# Clinical Review

**Lisa Wiltrout**  
**NDA 209501**  
**Lyrica CR (pregabalin ER)**

## CLINICAL REVIEW

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<tr>
<td>Priority or Standard</td>
<td>Standard</td>
</tr>
<tr>
<td>Submit Date(s)</td>
<td>15 December 2016</td>
</tr>
<tr>
<td>Received Date(s)</td>
<td>15 December 2016</td>
</tr>
<tr>
<td>PDUFA Goal Date</td>
<td>15 October 2017</td>
</tr>
<tr>
<td>Division/Office</td>
<td>Division of Anesthesia, Analgesia and Addiction Products/ ODE 2</td>
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<tr>
<td>Reviewer Name(s)</td>
<td>Lisa Wiltrout, MD</td>
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<tr>
<td>Review Completion Date</td>
<td>8 September 2017</td>
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<tr>
<td>Established Name</td>
<td>Pregabalin extended release (ER) tablets</td>
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<tr>
<td>(Proposed) Trade Name</td>
<td>Lyrica CR</td>
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<td>Applicant</td>
<td>Pfizer Inc.</td>
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<td>Formulation(s)</td>
<td>82.5 mg, 165 mg, and 330 mg</td>
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<td>Dosing Regimen</td>
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<td>Management of neuropathic pain associated with diabetic peripheral neuropathy at doses ranging from 165 mg to 330 mg, management of post-herpetic neuralgia at doses ranging from 165 mg to 660 mg, and management of fibromyalgia at doses ranging from 165 mg to 660 mg</td>
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CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)
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Glossary

AC  advisory committee
AE  adverse event
ACR  American College of Rheumatology
BID  two times per day
BL  baseline
BLA  biologics license application
BPCA  Best Pharmaceuticals for Children Act
BRF  Benefit Risk Framework
CBER  Center for Biologics Evaluation and Research
CDER  Center for Drug Evaluation and Research
CDRH  Center for Devices and Radiological Health
CDTL  Cross-Discipline Team Leader
CFR  Code of Federal Regulations
CLcr  creatinine clearance
CMC  chemistry, manufacturing, and controls
COSTART  Coding Symbols for Thesaurus of Adverse Reaction Terms
CR  controlled release
CRF  case report form
CRO  contract research organization
CRT  clinical review template
CSR  clinical study report
CSS  Controlled Substance Staff
C-SSRS  Columbia Suicidality Severity Rating Scale
DB  double-blind
DMC  data monitoring committee
ECG  electrocardiogram
eCTD  electronic common technical document
EOT  end-of-therapy
ER  extended-release
ETASU  elements to assure safe use
FDA  Food and Drug Administration
FDAAA  Food and Drug Administration Amendments Act of 2007
FDASIA  Food and Drug Administration Safety and Innovation Act
FM  Fibromyalgia
GCP  good clinical practice
GRMP  good review management practice
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ICH    International Conference on Harmonization
IND    Investigational New Drug
IR     immediate-release
ISE    integrated summary of effectiveness
ISS    integrated summary of safety
ITT    intent to treat
Loge   log transformed
LTR    loss of therapeutic response
MedDRA Medical Dictionary for Regulatory Activities
mITT   modified intent to treat
NCI-CTCAE National Cancer Institute/Common Terminology Criteria for Adverse Event
NDA    new drug application
NME    new molecular entity
OCS    Office of Computational Science
OPQ    Office of Pharmaceutical Quality
OSE    Office of Surveillance and Epidemiology
OSI    Office of Scientific Investigation
OTC    over-the-counter
PBRER  Periodic Benefit-Risk Evaluation Report
PD     pharmacodynamics
PHN    post-herpetic neuralgia
PI     prescribing information
PK     pharmacokinetics
PMC    post-marketing commitment
PMR    post-marketing requirement
PP     per protocol
PPI    patient package insert
PREA   Pediatric Research Equity Act
PRO    patient reported outcome
PSUR   Periodic Safety Update report
REMS   risk evaluation and mitigation strategy
SAE    serious adverse event
SAP    statistical analysis plan
SB     single-blind
SGE    special government employee
SOC    standard of care
TEAE   treatment emergent adverse event
TID    three times per day
1 Executive Summary

1.1. Product Introduction

[Pregabalin is a gamma-aminobutyric acid (GABA) analogue that binds to the alpha-2-delta (α2δ) receptor site (a subunit of voltage-gated calcium channels) in the central nervous system. Pregabalin has analgesic and anticonvulsant activity. The immediate-release (IR) formulation is administered two times per day (BID) to three times per day (TID) and is approved in the US for the following indications: neuropathic pain associated with diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), fibromyalgia (FM), adjunctive therapy for adults with partial onset seizures, and neuropathic pain associated with spinal cord injury (SCI). The Applicant (Pfizer Inc.) has formulated a longer acting version of pregabalin, currently known as pregabalin extended-release (ER) tablets, with a proposed proprietary name of LYRICA CR. The proposed dosing of pregabalin ER is once daily, following an evening meal. The ER formulation is designed to reside in the stomach longer than the IR formulation and slowly release pregabalin for absorption in the small intestine and proximal colon. The Applicant postulates that once daily dosing may enhance patient compliance, may provide for patient convenience or ease of clinical use, and may potentially improve medication adherence.]

1.2. Conclusions on the Substantial Evidence of Effectiveness

[This is a 505(b)(1) application for which the Applicant owns all of the data for the active drug, pregabalin. Since the Agency has found pregabalin effective for the indications noted in Section 1.1, we agreed that a single adequate and well-controlled study in each condition (peripheral neuropathic pain, FM, and epilepsy) would suffice as evidence of effectiveness for the ER formulation. The Applicant conducted a successful study in PHN to support the neuropathic pain indications. The Applicant’s studies in epilepsy and FM failed. The data contained in this submission support a finding of efficacy for the peripheral neuropathic pain indications, PHN and DPN.]

1.3. Benefit-Risk Assessment

[The pregabalin moiety has known activity in neuropathic pain, FM, and epilepsy. The approved immediate-release formulation of pregabalin requires BID to TID dosing. The Applicant formulated an extended-release formulation of pregabalin, presumably for patient convenience and enhanced patient compliance. No novel indications for the new formulation were pursued during the drug development program; peripheral neuropathic pain, FM, and seizure disorder were investigated. Because epilepsy is outside the scope of the Division of Anesthesia, Analgesia, and Addiction Product’s (DAAAP) jurisdiction and the study of the new formulation in epilepsy failed, this review will not discuss the epilepsy indication further.]
The non-epilepsy indications sought by the Applicant are peripheral neuropathic pain (PHN and DPN) and FM. These are important painful conditions of high prevalence. However, as I will discuss in Section 2.2 of this review, a substantial armamentarium exists for these indications including immediate-release pregabalin.

The Applicant conducted two Phase 3 clinical studies. One study assessed LYRICA CR against placebo in a randomized, double-blind study in patients with PHN. This study showed a clinically meaningful and statistically significant difference between LYRICA CR and placebo in the change in pain intensity from baseline (BL) to 13 weeks. A similar study in patients with FM failed to show a significant difference between LYRICA CR and placebo in the change in pain intensity from BL to 13 weeks. Consistent with prior agreements between the Agency and the Applicant, the finding of efficacy in PHN can be extrapolated to DPN, another painful peripheral neuropathy.

The clinical development program generated safety data for 1455 subjects who were exposed to the new formulation for up to 4.75 months. The mechanism to extend release in LYRICA CR does not pose specific predictable risks although the Applicant notes that the ER formulation increases gastric residence time. I conducted a thorough examination of the safety data for LYRICA CR against the placebo-controlled portions of the controlled trials. I identified no evidence of formulation-related safety issues. I reviewed the safety profile of the pregabalin ER and IR formulations overall. I also reviewed the safety profile of the ER and IR formulations by indication. Considering differences in the patient populations based on indication, the adverse event profile appears comparable between the pregabalin ER and IR formulations and across indications.

In summary, the Applicant appropriately assessed the risks and benefits of this new formulation of pregabalin in patients with PHN, FM, and epilepsy. The FM and epilepsy trials failed to meet standards for substantial evidence of efficacy. The adverse event profile for LYRICA CR appears to be consistent and justified for the treatments in which the ER formulation has been shown to be efficacious. Per FDA policy and prior agreement with the Applicant, the findings in the PHN study can be extrapolated to the DPN indication. The benefits of LYRICA CR outweigh the risks for the PHN and DPN indications. No efficacy was demonstrated with the pregabalin ER formulation for FM or epilepsy.

Reference ID: 4150575
2 Therapeutic Context

2.1. Analysis of Condition

[The Applicant seeks marketing of pregabalin ER tablets in the United States for the proposed indications of DPN, PHN, and FM.

Neuropathic pain is a complex condition involving damaged, dysfunctional or injured nerve fibers that transmit incorrect signals to other pain centers in the body resulting in chronic waxing and waning numbness, tingling, and pain. Many etiologies for neuropathic pain exist including trauma, infection, cancer, vitamin deficiency, chronic disease, alcohol use, and chemotherapy. Neuropathic pain may worsen over time and may lead to disability. Chronic pain negatively impacts quality of life. Patients with neuropathic pain may experience infection, injury, sleep deprivation, mood disorders, loss of functionality, and loss of income. Neuropathic pain responds poorly to standard pain treatments; therefore, the approach to neuropathic pain management must be multidisciplinary. The two proposed neuropathic pain indications for which the Applicant seeks marketing of pregabalin ER tablets in the United States are discussed below.

PHN

PHN is the most frequent chronic complication of herpes zoster (also known as shingles). It is also the most common neuropathic pain condition resulting from infection. Herpes zoster is a painful, vesicular skin rash that results from reactivation of dormant varicella zoster virus in a sensory ganglion. As cellular immunity decreases with age or because of weakened immunity, the varicella zoster virus reactivates and moves along the sensory nerves to the skin causing prodromal symptoms, such as pruritus, dysesthesia and pain, followed by a distinctive skin eruption in a dermatomal distribution. It is estimated that approximately 1 in 3 people will get herpes zoster at some point in their lifetime. In the United States each year, about 1,000,000 people develop herpes zoster.

PHN is defined as pain persisting for more than 3 months after the vesicular rash has resolved. It is estimated that 1 in 5 patients (roughly 20%) with herpes zoster will develop PHN. Older age is the most significant risk factor for developing PHN. At 60 years of age, approximately 60% of patients with herpes zoster develop PHN, and at 70 years of age, approximately 75% of patients with herpes zoster develop PHN. Other risk factors for PHN include the following: severe rash or pain, rash on the face or torso, immunocompromised state, or other chronic illness.
The pain of PHN is a direct consequence of the varicella zoster virus damaging peripheral nerve fibers. The damaged nerve fibers cannot properly transmit messages from the skin to the brain; therefore, the damaged nerve fibers send random, chaotic messages to the brain. Patients describe these random, chaotic messages as pain that can last months or years. The pain may be characterized as burning, sharp and jabbing, or deep and aching. In some instances, patients describe sensitivity to light touch, known as allodynia, sensitivity to temperature change, and, less commonly, itching and numbness.

PHN is not fatal; however, it is debilitating and results in suffering and reduced quality of life for those who have the medical condition. PHN affects both sexes. Patients with PHN may have reduced physical functioning and impaired psychological well-being. Some patients may no longer be able to care for themselves and necessitate transition from independent functioning to dependent care. The complications of PHN include depression, fatigue, difficulty sleeping, lack of appetite, and difficulty concentrating. PHN has both individual and societal health care costs.

**DPN**

DPN is the most common complication of diabetes mellitus (DM) with an overall annual incidence of 2%. DPN affects roughly 50% of older patients with Type 2 DM. Neuropathy may be present in 7.5% of patients at the time of initial DM diagnosis. Up to 50% of patients with DPN may be asymptomatic; however, 10-20% of patients with DPN may experience symptoms that warrant therapy.

DPN has a gradual, insidious onset. Chronic sensorimotor neuropathy is the most common form of DPN. Patients experience numbness, loss of sensation and sometimes pain in the feet, legs, fingers or hands. On clinical examination, patients have stocking and glove sensory loss and diminished or absent ankle reflexes. Descriptive terms used by patients to characterize the sensory neuropathy symptoms are as follows: numbness, tingling, pins and needles, prickling, burning, cold, pinching, buzzing, sharp and stabbing. Patients with sensorimotor neuropathy may also experience touch sensitivity, muscle weakness, balance problems, and coordination problems. These patients are at risk for developing skin wounds and potentially skin infections as impaired sensation may limit their ability to identify foot, leg, finger, and hand injuries.

Sensorimotor neuropathy may be accompanied by autonomic dysfunction. Signs of autonomic dysfunction include indigestion, nausea or vomiting, diarrhea or constipation, hypoglycemia unawareness, dizziness or faintness with change in position due to hypotension, urinary incontinence or urinary tract infections, erectile dysfunction, and increased or decreased sweating.

The prevalence of DPN increases with age and duration of DM. DPN occurs more commonly in those with poor glycemic control. DPN has equal prevalence among males and females;
however, males with Type 2 DM may develop DPN earlier than females. Females with DPN have a higher morbidity rate than males. Risk factors for the development of DPN include the following: advanced age, heavy alcohol use, cigarette smoking, hyperglycemia, hyperlipidemia, hypertension (HTN), kidney disease, obesity, and long duration of DM. The causes of DPN are multifactorial involving metabolic, neurovascular, autoimmune, and lifestyle factors as well as inherited traits and mechanical injury. It is believed that oxidative stress, advanced glycation end products and the polyol pathway all contribute to the development of DPN.

Despite the high burden of disease, DPN remains underdiagnosed and undertreated. Many patients with DPN do not report their symptoms and less than half of those with DPN are treated for their pain. Quality of life is severely decreased for those with DPN. Symptoms may persist for years. Though the primary symptoms of numbness, loss of sensation and pain may be unpleasant, the secondary complications, which include falls, foot ulcers, ileus, and cardiac arrhythmias, are more serious and may lead to fractures, limb amputations and even death.

**FM**

FM is a neurologic health condition characterized by widespread pain and diffuse tenderness that fluctuate and move throughout the body. People with this chronic illness often experience fatigue and sleep problems as well. Additional symptoms that may be reported include the following: morning stiffness, jaw or facial tenderness, temporomandibular joint disorder (TMJ), cognitive and memory problems, irritable bowel syndrome (IBS) or gastroesophageal reflux disease (GERD), migraine or tension headaches, irritable or overactive bladder, numbness or tingling in the extremities, painful menses, anxiety or depression, temperature sensitivity, and a feeling of swelling in the hands and feet.

FM affects an estimated 5 million Americans age 18 or older. Between 80 and 90% of those affected with FM are female; however, males and children may be affected as well. FM is most commonly diagnosed during middle age. Primary risk factors for FM are female sex, past medical history of a rheumatic disease or family history of FM.

The American College of Rheumatology (ACR) initially established criteria for the diagnosis of FM in 1990. These criteria were then modified in 2010 with elimination of the requirement for pain in 11 out of 18 tender points on examination. The most current ACR FM diagnostic criteria are presented in the table below.

| Table 1 | 2010 ACR Preliminary Diagnostic Criteria for FM |
Researchers believe that FM amplifies painful sensations and alters the way the central nervous system (CNS) processes pain. FM causes significant pain and fatigue with no inflammation or damage to muscles, joints or other tissues. For those with severe symptoms, FM can be extremely debilitating and can interfere with activities of daily living.

FM is not fatal and is not progressive. Those with FM may improve over time. The symptoms are typically worse in the morning, in the late afternoon, and in the evening and also worse with fatigue, tension, inactivity, weather changes, stress, overexertion, and depression.

The cause of FM remains unknown. Often FM is associated with a physically or emotionally traumatic event, or with repetitive injuries or chronic illness. At times, FM may occur spontaneously. Current thinking is that the etiology may be multifactorial with contributions from genetics, environment, infections, physical trauma, and emotional trauma.

2.2. Analysis of Current Treatment Options
[The treatment armamentarium for PHN, DPN, and FM includes not only FDA approved treatment options but also FDA unapproved treatment options and non-pharmacologic treatment options. The following section reviews the treatment options currently available for the management of PHN, DPN, and FM.

**FDA approved treatment options for PHN, DPN, and FM**

The primary goal of PHN treatment is symptom control. Current FDA approved treatment consists of the following:

- Anticonvulsants (gabapentin, extended-release gabapentin, pregabalin)
- Lidocaine 5% patch
- Capsaicin 8% patch
- OTC products – capsaicin creams and topical analgesics

No disease modifying therapies exist for PHN at this time. Prevention of PHN with use of the herpes zoster vaccine (Zostavax) in adults age 50 or older is recommended.

The primary goals of DPN treatment are limiting nerve damage and slowing progression of the neuropathy by maintaining blood glucose as close to normal as possible. The secondary goal of DPN treatment is pain management. Current FDA approved pain management options are as follows:

- Duloxetine
- Pregabalin
- Tapentadol extended release

Treatment for FM is best approached from a multidisciplinary perspective. Medications may help address the pain, sleep disturbance, and fatigue associated with FM. PT, occupational therapy (OT), and counseling may help minimize the impact the disease has on your body and mind. Complementary and alternative therapies, such as acupuncture, yoga, and massage therapy, may help with both pain and stress management. Current FDA approved medications consist of the following:

- Duloxetine
- Pregabalin
- Milnacipran

The table below provides a synopsis of approval dates, dosing information, route of administration, efficacy information, and safety issues for FDA approved medications currently used in the management of PHN, DPN, and FM.]

