients	MedDRA PT	No. (%) of Patients
Dizziness	2076 (14.5%)	Myoclonus	2 (15.4)
Somnolence	1470 (10.3%)	Pain	2 (15.4)
Weight increased	947 (6.6%)	Vision blurred	2 (15.4)
Oedema peripheral	857 (6.0%)	Akathisia	1 (7.7)
Drug ineffective	826 (5.8%)	Altered state of consciousness	1 (7.7)
Nausea	649 (4.5%)	Cystostomy	1 (7.7)
Vision blurred	540 (3.8%)	Dizziness	1 (7.7)
Pain	522 (3.7%)	Drug interaction	1 (7.7)
Confusional state	505 (3.5%)	Erythema	1 (7.7)
Fatigue	424 (3.0%)	Fall	1 (7.7)
Tremor	422 (3.0%)	Gait disturbance	1 (7.7)
Headache	363 (2.5%)	Headache	1 (7.7)
Fall	358 (2.5%)	Hyperhydrosis	1 (7.7)
Vomiting	326 (2.3%)	Hypoglycaemia	1 (7.7)
Malaise	315 (2.2%)	Insomnia	1 (7.7)
Vertigo	308 (2.2%)	Malaise	1 (7.7)
Feeling abnormal	297 (2.1%)	Muscle spasms	1 (7.7)
Rash	296 (2.1%)	Muscle twitching	1 (7.7)
Gait disturbance	292 (2.0%)	Myalgia	1 (7.7)
		Pancytopenia	1 (7.7)
		Peripheral coldness	1 (7.7)
		Rash erythematous	1 (7.7)
		Thrombocytopenia	1 (7.7)
		Urinary incontinence	1 (7.7)
		Vaginal haemorrhage	1 (7.7)
		Weight increased	1 (7.7)

Source data: Appendix SA3.1 and SA3.2.
 NP=neuropathic pain, CNP=central neuropathic pain, N=total number of reported cases, MedDRA=Medical Dictionary for Regulatory Activities.

Source: Applicant's Integrated Summary of Safety, p 117.

Table 56. Summary of Most Commonly Reported Pregabalin Postmarketing AEs in at Least 2% of Cases For the ISS and SU Periods: Combined Patient Population with Various Types of Neuropathic Pain.

ISS Period (N=14,276)		SU Period (N=1257)	
MedDRA PT ^a	No. (%) of Cases	MedDRA PT ^a	No. (%) of Cases
Dizziness	2076 (14.5%)	Dizziness	157 (12.5)
Somnolence	1470 (10.3%)	Somnolence	148 (11.8)
Weight increased	947 (6.6%)	Weight increased	83 (6.6)
Oedema peripheral	857 (6.0%)	Pain	70 (5.6)
Drug ineffective	826 (5.8%)	Drug ineffective	61 (4.9)
Nausea	649 (4.5%)	Oedema peripheral	59 (4.7)
Vision blurred	540 (3.8%)	Fall	42 (3.3)
Pain	522 (3.7%)	Nausea	41 (3.3)
Confusional state	505 (3.5%)	Vision blurred	36 (2.9)
Fatigue	424 (3.0%)	Headache	35 (2.8)
Tremor	422 (3.0%)	Feeling abnormal	33 (2.6)
Headache	363 (2.5%)	Fatigue	31 (2.5)
Fall	358 (2.5%)	Visual acuity reduced	30 (2.4)
Vomiting	326 (2.3%)	Dyspnoea	28 (2.2)
Malaise	315 (2.2%)	Vomiting	25 (2.0)
Vertigo	308 (2.2%)		
Feeling abnormal	297 (2.1%)		
Rash	296 (2.1%)		
Gait disturbance	292 (2.0%)		

Source data: ISS Appendix SA3.1 and SU Appendix SU_SA3.1.
 HCP=health care professional, IBD=International Birth Date, ISS=Integrated Summary of Safety, SU=Safety Update, NP=neuropathic pain, N=total number of reported cases, MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred term.
^a MedDRA Version 14.1.

Source: Applicant's Safety Update, p 15.

9 Appendices

9.1 Literature Review/References

The Applicant submitted 39 literature references in support of this supplemental application. The majority of the references considered the epidemiology, demography, and disease characteristics of spinal cord injury and the associated complication of neuropathic pain. While some of the references review treatment options, there is limited published data on the use of pregabalin in neuropathic pain associated with spinal cord injury. However, review of the provided literature reveals no new safety signals that would alter the risk-benefit profile of pregabalin in this population.

9.2 Labeling Recommendations

Based on review of the proposed labeling provided in the submission, this reviewer has the following recommendations. My comments are italicized and, they follow the Applicant's proposed wording as it appears in the referenced section of the proposed label (bolded).

