CLINICAL REVIEW

Application Type	NDA Postmarketing Requirement
Application Number(s)	21446/S-032 and 22488/S-011
Priority or Standard	Standard
Submit Date(s)	29 February 2016
Received Date(s)	29 February 2016
PDUFA Goal Date	December 29, 2016
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products/ODE 2
Reviewer Name(s)	Robert A. Levin, MD
Review Completion Date	23 November 2016
Established Name	Pregabalin
(Proposed) Trade Name	Lyrica
Therapeutic Class	alpha-2-delta ligand
Applicant	Pfizer
Formulation(s)	25, 50, 75, 100, 150, 200, 225 and 300 mg capsules
Dosing Regimen	Lyrica is to be administered orally BID
Indication(s)	For the management of fibromyalgia
Intended Population(s)	Pediatric

Template Version: March 6, 2009

APPEARS THIS WAY ON ORIGINAL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approving this labeling supplement for LYRICA (pregabalin) with the modified language shown in Section 9.2 (Labeling Recommendations) of this review. (b) (4) . This recommendation is based on the Applicant failing to demonstrate efficacy in an adequate and well-controlled study. However, this study does fulfill Pfizer's pediatric postmarketing requirements for NDA 21446 (LYRICA capsules) and NDA 22488 (LYRICA oral solution).

1.2 Risk Benefit Assessment

Risk Benefit Assessment

(b) (4) efficacy was not demonstrated in adolescent patients with fibromyalgia. The safety profile for pregabalin in the fibromyalgia studies in pediatric patients was generally consistent with the known profile for pregabalin in fibromyalgia adult studies.

Benefit

Efficacy was not demonstrated in Study A0081180 (hereafter referred to as Study 1180), a randomized, double-blind, placebo-controlled, flexible-dose, 15-week study of pregabalin in 107 pediatric patients with fibromyalgia, age 12 to 17 years, at LYRICA total daily doses of 75-450 mg/day. The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11-point daily pain numeric rating scale) showed numerically greater improvement for the pregabalin-treated patients compared to placebo-treated patients, but did not reach statistical significance. Based on Pfizer's prespecified analysis, a treatment difference of (b) (4) was reported by the Applicant for pregabalin relative to placebo in endpoint mean pain score. Although sensitivity analyses (BOCF, mBOCF, LOCF, MMRM at Week 15) also showed greater numerical improvements for pregabalin compared to placebo, they were not statistically significant. The secondary endpoint Patient Global Impression of Change at Week 15 trended in favor of the pregabalin group. The FDA statistician, confirmed the Sponsor's overall findings and determined a treatment difference of (b) (4) for the primary endpoint.

Risk
In the LYRICA pediatric development program for fibromyalgia, a total of 84 patients were exposed to at least one dose of pregabalin during efficacy Study 1180 and open-label extension safety Study A0081231 (hereafter referred to as Study 1231). In Study 1180, 54 patients were treated with pregabalin and in extension Study 1231 of the 63 patients treated with pregabalin, 33 subjects had previously been treated with pregabalin and 30 subjects with placebo. The safety data obtained from this limited number of patients revealed no new safety concerns in adolescents. The currently approved label for LYRICA for adults states that antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. During Study 1180, there did not appear to be a significant difference in the incidence of suicidal ideation between the placebo and LYRICA treatment arms and no suicidal behavior was reported in either treatment group but given the small size of the study a treatment difference would not be expected. LYRICA treatment may cause weight gain in adults. During Study 1180, approximately 22% of subjects treated with pregabalin had weight gain compared to no subjects in the placebo arm.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

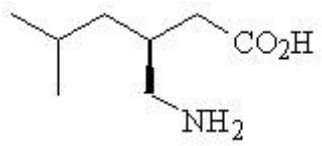
1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

2.1 Product Information

Pregabalin is described chemically as (*S*)-3-(aminomethyl)-5-methylhexanoic acid. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



Pregabalin binds with high affinity to the alpha-2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results with genetically modified mice and with compounds structurally related to pregabalin (such as

gabapentin) suggest that binding to the alpha-2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are currently no FDA approved products for the treatment of fibromyalgia in adolescents. FDA products approved for the treatment of fibromyalgia in adults include: pregabalin (Lyrica), duloxetine hydrochloride (Cymbalta) and milnacipran HCI (Savella).

2.3 Availability of Proposed Active Ingredient in the United States

Pregabalin is currently available in the United States as an approved treatment in adults for the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, adjunctive therapy for adult patients with partial onset seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury.

2.4 Important Safety Issues With Consideration to Related Drugs

Lyrica is associated with the potentially serious safety issues of increased risk of suicidal thoughts or behavior (this risk applies to all antiepileptic drugs used for any indication), peripheral edema, dizziness and somnolence, angioedema (e.g. swelling of the throat, head and neck), hypersensitivity reactions (e.g. hives, dyspnea, and wheezing), and increased seizure frequency in patients with seizure disorders if Lyrica is rapidly discontinued.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 displays highlights of the regulatory activity that occurred during the clinical development program for Lyrica for the treatment of fibromyalgia in adolescents.

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant

Date	Topics
June 21, 2007 NDA 21446 approved	• Lyrica approved for the management of fibromyalgia in adults • Pediatric study requirements waived for ages 0 to 12 years • Pediatric study requirements deferred for ages 13 to 16 years with a final report submission date of January 31, 2012
January 30, 2008 New protocol	Pfizer submitted a new pediatric protocol (A0081180) for fulfill their required pediatric study requirement

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant	
January 9, 2009 FDA Advice Letter	The Division made the following comments about Protocol A0081180: • Your proposed pediatric study is primarily a safety and tolerability study and is not designed to demonstrate efficacy. Demonstration of efficacy and safety are necessary. • You will need to demonstrate efficacy with at least 12 weeks of double-blind therapy. • The Yunus and Masi criteria are acceptable for diagnosing juvenile fibromyalgia syndrome. • Flexible dosing with of 75 to 450 mg/day is acceptable. • Enroll patients ages 12 to 16 years old, inclusive. • Female reproductive hormone levels should be monitored.
January 4, 2010 NDA 22488 approved	• Lyrica Oral Solution approved for neuropathic pain associated with DPN and PHN, adjunctive therapy of patients with partial onset seizures and fibromyalgia. • Pediatric study requirement waived for ages 0 to 16 years for patients with neuropathic pain associated with DPN and PHN • Pediatric study requirement waived for ages 0 to 12 years in patients with fibromyalgia because pediatric fibromyalgia studies are impossible or highly impracticable to conduct due to the low incidence of this condition. • Pediatric study requirement deferred for ages 13 to 16 years with a final report submission date of January 31, 2012
December 19, 2012 Deferral extension request	Pfizer requested a deferral extension for the clinical study report for Study 1180 to December 31, 2017 due to the slow recruitment of adolescent fibromyalgia patients.
January 8, 2013 FDA Advice Letter	The Division made the following comments and recommendations for Protocol A0081180: • We note that you plan to monitor subjects for suicidality using the Suicidality Tracking Scale. This instrument does not adequately capture key categories of suicidal ideations and behaviors. • We recommend use of the Columbia-Suicide Severity Rating Scale (C-SSRS) or another instrument that will capture the information described in the Draft Guidance. • You propose to use LOCF imputation for the efficacy pain measure for all patients who discontinue for any reason. Single imputation methods such as LOCF are not

Table 1: Presubmission Regulatory Interactions between FDA and the Applicant	
	currently preferred for efficacy analyses. Consult the National Academy of Sciences report on missing data. We favor approaches that attribute poor outcomes to those patients that discontinue prior to the end of the study.
April 8, 2013 New Postmarketing Requirement Date	The Division revised the Final Report Submission date to December 31, 2017 and included 17 year olds in the population to be evaluated.
March 4, 2014 Type C Written Response	The Division provided the following written responses to Pfizer's request for a Type C Meeting: • The Division agreed with the proposed imputation and analyses. • The Division agreed with the proposed change in sample size of 106 subjects. • The Division noted that if Pfizer plans to enroll only 106 patients there may only be two patients with monitoring by the C-SSRS. • The Division stated, "However, as an approved product that is already labeled with a suicide warning, the data you have will be sufficient to support filing your application and the adequacy of the data collected on suicidal ideation and behavior will be a review issue. If, after review of the data, we believe additional data on suicidality is needed for this patient population, we may consider available options such as a new postmarketing requirement."
June 15, 2015 Submission of CSR study A0081180	• Final CSR for Study A0081180 to fulfill the pediatric post marketing requirement submitted.
December 8, 2015 Submission of CSR study A0081231	• Final CSR for Study A0081231 an open-label extension to PMR study A0081180 submitted.
February 29, 2016	• Pediatric sNDA submitted: NDA 21446/S-032 and NDA 22488/S-011.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted in Electronic Common Technical Document (eCTD) format. There were no issues with the quality of the submission that affected my ability to complete this review.

3.2 Compliance with Good Clinical Practices

Randomized, double-blind efficacy Study 1180 and open-label safety Study 1231 were conducted in accordance with Good Clinical Practice (GCP) guidelines and in accordance with the Declaration of Helsinki.

No inspections of clinical sites were requested. It was decided that inspections were unlikely to be informative for this application because no specific safety or efficacy concerns were identified in the failed efficacy study or open-label safety extension study.

3.3 Financial Disclosures

Pfizer has submitted financial disclosure information on Study 1180 for the time period from the start of the study through one year after the completion of the study. Pfizer submitted Debarment Certification and FDA form 3454 certifying that none of the financial interests or arrangements described in 21 CFR Part 54 exists for 109 of the 114 clinical investigators who participated in the covered study listed above. Pfizer was unable to obtain a completed Financial Disclosure Form for three Clinical Investigators (Cathy Henderson, Caitlyn Eliza Toffler and Jesdit Diaz), despite multiple attempts. For those investigators no longer at the institution where the study was conducted, Pfizer is certifying that it has conducted reasonable efforts to contact the Clinical Investigator to obtain disclosable financial information. Pfizer identified no clinical investigators who were full-time or part-time employees of the sponsor of the covered study. Pfizer identified two clinical investigators (b) (6) that had financial information to report and provided FDA Form 3455, Disclosure Statement, for each of these clinical investigators who received payment in excess of $25,000.

A copy of the completed Clinical Investigator Financial Disclosure Review form follows.

Application Number: 21446

Submission Date(s): February 29, 2016

Applicant: Pfizer

Product: Lyrica (pregabalin)

Reviewer: Robert A. Levin, MD

Date of Review: October 4, 2016

Covered Clinical Study (Name and/or Number): A0081180

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 114		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: ____ Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: ____ Significant equity interest held by investigator in sponsor of covered study: ____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Pfizer has adequately disclosed financial arrangements with clinical investigators. Two investigators, (b) (6) received payments from Pfizer exceeding $25,000 for consulting and as honorarium. The FDA statistician repeated the analysis of the primary efficacy endpoint without subjects from these two investigators and the three investigators without a completed Financial Disclosure Form and found similar results with a numerically greater improvement for pregabalin compared to placebo. Therefore, it can be concluded that investigators with financial disclosure problems did not favorably influence the efficacy findings.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable

4.2 Clinical Microbiology

Not applicable

4.3 Preclinical Pharmacology/Toxicology

Not applicable

4.4 Clinical Pharmacology

A detailed discussion of the pharmacology issues is contained in the review by Dr. Srikanth Nallani, the pharmacology reviewer.

4.4.1 Mechanism of Action

Pregabalin (LYRICA) is an alpha-2-delta ligand that binds with high affinity to this auxiliary subunit of voltage-gated calcium channels in central nervous system tissues.

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Study A0081180 confirmed the findings from a previous PK study in pediatric subjects with epilepsy that for the same mg dose, pregabalin exposure in pediatric patients 12 to 16 years of age is similar to adults. It is recommended that this information be included in the label (refer to Section 9.2 Labeling Recommendations).

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The LYRICA clinical development program for fibromyalgia in adolescents includes two Phase 3 clinical studies: Study A0081180 a double-blind randomized efficacy and safety study and Study A0081231 an open-label extension safety study (Table 2).

Table 2: Phase 3 Studies

Study	Title	Number of Subjects/Dose
1180 Efficacy	A 15 Week, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Flexible-Dose, Safety and Efficacy Study of Pregabalin in Adolescents (12-17 Years Old) with Fibromyalgia	107 subjects treated: 54 pregabalin and 53 placebo Pregabalin 75, 150, 300, or 450 mg/day (dosed BID)
81231 Safety	A 6-Month, Open-Label, Safety Trial of Pregabalin in Adolescent Patients with Fibromyalgia	63 subjects continued from Study 1180 into the open-label study (33 subjects previously treated with pregabalin and 30 subjects with placebo) Pregabalin 75, 150, 300, or 450 mg/day (dosed BID)

5.2 Review Strategy

Efficacy
Study 1180 was the only study submitted by the Applicant (b) (4) and is reviewed in detail in Section 5.3. Study 1180 failed to demonstrate efficacy with the prespecified primary endpoint of change from baseline to Week 15 in average pain intensity.

Safety
Safety findings from the double-blind study (Study 1180) and the open-label extension study (Study 1231) are discussed in Section 7 on Safety.

5.3 Discussion of Individual Studies/Clinical Trials

(b) (4) the Applicant conducted Study A0081180, hereafter referred to as Study 1180. The following summary of the design of Study 1180 was derived from Final Protocol Amendment 3, dated March 14, 2014. Important modifications to the original protocol are summarized at the end of the protocol.

Title: A 15 WEEK, RANDOMIZED, DOUBLE BLIND, PARALLEL-GROUP, PLACEBO-CONTROLLED, FLEXIBLE-DOSE, SAFETY AND EFFICACY STUDY OF PREGABALIN IN ADOLESCENTS (12-17 YEARS OLD) WITH FIBROMYALGIA

Dates Conducted: The first patient enrolled May 7, 2010 and last patient completed December 8, 2014.

Objectives

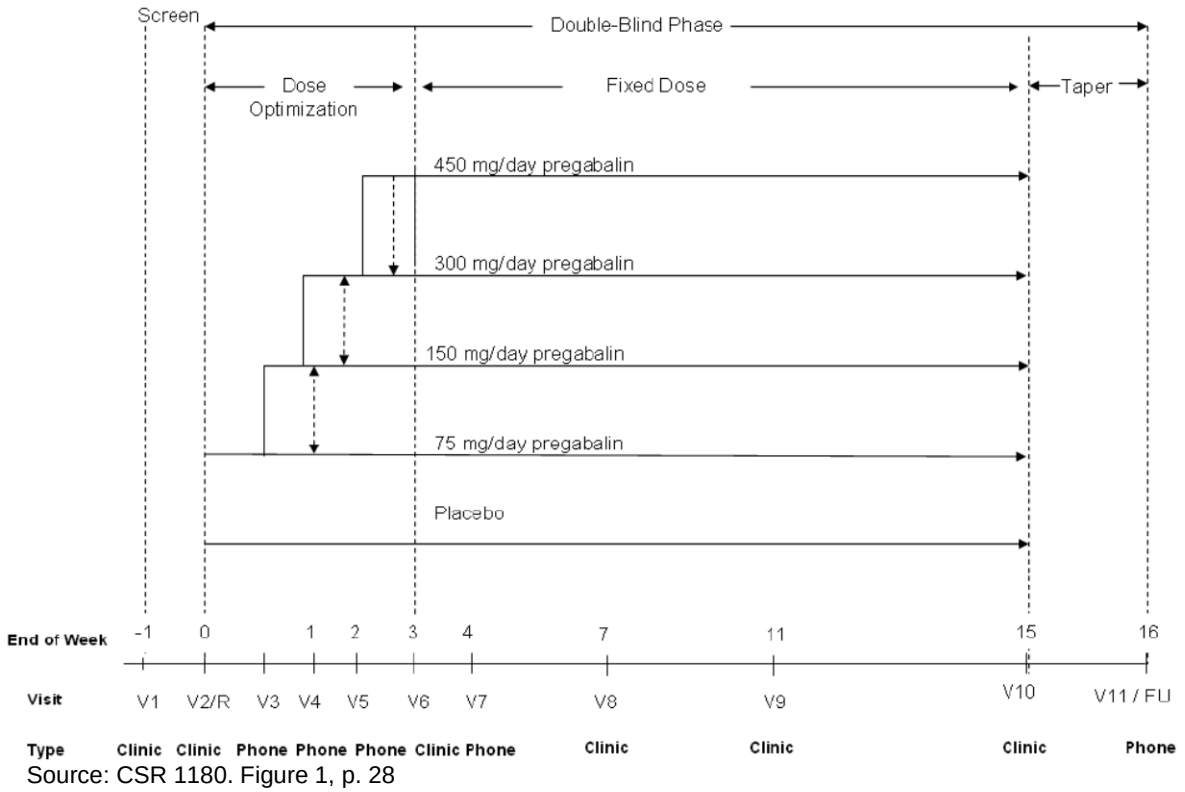
The primary objective was to have been:
- To evaluate the safety and efficacy of pregabalin (75-450 mg/day) compared with placebo in an adolescent fibromyalgia population.