[Table 2 Summary of the FDA Approved Treatment Armamentarium Relevant to the Proposed Indications for pregabalin ER tablets]
<table>
<thead>
<tr>
<th>Product (s) Name</th>
<th>Relevant Indication</th>
<th>Year of Approval</th>
<th>Dosing/Administration</th>
<th>Efficacy Information</th>
<th>Important Safety and Tolerability Issues</th>
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<tbody>
<tr>
<td>Lidocaine 5% patch</td>
<td>PHN</td>
<td>1999</td>
<td>Apply a maximum of 3 patches for up to 12 hours within a 24 hour period to intact skin</td>
<td>Efficacy was seen with use of lidocaine 5% patch as compared to placebo patch; results showed a statistically better decrease in pain intensity from 4 to 12 hours and statistically different times to withdrawal from the trial (14 days for lidocaine 5% patch vs. 3.8 days for placebo patch)</td>
<td>Accidental exposure in children and pets from chewing or ingesting new or used lidocaine patches; application site reactions; anaphylactic and allergic reactions may occur; systemic adverse reactions possible with excessive dosing – CNS excitation or depression, bradycardia, hypotension and CV collapse leading to arrest</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PHN</td>
<td>2002</td>
<td>300 to 600 mg TID</td>
<td>Efficacy seen for all 3 tested doses as compared to placebo; results showed a reduction in weekly mean pain scores and maintenance of the reduction in weekly mean pain scores through end of treatment</td>
<td>DRESS; anaphylaxis and angioedema; driving impairment; somnolence, sedation and dizziness; increased seizure frequency if medication is discontinued abruptly; increased risk of suicidal thoughts or behaviors</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>PHN</td>
<td>2004</td>
<td>300 to 600 mg per day divided BID or TID</td>
<td>Efficacy seen for all tested doses as compared to placebo; results showed a statistically significant improvement in endpoint mean pain scores and a statistically significant increase in the proportion of patients with at least a 50% reduction in pain scores from baseline</td>
<td>Angioedema may occur; hypersensitivity reactions may occur; increased seizure frequency may occur if medication is discontinued abruptly; increased risk of suicidal thoughts or behaviors; peripheral edema, somnolence, dizziness, and weight gain may occur</td>
</tr>
<tr>
<td>Capsaicin 8% patch</td>
<td>PHN</td>
<td>2009</td>
<td>Single 60 minute of up to 4 patches on intact skin; may repeat every 3 months</td>
<td>Efficacy seen for capsaicin 8% patch as compared to low-dose control; results showed a greater reduction in pain at week 8 and a larger proportion of patients experiencing ≥ 30% reduction in pain intensity from baseline for each week through Week 12</td>
<td>Application site reactions may occur; transient increases in BP may occur; if irritation of eyes or airway occurs, remove affected person from the vicinity of capsaicin patch and flush mucous membranes or eyes with water</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>PHN</td>
<td>2012</td>
<td>600 mg BID</td>
<td>Efficacy seen for all 3</td>
<td>Driving impairment;</td>
</tr>
<tr>
<td>Drug</td>
<td>Type</td>
<td>Year</td>
<td>Daily Dose</td>
<td>Schedule</td>
<td>Efficacy</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
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<td>------------</td>
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<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>encarbil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>DPN</td>
<td>2004</td>
<td>150 to 300 mg per day</td>
<td>TID</td>
<td>Efficacy seen for all tested doses as compared to placebo; results showed a statistically significant improvement in endpoint mean pain scores and a statistically significant increase in the proportion of patients with at least a 50% reduction in pain scores from baseline</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>DPN</td>
<td>2004</td>
<td>60 mg</td>
<td>QD</td>
<td>Efficacy seen for two tested doses as compared to placebo; results showed a statistically significant improvement in endpoint mean pain scores and a statistically significant increase in the proportion of patients with at least a 50% reduction in pain scores from baseline</td>
</tr>
<tr>
<td>Tapentadol extended release</td>
<td>DPN</td>
<td>2012</td>
<td>100 to 250 mg per day</td>
<td>BID</td>
<td>Efficacy seen for tested doses as compared to placebo; results showed a significantly greater reduction in pain intensity from baseline to the end of Week 12</td>
</tr>
<tr>
<td>Drug</td>
<td>Route</td>
<td>Year</td>
<td>Dosage</td>
<td>Efficacy</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>---------------</td>
<td>-------</td>
<td>------</td>
<td>-------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>FM</td>
<td>2007</td>
<td>300 to 450 mg per day divided BID</td>
<td>Efficacy was seen for all tested doses as compared to placebo; results showed a difference in endpoint mean pain scores and in percentage of improvement in PGIC scores from baseline.</td>
<td>Angioedema may occur; hypersensitivity reactions may occur; increased seizure frequency may occur if medication is discontinued abruptly; increased risk of suicidal thoughts or behaviors; peripheral edema, somnolence, dizziness, and weight gain may occur.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>FM</td>
<td>2008</td>
<td>30 to 60 mg QD</td>
<td>Efficacy seen for two tested doses as compared to placebo; results showed a statistically significant improvement in endpoint mean pain scores and a statistically significant increase in the proportion of patients with at least a 50% reduction in pain scores from baseline.</td>
<td>Increased risk of suicidality, orthostatic hypotension and syncope, seizures, abnormal bleeding, hepatotoxicity, hyponatremia, and urinary hesitation and retention; serotonin syndrome or NMS-like reactions may occur; activation of mania or hypomania may occur; discontinuation may result in symptoms.</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>FM</td>
<td>2009</td>
<td>100 to 200 mg per day divided BID</td>
<td>Efficacy seen for two tested doses as compared to placebo; results showed a larger proportion of those treated with test drug met criteria for treatment response (improvement in pain, physical function, and PGIC), experienced at least a 30% reduction in pain from baseline and had improvement in PGIC.</td>
<td>Increased risk of suicidal behavior and ideation; serotonin syndrome, elevated BP, elevated heart rate, seizures, hepatotoxicity, and abnormal bleeding may occur; withdrawal symptoms may occur with discontinuation.</td>
</tr>
</tbody>
</table>

**FDA unapproved treatment options**

Current FDA unapproved treatment for PHN consists of the following:

- Tricyclic antidepressants (amitriptyline and nortriptyline)
- Serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine)
Current FDA unapproved treatment for DPN consists of the following:
- Tricyclic antidepressants (amitriptyline and nortriptyline)
- Serotonin-norepinephrine reuptake inhibitors (venlafaxine)
- Anticonvulsants (gabapentin and sodium valproate)
- Opioids
- Dextromethorphan
- Capsaicin cream
- Lidocaine patch

Current FDA unapproved treatment for FM consists of the following:
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors
- Benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam)
- Muscle relaxants (cyclobenzaprine)
- Anticonvulsants (gabapentin)
- Opioids

The table below provides a summary of the benefits and safety concerns associated with each class of FDA unapproved medication currently used in the management of PHN, DPN, and FM.

**[Table 3 Summary of the FDA Unapproved Treatment Armamentarium Relevant to the Proposed Indications for pregabalin ER tablets]**

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Relevant Indication</th>
<th>Benefits</th>
<th>Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>PHN, DPN, FM</td>
<td>Effective in clinical treatment of neuropathic pain and FM; mechanism of action unclear but believed to inhibit the reuptake of serotonin and norepinephrine; also known to antagonize NMDA receptors</td>
<td>Dry mouth; dry eyes; constipation; cognitive and/or memory impairment; anxiety; apathy; dizziness; sexual dysfunction; hypotension; tachycardia; in overdose, CNS and CVS toxicity</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>DPN and FM</td>
<td>Used for chronic pain, depression, anxiety disorders; inhibit reuptake of serotonin</td>
<td>Akathisia; increased risk of suicidal ideation; sexual dysfunction</td>
</tr>
<tr>
<td>Serotonin-norepinephrine</td>
<td>PHN and DPN</td>
<td>Used for chronic pain,</td>
<td>Drowsiness; dizziness;</td>
</tr>
</tbody>
</table>

Reference ID: 4150575
<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Action</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reuptake inhibitors</td>
<td>Antidepressants</td>
<td>Disrupt the balance of neurotransmitters in CNS and stimulate descending inhibitory pathways to alleviate pain</td>
<td>Depression, anxiety disorders, increased blood pressure, increased risk of suicidal ideation, sexual dysfunction</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Antidepressants</td>
<td>Used for neuropathic pain; inhibit voltage-gated sodium channels resulting in reduced peripheral nerve excitability</td>
<td>Drowsiness, dizziness, headache, blurred vision, nausea/vomiting, rash, increased risk of suicide, boxed warning about skin reaction, aplastic anemia, and agranulocytosis</td>
</tr>
<tr>
<td>Carboxamides</td>
<td>DPN</td>
<td>Used for neuropathic pain; inhibit voltage-gated sodium channels resulting in reduced peripheral nerve excitability</td>
<td>Dizziness, nausea/vomiting, weight gain, worsening of glycemic control, depression, aggression, hyperactivity, hearing loss, pancreatitis, thrombocytopenia, ataxia, vasculitis, hepatotoxicity, increased risk of suicidal ideation</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>DPN</td>
<td>Used for neuropathic pain; mechanism of action unknown</td>
<td>Dizziness, nausea/vomiting, weight gain, worsening of glycemic control, depression, aggression, hyperactivity, hearing loss, pancreatitis, thrombocytopenia, ataxia, vasculitis, hepatotoxicity, increased risk of suicidal ideation</td>
</tr>
<tr>
<td>GABA analogs</td>
<td>DPN and FM</td>
<td>Used for neuropathic pain; analgesic effect through inhibition of the α2δ unit of the presynaptic calcium channel</td>
<td>Drowsiness, dizziness, ataxia, nystagmus, peripheral edema, increased risk of suicidal ideation, anxiety or aggression, depression</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>FM</td>
<td>Sedating, hypnotic, anxiolytic, muscle relaxant, and amnesic properties</td>
<td>Cognitive impairment, aggression or behavioral disinhibition, respiratory depression, increased risk of suicide, risk of physical dependence and withdrawal with long-term use, risk of toxicity and fatal overdose when combined with other CNS depressants such as alcohol and opioids</td>
</tr>
<tr>
<td>Opioids</td>
<td>PHN, DPN, and FM</td>
<td>Used for chronic pain; modulate pain signals by</td>
<td>Nausea, constipation, itching, dizziness,</td>
</tr>
</tbody>
</table>

Reference ID: 4150575
activating spinal and supraspinal mechanisms via μ, δ, and κ type opioid receptors

<table>
<thead>
<tr>
<th>NMDA receptor antagonists (dextromethorphan)</th>
<th>DPN</th>
<th>Used for neuropathic pain; similar chemical structure as morphine and codeine;</th>
<th>Drowsiness; dizziness; nausea/vomiting; diarrhea; nervousness; restlessness; euphoria and dissociative effects in overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin cream</td>
<td>DPN</td>
<td>Used for neuropathic pain; causes a depletion of axonal substance P that subsequently results in desensitization of the skin due to decreased transmission of painful signals to the brain</td>
<td>Burning sensation; erythema and itching; associated with complete or nearly complete epidermal denervation and impaired nerve regeneration; patients with DM at increased risk for foot ulceration due to denervation</td>
</tr>
<tr>
<td>Lidocaine patch (5%)</td>
<td>DPN</td>
<td>Used for neuropathic pain</td>
<td>Application site reactions; anaphylactic and allergic reactions may occur; systemic adverse reactions possible with excessive dosing – CNS excitation or depression, bradycardia, hypotension and CV collapse leading to arrest</td>
</tr>
</tbody>
</table>

**Non-pharmacologic treatment options**

Current non-pharmacologic treatment for PHN consists of the following:
- Transcutaneous electrical nerve stimulation (TENS)
- Spinal cord or peripheral nerve stimulation

Current non-pharmacologic treatment for DPN consists of the following:
- Bed cradle (used to prevent sheets or blankets from touching sensitive skin)
- Acupuncture
- Biofeedback
- Transcutaneous electrical nerve stimulation (TENS)
- Physical therapy (PT)

Current non-pharmacologic treatment for FM consists of the following:
- Healthy diet, regular exercise, and adequate sleep
- Cognitive behavioral therapy
- Mindfulness based stress reduction
Clinical Review  
Lisa Wiltrout  
NDA 209501  
Lyrica CR (pregabalin ER)

 Massage, movement or chiropractic therapy  
Acupuncture  
Occupational therapy (OT) and/or PT

3  Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

[The IR formulation of pregabalin has been marketed in the United States for over ten years. Pregabalin was initially approved by the FDA in December 2004 for the following indications: management of neuropathic pain associated with DPN, management of neuropathic pain associated with PHN, and adjunctive therapy for partial onset seizures. Three years later, in June 2007, pregabalin was approved by the FDA for the management of FM. New safety information about the use of pregabalin and other antiepileptic drugs emerged in 2008 as a result of post-marketing surveillance. This safety information showed a risk of suicidal behavior and suicidal ideation associated with use of any antiepileptic drug. Therefore, pregabalin - along with all other drugs in the antiepileptic class - underwent a safety labeling change in 2009. Information pertaining to increased risk of suicidal thoughts and behavior was added to the Warnings section of the prescribing information and a medication guide informing patients of this increased risk was required for all antiepileptic drugs. In June 2012, pregabalin was approved by the FDA for the management of neuropathic pain associated with spinal cord injury. The Applicant has fulfilled multiple post-marketing study commitments. Most recently in 2016, the Applicant fulfilled a post-marketing commitment to complete a pediatric study under PREA for the management of FM in pediatric patients ages 13 to 16.]

3.2. Summary of Presubmission/Submission Regulatory Activity

[Pregabalin ER drug development was conducted under multiple INDs and required the input of two divisions within the Office of New Drugs (OND), IND 53763 and IND 107333 were submitted to and reviewed by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the neuropathic pain indications. Table 1 summarizes the highlights of the regulatory activity that occurred during the clinical development program for pregabalin ER tablets.]
<table>
<thead>
<tr>
<th>Presubmission Regulatory Activity between the FDA and the Applicant</th>
</tr>
</thead>
</table>
| **August 2008**  
Type B End of Phase 2 meeting  
IND 53763 | DAARP (predecessor of DAAAP) responded to the Applicant’s questions regarding development plans for a once daily pregabalin formulation. DAARP stated that, in principle, a BE approach with AUC comparison of the proposed commercial ER formulation of pregabalin under fed conditions appeared acceptable. DAARP recommended the following:  
- multiple-dose BE studies comparing all the ER product strengths to the equivalent dose of IR product under fed conditions  
- food effect study must include a fasting arm, assess PK dose proportionality for the proposed ER strengths  
- conduct in vitro alcohol-drug interaction studies  
- propose appropriate dose adjustment recommendations for use of ER product in the elderly and in those with renal impairment  
- address the requirements for the epilepsy indication with DNP  
DAARP was undecided as to whether the Applicant’s proposal to use predicted similarities in efficacy between IR and ER formulations based on PK/PD analyses is sufficient information to support the filing of a supplement for the neuropathic pain (PHN and DPN) and FM indications. The Division stated it would communicate with the Applicant once a final decision had been made. |
| **November 2008**  
Type B meeting | (b) (4) |
| **March 2009**  
FDA Advice letter  
IND 53763 | In follow up to the August 2008 meeting, DAARP stated that at least one efficacy trial in one neuropathic pain population (DPN or PHN) (b) (4) required to confirm that a change in the PK profile of pregabalin does not alter the efficacy when changing from an IR to an ER formulation. |
| **February 2010**  
New protocol submission  
IND 107333 | Protocol A0081239 (Phase 1 single dose trial) and Protocol A0081224 (Phase 3 repeat dose trial) evaluating pregabalin ER tablets for treatment of neuropathic pain due to PHN submitted to DAAAP. |
| **March 2010**  
Partial clinical hold notification  
IND 107333 (teleconference with DAAAP) | IND 107333 placed on partial clinical hold because the Applicant provided insufficient information to assess the safety of the Kollidon SR excipient for repeat-dose clinical trials. Protocol A0081239 was deemed safe to proceed. Protocol A0081224 was put on hold. Full details were provided to the Applicant in a follow-up letter. |
| **July 2010**  
Remove partial clinical hold letter  
IND 107333 | Protocol A0081224 allowed to proceed as the Applicant provided adequate scientific justification to support the safety of repeated exposure to Kollidon SR at the levels found in pregabalin ER tablets. |
Presubmission Regulatory Activity between the FDA and the Applicant
for clinical trials up to four months in duration.

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
<th>Notes</th>
</tr>
</thead>
</table>
| August 2010| FDA Advice letter IND 107333                         | DAAAP stated the design of Protocol A0081224 was acceptable and recommended the following:  
  - also conduct an analysis comparing the differences in pain between baseline and end-of-therapy; the results should support the findings from the primary analysis (LTR)  
  - treat all patients who withdraw from the study as experiencing treatment failure at the time of withdrawal  
  - you must establish standard operating procedures if you plan to adjust sample size during the trial  
  - control for multiple endpoints if you intend to use any data from secondary endpoints to support claims in the label  
  - sleep outcomes secondary endpoint data will not be able to support a claim in labeling |
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 2010</td>
<td>FDA Advice letter&lt;br&gt;IND 107333/Protocol A0081224&lt;br&gt;DAAAP responded to the Applicant’s amendment to and SAP for protocol A0081224 with the following:&lt;br&gt;1. Your proposal to treat subjects who withdraw prematurely due to lack of efficacy or an adverse event as having experienced loss of therapeutic response is acceptable provided that the reason for withdrawal is well documented and adjudicated&lt;br&gt;2. Prespecify your method for how the primary endpoint will be determined when a subject misses more than 3 daily diary entries in a 7 day period but does not withdraw from the study</td>
</tr>
<tr>
<td>November 2010</td>
<td>New protocol submission&lt;br&gt;IND 107333&lt;br&gt;Protocol A0081245 (Phase 3 trial evaluating pregabalin ER tablets for treatment of FM) submitted to DAAAP</td>
</tr>
<tr>
<td>June 2015</td>
<td>Type C Meeting&lt;br&gt;Written Responses Only&lt;br&gt;IND 107333</td>
</tr>
<tr>
<td>December 2015</td>
<td></td>
</tr>
</tbody>
</table>
## Presubmission Regulatory Activity between the FDA and the Applicant

<table>
<thead>
<tr>
<th>FDA Advice letter IND 107333</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2016 iPSP submission IND 107333</td>
</tr>
<tr>
<td>iPSP to IND 107333 submitted to DAAAP requesting full waivers for the following indications:</td>
</tr>
<tr>
<td>- NoP associated with DPN</td>
</tr>
<tr>
<td>- PHN</td>
</tr>
<tr>
<td>- FM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>April 2016 Pre-NDA meeting IND 107333</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAAAP stated the following:</td>
</tr>
<tr>
<td>- Kollidon SR appears to be adequately qualified for use in pregabalin ER tablets</td>
</tr>
<tr>
<td>- Clinical use of crosdioxide in pregabalin ER tablets appears to be adequately qualified for safety</td>
</tr>
<tr>
<td>- Clinical use of crosopovidone in pregabalin ER tablets appears adequately qualified for safety</td>
</tr>
<tr>
<td>- Provide a letter of authorization to reference the drug master file for polyethylene oxide</td>
</tr>
<tr>
<td>- Final determination of the adequacy of your drug product formulation will be a review issue</td>
</tr>
<tr>
<td>- You must conduct a 90-day repeat-dose toxicology study to qualify any impurity that exceeds ICH thresholds to support the proposed indication for a chronic-use drug product</td>
</tr>
<tr>
<td>- The proposed summary of data to support the clinical pharmacology and biopharmaceutics review appears acceptable; confirm that the to-be-marketed formulation was used in all the supporting clinical pharmacology and biopharmaceutics studies</td>
</tr>
<tr>
<td>- In addition to the planned comparisons of results by age, sex and race, provide a comparison of efficacy by dose</td>
</tr>
<tr>
<td>- Include in the summary of treatment exposure, the duration of exposure for each dose by indication, and any adverse events due to adverse events a comparison of adverse event incidence by indication and dose; also focus on CNS adverse events of special interest</td>
</tr>
<tr>
<td>- Include subject narratives for deaths, nonfatal SAEs and subjects who were discontinued due to AEs regardless of the</td>
</tr>
</tbody>
</table>
### Presubmission Regulatory Activity between the FDA and the Applicant

- Relatedness assessment; *(b)(4)* are not acceptable
- Include CRFs for all deaths, nonfatal SAEs and patients who discontinued treatment due to AES for all clinical studies
- Include sufficient documentation to link the datasets to all results presented in the CSRs, ISS and ISE

- Although DPN was not studied with Lyrica CR, Section 6 of the USPI should include relevant safety information for DPN patients based on Lyrica IR studies
- We would not grant a waiver for the 120-day safety update; however, if no new safety information is available, then the safety update can simply report that

**July 2016**
**Agreed iPSP- agreement**

**DAAAP agreed with the Applicant’s request for waivers for DPN, PHN, and FM.** DAAAP also agreed with the Applicant’s stated justification for the waiver requests for DPN, PHN, and FM.

### 3.3. Foreign Regulatory Actions and Marketing History

[The IR formulation of pregabalin was first approved for sale in the European Union in July 2004. Pregabalin is now marketed throughout the world with indications for neuropathic pain, CDER Clinical Review Template 2015 Edition]

*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*
epilepsy, and generalized anxiety disorder. There have been no significant post-marketing safety concerns internationally to date.]

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

[Four international sites were selected for Office of Scientific Investigations (OSI) clinical site inspections for Study 1224. The sites selected had the highest level of subject enrollment for the double blind (DB) phase of the trial, the driving factor for efficacy determination. The four selected sites were as follows:

Dr. Alina Agafina in Saint-Petersburg, Russia
Dr. Nataliya Shilkina in Yaroslavl, Russia
Dr. Oleg Nadashkevich in Lviv, Ukraine
Dr. Mohammed Siddique Tayob, in Middleburg, South Africa

The final classification of the inspections of Drs. Agafina and Shilkina was no deviation from regulations (NAI). The preliminary classification of the inspection of Dr. Nadashkevich was no deviation from regulations (NAI) as well. The preliminary classification of the inspection of Dr. Tayob based on communication with the field investigator was deviations from regulations (VAI). The primary OSI reviewer, Dr. Damon Green, concluded that Study 1224 appears to have been conducted adequately and that the data generated by these sites appear acceptable in support of the respective application.

