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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 6, 2012
From	Frank Pucino, PharmD, MPH, Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA # / Supplement #	NDA 021446 / S-028
Applicant	Pfizer, Inc., for PF PRISM CV
Date of Submission	December 20, 2011
PDUFA Goal Date	June 20, 2012
Proprietary Name / Established (USAN) Names	Lyrica (pregabalin)
Dosage Forms / Strength	Capsules: 25, 50, 75, 100, 150, 200, 225, 300 mg Oral Solution: 20 mg/mL
Proposed Indication	Management of Neuropathic Pain Associated with Spinal Cord Injury
Recommended	Approval

Material Reviewed/Consulted	
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CMC =	Chemistry, Manufacturing, and Controls	OB =	Office of Biostatistics
DAAAP =	Division of Anesthesia, Analgesia, and Addiction Products	OCP =	Office of Clinical Pharmacology
DCDP =	Division of Consumer Drug Promotion	OMPI =	Office of Medical Policy Initiatives
DCP-2 =	Division of Clinical Pharmacology 2	ONDQA =	Office of New Drug Quality Assessment
DGCPC =	Division of Good Clinical Practice Compliance	OPDP =	Office of Prescription Drug Promotion
DMPP =	Division of Medical Policy Programs	OPS =	Office of Pharmaceutical Science
DPDP =	Division of Professional Drug Promotion	SRS =	Science and Research Staff
IO =	Immediate Office		

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ABBREVIATIONS

AE	Adverse Event	MOS	Medical Outcome Study
ANCOVA	Analysis of Covariance	N	Number
BOCF	Baseline Observation Carried Forward	NA	Not Applicable
CFR	Code of Federal Regulations	NDA	New Drug Application
CI	Confidence Interval	NP-SCI	Neuropathic Pain Associated with Spinal Cord Injury
CMC	Chemistry, Manufacturing and Controls	NSAID	Nonsteroidal Anti-inflammatory Drug
CMH	Cochran-Mantel-Haenszel	OB	Office of Biostatistics
CNS	Central Nervous System	OCP	Office of Clinical Pharmacology
COX-2	Cyclooxygenase-2	OMPI	Office of Medical Policy Initiatives
CrCl	Creatinine Clearance	ONDQA	Office of New Drug Quality Assessment
CYP	Cytochrome P450	OPDP	Office of Prescription Drug Promotion
DAAC	Duration Adjusted Average Change	OPS	Office of Pharmaceutical Science
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products	OSI	Office of Scientific Investigations
DCDP	Division of Professional Drug Promotion	PCS	Pain Catastrophizing Scores
DCP-2	Division of Clinical Pharmacology 2	PE	Pulmonary Embolism
DGCP	Division of Good Clinical Practice Compliance	PeRC	Pediatric Research Committee
Diff	Difference	PGIC	Patient Global Impression of Change
DMPP	Division of Medical Policy Programs	PHN	Postherpetic Neuralgia
DPDP	Division of Professional Drug Promotion	PI	Pain Intensity
DPN	Diabetic Peripheral Neuropathy	PT	Preferred Term
DPRS	Daily Pain Rating Scale	SAE	Serious Averse Event
DVT	Deep Venous Thrombosis	SAP	Statistical Analysis Plan
FDA	Food and Drug Administration	SCI	Spinal Cord Injury
GABA	Gamma-Aminobutyric Acid	SD	Standard Deviation
GCP	Good Clinical Practice	SE	Standard Error
HADS	Hospital Anxiety and Depression Scale	SF-MPQ	Short-Form-McGill Pain Questionnaire
IND	Investigational New Drug	sNDA	Supplemental New Drug Application
IO	Immediate Office	SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
ITT	Intent-To-Treat	SOC	System Organ Class
LOCF	Last Observation Carried Forward	SPA	Special Protocol Assessment
LS	Least Squares	SRS	Science and Research Staff
Max	Maximum	SSRI	Selective Serotonin Reuptake Inhibitors
mBOCF	Modified Baseline Observation Carried Forward	TEAE	Treatment-Emergent Adverse Event
Min	Minimum	VAS	Visual Analog Scale
mITT	Modified Intent-To-Treat	Wk	Week

1. INTRODUCTION

Lyrica (pregabalin) is a gamma-aminobutyric acid (GABA) analog currently approved as adjunctive therapy for adult patients with partial onset seizures, and for the management of postherpetic neuralgia (PHN), fibromyalgia and neuropathic pain associated with diabetic peripheral neuropathy (DPN). Although the mechanisms of action for the currently approved pain indications have not been fully elucidated, it is thought that binding of Lyrica to the alpha2-delta subunits of voltage-gated calcium channels may disrupt calcium channel trafficking and/or reduce calcium currents involved in nociception.

On December 20, 2012, Pfizer (henceforth referred to as the Applicant) submitted a supplemental New Drug Application (sNDA 021446/S-028) for the following additional indication: management of neuropathic pain associated with spinal cord injury (NP-SCI). Neuropathic pain following SCI has been reported in approximately 40% of patients following SCI. Symptoms associated with this condition may be disabling and significantly impact the quality of life of these individuals. There are no approved products for this condition in the United States. The Agency recognizes this unmet medical need, which is why this application was reviewed on a priority basis with a six-month time line.

To support the safety and efficacy of Lyrica at the proposed doses of 150 to 600 mg/day for the NP-SCI indication, the Applicant submitted the results from two double-blind, placebo-controlled, multicenter clinical trials (Studies A0081107 and 1008-125) and a long-term open-label trial (Study 1008-202; extension of Study 1008-125). Additionally, the 28-week interim safety results from a second ongoing open-label trial (Study A0081252; extension of Study A0081107) were submitted to this application. Throughout the remainder of this review, the leading designations in the study numbers (i.e., product identifiers) are removed, and these clinical trials will be referred to as follows:

- 1008-125 as Study 125
- 1008-202 as Study 202
- A0081107 as Study 1107
- A0081252 as Study 1252

This review will focus primarily on the adequacy of the data submitted from these clinical trials to support the application. An overview of the regulatory history of this product and issues and concerns related to the efficacy and safety of Lyrica for the proposed dose and indication will be presented.

2. BACKGROUND

Lyrica was first approved by the Agency for the management of neuropathic pain associated with DPN and PHN on December 30, 2004. Subsequently it was approved

as adjunctive therapy for adult patients with partial onset seizures (June 10, 2005) and for the management of fibromyalgia (June 21, 2007). At the time of approval for these indications, it was only available as a capsule formulation. On January 4, 2010, an oral solution was also approved. Lyrica is currently commercially available as hard gelatin capsules, containing 25, 50, 75, 100, 150, 200, 225, 300 mg of pregabalin, and as a 20 mg/mL oral solution. The approved indications and doses of Lyrica are presented in Table 1 below.

Table 1: Approved Indications and Dosing Recommendations for Lyrica

INDICATION	DOSING REGIMEN	MAXIMUM DOSE
DPN Pain	3 divided doses per day	300 mg/day within 1 week
PHN	2 or 3 divided doses per day	300 mg/day within 1 week. Maximum dose of 600 mg/day.
Adjunctive Therapy for Adult Patients with Partial Onset Seizures	2 or 3 divided doses per day	Maximum dose of 600 mg/day.
Fibromyalgia	2 divided doses per day	300 mg/day within 1 week. Maximum dose of 450 mg/day.

Source: Modified from the revised Lyrica product label for this application.

In addition to the clinical use of Lyrica in the United States, pregabalin is also available in 110 other countries, and there is extensive clinical experience with this medication worldwide. Further, although there are currently no products approved in the United States for central neuropathic pain (e.g., the NP-SCI indication), the European Union has approved Lyrica for the treatment of both peripheral and central neuropathic pain in adults.

A review of the regulatory history for Lyrica related to the current application is discussed in detail in the clinical review by Joshua Lloyd, MD, the clinical reviewer for this efficacy supplement. The milestone meetings and regulatory actions for this product are depicted in Table 2 below.

Table 2: Milestone Meetings and Regulatory Actions

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 continuous responder analysis
8/28/2006	Post Type A Meeting teleconference	<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

Date	Meeting/ Submission Type	Comments
		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: Reproduced from Dr. Joshua Lloyd's Clinical Review, Table 1, p. 11-12.