The secondary objective was to have been:
- To evaluate the pharmacokinetics (PK) of pregabalin in an adolescent fibromyalgia population.

Overall Design: Study 1180 was a Phase 4, 15-week, multicenter, randomized, double-blind, parallel group, placebo-controlled study consisting of 4 phases: screening/baseline (1 week), dose optimization (3 weeks), fixed dose (12 weeks) and

follow-up/taper (1 week). At Visit 1 (screening), subjects were to be given a pain and quality of sleep diary which they were instructed to complete on a daily basis. At Visit 2 (randomization), at least 4 pain diaries were to be completed satisfactorily within the last 7 days and the average pain score had to be ≥4. Subjects who met the eligibility criteria at randomization were to receive blinded treatment of either placebo or pregabalin in a ratio of 1:1. Subjects were to initiate dosing at 75 mg/day and have their dose optimized over a 3 week period, based on tolerability and response, to a dose of 75 mg/day, 150 mg/day, 300 mg/day or 450 mg/day (Figure 1). Guidelines for dose escalation are described in Table 4. Study drug dose could only be increased at scheduled visits but could be decreased at, or between the visits, up to and including Day 21. The dose could only be changed by one step up or down at a time (eg, 75 mg/day to 150 mg/day or 450 mg/day to 300 mg/day etc.). After this 3 week optimization period, subjects were to remain at the optimized dose for 12 weeks with no further dose adjustment allowed. Subjects unable to tolerate the fixed dose of study medication were to discontinue from the study. At the end of the 12 week period, subjects were to taper their study medication over a 1-week period and given the option to enter into an open-label extension study. The initial planned sample size of 162 subjects was reduced in Protocol Amendment 3 to a minimum of 106 subjects.

Figure 1: Study Design



Source: CSR 1180. Figure 1, p. 28

Inclusion Criteria:
Patients were to have met all of the following criteria:

1. Male or female 12-17 years of age, inclusive.
2. Subjects and one parent (or legal guardian) must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. Study medication will not be dispensed to a minor; a parent/guardian/caregiver must be available to pick up study medication. Dose adjustments (except dose reductions required for safety reasons) will not be made without parent/guardian/caregiver agreement.
3. Subjects and one parent (or legal guardian) must have signed a written informed assent and consent prior to admission to the study.
4. At screening (Visit 1), subjects must meet the Yunus and Masi criteria (1985) for fibromyalgia: generalized musculoskeletal aching at 3 or more sites for 3 or more months, 5 or more tender points, and 3 or more of the following 10 minor criteria should be present:
    - Chronic anxiety or tension
    - Fatigue
    - Nonrestorative sleep, defined as waking from sleep feeling tired
    - Chronic headaches
    - Irritable Bowel Syndrome, defined as altered bowel habits associated with abdominal pain or discomfort
    - Subjective soft tissue swelling
    - Numbness
    - Pain modulation by physical activities
    - Pain modulation by weather factors
    - Pain modulation by anxiety or stress

    If 5 of the above minor criteria are present, 4 tender points will satisfy the criteria.
5. At screening (Visit 1) and randomization (Visit 2), patients must have a score of ≥4 on the Weekly Pain Numeric Rating Scale.
6. At randomization, at least 4 pain diaries must be completed satisfactorily within the preceding 7 days and the average daily pain score must be ≥4.

Exclusion Criteria:
Patients were to have been excluded if any of the following applied:

1. Subjects with pain due to other conditions that may confound assessments of the pain associated with fibromyalgia.
2. Subjects with systemic inflammatory musculoskeletal disorders or rheumatic diseases other than fibromyalgia, serious active infections, or untreated endocrine disorders. Subjects with a history of Juvenile Rheumatoid Arthritis (JRA) in remission and no longer being treated were eligible for enrollment.

3. Previous participation in a clinical trial with pregabalin, failed pregabalin treatment due to lack of efficacy, intolerance to pregabalin or any pregabalin ingredient, or taking pregabalin within the last 30 days for any condition.
4. Subjects with unstable depressive disorders, unstable Attention Deficit Hyperactivity Disorder (ADHD), or any history of bipolar (mania or hypomania) or psychotic disorder, as assessed by structured interview using the Mini International Neuropsychiatric Interview (MINI-KID) assessment. Subjects with any clinically significant psychiatric disorder that in the judgment of the investigator would make the patient inappropriate for this trial. For subjects with a current DSM diagnosis of a depressive disorder, anxiety disorder, or ADHD (or who meet criteria for one of these conditions based upon the MINI-KID), the following criteria must have been met to be eligible:
    - Subjects with an anxiety disorder or depressive disorder: Must have stable symptoms that do not require pharmacologic treatment, OR be treated for these symptoms for at least 3 months, with the last 2 months prior to Visit 1 at a stable dose and not considering a further increase in dose at study entry.
    - Subjects with ADHD: Must have stable symptoms that do not require pharmacologic treatment, OR must be on a pharmacologic treatment for ADHD for at least 3 months with the last 2 months at a stable dose and unlikely to require a dose adjustment during the study.
    - Any non-pharmacological treatments must be stable.
5. Any subject at risk of suicide or self-harm based on investigator judgment and/or details of a risk assessment by a qualified mental health professional.
6. Subjects with serious hepatic, respiratory, neurologic (epilepsy, multiple sclerosis), cardiovascular, hematologic or immunologic illnesses, or any other severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or study drug administration.
7. Pregnant or nursing females; patients who are unwilling or unable to use an acceptable method of contraception (or abstinence) from screening until completion of follow-up procedures. Females must have a negative serum pregnancy at screening prior to randomization.
8. Subjects with active malignancy of any type or any history of a malignancy.
9. Subjects who are immunocompromised.
10. Subjects with a history of illicit drug or alcohol abuse within the last 2 years. Subjects will not be randomized if a urine drug screen for non-therapeutic drugs is positive at screening. Subjects testing positive for opioid use may have a repeat urine drug screen at the discretion of the investigator, and may be randomized if the repeat test is negative.
11. Creatinine clearance (CLcr) ≤80 mL/min (Cockroft-Gault equation).
12. Platelet count <100x 10^9/L; white blood cell (WBC) count <2.5 x 10^9/L; neutrophil count <1.5 x 10^9/L.
13. C-reactive protein ≥2.00 mg/L.
14. Rheumatoid factor (RF>80 IU/mL).

15. Abnormal (clinically relevant) 12-lead electrocardiogram (ECG); must be reviewed/confirmed by investigator.
16. Subjects taking any other investigational drugs within 30 days of screening.
17. Subjects with active gastrointestinal disease (GI) including any GI surgery that in the opinion of the investigator would interfere with the absorption.
18. Subjects with difficulty swallowing capsules or unable to tolerate oral medication.
19. Unwilling or unable to comply with the Life Style Guidelines including not having elective surgery or consuming alcohol during the study.
20. Use of certain medications for pain, sleep or the treatment of fibromyalgia are prohibited, as listed in Table 5. Certain antidepressants, sleep medications, and medications for the treatment of ADHD are allowable under specific conditions (refer to section on allowable medications). Non-steroidal anti-inflammatory drugs (NSAIDS) and selective COX-2 inhibitors are permitted. Acetaminophen (up to 3 g/day) as rescue medication is permitted.
21. Clinically significant or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise participation in the study.

Randomization Criteria

For randomization at Visit 2 and entry into the double-blind period, subjects were to have met the following criteria:

1. At Visit 2 at least 4 pain diaries must have been completed satisfactorily within the preceding 7 days, and the average daily pain score had to be ≥4.
2. No subject was to be randomized until confirmed ECG and lab reports had been received from the central ECG reader and central laboratory by the site and verified by the Investigator that the subject met all eligibility criteria.
3. Females of child-bearing potential must have had a negative serum pregnancy test prior to randomization.
4. Prior to randomization, the need for a risk assessment by a qualified mental health professional (MHP) was to be determined based on results of screening suicidality assessment. If a subject met criteria for a risk assessment, the subject could not be randomized until the risk assessment had been completed and eligibility determined by the investigator in conjunction with the MHP (or investigator alone if qualified).

Study Procedures

The Schedule of Activities (Table 3) provides an overview of the visits and procedures.

Table 3: Schedule of Activities

Activity	Washout[b] (V0)	Wk -1 V1	Day 0 V2	Day 3 V3[c]	Wk 1 V4[c]	Wk 2 V5[c]	Wk 3 V6	Wk 4 V7[c]	Wk 7 V8	Wk 11 V9	Wk 15 V10/ET	Wk 16[d] V11
Visit Detail[a]	Clinic	Clinic	Clinic	Phone	Phone	Phone	Clinic	Phone	Clinic	Clinic	Clinic	Phone
Visit Type	Washout	Screening	Randomi-zation	Dose Optimization	Dose Optimization	Dose Optimization	End of Dose Optimization	Fixed Dose	Fixed Dose	Fixed Dose	Start Taper	Follow-up
Day[a]	N/A	-21 to -7	0	3	7	14	21	28	49	77	105	112
Visit Window (days)	N/A	N/A	7-21	+1	±3	±3	±3	±3	±3	±3	±3	+7
Informed Consent and Child Assent	(X)	X										
Inclusion / Exclusion Criteria	(X)	X----------X										
Fibromyalgia Diagnostic Criteria[e]		X										
Medical History / Demography	(X)	X										
Physical and Abbreviated Neurological Examination		X									X	
Vital Signs/Weight/Height[f]		X	X				X		X	X	X	
Assessment of pubertal status (Tanner Staging) – Females only		X									X	
Menstrual History – Females only		X									X	
Mini International Neuropsychiatric Interview (MINI-KID)		X										
Suicide Behavior Questionnaire - Revised (SBQ-R)		X										
Sheehan Suicidality Tracking Scale (STS)[g]		X	X				X		X	X	X	
Columbia Suicide Severity Rating Scale (C-SSRS)[g]		X	X				X		X	X	X	
Assessment of need to complete a risk assessment[h]		X	X				X		X	X	X	
12- Lead Electrocardiogram		X									X	
Clinical Laboratory: Hematology, Chemistry, Urinalysis, Pregnancy test		X					X				X	
Clinical Laboratory: C-reactive Protein		X										
Clinical Laboratory: Urine Drug testing		X									X	
Clinical Laboratory: Reproductive hormone evaluation[i] – Females only		X									X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic Sampling							X					

Activity	Washout[b] (V0)	Wk -1 V1	Day 0 V2	Day 3 V3[c]	Wk 1 V4[c]	Wk 2 V5[c]	Wk 3 V6	Wk 4 V7[c]	Wk 7 V8	Wk 11 V9	Wk 15 V10/ET	Wk 16[d] V11
Weekly Pain Numeric Rating Scale[f]		X	X								X	
Daily Pain and Sleep Quality Diaries		X	X[k]	X	X	X	X	X	X	X	X	
Fibromyalgia Impact Questionnaire for Children (FIQ-C)			X								X	
Patient Global Impression of Change											X	
Parent Global Impression of Change											X	
Study Drug Review			X[l]	X	X	X[m]	X	X	X	X	X[n]	X[o]
Study Drug Dispensing			X				X		X	X	X	
Study Drug Dosing Diary and Dosing Instruction Cards		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X

a) The following visit windows applied: V3 (+1 day), V4 to V10 (±3 days), V11 (+7 days from V10). Phone visits required contact via telephone with the subject and parent/guardian/caregiver; subjects may have been asked to come into the clinic as necessary for appropriate clinical management (for instance, to more fully assess an adverse event). V1 may have occurred between 21 days and 7 days prior to V2, based on the amount of time required for screening procedures such as risk assessment by qualified mental health professional. The duration between V1 and V2 was approximately 7 days. A 7-day minimum baseline between V1 and V2 was required to establish baseline pain level. The maximum 21-day screening period did not include prior completion of the informed consent.

b) V0 for subjects requiring washout of prohibited medications. Informed consent and child assent must have been obtained prior to washout of any prohibited medication. If consent/assent, medical history and demography were obtained at V0 they did not need to be repeated at V1. Eligibility criteria were to be assessed until randomization.

c) V3, V4, V5 and V7 may have been handled as phone visits if the subject was tolerating study drug. However, if a subject was not tolerating the study drug, they needed to be seen in the clinic.

d) Follow-up visit only for subjects discontinuing study drug and not entering open-label protocol. Study drug must have been returned to clinic as well.

e) Yunus and Masi and ACR criteria were to be assessed. Eligibility for the study was determined based upon Yunus and Masi criteria.

f) Vital signs including blood pressure and pulse and weight was to be completed at specified visits, height was to be done at V1 and V10 only.

g) "Lifetime" version of Sheehan Suicidality Tracking Scale (STS) at screening only. All other visits used STS for suicidality risk assessment "since last visit". The STS was to be administered any time the subject came in for a clinic visit, including unscheduled clinic visits. The Columbia Suicide Severity Rating Scale (C-SSRS) "Lifetime" was to be performed at V1, and the C-SSRS "since last visit" was to be performed at all subsequent visits. The C-SSRS "since last visit" was to be administered any time the subject came in for an unscheduled clinic visit. For subjects without the C-SSRS "Lifetime" performed at screening, this assessment was to be performed at their next visit. The C-SSRS "since last visit" was to be performed at all subsequent visits.

h) A risk assessment had to be performed and documented if the subject met the criteria.

i) Reproductive hormone monitoring for females only, included luteinizing hormone, follicle stimulating hormone, and estradiol levels.

j) Completed in clinic; 1-week recall period.

k) At V2, at least 4 pain diaries must have been completed within the preceding 7 days.

l) First dose of study drug occurred the morning following the randomization visit. Used and unused study drug was to be returned to the center at all clinic visits and accountability performed.

m) Subjects were to be reminded that a pharmacokinetic sample was to be taken at their next clinic visit (V6) and to record the time of their last meal before attending the clinic visit and the time of the previous evening's dose. Subjects with a morning clinic visit (V6) were instructed not to take the morning dose the day of the visit. Subjects with an upcoming afternoon clinic visit (V6) were instructed to take their morning dose the day of the visit.

n) Dispense double-blind taper medication to all subjects.

o) At V11, study drug must have been returned to the center for subjects not entering the open-label extension study.

Abbreviations: V=visit, Wk=week, ET=early termination, N/A=not applicable

Source: CSR 1180. Schedule of Activities, p. 43-45

Washout (Visit 0)

Informed consent and child assent was to have been obtained prior to undergoing any washout of prohibited medications (Table 7).

Screening (Visit 1)

Visit 1 was to have occurred between 21 days and 7 days prior to Visit 2 (randomization). The following procedures were to have been conducted at this visit:

- Written Informed Consent and assent obtained unless previously at Visit 0.
- Review inclusion/exclusion criteria, including diagnosis of fibromyalgia per Yunus and Masi criteria. Determine whether patient also meets the American College of Rheumatology (ACR) criteria for fibromyalgia (not a requirement for study eligibility).
- Review medical history, concomitant medications and non-drug treatments.