Please see the clinical inspection summary of Dr. Damon Green for additional information.]

4.2. Product Quality

[Pregabalin ER tablets consist of the drug substance, pregabalin, and the excipients, Kollidon SR, crospovidone, polyethylene oxide, carbomer and magnesium stearate. Pregabalin is a white to off-white solid that is classified as a BCS Class I compound given its high permeability and high solubility. Pregabalin ER tablets are available as almond shaped tablets with different film coating colors to distinguish the three dosage strengths of 82.5 mg, 165 mg, and 330 mg.]

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)
Generic name: Pregabalin ER
Trade name: LYRICA CR® extended-release tablets
Chemical name: (S)-3-(aminomethyl)-5-methylhexanoic acid
Molecular formula: C₈H₁₇NO₂
Molecular weight: 159.23
Chemical structure of pregabalin is:

![Chemical structure of pregabalin](image)

The drug product used in the later phases of clinical development was to be marketed product. Pregabalin ER tablets have a 30 month shelf life based on the Applicant’s 36-month stability data.

The benefits of pregabalin include pain relief and seizures. The well-known side effects of pregabalin include somnolence, dizziness, fatigue, peripheral edema, and weight gain.

The CMC acting team lead, Dr. Ciby Abraham, communicated no concerns regarding the approvability of pregabalin ER tablets in the wrap up meeting. Please see the review of the CMC drug product primary reviewer, Chris Hough, Ph.D., for additional information.

4.3. **Clinical Microbiology**

[Not applicable]

4.4. **Nonclinical Pharmacology/Toxicology**

[The nonclinical pharmacology and toxicology of the pregabalin drug substance were reviewed for the LYRICA NDA(s) and no outstanding issues were identified. The impurities and degradants in the pregabalin ER drug product that exceed ICH Q3A and Q3B requirements have been adequately qualified. Qualification studies of the novel excipient, Kollidon SR, were previously reviewed and deemed adequate during the drug development process.

Please see the review of the primary pharmacology/toxicology reviewer, Kevin Snyder, Ph.D., for more information on the nonclinical pharmacology/toxicology of pregabalin ER tablets.]

4.5. **Clinical Pharmacology**
[Phase 1 studies using pilot pregabalin ER formulations showed differences in relative bioavailability (BA) between the pilot pregabalin ER formulations and the LYRICA capsule formulation. The Phase 1 studies Consequently, the Applicant developed final pregabalin ER tablet dose strengths of 82.5 mg, 165 mg, and 330 mg. These final pregabalin ER formulations were used in the clinical pharmacology studies as well as the Phase 3 clinical trials conducted in the later stages of drug development. These final pregabalin ER formulations (pregabalin ER 82.5 mg, 165 mg, and 330 mg) are also the Applicant’s proposed commercial tablet strengths.

The Applicant conducted twelve clinical pharmacology Phase 1 studies using the proposed commercial dosages of pregabalin ER tablets in healthy adult volunteers. The Applicant evaluated the PK and relative bioavailability of pregabalin ER compared to equivalent doses of pregabalin IR in both single dose and multiple dose studies. The Applicant also evaluated dose proportionality in multiple dose studies.]

4.5.1. **Mechanism of Action**

[Pregabalin is classified as a GABA analogue and gabapentinoid. It is a close analogue of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). Pregabalin selectively binds to the α2δ subunit of voltage-gated calcium channels in the central nervous system. It increases extracellular GABA concentrations in the brain by producing dose-dependent increases in L-glutamic acid decarboxylase (GAD), the enzyme responsible for making GABA.

Pregabalin does not bind to GABA<sub>A</sub>, GABA<sub>B</sub>, or benzodiazepine receptors, does not alter rat brain GABA concentration, does not augment GABA<sub>A</sub> responses in cultured neurons, or have rapid effects on GABA uptake or degradation. With extended application of pregabalin in cultured neurons, the density of GABA transporter protein increases and the rate of functional GABA transport increases. Pregabalin remains inactive at serotonin and dopamine receptors and does not affect serotonin, dopamine or noradrenaline reuptake. Pregabalin does not block sodium channels, remains inactive at opioid receptors, and does not interfere with cyclooxygenase enzyme activity.

The mechanism of action of pregabalin is not fully understood. Animal studies suggest that binding to the α2δ subunit may be involved in the drug’s anti-nociceptive and anticonvulsant effects. Animal models of nerve damage show that pregabalin reduces calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord. Pregabalin may disrupt α2δ containing calcium-channel trafficking, may reduce calcium currents, or may interact with noradrenergic and serotonergic pathways that are involved in modulating pain transmission in the spinal cord.]

4.5.2. **Pharmacodynamics**
4.5.3. **Pharmacokinetics**

[The Applicant conducted numerous single dose studies to evaluate the effect of food, of variations in caloric content, and of variations in study medication administration time on the PK of pregabalin ER tablets. Study A0081238 is a representative example of these single dose studies. In this study, the single-dose PK of pregabalin ER 330 mg administered in three different settings – following a 400-500 calorie evening meal, following a 600-750 calorie meal and, at bedtime approximately 4 hours following a 600-750 calorie meal - was compared to pregabalin IR 300 mg administered fasted in the evening. The results of this study are presented in both graphical format and tabular format below. The C\text{max} values were lower for all three ER tablets regardless of food exposure or caloric content as compared to the IR formulation. The C\text{max} value for the ER tablet administered fasted occurred earlier and was approximately 15% lower than the C\text{max} values for the ER tablets administered fed. The T\text{max} values were later for all three ER tablets as compared to the IR formulation as well. The ER tablets administered following an evening meal, regardless of variations in caloric content, had a total exposure that was comparable to that achieved with the IR formulation. The ER tablet administered fasted had a lower total exposure as compared to both the IR formulation and the ER tablets administered fed.]

**Figure 1**  Mean Plasma Pregabalin Concentration-Time Plot (Study 1238)
Table 5  Summary of Plasma Pregabalin PK Parameter Values (Study 1238)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Parameter Summary Statisticsa by Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>330 mg CR 400-500 calories Morning Meal</td>
</tr>
<tr>
<td>N1, N2</td>
<td>23, 23</td>
</tr>
<tr>
<td>AUCint (μg•h/mL)</td>
<td>54.39 (25)</td>
</tr>
<tr>
<td>AUClast (μg•h/mL)</td>
<td>53.52 (25)</td>
</tr>
<tr>
<td>Cmax (μg/mL)</td>
<td>3.373 (19)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>8.00 (5.00-12.0)</td>
</tr>
<tr>
<td>Tlag (h)</td>
<td>0.00 (0.00-5.33)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>6.903 (16)</td>
</tr>
</tbody>
</table>

Source: Table 14.4.3.1.

N1 was the number of subjects in the treatment group; N2 was the number of subjects included in the analysis. Parameters are defined in Table 4.

CR = controlled-release; IR = immediate-release; CV = coefficient of variation.

a Geometric mean (%CV) was calculated for all parameters except for Tmax and Tlag (median [range]) and t1/2 (arithmetic mean [%CV]).

Source: CSR, Study 1238, Table 13, p. 46
The Applicant conducted one preliminary, multiple dose, crossover, PK and relative BA study (Study A0081225) and four multiple dose, crossover, PK, relative BA and dose proportionality studies (Study A0081198, Study A0081215, Study A0081216, and Study A0081226) to further determine the PK of pregabalin ER tablets. These studies generated the results displayed below in Table 6. The Applicant evaluated AUC, \(C_{\text{max}}\), and \(C_{\text{min}}\) for all proposed commercial doses of pregabalin ER tablets administered once daily following an evening meal relative to comparative doses of pregabalin IR capsules administered twice or three times daily without food. The Applicant’s analysis of these results led to the following conclusions:

- Total daily AUC for pregabalin ER tablets (82.5 mg, 165 mg, 330 mg, and 660 mg/day) administered once daily following an evening meal is equivalent to the comparative total daily AUC for pregabalin IR capsules (75 mg, 150 mg, 300 mg, and 600 mg/day) administered BID or TID without food
- The steady-state \(C_{\text{max}}\) of pregabalin ER tablets administered once daily following an evening meal is lower than the steady-state \(C_{\text{max}}\) of pregabalin IR capsules administered fasted twice or three times daily
- The steady-state \(C_{\text{min}}\) of pregabalin ER tablets administered once daily following an evening meal is lower than the steady-state \(C_{\text{min}}\) of pregabalin IR capsules administered fasted twice or three times daily

<table>
<thead>
<tr>
<th>Study (A008)</th>
<th>Study Design(^a)</th>
<th>Pregabalin Dose (mg)</th>
<th>Test/Ref Ratio (90% CIs)(^b,c)</th>
<th>AUC</th>
<th>(C_{\text{max}})</th>
<th>(C_{\text{min}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary Multiple Dose Study Evaluating the PK and Relative BA of 330 mg Pregabalin ER Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 without Food</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1225(^e)</td>
<td>ER: 600 kcal, med-fat, evening&lt;br&gt;IR: Fasted, evening</td>
<td>1 x 330 q24&lt;br&gt;1 x 150 q12</td>
<td>99.03&lt;br&gt;(95.27, 102.94)</td>
<td>97.26&lt;br&gt;(91.44, 103.45)</td>
<td>67.89&lt;br&gt;(62.50, 73.74)</td>
<td></td>
</tr>
</tbody>
</table>

Multiple Dose Studies Evaluating the PK, Relative BA, and Dose Proportionality of Proposed Commercial Pregabalin ER Tablets Administered QD Following an Evening Meal (600-750 Calorie, 30% Fat) Relative to Pregabalin IR Administered q12 or TID without Food |
| 1198 | ER: 600 kcal, med-fat, evening<br>IR: Fasted, evening | 2 x 165 q24<br>1 x 150 q12 | 94.56<br>(92.05, 97.14) | 63.84<br>(60.82, 67.00) | 73.32<br>(69.24, 77.63) |
| 1215 | ER: 600 kcal, med-fat, evening<br>IR: Fasted, evening | 1 x 82.5 q24<br>1 x 25 TID | 96.02<br>(92.84, 99.30) | 82.19<br>(77.05, 87.67) | 63.71<br>(59.20, 68.56) |
| 1216 | ER: 600 kcal, med-fat, evening<br>IR: Fasted, evening | 2 x 330 q24<br>1 x 300 q12 | 96.29<br>(92.35, 100.41) | 68.34<br>(63.76, 73.24) | 84.44<br>(74.49, 95.33) |
| 1226 | ER: 600 kcal, med-fat, evening<br>IR: Fasted, evening | 2 x 82.5 q24<br>1 x 75 q12 | 95.21<br>(92.52, 97.97) | 63.79<br>(61.00, 66.71) | 73.32<br>(69.27, 77.62) |
| ER: 600 kcal, med-fat, evening<br>IR: Fasted, evening | 1 x 165 q24<br>1 x 75 q12 | 93.05<br>(90.47, 95.71) | 62.62<br>(59.92, 65.43) | 74.15<br>(70.11, 78.41) |

Source: Summary of Clinical Pharmacology Studies, Table 2.7.2.12, p. 28

The figure below is a representative example (taken from Study 1198) of a multiple dose concentration time curve comparing the PK of pregabalin ER administered daily to the PK of pregabalin administered two times per day. The significant findings in this concentration time
curve are the consistently lower $C_{\text{min}}$ values at time points $C_0$ and $C_{24}$ for pregabalin ER dosed daily as compared to pregabalin dosed BID.

**Figure 2** Mean Plasma Concentration-Time Curves Following Day 4 Evening Administration: 2 x 165mg and 1 x 330mg pregabalin ER tablets QD and 1 x 150mg pregabalin capsule BID

![Mean Plasma Concentration-Time Curves](image)

Source: CSR Study 1198, p.44

**Reviewer Comment:** The pharmacokinetics of pregabalin ER differ from the pharmacokinetics of LYRICA and likely impact the efficacy of this drug product. Firstly, the drug dosage in the pregabalin ER formulation must be increased by 10% to provide a comparable BA to that of the LYRICA formulation. Secondly, pregabalin ER must be administered after an evening meal to yield optimal drug concentration and to provide a total exposure that is comparable to that of the LYRICA formulation administered fasted two or three times per day. Thirdly, even with a 10% dosage increase and administration after an evening meal, the pregabalin ER formulation has steady state $C_{\text{max}}$ and $C_{\text{min}}$ values that remain lower than the LYRICA formulation. All of these factors contribute to less drug availability systemically and potentially less efficacy particularly in those populations with relatively normal renal function with rapid excretion of pregabalin ER.

Please see the review of the primary clinical pharmacology reviewer, Srikanth Nallani, Ph.D., for a more detailed discussion of the clinical pharmacology of pregabalin ER tablets.]

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Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)
4.6. Devices and Companion Diagnostic Issues

[Not applicable]

4.7. Consumer Study Reviews

[Not applicable]

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

[The pregabalin ER clinical development program supporting the 505(b)(1) NDA submission included one Phase 3 clinical trial in the PHN population to support the DPN and PHN indications, one Phase 3 clinical trial in the FM population to support the FM indication, and one Phase 3 clinical trial in the epilepsy population. Study A0081194, a randomized, double-blind parallel group trial in the epilepsy population, failed to meet its primary efficacy endpoint.]

Reference ID: 4150575
**Table 7  Phase 3 Clinical Trials**

<table>
<thead>
<tr>
<th>Trial Identity</th>
<th>Trial Design</th>
<th>Medication regimen</th>
<th>Trial Endpoints</th>
<th>Treatment Duration</th>
<th>No. of patients randomized</th>
<th>Trial Population</th>
<th>No. of Centers and Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controlled Trials to Support Efficacy and Safety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A0081224</td>
<td>SB enrichment phase followed by DB, R, PC withdrawal phase</td>
<td>Pregabalin ER tablets: 82.5, 165, 247.5 or 330 mg po QD (impaired renal function)</td>
<td>1° Time to LTR* 2° Time to secondary LTR*; NRS (daily pain and 1 week recall)</td>
<td>Baseline phase: 1 week SB Phase: 6 wks 4 wks, dose optimization; 2 wks, fixed dose DB Phase: 13 weeks, fixed dose Taper phase: 1 week</td>
<td>SB Phase: 801 DB Phase: 418</td>
<td>Adults with PHN</td>
<td>129 centers/17 countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pregabalin ER tablets: 165, 330, 495 or 660 mg po QD (normal renal function)</td>
<td>Safety – AEs, physical and neurological exams, vital signs, suicidality</td>
<td></td>
<td></td>
<td></td>
<td>Enrollment: 116 centers/16 countries</td>
</tr>
<tr>
<td>A0081245</td>
<td>SB enrichment phase followed by DB, R, PC withdrawal phase</td>
<td>Pregabalin ER tablets: 165, 330 or 495 mg po QD</td>
<td>1° Time to LTR* 2° NRS (daily pain and 1 week recall)</td>
<td>Baseline phase: 1 week SB Phase: 6 wks 3 wks, dose optimization; 3 wks, fixed dose DB Phase: 13 weeks, fixed dose Taper phase: 1 week</td>
<td>SB Phase: 441 DB Phase: 122</td>
<td>Adults with FM</td>
<td>50 centers/4 countries</td>
</tr>
</tbody>
</table>

Reference ID: 4150575
## Trials to Support Safety

<table>
<thead>
<tr>
<th>Trial Identity</th>
<th>Trial Design</th>
<th>Medication regimen</th>
<th>Trial Endpoints</th>
<th>Treatment Duration</th>
<th>No. of patients randomized</th>
<th>No. of Centers and Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0081194</td>
<td>R, DB, PC parallel group</td>
<td>Pregabalin ER tablets: 165 mg po QD 330 mg po QD OR Placebo</td>
<td>1° log_{10} 28-day seizure rate for all partial onset seizures in DB treatment phase* 2° responder rate*; % change in 28-day partial seizure rates by treatment group; frequency of SGTC</td>
<td>Baseline observation phase: 8 weeks DB Phase: 14 or 15 wks 2 wks, dose escalation 12 wks, maintenance 1 week, optional taper</td>
<td>325</td>
<td>Adults with dx of epilepsy with partial onset seizures minimum of 3 during 28 days prior to first screening visit</td>
</tr>
</tbody>
</table>

* LTR defined as < 30% pain response relative to SB Phase baseline, patient discontinuation due to lack of efficacy or due to AEs;  
  * secondary LTR defined as: 1) at least a 30% increase in the 5 days mean pain score during DB Phase relative to the 5-day randomization baseline pain score and; 2) a 5 days mean pain score ≥4; or patient discontinuation due to lack of efficacy or due to AEs;  
  * DB treatment phase = dose escalation phase + maintenance phase;  
  * Responder rate – proportion of subjects who had ≥50% reduction in the 28-day partial seizure rate from baseline during the DB treatment phase.
5.2. Review Strategy

[I reviewed the study design, study conduct, statistical methods, and efficacy data from Study 1224 and Study 1245 to assess the Applicant’s efficacy submission. I did not review the study design, study conduct, statistical methods, and efficacy data from Study 1194 as this clinical trial failed to meet its primary efficacy endpoint. I also compared the study design, study conduct, and efficacy data from Study 1245 to Study A0081059 entitled, “A Six-Month, Double-Blind, Placebo-Controlled Durability of Effect Study of Pregabalin for Pain Associated with Fibromyalgia”. Study 1059 is a previously published clinical trial submitted by the Applicant under sNDA 21-446/S010 in support of the FM indication for pregabalin capsules.

I analyzed Studies 1224 and 1245 looking for the following hallmarks of adequate and well-controlled research as stated in 21 CFR 314.126:

- Clearly stated objectives
- Use of a study design that allows valid comparison with a control and provides quantitative assessment of drug effect
- Use of a placebo control with maintenance of blinding
- Selection of subjects who have the disease or condition being studied
- Use of randomization to minimize bias and assure comparability between the test group and the control group
- Adequate measures taken to minimize bias on the part of subjects, observers, and researchers (all involved in the studies)
- Well-defined and reliable methods for assessment of subjects’ response
- Capability to make an adequate assessment of the effects of the study drug from analysis of the study results

All statistical analyses discussed in my review have been confirmed by the statistical team.

I reviewed the integrated safety data for the multiple dose Phase 1 studies, the integrated safety data for the two Phase 3 pain studies (Study 1224 and 1245), and the individual study safety data from Studies 1224, 1245, and 1194 to assess the Applicant’s safety submission.]

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. [Protocol A0081224]

6.1.1. Study Design

Overview and Objective
[The Applicant conducted Protocol A0081224 which hereafter will be referred to as Study 1224 to support efficacy for the indications of neuropathic pain associated with PHN and DPN for this submission. The following summary of the design of Study 1224 was derived from Final Protocol Amendment 4, dated December 18, 2012. Important modifications to the original protocol are summarized at the end of this protocol summary.

**Title:** “A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of Once Daily Controlled Release Pregabalin in the Treatment of Patients with Postherpetic Neuralgia”

**Dates Conducted:** The first subject was enrolled in Study 1224 on April 8, 2011 and the last subject completed Study 1224 on September 8, 2014.

**Study Duration:** 21 weeks

**Number of centers:** 129

**Number of countries:** 17

**Objectives:**
The primary objective was to have been -
- To evaluate the efficacy of pregabalin ER compared with placebo in the durability of effect for the treatment of pain associated with PHN among patients who initially respond to single-blind pregabalin

The secondary objectives were to have been -
- To evaluate the efficacy of pregabalin ER compared with placebo to relieve pain and to improve global assessment, functional status and sleep;
- To assess treatment satisfaction with pregabalin ER compared with placebo;
- To assess the safety and tolerability of the pregabalin ER formulation
[Trial Design]

Study 1224 was a Phase 3, 17 week, multicenter, randomized withdrawal trial consisting of 4 phases: screening/baseline (1 week), single-blind treatment (dose optimization 4 weeks/fixed dose 2 weeks), double-blind, placebo-controlled treatment (fixed dose 13 weeks) and double-blind taper (1 week).