It is important to note that, during the April 21, 2005, Type C meeting, the Applicant was told that two adequate and well-controlled clinical trials would be required to support a specific central pain indication such as spinal cord injury. Further, throughout the regulatory history of this application, the Agency has repeatedly recommended the use of a landmark analysis for evaluation of the primary efficacy parameter, the use of conservative imputation strategies, and performing continuous responder analyses for the proposed Phase 3 trials.

3. Chemistry, Manufacturing, and Controls (CMC)

There were no changes in the manufacturing process of the drug substance, pregabalin, or no new CMC data submitted for review with this supplemental application.

There are no outstanding CMC issues that would preclude approval of this supplement.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

The mechanisms of action by which Lyrica may relieve neuropathic pain in SCI patients are unknown. According to the approved Lyrica label, nonclinical studies using murine models suggests that Lyrica binds with high affinity to the alpha2-delta subunit of the voltage-gated calcium channel felt to be involved in Lyrica's anti-nociceptive and antiseizure pharmacodynamic effects. Animal studies also provide some evidence that Lyrica may reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, by potentially disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents. Additionally, product labeling suggests that the anti-nociceptive effects of Lyrica may be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

The Applicant did not submit any new nonclinical pharmacology or toxicology data to review with this supplemental application.

There are no outstanding pharmacology or toxicology issues that would preclude approval of this sNDA.

5. CLINICAL PHARMACOLOGY/BIPHARMACEUTICS

Following oral administration, Lyrica is well absorbed, with peak plasma concentrations occurring within 1.5 hours. It does not bind to plasma proteins, and the apparent volume of distribution is approximately 0.5 L/kg. Steady state serum concentrations are achieved within 24 to 48 hours, and Lyrica is largely eliminated unchanged by renal elimination. In patients with normal renal function, the elimination half-life is 6.3 hours. Dosage adjustments are recommended and labeled for patients with reduced renal function (i.e., creatinine clearance [CrCl] < 60 mL/min), and since approximately 50% of Lyrica is cleared from the plasma during a 4-hour hemodialysis procedure, supplemental doses are recommended following hemodialysis.

Since SCI patients participating in Studies 125 and 1107 were to be excluded if their estimated CrCl was < 60 mL/min, there is limited information regarding patient tolerance and adverse reactions using the recommended dosage adjustment in the approved Lyrica label for SCI patients with reduced renal function.

Lyrica is not protein bound and does not induce or inhibit cytochrome P450 (CYP) isoenzymes. Therefore, the Applicant felt that pharmacokinetic interactions with medications commonly used by SCI patients, including nonsteroidal anti-inflammatory drugs (NSAIDs), amitriptyline, selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) would not be expected.

In his review, Dr. Lloyd noted that approximately 76% of subjects in the Lyrica treatment arm of Study 125 were taking concomitant analgesics, anti-inflammatory agents, and antidepressants.

Although pharmacokinetic drug-drug interactions are not anticipated with Lyrica, potential pharmacodynamic interactions with other central nervous system (CNS) active drugs are possible. The approved Lyrica label includes adequate precautions regarding the potential for additive CNS side effects with CNS depressants, including alcohol.

Dr. Lloyd noted that the Applicant analyzed the frequency of somnolence in their controlled studies, and reported that the frequency of somnolence was 46.6% and 30.6% among subjects who did and did not take concomitant benzodiazepines, respectively. The placebo treatment arms also resulted in higher frequencies of somnolence in patients taking benzodiazepines (i.e., 15.4% vs. 9.2%).

The Applicant did not submit any new biopharmaceutics or clinical pharmacology studies to support this application. There are no outstanding clinical pharmacology issues that preclude approval.

6. CLINICAL MICROBIOLOGY

Since Lyrica is not a therapeutic antimicrobial, clinical microbiology data were not required or submitted for this application.

7. CLINICAL/STATISTICAL - EFFICACY

The primary clinical review for this application was conducted by Joshua Lloyd, MD, and the primary statistical review was conducted by David Petullo, MS, with concurrence from Dionne Price, PhD.

The application included two Phase 3 trials, Studies 125 and 1107, to support the efficacy of Lyrica for the management of NP-SCI in adults. Study 125 was not conducted under an IND; therefore the study protocol was not reviewed by the Agency prior to the submission of the application. The study characteristics and designs of these clinical trials are presented in Table 3 below.

Table 3: Study Features of the Phase 3 Clinical Trials

Study Identifier	Study Design	Treatment Duration	Treatment Group	Number of Patients n (Male/Female)
125	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	14 weeks 1 week baseline 3 weeks dose titration 9 weeks fixed-dose 1 week follow-up	Lyrica 150-600 mg/d Placebo	70 (60/10) 67 (54/13)

Study Identifier	Study Design	Treatment Duration	Treatment Group	Number of Patients n (Male/Female)
1107	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	20 weeks 2 weeks screening 4 weeks dose titration 12 weeks fixed-dose 1 week taper	Lyrica 150-600 mg/d Placebo	112 (85/27) 107 (91/16)

Source: Adapted from the clinical and statistical reviews, Dr. Joshua Lloyd's and Mr. David Petullo's.

A summary description of the Phase 3 trials and the respective efficacy findings will be presented. For more detailed descriptions and discussions of these clinical trials refer to the statistical and clinical reviews by Mr. Petullo and Dr. Lloyd, respectively.

STUDY 125

Title: *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.*

Objective: The primary objective of this trial was to evaluate the efficacy of Lyrica compared with placebo for the treatment of central neuropathic pain in spinal cord injury.

Design: This trial was designed as a randomized, double-blind, placebo-controlled, multicenter study.

Duration: The study duration for this trial was 14 weeks (12 weeks on study medications), including a 1-week baseline phase, a 3-week dose titration phase, a 9-week fixed-dose maintenance phase, and a 1-week follow-up visit (Figure 1). At the end of study, eligible patients could continue Lyrica treatment in open-label Study 202 after the termination visit.

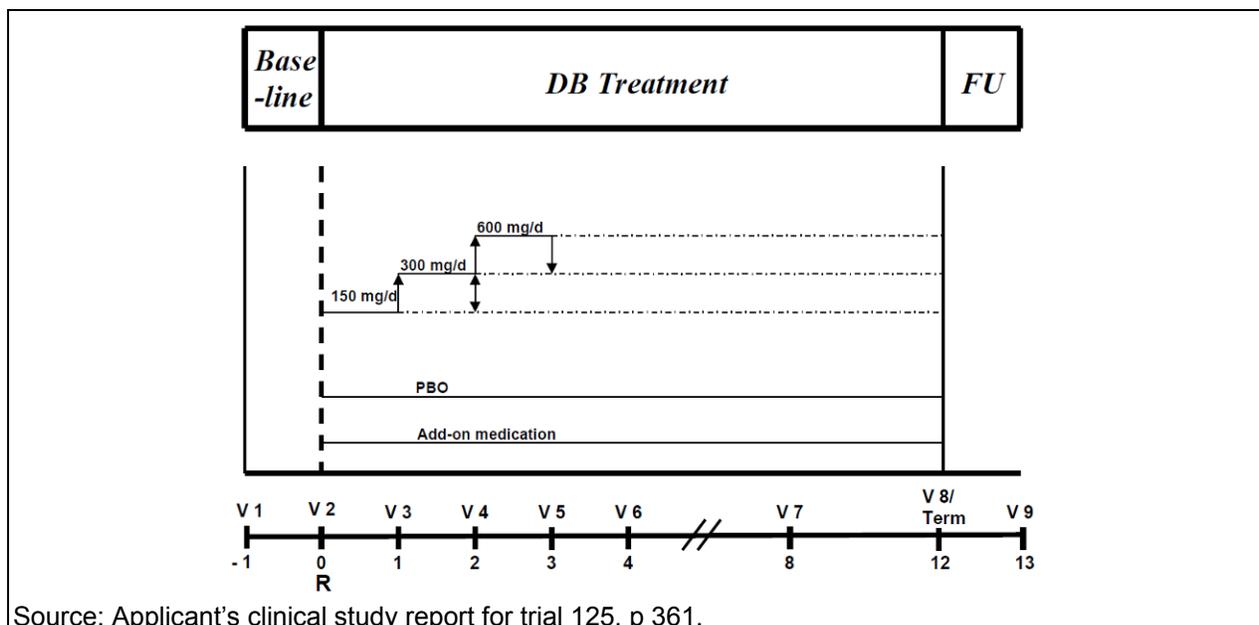
Setting: The trial was conducted from June 2002 to July 2004 at eight centers in Australia.