- Physical examination (including height, weight, pulse, blood pressure).
- Abbreviated neurological examination (muscle strength, gait and reflexes).
- Assessment of pubertal status (Tanner Staging) and menstrual history– females only.
- Mini International Neuropsychiatric Interview- KID (MINI-KID).
- Suicidality Tracking Scale (STS).
- Columbia Suicide Severity Rating Scale (C-SSRS) (added Amendment 3)
- Suicide Behaviors Questionnaire-Revised (SBQ-R).
- Assessment of need to complete a risk assessment.
- Weekly Pain Numeric Rating Scale (Pain-NRS).
- 12-lead ECG.
- Clinical laboratory tests (hematology, chemistry with estimated serum creatinine clearance (CLcr), C-reactive protein, urinalysis, drug testing and serum pregnancy.
- Reproductive hormone evaluations – females only.
- Subjects instructed in proper completion of daily diaries for pain and sleep.

Suicidality Risk Assessment During Screening

If the subject had suicide ideation with actual intent, method, or plan at any time in their lifetime or any previous lifetime history of suicide behaviors, or current major psychiatric disorders that were not explicitly permitted in the inclusion/exclusion criteria, a subject should have been excluded based on the judgment of the investigator, or a risk assessment by a clinically qualified mental health professional should have been done. Subjects meeting the following criteria were to have been excluded from the study or may have been allowed to proceed if deemed appropriate after a documented risk assessment:

1. The subject has had suicide ideation associated with actual intent and/or plan at any time in their lifetime, or any positive response (score ≥1) on STS items 1a, 1b, both 3 and 4, or 5 or “yes” response to C-SSRS items 4 or 5; or
2. A score ≥8 on the SBQ-R, or
3. Any previous lifetime history of suicide behaviors:
   - any positive response on STS items 1a, 1b, 6 or 8; or
   - an answer of “yes” to any of the suicidal behavior items of the C-SSRS; or
4. The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria. If a subject has a DSM anxiety disorder, DSM depressive disorder, or ADHD (or meet criteria for one of these conditions based on the MINI-KID) and is stable (treated or untreated), the subject will be eligible to participate in the study without a risk assessment for suicidality if no risk assessment criteria have been met. However, if the investigator feels anxiety, depressive symptoms or impulsive behaviors are significant enough to warrant a risk assessment, this approach would be supported by the sponsor; or

5. In the investigator's judgment a risk assessment or exclusion is required.

It was recommended that the risk assessment be done by a clinically-qualified child and adolescent Mental Health Professional (MHP).

Randomization (Visit 2)
Subjects were to have been randomized in a ratio of 1:1 to receive either placebo or active treatment. Pregabalin or matching placebo capsules were to have been administrated orally, BID for 15 weeks (3 week dose optimization phase and 12 weeks fixed-dose phase).

Study Drug
LYRICA Capsules were supplied in the following strengths: 25mg, 50mg, 75mg, 150mg and 225mg. Study drug was supplied as blinded capsules of pregabalin and matching placebo. On the day of randomization, drug supply consisting of 4 blister packages, was provided to the subject's parent/guardian/caregiver, as follows:

- Pregabalin 75 mg/day (25 mg morning and 50 mg evening) or placebo.
- Pregabalin 150 mg/day (75 mg BID) or placebo.
- Pregabalin 300 mg/day (150 mg BID) or placebo.
- Pregabalin 450 mg/day (225 mg BID) or placebo.

Dose Titration
Subjects were to initiate dosing at 75 mg/day with pregabalin or matching placebo the morning after randomization (Visit 2). Subjects were to take one capsule in the morning and one capsule in the evening. During the dose optimization phase (Weeks 1, 2, and 3), the dose was escalated in a blinded fashion (ie, the investigator and subject were unaware as to whether active or placebo was being administered) in order to reach the optimal dose for each subject. Study drug dose could only be increased at scheduled visits (including phone visits) but could be decreased at, or between the visits, up to and including Day 21. Based on tolerability and response, the dose could be titrated from the initiating dose of 75 mg/day to 150 mg/day, 300 mg/day or 450 mg/day (Figure 1). Guidelines for dose escalation are described in Table 5. Patients were to have remained on these doses for an additional 12 weeks without further dose adjustment.

Table 4: Dose Escalation Guidelines

Visit	Day	Dose Achieved by Visit [a]	Response [a]	Action*, [a]
2	1	Not applicable	All subjects begin with regimen of 75 mg/day for 3 days.	Subjects unable to tolerate 75 mg/day will be discontinued.
3	3	75 mg/day	Subject tolerates any side effects [b]	Increase dose to 150 mg/day starting on Day 4
			Subject unable to tolerate side effects	Discontinue subject
4, 5, 6	7, 14, 21	75 mg/day	Subject unable to tolerate side effects	Discontinue subject
			Good pain relief, good tolerability	Subject remains at 75 mg/day
			Inadequate pain relief, good tolerability	Escalate to 150 mg/day
		150 mg/day	Subject unable to tolerate side effects	Decrease to 75 mg/day
			Good pain relief, good tolerability	Subject remains at 150 mg/day
			Inadequate pain relief, good tolerability	Escalate to 300 mg/day
		300 mg/day	Subject unable to tolerate side effects	Decrease to 150 mg/day
			Good pain relief, good tolerability	Subject remains at 300 mg/day
			Inadequate pain relief, good tolerability	Escalate to 450 mg/day
		450 mg/day	Subject unable to tolerate side effects	Decrease to 300 mg/day
			Good pain relief, good tolerability	Subject remains at 450 mg/day
			Inadequate pain relief, good tolerability	No further escalation is permitted. Assess if pain level is tolerable to complete study or withdraw subject from study due to lack of efficacy

a Doses described in the table and footnotes refer to the pregabalin dose and its matching placebo.

b If in the investigator's judgment, the subject likely would not tolerate a dose increase to 150 mg/day, the subject could remain at 75 mg/day, although dose escalation to 150 mg/day was preferred.

* Subjects who had good tolerability but inadequate pain relief could increase to the next dose level up to 450 mg/day, at the next clinic visit, at the investigator's discretion. If the subject was unable to tolerate the side effects at the increased dose, the subject was to be reduced by a dose level (eg, from 300 mg/day to 150 mg/day). This dose reduction could occur outside of the scheduled visit. Subjects unable to tolerate a dose of 75 mg/day were to discontinue from the study. Clinic Visit 6 was the last opportunity to adjust the subject's dose.

Source: CSR 1180. Table 1, p. 29

Suicidality Risk Assessment During the Clinical Trial

At the baseline (randomization) and post-baseline visits, if there is any positive response on STS items 1a, 1b, both 3 and 4, 5, 6, or 8 (score of ≥1), a risk assessment must be done by a qualified MHP to determine whether it is safe for the subject to continue to participate in the trial. Subjects who have a positive response on STS

items 1a, 1b, both 3 and 4, 5, 6, or 8 (score of ≥1) on more than one occasion during a trial must have their potential suicidality managed appropriately by the investigator together with a qualified MHP (or the investigator alone if the investigator is a qualified MHP), or be discontinued from the trial. The investigator should consult with the Pfizer medical monitor regarding this issue.

Anytime a subject came into the clinic, including an unscheduled clinic visit, suicidality assessments (Sheehan Suicidality Tracking Scale - since last visit version and Columbia Suicide Severity Rating Scale – since last visit version) were to have been administered. Beginning with Visit 2, if there are any positive responses on items 4, 5, or on any behavioral question of the C-SSRS (Since Last Visit version), a risk assessment must be done by a qualified MHP to determine whether it is safe for the subject to continue in the trial. A suicidality narrative must be constructed for subjects who receive study treatment who have undergone any risk assessment as part of the study (baseline or during the study), using information from the STS assessment, C-SSRS assessment, the MHP assessment(s), and prior screening and baseline information, utilizing the supplemental relevant case report forms.

Visits 3, 4, 5 (Day 3, Wk 1, and Wk 2) – Phone Visits
If the subject was tolerating the study medication, these visits could be completed by phone. Subjects unable to tolerate a dose of 75 mg were to have been discontinued from the study. Dose adjustment was to have been discussed during this visit and the dose confirmed at this time should be administered at the next dose.

Visit 6 (Week 3) – Clinic Visit
The following procedures were to have been conducted at this visit:

- Vital signs (pulse, blood pressure and weight).
- Clinical laboratory tests (hematology, chemistry, urinalysis, and serum pregnancy).
- Collection of pharmacokinetic samples.
- Review concomitant medications and nondrug treatments.
- Daily pain and sleep quality diary review and reminder to complete diaries until the next scheduled visit.
- Assess and record adverse events.
- Suicidality Tracking Scale (STS).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess need to complete a risk assessment.
- Collection of blister packs (used and unused). Review of study medication compliance and dosing diary. Discuss potential dose adjustment. Subjects unable to tolerate a dose of 75 mg/day were to have been discontinued from the study. This was to have been the last opportunity for dose optimization; after this visit no further dose changes were allowed.

Visit 7 (Week 4) – Phone Visit
If the subject was tolerating the study medication, this visit may have been completed by phone. The following procedures were to have been completed at this visit:

- Documentation of pain and other fibromyalgia symptoms over the past week.
- Daily pain and sleep quality diary review.
- Assess and record adverse events.
- Review of study medication compliance and dosing diary.
- Review concomitant medications and nondrug treatments.
- Study personnel to confirm study medication dose.
- Review with parent/guardian/caregiver that an adult must be closely involved in supervising the administration of study medication.

Visit 8 (Week 7) – Clinic Visit
The following procedures were to have been conducted at this visit:

- Vital signs (pulse, blood pressure and weight).
- Review concomitant medications and nondrug treatments.
- Daily pain and sleep quality diary review.
- Assess and record adverse events.
- Suicidality Tracking Scale (STS).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess need to complete a risk assessment.
- Collection of blister pack with unused capsules and dispensing of new blister pack.
- Review of study medication compliance and dosing diary.
- Study personnel to confirm study medication dose to be administered

Visit 9 (Week 11) – Clinic Visit
The following procedures were to have been conducted at this visit:

- Vital signs (pulse, blood pressure and weight).
- Review concomitant medications and nondrug treatments.
- Daily pain and sleep quality diary review.
- Assess and record adverse events.
- Suicidality Tracking Scale (STS).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess need to complete a risk assessment.
- Collection of blister pack with unused capsules and dispensing of new blister pack.
- Review of study medication compliance and study medication dosing diary.
- Introduce the open-label extension study A0081231 to the subject and parent/guardian and provide a copy of the Informed Consent/Assent.

Visit 10 Termination Visit (Week 15) – Clinic Visit
The following procedures were to have been conducted at this visit:

- For subjects entering open-label extension Study A0081231, Informed Consent/Assent must be obtained.
- Physical examination (including height, weight, pulse, blood pressure).
- Abbreviated neurological examination (muscle strength, gait and reflexes).
- Assessment of pubertal status (Tanner Staging) – females only.
- 12-lead ECG.
- Clinical laboratory tests: (hematology, chemistry with estimated serum CLcr, urinalysis, drug testing and serum pregnancy tests).
- Reproductive hormone evaluations for females only.
- Weekly Pain Numeric Rating Scale (Pain-NRS).
- Parent Global Impression of Change (Parent-GIC).
- Patient Global Impression of Change (PGIC).
- Fibromyalgia Impact Questionnaire for Children (FIQ-C).
- Suicidality Tracking Scale (STS).
- Columbia Suicide Severity Rating Scale (C-SSRS).
- Assess need to complete a risk assessment.
- Daily pain and sleep quality diary review.
- Record and assess adverse events.
- Review concomitant medications and nondrug treatment.
- Collection of blister pack with unused medication.
- Review study medication compliance and dosing diary.
- Study personnel to confirm study medication dose to be administered and dispense medication for study medication taper.

Drug Taper
Following the treatment phase, all patients were to have tapered study medication over 1 week as shown in Table 6 below and be given the option to enter the open-label extension study. For subjects who have not taken study medication for the past 24 hours or more, there was no requirement to dispense the taper medication.

Table 5: Study Drug Taper Schedule

Final Dose	Day 1 (mg/day)	Day 2 (mg/day)	Day 3 (mg/day)	Day 4 (mg/day)	Day 5 (mg/day)	Day 6 (mg/day)	Day 7 mg/day)
PGB 450 mg/day	300	300	150	150	75	PBO	PBO
PGB 300 mg/day	150	150	75	PBO	PBO	PBO	PBO
PGB 150 mg/day	75	PBO	PBO	PBO	PBO	PBO	PBO
PGB 75 mg/day	PBO	PBO	PBO	PBO	PBO	PBO	PBO

Abbreviations: PGB=pregabalin, PBO=placebo
Source: Study 1180 Clinical Study Report. Table 5, p. 39

Visit 11 Follow-up Visit (Week 16) –Clinic/Phone
If the subject was not entering open-label extension Study 1231, this visit may have been completed by phone. If the subject was entering the open-label extension study, this visit was to have been conducted in the clinic and was considered V1.

Rescue Medication
Acetaminophen up to 3 g/day as rescue medication was permitted.

Prohibited Pain/Sleep Medications
Table 7 lists concomitant medications that might affect the pain or sleep disturbance associated with fibromyalgia that were to have been discontinued prior to Visit 1. Also, consumption of alcohol was to be avoided during the study.

Table 6: Prohibited Medications

Class of Medication	Examples[a]	Minimum Washout Period[b]
Medications used for relief of pain associated with fibromyalgia	Serotonin-norepinephrine reuptake inhibitors (eg, duloxetine, milnacipran)	At least 7 days prior to Visit 1
	Tricyclic antidepressants (eg, amitriptyline)	
	Other antidepressants (eg, trazodone), except 1 SSRI or bupropion as per Section 9.4.10.2	
	Skeletal muscle relaxants (eg, Soma, Flexeril)	
	Antiepileptic agents (including gabapentin)	
	Systemic corticosteroids	
	Benzodiazepines	
	Narcotic analgesics including opioids	
	Levodopa, dopamine agonists or other agents for Parkinson's disease	
	Capsaicin or other topical or local anesthetics	
	Cannabinoids	
	Mexiletine	
	Tramadol	At least 2 days prior to Visit 1
	Tender point injections	Last injection must be at least 1 month prior to Visit 1
Medications used for relief of insomnia	Anxiolytics including benzodiazepines (eg, alprazolam) and barbiturates	At least 7 days prior to Visit 1
Over the counter sleep medications that are in combination with analgesics were not permitted. Refer to Section 9.4.10.2 for information regarding permitted sleep medications.		

[a] Not a comprehensive list
[b] Clinical judgment was to be exercised regarding washout periods as subjects may have required significantly longer periods to taper/stabilize
Abbreviations: SSRI= selective serotonin reuptake inhibitor
Source: CSR1180. Table 1, p. 41

Allowable Medications/Nonpharmacologic Therapies
The following medications and nonpharmacologic therapies were to have been allowed:

Antidepressants
The use of one antidepressant for anxiety or depressive symptoms, either a selective serotonin reuptake inhibitor (SSRI) or bupropion (Wellbutrin), was permitted if it had been taken for at least 3 months prior to Screening (Visit 1) and at a stable dose for the 2 months prior to Visit 1. The use of other antidepressants was not permitted (Table 7).

Attention Deficit Hyperactivity Disorder (ADHD) Medications
The use of one pharmacologic treatment for ADHD (a psychostimulant, or the nonstimulant atomexetine/Straterra only) was to have been permitted if the dose had been taken for at least 3 months prior to screening (Visit 1) and at a stable dose for the 2 months prior to Visit 1.

Sleep Medications
Bedtime use of the following medications for sleep was to have been allowed if the pattern of use had been stable for the 30 days prior to Screening (Visit 1) and the conditions below were met:

- Zolpidem (Ambien) and eszopiclone (Lunesta), if used 3 nights or fewer per week.
- Over the counter sleep medications allowed if used 3 nights or fewer per week.
- The daily use of herbal sleep aids such as melatonin and valerian root permitted.

Diphenhydramine (Benadryl) for topical use was to have been permitted. Acute use of oral Benadryl as per product labeling was to have been allowed not more than 3 days weekly for allergies and allergic reactions and as a sleep aid.

Use of anxiolytics including benzodiazepines (eg, alprazolam) and barbiturates for sleep was not to have been permitted (Table 7). Sleep medications should not have been initiated during the Double-Blind Phase of the study.