Visit 0 (washout) was to have been scheduled for subjects who required a wash-out of prohibited medications. At Visit 1 (screening), subjects were to have been given instructions on completing daily pain and daily sleep diaries during the baseline period. At Visit 2 (enrollment) one week later, subjects were to have completed at least 4 pain diary entries satisfactorily within the last 7 days and were to have an average daily pain score ≥ 4 in order to meet eligibility criteria.

Subjects, who met study entry criteria, including a washout of prohibited medications, were to have been enrolled in the single-blind Phase of the trial. The optimal dose of pregabalin ER was to have been determined in the first 4 weeks of this phase. The optimized dose was then to have been used in a fixed manner during the last 2 weeks of this phase. Pregabalin ER was to have been administered once daily within 1 hour after the evening meal. The starting dose was to have been 82.5 mg pregabalin ER daily for patients with low creatinine clearance (>30 to <60 mL/min) and 165 mg pregabalin ER daily for patients with normal creatinine clearance. The medication dosage was to have been escalated at weekly intervals, based on efficacy and tolerability, up to a maximum of 330 mg pregabalin ER daily for patients with low creatinine clearance and up to a maximum of 660 mg pregabalin ER daily for patients with normal creatinine clearance. At the end of 6 weeks, subject pain response was to have been assessed using the daily pain diary. Responders were to have been defined as those with at least 50% improvement in pain from single-blind baseline to end of the single-blind Phase.

Responders from the single-blind Phase of the trial were to have been considered for participation in the double-blind Phase of the trial. Patients who met eligibility criteria and agreed to participate in the double-blind Phase were to have been randomized either to continue pregabalin ER for 13 weeks, at the optimized dose determined in the single-blind Phase, or to continue matching placebo for 13 weeks. Those randomized to placebo were to have been tapered off active medication during the first week of the double-blind Phase. Pain was to have been assessed by comparing average weekly pain scores to single-blind baseline with calculation of the percent reduction in pain score. Patients with less than 30% pain reduction relative to baseline, who discontinued due to lack of efficacy or who discontinued due to adverse events were to have been categorized as experiencing the event of loss of therapeutic response (LTR). All patients were to have completed a one week taper off study drug at the end of both the single-blind and double-blind Phases of the trial.

Figure 1  Study Design for Study 1224
**Inclusion Criteria:**
Patients were to have been included in the trial if all of the following criteria were met:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
2. Male or female of any race, at least 18 years of age, and using appropriate methods of contraception. Women of childbearing potential must have a confirmed negative serum pregnancy test prior to enrollment.
3. Patients must have pain present for more than 3 months after the healing of the herpes zoster skin rash.
4. At screening (V1) and enrollment (V2), patients must have a score of ≥4 on the pain NRS (1 week recall period).
5. At enrollment (V2), at least 4 pain diaries must be completed satisfactorily within the last 7 days and the average pain score must be ≥4.
6. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

**Exclusion Criteria:**
Patients were to have been excluded from the trial if any of the following were met:

1. Patients having other severe pain that may confound assessment or self-evaluation of the pain due to PHN.
2. Neurolytic or neurosurgical therapy for PHN.

Source: CSR Study 1224, p. 37

*Low creatinine clearance patients: 82.5-330 mg/day*
3. Skin conditions in the affected dermatome that could alter sensation.
4. Creatinine clearance (CLcr) ≤ 30 mL/min (estimated from serum creatinine).
5. Have failed pregabalin treatment due to lack of efficacy at efficacious doses (300 to 600 mg), have hypersensitivity or intolerance to pregabalin or other a2δ ligands (e.g. gabapentin), or have participated in a pregabalin clinical trial. Patients previously taking pregabalin IR may be eligible if they do not meet these exclusions.
6. Pregabalin use in the last 30 days. Subjects taking pregabalin in the last 30 days should be washed out of pregabalin for at least 30 days prior to screening visit.
7. Use of prohibited medications in the absence of appropriate washout periods.
8. Participation in any clinical trial within the 30 days prior to screening and/or during study participation.
9. Subjects with any clinically unstable cardiovascular, hematological, autoimmune, endocrine, renal, hepatic, retinal or gastrointestinal disease.
10. Any subject considered at risk of suicide or self-harm based on investigator judgment and/or the results of a risk assessment.
11. Screening ECG with any clinically significant abnormality.
12. Subjects with a history of life-threatening neoplasms within 5 years prior to study entry, other than carcinoma in situ of the cervix or basal cell carcinoma of the skin.
13. Subjects with active GI disease including any GI surgery that in the opinion of the investigator would interfere with the absorption of study medication. Conditions such as irritable bowel syndrome (IBS) are not excluded.
14. Subjects with difficulty swallowing tablets or unable to tolerate oral medication.
15. Platelet count < 100 x 10^9/L; white blood cell count < 2.5 x 10^9/L; neutrophil count < 1.5 x 10^9/L.
16. Clinically significant liver disease which may prevent the patient from completing the study, or an elevation in AST or ALT > 3x upper limit of normal, or Tbili > 2x upper limit of normal. Laboratory assays may be repeated once, prior to enrollment, to confirm unacceptability of any patient.
17. Alcohol or substance abuse or dependence within the previous year.
18. Are pregnant, nursing, or intend to become pregnant during the course of the trial.
19. Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into the trial.

Randomization Criteria:
For randomization into the double-blind Phase of the trial, patients were to have met the following criteria:

- Patients must have ≥ 50% mean pain improvement from single-blind baseline to the end
of single-blind Phase of the trial
- Patients must have at least 4 completed diaries within the last 7 days

Study Procedures:
The tables below provide an overview of the visits and procedures for the baseline visit, the SB Phase, and the DB phase of Study 1224.

Table 8  Schedule of Activities for Baseline Visit and SB Phase of Study 1224

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Baseline (1 week, V1 to V2)</th>
<th>Single-Blind Treatment Phase (6 weeks)</th>
<th>Single-Blind Follow-Up 9 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Visit No.</td>
<td>V0</td>
<td>V1</td>
<td>V2</td>
</tr>
<tr>
<td>Study Day</td>
<td>Washout</td>
<td>Screening</td>
<td>Clinic</td>
</tr>
<tr>
<td>Visit Window</td>
<td>N/A</td>
<td>N/A</td>
<td>+3 days</td>
</tr>
</tbody>
</table>

Observation/Procedure
- Informed Consent
- Inclusion/Exclusion
- Medical History
- Physical & Neurological Examination
- 12-Lead Electrocardiogram (ECG)
- Clinical Laboratory
- Review Hy’s Law (Drug Induced Liver Toxicity)
- Patient Health Questionnaire-8 (PHQ-8)
- Columbia Suicidality Severity Rating Scale (C-SSRS)
- Concomitant/Rescue Medications
- Study Medication Dispensing
- Daily Pain- and Sleep Diary
- Numeric Rating Scale for Pain (NRS-Pain)
- Brief Pain Inventory Short Form (BPI-SF)
- Patient Global Impression of Change (PGIC)
- Benefit, Satisfaction, Willingness to Continue Measure (BSW)
- Medical Outcomes Study Sleep Scale (MOS-SS)
- Short-Form 36 Health Survey (SF-36)
- Hospital Anxiety and Depression Scale (HADS)
- Pharmacokinetic Assessment
- Dosing Diary

Abbreviations: ET = early termination; FU = follow-up; N/A = not applicable; V = visit

Source: CSR Study 1224, pp. 48-49

Table 9  Schedule of Activities for DB Phase of Study 1224

Source: CSR Study 1224, pp. 48-49

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)
**Reviewer Comment:** The enrichment design of the trial (initial SB Phase with individual patient dose adjustment for 4 weeks and then fixed dose for 2 weeks) is reasonable as it selects for patients who are responsive to pregabalin ER.

**Washout/Visit 0**
Informed consent was to have been obtained prior to subjects undergoing any washout of prohibited medications.

**Screening/Visit 1 (1 week before Visit 2) – Clinic Visit**
The following procedures were to have been conducted at this visit:

- Obtain written informed consent unless previously obtained at Visit 0
- Review medical history, concomitant medications, prior treatments for PHN, any non-drug treatments and adverse events
- Complete weekly pain numeric rating scale (Pain-NRS)
- Complete physical examination including edema assessment and neurological examination

---

**Table: Study Phase Schedule**

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Double-Blind Treatment Phase (13 weeks)</th>
<th>Double-Blind FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Visit No.</td>
<td>V7</td>
<td>V8</td>
</tr>
<tr>
<td>End of Study Week</td>
<td>Week 0 (Randomization)</td>
<td>Week 11</td>
</tr>
<tr>
<td>Study Day:</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>Visit Type:</td>
<td>Clinic</td>
<td>Clinic</td>
</tr>
<tr>
<td>Visit Window:</td>
<td>±3 days</td>
<td>±3 days</td>
</tr>
</tbody>
</table>

**Observations/Procedures**

1. Physical and Neurological Examination
2. Electrocardiogram
3. Clinical Laboratory
4. Monitor Hy’s Law (Drug Induced Liver Toxicity, Hepatotoxicity)
5. Columbia Suicidality Severity Rating Scale (C-SSRS)
6. Adverse Events
7. Concomitant/Rescue Medication
8. Study Medication Disposition
9. Daily Pain- and Sleep Diary
10. Numeric Rating Scale for Pain (NRS-Pain)
11. Brief Pain Inventory Short Form (BPI-sf)
12. Patient Global Impression of Change (PGIC)
13. Medical Outcomes Study Sleep Scale (MOS-SS)
14. Short-Form 36 Health Survey (SF-36)
15. Hospital Anxiety and Depression Scale (HADS)
16. Pharmacokinetic Assessment
17. Dosing Diary

**Abbreviations:**
- ECG = electrocardiogram
- ET = early termination
- FU = follow-up
- V = visit

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Source: CSR Study 1224, p. 50
Clinical Review
Lisa Wiltrout
NDA 209501
Lyrica CR (pregabalin ER)

- Laboratory tests to include CBC, electrolytes, BUN/creatinine with estimation of serum Clcr using the Cockcroft and Gault equation, glucose, amylase, AST/ALT, total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, T4, thyroid stimulating hormone (TSH), B12, folate and urinalysis as well as serum pregnancy for females of childbearing potential
- 12-lead ECG
- Complete and review Columbia Suicidality Severity Rating Scale (C-SSRS) baseline and Patient Health Questionnaire-8 (PHQ-8) to determine whether risk assessment is required

For subjects who continued to meet eligibility criteria following completion of the above procedures, the following were to have been completed:
- Instruct each subject on daily completion of pain and sleep diaries
- Schedule the next clinic visit (Visit 2)

Suicidality Risk Assessment during Screening
The investigator was to have reviewed each subject’s medical history as well as the results of the C-SSRS baseline and the PHQ-8. The following criteria were to have indicated a potential risk and were to have triggered a risk assessment:
- PHQ-8 score ≥ 15
- Suicidal ideation with actual intent and/or plan in the past year based on C-SSRS assessment
- Any previous lifetime history of suicide behaviors based on C-SSRS assessment
- Investigator’s judgment that a risk assessment is required

If a subject met any of the criteria listed above and also met eligibility criteria for trial participation, then a risk assessment was to have been conducted by a qualified mental health professional (MHP). The investigator was to have obtained and reviewed the completed risk assessment before a subject was to have been allowed to continue in the trial. A written copy of the risk assessment was to have been included in the subject’s clinical record.

Enrollment/ Visit 2 (Day 1) – Clinic Visit
The following procedures were to have been conducted at this visit:
- Review concomitant medications, adverse events and any non-drug treatments
- Review screening labs for eligibility and for assessment of Hy’s Law
- Review pain and sleep diaries
- Complete weekly pain-NRS
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Review inclusion and exclusion criteria to determine if subjects meet study entry criteria

For subjects who continued to meet eligibility criteria following completion of the above procedures, the following were to have been completed:
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- Complete the Brief Pain Inventory – Short Form (BPI-sf), the Short Form 36 Health Survey (SF-36), the Medical Outcomes Study – Sleep Scale (MOS-SS), and the Hospital Anxiety and Depression Scale (HADS)
- Remind the subject to continue completing the daily pain and sleep diaries
- Dispense study medication and instruct subject to begin dosing the evening of Visit 2
- Schedule the next clinic visit (Visit 3)

Study Drug
Pregabalin ER tablets were to have been supplied by Pfizer in the following strengths: 82.5 mg, 165 mg and 330 mg. Study drug was to have been supplied as blinded capsules of pregabalin ER and matching placebo. Dosage strengths of 247.5 mg, 495 mg and 660 mg or matching placebo were to have been achieved by having subjects take two tablets daily in the evening. All study medication was to have been supplied in non-subject specific bottles. Documentation of study drug dispensation was to have been documented in the CRF with notation of the date of receipt by subject, the amount dispensed to subject and the amount returned by subject. Study drug was to have been dispensed at Visits 2, 3, 4, 5, 6, 7, 8, 9 and at Visit 10.

Dose Selection
In Phase 1 clinical pharmacology studies, specifically Study A0081174 and Study A0081206, the Applicant identified the 300 mg pregabalin ER formulation administered following an evening meal as the formulation most likely to support QD dosing given that this formulation achieved sustained plasma concentration-time profiles. The 300 mg pregabalin ER formulation also achieved AUC values comparable to that of the pregabalin IR 300 mg capsule - AUC values in the 85% to 91% range which met FDA’s acceptance criteria for bioequivalence based on AUC. In order to match the bioavailability of the pregabalin ER formulation with that of the IR formulation, the strengths of the pregabalin ER tablets for Phase 3 studies containing 82.5 mg, 165 mg or 330 mg of pregabalin per tablet. Additional data from clinical pharmacology study A0081225 showed that the pregabalin ER formulations were equivalent to the marketed pregabalin IR formulations based on AUC and were anticipated to support QD dosing. The doses of pregabalin ER were then selected based on the approved dosage and administration guidelines for the pregabalin IR formulation for the management of PHN as listed in the package insert. The dosage and administration guidelines recommend a starting dose of 150 mg/day divided BID to TID with an increase up to 300 mg/day divided BID to TID in the first week and then a maximum dose increase up to 600 mg/day divided BID to TID.

Study Drug Administration
Subjects were to have been instructed to take 1 or 2 tablets of study medication orally once daily within 1 hour after completion of the evening meal. Subjects were to have been specifically instructed not to take the tablet at the start of the evening meal. If subjects did not...
take the study medication within 1 hour of completion of the evening meal, then subjects were to have been instructed to take study medication prior to bedtime with food. If subjects did not take the study medication within 1 hour after completion of the evening meal or at bedtime, then subjects were to have been instructed to take study medication the following morning with food. Doses of study medication not taken by the following morning were to have been omitted and the next dose of study medication was to have been taken as regularly scheduled in the evening. Subjects were to have been provided enough study medication to cover the visit duration with adequate excess to cover the visit window. Subjects were to have returned any unused study medication in each bottle to the site. Any study medication errors and any associated adverse events were to have been captured on the adverse event page of the CRF and on the SAE form when appropriate. The Applicant was to have been notified in the event of a medication dosing error.

**Study Drug Dose Titration**

During the initial week of the single-blind Phase, subjects with normal CLcr were to have been treated with pregabalin ER 165 mg/day and subjects with low CLcr were to have been treated with pregabalin ER 82.5 mg/day. At each subsequent weekly visit (Visits 3, 4 and 5), study drug dose was to have been increased based on individual subject efficacy and tolerability. At Visit 3, pregabalin ER was to have been increased to 330 mg/day for normal CLcr or 165 mg/day for low CLcr in subjects who did not experience adequate pain relief at the starting dose and who tolerated treatment. The pregabalin ER dosage was to have been escalated further to 495 mg/day for normal CLcr or 247.5 mg/day for low CLcr at Visit 4 in subjects with insufficient pain relief and good tolerance of treatment. At Visit 5, the pregabalin ER dosage was to have been escalated one final time to 660 mg/day for normal CLcr and 330 mg/day for low CLcr in subjects with continued insufficient pain relief and good tolerance of treatment. At Visit 6, no further dose optimization was to have been permitted. For the last 2 weeks of the single-blind Phase of the study, subjects were to have remained on fixed dose pregabalin ER treatment at the optimized dose determined in the prior 4 weeks. Subjects unable to tolerate the fixed dose of study medication were to have been discontinued from the study.

**Method of Assigning to Treatment Groups/Blinding**

Subjects were to have been assigned a single subject identification number (SSID) at the time of screening using an Interactive Voice Response System (IVRS). This number was to have been retained throughout the study. A separate randomization number was to have been assigned by the IVRS at randomization and recorded in the CRF. Subjects were to have been informed before entry into the study of the potential to receive either pregabalin ER or placebo during the study. Subjects were to have been blinded to their treatment assignment during the entire course of the study. Subjects were also to have been blinded as to the point of transition from the SB to the DB Phase of the study. Investigators were to have been aware of subjects’ treatment during the SB Phase but blinded during the DB Phase. All subjects were to have received pregabalin ER during the first 6 weeks of the study (SB Phase) and were to have been
randomized to receive either pregabalin ER or placebo for the final 13 weeks of the study (DB Phase).

At the start of the study, investigational sites were to have been instructed on the appropriate method for breaking the blind. Blinding codes were to have been broken only in emergency situations for reasons of subject safety. The investigator was to have contacted Pfizer, Inc. before breaking the blind. The reason for breaking the blind was to have been documented and recorded in the CRF.

Suicidality Risk Assessment during the Study
Beginning with Visit 2, a risk assessment was to have been conducted by a qualified MHP if a subject had any positive responses to items 4, 5 or to any behavioral question on the C-SSRS (since the last visit version). This risk assessment was to have been conducted in order to determine whether it was safe for a subject to continue trial participation. Suicidal risk was to have been managed by the clinical investigator in conjunction with a qualified MHP. Additionally, the investigator was to have consulted the Applicant’s designated medical monitor to determine whether a subject could continue the trial. Using relevant information from the C-SSRS and the risk assessment, a narrative was to have been developed for subjects who underwent any post-baseline risk assessment. This narrative was to have been included in the subject’s medical record.