Patients: Adult patients (≥ 18 years of age) with a diagnosis of traumatic SCI of at least one year duration with a nonprogressive stage of at least six months, who presented with central neuropathic pain that persisted continuously for at least three months or with remissions and relapses for at least 6 months, were eligible to participate in this trial. Additionally, patients must have completed at least four pain evaluations at baseline during the seven days prior to randomization, with an average pain score of four or higher (on an 11-point numerical scale), and have had a screening and

randomization pain score of at least 40 mm on the 100 mm visual analogue scale (VAS) of the Short-Form-McGill Pain Questionnaire (SF-MPQ).

A sample size of 132 patients (66 per treatment arm) would provide greater than 90% power to detect a clinically meaningful difference of 1.3 points in endpoint mean pain scores.

Figure 1: Study Design Diagram (Study 125)



Source: Applicant's clinical study report for trial 125, p 361.

Intervention: Patients were randomized in a 1:1 allocation scheme to receive either weekly escalating doses of Lyrica (150 to 300 to 600 mg/day, adjusted based on response and tolerability) or placebo administered as a split twice daily dose.

Patients were allowed to take narcotic and nonnarcotic analgesics, tricyclic antidepressants, SSRIs, and NSAIDs, but must have been on a stable dosing regimen (for antidepressants and narcotic analgesics, the dose was required to have been stable for at least 30 days prior to screening). Transcutaneous electrical nerve stimulation and antiepileptic drugs (excluding gabapentin) were permitted at stable levels/dosages, and benzodiazepines were allowed as needed but not within six hours of a clinic visit.

Primary Efficacy Endpoint: The prespecified primary efficacy outcome for this trial was the endpoint weekly mean pain intensity (PI) score, defined as the mean of the last seven post-randomization pain scores including the day after the last day of dosing.

Secondary Efficacy Endpoints: The key secondary efficacy endpoints for this trial 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

Additionally, the weekly mean pain score (i.e., the mean of the seven entries of the daily pain diary from that week) was determined during the double-blind treatment phase.

Mr. Petullo also evaluated the weekly mean pain-related sleep interference scores, percentage of patients that achieved at least a 30% reduction in baseline PI at Week 12, and PGIC.

Statistical Analysis Plan (SAP): Mr. Petullo noted that the Applicant's SAP for this study was not submitted to the Agency for review prior to submission of the application. The following is an excerpt from his review describing his statistical approach for analyzing the efficacy data for this study.

As previously stated, the protocol and Statistical Analysis Plan (SAP) for this study was not submitted to the Agency for review prior to submission of the NDA. The applicant's primary efficacy endpoint was defined as "endpoint mean pain score". Endpoint was defined as the mean pain score of the last seven post-randomization entries. This type of approach is analogous to a LOCF strategy to account for missing data. In my analyses, I focused on the change in baseline PI at Week 12 as it had the most relevance based on advice consistently given by the division over the past several years. I utilized both a BOCF and a modified or hybrid approach (mBOCF) to account for missing data at Week 12. The mBOCF approach utilized LOCF for discontinuations due lack of efficacy and BOCF for all other reasons. In July 2010, the National Academy of Sciences issued a report on the prevention and treatment of missing data. The NAS report discourages single imputation methods; however, I justified the use of single imputation strategies in this study since it was conducted prior to the NAS report. Although it is unclear which alternative methods are most desirable, I conducted a cumulative responder analysis which may address some of the concerns outlined in the report. Further, the methods I utilized were unlikely to impute a treatment effect for a patient that withdrew due to an undesirable outcome, i.e. adverse event.

The applicant defined the intent-to-treat (ITT) population as all randomized patients that received at least one dose of study drug and had at least one post-randomization efficacy assessment. Patients were analyzed as randomized regardless of the treatment actually received. All efficacy analyses conducted by the applicant used the ITT population.

To evaluate efficacy, the applicant compared the endpoint mean pain score for the Lyrica group compared to the placebo group using an analysis of covariance (ANCOVA) model with treatment and center as main effects and the baseline PI score as a covariate. If less than seven observations were available, the applicant used what data were available. In my analysis, a patient had to have at least 4 pain scores during Week 12, otherwise the Week 12 pain score was considered missing and was imputed according to the above rules. This approach was not explicitly stated in the protocol for Study 125; however, it was stated for Study 1107.

Secondary outcomes were also evaluated. The percentage of patients that achieved at least a 30% reduction in baseline PI at the end of the study were analyzed using logistic regression with treatment, center, and baseline PI score in the model. PGIC scores were compared between treatment groups using a Cochran-Mantel-Haenszel (CMH) test. Mean sleep interference scores were analyzed using the same ANCOVA model used for the primary endpoint. Treatment and center were included as main effects and the baseline PI score as a covariate.

In his review, Dr. Lloyd also noted that the Applicant conducted the following supplemental analyses:

- 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

Patient Demographics and Disposition: The baseline demographics for the patient population (n=165 screened; 137 randomized) included predominantly male Caucasians with a mean age of approximately 50 years. There does not appear to be any significant imbalances in demographics between the treatment groups (Table 4). However, regarding patient disposition, Mr. Petullo noted that the discontinuation rate was high regardless of treatment (45% and 30% in the placebo and Lyrica treatment arms, respectively). Further, as anticipated, higher numbers of patients discontinued study due to lack of efficacy in the placebo arm and due to AEs in the Lyrica treatment arm.

Table 4: Baseline Demographic Characteristics and Disposition (Study 125)

	Placebo N=67	Lyrica N=70	Total N=137
Demographic Characteristics			
Age (y)			
Mean (SD)	49.8 (14.2)	50.3 (14.3)	50.1 (14.2)
Median	52	51	51
Range	21 – 80	23 – 78	21 – 80
Gender, n (%)			
Female	13 (19.4)	10 (14.3)	23 (16.8)
Male	54 (80.6)	60 (85.7)	114 (83.2)
Race, n (%)			
Caucasian	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)			
Mean (SD)	77.2 (17.6)	79.4 (17.2)	78.3 (17.4)
Median	77	78.3	77.6
Range	41 – 140	50 – 126	41 – 140
Height (cm)			
Mean (SD)	172.5 (10.5)	173.6 (9.5)	173 (10)
Median	173	174.6	173
Range	145 – 199	153 – 193	145 – 199
Baseline Pain Score			
Mean (SD)	6.7 (1.3)	6.5 (1.3)	Not provided
Range	3.9 – 10	3.6 – 9.6	Not provided
Patient Disposition			
Reason for Discontinuation			
Lack of Efficacy, n (%)	20 (30)	5 (7)	25 (18)
Adverse Event, n (%)	9 (14)	15 (22)	24 (18)
Other, n (%)	1 (1)	1 (1)	2 (1)

Source: Adapted from the Applicant's Clinical Study Report for Study 125, p 38, and Mr. Petullo's Statistical Review, Tables 1 and 2, p 7.

Results:

Primary Efficacy Analysis. The results for the Applicant's primary efficacy analysis (i.e., endpoint weekly mean PI score) are presented in Table 5. The Applicant demonstrated superiority over placebo for Lyrica using the prespecified LOCF imputation approach for missing data.

Table 5: Applicant's Primary Efficacy Analysis (Study 125)

	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: Applicant's Clinical Study Report for Study 125, Table 11, p 54.

Because of concerns related to use of a LOCF imputation approach for missing data (i.e., the potential to impute a good score for a patient with a bad outcome), Mr. Petullo reanalyzed the primary efficacy data using more conservative imputation strategies (Table 6).