Pain Relief or Cardiovascular Prophylaxis
The following medications were to have been permitted for additional pain relief or cardiovascular prophylaxis:

- Non-steroidal anti-inflammatory agents (NSAIDs) or selective COX-2 inhibitors.
- Aspirin.
- Acetaminophen, 3 grams/day maximum.

Nonpharmacologic Therapies
Subjects were permitted to continue with stable (ie, for at least 30 days before Visit 1) nonpharmacologic therapy (ie, physical and psychological therapy, massage, chiropractic care, exercise program, etc.) during the study.

Contraceptive Measures

Males and females of childbearing potential were to have used an acceptable method of contraception from screening until completion of follow-up procedures. Acceptable methods of contraception included:

- Oral contraceptive agents, intrauterine devices, implantable contraceptives, transdermal hormonal contraceptives, and injectable contraceptives.
- Barrier methods of contraception (eg, condom and/or diaphragm) with concomitant use of a spermicide.
- Abstinence during the entire study period.
- Vasectomy.

Male subjects were to agree that female spouses/partners would use adequate contraception (as defined above) or were of non-childbearing potential (ie, surgically sterile).

Compliance

Lack of study compliance was to have included any of the following:

- Missing 3 or more consecutive days of study drug.
- Less than 80% or greater than 120% study drug compliance for >2 clinic and/or phone visits; if this occurred, this was to be recorded as a protocol deviation (except if doses were missed due to an AE).
- Missing a required study visit (or 2 phone contacts).
- Starting any prohibited treatment.
- If a capsule count of returned medication at any clinic visit indicated that the subject had not taken all prescribed study drug, the subject was to be counseled about the importance of compliance and reminded of the instructions for taking study drug.
- If the subject had been non-compliant in any area as defined above, the subject's participation in the study was to be re-evaluated. Any discontinuation was to be done in consultation with Pfizer.

Subject Withdrawal

Subjects were to have been allowed to withdraw from the study at any time at their own request, or withdrawn at any time at the discretion of the investigator for safety or behavioral reasons, or inability to comply with the protocol. Subjects were to have been withdrawn for the following reasons:

- If a female subject became pregnant during the study.
- If alanine aminotransferase (ALT) or aspartate aminotransferase (AST) was above 3 times ULN repeatedly during 2 weeks, or above 5 times ULN.

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was to have been the following:

- Change from baseline to Week 15 in mean pain intensity (derived from an 11-point daily pain numeric rating scale).

Secondary Efficacy Endpoints

The following secondary efficacy endpoints were to have been measured:

- Weekly mean pain score at each week derived from the daily pain numeric rating scale (NRS) (24-hour recall).
- 30% and 50% pain responders.
- Weekly pain NRS at Week 15 (1-week recall).
- Weekly mean sleep quality score (from the daily sleep diary) at end of study using the mean of the last 7 diary entries prior to Week 15.
- Weekly mean sleep quality score at each week, from the daily sleep diary.
- Patient Global Impression of Change (PGIC) at Week 15.

Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints were to have been measured:

- Parent Global Impression of Change (Parent-GIC) at Week 15.
- Fibromyalgia Impact Questionnaire for children (FIQ-C) at Week 15.

Safety Assessments

Safety was to have been assessed by the following:

- Incidence and severity of AEs.
- Physical and neurological examinations.
- Vital signs.
- Electrocardiogram (ECG) at V1 and V10.
- Laboratory assessment.
- Tanner staging at V1 and V10.
- Reproductive hormones (LH, FSH, and Estradiol) collected at V1 and V10 for female patients only.
- Suicidality assessment.

Clinical Laboratory Tests

The following serum chemistry, hematology and urinalysis tests were to have been obtained at V1, V6 and V10 unless otherwise specified:

Serum Chemistry: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Albumin, Alkaline Phosphatase, Amylase, Blood Urea Nitrogen, Creatine Kinase, Serum Creatinine, Estimated Creatinine Clearance (Calculated at V1 and V10 only), Sodium, Potassium, Chloride, Calcium, C-reactive protein (V1 Only), Glucose, Pregnancy Test,

Rheumatoid Factor (V1 Only), Thyroid-Stimulating Hormone (TSH) and T4 (V1 Only), Total Protein, Total Bilirubin, Uric Acid

Hematology: Hemoglobin, Hematocrit, Red Blood Cell (RBC) Count, Platelet Count, White Blood Cell (WBC) Count, Differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)

Urinalysis: pH, Specific Gravity, Glucose, Microscopic Sediment Examination (if indicated), Drug screen (V1 and V10 only and as indicated)

Reproductive Hormones
The following reproductive hormone levels were to have been obtained in female patients at V1 and V10: luteinizing hormone (LH), follicle-stimulating hormone (FSH) and, Estradiol.

Electrocardiogram
A 12-lead ECG was to have been obtained at Visit 1 (Screening) and Visit 10/Termination.

Pharmacokinetic Endpoint
Two pharmacokinetic (PK) samples were to have been collected at Visit 6 (Week 3). The first sample was to be collected as soon as possible upon arrival at the clinic, and the second sample just prior to leaving the clinic. Subjects with a clinic visit scheduled in the morning should not have taken their morning dose until immediately after the first PK sample was drawn. The dose taken in the clinic was to be taken from the previously dispensed blister pack. Subjects with a clinic visit scheduled in the afternoon should have taken their morning dose at the usual time, collect the PK samples upon arrival and departure, and no dose was to be administered during the clinic visit. Subjects with a clinic visit scheduled in the evening should not have taken their evening dose until immediately after the first PK sample was drawn. The dose taken in the clinic was to be taken from the previously dispensed blister pack.

Statistical Analysis

Full Analysis Set (FAS)
The FAS includes all randomized subjects who received at least one dose of study drug. The FAS population was the primary population for efficacy analyses.

Primary Analysis
The primary analysis of change from baseline to endpoint in weekly mean pain scores was carried out based on the FAS population using analysis of covariance (ANCOVA) with baseline mean pain score, center and treatment. Baseline was defined as the mean of the daily pain scores recorded in the 7 days prior to randomization. Endpoint

was defined as the mean of the daily pain scores recorded in the 7 days prior to final dose of study drug.

Sensitivity Analyses of the Primary Endpoint
The following sensitivity analyses were performed to assess the robustness of the primary analysis:

- Mixed model repeated measures (MMRM) analysis without any imputation for missing data
- ANCOVA model with BOCF imputation method
- ANCOVA model with LOCF imputation method
- ANCOVA model with modified BOCF imputation method where BOCF was applied for subjects discontinued due to AEs and LOCF was applied for subjects discontinued due to any other reasons

Method of Imputation for Missing Data
The method of imputation for missing data will be derived using the following methods:

- For subjects who discontinue for reasons other than tolerability or lack of efficacy, the Week 15 mean pain score will be assigned based on the distribution of post randomization weekly mean pain scores.
- For subjects who withdraw due to an adverse event or discontinue due to lack of efficacy, the Week 15 mean pain scores will be assigned according to the distribution of baseline mean pain scores.

Protocol Amendments

Original Protocol, January 28, 2008
No patients were enrolled under the original protocol.

Amendment 1, October 29, 2009
Amendment 1 was issued prior to enrolling any subjects in the study. This amendment revised the study from a short-term (6-week) safety and tolerability study to a 12-week efficacy and safety study (as requested by the FDA).

Amendment 2, April 24, 2012
The following were changes made in Amendment 2:

- The patient population age range was expanded from 12-16 years to 12-17 years.
- Narratives for risk assessments required.
- Time between screening to randomization increased to 21 days.
- Certain antidepressants, sleep meds, ADHD meds allowed.

Amendment 3, March 14, 2014
The following were changes made to the protocol in Amendment 3:

- Secondary endpoints were clarified to include weekly pain scores and weekly sleep quality scores at each week
- Columbia Suicide Severity Rating Scale (C-SSRS) added in addition to the STS. (Reviewer's Note: Only 3 patients actually completed this assessment)
- Sample size changed from 162 randomized patients (81 in each treatment arm) to 106 patients based on ongoing Study 1180 blinded database and the previously completed placebo-controlled studies in adults with fibromyalgia.
- Analysis of primary efficacy endpoint modified and sensitivity analyses added.

Efficacy Results
A detailed discussion of the efficacy results is presented in Section 6.

Summary of Primary Efficacy Endpoint
The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11-point daily pain numeric rating scale) was not statistically significant but showed numerically greater improvement for the pregabalin-treated patients compared to placebo-treated patients. Based on Pfizer's prespecified analysis, a treatment difference of (b) (4) was reported by the Applicant for pregabalin relative to placebo in endpoint mean pain score. The FDA statistician, confirmed the Sponsor's overall findings and determined a treatment difference of (b) (4) for the primary endpoint.

Safety Results
A detailed discussion of the safety findings is presented in Section 7.

The following is a summary of Protocol A0081231.

Title: A 6-MONTH, OPEN-LABEL, SAFETY TRIAL OF PREGABALIN IN ADOLESCENT PATIENTS WITH FIBROMYALGIA

Dates Conducted: The first patient enrolled September 1, 2010 and the last patient completed June 1, 2015.

Objective:
The objective of this study was to evaluate the safety of pregabalin at doses of 75-450 mg/day (taken twice daily) in subjects who participated in double-blind study A0081180 and who wished to receive open-label pregabalin therapy.

Overall Design:
This was a 6-month (25-week) open-label extension study of the double-blind randomized fibromyalgia study A0081180. After the termination visit and study drug taper in study A0081180, subjects had an option of starting pregabalin at a dose of 75 mg/day under open-label conditions. The study consisted of 3 phases: dose

optimization (3 weeks), flexible dose (21 weeks), and follow-up/taper (1 week). Day 1 of this open-label study (Visit 1) was the same day as Visit 11 in study A0081180. Subjects initiated pregabalin dosing at 75 mg/day and had their dose optimized over a 3-week period, based on tolerability and response, to a dose of 75 mg/day, 150 mg/day, 300 mg/day, or 450 mg/day. The dose could only be changed by 1 step (up or down) at a time. After the initial 3-week optimization period, the dose could be adjusted for the remainder of the study to optimize pain control and to minimize AEs. The minimum daily dose of pregabalin was 75 mg/day and the maximum daily dose was 450 mg/day. At the end of the study, subjects tapered the dose over a 1-week period. A maximum of 12 visits were scheduled in the study; 5 visits conducted in the clinic and 7 visits by telephone (Table 8).

Table 7: Schedule of Activities Study 1231

Protocol Activity	Screening Baseline V1	Day 3 V2[a]	Week 1 V3[a]	Week 2 V4[a]	Week 3 V5	Week 4 V6[a]	Week 8 V7	Week 12 V8[a]	Week 16 V9	Week 20 V10[a]	Week 24 ET V11	Week 25 FU V12[a]
Visit Type	Clinic Visit	Phone Visit	Phone Visit	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit	Phone Visit	Clinic Visit	Phone Visit
Visit Detail[b]	Begin Dose Optimi-zation	Dose Optimi-zation	Dose Optimi-zation	Dose Optimi-zation	End Dose Optimi-zation	Flexible Dosing	Flexible Dosing	Flexible Dosing	Flexible Dosing	Flexible Dosing	Start Taper	Follow-up
Day[c]	0	3	7	14	21	28	56	84	112	140	168	175
Physical and Abbreviated Neurological Examination	(X)								X		X	
Assessment of pubertal status (Tanner Staging) – Females Only	(X)										X	
12- Lead Electrocardiogram	(X)										X	
Clinical Labs: Hematology, Chemistry, Urinalysis, Urine Drug test and Serum Pregnancy test[d]	(X)				X		X				X	
Clinical Labs: Reproductive hormone evaluations[e]	(X)										X	
Informed Consent and Child Assent	X											
Inclusion / Exclusion Criteria	X											
Vital Signs / Weight / Height[f]	X				X		X		X		X	
Suicidality Tracking Scale (STS)[g]	X				X		X		X		X	
Columbia Suicide Severity Rating Scale (C-SSRS)[g]	X				X		X		X		X	
Assessment of need to complete a risk assessment[h]	X				X		X		X		X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Pain Numeric Rating Scale (pain NRS)[i]	X				X		X		X		X	
Study Drug Review	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensing	X				X		X		X		X[j]	
Study Drug Dosing Diary	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X

Note: if the procedures at Visit 1 marked with (X) were completed previously in study A0081180 (at Visit 10/ET), they did not need to be repeated at this Visit 1.

a) Phone visits required contact via telephone with the subject; subjects were asked to come into the clinic as necessary for appropriate clinical management (eg, to more fully assess an adverse event).
b) Subjects were seen in the clinic at Visits 1, 5, 7, 9 and 11 (Weeks 0, 3, 8, 16, and 24). Visits 2, 3, 4, 6, 8 and 10 (Day 3 and Weeks 1, 2, 4, 12, and 20) could be handled as phone visits if the subject was tolerating study drug. If a subject was not tolerating the study drug, however, the subject needed to be seen in the clinic.
c) The following visit windows applied: V1 (±3 days), V2 (±1 day), V3 – V6 (±3 days), V7 – V11 (±7 days), V12 (+7 days).
d) Pregnancy testing could be repeated at the investigator's discretion, per request of IRB/IECs, or if required by local regulation at any time.
e) Reproductive hormone monitoring for females only (included luteinizing hormone, follicle stimulating hormone, and estradiol levels).
f) Vital signs including blood pressure, pulse, and weight were to be completed at all specified visits; height was to be assessed at V1 and V11 only.
g) All clinic visits used the Suicidality Tracking Scale (STS) "since last visit" version for suicidality risk assessment. The STS was to be administered any time the subject came in for a clinic visit, including unscheduled clinic visits. The Columbia Suicide Severity Rating Scale (C-SSRS) "since last visit" was to be performed at all visits including unscheduled clinic visits. For subjects without the C-SSRS "lifetime" performed at any previous visit, this assessment was to be performed at their next visit. The C-SSRS "since last visit" was to be performed at all subsequent visits.
h) A risk assessment was to be performed and documented if the subject met the criteria.
i) Completed in clinic; 1-week recall period.
j) Dispense of taper medication.

Abbreviations: V=visit; ET=early termination; FU=follow-up; IRB=Institutional Review Board; IEC=Independent Ethics Committee; N/A=not applicable

Source: CSR A0081231. Table 4, p.33

Key Eligibility Criteria:

- Subject and 1 parent were able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
- Subject and 1 parent signed written informed assent and consent.
- Subjects must have met the inclusion criteria for the preceding fibromyalgia study 1180 (12-17 years old at time of enrollment in Study 1180, and have met the Yunus and Masi criteria for fibromyalgia), have received study drug under double-blind conditions, and have completed study 1180.
- Subjects who experienced a serious adverse event during study 1180 which was considered related to study medication were not eligible to participate.
- Subjects with white blood cell count <2.5 x 10^9/L, neutrophil count <1.5 x 10^9/L, platelet count <100 x 10^9/L, or creatinine clearance <80 mL/min were not eligible to participate.
- Female subjects were to continue to use adequate birth control methods and have a negative pregnancy test at open-label Visit 1 (Visit 10/early termination of study 1180) and at the indicated intervals during the open-label study.

Study Drug

Subjects who met the eligibility criteria received open-label treatment with pregabalin. Subjects optimized their dose based on efficacy and tolerability over a 3-week period to one of the following pregabalin doses: 75 mg/day (minimum allowable dose), 150 mg/day, 300 mg/day, or 450 mg/day (maximum allowable dose). At the end of the study, all subjects tapered their dose over a 1-week period.

Duration of Treatment: Up to 25 weeks

Efficacy Assessments

- Pain Numeric Rating Scale (NRS)

Safety Assessments

- Frequency and severity of adverse events (AEs)
- Physical and neurological examinations
- Vital signs
- Electrocardiogram (ECG)
- Laboratory assessment
- Tanner staging
- Suicidality assessment

Summary of Results

A detailed discussion of the safety findings is presented in Section 7.

Enrollment: A total of 63 subjects were enrolled in this open-label extension study and treated with pregabalin. Of these 63 subjects, 33 had previously been treated with pregabalin and 30 subjects with placebo.