Visit 3 (Week 1) – Clinic Visit
The following were to have been completed at this visit:
- Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
- Remind subject to continue completing daily diaries
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Determine and discuss the pregabalin ER dosage to be administered
- Dispense study medication and provide instructions to subject for dose administration (blinding must be maintained with the subject)
- Schedule the next clinic visit (Visit 4)
- Remind subject to bring study medication (used and unused bottles) to the clinic visit

Visit 4 (Week 2) – Clinic Visit
The following were to have been completed at this visit:
- Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
- Remind subject to continue completing daily diaries
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
• Determine and discuss the pregabalin ER dosage to be administered
• Dispense study medication and provide instructions to subject for dose administration (blinding must be maintained with the subject)
• Schedule the next clinic visit (Visit 5)
• Remind subject to bring study medication (used and unused bottles) to the clinic visit

Visit 5 (Week 3) – Clinic Visit
The following were to have been completed at this visit:
• Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
• Remind subject to continue completing daily diaries
• Complete and review C-SSRS since last visit to determine whether risk assessment is required
• Determine and discuss the pregabalin ER dosage to be administered
• Dispense study medication and provide instructions to subject for dose administration (blinding must be maintained with the subject)
• Schedule the next clinic visit (Visit 6)
• Remind subject to bring study medication (used and unused bottles) to the clinic visit

Visit 6 (Week 4) – Clinic Visit
The following were to have been completed at this visit:
• Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
• Remind subject to continue completing daily diaries
• Complete and review C-SSRS since last visit to determine whether risk assessment is required
• Determine and discuss the pregabalin ER dosage to be administered
• Dispense study medication and provide instructions to subject for dose administration (blinding must be maintained with the subject)
• Schedule the next clinic visit (Visit 7)
• PK sampling
• Remind subject to bring study medication (used and unused bottles) to the clinic visit

End of Single-Blind Phase/ Randomization for Double-Blind Phase/ Visit 7 (Week 6) or Early Termination Visit – Clinic Visit
The following were to have been completed at this visit:
• Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
• Complete physical examination to include edema assessment and neurological examination
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Lyrica CR (pregabalin ER)

- Complete weekly pain-NRS
- Laboratory assessments with monitoring of labs for Hy’s Law
- PK sampling
- ECG only for subjects terminating from the study
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Complete the PGIC, BSW, BPI-sf, SF-36, MOS-Sleep Scale and HADS assessments

For subjects who discontinued from the study, the following were to have been completed:
- Dispense a bottle of taper medication
- Schedule follow up clinic visit in approximately 9 days
- Remind subject to continue completing the daily dosing diary
- Remind subject to bring study medication (used and unused) to the clinic visit

For subjects who had a ≥50% pain improvement relative to baseline, the following were to have been completed:
- Randomize the subject
- Dispense study medication and provide instructions to subject for dose administration
- Remind subject to continue completing daily diaries
- Schedule next clinic visit (Visit 8)
- Remind subject to bring study medication (used and unused) to the clinic visit

Study Drug Taper
Subjects who discontinued from the study at the end of the single-blind Phase were to have completed a taper off study medication with a follow up visit approximately 9 days after the start of the taper phase. The study medication taper schedule is described in the tables below:

Table 10  Study Medication Taper Schedule - Normal CLcr

<table>
<thead>
<tr>
<th>Pregabalin Dose</th>
<th>Taper Day 1 (mg QD)</th>
<th>Taper Day 2 (mg QD)</th>
<th>Taper Day 3 (mg QD)</th>
<th>Taper Day 4 (mg QD)</th>
<th>Taper Day 5 (mg QD)</th>
<th>Taper Day 6 (mg QD)</th>
<th>Taper Day 7 (mg QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>165 mg</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>330 mg</td>
<td>165</td>
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<td>165</td>
<td>165</td>
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<td>165</td>
<td>165</td>
</tr>
<tr>
<td>495 mg</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>660 mg</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
</tbody>
</table>

Abbreviations: QD = once daily, CLcr = creatinine clearance.

Source: CSR Study 1224, p.43

Table 11  Study Medication Taper Schedule - Low CLcr

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Reference ID: 4150575
Visit 8 (Week 11) and Visit 9 (Week 15) – Clinic Visits

The following were to have been completed at these visits:

- Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
- PK sampling at Visit 8 only
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Dispense study medication and provide instructions to subject for dose administration
- Schedule the next clinic visit (Visits 9 and 10 respectively)
- Remind subject to bring study medication (used and unused) to the clinic visit

End of Double-Blind Phase/ Visit 10 (Week 19) or Early Termination Visit – Clinic Visit

The following were to have been completed at this visit:

- Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
- Complete physical examination to include edema assessment and neurological examination
- Complete weekly pain-NRS
- Laboratory assessments with monitoring of labs for Hy’s Law
- ECG
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Complete the PGIC, BSW, BPI-sf, SF-36, MOS-Sleep Scale and HADS assessments
- PK sampling only for subjects terminating from the study early (before Visit 8)
- Dispense bottle of taper medication and provide instructions to subject for dose administration
- Schedule follow up visit in approximately 9 days

End of Single-Blind Phase Follow-up (Week 7) and End of Double-Blind Phase Follow-up/ Visit 11 (Week 20) – Clinic Visits
All subjects discontinuing from the study were to have completed a follow-up visit. Subjects who completed the study at the end of the single-blind Phase were to have completed an end of single-blind Phase follow-up visit. Subjects who completed the study at the end of the double-blind Phase were to have completed an end of double-blind Phase follow-up visit. Follow-up visits were to have been scheduled to occur approximately 9 days after the start of the study drug taper to allow for a 7-day taper and a 2-day pregabalin ER washout.

The following were to have been completed at these visits:
- Review adverse events, daily pain diary, daily sleep diary, daily dosing diary, concomitant medications, and non-drug treatments
- Complete and review C-SSRS since last visit to determine whether risk assessment is required
- Collect all used and unused study medication from each subject

Allowable Medications
The following classes of medications were to have been permitted during the study:

**Analgesics**
Subjects were to have been allowed to use narcotic and non-narcotic analgesics with a maximum dosage of 80 mg oral morphine equivalents per day. Subjects were to have been on stable doses of these medications for at least 30 days prior to Visit 1. Chronic therapy was not to have been initiated during the study. Subjects were to have been allowed to use acetaminophen at a maximum dose not to exceed 3 grams per day.

**Anti-inflammatories**
Subjects were to have been allowed to use NSAIDS and COX-2 inhibitors. Subjects were to have been on stable doses of these medications for at least 30 days prior to Visit 1. Chronic therapy was not to have been initiated during the study. Subjects were to have been allowed to use aspirin up to 325 mg per day for myocardial infarction and stroke prophylaxis.

**Antidepressants**
Subjects were to have been allowed to use tricyclic/other antidepressants, SSRIs, Effexor and Wellbutrin. Subjects were to have been on stable doses of these medications for 30 days prior to Visit 1. A maximum of one antidepressant may be used during the study.

**Benzodiazepines**
Subjects were to have been allowed to use lorazepam only if dose at bedtime and only if prescribed for sleep. Subjects were to have been on stable doses of this medication for at least 30 days prior to Visit 1. Therapy with this medication was not to have been initiated during the study. Diazepam was not to have been allowed.

Reference ID: 4150575
GABA<sub>A</sub> partial agonists
Subjects were to have been allowed to use zolpidem and eszopiclone. Subjects were to have been on stable doses of these medications for at least 30 days prior to Visit 1. Therapy with these medications was not to have been allowed during the study. These medications were not to have been used in conjunction with a benzodiazepine.

Prohibited Medications
Subjects were to have discontinued any prohibited concomitant medications before Visit 1. Prohibited medications were to have included but were not limited to those listed in the table below.

Table 12 Prohibited Medications

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Examples (not a comprehensive list)</th>
<th>Washout Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other medications used for relief of PHN</td>
<td>Benzodiazepines (if not given at a stable bedtime dose for sleep), skeletal muscle relaxants, and steroids</td>
<td>At least 7 days or 5 half-lives prior to Visit 1.</td>
</tr>
<tr>
<td>Local/topical agents for relief of PHN</td>
<td>Lidoderm patch or other local anesthetics, steroids, capsaicin, and topical opioid analgesics</td>
<td>At least 7 days prior to Visit 1 or 5 half-lives.</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, vigabatrin, gabapentin, and pregabalin (apart from study medication)</td>
<td>At least 7 days prior to Visit 1. Pregabalin use within 30 days prior to Visit 1 was prohibited.</td>
</tr>
<tr>
<td>Injections for relief of pain</td>
<td>Local anesthetics and steroids</td>
<td>At least 1 month prior to Visit 1.</td>
</tr>
</tbody>
</table>

This was not a comprehensive list and the study team was available to answer questions related to medications anytime. It was strongly encouraged that study management was to be consulted if there was any doubt about prohibited medications.

Source: CSR Study 1224, p. 46

Contraceptive Measures
Females were to have been surgically sterile, post-menopausal or were to have agreed to use of effective contraception during the study and for at least 30 days after treatment completion. Males were to have been surgically sterile or were to have agreed to use of effective contraception during the study and for at least 30 days after treatment completion. The choices of effective contraception were to have been determined by the principal investigator or a designated associate.
Compliance
Subjects were to have recorded dose and meal information daily in a diary. Study medication and administration compliance were to have been evaluated by the site at each clinic visit following Visit 2. Any compliance deviations were to have been recorded with an explanation provided. Dosing compliance was to have been derived using the following calculation:

\[
\% \text{ compliance} = \frac{\text{number of tablets taken}}{\text{number of tablets expected to have taken}} \times 100
\]

Subjects were to have been considered non-compliant with study medication dosing if the percentage compliance was < 80% or > 120% using the above calculation. Subjects’ participation in the study was to have been re-evaluated at a given visit for those who were non-compliant with study medication dosing and/or administration. Any discontinuation was to have been done in consultation with the Applicant.

Compliance with daily pain and sleep diary completion was also to have been evaluated at each clinic visit. Subjects were to have completed at least 8 daily pain and sleep diaries over each 14 day period (consecutive days) in the study. A protocol deviation was to have been recorded for each instance of completion of fewer than 8 daily pain or sleep diaries over the course of 14 days. Subjects’ participation in the study was to have been re-evaluated at a given visit for those who were non-compliant with diary completion. Any discontinuation was to have been done in consultation with the Applicant.

Subject Withdrawal
Subjects were to have been able to withdraw from the study at any time at their own request. Subjects were to have also been withdrawn at any time at the discretion of the investigator or the Applicant for safety or behavioral reasons or the inability of subjects to comply with protocol required study visits or procedures at a given site. Every effort was to have been made to contact any subjects who did not return for scheduled visits. Every effort was also to have been made to document subject outcome, if possible. Investigators were to have inquired about the subject’s reason for withdrawal, were to have requested the return of all unused study medication and were to have requested subjects return for a final visit if possible. The investigators were also to have followed-up with subjects regarding any unresolved adverse events. Subjects who withdrew from the study and also withdrew consent for disclosure of future information were to have no further evaluations and no additional data collected. The Applicant was to have retained and was to have continued to use any data collected before the subject’s withdrawal of consent.

Trial Endpoints

Efficacy Endpoints:
Primary Efficacy Endpoint
The primary efficacy endpoint was to have been the following:
Loss of Therapeutic Response (LTR) defined as either: 1) < 30% pain response relative to the SB baseline pain score or 2) patient discontinuation due to lack of efficacy or adverse events in the DB Phase of the study. SB baseline pain score was to have been defined as the mean of the last 7 observations prior to the start of the SB treatment. SB baseline pain score was to have been compared to the 7 day rolling average of daily pain responses in the DB treatment phase.

- Primary Efficacy Parameter: Daily Pain Diary
  - The primary efficacy endpoint was derived from information collected in the daily pain diary. The daily pain diary was to have been completed by subjects daily upon awakening using an IVRS. Subjects are asked to rate their pain during the previous 24 hours using a pain rating scale that consists of 11 points ranging from 0 (no pain) to 10 (worst possible pain). Daily pain diaries were to have been administered from Visit 1 (Baseline) through Visit 10 (End of DB Phase) or Early Termination.

Secondary Efficacy Endpoints
The secondary efficacy endpoints were to have been the following:

- Secondary LTR defined as both: 1) at least a 30% increase in the 5 days mean pain score (also defined as the 5 day rolling average of daily pain scores) during the DB treatment phase relative to the 5-day randomization baseline pain score and 2) a 5 days mean pain score ≥ 4. Subjects who discontinued due to lack of efficacy or adverse events in the DB Phase of the study were also counted as an LTR. The 5-day randomization baseline pain score was to have been compared to the 5 day rolling average of daily pain responses in the DB treatment phase.
  - Secondary Efficacy Parameter: Daily Pain Diary
    - The secondary LTR endpoint was derived from information collected in the daily pain dairy as described above for the primary efficacy parameter.

- Pain numeric rating scale (NRS) – 1 week recall period
  - Subjects are asked to rate their pain over the last week using a pain rating scale that consists of 11 points ranging from 0 (no pain) to 10 (worst possible pain).

- Medical Outcomes Study – Sleep Scale (MOS-SS) total score and each sub-domain
  - A self-administered, validated questionnaire consisting of twelve items that assess key constructs of sleep. Subjects are asked to recall sleep-related activities over the past week.

- Patient Global Impression of Change (PGIC)
  - A patient-rated instrument used in chronic pain and FM studies to rate change in a patient’s overall status.

- Short Form 36 Health Survey (SF-36)
  - A self-administered, validated questionnaire that measures numerous aspects of health to include physical functioning, social functioning, bodily pain, mental...
health, role limitations due to physical problems and/or emotional problems, vitality and general health perception over the past week.

- **Daily sleep interference diary**
  - A self-administered pain-related sleep interference rating scale that consists of 11 points ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes (unable to sleep due to pain)). Subjects are asked to rate how pain has interfered with their sleep during the past 24 hours. The daily sleep interference diary was to have been completed daily upon awakening. Sleep interference diaries were to have been administered from Visit 1 (Baseline) through Visit 10 (End of DB Phase) or Early Termination.

- **Hospital Anxiety and Depression Scale (HADS)**
  - A self-administered questionnaire designed to screen for the presence of a mood disorder in medically ill patients. Subjects are asked to recall how they have felt over the past week.

- **Brief Pain Inventory (BPI-sf)**
  - A self-administered questionnaire designed to assess the severity of and the impact of pain on daily functions during the preceding 24-hour period. Subjects are asked to recall their pain over the last 24 hours.

- **Benefit, Satisfaction, Willingness to Continue Measure (BSW)**
  - A questionnaire administered by the investigator or designated site personnel designed to capture the patient’s perception of the effect of treatment with regard to the relative benefit, their satisfaction and their willingness to continue on therapy.

**Safety Endpoints:**

The safety endpoints were to have been the following:

- Laboratory assessments at Visit 1, Visit 7/Termination and Visit 10/Termination
- Physical and neurological examinations to include vital signs, weight assessment and edema assessment at Visit 1, Visit 7/Termination and Visit 10/Termination
- ECGs at Visit 1 and Visit 10 or upon early termination from the study
- Suicidality assessment
  - Patient Health Questionnaire-8 (PHQ-8)
    - A self-administered version of the PRIME-MD diagnostic instrument for common mental disorders. The PHQ-8 is a validated subset of the PHQ-9 which is the depression module from the PRIME-MD which scores each of the 9 DSM-IV criteria as 0 (not at all) to 3 (nearly every day).
  - Sheehan-Suicidality Tracking Scale (S-STS)
    - An 8 item prospective rating scale administered by a clinician or subject through self-report that tracked treatment emergent suicidal
ideation and behaviors.
- This scale was used for subjects who entered the study prior to initiation of Amendment 3.
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
    - A semi-structured interview completed by a trained clinician used in this trial to provide a summary measure of suicidal risks.
    - This scale was used for subjects who entered the study after initiation of Amendment 3.

Pharmacokinetic Endpoints:

Pharmacokinetic (PK) samples were to have been collected at Visits 6, 7 and 8. Additional PK sampling was to have been required at the early termination visit for subjects who terminated from the study prior to completion of Visit 8. The blood samples were to have been collected from subjects at random times post-study drug dosing in order to provide a wide distribution of PK sample collection times post-dose. The time of the blood sample collection, the time of the last dose of study drug administration and the time of the meal prior to the last dose of study drug were to have been recorded.

Statistical Analysis Plan

Statistical Hypotheses
The null hypothesis for Study 1224 assumed that there was no difference between pregabalin ER and placebo. The alternative hypothesis assumed that there was a difference between pregabalin ER and placebo. The weight of treatment effects was to be estimated by use of adjusted means and associated 95% CIs. For survival analyses, the weight of treatment effects was to be estimated by use of median time and associated 95% CIs if estimable. Descriptive statistics were to be performed on the single-blind analysis set (SBAS) for the SB Phase of the study. The primary and secondary efficacy analyses were to be performed on the full analysis set (FAS) for the DB Phase of the study.

The Applicant selected a sample size in order to achieve 90% power to detect a difference in the primary endpoint, LTR, defined as <30% pain response relative to the SB baseline or subject discontinuation due to lack of efficacy or AEs during the DB Phase of the study. Data from a previous randomized withdrawal design study of pregabalin IR (Study A0081059) were used to estimate sample size for Study 1224. The Applicant originally estimated that a total of 74 LTR events would need to be observed in the DB Phase of the study. Therefore, the Applicant estimated that approximately 145 subjects would need to participate in the DB Phase of the study in order to yield 74 LTR events. It was further estimated that about 50% of the subjects who entered the SB Phase of the study would be eligible for randomization into the DB Phase of the study. Therefore, the Applicant estimated that 290 subjects would need to participate in the SB Phase of the study.
The Applicant tracked the total number of LTR events in both treatment arms during the DB Phase of the study. Given that a lower number of events than expected occurred during the tracking period, the number of subjects enrolled and randomized was increased in order to obtain the required number of LTR events (see Amendment 4 to the study protocol). The Applicant stated that the number of LTR events was not discussed with investigators or investigational site personnel and that the tracking of LTR events remained blinded with no reference to treatment arms. The Applicant concluded that this interim look at the data had no impact on Type I error rate.

Interim Analysis, Final Analyses, and Unblinding
For administrative reasons, an interim analysis (IA) was to be conducted by an external Data Monitoring Committee (DMC) statistician and clinician when approximately 45 LTR events were observed. If the conditional probability of success of the study was less than 40% based on the observed treatment hazard ratio, then a futility decision was to be made by the external DMC members in accordance with the IA charter. The IA results, excluding the futility decision, if applicable, were not to be disseminated to anyone outside the external DMC. No efficacy claim was to be allowed at the IA; therefore, no adjustment was made to the p-value on final analyses.
Final analyses were to be conducted after requirements for final release of the randomization codes were met and the official database was released.
The DMC charter was to have provided an explanation of the external DMC membership, responsibilities, rules of conduct, and meeting format.

Statistical Decision Rules
Survival analyses were to have been estimated using median time to event and associated 95% confidence intervals. The magnitude of treatment effects was to have been estimated using adjusted means and associated 95% confidence intervals. A two-sided 0.05 level was to have been applied when significance testing was to be used.

Analysis Sets:
Full Analysis Set
The full analysis set (FAS) is the primary efficacy analysis set. The FAS consists of all subjects randomized to the double blind Phase of the study who received at least one dose of study medication. Subjects were to have been reported under the treatment to which they were randomized.

Single-Blind Analysis Set
The single-blind analysis set (SBAS) consists of all subjects enrolled into the single-blind Phase of the study who received at least one dose of study medication.
Safety Analysis Set
The safety analysis set consists of all subjects who received at least one dose of study medication. Subjects were to have been reported under the treatment which they received.

Treatment Misallocations:
Treatment misallocations were to be handled in the following manner:
- Subjects who were treated in the SB Phase and randomized but not treated in the DB Phase were to have been excluded from the FAS as they did not take at least one dose of study medication in the DB Phase. They were to have been included in the SBAS and in the safety analysis.
- Subjects who were randomized but not treated in either the SB or DB phases were to have been excluded from the efficacy analyses (SBAS, FAS) and the safety analyses as they did not take any study medication.
- Subjects who were randomized but took the incorrect treatment in the DB Phase were to have been reported under their randomized treatment group for all efficacy analyses based on the FAS. These subjects were to have been included in the SBAS as well.

Primary Efficacy Analysis:
The primary efficacy analysis (time to LTR) was to have been performed on the FAS population using survival techniques to compare time to LTR between the pregabalin ER treatment group and the placebo treatment group. LTR was defined as any of the following in the DB Phase of the study:
- Less than 30% pain response relative to the SB baseline pain score
- Patient discontinuation due to lack of efficacy
- Patient discontinuation due to adverse events
Subjects who did not experience an LTR event were to have been analyzed as censored observations. Kaplan-Meier estimates were to have been calculated and the log-rank test was to have been used to compare the treatment groups. P-values, median times to LTR and 95% CIs were to have been presented if estimable. Missing values were not to have been replaced.