Table 6: Agency's Primary Efficacy Analysis (Study 125)

Imputation	Treatment	N	Mean Pain Intensity (SE)			
			Baseline	WeeK12	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

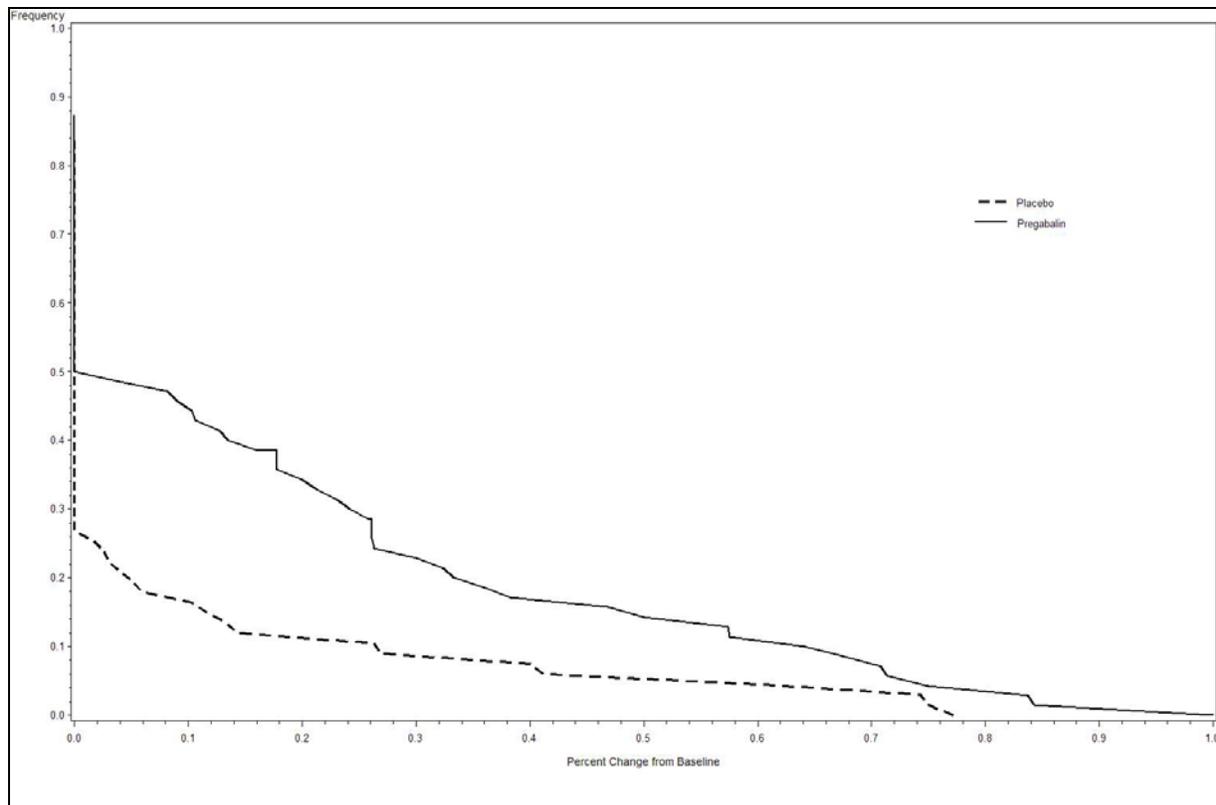
Source: Adapted from Mr. Petullo's Statistical Review, Tables 1 and 2, p 7.

All imputation approaches for the primary efficacy analyses (i.e., LOCF, BOCF and mBOCF) resulted in a significant treatment effect in favor of Lyrica over placebo.

Secondary Efficacy Analyses. In this trial, Mr. Petullo further explored pain response using a cumulative response profile. Results for the continuous responder analysis were supportive of the primary efficacy analysis (Figure 2). Mr. Petullo reported that there was a clear separation in the two curves with Lyrica having a better response profile.

Further, the two curves were significantly different using both the Van der Waerden test ($p < 0.001$) and the Wilcoxon Ranks Sum test ($p = 0.004$).

Figure 2: Continuous Responder Analysis Curves Using BOCF (Study 125)



Source: David Petullo's Statistical Review, Figure 1, p. 10.

Reanalysis of other secondary efficacy variables, i.e., proportion of patients with a 30% reduction in baseline PI at study endpoint using a BOCF approach ($p = 0.02$), PGIC ($p < 0.001$), and weekly mean sleep interference score ($p = 0.002$) also favored Lyrica over placebo.

Secondary endpoint and supplemental analyses conducted by the Applicant also favored Lyrica over placebo. However, as noted by Dr. Lloyd, in his review, 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.

Interpretation/Conclusions:

In the summary conclusions of his review, Mr. Petullo stated the following:

For Study 125, the analysis of the applicant's primary efficacy endpoint, endpoint mean pain score, demonstrated a significant treatment effect in favor of Lyrica. Endpoint was defined as the mean pain score of the last seven post-randomization

entries. My analyses of the mean change in pain at Week 12, using an imputation approach that was unlikely to assign a positive treatment effect to dropouts due to adverse events, was also significant in favor of Lyrica. These results were supported by the findings from analyses of various secondary endpoints such as PGIC and pain related sleep interference. Further when I examined the proportion of patients that demonstrated a reduction of moderate pain to mild pain, there were significantly more patients in the Lyrica arm than the placebo arm that experienced the reduction. This study was conducted entirely outside of the United States; however, the standard of care is considered to be similar, and there were no concerns expressed by the clinical review team.

I concur with the efficacy findings and conclusions of the statistical reviewers.

STUDY 1107

Title: *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.*

Objective: The primary objective of the clinical trial was to evaluate the efficacy of Lyrica 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.

Design: This clinical trial was designed as a randomized, double-blind, placebo-controlled, two-arm, parallel-group, flexible-dose, multicenter clinical trial.

Duration: The study duration for this trial was 20 weeks (17 weeks on study medications), including a 2-week screening phase, a 4-week dose adjustment phase, a 12-week maintenance phase, a 1-week taper phase and a 1-week off treatment phase (Figure 3).

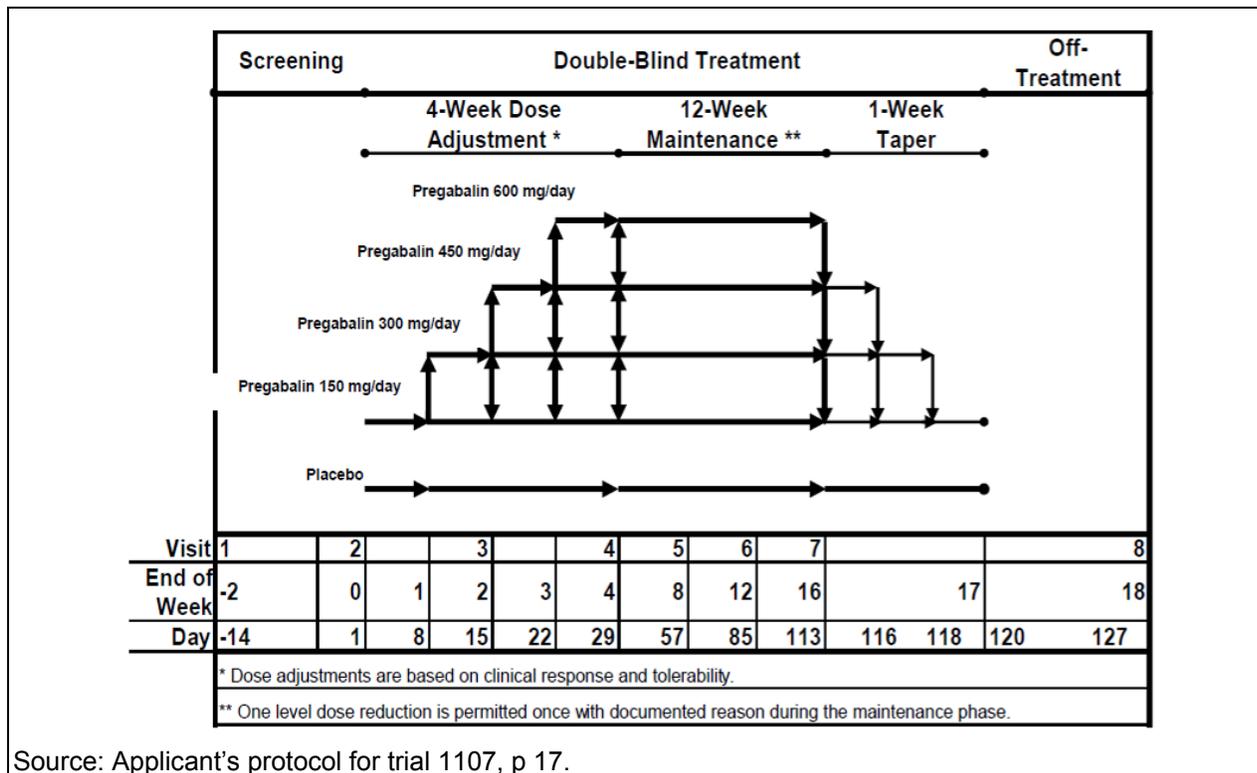
Setting: The trial was conducted from January 2007 to February 2011 at 60 centers in 10 countries, including the United States.