Disposition: Of the 14 subjects that discontinued, 7 subjects had been treated in study 1180 with pregabalin, and 7 subjects with placebo. Two subjects discontinued due to adverse events, 3 subjects due to lack of efficacy, 5 subjects no longer willing to participate, 1 subject lost to follow-up and 3 subjects other.

Deaths: There were no deaths.

Serious Adverse Events: There were 3 (4.8%) subjects who had SAEs during the study. These resulted in hospitalization due to migraine, appendicitis, and joint instability. The SAE of severe migraine may have been related to the study drug but the patient had a history of headaches.

Discontinuations due to AEs: There were 2 (3.2%) subjects who discontinued study drug due to adverse events. Dizziness, fatigue and nausea in 1 subject were considered related to the study drug, and spinal stenosis in 1 subject was not considered related to the study drug.

Common Adverse Events: A total of 45 (71.4%) subjects experienced at least one adverse event. The most frequently reported adverse events were dizziness and fatigue.

Weight Gain: A weight gain of at least 7% was reported for 18 (29.0%) subjects.

Suicidality: There were no suicide attempts or completed suicides during the study. No suicidal behavior was reported. During the study, 6 (9.5%) subjects reported suicidal ideation, without plan or intent; these subjects all had a history of suicidal ideation noted at the time of screening for study 1180.

6 Review of Efficacy

Efficacy Summary

Statistical significance was not demonstrated with the primary efficacy endpoint of change from baseline to Week 15 in mean pain score, derived from the daily pain NRS (24-hour recall) but the results were numerically in favor of pregabalin. The patient global impression of change also showed greater improvement rates in the pregabalin group compared to the placebo group. The reason the study failed to demonstrate efficacy is unclear but the FDA statistician noted that the study was not adequately powered to demonstrate efficacy with respect to the primary efficacy endpoint.

(b) (4)

6.1.1 Methods

The Applicant submitted one efficacy study (Study 1180) (b) (4) This study was an adequate and well-controlled (i.e., randomized, double-blind, placebo-controlled) study in subjects with fibromyalgia. The primary efficacy endpoint was change from baseline to Week 15 in mean pain intensity (derived from an 11-point daily pain numeric rating scale). The study design and primary endpoint meet the Division's standards.

6.1.2 Demographics

The demographic characteristics for the pregabalin and placebo treatment groups were similar with respect to age, sex, race and weight (Table 9). In the pregabalin treatment group the mean age was 14.6 years and in the placebo group 14.7 years. Most subjects were 14 to 16 years old with only a few subjects (1.9%) 17 years old, likely due to this age group being added with Amendment 2 after initiation of the study. The majority of subjects were White (57%) or Asian (34%). In the pregabalin group 89% of the subjects were female and in the placebo group 83% of the subjects were female. All but two of the female subjects (2.2%) were in menarche.

Table 8: Demographic Characteristics for Pregabalin and Placebo Treatment Groups			
Demographic Characteristic	**Pregabalin (N=54)**	**Placebo (N=53)**	**Total (N=107)**
Gender			
Male	6 (11)	9 (17)	15 (14)
Female	48 (89)	44 (83)	92 (86)
Premenarchal	1 (2.2)	1 (2.3)	2 (2.2)
Menarche	47 (97.9)	43 (97.7)	90 (97.8)
Age (years)			
Mean (SD)	14.6 (1.2)	14.7 (1.2)	14.7 (1.2)
Range	12-17	12-16	12-17
Age group			
12 years	4 (7.4)	3 (5.7)	7 (6.5)
13 years	5 (9.3)	6 (11.3)	11 (10.3)
14 years	15 (27.8)	8 (15.1)	23 (21.5)
15 years	18 (33.3)	21 (39.6)	39 (36.4)
16 years	10 (18.5)	15 (28.3)	25 (23.4)
17 years	2 (3.7)	0	2 (1.9)
Race			
White	29 (53.7)	32 (60.4)	61 (57)
Black	2 (3.7)	3 (5.7)	5 (4.7)
Asian	21 (38.9)	15 (28.3)	36 (33.6)
Other	2 (3.7)	3 (5.7)	5 (4.7)
Weight (kg)			
Mean (SD)	60.4 (21.4)	59.7 (17.7)	60.1 (19.6)
Range	28.5-154.7	39.0-127.6	28.5-154.7
Height (cm)			
Mean (SD)	160 (7.6)	162 (8.2)	161 (7.9)
Range	141-178	147-183	141-183

Source: CSR 1180. Table 13, p.77

6.1.3 Subject Disposition

Subject Disposition

Enrollment/Randomization: Of the 147 subjects screened for this study, 107 subjects were randomized to treatment, 54 patients to receive pregabalin and 53 patients to receive placebo.

Double-blind Treatment Period: All 107 randomized subjects took at least one dose of study drug. A total of 44 (81.5%) subjects in the pregabalin group and 36 (67.9%) subjects in the placebo group completed the study. Table 10 summarizes subject

disposition in Study 1180. Within the pregabalin group, 10 (18.5%) subjects discontinued study drug early for the following reasons: adverse event 7.4% (4/54), lack of efficacy no subjects, no longer willing to participate 9.3% (5/54), other 1.9% (1/54) and protocol violation no subjects. Within the placebo group, 17 (32.1%) subjects discontinued study drug early for the following reasons: adverse event 7.5% (4/53), lack of efficacy 5.7% (3/53), no longer willing to participate 13.2% (7/53), other 1.9% (1/53) and protocol violation 3.8% (2/53). As expected there were more discontinuations due to lack of efficacy in the placebo group. Discontinuations due to adverse events were numerically similar in both groups but the specific adverse events resulting in study discontinuation were more likely due to study drug in the pregabalin group where two subjects discontinued due to weight gain (Section 7.3.3).

Table 9: Subject Disposition (Study 1180)

	Pregabalin n (%*)	Placebo n (%*)
Randomized	54	53
Completed Study	44 (81.5%)	36 (67.9%)
Discontinued Study	10 (18.5%)	17 (32.1%)
Adverse Event	4 (7.4%)	4[1] (7.5%)
Lack of Efficacy	0	3 (5.7%)
No longer willing to participate	5 (9.3%)	7 (13.2%)
Other	1 (1.9%)	1 (1.9%)
Protocol Violation	0	2[2] (3.8%)

* Percent of randomized subjects
Source: CSR 1180. Modified from Table 10, p.73

Protocol Violations

Protocol deviations included subjects who did not meet all inclusion/exclusion criteria, deviations in the conduct of the study (eg, incorrect dosing of investigational product, prohibited concomitant medication), deviations from study assessments as required by the protocol, deviations due to adverse events, informed consent deviations, and deviations due to other criteria. Major protocol deviations were defined as those deviations from the protocol likely to have an impact on the subject's rights, safety, or well-being, and/or on the validity of the data for analysis. A summary of protocol violations is provided in Table 11. A total of 22% (23/107) of randomized subjects had a protocol violation. The incidence was similar in the pregabalin group 24% and placebo group 19%. Across all subjects, the most common category for major protocol deviations was a deviation related to study drug administration/study treatment.

Table 10: Protocol Deviations (Randomized Subjects)

Protocol Deviations	Pregabalin (N=54) n (%)	Placebo (N=53) n (%)	Total (N=107) n (%)
Major	13 (24.1)	10 (18.9)	23 (21.5)
Disallowed medications	3 (5.6)	1 (1.9)	4 (3.7)
Inclusion/Exclusion criteria	0	3 (5.7)	3 (2.8)
Study drug administration/Study treatment	7 (13.0)	4 (7.5)	11 (10.3)
Other	3 (5.6)	3 (5.7)	6 (5.6)
Procedures/Tests	2 (3.7)	1(1.9)	3 (2.8)
Visit schedule	1 (1.9)	0	1 (0.9)
Minor	50 (92.6)	44 (83.0)	94 (87.9)
Adverse event/Serious adverse event	2 (3.7)	0	2 (1.9)
Disallowed medications	6 (11.1)	6 (11.3)	12 (11.2)
Inclusion/Exclusion criteria	2 (3.7)	2 (3.8)	4 (3.7)
Informed consent	21 (38.9)	14 (26.4)	35 (32.7)
Study drug administration/Study treatment	16 (29.6)	13 (24.5)	29 (27.1)
Other	32 (59.3)	33 (62.3)	65 (60.7)
Procedures/Tests	19 (35.2)	19 (35.8)	38 (35.5)
Visit schedule	1 (1.9)	2 (3.8)	3 (2.8)

Note: Subjects could contribute to more than one deviation category.

Source: CSR 1180. Table 11, p74

6.1.4 Analysis of Primary Endpoint(s)

Primary Efficacy Endpoint

The primary endpoint was change from baseline to Week 15 in mean pain score derived from the daily pain numeric rating scale (24-hour recall) from the daily pain diary. Based on the prespecified analysis using the full analysis set (FAS) population, the Applicant reported a placebo-adjusted treatment difference of (b) (4) favoring pregabalin, which was not a statistically significant difference (b) (4). The FAS population consisted of all randomized subjects who received at least one dose of study drug. Pregabalin-treated subjects experienced an improvement in LS mean changes of (b) (4) points from baseline while placebo-treated subjects experienced a (b) (4) point improvement from baseline (Table 12). The FDA statistician, Dr. Yan Zhou, confirmed the Sponsor's overall findings and determined a treatment difference of (b) (4) (Table 13).

Table 11: Applicant's Analysis of Primary Endpoint - Change from Baseline to Week 15 in Weekly Mean Pain Score - Daily Pain NRS

(b) (4)

Source: CSR 1180. Table 17, p.81

Table 12: FDA Analysis of Primary Efficacy Endpoint

(b) (4)

Source: FDA Statistical Review. Table 3, p.10

Sensitivity Analyses of Primary Endpoint

The Applicant reports results of sensitivity analyses of the primary endpoint using alternate imputation approaches or based on the per protocol analysis were not statistically significant but treatment differences favored pregabalin treatment (Table 14). The FDA statistician confirmed that using alternate imputation approaches were similar in nature to the primary efficacy analysis, numerically favoring pregabalin but not statistically significant.

Table 13: Summary of Applicant's Sensitivity Analyses - Change from Baseline to Week 15 in Weekly Mean Pain Score - Daily Pain NRS (24-Hour Recall)

(b) (4)

Source: CSR 1180. Table 18, p.82

6.1.5 Analysis of Secondary Endpoints(s)

Secondary Efficacy Endpoints
The Division does not consider any of the secondary efficacy endpoints to be statistically significant since the study failed to demonstrate statistical evidence of efficacy with the prespecified primary endpoint.

Weekly Mean Pain Score at Each Week – Derived from Daily Pain Numeric Rating Scale (24-Hour Recall)

(b) (4)

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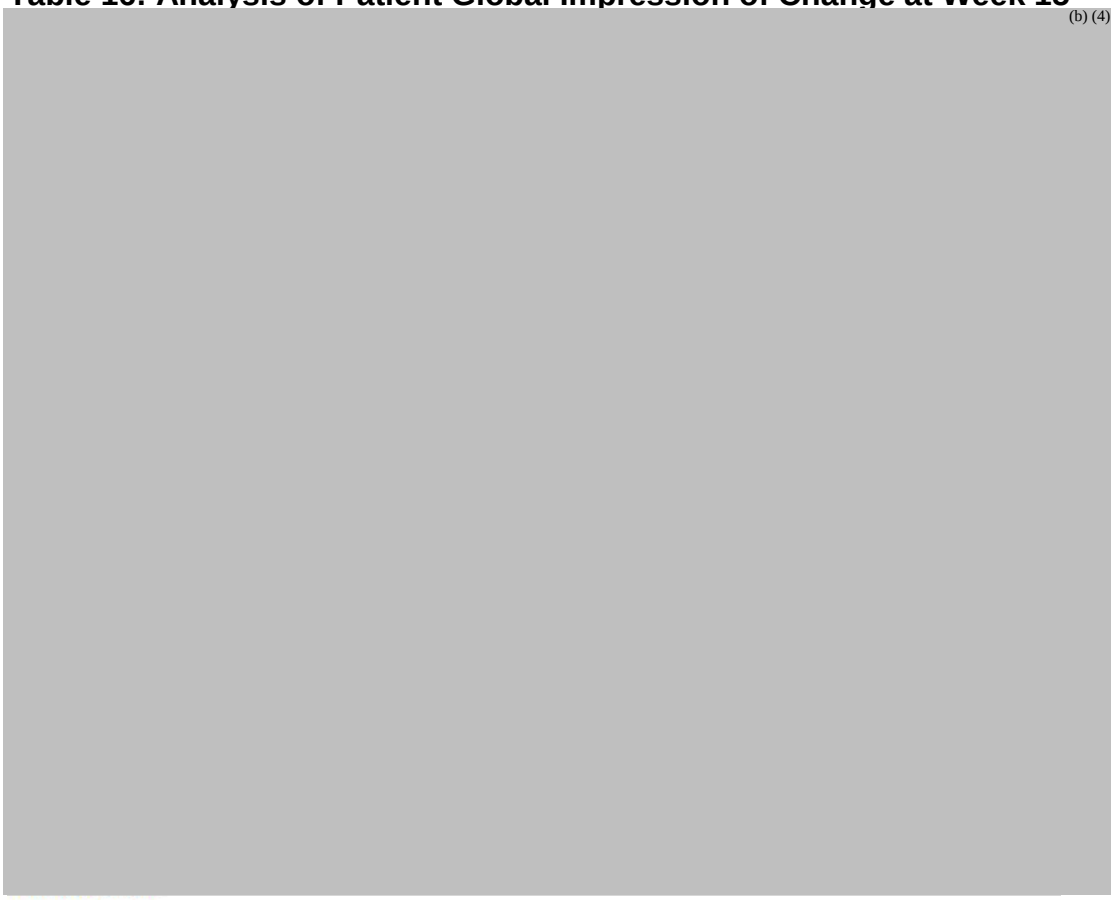
Table 16: Analysis of Patient Global Impression of Change at Week 15

(b) (4)



Source: CSR 1180. Table 23, p.89

Rescue Medication Use

The number of doses and milligrams of rescue medication taken during the study was not collected. Pfizer did collect information regarding the number of subjects taking concomitant medications and the duration of use but this limited information on rescue medication makes it impossible to assess study drug efficacy based on rescue medication use.

Pfizer provided Table 18 summarizing the mean duration and number of patients taking concomitant medications during the Double-Blind Phase, with similar information provided for the Baseline Phase as reference. The most commonly used medications during the Double-Blind Phase were ibuprofen and paracetamol. Ibuprofen was used by 23 (42.6%) pregabalin-treated subjects for an average of 5.7 days/week and 18 (34.0%) placebo-treated subjects for an average of 6.2 days per week. Paracetamol was used by 19 (35.2%) of pregabalin-treated subjects for an average of 5.5 days/week and 19 (35.8%) of placebo treated subjects for an average of 5.2 days/week. Overall, the number of subjects taking rescue medication and duration of treatment appeared similar but without knowing the actual dose this information is of limited value.

Table 17: Applicants Analysis of Duration of Use of NSAIDs, COX-2 Inhibitors, and Acetaminophen- and Aspirin- Containing Medications

Medication	Pregabalin (N=54)			Placebo (N=53)		
	Double-Blind Phase		7-Day Baseline	Double-Blind Phase		7-Day Baseline
	N (%)	Duration (Mean Days/week)	Duration* (Mean Days/week)	N (%)	Duration (Mean Days/week)	Duration* (Mean Days/week)
Ibuprofen	23 (42.6)	5.7	5.6	18 (34.0)	6.2	6.6
Meloxicam	4 (7.4)	5.9	7.0	4 (7.5)	7.0	7.0
Naproxen	9 (16.7)	5.7	4.0	7 (13.2)	3.8	3.0
Naproxen Sodium	2 (3.7)	7.0	7.0	3 (5.7)	0.1	0
Paracetamol	19 (35.2)	5.5	5.0	19 (35.8)	5.2	4.8

N=number of subjects
* For patients who took the medication in double blind but not in the 7-day baseline period, the baseline value is set to 0 days.
Source: Study 1180. Pfizer Response to Information Request. Table 1, p.2

6.1.6 Other Endpoints

Not Applicable

6.1.7 Subpopulations

Efficacy Study 1180 failed to demonstrate efficacy in adolescents based on the primary prespecified endpoint. Several possible factors were considered as to why this study may have failed to demonstrate efficacy in adolescents while in adults efficacy has been demonstrated. (b) (4) The FDA statistician believes that this study was not adequately powered to detect statistically significant differences in treatment group comparisons. Subgroup analyses of the other factors listed above were performed by the statistician.