A secondary time to LTR (S-LTR) analysis was to have been performed on the FAS population, using the same survival techniques as used for the primary efficacy analysis, to compare the time to S-LTR between the pregabalin ER treatment group and the placebo treatment group. S-LTR was defined as the following in the DB Phase of the study:
- at least a 30% increase in the 5 days mean pain score (also defined as the 5 day rolling average of daily pain scores) during the DB treatment phase relative to the 5-day randomization baseline pain score; OR
- patient discontinuation due to lack of efficacy or AEs; AND
- 5 days mean pain score ≥ 4
Time to S-LTR was defined as the number of days from randomization to the date of the 5-day S-LTR, or the date of discontinuation due to lack of efficacy or AEs, whichever came first.
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In addition to the Kaplan-Meier analyses described above, secondary Cox proportional hazards model analyses were performed on time to LTR events, adjusting for 7-day SB baseline pain score on the FAS population for the primary analysis and for 5-day (prior to randomization) DB baseline pain score on the FAS population for the secondary S-LTR analysis.

Sensitivity Analyses of the Primary Endpoint:
Four sensitivity analyses of the primary endpoint were to have been performed to assess the robustness of the primary analysis by altering assumptions with regard to the censoring mechanism. Kaplan-Meier estimates were to have been performed on the following modified FAS populations:

- All subjects who withdrew from the study for any reason were assumed to have experienced LTR;
- Subjects who withdrew due to lack of efficacy prior to LTR but did not also experience LTR based on the daily pain diaries were defined as having experienced LTR. All other withdrawals (including AEs) were counted as censored;
- All subjects who withdrew within the first week of DB treatment were assumed to be censored, regardless of reason for withdrawal;
- Subjects who withdrew based on lack of efficacy, but did not also experience LTR based on the daily pain diaries were defined as censored rather than having experienced LTR.

An additional sensitivity analysis of the primary endpoint was created during the blinded review of protocol deviations and incorporated into the SAP with Amendment 2. This analysis was to have been performed using Kaplan-Meier estimates based on a modified FAS population that excluded subjects who experienced a dosing error that may have confounded randomization or the occurrence of an LTR. Those subjects who were to be excluded from the modified FAS had to meet the following criteria:

1) Subjects who received a higher dose than intended per protocol; and
2) Dosing error occurred within 2 weeks prior to randomization or prior to observed LTR; and
3) Dosing error was followed by a change in weekly mean pain score which then fulfilled randomization criteria (≥50% response from SB baseline) or met LTR criteria (≤30% response from SB baseline). Mean pain score data prior to the dosing error would otherwise not have qualified the subject for randomization or LTR criteria.

Secondary Analyses:
All secondary analyses were to have used analysis of covariance (ANCOVA) to compare changes from the relevant baseline score between the pregablin ER treatment group and the placebo treatment group for the DB Phase of the study using the FAS population. Analyses of secondary endpoints were to have been performed separately for data collected during the SB and DB Phases. Terms for the relevant baseline score, center, and treatment were to have been fitted in the model. This model was to have been used to estimate and present treatment

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differences, with associated 95% 2-sided CI’s and p-values. Adjusted means and 95% CI’s for each treatment group were to have been presented as well.

Handling of Missing Values:
For the primary efficacy analysis (time to LTR), the Applicant was to have handled dropouts in the following manner:
- Subjects who completed the DB Phase of the study or who withdrew not due to AEs or lack of efficacy prior to LTR were right-censored
- Subjects with no post-baseline observations were right-censored at DB Day 1
- Right-censoring is defined as a subject having no events up to a certain time point after which there are no additional data

For the primary efficacy analysis (time to LTR), the Applicant was to have handled missing data in the following manner:
- The method of last observation carried forward (LOCF) was to have been used for all endpoint analyses that occurred at more than 1 visit.
- For diary measures, the last 7 diary entries while on study drug were used to calculate the endpoint mean pain score and the endpoint mean sleep interference score. If less than 4 diary entries were present in the last 7 days, then the entries for the previous days were included until there were 4 non-missing pain entries.

Safety Analysis:
The safety analysis was to have included summaries of the following information:
- All AEs
- Repeated physical and neurological examinations
- Weight assessments
- Vital signs
- C-SSRS or S-STS results
- 12-lead ECG results
- Laboratory test results

Safety data was to have been presented separately for the SB (SBAS population) and DB (FAS population) phases of the study and as a combined analysis for the safety analysis set.

Protocol Amendments

[Original Protocol, February 15, 2010]
No subjects were enrolled under the original protocol.

Amendment 1, October 8, 2010
Amendment 1 was issued prior to enrolling any subjects in the trial. The following changes were made in this amendment:
- The original key secondary endpoints were removed.
MOS-SS total score and each sub-domain were changed to secondary endpoints.
Definition of LTR changed to include withdrawals due to AEs (as requested by FDA).
The sample size was increased in the SB Phase from 260 to 290 subjects and in the DB Phase from 130 to 145 subjects in order to capture a total of 74 LTR events in the DB Phase of the trial.

Amendment 2, November 11, 2010
Amendment 2 was issued prior to enrolling any subjects in the trial. This amendment incorporated the S-STS into clinical visits 3, 4 and 6 as FDA guidance requires monitoring of suicidality at all clinic visits.

Amendment 3, March 16, 2011
The following changes were made in this amendment:
- The suicidality assessment was changed from S-STS to C-SSRS (as requested by FDA). Subjects enrolled prior to the implementation of Amendment 3 were to complete the S-STS and subjects enrolled after implementation of Amendment 3 were to complete the C-SSRS. Data from both the S-STS and the C-SSRS were mapped to C-CASA categories which were then used to derive a summary of the suicidality assessment results.
- Definition of LTR changed to include withdrawals due to AEs (missed in Amendment 2).

Amendment 4, December 18, 2012
The following changes were made in this amendment:
- Addition of the secondary LTR endpoint – measurement of the 5 day rolling average pain score during DB Phase compared to the 5 day randomization baseline pain score - as a more sensitive definition to detect more LTRs (LTR events observed to date lower than anticipated).
- Increase the screening population to approximately 1100 subjects with goal to enroll 800 subjects in the SB Phase and randomize 400 subjects in the DB Phase in order to achieve the protocol targeted goal of 74 LTR events (LTR events observed to date lower than anticipated).
- A paragraph was added to explain the need for an interim analysis (IA) given the lower than expected rate of LTRs.
- A paragraph was added to explain that the trial will use an Internal Review Committee (IRC) to monitor safety and an external Data Monitoring Committee (DMC) to conduct the IA for futility.
- A clarification of the laboratory criteria that require further evaluation with regard to potential cases of drug-induced liver toxicity.
- A clarification of the SAE reporting period to include reporting all SAEs that occur in the post-active reporting period in order to align with EU ‘CT-3’ guidance and FDA final rule.
- Addition of a potential suicide risk criterion: PHQ-8 score ≥15
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- Clarification that medication errors are reportable events that must be documented in the CRF regardless of their association or lack of association with an AE (alignment with EU ‘CT-3’ guidance)

Data Quality and Integrity: Sponsor’s Assurance

[The Applicant has stated that periodic monitoring visits were conducted to ensure that the protocol and GCPs were followed. During these monitoring visits, the clinical sites provided the Applicant’s monitors with direct access to source documents. The monitors used these source documents to authenticate that the data recorded on CRFs were veracious. The clinical sites were also subject to inspection by regulatory authorities, to quality assurance audits by the Applicant and to review by the IRB or IEC. Study and site level oversight was provided by compliance oversight leads in order to ensure that the study met high quality standards. Compliance oversight leads conducted oversight both on-site and remotely to evaluate monitoring effectiveness and to ensure compliance with the study protocol by investigational sites according to local regulation, applicable standard operating procedures, and ICH/GCP.]

6.1.2. Study Results

Compliance with Good Clinical Practices

[The Applicant has provided attestation that Study 1224 was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidance for Good Clinical Practice (GCP) (International Conference on Harmonisation [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008).]

Financial Disclosure

[The Applicant has submitted financial disclosure information on Study 1224 for the time period from the start of the study through one year after completion of the study. The Applicant has submitted Debarment Certification and FDA form 3454 certifying that none of the financial interests or arrangements described in 21 CFR Part 54 exists for 525 of 535 clinical investigators who participated in the covered study listed above. The Applicant was unable to obtain a completed Financial Disclosure Form, despite multiple attempts, for the following seven clinical investigators who participated in Study 1224: Dr. Sundernag Ganjekar, Katherine M. Rogers, Dr. Diana L. Besleaga, Dr. Kerri D. Copponex, Dr. LaKeisha K. Crawford, Dr. Laura M. Tunke, and Dr. Brandon L. Williams. For those clinical investigators no longer at the institution where the study was conducted, the Applicant has certified that reasonable attempts were made to contact the clinical investigator to obtain disclosable financial information. The Applicant has identified no clinical investigators who were full-time or part-time employees of the sponsor of Study 1224.]

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the covered study. The Applicant has identified three clinical investigators who 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.

See the completed Clinical Investigator Financial Disclosure Review Form below.

**Covered Clinical Study (Name and/or Number): Study 1224**

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes ☒</th>
<th>No ☐ (Request list from Applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>535</td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are Sponsor employees (including both full-time and part-time employees):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

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)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payments of other sorts: 3
- Proprietary interest in the product tested held by investigator: 0
- Significant equity interest held by investigator in Sponsor of covered study: 0

<table>
<thead>
<tr>
<th>Is an attachment provided with details of the disclosable financial interests/arrangements:</th>
<th>Yes ☒</th>
<th>No ☐ (Request details from Applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is a description of the steps taken to minimize potential bias provided:</td>
<td>Yes ☒</td>
<td>No ☐ (Request information from Applicant)</td>
</tr>
<tr>
<td>Number of investigators with certification of due diligence (Form FDA 3454, box 3):</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Is an attachment provided with the reason:</td>
<td>Yes ☒</td>
<td>No ☐ (Request explanation from Applicant)</td>
</tr>
</tbody>
</table>

The Applicant has adequately disclosed financial interests with clinical investigators. Three investigators received payments from the Applicant exceeding $25,000 for consulting and as honorarium. Site enrolled patients (% of the study population), Site.
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enrolled (b)(4) patients (b)(4) % of the study population), and Site (b)(4) enrolled (b)(4) patients (b)(4) % of the study population) in the DB Phase of Study 1224. Each clinical investigator with a financial interest in excess of $25,000 provided a minimal contribution to the study data when the data are considered as a whole. Therefore, the clinical investigators with significant financial interests did not favorably influence the efficacy findings for this study.

Patient Disposition

[The disposition of subjects and the primary reasons for subject discontinuation in both the SB and DB phases of Study 1224 are summarized in the outline below.

Subject disposition during the single-blind/enrichment phase of the study:

Number of subjects screened for inclusion 1117
Number of subjects who received at least 1 dose of pregabalin ER in SB Phase 801
Number of subjects who discontinued from the study during the SB Phase 141 (17.6%)
Number of subjects who completed SB treatment 660 (82.4%)

Reasons for discontinuations during the SB Phase of the study:
- Study drug related adverse event 46 (5.7%)
- Insufficient clinical response 32 (4.0%)
- No longer willing to participate 29 (3.6%)
- Lost to follow-up 10 (1.2%)
- Protocol violation 8 (1.0%)
- Other 8 (1.0%)

Subject disposition during the double-blind Phase of the study:

Number of subjects screened for inclusion in DB Phase 660 (82.4%)
Number of subjects discontinued from study before randomization 242 (30.2%)
Number of subjects randomized 418 (52.2%*)
Number of subjects randomized but discontinued before receiving treatment 5
Number of subjects who received at least 1 dose of pregabalin ER in DB Phase 413 (51.6%)
- pregabalin ER treatment group 208 (26.0%)
- placebo treatment group 205 (25.6%)
Number of subjects who discontinued from the study during the DB Phase 71 (17.2%)
- pregabalin ER treatment group 26 (12.5%)
- placebo treatment group 45 (22%)
Number of subjects who completed DB treatment 342 (82.8%)
- pregabalin ER treatment group 182 (87.5%)
- placebo treatment group 160 (78%)

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Reasons for discontinuation from DB Phase of study for pregabalin ER treatment group:
- Other 7 (3.4%)
- No longer willing to participate 6 (2.9%)
- Study drug related AE 5 (2.4%)
- Protocol and GCP non-compliance 4 (1.9%)
- Insufficient clinical response 2 (1.0%)

Reasons for discontinuation from DB Phase of study for placebo treatment group:
- No longer willing to participate 15 (7.3%)
- Insufficient clinical response 11 (5.4%)
- Study drug related AE 7 (3.4%)
- Other 4 (2.0%)
- Protocol and GCP non-compliance 3 (1.5%)

Reviewer comment: Subjects have been appropriately accounted for by the Applicant throughout Study 1224. The most common reasons for discontinuation during the SB Phase of the study were study drug related adverse events, insufficient clinical response and no longer willing to participate. The most common reasons for discontinuation during the DB Phase of the study for pregabalin ER treated subjects were “other”, no longer willing to participate, and study drug related AEs. The most common reasons for discontinuation during the DB Phase of the study for placebo treated subjects were no longer willing to participate, insufficient clinical response, and study drug related AEs. More subjects in the placebo treatment group than in the pregabalin ER treatment group discontinued due to insufficient clinical response, due to no longer willing to participate, or due to study drug related AEs. Fewer subjects in the placebo treatment group than in the pregabalin ER treatment group discontinued due to “other”. The rate of discontinuation due to protocol and GCP non-compliance was comparable between both treatment groups.

The percentage result for number of subjects randomized is asterisked because I included my percentage calculation of 52.2% instead of the Applicant’s percentage calculation of 51.5%. I concluded that the Applicant made a minor mathematical error when calculating this result – 418/801 x 100 = 52.2% (not 51.5%).

Protocol Violations/Deviations

[Overall, 188 subjects (23.5%) had one major protocol violation and 197 subjects (24.6%) had one minor protocol violation during the course of Study 1224. The most frequent major protocol violations were in the category of IP administration and study treatment with 88 (11%) occurrences and 89 (11%) occurrences in the SB and DB phases, respectively. The rate of major protocol violations was comparable between the pregabalin ER treatment group and the placebo treatment group in the DB Phase of the study as detailed in Table 13.]
Table 13  Major Protocol Deviations by Category and by Treatment Assignment

<table>
<thead>
<tr>
<th>Issue category</th>
<th>Pregabalin CR SB(^a)</th>
<th>SB Pregabalin CR → DB Pregabalin CR(^b)</th>
<th>SB Pregabalin CR → DB Placebo(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE/SAE</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Disallowed Medications</td>
<td>5 (0.6%)</td>
<td>6 (0.7%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>8 (1.0%)</td>
<td>4 (0.5%)</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Informed Consent</td>
<td>4 (0.5%)</td>
<td>3 (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>IP Administration and Study Treatment</td>
<td>88 (11%)</td>
<td>44 (5.5%)</td>
<td>45 (5.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (3.6%)</td>
<td>14 (1.7%)</td>
<td>15 (1.9%)</td>
</tr>
<tr>
<td>Procedures/Tests</td>
<td>11 (1.4%)</td>
<td>4 (0.5%)</td>
<td>5 (0.6%)</td>
</tr>
</tbody>
</table>

A total of 108 medication errors were identified in 64 out of 801 treated subjects during Study 1224. The majority of errors (102 out of 108) occurred during the SB dose optimization phase. Six medication errors occurred during DB treatment. The medication errors were grouped as follows:

- Subject dose administration errors (subject misunderstanding of dosing instructions; 50 errors)
- Site dispensing errors (site personnel giving incorrect dosing instructions; 31 errors)
- IVRS dispensing errors (programming errors leading to incorrect bottle dispensing; 18 errors)
- Site data entry errors (incorrect entry of subject’s CLcr value with subsequent dispensing of incorrect medication dosage; 9 errors)

The Applicant and the study teams conducted safety reviews of all medication errors and determined that none of the errors resulted in any SAEs. Non-serious AEs that occurred in subjects with medication errors were consistent with AEs seen during the study as well as the known safety profile of pregabalin. Sixty subjects with medication errors were randomized to the DB Phase. Of these 60 subjects, two subjects whose medication errors may have positively impacted their fulfillment of DB randomization criteria were identified. An efficacy sensitivity
analysis excluding these two subjects was conducted and did not reveal any difference in interpretation of the primary efficacy results. The Applicant concluded that medication errors did not adversely impact data integrity or data quality for either safety or efficacy.]

**Table of Demographic Characteristics**

[The demographic characteristics for the pregabalin ER and placebo treatment groups in the DB Phase of Study 1224 were similar with respect to age, gender, race, and weight. The mean age was 61.9 in the pregabalin ER group and 62.2 in the placebo group. More than half of the subjects were female in both groups – 64.4% in the pregabalin ER group and 59.5% in the placebo group. The majority of subjects were white for both groups – 76.0% in the pregabalin ER group and 77.1% in the placebo group. The mean weight for subjects was 77.8 kg in the pregabalin group and 76.8 in the placebo group. See the table below for details.]

**[Table 14 Demographic Characteristics for Pregabalin ER and Placebo Treatment Groups in the DB Phase for Study 1224]**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Pregabalin ER (N=208) (100.0%)</th>
<th>Placebo (N=205) (100.0%)</th>
<th>Total (N=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>74 (35.6%)</td>
<td>83 (40.5%)</td>
<td>157 (38.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>134 (64.4%)</td>
<td>122 (59.5%)</td>
<td>256 (62.0%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>61.9 (13.5)</td>
<td>62.2 (13.9)</td>
<td>62.1 (13.7)</td>
</tr>
<tr>
<td>Min, max (years)</td>
<td>22, 86</td>
<td>21, 85</td>
<td>21, 86</td>
</tr>
<tr>
<td><strong>Age Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18 – 44 years</td>
<td>26 (12.5%)</td>
<td>24 (11.7%)</td>
<td>50 (12.1%)</td>
</tr>
<tr>
<td>45 – 64 years</td>
<td>86 (41.3%)</td>
<td>78 (38.0%)</td>
<td>164 (39.7%)</td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>96 (46.2%)</td>
<td>103 (50.2%)</td>
<td>199 (48.2%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>158 (76.0%)</td>
<td>158 (77.1%)</td>
<td>316 (76.5%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>31 (14.9%)</td>
<td>36 (17.6%)</td>
<td>67 (16.2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (4.8%)</td>
<td>8 (3.9%)</td>
<td>18 (4.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.3%)</td>
<td>3 (1.5%)</td>
<td>12 (2.9%)</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean kg (SD)</td>
<td>77.8 (19.3)</td>
<td>76.8 (17.5)</td>
<td>77.3 (18.4)</td>
</tr>
<tr>
<td>Min, Max (kg)</td>
<td>43.4, 179.2</td>
<td>40.0, 135.6</td>
<td>40.0, 179.2</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

[Other relevant baseline characteristics for the pregabalin ER treatment group and the placebo treatment group in the DB Phase of Study 1224 are presented in the table below. The pregabalin ER treatment group and the placebo treatment group were comparable with respect to creatinine clearance (CLcr) at screening, duration since diagnosis of PHN in years, and other diseases present at screening.]