Patients: Adult patients (≥ 18 years of age) with a diagnosis of SCI of at least one year duration, with consistent neurological examination findings and/or radiographic/imaging studies demonstrating a corresponding anatomical lesion, and a neurological level of injury from C2-T12 inclusive were eligible to participate in this trial. The pain following SCI must have persisted continuously for at least three months or, with remissions and relapses, for at least 6 months, and be classified as below-level, type 14 or 15 neuropathic pain according to the Bryce-Ragnarsson SCI pain taxonomy.

Key exclusion criteria included renal dysfunction (i.e., CrCl < 60 mL/min); decreased white blood ($< 2500/\text{mm}^3$), neutrophil ($< 1500/\text{mm}^3$) or platelet ($< 100 \times 10^3/\text{mm}^3$) counts; or clinically significant findings on electrocardiogram.

Based on the results of Study 125, the Applicant estimated that a sample size of 200 patients (100 per treatment arm) would provide greater than 82% power to detect a 0.9 point difference in change from baseline to endpoint mean pain score using a mBOCF analysis.

Figure 3: Study Design Diagram (Study 1107)



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

Intervention: Patients were randomized in a 1:1 allocation scheme to receive either weekly escalating doses of Lyrica (150 to 300 to 450 to 600 mg/day, adjusted based on response and tolerability) or placebo administered as a split twice daily dose.

Acetaminophen (up to 1.5 g per day) and NSAIDs, including COX-2 inhibitors, were allowed as rescue therapy, but they were recorded as concomitant treatment. Medications commonly used for relief of neuropathic pain (e.g., anti-inflammatory agents [i.e., acetylsalicylic acid], opioids, antidepressants, antiepileptic drugs [excluding pregabalin and gabapentin], benzodiazepines, etc.) were also permitted if patients were on a stable dose for 30 days prior to the screening visit.

Primary Efficacy Endpoint: The prespecified primary efficacy outcome for this trial was the duration adjusted average change (DAAC). This endpoint 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. As with the LOCF imputation strategy, the DAAC also potentially assigns a good score for patients with a bad outcome.

Secondary Efficacy Endpoints: The key secondary efficacy endpoints for this trial included:

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

Statistical Analysis Plan (SAP): The Applicant chose the DAAC as their primary efficacy endpoint, even though the Agency had informed them at several milestone meetings and in the SPA No Agreement letters that a landmark analysis would be required (i.e., change in baseline PI at Week 16). However, a landmark analysis was included as a key secondary endpoint only to be tested if their primary was significant. Mr. Petullo focused his review on this secondary efficacy endpoint. The following excerpt from his review describes the statistical approach he used in analyzing the efficacy data for this study.

The applicant defined the ITT population as all randomized patients who received at least one dose of study treatment. There was one patient that was randomized but did not receive study drug. The modified intent to treat (mITT) population excluded the eight patients that were randomized under the fixed dose paradigm and was the applicant's primary analysis population.

The applicant's primary endpoint, DAAC, was compared between treatment groups using an ANCOVA model with baseline pain and pain catastrophizing scores (PCS) as covariates. By definition, DAAC does not impute missing data. Key secondary endpoints included change in PI from baseline to Week 16, 30% reduction in baseline PI, PGIC, and pain related sleep interference scores. The analysis of the change in PI mimicked that of the primary endpoint. Missing data at Week 16 was imputed using three separate approaches, BOCF, mBOCF, and LOCF. The results for PGIC were analyzed via a CMH test adjusting for center. Responder status (30%) was analyzed using a logistic regression model with treatment, center, and baseline PI and PCS. The results for sleep interference scores were compared between treatment groups utilizing an ANCOVA model with baseline pain as a covariate. Missing data was imputed using LOCF.

If the applicant's primary analysis was significant, the key secondary endpoints were tested sequentially; change in PI from baseline to Week 16, 30% reduction in PI at Week 16, PGIC, and change from baseline in the pain related sleep interference score.

Patient Demographics and Disposition: Similar to Study 125, the baseline demographics for the patient population (n=220 screened; 219 randomized) included predominantly male patients with a mean age of approximately 46 years. However, a greater proportion of patients of Asian descent (approximately 50%) were enrolled in this study. In general, the demographic characteristics and patient disposition appeared to be balanced between the treatment groups (Table 7).

Table 7: Demographic Characteristics and Patient Disposition (Study 1107)

	Placebo N=107	Lyrica N=112	Total N=219
Demographic Characteristics			
Age (y)			
Mean (SD)	46 (14)	46 (13)	
Median			
Range	19 – 81	22 – 72	19 – 81
Gender, n (%)			
Female	16 (15)	27 (24)	43 (20)
Male	91 (85)	85 (76)	176 (80)
Race, n (%)			
Caucasian	42 (39)	43 (39)	85 (39)
Black	8 (7)	6 (5)	14 (6)
Asian	53 (50)	57 (51)	110 (50)
Other	4 (4)	6 (5)	10 (5)
Weight (kg)[†]			
Mean (SD)	73.4 (18)	69.9 (16)	71.7 (17)
Median	72.3	68.4	70.9
Range	38.6 – 134	40 – 118	38.6 – 134
Height (cm)[‡]			
Mean (SD)	172 (9.7)	171 (10)	171 (9.9)
Median	172	170	171
Range	144 – 203	143 – 193	143 – 203
Baseline Pain Score			
Mean (SD)	6.5 (1.4)	6.5 (1.4)	6.5 (1.4)
Range	3.4 – 10	3.3 – 10	3.3 – 10
Patient Disposition			
Reason for Discontinuation			
Lack of Efficacy, n (%)	2 (2)	1 (1)	3 (1)
Adverse Event, n (%)	8 (7)	8 (7)	16 (7)
Protocol Violation, n (%)	3 (3)	5 (4)	8 (4)
Other, n (%)	–	2 (2)	2 (1)
Withdrew Consent, n (%)	3 (3)	3 (3)	6 (3)

Source: Adapted from Mr. Petullo's Statistical Review, Tables 10 and 11, p 13.

[†] Nine patients (3 placebo and 6 Lyrica) were missing baseline weights.

[‡] Three patients (2 placebo, 1 Lyrica) were missing baseline heights.

Results:

Primary Efficacy Analysis. Although the results on the DAAC alone would be insufficient to support the effectiveness of Lyrica for the proposed indication, Mr. Petullo included the Applicant's results in his review for completeness (Table 8). The Applicant demonstrated superiority over placebo for Lyrica using this prespecified endpoint.

Table 8: Applicant's Primary Efficacy Analysis (ANCOVA) and Summary of DAAC (Study 1107)

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Lyrica	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: Adapted from the Applicant's Clinical Study Report for Study 1107, Table 14, p 81.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; DAAC, Duration Adjusted Average Change; Diff, difference; DPRS, Daily Pain Rating Scale; LS, least squares; Max, maximum; Min, minimum; MITT, modified intent to treat; N, number of subjects in MITT Population; n, number of subjects analyzed for this endpoint; NA, not applicable; SD, standard deviation; SE, standard error.

Mr. Petullo reanalyzed the data using a landmark analysis (i.e., change in baseline PI at Week 16), the efficacy analysis of interest to the Division (Table 9).