Section 2.5 Neuropathic Pain Associated with Spinal Cord Injury

Because LYRICA is eliminated primarily by renal excretion, the dose (b) (4) patients with reduced renal function (b) (4) [see *Dosage and Administration (2.6)*].

Criteria for renal dosing are detailed in Section 2.6 of the proposed label. To remain consistent with the other labeled indications, I recommend removing the (b) (4) from Section 2.5. Therefore, I recommend changing the wording to:

*“Because LYRICA is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function [see *Dosage and Administration (2.6)*].”*

Section 5.6 Dizziness and Somnolence

(b) (4)

Section 7 Drug Interactions

In addition, no pharmacokinetic interactions are expected between pregabalin and the following treatments: amitriptyline, NSAIDs, SSRIs and SNRIs.

No data was specifically submitted that addressed pharmacokinetic interactions between pregabalin and the above referenced drugs. However, based on pregabalin's known pharmacokinetic profile (predominantly excreted unchanged in the urine and negligible metabolism in humans), it is unlikely for pregabalin to interact with these drugs pharmacokinetically.

Section 14.5 Management of Neuropathic Pain after Spinal Cord Injury

1. Patients were allowed to take nonsteroidal anti-inflammatory drugs, opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants and antidepressant drugs if dose was stable for 30 days prior to screening. Patients were allowed to take acetaminophen during the studies; 18.1 % of LYRICA patients and 19.5% of placebo patients received acetaminophen as a concomitant medication.

Subjects were allowed to take nonsteroidal anti-inflammatory drugs as rescue medications and were not required to be on a stable dose 30 days prior to screening. Therefore, I recommend removing nonsteroidal anti-inflammatory drugs from the list of drugs that required stable dosing for 30 days prior to screening and placing them in the sentence with acetaminophen. Subjects could take the other drugs listed as long as the dose was stable 30 days prior to screening.

Acetaminophen could be used as rescue therapy for pain control, however, it was not the only medication that could be used for rescue therapy. Therefore, only reporting the frequency of acetaminophen use in the label could mislead the reader regarding concomitant medication use in the clinical trials. Based on these findings I recommend changing the wording to:

"Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if the dose was stable for 30 days prior to screening. Patients were allowed to take

acetaminophen and nonsteroidal anti-inflammatory drugs during the studies.”

2. Study SCI 1: This 12 week, randomized, double-blind, parallel-group, multicenter, flexible dose (150-600 mg/day) study compared pregabalin with placebo. Treatment with LYRICA 150-600mg/day statistically significantly improved the endpoint weekly mean pain score and increased the proportion of patients with at least 30% and 50% reduction in pain score from baseline. (b) (4) in Figure 10. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 10: (b) (4)t

The study design included a 3-week dose adjustment phase and a 9-week dose maintenance phase. I recommend the labeling be revised to include this information. I recommend the (b) (4), as referenced in the text and in the title for Figure 10, be changed to remain consistent with the other labeled indications. Therefore, I recommend changing the wording to:

“Study SCI 1: This 12-week, randomized, double-blind, parallel-group, multicenter, flexible dose (150-600 mg/day) study compared pregabalin with placebo. The 12-week study consisted of a 3-week dose adjustment phase and a 9-week dose maintenance phase. Treatment with LYRICA 150-600 mg/day statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to Week 12 is presented in Figure 10. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 10: Patients Achieving Various Levels of Improvement in Pain Intensity – Study SCI 1”

3. Study SCI 2: This 16 week, randomized, double-blind, placebo-controlled, parallel-group, multi-center flexible dose (150-600 mg/day, in increments of 150 mg) study compared the efficacy, safety and tolerability of pregabalin with placebo. Treatment with LYRICA statistically significantly improved the

(b) (4)

(b) (4) is presented in Figure 11. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 11: (b) (4) percent

The study design included a 4-week dose adjustment phase and a 12-week dose maintenance phase. I recommend the labeling be revised to include this information. (b) (4) is not an acceptable primary endpoint; therefore, I recommend removing it from the label, and replacing it with the preferred primary endpoint. I recommend the (b) (4) as referenced in the text and in the title for Figure 11, be changed to remain consistent with the other labeled indications. Therefore, I recommend changing the wording to:

“Study SCI 2: This 16-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, flexible dose (150-600 mg/day, in increments of 150 mg) study compared the efficacy, safety and tolerability of pregabalin with placebo. The 16-week study consisted of a 4-week dose adjustment phase and a 12-week dose maintenance phase. Treatment with LYRICA statistically significantly improved the endpoint weekly mean pain score, and increased the proportion of patients with at least a 30% and 50% reduction in pain score from baseline. The fraction of patients achieving various levels of improvement in pain intensity from baseline to Week 16 is presented in Figure 11. Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 11: Patients Achieving Various Levels of Improvement in Pain Intensity – Study SCI 2”