Table 15 Other Baseline Characteristics for Pregabalin ER and Placebo Treatment Groups in the FAS Population

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Pregabalin ER (N=208) (100%)</th>
<th>Placebo (N=205) (100%)</th>
<th>Total (N=413)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening CLcr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&gt;30 and &lt;60 mL/min)</td>
<td>37 (17.8%)</td>
<td>41 (20.0%)</td>
<td>78 (18.9%)</td>
</tr>
<tr>
<td>Mean mL/min (SD)</td>
<td>50.2 (6.7)</td>
<td>48.0 (6.7)</td>
<td>49.1 (6.7)</td>
</tr>
<tr>
<td>Min, max (mL/min)</td>
<td>32.0, 59.0</td>
<td>33.0, 59.0</td>
<td>32.0, 59.0</td>
</tr>
<tr>
<td>Normal (≥60 mL/min)</td>
<td>171 (82.2%)</td>
<td>164 (80.0%)</td>
<td>335 (81.1%)</td>
</tr>
<tr>
<td>Mean mL/min (SD)</td>
<td>96.8 (35.1)</td>
<td>94.1 (27.6)</td>
<td>95.5 (31.4)</td>
</tr>
<tr>
<td>Min, max (mL/min)</td>
<td>60.0, 322.0</td>
<td>60.0, 191.0</td>
<td>60.0, 322.0</td>
</tr>
<tr>
<td>Duration since diagnosis of PHN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years</td>
<td>2.7</td>
<td>2.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Min, max (years)</td>
<td>0.0, 36.7</td>
<td>0.1, 40.1</td>
<td>0.0, 40.1</td>
</tr>
<tr>
<td>Another disease present at screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI disorder</td>
<td>43 (21.0%)</td>
<td>45 (21.6%)</td>
<td>88 (21.3%)</td>
</tr>
<tr>
<td>GE reflux disease</td>
<td>19 (9.3%)</td>
<td>23 (11.1%)</td>
<td>42 (10.2%)</td>
</tr>
<tr>
<td>Immunology disorder</td>
<td>23 (11.2%)</td>
<td>26 (12.5%)</td>
<td>49 (11.9%)</td>
</tr>
<tr>
<td>Seasonal allergies</td>
<td>15 (7.3%)</td>
<td>21 (10.1%)</td>
<td>36 (8.7%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>77 (37.6%)</td>
<td>61 (29.3%)</td>
<td>138 (33.4%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>20 (9.8%)</td>
<td>13 (6.3%)</td>
<td>33 (8.0%)</td>
</tr>
<tr>
<td>MS and connective tissue disorders</td>
<td>53 (25.9%)</td>
<td>65 (31.3%)</td>
<td>118 (28.6%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>20 (9.8%)</td>
<td>24 (11.5%)</td>
<td>44 (10.6%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>89 (43.4%)</td>
<td>100 (48.1%)</td>
<td>189 (45.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>70 (34.1%)</td>
<td>78 (37.5%)</td>
<td>148 (35.8%)</td>
</tr>
</tbody>
</table>

Source: CSR Study 1224, pp. 94-98]
Treatment Compliance, Concomitant Medications, and Rescue Medication Use

[The proportion of subjects on prior medications before start of the study was comparable between the pregabalin ER treatment group and the placebo treatment group for the DB Phase of Study 1224. In the pregabalin ER treatment group, 172 subjects (82.7%) were on prior medications before the start of the study. In the placebo treatment group, 159 subjects (77.6%) were on prior medication before the start of the study. The more common medications taken prior to Study 1224 were as follows: acetylsalicylic acid, gabapentin, paracetamol, simvastatin, multivitamins, lisinopril, and ibuprofen. The washout period for most prohibited medications was 7 days or 5 half-lives (whichever was greater) prior to Visit 1. The washout period for pregabalin was 30 days prior to Visit 1.

The proportion of subjects having any concomitant medications was also comparable between treatment groups in the DB Phase. In the pregabalin ER treatment group 166 subjects (79.8%) were using concomitant medications during the study. In the placebo treatment group, 157 subjects (76.6%) were using concomitant medications during the study. The more common concomitant medications used during Study 1224 included the following: acetylsalicylic acid, paracetamol, simvastatin, multivitamins, lisinopril, ibuprofen, and omeprazole.

Subjects were generally compliant with study treatment during both phases of the study. In the SB Phase, 755 subjects (94.3%) had overall compliance ranging from >90% to 100%. In the DB Phase, 203 subjects (97.6%) in the pregabalin ER treatment group and 199 subjects (97.1%) in the placebo arm had overall compliance ranging from >90% to 100%.

Table 16  Study Medication Compliance Overall
With regard to medication compliance within one hour of any meal, 739 (92.3%) had >90 to 100% compliance during the SB Phase. In the pregabalin ER treatment group, 200 subjects (96.2%) had >90 to 100% medication compliance during the DB Phase. In the placebo treatment group, 196 subjects (95.6%) had >90 to 100% compliance during the DB Phase. The medication compliance rate when medication was dosed within one hour of any meal was comparable between treatment groups during the DB Phase of Study 1224.

### Table 17  Study Medication Compliance within 1 Hour of Any Meal

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Pregabalin CR SB N=801</th>
<th>Pregabalin CR DB N=208</th>
<th>Placebo DB N=205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>17 (2.1)</td>
<td>5 (2.4)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>80% to 90%</td>
<td>32 (4.0)</td>
<td>1 (0.5)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>&gt;90%-100%</td>
<td>739 (92.3)</td>
<td>200 (96.2)</td>
<td>196 (95.6)</td>
</tr>
<tr>
<td>&gt;100%-120%</td>
<td>4 (0.5)</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>&gt;120%</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>97.8 (6.17)</td>
<td>98.5 (5.05)</td>
<td>98.7 (3.0)</td>
</tr>
<tr>
<td>Range</td>
<td>16.7 - 102.6</td>
<td>56.1 - 102.5</td>
<td>81.2 - 100.7</td>
</tr>
</tbody>
</table>

Source: Section 14.4, Table 14.4.1.4.13.3

Abbreviations: CR = controlled release; DB = double-blind; N = number of subjects in treatment group; SB = single-blind; SD = standard deviation

1 Overall refers to SB phase in pregabalin SB column and DB phase in pregabalin DB and Placebo DB columns.
With regard to medication compliance within one hour of the evening meal, 662 subjects (82.6%) had >90% to 100% compliance during the SB Phase. In the pregabalin ER treatment group, 182 subjects (87.5%) had >90 to 100% medication compliance during the DB Phase. In the placebo treatment group, 185 subjects (90.2%) had >90% to 100% medication compliance during the DB Phase. Consequently, the medication compliance rate when medication was dosed within one hour of the evening meal (as recommended in labeling) was comparable between treatment arms during the DB Phase of the study.

**Table 18  Study Medication Compliance within One Hour of the Evening Meal**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Pregabalin CR SB N=801</th>
<th>Pregabalin CR DB N=208</th>
<th>Placebo DB N=205</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>64 (8.0)</td>
<td>14 (6.7)</td>
<td>8 (3.9)</td>
</tr>
<tr>
<td>80% to 90%</td>
<td>59 (7.4)</td>
<td>10 (4.8)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>&gt;90% to 100%</td>
<td>662 (82.6)</td>
<td>182 (87.5)</td>
<td>185 (90.2)</td>
</tr>
<tr>
<td>&gt;100% to 120%</td>
<td>2 (0.2)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>&gt;120%</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>94.6 (12.49)</td>
<td>95.2 (12.76)</td>
<td>96.5 (10.82)</td>
</tr>
<tr>
<td>Range</td>
<td>4.1 - 102.5</td>
<td>4.1 - 102.5</td>
<td>9.8 - 100.7</td>
</tr>
</tbody>
</table>

Source: Section 14.4, Table 14.4.1.4.13.2
Abbreviations: CR = controlled release; DB = double-blind; N = number of subjects in treatment group; SB = single-blind; SD = standard deviation.
1 Overall refers to SB phase in pregabalin SB column and DB phase in pregabalin DB and placebo DB columns.

**Efficacy Results – Primary Endpoint**

[The Applicant selected time to LTR as the primary endpoint for Study 1224. However, DAAAP recognizes the landmark endpoint of change in pain from baseline to end-of-therapy as more clinically meaningful than time to LTR and, therefore, most applicable when determining drug efficacy. The Applicant was informed of the importance of the landmark endpoint in an FDA advice letter dated August 2010 and again at the pre-NDA meeting in April 2016. Consequently, I will present the Applicant’s efficacy results on change in pain as the primary endpoint and the Applicant’s efficacy results on time to LTR as one of the secondary endpoints.

**Change in Mean Daily Pain (NRS-Pain)**
The pregabalin ER treatment group showed a decrease in mean daily pain score from SB baseline to DB endpoint as compared to the placebo treatment group. The numeric result was a statistically significant least square (LS) means difference of -0.9. The pregabalin ER
treatment group also showed a decrease in mean daily pain score from DB baseline to DB endpoint as compared to the placebo treatment group. The numeric result was a statistically significant LS means difference of -0.9 (see Table 28 below).

Table 19 Change in Mean Daily Pain Scores at DB Endpoint (Week 19) - FAS Population (LOCF)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>LS Mean</th>
<th>SE</th>
<th>LSMD</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SB baseline to DB endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin CR</td>
<td>206</td>
<td>-4.9</td>
<td>0.12</td>
<td>-0.9</td>
<td>(-1.26, -0.62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>-4.0</td>
<td>0.12</td>
<td>-0.9</td>
<td>(-1.21, -0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DB baseline to DB endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin CR</td>
<td>206</td>
<td>0.0</td>
<td>0.11</td>
<td>-0.9</td>
<td>(-1.21, -0.61)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>205</td>
<td>0.9</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval; CR=controlled release; DB=double-blind; FAS=full analysis set; LS=least squares; LSMD=differences in least squares means; n=number of subjects with data analysed; SB=single-blind; SE=standard error.

Note: Decreases in scores indicate improvement.
Note: SB baseline refers to Visit 2 (Enrollment); DB baseline refers to Visit 7 (Week 6).
Note: Estimates and p-values are from an analysis of covariance main effects model with baseline value, pooled center decided before unblinding, and treatment in the model.

Source: Study 1224 CSR, Table 27, p. 110

Reviewer Comment: The primary statistical reviewer, Yan Zhou, Ph.D., was able to replicate the Applicant’s results for change in pain using the LOCF imputation method; however, the FDA does not view LOCF as an acceptable imputation method. Therefore, the statistician conducted another primary analysis of the change in pain endpoint using the multiple imputation method. The results showed a statistically significant LS mean difference from SB baseline and DB baseline to DB endpoint in favor of pregabalin ER. Please see the statistical review of Dr. Yan Zhou for more details.

Change in Mean Weekly Pain Score (NRS – 1 week recall)
The pregabalin ER treatment group showed a decrease in mean weekly pain score from SB baseline to DB endpoint as compared to the placebo treatment group. The numeric result was a statistically significant LS means difference of -1.1. The pregabalin ER treatment group also showed a decrease in mean weekly pain score from DB baseline to DB endpoint as compared to the placebo treatment group. The numeric result was a statistically significant LS means difference of -1.0 (see Table 29 below).
Clinical Review
Lisa Wiltrout
NDA 209501
Lyrica CR (pregabalin ER)

Table 20  Change in Mean Weekly Pain Scores at DB Endpoint (Week 19) - FAS Population (LOCF)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Mean</th>
<th>SE</th>
<th>LSMD</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin CR</td>
<td>-5.0</td>
<td>0.13</td>
<td>-1.1</td>
<td>-1.47, -0.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>-3.9</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregabalin CR</td>
<td>-0.1</td>
<td>0.13</td>
<td>-1.0</td>
<td>-1.34, -0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.9</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Section 14.2, Table 14.2.3.1.
Abbreviations: CI = confidence interval; CR = controlled release; DB = double-blind; FAS = full analysis set; LS = least squares; LSMD = differences in least squares means; n = number of subjects with data analysed; NRS-Pain = Numeric Rating Scale for Pain; SB = single-blind; SE=standard error.
Note: Decreases in scores indicate improvement.
Note: SB baseline refers to Visit 2 (Enrollment); DB baseline refers to Visit 7 (Week 6).
Note: Estimates and p-values are from an analysis of covariance main effects model with SB baseline value, center, and treatment in the model.

Efficacy Results - Sensitivity Analyses of the Primary Efficacy Endpoint

[No sensitivity analyses of the change in pain endpoint were conducted by the Applicant.]

Data Quality and Integrity – Reviewers’ Assessment

[This NDA was submitted in Electronic Common Technical Document (eCTD) format. The datasets were submitted in SAS format. Earlier in the review process, the review team identified that the Applicant did not submit SDTM datasets for the pivotal clinical trials (Studies 1224 and 1245). An information request was sent in the 74-day letter and a teleconference was held on March 9, 2017 with the Applicant, the clinical team, and the statistical team to clarify the missing data needed for completion of FDA’s statistical review of this NDA. Subsequent to this teleconference, the Applicant successfully submitted the necessary SDTM datasets and statistical programming requested by the FDA on March 23, 2017.

I noted some minor mathematical errors during my review of the safety data for this NDA – none of these mathematical errors had any impact on the findings of safety for pregabalin ER. I also noted a number of inconsistencies between the clinical safety narratives and the case report forms submitted by the Applicant – medical diagnoses listed in the clinical safety narrative as possible causality for an SAE but not documented in the CRF; incorrect medical diagnoses documented in PMH section of the CRF; or medical diagnoses documented in the...
PMH section of the CRF but no corresponding medication documented in the medication section of the CRF. I queried the Applicant regarding a small portion of these inconsistencies and the Applicant replied with plausible explanations for the inconsistencies. I concluded that these inconsistencies had no impact on the findings of safety for pregabalin ER.

I found no additional issues with the quality or integrity of the submission that affected my ability to complete this review. The Applicant responded to clinical information requests in a timely manner. Currently, there are no outstanding clinical information requests.

Efficacy Results – Secondary and other relevant endpoints

Time to LTR
The Applicant used the prespecified FAS population to analyze the efficacy of pregabalin ER using Kaplan-Meier estimates of time to LTR for the DB Phase of the study. The prespecified primary efficacy endpoint was time to LTR defined as <30% pain response as compared to the SB baseline pain score or subject discontinuation due to lack of efficacy or AEs in the DB Phase of the study. Ninety-two subjects experienced an LTR event. Of these 92 subjects, 29 subjects (13.9%) were in the pregabalin ER treatment group and 63 subjects (30.7%) were in the placebo treatment group. The results of the Kaplan-Meier analysis showed statistical significance in favor of pregabalin ER (p<0.0001). See the Kaplan-Meier plots in the figure below.

Figure 3 Kaplan-Meier Plot of Time to LTR in the DB Phase of Study 1224 (FAS Population)
The Applicant was unable to estimate the median time in days from randomization to LTR during the DB Phase as less than half of the subjects in both treatment groups experienced LTR during the DB Phase of the study. The first quartile time to LTR for the placebo treatment group was 46 days. The first quartile time to LTR for the pregabalin ER treatment group was not estimable because less than one quarter of subjects experienced LTR during the DB Phase. See the table below for a summary of the Kaplan-Meier estimates.

**Table 21** Kaplan-Meier Estimates of Time to LTR in the DB Phase of Study 1224 (FAS Population)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>1st quartile (days)</th>
<th>95% CI</th>
<th>Median</th>
<th>95% CI</th>
<th>p-value (log-rank test)</th>
<th>Failed</th>
<th>Censored</th>
<th>Percent censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>205</td>
<td>46</td>
<td>31-77</td>
<td>-</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>63</td>
<td>142</td>
<td>69.27</td>
</tr>
<tr>
<td>Pregabalin CR</td>
<td>208</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>&lt;0.0001</td>
<td>29</td>
<td>179</td>
<td>86.06</td>
</tr>
</tbody>
</table>

Source: Study 1224 CSR, Figure 3, p. 106
Secondary Loss of Therapeutic Response (S-LTR) Endpoint

An analysis of the S-LTR endpoint, based on the 5-day rolling average pain diary results, was performed on the FAS population. The number of subjects experiencing S-LTR was smaller in the pregabalin ER treatment group (49 out of 208 subjects; 23.6%) as compared to the placebo treatment group (87 out of 205 subjects; 42.2%) and showed statistical significance in favor of the pregabalin ER treatment group (p<0.0001).

Figure 4 Kaplan-Meier Plot of Time to Five Day Rolling Average LTR in the DB Phase of Study 1224 (FAS Population)

Source: CSR Study 1224, Figure 14.2.1.12, p. 527

Continuous Responder Rates
Responder rates (defined as 30% and 50% improvement from BL to DB endpoint) were analyzed using the Cochran-Mantel-Haenszel (CMH) method with missing values replaced according to the LOCF approach for the DB phase. At the DB endpoint, 197 subjects (95.6%) in the pregabalin ER group and 171 subjects (83.8%) in the placebo group had at least a 30% reduction in mean pain score. At the DB endpoint, 182 subjects (88.3%) in the pregabalin ER group and 140 subjects (68.6%) in the placebo group had at least a 50% reduction in mean pain score. This above-mentioned information is presented in the table below.

**Table 22** Analysis of 30% and 50% Responder Rates at DB Endpoint in Study 1224 - FAS Population (using LOCF)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Responder</th>
<th>Pregabalin DB (n=206)</th>
<th>Placebo DB (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NUMBER OF SUBJECTS ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>responder</td>
<td>197 (95.6)</td>
<td>171 (83.8)</td>
</tr>
<tr>
<td></td>
<td>nonresponder</td>
<td>9 (4.4)</td>
<td>33 (16.2)</td>
</tr>
<tr>
<td>30% responders</td>
<td>p-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>50% responders</td>
<td>NUMBER OF SUBJECTS ASSESSED</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>responder</td>
<td>182 (88.3)</td>
<td>140 (68.6)</td>
</tr>
<tr>
<td></td>
<td>nonresponder</td>
<td>24 (11.7)</td>
<td>64 (31.4)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

FAS = Full Analysis Set, DB = Double-Blind
Source: CSR Study 1224, Table 14.2.1.9.1, p. 358

**Other Endpoints (Mean Daily Sleep Interference Scores, MOS-SS, BPI-sf, PGIC, SF-36, HADS, and BSW)**

The Applicant analyzed numerous other secondary endpoints that assessed different aspects of sleep; pain severity and pain interference indices; patient global impression of change; physical, social, and emotional functioning; anxiety and depression; and subjects’ satisfaction with treatment, perceived benefit from treatment, and willingness to continue treatment. Some of these analyses produced statistically significant results in favor of pregabalin ER and some of these analyses trended in favor of pregabalin ER but did not yield statistical significance. The Applicant is not using any of these secondary endpoints to support labeling claims for pregabalin ER; therefore, I will not review any of these secondary endpoints in detail.

**Dose/Dose Response**

[The pregabalin ER tablet dose strengths of 165 mg, 330 mg, 495 mg, and 660 mg selected for Study 1224 were chosen to correspond with Lyrica capsule doses of 150, 300, 450, and 600 mg/day as is recommended in the approved label dosing guidelines for Lyrica capsules for the management of PHN. Treatment was adjusted based on CLcr with lower dose strengths of pregabalin ER tablets - 82.5 mg, 165 mg, 247.5 mg and 330 mg - given to those with impaired
renal function. The dose optimization approach allowed for flexible dosing during the first four weeks of the SB Phase, and then fixed dosing at the optimized dose level for the last two weeks of the SB Phase and the entire DB phase. In total, six pregabalin ER dose groups (82.5 mg, 165 mg, 247.5 mg, 330 mg, 495 mg, and 660 mg) were evaluated for efficacy in Study 1224.

The Applicant conducted clinical pharmacology studies that demonstrated the following information in support of the use of the above-listed pregabalin ER dose strengths:
- the need for a 10% drug dosage increase in the pilot pregabalin ER formulation to provide comparable BA to that of the Lyrica formulation
- bioequivalence between the final pregabalin ER formulation administered within one hour of the evening meal and Lyrica capsules administered fasted

Pregabalin ER tablets in dose strengths of 82.5mg, 165 mg, 247.5 mg, 330 mg, 495 mg, and 660 mg/day proved efficacious as compared to placebo for the PHN indication.

Durability of Response

[The durability of response was demonstrated for pregabalin ER tablets with the Kaplan-Meier analysis of LTR in Study 1224. The percentage of subjects who maintained pain response during the DB Phase of the study was higher in the pregabalin ER treatment group (71%) than in the placebo treatment group (37%).]