Table 9: Reviewer's Primary Efficacy Analysis (Study 1107)

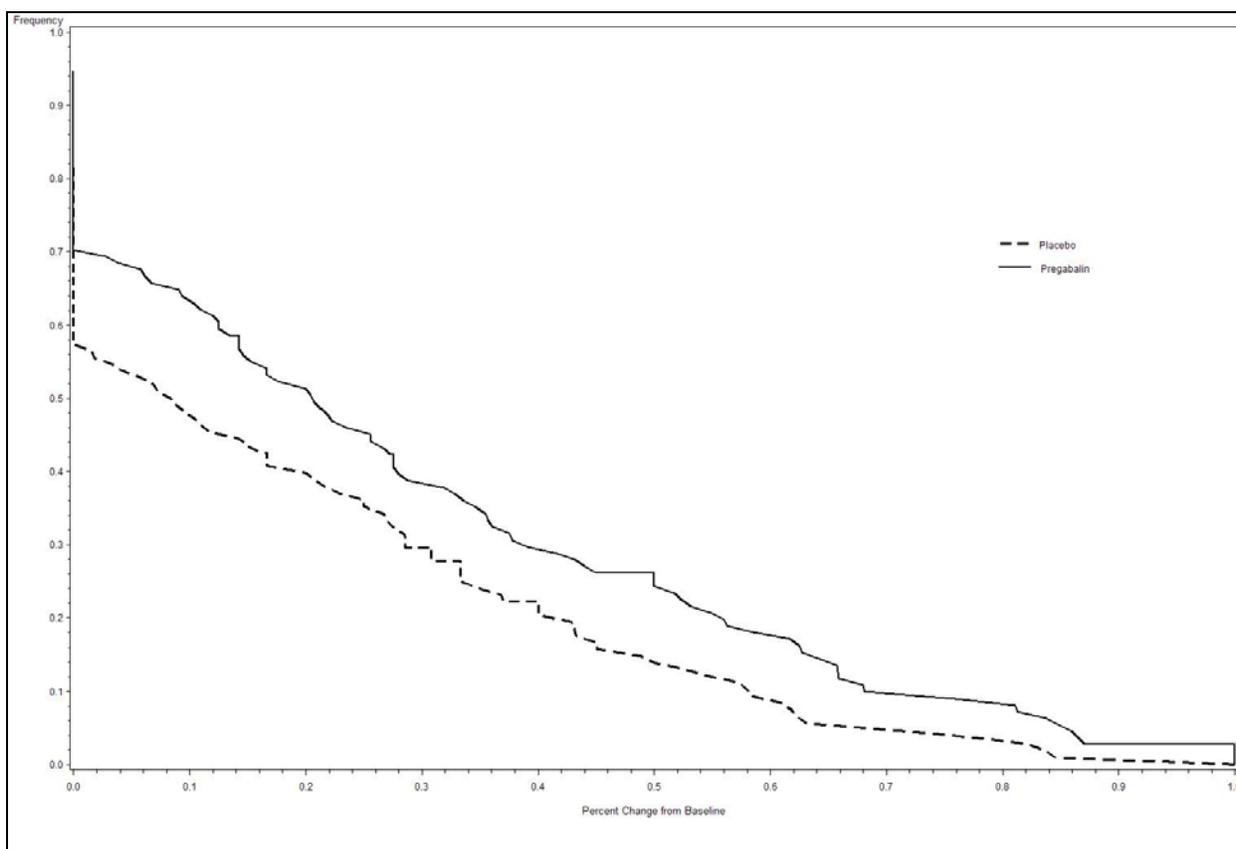
Imputation	Treatment	N	Mean Pain Intensity (SE)				
			Baseline	Wk16	Change	Diff	p-value
BOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.014
mBOCF	Placebo	108	6.5 (0.1)	5.4 (0.2)	1.1 (0.2)	-	-
	Lyrica	111	6.4 (0.1)	4.7 (0.2)	1.7 (0.2)	0.6	0.015

Source: Mr. Petullo's Statistical Review, Tables 13, p 7.

Since only three patients withdrew due to lack of efficacy, both imputation strategies used in the analysis (i.e., BOCF and mBOCF) resulted in a similar treatment effect in favor of Lyrica over placebo ($p < 0.05$).

Secondary Efficacy Analyses. Mr. Petullo also explored the pain response profile using a cumulative response approach. Results for this continuous responder analysis were supportive of the primary efficacy analysis (Figure 4). As observed in Study 125, there was a separation in the two curves, with Lyrica having a better response profile. The two curves were also significantly different using both the Van der Waerden test ($p=0.001$) and the Wilcoxon Ranks Sum test ($p=0.003$).

Figure 4: Continuous Responder Analysis Curves Using BOCF (Study 1107)



Source: David Petullo's Statistical Review, Figure 2, p. 16.

Since the mean change in PI was significant, the proportion of patients with at least a 30% response rate was evaluated according to the sequential testing strategy. The Applicant's use of LOCF for patients missing Week 16 data was considered unacceptable. Therefore, Mr. Petullo performed this same analysis classifying patients that withdrew prior to Week 16 or had missing PI scores for Week 16 as non-responders. The results of these analyses are presented in Table 16. Since a significant treatment effect was not observed in his analysis of the data, the sequential testing would stop.

Table 10: Proportion of Patients with at Least a 30% Reduction in Baseline Pain at Week 16 (Study 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's Statistical Review, Table 16, p. 17.

Reanalysis of other secondary efficacy variables, PGIC ($p=0.04$) and weekly mean sleep interference score ($p=0.0002$), favored Lyrica over placebo, and these were in agreement with the analyses submitted by the Applicant.

Interpretation/Conclusions:

In the summary conclusions of his review, Mr. Petullo stated the following:

In Study 1107, there was a significant treatment effect for the applicant's primary efficacy endpoint, DAAC, and the change in baseline PI at Week 16. Regardless of the analysis population utilized, this finding was consistent. The efficacy of Lyrica was also supported by various secondary endpoints such as PGIC and pain related sleep interference scores. This study was multi-national but included patients from the United States. Evaluation of the subgroup of US patients did not yield a statistically significant difference; however, the difference numerically favored Lyrica.

I concur with the efficacy findings and conclusions of the statistical reviewers.

SUMMARY OF EFFICACY

Based on the review and analysis of data from the two Phase 3 clinical trials, Studies 125 and 1107, the clinical and statistical reviewers felt that there is evidence to support the efficacy of Lyrica for the proposed indication. In his review, Mr. Petullo stated that the analyses of the efficacy endpoints of primary interest to the Division (i.e., a landmark analysis of change in baseline pain intensity to endpoint) were statistically significant in favor of Lyrica, and that these results were further supported by the analyses of secondary endpoints.

I concur with their conclusions that the data from these two clinical trials provide sufficient evidence of effectiveness to support approval of Lyrica for the management of NP-SCI.

8. SAFETY

The review of clinical safety was conducted by Dr. Lloyd. Refer to his review for a detailed discussion of the safety assessment for this application.

The safety database for the NP-SCI clinical development program included the pooled safety data for the two controlled trials (Studies 125 and 1107) and the data for the combined controlled and uncontrolled trials (Studies 125, 1107 and 202). A total of 356 NP-SCI patients from the two completed Phase 3 trials were available for safety assessments, of which 182 patients were exposed to at least one dose of Lyrica. The combined controlled and uncontrolled trials included 235 patients who received at least one dose of Lyrica (Table 11). In his review, Dr. Lloyd noted that eighty-four (35.7%) patients received Lyrica at any dose for at least 24 weeks, and 68 (28.9%) patients received Lyrica at any dose for at least 52 weeks.

MAJOR SAFETY RESULTS

Deaths

During the NP-SCI clinical development program, there was a single death reported in the open-label extension trial (Study 202). Dr. Lloyd noted that the cause of death, i.e., progression of metastatic cancer, was unrelated to Lyrica.

Serious Adverse Events (SAEs)

Dr. Lloyd assessed all SAEs. In the controlled trials (Studies 125 and 1107), he noted that the number of patients experiencing at least one nonfatal SAE was similar between the placebo (n=13; 7.5%) and Lyrica (n=14; 7.7%) treatment arms. Following review of each case, Dr. Lloyd felt that the following SAEs were not related to Lyrica: fecal impaction; urinary tract infection; cellulitis; hypotension; pneumonia; leg pain; dysuria; bradycardia; angina; and ulna fracture. SAEs that he considered as possibly related to Lyrica included: withdrawal reaction; increased muscle spasms; decreased platelet count; edema/hemodilution; hypoglycemia; and cholelithiasis.

In the Lyrica treatment arm, all SAEs resolved with the exception of one subject with an ulna fracture, whose outcome was “not recovered” at the time of reporting. In his review, Dr. Lloyd concluded that there were no new or unexpected safety signals identified from review of the narratives of these events.

I concur with this assessment.