Subgroup Analysis by Fibromyalgia Diagnostic Criteria

Subjects must have met the Yunus and Masi criteria for diagnosing fibromyalgia to be eligible for participation in Study 1180. These criteria required: generalized musculoskeletal aching at 3 or more sites for 3 or more months, 5 or more tender points, and 3 or more of the following 10 minor criteria:

- Chronic anxiety or tension
- Fatigue
- Nonrestorative sleep, defined as waking from sleep feeling tired
- Chronic headaches
- Irritable Bowel Syndrome, defined as altered bowel habits associated with abdominal pain or discomfort
- Subjective soft tissue swelling

- Numbness
- Pain modulation by physical activities
- Pain modulation by weather factors
- Pain modulation by anxiety or stress

The 1990 American College of Rheumatology (ACR) criteria used to determine eligibility in adult studies was not a requirement for entry into Study 1180 in adolescents. ACR criteria require a history of widespread pain present for at least 3 months with pain in 11 of 18 tender point sites on digital palpation.

Of the 107 randomized subjects, 95 (88.8%) subjects met the ACR fibromyalgia diagnostic criteria in addition to the Yunus and Masi criteria, which were a study eligibility requirement. In the pregabalin group 92.6% (50/54) met the ACR diagnostic criteria at screening and in the placebo group 84.9% (45/53) met the criteria. When the FDA statistician excluded subjects who did not meet the ACR criteria the efficacy results appeared similar (treatment difference (b) (4)).

Subgroup Analysis by Dose

In adults the recommended dose of LYRICA for fibromyalgia is 300 to 450 mg/day. In Study 1180 doses of 75 mg/day and 150 mg/day were included to allow for smaller, low-weight adolescents. There was lower exposure compared to adults with pediatric subjects dosed with 75 mg and 150 mg/day. Approximately half of the patients in Study 1180 received doses that are lower than the doses demonstrated to be effective in adults. Table 19 presents subgroup analyses results by dose group performed by the FDA statistician. The results were only numerically in favor of the lowest and highest dose of pregabalin.

Table 18: FDA Subgroup Analyses by Dose Group

(b) (4)

Source: FDA Statistical Review. Table 5, p.13

Subgroup Analysis by Country
In Study 1180, 67 patients were enrolled in sites in the U.S. and 40 patients were enrolled in three countries outside the U.S. Table 20 presents subgroup analyses results by country. The results were similar between the U.S. and the other countries.

Table 19: FDA Subgroup Analyses by Country

(b) (4)

Source: FDA Statistical Review. Table 6, p.13

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Refer to the discussion on Subgroup Analysis by Dose in the section above.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not Applicable

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety of LYRICA for the treatment of fibromyalgia in adolescents was evaluated in two clinical studies: Study 1180 and Study 1231.

- Study 1180 was a 15-week, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose, study in adolescents with fibromyalgia. A total of 107 subjects were treated, 54 with pregabalin and 53 with placebo.
- Study 1231 was a 6-month, open-label safety study with 63 subjects continuing from Study 1180.

7.1.2 Categorization of Adverse Events

All adverse events were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) with Version 17.1 used for Study 1180 and Version 18.0 used for Study 1231.

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

Adverse events from the two studies were not combined due to the difference in study designs. Study 1180 was a randomized, double-blind, placebo-controlled study and Study 1231 was an open-label extension study. Safety data was analyzed separately for each study.

7.2 Adequacy of Safety Assessments

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

Exposure for Study 1180
The duration of treatment for Study 1180 including dose optimization, maintenance and the taper phase is summarized in Table 21. A total of 44 patients were exposed to pregabalin for greater than 90 days. The mean and median pregabalin doses during the fixed dose period were 244.5 mg/day and 262.3 mg/day, respectively. Mean and median doses were higher for male subjects and for subjects weighing at least 50 kg. During the fixed dose period approximately 40% of subjects were treated with 450 mg/day, 15% of subjects were treated with 300 mg/day, 19% with 150 mg/day, and 25% with 75 mg/day. A total of 29 subjects approximately 55% were treated at a dose level of 300-450 mg/day, the approved dose range for adult fibromyalgia subjects in the US.

Table 20: Duration of Treatment Study 1180

	Pregabalin (N=54)	Placebo (N=53)
Duration Category (Days)		
≤1	0	0
2-7	0	2
8-14	0	2
15-28	2	3
29-60	5	2
61-90	3	5
91-108	21	2
≥109	23	37
Median Duration	108.0	112.0
Range	21-117	3-129

Source: CSR 1180. Table 26, p.94

Combined Exposure for Studies 1180 and 1231

The combined duration of treatment for Study 1180 and Study 8123 including the 3-week dose optimization for each study, 12-week fixed dose phase in Study 1180, 21-week flexible dosing phase in Study 81231, and 1-week taper for each study is summarized in Table 22. In Study 1180, 54 subjects were randomized to pregabalin treatment and 53 to placebo. A total of 63 subjects were subsequently treated with pregabalin in Study 1231, 33 (52.4%) of whom had previously been treated in Study 1180 with pregabalin, and 30 (47.6%) with placebo. A total of 84 subjects were treated with pregabalin across studies 1180 and 1231, for a median duration of treatment of 172 days. A total of 5 (6%) subjects received pregabalin for 2-28 days, 11 (13%) subjects for 29-90 days, 37 (44%) subjects for 91-180 days, and 31 (37%) subjects for 181-300 days (Table 22).

Table 21: Duration of Treatment by Dose, Combined Controlled and Uncontrolled Studies (A0081180 and A0081231)

	Total Daily Dose of Pregabalin (mg/day)[a]					Any Dose[b]
	>0 to <75	75 to <150	150 to <300	300 to <450	≥450	
Number of Subjects	27	84	65	59	34	84
Duration (Days) [c]						
≤1	20	0	0	1	1	0
2-14	5	52	28	20	0	1
15-28	2	14	15	13	0	4
29-90	0	2	11	4	11	11
91-120	0	3	3	4	7	12
121-150	0	2	4	2	7	3
151-180	0	4	2	13	1	22
181-210	0	2	1	1	2	3
211-240	0	0	0	0	3	2
241-270	0	3	1	1	2	2
271-300	0	2	0	0	0	24
Median Duration (Days)	1.0	9.5	18.0	18.0	105.3	172.0
Range (Days)	1-25	2-288	3-254	1-260	1-247	10-289

Source: Table 14.4.2.a
[a] Each subject is counted in only one row within a column, but subjects who received more than one dose of pregabalin will appear in multiple columns.
[b] Indicates days on all specified pregabalin doses. Does not include days off drug and days when dose was unknown.
[c] Duration defined as the total dosing days from first to last day of each study treatment, inclusive.
All study phases are included in the duration, as follows: Dose Optimization for each study, Fixed Dose phase in Study A0081180, Flexible Dosing phase in study A0081231, and Taper for each study. Days with missing dose or zero doses are excluded.

7.2.2 Explorations for Dose Response

Refer to Section 7.2.1 for the number of subjects exposed at various doses for various durations.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the pediatric clinical trials for Lyrica appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pregabalin is approved in adults and the adverse event profile in this population is well known.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths during the LYRICA development program for fibromyalgia in adolescents.

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events
Of the 107 patients (54 on pregabalin and 53 on placebo) enrolled in double-blind Study 1180, one patient on pregabalin (2%) had 2 SAEs (cholelithiasis and major depression resulting in hospitalization). No patient on placebo in Study 1180 had an SAE. In open-label safety Study 1231, three of 63 patients on pregabalin (5%) each had one SAE (migraine, joint instability and appendicitis). Narratives of all SAEs were reviewed. Pregabalin cannot be excluded as a contributing factor to the SAEs of major depression, cholelithiasis, and migraine. Summaries of the two patients with these three SAEs are provided below.

Individual Patient Summaries of Nonfatal Serious Adverse Events

Subject Number: 10031002 (Pregabalin)
Study Number: 1180
Serious Adverse Events: Cholelithiasis and major depression

Patient 10031002 was a 14-year-old white female who started treatment with pregabalin in Study 1180 on (b) (6) and stopped treatment after 60 days on (b) (6). Following dose escalation, the subject was taking pregabalin 150 mg/day as of 14-Aug-2010 and throughout the rest of the study.

Her medical history at study entry included gastroesophageal reflux, insomnia, metabolic syndrome, migraine, tension headache, polycystic ovaries, restless leg syndrome, and vitamin D deficiency. Past medical history was significant for depression. Treatments ongoing at study entry included ergocalciferol, ibuprofen, metformin hydrochloride, riboflavin, and vitamin B complex.

At screening, the subject's scores on self-reported suicidal ideation and behavior questionnaires, which included the Sheehan Suicidality Tracking Scale (STS), Quick

Inventory of Depressive Symptomatology (QIDS), and Suicide Behavior Questionnaire – Revised (SBQ-R), all met protocol criteria requiring a mental health risk assessment (MHRA). The subject had a score of 11 on the QIDS, which reflects clinically significant depression. The subject also had a score of 8 on the SBQ-R, reporting that "I have attempted to kill myself, but did not want to die." The STS score met protocol criteria for MHRA based on items 3 and 4. The MHRA conducted on 08-Jul-2010 found that she denied suicidal ideation, her mood was good and she denied any current depressive episode. Based on the outcome of the MHRA, the investigator considered the subject appropriate to enter the study. The subject completed subsequent STS assessments on (b) (6) (at randomization), 02-Sep-2010, and 12-Oct-2010 with no report of suicidal ideation or behavior, and the subject did not require MHRA based on these evaluations.

On (b) (6) (Study Day 41), the subject experienced the SAE of cholelithiasis requiring hospitalization. At that time her pregabalin dose was 150 mg/day. The subject took morphine on (b) (6), hydromorphone on (b) (6), and Vicodin for abdominal pain from (b) (6) through (b) (6) Study Day 35 to 66. No action was taken with regard to the study drug. The event resolved on Study Day 47 (b) (6) after removal of the gallbladder. The subject had several risks factors for gallstones including being female, overweight and metabolic syndrome. The investigator considered the event of cholelithiasis unrelated to study drug.

On (b) (6) (Study Day 73), the subject was admitted to the hospital due to major depression. Her last dose of pregabalin 75 mg/day was taken 10 days earlier on (b) (6) (Study Day 63). The subject's mother reported that the subject had been doing well and went to her homecoming dance the night of (b) (6). The next day ((b) (6)), the subject reported increased pain and fatigue. On (b) (6), the subject took 10 pills of an over the counter cold medicine (name unknown) to try to alleviate her pain. The subject became concerned about taking that much medicine and made herself vomit. She asked her mother in the morning to take her to the hospital for help. The mother reported that the subject denied suicidal ideation and did not take the medication to hurt herself. She was assessed by the physician at the hospital as having major depression and was admitted for observation. Assessments of suicidal ideation and behavior were not reported during the subject's hospitalization or after (b) (6). On Study Day 76 (b) (6), the subject was discharged from the hospital and the SAE of major depression was considered resolved but she continued to have depression of moderate intensity which required ongoing treatment (escitalopram and psychotherapy); the event was still present at last reporting.

The investigator and sponsor considered the event of major depression related to study drug. The subject was lost to follow-up and was contacted multiple times with no response. The subject was permanently discontinued from the study on 15-Nov-2010 due to the event of depression.

Impression
The SAE of cholelithiasis in a 14-year old is unusual but the patient had several known risk factors for cholelithiasis. However, pregabalin cannot be excluded as a contributing factor considering the current label includes cholelithiasis in the list of infrequent treatment-emergent adverse reactions (occurring in 1/100 to 1/1000 patients). Her SAE of depression may be due to her history of depression and suicidal ideation but LYRICA cannot be completely excluded as a contributing factor. It is noted that no suicidal ideation was reported with her SAE of depression and she denied suicidal ideation, but since no formal suicidal assessment was completed in the hospital it may have been missed.

Subject Number: 10071001 (Pregabalin)
Study Number: A0081231
Serious Adverse Events: Migraine

This 14-year-old white female subject, treated with placebo in double-blind study 1180, started treatment with pregabalin in study 1231 on (b) (6) (Study Day 1). She completed the study and treatment was stopped on (b) (6) (Study Day 175).

Medical history present at study entry included acne, asthma, cough, fatigue, headache, hypermobility syndrome, osteochondrosis, paraesthesia, seasonal allergy, sinus arrhythmia, somnambulism, and syncope. Treatments at study entry included benzaclin topical, fexofenadine, fluticasone, minocycline, montelukast, paracetamol, salbutamol, and tretinoin. The subject had a history of headaches which had not previously been diagnosed as migraine. The subject had a known allergy to celebrex with reactions of headache.

On Study Day 4 (b) (6), when the subject was on pregabalin 150 mg/day, she reported a headache that led to hospitalization; the diagnosis was first time migraine. This had occurred on a background of daily headaches associated with fibromyalgia. The subject was given intravenous (IV) ketorolac and metoclopramide and was discharged after 12 hours. The migraine had improved, but not fully resolved. This event was considered an SAE due to hospitalization. No action was taken with regard to the study drug.

The subject increased the dose of study drug to 225 mg/day twice daily (BID) on (b) (6) (Study Day 17), but then started tapering on (b) (6) (Study Day 27) to determine if the study drug was causing the migraine. The subject decreased the dose to 75 mg/day, but this made no difference to the migraine, however, fibromyalgia pain was worsening. The subject therefore increased the dose back up to 225 mg/day on (b) (6) (Study Day 51).

On (b) (6) (Study Day 100), the subject was admitted to the children's medical center to receive a dihydroergotamine (DHE) protocol for her migraine. She received a total of 14 doses of DHE and her migraine improved.

The subject was discharged on (b) (6) (Study Day 105) and was instructed to take amitriptyline 10 mg for 1 week and 20 mg for another week, but then stopped as it was not helping the migraine. The subject continued to receive study drug pregabalin 225 mg/day BID from (b) (6) (Study Day 51) to (b) (6) (Study Day 170), and then started a taper until the medicine was stopped on (b) (6) (Study Day 175).

As of the investigator's conversation with subject's mother on (b) (6) (Study Day 127), the investigator considered that this subject still had a constant migraine. The investigator and sponsor considered there was a reasonable possibility that the event of migraine was related to pregabalin. The subject had a history of headaches, which had not previously been diagnosed as migraine; the migraine diagnosis was made after the headache increased in intensity and did not respond to multiple interventions.

Impression
Pregabalin cannot be excluded as a cause of her migraine headache based on the temporal relationship (headache started on Day 4 of treatment). However, the patient had a prior history of daily headaches associated with fibromyalgia. This raises the possibility that some of her previous headaches may have been migraine headaches but attributed to her fibromyalgia.

Summary of Serious Adverse Events
There were two serious adverse events (SAEs) in one patient on LYRICA in Study 1180 and three SAEs in Study 1231. LYRICA cannot be completely excluded as the cause of the serious adverse events of cholelithiasis, depression and migraine headache. Depression and cholelithiasis are adverse events listed in the current label. The etiology of the cholelithiasis is unclear but pregabalin cannot be completely excluded as a cause considering cholelithiasis is listed in the current label as an adverse event. Although migraine headache is not listed in the label, headache is included in the label. It is possible that migraine headaches were previously present in this patient with a history of headaches prior to starting pregabalin but not diagnosed as migraine headaches.

7.3.3 Dropouts and/or Discontinuations

A summary of subject disposition during placebo-controlled, double-blind Study 1180 is provided in Table 23. As expected a larger percentage of placebo group subjects (5.7%) discontinued due to lack of efficacy compared with pregabalin group (0%). Discontinuation from the study due to adverse events was similar in the placebo group

and pregabalin group (7.5% vs 7.4%). However, in the pregabalin group the adverse events appeared related to pregabalin and are discussed below.