Additional Labeling Issues

The currently approved labeling for pregabalin contains data, in Sections 5.5, 5.6, 5.7, 5.10, 5.11, 5.12, and 6.1, regarding adverse events and clinical laboratory parameters for premarketing controlled trials of all populations combined. To verify this information with the CNP-SCI population included, we emailed two information requests (dated 5/10/2012 and 5/21/2012) and subsequent clarification (dated 5/15/2012) to the Applicant. At the time of this review, the Applicant has submitted a formal, partial, electronic response (dated 5/23/2012) and informal email responses (dated 5/15/2012, 5/18/2012, 5/23/2012, and 5/24/2012) to the information requests. The Applicant plans to formally submit all responses electronically.

As part of the formal, electronic response (dated 5/23/2012), the Applicant submitted a list of infrequent or rare TEAEs regardless of causality reported for patients treated with

pregabalin during spinal cord injury trials that are not otherwise represented in the draft prescribing information for neuropathic pain associated with spinal cord injury. This list contains adverse events where a clear causal relationship cannot be established with the study medication, that are currently addressed in labeling (i.e., through warnings and precautions), or were not classified as serious. Neutropenia, a potentially clinically relevant AE, was listed and classified as rare. Although this event was not characterized as serious (i.e., no SAE for neutropenia was reported), it is potentially clinically relevant. Therefore, an information request will be sent to the Applicant to gather more information regarding this event (i.e., case report forms and case narratives). The response will be reviewed and any appropriate changes in labeling will be made at that time.

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held.

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

/s/

JOSHUA M LLOYD
05/27/2012

FRANK PUCINO
05/27/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>well-controlled studies in the application?</p> <p>Pivotal Study #1: Protocol Number: A0081107; A 17-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin for the Treatment of Chronic Central Neuropathic Pain After Spinal Cord Injury</p> <p style="padding-left: 40px;">Indication: management of neuropathic pain associated with spinal cord injury</p> <p>Pivotal Study #2: Protocol Number 1008-000-125; A 12-week randomized, double-blind, placebo-controlled, parallel-group multicenter study of pregabalin for treatment of chronic central neuropathic pain after spinal cord injury</p> <p style="padding-left: 40px;">Indication: management of neuropathic pain associated with spinal cord injury</p>				included a 3-week dose adjustment phase and a 9-week dose maintenance phase. This will be a review issue.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Study 1008-000-125 included a 3-week dose adjustment phase and a 9-week dose maintenance phase. This will be a review issue.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.		X		The sponsor did not adhere to DAAAP's previous recommendations regarding primary efficacy endpoints.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		This is yet to be determined as submitted exposure data is tabulated so

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					that each subject could be counted in more than one row within a column and the long term open label study (1008-000-202) included mandatory drug holidays (up to 28 days) every 3 months. Study designs included a flexible dosing regimen.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		Will request from sponsor
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			per stats
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			per stats
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Will expect completed CRFs for deaths, serious adverse events, and adverse dropouts for the ongoing open label study (1252) at the 4-month safety update.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- In section 5.3.5.3.28, we note in Table 3.3.b (Summary of Cumulative Exposure to Pregabalin by Daily Dose Range, Appendix 1-9 - safety tables and listings, p 100) that each subject could be counted in more than one row within a column. Provide an algorithm or rationale to calculate exposure totals (i.e., exposure data without duplicate representation of subjects within a column).
- Provide a rationale for mandatory drug holidays in study 1008-000-202 and for deriving chronic exposure data despite intermittent dosing in that study.
- Provide narratives (not MedWatch reports) for all SAEs and all discontinuations secondary to AEs.
- Provide case report forms (CRFs) and narratives for the following subjects who discontinued secondary to “other” or “no longer willing to participate”:
 - A0081107: 1078-1001
 - A0081107: 1161-1002
 - A0081107: 1148-1002

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

- 1008-000-125: 2-2012
- 1008-000-125: 2-2013
- 1008-000-125: 4-4001
- 1008-000-125: 4-4037
- 1008-000-125: 6-6014
- 1008-000-125: 8-8006
- A0081063: All 6 subjects in study who discontinued secondary to “other” or “no longer willing to participate”
- Provide CRFs and narratives for all deaths (if any occur), SAEs, and discontinuations secondary to AEs for ongoing study A0081252.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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

/s/

JOSHUA M LLOYD
01/31/2012

JACQUELINE A SPAULDING
01/31/2012