Table 11: Summary of Clinical Trials Used to Evaluate Safety in the NP-SCI Clinical Developmental Program

Study	Design	Treatment Duration	Treatment	Randomized (n)			
Completed Controlled Trials							
125	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	12 Weeks	Lyrica 150-600 mg/d	70			
			Placebo	67			
1107	Randomized Double-blind Placebo-controlled Flexible-dose Multicenter	17 Weeks	Lyrica 150-600 mg/d	112			
			Placebo	107			
Completed Open-Label Extension Trial of Study 125							
202	Open-label	9 Months	Lyrica 150-600 mg/d	103*			
Total Number of Patients Exposed to Lyrica : 235							
Cumulative Exposure in Controlled and Uncontrolled NP-SCI Trials							
	Number of Subjects						
	Total Daily Dose of Lyrica (mg/day)						
Duration of Exposure	>0 to <75	75 to <150	75 to <150	150 to <300	450 to <600	≥ 600	Any Dose
<24 Wks	0	137	211	187	119	97	151
≥24 Wks to <36 Wks	0	0	6	8	2	3	8
≥36 Wks to <52 Wks	0	0	4	5	3	0	8
≥52 Wks to <104 Wks	0	0	10	9	6	11	27
≥104 Wks to <156 Wks	0	0	3	4	4	15	34
≥156 Wks	0	0	1	0	0	0	7

*53 Placebo-treated patients enrolled into Study 202 from Study 125 were treated with Lyrica.

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

Serious Adverse Events (SAEs)

Dr. Lloyd assessed all SAEs. In the controlled trials (Studies 125 and 1107), he noted that the number of patients experiencing at least one nonfatal SAE was similar between the placebo (n=13; 7.5%) and Lyrica (n=14; 7.7%) treatment arms. Following review of each case, Dr. Lloyd felt that the following SAEs were not related to Lyrica: fecal impaction; urinary tract infection; cellulitis; hypotension; pneumonia; leg pain; dysuria; bradycardia; angina; and ulna fracture. SAEs that he considered as possibly related to

Lyrica included: withdrawal reaction; increased muscle spasms; decreased platelet count; edema/hemodilution; hypoglycemia; and cholelithiasis.

In the Lyrica treatment arm, all SAEs resolved with the exception of one subject with an ulna fracture, whose outcome was “not recovered” at the time of reporting. In his review, Dr. Lloyd concluded that there were no new or unexpected safety signals identified from review of the narratives of these events.

I concur with this assessment.

Discontinuations Due to TEAEs

The following excerpt from Dr. Lloyd’s review summarizes patient discontinuations due to TEAEs reported in Studies 125 and 1107:

In the controlled trials (125 and 1107), the frequency of discontinuation due to adverse events (AEs) was 12.6% (23/182) for the Lyrica group and 9.8% (17/174) for the placebo group. The combined controlled and uncontrolled population (Studies 125, 1107, and 202) had a discontinuation frequency of 15.7% (37/235) for Lyrica-treated subjects. Among the 23 subjects in the Lyrica 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 Lyrica group and three weeks for the placebo group.

The TEAEs for Lyrica-treated patients in the controlled and uncontrolled clinical trials for the NP-SCI clinical development program are presented in Table 12 below. Following review of the narratives, Dr. Lloyd felt that the following TEAEs may have been related to Lyrica: anxiety; blurred vision; choking sensation; constipation; drowsiness; dry mouth; euphoria; exacerbation of bipolar disorder; fatigue; headache; irritability; memory loss; nausea; photophobia; photosensitive rash; physical collapse; posterior head pain; vomiting; and worsening rash. The TEAEs for the Lyrica-treated patients in the controlled and uncontrolled clinical trials for the NP-SCI clinical development program are presented in Table 12 below.

**Table 12: Discontinuations Due to Adverse Events for Lyrica-Treated Subjects
(Studies 125 , 1107 and 202)**

MedDRA Preferred Term	Number (%) of Subjects (N=235)
Any Adverse Event	37 (15.7)
Somnolence	7 (3)
Fatigue	4 (1.7)
Edema	4 (1.7)
Balance disorder	2 (0.9)
Disturbance in attention	2 (0.9)
Muscular weakness	2 (0.9)
Edema 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)
Diarrhea	1 (0.4)
Eczema	1 (0.4)
Euphoric mood	1 (0.4)
Hemodilution	1 (0.4)
Hypoglycemia	1 (0.4)
Hypoglycemia	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: Applicant's Integrated Summary of Safety, p 67.

ADDITIONAL SAFETY EVALUATIONS

Somnolence

The incidence of somnolence observed in the SCI population was higher than what was observed in other patient populations for which Lyrica is approved.

- Neuropathic pain associated with spinal cord injury – 35.7%
- Neuropathic pain associated with diabetic peripheral neuropathy 12% to 16%
- Postherpetic neuralgia – 16% to 25%
- Adult partial onset seizure – 22% to 28%
- Fibromyalgia – 20% to 22%

This common AE is discussed in greater detail in Dr. Lloyd's review as follows:

The Applicant analyzed the frequency of somnolence in the controlled NP-SCI population with respect to concomitant benzodiazepines. Among Lyrica-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 NP-SCI subjects in the Lyrica 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 NP-SCI population as its frequency among Lyrica-treated subjects *not* taking concomitant benzodiazepines is higher than its frequency among Lyrica 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 NP-SCI population. Potentially sedating concomitant medications (e.g., baclofen, opioids, amitriptyline, and oxybutynin), in addition to benzodiazepines, were commonly used by subjects in the Lyrica and placebo groups.

Venous Embolic and Thrombotic Disorders

Due to the risk for deep venous thrombosis (DVT) and pulmonary embolism (PE) among SCI patients, particularly in the first several months following injury, the Applicant provided an analysis of venous embolic and thrombotic disorders for this population. There were no subjects in the controlled trials (Studies 125 and 1107), who experienced a thromboembolic event. However, during the open-label trial (Study 202), two patients developed embolic AEs (i.e., PE following 24 weeks on Lyrica 600 mg/day; and "bilateral lower extremity blood clots"). Dr. Lloyd felt that with only two events, there was insufficient evidence to conclude that Lyrica use is associated with increased venous embolic and thrombotic disorders.

I concur with the assessment that there is insufficient evidence that Lyrica is associated with thromboembolic events, especially considering the other predisposing factors (e.g., immobility, polypharmacy, and comorbidities) common to the NP-SCI patient population.

Common Adverse Events

In the controlled trials (Studies 125 and 1107), 89% (162/182) of the Lyrica-treated patients and 77% (134/174) of patients receiving placebo developed TEAEs. For the entire safety database, 91.9% (216/235) of Lyrica-treated patients experienced at least one AE, of which 27.2% (64/235) were classified as severe. AEs were also more commonly reported for the nervous system disorders system organ class (SOC), and they were reported more frequently in the Lyrica-treated patients (61% vs. 31.6%). The common TEAEs, by preferred term and in decreasing order of frequency, for more than 2% of Lyrica-treated subjects in the controlled trials, are presented in Table 13.

Table 13: TEAEs Occurring in >2% of Lyrica-treated Patients in Phase 3 Trials (Studies 125 and 1107)

System Organ Class Preferred Term	PGB* (N=182)	Placebo (N=174)
	%	%
Ear and labyrinth disorders		
Vertigo	2.7	1.1
Eye disorders		
Vision blurred	6.6	1.1
Gastrointestinal disorders		
Dry mouth	11.0	2.9
Constipation	8.2	5.7
Nausea	4.9	4.0
Vomiting	2.7	1.1
General disorders and administration site conditions		
Fatigue	11.0	4.0
Edema peripheral	10.4	5.2
Edema	8.2	1.1
Pain	3.3	1.1
Infections and infestations		
Nasopharyngitis	8.2	4.6
Investigations		
Weight increased	3.3	1.1
Blood creatine phosphokinase increased	2.7	0
Musculoskeletal and connective tissue disorders		
Muscular weakness	4.9	1.7
Pain in extremity	3.3	2.3
Neck pain	2.7	1.1
Back pain	2.2	1.7
Joint swelling	2.2	0
Nervous system disorders		
Somnolence	35.7	11.5
Dizziness	20.9	6.9
Disturbance in attention	3.8	0
Memory impairment	3.3	1.1
Paresthesia	2.2	0.6

System Organ Class Preferred Term	PGB* (N=182)	Placebo (N=174)
	%	%
Psychiatric disorders		
Euphoric mood	2.2	0.6
Insomnia	3.8	2.9
Skin and subcutaneous tissue disorders		
Decubitus ulcer	2.7	1.1
Renal and urinary disorders		
Urinary incontinence	2.7	1.1
Vascular disorders		
Hypertension	2.2	1.1
Hypotension	2.2	0

Source: Modified from the revised Lyrica product label for this application.