Table 22: Patient Disposition by Treatment Group for Study 1180

Analysis Group	**Pregabalin N=54 n (%)**	**Placebo N=53 n (%)**
Discontinued study	10 (18.5)	17 (32.1)
Adverse event	4 (7.4)	4 (7.5)
Lack of efficacy	0	3 (5.7)
No longer willing to participate	5 (9.3)	7 (13.2)
Protocol violation	0	2 (3.8)
Other	1 (1.9)	1 (1.9)

N=number of patients; n=number of patients in subgroup.
Source: CSR Protocol 1180. Table 10, p73

Four (7.4%) patients in the pregabalin group and four (7.5%) patients in the placebo group reported adverse events causing discontinuation form the study (Table 24). In the pregabalin group weight increased was reported by two patients and depression and loss of consciousness were each reported by one patient. All AEs causing discontinuation in the pregabalin group were reviewed and considered possibly related to study drug. A summary of these SAEs is provided below. Depression was also reported by one patient in the placebo group.

Table 23: Adverse Events Causing Discontinuation During Study 1180

MedDRA Preferred Term	**Pregabalin N=54 n (%)**	**Placebo N=53 n (%)**
Number of patients with an AE causing discontinuation	4 (7.4%)	4 (7.5%)
Weight increased	2 (3.7%)	0
Depression[1]	1 (1.9%)[2]	1 (1.9%)
Loss of consciousness	1 (1.9%)	0
Arthralgia	0	1 (1.9%)
Vertigo	0	1 (1.9%)
Headache	0	1 (1.9%)

[1]Term depression includes the preferred terms: major depression for Patient 10031002 on pregabalin and depressed mood for Patient 10221008 on placebo.
[2] Patient 10031002 described in section on SAE
Source: CSR 1180. Section 14.3.3.3.1. Narratives for AEs Resulting in Permanent Discontinuation

During open-label extension Study 1231, two patients on pregabalin reported adverse events causing discontinuation form the study. Subject 10021005 developed dizziness,

fatigue, and nausea considered related to study drug and a summary of this patient is provided below. Subject 10531004 developed low back pain secondary to spinal stenosis considered unrelated to pregabalin.

Individual Patient Summaries of Adverse Events Resulting in Discontinuation

Subject Number: 10011003 (Pregabalin)
Study Number: A0081180
Reason Drug Discontinued: Weight gain

This 15-year-old white female subject with fibromyalgia started treatment with pregabalin on 11-Dec-2010. Following dose escalation, the subject was taking pregabalin 150 mg/day as of 04-Jan-2011. Her medical history was significant for increased triglycerides, depression, diarrhea, headache, and insomnia. Prior medications continued during the study were azelastine hydrochloride, fluoxetine, and marvelon.

On Study Day 52 (31-Jan-2011), the subject experienced weight increased of mild intensity. The subject weighed 163 lb. at screening on 02-Dec-2010, and was 65 inches in height. On 10-Dec-2010, the day of randomization, the subject weighed 167 lb. On 03-Jan-2011, the subject's weight was 169 lb., and on 31-Jan-2011 she weighed 172 lb. On 28-Feb-2010 and 07-Mar-2011, she weighed 174 lb., for a weight gain since randomization of approximately 7 lb. The investigator considered the event of weight increased as related to study drug. The study drug was permanently discontinued and the subject withdrawn from the study on 07-Mar-2011 due to this AE. The duration of treatment was 87 days. The event was still present at last reporting.

Impression
This subject gained 7 lb. (4%) while on LYRICA over a period of 11 weeks from the time of randomization. It is possible that some of the weight gain may not be related to Lyrica, considering she gained 4 lb. in eight days while not on study drug from the day of screening to randomization.

Subject Number: 10281001 (Pregabalin)
Study Number: A0081180
Reason Drug Discontinued: Loss of consciousness (syncope)

This 15-year-old Asian female with fibromyalgia started treatment with pregabalin in Taiwan on 12-Apr-2011. Following dose escalation, the subject was taking a fixed dose of pregabalin 450 mg/day as of 26-Apr-2011 (Study Day 15). The subject had been experiencing fibromyalgia symptoms since Nov-2010 and was diagnosed with fibromyalgia in Jan-2011. No other medical history was provided at study entry. Concomitant medications during the study included combevit C.

On 13-Jun-2011 (Study Day 63), the subject first experienced loss of consciousness which resolved the same day. On the same date, she also experienced dizziness and vomiting. The investigator stated that "the patient had one syncope episode on 13-Jun-2011." Study drug dose at the time was 450 mg. The subject temporarily stopped study drug from 14 to 19 June 2011 (Study Days 64-69) due to the vomiting AE and due to the loss of consciousness for which study drug was initially stopped temporarily and subsequently permanently discontinued. After the investigator saw her on 20-Jun-2011, she restarted the medication that afternoon. The subject also took difenidol hydrochloride for dizziness from 20-Jun-2011 to 27-Jun-2011.

The investigator reported another episode of syncope happened on 21-Jun-2011 at school (Study Day 71), and that subsequently the patient decided to drop out of the trial. The event was reported as loss of consciousness, which the investigator considered of mild severity. The site reported that the subject fell down "in a swoon for few seconds at school." The subject's teacher called her name many times but there was no response. The subject awoke "after 5-10 seconds." In addition on 21-Jun-2011, the subject experienced mild headache and mild memory loss. The patient totally recovered soon after this episode in school. The study drug was permanently discontinued due to the second event of loss of consciousness

The patient saw the investigator on 30-Jun-2011 (Study Day80) with no sequelae. It is noted that the subject experienced a 5-kg weight loss between Study Days 52 and 80, during the timeframe of the episodes of syncope. Physical and neurological examination, vital signs (pulse and blood pressure), and electrocardiogram (ECG) performed at this visit on 30-Jun-2011 were otherwise normal. Throughout the study, laboratory assessments were normal with the exception of elevated eosinophils on Study Day 24, which were normal at the next evaluation on Study Day 80.

Impression
The exact etiology of her adverse event coded as loss of consciousness but characterized by the investigator as syncope is unclear. Pregabalin cannot be excluded as the cause of the event. She had dizziness and vomiting on the day of the first event which is consistent with a syncopal episode.

Subject Number: 10571005 (Pregabalin)
Study Number: A0081180
Reason Drug Discontinued: Weight gain

This 14-year-old white female subject discontinued study drug on Day 82 due to the adverse event of weight gain (approximately 10 pounds) since beginning the study. She started treatment with pregabalin on 20-May-2011. Following dose escalation, the subject was taking pregabalin 450 mg/day from Study Day 22 (10-Jun-2011).

Her medical history included fibromyalgia symptoms since 2009 and headache. Prior treatments ongoing at study entry were meloxicam and paracetamol. Concomitant treatments during the study were cetirizine hydrochloride (stopped on Study Day 1), fexofenadine hydrochloride, gabapentin, and herbal preparation (butterbur).

On Study Day 22 (10-Jun-2011), the subject experienced increased weight of moderate intensity and study drug was permanently discontinued on 22-Aug-2011 after 82 days of treatment due to a 10 lb. weight gain.

Impression
This subject's weight gain of 10 lb. from baseline was likely related to pregabalin. The weight gain was first noticed on Day 22 of treatment with pregabalin.

Subject Number: 10021005 (Pregabalin)
Study Number: A0081231
Reason Drug Discontinued: Dizziness, Fatigue, and Nausea

This 13 year old white female discontinued pregabalin on Study Day 10 due to the adverse events of dizziness, fatigue, and nausea. She was treated with placebo in the preceding double-blind study A0081180 and started treatment with pregabalin in study A0081231 on 15-Oct-2011 (Study Day 1) and stopped treatment on 24-Oct-2011 (Study Day 10).

Medical history present at study entry included arthralgia and acne. Past medical history included cataract, gastroenteritis viral, ligament sprain, and wrist fracture. Prior treatments ongoing at study entry included adapalene, benzoyl peroxide/clindamycin, minocycline hydrochloride, sulfacet, and tretinoin.

On Study Day 4 (18-Oct-2011), the subject experienced AEs of dizziness, fatigue, and nausea, all of moderate intensity while on pregabalin 150 mg/day. The study drug was permanently discontinued due to these events on Study Day 10. The events resolved on Study Day 12 (26-Oct-2011), 2 days after study drug was discontinued.

Impression
The adverse events of dizziness, fatigue, and nausea resulting in study drug discontinuation were likely related to pregabalin. The onset of symptoms was on Day 4 of treatment and symptoms resolved two days after study drug was discontinued.

7.3.4 Significant Adverse Events

Discussed in Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

Suicidal Behavior and Ideation

Approved Label: The currently approved label for LYRICA contains the following warning on suicidal behavior and ideation:

> Antiepileptic drugs (AEDs), including LYRICA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication… The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed.

Background: The Division made the following comment on the preferred assessment to use for monitoring suicidal behavior and ideation in an Advice Letter dated January 18, 2013.

> We note that you plan to monitor subjects for suicidality using the Suicidality Tracking Scale. This instrument does not adequately capture key categories of suicidal ideations and behaviors that are noted in the Draft Guidance for Industry on Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials and is not acceptable. We recommend use of the Columbia-Suicide Severity Rating Scale (C-SSRS) or another instrument that will capture the information described in the Draft Guidance.

Based on the Division's recommendation, Pfizer added the Columbia-Suicide Severity Rating Scale (C-SSRS) to the ongoing study. However, the Division noted that if Pfizer planned to enroll only 106 patients in Study 1180 and given the enrollment at the time, this might result in at most, two patients with monitoring by the C-SSRS. Therefore, the Division provided the following comment to Pfizer on March 4, 2014 on how this might impact the filing and review of the proposed NDA:

> …However, as an approved product that is already labeled with a suicide warning, the data you have will be sufficient to support filing your application and the adequacy of the data collected on suicidal ideation and behavior will be a review issue. If, after review of the data, we believe additional data on suicidality is needed for this patient population, we may consider available options such as a new postmarketing requirement.

Suicidality Screening: During Study 1180 patients completed a suicidality risk assessment at screening, randomization, and weeks 3, 7, 11 and 15. The "lifetime" version of the Sheehan Suicidality Tracking Scale (STS) was completed at screening only and all other visits used STS for suicidality risk assessment "since last visit". The STS was administered any time the subject came in for a clinic visit, including unscheduled clinic visits. The Columbia Suicide Severity Rating Scale (C-SSRS) "Lifetime" was to be performed at screening, and the C-SSRS "since last visit" was to be performed at all subsequent visits and any time the subject came in for an unscheduled clinic visit. The timing of the suicidality assessments at baseline and at each clinic visit

is considered adequate. For Study 1180, two of the 54 patients randomized to pregabalin were assessed using the C-SSRS and one of the 53 patients randomized to placebo was assessed using the C-SSRS. The adequacy of the suicidal assessments used is reviewed in the discussion section.

Results

There were no completed suicides, suicide attempts or reports of suicidal behavior during Study 1180 or Study 1231. During placebo-controlled Study 1180 suicidal ideation was reported by 3 subjects (5.6%) in the pregabalin group and by 2 subjects (3.8%) in the placebo group. All the subjects with suicidal ideation during the study reported suicidal ideation during the screening assessment. At screening, 8 subjects in each treatment group reported suicidal ideation. During open-label safety study 1231, 6 (9.5%) subjects reported suicidal ideation, without plan or intent; these subjects all had a history of suicidal ideation noted at the time of screening for study 1180. No positive responses for suicidal ideation or behavior were recorded in the three subjects assessed with the C-SSRS. All of the required narratives based on mental health assessments were reviewed in both studies and no unexpected findings were noted.

Discussion

During placebo-controlled study 1180, there did not appear to be a significant difference in the incidence of suicidal ideation between the placebo and LYRICA treatment arms and no suicidal behavior was reported in either treatment group but given the small size of the study a treatment difference would not be expected. During open-label safety study 1231, the six subjects with suicidal ideation all had a history of suicidal ideation at the time of screening. The frequency of suicidality assessments performed during the studies was adequate. The C-SSRS scale is the preferred assessment of the FDA. The FDA Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (Draft 2012) describes the preferred terms that the FDA considers important and include five levels of suicidal ideation, five levels of suicidal behavior, and the category self-injurious behavior, no suicidal intent. The 11 categories are listed below:

Suicidal ideation

1. Passive suicidal ideation: wish to be dead
2. Active suicidal ideation: nonspecific (no method, intent, or plan)
3. Active: suicidal ideation: method, but no intent or plan
4. Active: suicidal ideation: method and intent but no plan
5. Active: suicidal ideation: method, intent and plan

Suicidal behavior

1. Completed suicide
2. Suicide attempt
3. Interrupted suicide attempt
4. Aborted suicide attempt

5. Preparatory actions toward imminent suicidal behaviors

Self-injurious behavior, no suicidal intent

These categories increase the granularity for tracking suicidal ideation and behavior, following the C-SSRS structure. The more fine-grained subcategories (eg, ideation with method and intent, but no plan) are not part of the STS. However, the STS has good accuracy for identifying broad categories of suicidal ideation and behavior. Given the limited number of subjects enrolled in the study and few subjects identified with suicidal ideation, the difference in the two scales would not result in any significant overall difference in results and interpretation of the findings. Since the LYRICA label already contains a suicide warning and there were no unexpected findings, there is no need for the Applicant to collect additional safety information on suicidality.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 107 patients enrolled in Study 1180, there were 38 (70%) subjects in the pregabalin group and 34 (64%) subjects in the placebo group, who had at least 1 treatment-emergent adverse event (TEAE) during the study (includes 1 subject in the pregabalin group with a SAE). An overview of the most common treatment-emergent adverse events for Study 1180 and study 1231 is provided in Table 25. The most common adverse events in placebo-controlled study 1180 were: dizziness, 30% in the pregabalin group and 13% in the placebo group; nausea 22% in the pregabalin group and 9% in the placebo group; headache, 19% in the pregabalin group and 19% in the placebo group; weight increased, 17% in the pregabalin group and no subjects in the placebo group; fatigue, 15% in the pregabalin group and 8% in the placebo group and; somnolence 9% in the pregabalin group and 4% in the placebo group.

Of the 63 patients enrolled in Study 1231, there were 45 (71%) subjects on pregabalin who had at least 1 TEAE during the study. The most commonly reported TEAEs by preferred term were: dizziness 22%, fatigue 8%, headache 10%, nausea 8%, abdominal pain 8%, abdominal pain upper 8%. The most common adverse events in the open-label study were similar to the double-blind study.

The most common AEs in the adolescent studies were dizziness, nausea, headache, weight gain, fatigue and somnolence. These adverse events are consistent with the adverse events observed in the adult studies except for nausea which was reported at a greater frequency in Study 1180. The Applicant provides the following additional details for Study 1180; 12 pregabalin-treated subjects and 5 placebo subjects reported nausea. In each treatment group, 4 of the events were considered study drug-related by the

investigator. The events which were not study drug-related were attributed by the investigator to other illness, co-occurrence with migraine or menstrual cramps, or situational concerns such as school stress.