Laboratory Findings, Vital Signs and Electrocardiograms

The clinical laboratory results, vital sign changes, and electrocardiogram findings, for the safety population, were consistent with the known safety profile of Lyrica and do not warrant further changes in the Lyrica package insert at this time.

SUMMARY OF SAFETY

Dr. Lloyd evaluated the safety profile of Lyrica in the NP-SCI population that consisted of 235 patients who received at least one dose of Lyrica. An excerpt from the safety summary of his clinical review is as follows:

Of the 235 subjects, 84 (35.7%) received Lyrica at any dose for at least 24 weeks, and 68 (28.9%) received Lyrica at any dose for at least 52 weeks.

Lyrica- and placebo-treated NP-SCI subjects experienced a higher frequency of somnolence 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 NP-SCI population.

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

In the safety database, the most commonly reported adverse events associated with Lyrica use, in the NP-SCI population, were somnolence and dizziness. The frequency of somnolence observed in this patient population was higher than what is currently reported in the Lyrica label for previously approved indications. However, the reported frequency of somnolence was also higher than expected in the placebo treatment arms, and the ratio of somnolence AEs in the Lyrica and placebo groups were relatively similar across all indications. Additionally, Lyrica has been available in the United States for more than seven years and is used in 110 countries world-wide for various pain indications, including central neuropathic pain.

I concur with Dr. Lloyd's conclusions that there were no unusual or unexpected safety findings, and that the balance of potential risks to benefits associated with the use of Lyrica in the management of NP-SCI is acceptable.

9. ADVISORY COMMITTEE MEETING

Since there is extensive clinical experience with Lyrica, and there were no challenging issues identified during the review cycle, an Advisory Committee was not convened for this supplemental application.

10. Pediatrics

The efficacy and safety studies submitted to this application only enrolled SCI patients who were at least 18 years of age. The Applicant requested a full waiver of the requirement to conduct pediatric studies for the management of NP-SCI, since these studies would be impossible or highly impractical to conduct based on the limited number and geographic dispersion of pediatric patients with this condition. On April 11, 2012, the Pediatric Review Committee (PeRC) reviewed and concurred with the Applicant's request for a full waiver.

11. OTHER RELEVANT REGULATORY ISSUES

The Division of Consumer Drug Promotion (DCDP) and the Division of Professional Drug Promotion (DPDP) were consulted for this supplemental application. Their recommendations were reviewed and incorporated into the proposed Lyrica labeling and presented to the Applicant. Labeling negotiations with the Applicant are in the final stages.

Compliance with Good Clinical Practices

In his clinical review, Dr. Lloyd stated that the clinical trials supporting this application were conducted in accordance with Good Clinical Practice (GCP) guidelines 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.

We requested that the Division of Good Clinical Practice Compliance (DGCPC)/Office of Scientific Investigations (OSI) inspect four clinical investigator sites (1072, 004, 006, and 1100) for the Phase 3 efficacy trials (i.e., Studies 125 and 1107). These sites were chosen for inspection primarily based on their relatively high subject enrollment.

The following summary of the inspection results was reproduced from Dr. Lloyd's review:

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 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.

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.

Financial Disclosures

The Applicant submitted Form FDA 3454 (i.e., Certification: Financial Interests and Arrangements of Clinical Investigator) 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. However, in accordance with 21 CFR 54, two investigators had financial interests to disclose; one received \$70,750.00, predominantly for speaking engagements, while the other investigator owned stock or options valued at \$108,400.00. These two investigators, both participating in Study (b) (6), randomized (b) (6) patients, respectively. Dr. Lloyd stated that given the small numbers of subjects randomized at individual clinical trial sites by the investigators with financial disclosures, the possibility of bias in the results based on financial interests is unlikely. One additional investigator is listed as a Due Diligence investigator.

I agree that the financial relationships between the Applicant and these investigators would not significantly influence the results of Study (b) (6).

12. LABELING

The date of the last approved labeling for Lyrica was on August 24, 2011. For the current submission, the Applicant originally proposed labeling that included updates and revisions primarily related to the NP-SCI indication and the supporting efficacy and safety information from their clinical trials (i.e., Studies 125, 1107 and 202). Sections that included relevant revisions are presented in Table 14 below.

As noted above, recommendations from the Division of Medical Policy Programs and the Division of Professional Drug Promotion were incorporated into the proposed labeling and conveyed to the Applicant.

Table 14: Proposed Labeling Changes

Labeling Section	Proposed Revisions
HIGHLIGHTS	Revise: Indications and Usage; Dosage and Administration; and Clinical Studies.
1 INDICATIONS AND USAGE (Section 1.5)	Include the proposed indication for the management of NP-SCI.
2 DOSAGE AND ADMINISTRATION (Section 2.5)	Add a table with instructions on dosage and administration for all Lyrica indications, including the proposed dosing for NP-SCI.
5 WARNINGS AND PRECAUTIONS (Section 5.6)	Revise the numbers for the incidence of dizziness and somnolence to include the NP-SCI safety data.
6 ADVERSE REACTIONS (Section 6.1)	Include adverse reaction information from the NP-SCI clinical development program.
7 DRUG INTERACTIONS (Section 7)	Remove text related to no drug-drug interactions expected between Lyrica and several medications used commonly in NP-SCI patients.
12 CLINICAL PHARMACOLOGY (Section 12.1)	Add the postulated mechanisms of action for gabapentin to be consistent with labeling of other gabapentin products.
14 CLINICAL STUDIES (Section 14.5)	Include the trial design and efficacy information from the Phase 3 trials (i.e., Studies 125 and 1107).
MEDICATION GUIDE	Add the NP-SCI indication, and revise the dosing instructions.

At this time, the Applicant has submitted sufficient information to support their proposed Lyrica labeling, and the Agency is currently in the final stages of labeling negotiations with the Applicant.

13. RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

RECOMMENDED REGULATORY ACTION

Approval

RISK-BENEFIT ASSESSMENT

The Applicant, Pfizer, submitted a supplemental New Drug Application to expand the use of Lyrica to include the indication: management of neuropathic pain associated with spinal cord injury (NP-SCI). There are currently no approved medications in the United States for this indication.

To support the safety and effectiveness of Lyrica for the proposed indication, the Applicant conducted two adequate and well-controlled clinical trials and one long-term open-label extension trial.

During the review of this application, there were no new or unexpected safety signals identified by Dr. Joshua Lloyd, the clinical reviewer for this application. In general, the safety profile of Lyrica in patients with NP-SCI is relatively consistent with what is currently contained in the approved labeling. Further, there is extensive clinical experience worldwide with the use of Lyrica, including its use for the management of peripheral and central neuropathic pain.

Of interest, somnolence was observed in 36% of NP-SCI patients, which is higher than what is currently reported in the Lyrica label for other indications (i.e., $\leq 22\%$ incidence). However, the frequency of somnolence was also higher than expected in the placebo treatment arms, and the ratio of somnolence adverse drug reactions in the Lyrica and placebo groups were relatively similar across all indications. Further, the NP-SCI patients are often taking concomitant medications with central nervous system depressant properties.

Regarding efficacy, the clinical and statistical reviewers determined that both Phase 3 trials (i.e., Study 125 and 1107) were designed and conducted in a reasonably adequate and well-controlled fashion, sufficient to rely upon for a determination of efficacy. The data was reanalyzed by Mr. David Petullo, the statistical reviewer, using a landmark analysis for the primary efficacy analysis and conservative imputation strategies that were acceptable to the Agency. Regardless of which imputation approach was employed, statistical superiority of Lyrica over placebo was demonstrated for the proposed dose and indication. The differences were also considered to be clinically meaningful. In addition, several key secondary outcomes for both trials were supportive, in favor of Lyrica.

I concur with the clinical and statistical assessments of the safety and efficacy findings from the clinical trial data submitted for this supplemental application. Further, considering the well known chemical and pharmacologic characteristics of pregabalin, and its established efficacy and safety profiles, I feel that the benefits of Lyrica outweigh potential risks for the proposed indication: management of neuropathic pain associated with spinal cord injury (NP-SCI).

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Commitments

None.

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/s/

FRANK PUCINO
06/07/2012