Table 24: Common Adverse Events Study 1180 and Study 1231 (Experienced by at least 4 subjects in the Pregabalin Treatment Group in Study 1180)

Preferred Term	Study 1180 (double-blind study)		Study 1231 (open-label study)
	Placebo (N=53) n (%)	Pregabalin (N=54) n (%)	Pregabalin (N=63) n (%)
Dizziness	7 (13.2)	16 (29.6)	14 (22.2)
Nausea	5 (9.4)	12 (22.2)	5 (7.9)
Headache	10 (18.9)	10 (18.5)	6 (9.5)
Weight increased	0 (0.0)	9 (16.7)	1 (1.6)
Fatigue	4 (7.5)	8 (14.8)	8 (12.7)
Somnolence	2 (3.8)	5 (9.3)	2 (3.2)
Oropharyngeal pain	2 (3.8)	4 (7.4)	2 (3.2)
Pain in Extremity	0 (0.0)	4 (7.4)	3 (4.8)
Pyrexia	3 (5.7)	4 (7.4)	3 (4.8)
Abdominal discomfort	3 (5.7)	1 (1.9)	1 (1.6)
Abdominal Pain	1 (1.9)	3 (5.6)	5 (7.9)
Abdominal Pain Upper	3 (5.7)	0 (0.0)	5 (7.9)

Source: CSR A0081180 Table 14.3.1.2.3.1 and Table 14.3.1.2.3.2 and CSR A008123 Table 14.3.1.2.3

7.4.2 Laboratory Findings

Serum chemistry, hematology and urinalysis tests were obtained at V1 (Screening), V6 (Week 3) and V10 (Week 15/Early Termination). The median changes in laboratory data from baseline to last observation did not appear to be clinically relevant for any of the parameters studied. However, it is noted that median platelet levels decreased from baseline by 7 x 10^3/mm^3 in pregabalin-treated subjects and by 4 x 10^3/mm^3 in placebo-treated subjects. Two subjects on pregabalin experienced thrombocytopenia considered related to study drug. One of these subjects, 10331006, had baseline thrombocytopenia (platelet value of 106 x 10^9/L, reference range 140-450 x 10^9/L) and an increase to 267 x 10^9/L (Day 21) before dropping to a low of 85 x 10^9/L (Day 105) and ending the study at 166 x 10^9/L (Day 116). Subject 10331010 had a baseline platelet value of 147 x10^9/L which dropped to 85 x10^9/L (Day 52) and ended the study at 108 x10^9/L (Day 121). There was no evidence of a pancytopenia in either of these patients. The finding of decreased platelets is consistent with the warning in the approved label below:

> LYRICA treatment was associated with a decrease in platelet count. LYRICA-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 10^3/\mu L$, compared to $11 \times 10^3/\mu L$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of LYRICA patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and less than $150 \times 10^3/\mu L$. A single LYRICA treated subject developed severe thrombocytopenia with a platelet count less than $20 \times 10^3/ \mu L$. In randomized controlled trials, LYRICA was not associated with an increase in bleeding-related adverse reactions.

Reproductive Hormone Levels

Due to nonclinical findings that pregabalin could have a negative effect on female fertility and possibly also affect sexual maturation, the Division requested that the Applicant measure reproductive hormones in their clinical studies.

The Applicant previously conducted two reproductive developmental toxicology studies in the juvenile rat. In the first study (RR 745-03267) conducted in male rats, sexual development was delayed, epididymal weight and sperm motility were reduced and when treated males were mated with untreated females decreased numbers of implants and live fetuses were seen. Female rat fertility was significantly lower than expected in all groups including controls (~60-70%). Therefore another study conducted only in juvenile females was undertaken (RR 745-03471). This study reported that when female rats were given pregabalin at doses of 50, 250 or 500 mg/kg for up to 9 weeks, vaginal opening was delayed, diestrus prolonged and fertility decreased. A NOAEL was not determined for these reproductive effects. The 50 mg/kg/day dose level concern was mainly driven by decreased fertility in females. This decrease was not statistically significant but appeared to be a trend which is dose-dependent in severity. The 83.3% (at 50 mg/kg/day) vs. 89.5% in the controls appeared to be a marginal decline. Based on these findings, the Division requested that the Applicant include measurement of reproductive hormones in their clinical studies.

Estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels were obtained at screening and end of study for placebo-controlled Study 1180 and at screening of Study 1231 if not previously performed at Week 15 of Study 1180, and at end of Study 1231.

Pfizer's Analysis of Reproductive Hormones

Pfizer submitted (July 22, 2016) a summary of their findings and concluded that no clinically relevant changes in reproductive hormones or Tanner stage were observed, and no reproductive system adverse events were reported suggestive of pregabalin induced alternations in reproductive hormones. Pfizer provided the following interpretation of the hormone levels but noted a variety of factors could influence the reproductive hormone levels.

Median changes from baseline to last observation in estradiol, FSH, and LH were determined for Study 1180 (pregabalin and placebo groups; Table 26 below) and Study 1231 (Table 27 below) across all subjects evaluated…

Median laboratory values (estradiol, FSH, LH) were found to be within normal ranges following treatment in both studies (including both pregabalin and placebo treatment groups in Study 1180)(Table 26). Generally, hormone evaluations at last observation either fell within normal limits by Tanner stage or were closer to normal ranges than for the same Tanner stage at baseline. It is noted that there are few subjects at earlier Tanner stages (e.g., 1-2 subjects at Tanner stages 1 and 2 in Study 1180).

Subjects whose reproductive hormone values were outside of the normal ranges appeared to reflect high mid-cycle levels (refer to Table 28 for mid-cycle reference ranges). Estradiol changes from baseline were not accompanied by substantive changes in FSH and LH (Table 26), suggesting that these were reflective of inter- and intra-subject variability and menstrual cycle timing; thus, none of the findings were considered to be clinically relevant.

Table 25: Study 1180 Hormone Levels: Median Changes from Baseline to Last Observation

Test	Units	Pregabalin				Placebo			
		Baseline		Change from Baseline		Baseline		Change from Baseline	
		N	Median	N	Median	N	Median	N	Median
Estradiol	pg/mL	45	79.00	38	-11.70	41	84.99	31	0.00
FSH	mIU/mL	47	6.50	42	-0.45	44	5.20	35	0.20
LH	mIU/mL	47	7.30	42	-2.10	44	5.35	35	-0.20

mIU: milliinternational units; mL: milliliters; N: number of subjects; pg: picograms.
Source: Pfizer July 22, 2016 Response to IR. Module 5.3.5.1 Table 1.2

Table 26: Study 1231 Hormone Levels: Median Changes from Baseline to Last Observation

Test	Units	Baseline		Change from Baseline	
		N	Median	N	Median
Estradiol	pg/mL	50	87.50	35	-17.40
FSH	mIU/mL	54	4.35	44	0.75
LH	mIU/mL	54	4.75	44	0.00

Baseline is defined as last observation before first active dose in Study 1231 including samples collected in Study 1180. mIU: milliinternational units; mL: milliliters; N: number of subjects; pg: picograms.
Source: Pfizer July 22, 2016 Response to IR. Module 5.3.5.2 Table 2.2

Table 27: Normal Ranges for Estradiol, FSH, and LH by Age and Phase

Age (years)	Phase	Estradiol (pg/mL)	FSH (mIU/mL)	LH (mIU/mL)
12-13	Not applicable	15.0 – 87	1.2 – 12.0	0.2 – 13.4
14-15	Prepubescent	15.0 – 87	1.2 – 12.0	0.2 – 13.4
14-15	Follicular	11 – 165	2.5 – 10.2	1.9 – 12.5
14-15	Midcycle Peak	146 – 526	3.4 – 33.4	8.7 – 76.3
14-15	Luteal	33 – 196	1.5 – 9.1	0.5 – 16.9
≥16	Follicular	11 – 165	2.5 – 10.2	1.9 – 12.5
≥16	Midcycle Peak	146 – 526	3.4 – 33.4	8.7 – 76.3
≥16	Luteal	33 – 196	1.5 – 9.1	0.5 – 16.9

mIU: milliinternational units; mL: milliliters; pg: picograms.
Source: Quintiles Laboratories, information on file

Source: Pfizer July 22, 2016 Response to IR.

Pfizer in their discussion below noted a variety of factors complicating the interpretation of their data.

> There are a variety of factors influencing reproductive hormone levels, resulting in a more complex interpretation. The results cover a wide range due to innate variability in the normal ranges. Between individuals, there are differences in hormone concentrations reflecting variations in the advancement of puberty. For patients who have experienced the onset of menarche, hormone levels fluctuate considerably during the menstrual cycle, with mid-cycle spikes of FSH and LH preceded by elevation of estrogen (e.g., estradiol)…Menstrual cycles are often irregular in adolescents (48% in one study), lending uncertainty to when peaks in hormone levels would be anticipated. Additionally, hormone levels vary across the day for any given individual…Lastly, there is inherent variability in Tanner staging by self-report compared with physical examination, particularly in younger adolescents. Recognizing these variables, the results obtained in the 2 studies are compatible with normal puberty and fluctuations in hormone levels throughout the menstrual cycle.

Division of Bone, Reproductive and Urologic Products Consult

The Division of Bone, Reproductive and Urologic Products (DBRUP) was consulted to determine whether the reproductive hormone laboratory assessments demonstrated any clinically relevant findings related to reproductive health. DBRUP concluded that the serum hormone laboratory data obtained are not clinically interpretable and provided the following additional comments.

> The rat reproductive system is significantly different than the human reproductive system. Rat reproduction is very heavily prolactin dependent. For example, many of the SSRI/SSNRIs have clinical effects on serum prolactin that can significantly affect rat reproductive behavior and fertility. In this reviewer's opinion, prolactin levels should have been evaluated in the rats and in humans. If there were effects of pregabalin on prolactin in rats and not in humans, that would lend support to a species-specific effect of pregabalin on the reproductive system.
>
> Although the Applicant provided publications with ranges of serum hormone levels in puberty in their response to a clinical request (See Applicant's response dated July 22,

2016), it is not possible to compare serum hormone levels because the publications were done many years ago with different laboratory kits that have different methodology and levels of detection. Also, the serum hormone data were not obtained with regard to the phase of the menstrual cycle. Even if the menstrual cycle data had been obtained, however, the hormone data may still be difficult to interpret as many adolescents girls have anovulatory or irregular cycles in early puberty resulting in unpredictable hormonal levels. The lack of menstrual diaries preclude the ability to detect increased rates of anovulation or oligovoluation. Finally, it is unknown whether most girls can accurately self-report Tanner stage which further complicates interpretation.

Seven subjects reported reproductive adverse events, five with dysmenorrhea, one with vaginal spotting and one with an ovarian cyst. These events are commonly reported in adolescents, especially within two to three years after initiation of menses.

It is not possible to identify infertility in adolescent girls. From this reviewer's perspective, the primary clinical conditions that could be monitored that could alter future fertility include anovulation, delayed puberty or premature ovarian failure. These conditions can be identified through menstrual diaries and serial visits over years to document whether the girls have normal menstrual cycles and are reaching appropriate milestones in development through Tanner staging. Also, growth charts and bone age could be useful if pubertal delay is identified. Since these evaluations often take several years of measurement, whether there are long-term effects of pregabalin on anovulation, pubertal milestones or premature ovarian failure is unknown with the available evidence. An important missing gap in assessing the relevance of the animal findings to humans is the drug's effect on prolactin. For example, if there were effects of pregabalin on prolactin in rats but not in humans, that would lend support to a species-specific effect of pregabalin on the reproductive system, and reduce the likelihood of clinical relevance.

Summary

The reproductive hormone data and self-reported Tanner staging are inconclusive and inadequate for determining whether there is an effect of pregabalin on future fertility and pubertal development. Although it is not possible to identify infertility in adolescent girls, it would be possible to monitor anovulation, delayed puberty or premature ovarian failure which could alter future fertility, but this would require documenting menstrual cycles and developmental milestones in a study lasting years. The approved label provides the nonclinical findings related to fertility in Section 8.4 Pediatric Use:

In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥50 mg/kg. The neurobehavioral changes of acoustic startle persisted at ≥250 mg/kg and locomotor activity and water maze performance at ≥500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma

pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established.

7.4.3 Vital Signs

For placebo-controlled study 1180, vital signs including blood pressure, pulse and weight were obtained at screening, randomization and visits at weeks 3, 7, 11 and 15. Height was done at screening and week 15 only. Review of the vital signs revealed no clinically relevant changes except for weight gain.

Weight Gain
During Study 1180, a total of 11 subjects had a weight gain of at least 7% compared to no patients in the placebo group (Table 29). Two subjects (3.7%) discontinued treatment during Study 1180 due to weight gain.

Table 28: Summary of Weight Gain from Baseline to Last Visit (Study A0081180)

Weight Gain	**Pregabalin N=51 n (%)**	**Placebo N=50 (%) n (%)**
Weight gain of at least 7%	11 (21.6)	0 (0.0)
Weight gain by category:		
≥ 7% to < 10%	8 (15.7)	0 (0.0)
≥ 10% to < 15%	3 (5.9)	0 (0.0)
≥ 15%	0 (0.0)	0 (0.0)

Only subjects with a post-baseline weight measurement are included in this table
Source: Study A0081180 Clinical Study Report. Table 14.3.4.2.5

The observed weight gain in adolescents is not unexpected since it is known that LYRICA may cause weight gain in adults. In LYRICA controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of LYRICA-treated patients and 2% of placebo-treated patients.

During Study 1180 there were no clinically significant differences in mean or median systolic or diastolic blood pressure or pulse rate between treatment groups. The number of subjects with a 30% or greater increase or decrease in pulse rate from baseline to last visit was similar in both treatment groups. A 30% increase in pulse rate was reported in 2 (3.8%) pregabalin subjects and 2 (4.0%) placebo patients and a 30% decrease was reported in no pregabalin patients and 1 (2.0%) placebo patient.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were recorded at screening and end of study or early termination. There were no clinically relevant changes in ECG parameters. The Applicant assessed

the number of “normal” and “abnormal, not clinically significant” ECGs at screening and end of treatment and found no significant difference (Table 30).

Table 29: Summary of Electrocardiogram Interpretation (Study 1180)

	Pregabalin (N=54)	**Placebo (N=53)**
Timepoint	**n (%)**	**n (%)**
Screening		
Number Assessed	54	53
Patient Status		
Normal	41 (75.9%)	45 (84.9%)
Abnormal, not clinically significant	13 (24.1)	8 (15.1)
Abnormal, clinically significant	0	0
End of Treatment (Week 15/Early Termination)		
Number Assessed	49	43
Patient Status		
Normal	37 (75.5)	38 (88.4)
Abnormal, not clinically significant	12 (24.5)	5 (11.6)
Abnormal, clinically significant	0	0

Source: CSR Study A0081180. Table 14.3.4.3.3

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not assessed

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The number of patients participating in the pediatric clinical development program for fibromyalgia was too small to for an analysis of dose dependency and adverse events. However, from the adult studies some of the adverse events appear to be dose dependent.

7.5.2 Time Dependency for Adverse Events

Not assessed

7.5.3 Drug-Demographic Interactions

Not assessed

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not assessed.

7.5.5 Drug-Drug Interactions

No drug-drug interaction studies were performed during the pediatric development program for fibromyalgia

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted.

7.6.2 Human Reproduction and Pregnancy Data

There were no pregnancies reported in Study 1180 or Study 1231.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not assessed

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not assessed

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

There is no postmarket experience with LYRICA for the treatment of fibromyalgia in adolescents.

9 Appendices

9.1 Literature Review/References

Not applicable

9.2 Labeling Recommendations

The existing label in Section 8.4 *Pediatric Use* contains the following clinical statement:

> The safety and efficacy of pregabalin in pediatric patients have not been established.

The Applicant proposes adding the following language to Section 8.4:

> Fibromyalgia
> (b) (4) a 15-week, placebo-controlled trial conducted with 107 pediatric patients with fibromyalgia, age 12-17, at LYRICA total daily doses of 75-450 mg/day. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.

The Division proposes modifying the Applicant's language by including a statement noting that the primary efficacy endpoint showed numerically greater improvement for pregabalin-treated patients but this did not reach statistical significance. The Division proposes the following language for Section 8.4:

> Fibromyalgia
> A 15-week, placebo-controlled trial was conducted with 107 pediatric patients with fibromyalgia, ages 12 through17 years, at LYRICA total daily doses of 75-450 mg/day. The primary efficacy endpoint of change from baseline to Week 15 in mean pain intensity (derived from an 11-point numeric rating scale) showed numerically greater improvement for the pregabalin-treated patients compared to placebo-treated patients, but did not reach statistical significance. The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue. The overall safety profile in adolescents was similar to that observed in adults with fibromyalgia.

The Division proposes the following changes for Section 12.3 *Pharmacokinetics*:
Delete the following statement under Pediatric Pharmacokinetics:

> (b) (4)

Add the following language under Pediatric Pharmacokinetics:

> In the pediatric age group of 12 years of age and older, systemic exposure of pregabalin is similar to adults at any given dose of LYRICA [*see Pediatric Use, (8.4)*].

9.3 Advisory Committee Meeting

No Advisory Committee Meeting was held for this product.

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

/s/

ROBERT A LEVIN
11/23/2016

JOHN J FEENEY
11/28/2016