Persistence of Effect

[Persistence of effect was demonstrated for pregabalin ER tablets with the Kaplan-Meier analysis of LTR in Study 1224. The majority of subjects who responded to pregabalin ER tablets in the SB Phase of the study maintained persistence of effect in the DB Phase of the study. Only 29 out of 208 subjects (13.9%) in the pregabalin ER treatment group experienced LTR as compared to 63 out of 205 subjects (30.7%) in the placebo treatment group. Time to LTR was statistically significant in favor of pregabalin ER. Additionally, the 30% and 50% responder rates were higher in the pregabalin treatment group as compared to the placebo treatment group.]

Additional Analyses Conducted on the Individual Trial

[No additional analyses were conducted on Study 1224.]

6.2. [Protocol A0081245]

6.2.1. Study Design

Overview and Objective
The Applicant conducted Protocol A0081245 which hereafter will be referred to as Study 1245 to support efficacy for the indication of fibromyalgia for this submission. Study 1245 was very similar in design and conduct to Study 1224; therefore, the summary below will highlight the key differences between the two studies. The summary of the design of Study 1245 was derived from Final Protocol Amendment 2, dated July 24, 2011. Important modifications to the original protocol are summarized at the end of this protocol summary.

**Title:** “A Phase 3 Double-Blind, Randomized, Placebo-Controlled, Safety and Efficacy Study of Once Daily Controlled Release Pregabalin in the Treatment of Patients with Fibromyalgia”

**Dates Conducted:** The first patient was enrolled in Study 1245 on March 2, 2011 and the last patient completed Study 1245 on July 30, 2012.

**Study Duration:** 21 weeks

**Number of center:** 50

**Number of countries:** 4

**Objectives:**
The primary objective was to have been –

- To evaluate the efficacy of pregabalin ER compared with placebo in the durability of effect for the treatment of FM among patients who initially respond to single-blind pregabalin

The secondary objectives were to have been –

- To evaluate the efficacy of pregabalin ER compared with placebo to relieve pain and to improve global assessment, functional status, tiredness and sleep
- To assess treatment satisfaction with pregabalin ER compared with placebo
- To assess safety and tolerability of the pregabalin ER formulation

**Trial Design**

[Study 1245 was a Phase 3, 17 week, multicenter, randomized withdrawal trial consisting of 4 phases: screening/baseline (1 week), single-blind treatment (dose optimization 3 weeks/fixed dose 3 weeks), double-blind, placebo-controlled treatment (fixed dose 13 weeks) and double-blind taper (1 week).

The main difference in study design between Study 1245 and Study 1224 is as described below:
Dose optimization and fixed dosing were to have lasted 3 weeks each during the single-blind treatment phase for Study 1245 instead of 4 weeks and 2 weeks, respectively, as stated for Study 1224.

The starting dose for Study 1245 was to have been 165 mg pregabalin ER daily with dose escalation weekly based on efficacy and tolerability up to a maximum of 495 mg pregabalin ER daily. There was no dose adjustment for renal impairment as this trial was to have enrolled only those with CLcr > 60 mL/min.

The main difference in the inclusion criteria between Study 1245 and Study 1224 is the enrollment of subjects with FM instead of PHN.

Inclusion Criteria:
Subjects were to have been included in the trial if all of the following criteria were met:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) had been informed of all pertinent aspects of the study.
2. Male or female of any race, at least 18 years of age, and was using appropriate methods of contraception as defined in the protocol. Women must have had a confirmed negative serum pregnancy test prior to enrollment.
3. At screening (Visit 1), subjects must have met the American College of Rheumatology (ACR) criteria for fibromyalgia (i.e., widespread pain present for at least 3 months, and pain in at least 11 of 18 specific tender point sites).
4. At screening (Visit 1) and enrollment (Visit 2), subjects must have scored ≥4 on the Numeric Rating Scale for Pain (1-week recall period).
5. At enrollment (Visit 2), at least 4 pain diaries must have been completed satisfactorily within the last 7 days and the average pain score must have been ≥4.
6. Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

The main differences in the exclusion criteria between Study 1245 and Study 1224 are described below in Table 23.

**Table 23 Comparison of Exclusion Criteria Differences between Studies 1245 and 1224**

<table>
<thead>
<tr>
<th>Exclusion Category</th>
<th>Study 1245</th>
<th>Study 1224</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other systemic disease</td>
<td>Inflammatory musculoskeletal disorders, rheumatic diseases (other than FM), active infections, untreated endocrine disorders or somatoform disorders</td>
<td>Any clinically unstable cardiovascular, hematological, autoimmune, endocrine, renal, hepatic, retinal or gastrointestinal disease</td>
</tr>
<tr>
<td>Medicolegal claims</td>
<td>Pending disability claims or currently receiving monetary compensation for FM or co-morbid diseases</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| Laboratory markers of inflammation | ESR > 40mm/h  
|                               | ANA (≥ 1:160 titer)  
|                               | RF > 80 IU/mL                                                       | Not applicable                                                                           |
| Renal function              | CLcr < 60 mL/min                                                          | CLcr < 30 mL/min                                                                            |

**Exclusion Criteria:**
Subjects were to have been excluded from the trial if any of the following were met:

1. Failed pregabalin treatment due to lack of efficacy, had hypersensitivity or intolerant to pregabalin or other α2δ ligands (e.g., gabapentin), or participated in a pregabalin clinical study. Subjects who previously took pregabalin IR were eligible if they did not meet these exclusions.
2. Pregabalin used in the last 30 days. Subjects taking pregabalin in the last 30 days were washed out of pregabalin for at least 30 days prior to screening visit.
3. Use of prohibited medications in the absence of appropriate washout periods.
4. Subjects with other severe pain due to other conditions (e.g., diabetic peripheral neuropathy or postherpetic neuralgia) that may have confounded assessment or self-evaluation of the pain associated with fibromyalgia.
5. Subjects with any widespread inflammatory musculoskeletal disorders, widespread rheumatic diseases other than fibromyalgia, active infections, untreated endocrine disorders, or somatoform disorder.
6. Subjects with severe depression that, in the judgment of the investigator, would have made the subject inappropriate for entry into the study.
7. Subjects with pending disability claims or who were receiving monetary compensation pertinent to the subject’s fibromyalgia or co-morbid diseases.
8. Erythrocyte sedimentation rate (ESR) >40 mm/h, abnormal antinuclear antibody ≥1:160 titer, or rheumatoid factor >80 IU/mL.
9. Estimated CLcr <60 mL/min (using Cockcroft-Gault equation). Subjects who had an estimated CLcr ≤60 mL/min by this screening method could have had their CLcr measured, at the investigator’s discretion, with a 24-hour urine collection performed at the central laboratory. If this 24-hour urine CLcr was >60 mL/min, the subject was not excluded.
10. Participation in any clinical study within the 30 days prior to screening and/or during study participation.
11. Subjects with any clinically unstable, cardiovascular, hematological, autoimmune, endocrine, renal, hepatic, retinal, or GI disease.
12. Any subject considered at risk of suicide or self-harm based on the investigator’s judgment, and/or the details of a risk assessment.
13. Screening electrocardiogram (ECG) with any clinically significant abnormality.
14. Subjects with a history of life-threatening neoplasms within 5 years prior to study entry, other than carcinoma in situ of the cervix or basal cell carcinoma of the skin.
15. Subjects with active GI disease including any GI surgery that in the opinion of the investigator would have interfered with the absorption of study medication (conditions such as irritable bowel syndrome were not excluded).
16. Subjects who had difficulties swallowing tablets or were unable to tolerate oral medication.
17. Platelet count <100x10^9/L; white blood cell (WBC) count <2.5x10^9/L; neutrophil count <1.5x10^9/L.
18. Clinically significant liver disease which may have prevented the subject from completing the study, or an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of greater than 3 times the maximum value of the laboratory assay normal range, or an elevation in total bilirubin of greater than 2 times the maximum value of the laboratory assay normal range. Laboratory assays could have been repeated once, prior to enrollment, to confirm the unacceptability of any subject.
19. Alcohol or substance abuse or dependence within the previous year.
20. Subjects who were pregnant, nursing, or intended to become pregnant during the course of the study.
21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or
investigational product administration or may have interfered with the interpretation of study results, and in the judgment of the investigator, would have made the subject inappropriate for entry into the study.

Randomization Criteria:
The randomization criteria that were to have been used for entry into the DB Phase of Study 1245 are identical with the randomization criteria used for Study 1224 (see p. 28 of this review).

Study Procedures
The tables below provide an overview of the visits and procedures for the baseline, single-blind and double-blind phases of Study 1245. The procedures and assessments that were to have occurred at Visit 0 (washout), Visit 1 (screening), Visit 2 (enrollment), and Visits 3 through 5 are comparable between Study 1224 and Study 1245. I will discuss the main differences in procedures and assessments between these two studies as I review each visit.

Table 24 Schedule of Activities for Baseline Visit and SB Phase of Study 1245

<table>
<thead>
<tr>
<th>Study Phase: Baseline (1 to 2 weeks, V1 to V2)</th>
<th>Baseline (6 weeks)</th>
<th>SB FU (approx 1 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinic Visit No.:</strong></td>
<td>V0</td>
<td>V1</td>
</tr>
<tr>
<td>Visit Type:</td>
<td>Clinic</td>
<td>Clinic</td>
</tr>
<tr>
<td>Study Day:</td>
<td>N/A</td>
<td>14-107</td>
</tr>
<tr>
<td>Visit Window:</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observation/Procedure</th>
<th>V0</th>
<th>V1</th>
<th>V2</th>
<th>V3</th>
<th>V4</th>
<th>V5</th>
<th>V6/ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent⁹</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical &amp; Neurological Examination³</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Laboratory (non-fasting)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacokinetics²</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Health Questionnaire-8 (PHQ-8)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Columbia Suicidality Severity Rating Scale (C-SSRS) or Suicidality Tracking Scale (SST-SSS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant/Rescue Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Study Medication Dispensing</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Daily IVRS diary (NRS-Pain, Tiredness NRS, and Subjective Sleep Questionnaire [SSQ])</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Actigraphy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>The Weekly NRS-Pain (1 week recall)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Patient Global Impression of Change (PGIC)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Benefit, Satisfaction, Willingness to continue measure (BSW)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medical Outcomes Study - Sleep Scale (MOS-SS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fibromyalgia Impact Questionnaire (FIQ)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Multidimensional Fatigue Inventory (MFI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Short-Form 36 Health Survey (SF-36)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Table 25  Schedule of Activities for DB Phase of Study 1245

<table>
<thead>
<tr>
<th>Study Phase:</th>
<th>Baseline (1 to 2 weeks, V1 to V2)</th>
<th>SB phase (6 weeks)</th>
<th>SB FU (approx 1 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Visit No.:</td>
<td>V0</td>
<td>V1</td>
<td>V2</td>
</tr>
<tr>
<td>Visit:</td>
<td>Washout</td>
<td>Screening</td>
<td>Enrollment</td>
</tr>
<tr>
<td>Study Day:</td>
<td>N/A</td>
<td>-14 to -7</td>
<td>1</td>
</tr>
<tr>
<td>Visit Type:</td>
<td>Clinic</td>
<td>Clinic</td>
<td>Clinic</td>
</tr>
<tr>
<td>Visit Window:</td>
<td>N/A</td>
<td>N/A</td>
<td>+3 days</td>
</tr>
</tbody>
</table>

Work Productivity and Activity Impairment (WPAI) Questionnaire
Pharmacokinetic Assessment
Dosing Diary

Abbreviations: approx=approximately, ECG=electrocardiogram, ET=early termination, FU=follow up; IVRS=interactive voice response system; NRS-Pain=numeric rating scale for pain; SB=single-blind; V=Visit.

Source: CSR Study 1224, Table 3, pp. 40-41

[Washout/Visit 0
No differences when compared to Study 1224

Screening /Visit 1 (1 to 2 weeks before Visit 2) – Clinic Visit
The main differences were as follows:
- Diagnosis of FM was to have been confirmed with tender point count performed by the investigator or physician.
Subjects were to have been given instructions on completing not only daily pain and daily sleep diaries but also completing the daily tiredness diary during the baseline period.

Subjects were to have been dispensed an Actiwatch with instructions on use until Visit 2.

**Suicidality Risk Assessment during Screening**

The investigator was to have reviewed each subject’s medical history as well as the results of the Sheehan Suicidality Tracking Scale (STS) (for subjects who entered the study prior to initiation of Study 1245 Protocol Amendment 2) or the C-SSRS baseline (for subjects who entered the study following approval/initiation of Study 1245 Protocol Amendment 2) and the PHQ-8. The main differences in criteria which were to have indicated a potential risk and triggered a risk assessment between the two studies were as follows:

- Any previous history of suicidal behaviors reported or documented within the past 10 years for Study 1245 (within past 1 year for Study 1224)
- A “yes” answer to any of the suicide behavior items of the C-SSRS for events that occurred within the past 10 years
- The presence of any current major psychiatric disorder that is not explicitly permitted in the entry criteria

As per Study 1224, subjects who met any criteria for potential risk and also met eligibility criteria for participation in Study 1245 were to have a risk assessment conducted by a qualified MHP. The investigator was to have obtained and reviewed the completed risk assessment before a subject was to have been allowed to continue in the trial. A written copy of the risk assessment was to have been included in the subject’s clinical record.

**Enrollment/Visit 2 (Day 1) – Clinic Visit**

The main differences were as follows:

- Subjects were to have returned the Actiwatch
- Subjects who met study entry criteria were to have completed the FIQ, MFI and WPAI assessments in addition to completing the MOS-SS, SF-36 and HADS used in Study 1224

**Study Drug**

Pregabalin ER was to have been supplied by Pfizer in the following strengths: 165 mg and 330 mg. Study drug was to have been supplied as blinded capsules of pregabalin ER and matching placebo. Dosage strengths of 495 mg or matching placebo were to have been achieved by having subjects take two tablets daily in the evening. All study medication was to have been supplied in non-subject specific bottles. Documentation of study drug dispensation was to have been documented in the CRF with notation of the date of receipt by subject, the amount dispensed to subject and the amount returned by subject. Study drug was to have been dispensed at Visits 2, 3, 4, 5, 6, 8 and at Visit 9.

**Dose Selection**
The Applicant referenced the same Phase 1 clinical pharmacology studies (Study A0081174, A0081206 and A0081225) discussed in Study 1224 as well as the approved dosage guidelines for the pregabalin IR formulation for the management of FM to support the use of pregabalin ER at doses of 165 mg, 330 mg and 495 mg for Study 1245.

**Study Drug Administration**
No differences when compared to Study 1224

**Study Drug Dose Titration**
The main differences were as follows:
- Normal CLcr was to have been an entry criterion, so starting dose of pregabalin ER was to have been 165 mg/day for all subjects
- Weekly dose escalation was to have been allowed based on subject efficacy and tolerability up to and including Visit 4, then fixed dose for the following 3 weeks
- Subjects unable to tolerate a dose of at least 330 mg/day by Visit 5 were to have been discontinued from the study

**Method of Assigning to Treatment Groups/Blinding**
No differences when compared to Study 1224

**Suicidality Risk Assessment during the Study**
Beginning with Visit 2, a risk assessment was to have been conducted by a qualified MHP if a subject had any positive responses to items 4, 5 or to any behavioral question on the C-SSRS (since the last visit version) or the STS if applicable. This risk assessment was to have been conducted in order to determine whether it was safe for a subject to continue trial participation. Suicidal risk was to have been managed by the clinical investigator in conjunction with a qualified MHP. Additionally, the investigator was to have consulted the Applicant’s designated medical monitor to determine whether a subject could continue the trial. Using relevant information from the C-SSRS or the STS and the risk assessment, a narrative was to have been developed for subjects who underwent any post-baseline risk assessment. This narrative was to have been included in the subject’s medical record.

**Visit 3 (Week 1) – Clinic Visit**
No differences when compared to Study 1224

**Visit 4 (Week 2) – Clinic Visit**
No differences when compared to Study 1224

**Visit 5 (Week 3) – Clinic Visit**
The main differences were as follows:
- PK sampling was to have been completed
Actiwatch was to have been dispensed

End of Single-Blind Phase/ Randomization for Double-Blind Phase/ Visit 6 (Week 6) or Early Termination Visit – Clinic Visit
Visit 6 in Study 1245 was comparable to Visit 7 in Study 1224 except for the following:
- Actiwatch was to have been returned to study site
- PK sampling was to have been completed
- Additional assessments (FIQ, MFI, WPAI) as mentioned for Visit 2

For subjects who discontinued from the study, there were no differences between Visit 6 in Study 1245 and Visit 7 in Study 1224.

For subjects who had a ≥ 50% pain improvement relative to baseline, there were no differences between Visit 6 in Study 1245 and Visit 7 in Study 1224.

Study Drug Taper
The study drug taper schedules were slightly different between the two studies as Study 1224 allowed for more dosing options when compared to Study 1245. The table below summarizes the study medication taper schedule for Study 1245.

Table 26 Study Medication Taper Schedule for Study 1245

<table>
<thead>
<tr>
<th>Pregabalin CR Dose (mg)</th>
<th>Taper Day 1 (mg QD)</th>
<th>Taper Day 2 (mg QD)</th>
<th>Taper Day 3 (mg QD)</th>
<th>Taper Day 4 (mg QD)</th>
<th>Taper Day 5 (mg QD)</th>
<th>Taper Day 6 (mg QD)</th>
<th>Taper Day 7 (mg QD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>165 mg (SB phase only)</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>330 mg</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
<tr>
<td>495 mg</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>330</td>
<td>165</td>
<td>165</td>
<td>165</td>
</tr>
</tbody>
</table>

Abbreviations: CR=controlled release; QD=once daily; SB=single-blind.

CSR Study 1245, p.37

Visit 7 (Week 11) and Visit 8 (Week 15) – Clinic Visits
The main differences were as follows:
- Actiwatch was to have been dispensed at Visit 7 and returned at Visit 8
- PK sampling was to have been completed at Visit 7

Visit 9 (Week 19) or Early Termination Visit – Clinic Visit
Visit 9 in Study 1245 was comparable to Visit 10 in Study 1224
End of Single-Blind Phase Follow-up (Week 7) and End of Double-Blind Phase Follow-up/ Visit 10 (Week 20) – Clinic Visits
The follow-up visits in Study 1245 were comparable to the follow-up visits in Study 1224

Allowable Medications and Non-drug Treatments
The following medications were permitted for additional pain relief or cardiovascular prophylaxis:
- Acetaminophen (paracetamol): Up to 3 grams/day as needed for pain
- Aspirin: ≤325 mg/day for myocardial infarction and stroke prophylaxis

Subjects were allowed to continue with stable (≥30 days before Visit 1) non-pharmacologic therapy belonging to one of the following categories:
- Physical therapy
- Heat/cold therapy
- Massage therapy
- Chiropractic therapy
- Psychological therapy
- Exercise/stretching program

Prohibited Medications
Subjects were to have discontinued any prohibited concomitant medications that might affect the pain or sleep disturbance associated with FM before Visit 1. Prohibited medications were to have included but were not limited to those listed in the table below.

Table 27 Prohibited Medications
Contraceptive Measures
No differences when compared to Study 1224

Compliance
No differences when compared to Study 1224

Subject Withdrawal
No differences when compared to Study 1224

Trial Endpoints

<table>
<thead>
<tr>
<th>Class of Medication</th>
<th>Examples</th>
<th>Minimum Washout Periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications Used for Relief of Pain</td>
<td>Skeletal muscle relaxants (e.g., carisoprodol-Soma, cyclobenzaprine/Flexeril)</td>
<td>At least 7 days prior to V1</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
<td>Pregabalin use within the 30 days prior to V1 is prohibited.</td>
</tr>
<tr>
<td></td>
<td>SSRIs and SSNRIs (e.g., fluoxetine(^a), venlafaxine, duloxetine, milnacipran)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reboxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antiepileptic agents (including gabapentin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Opioid analgesics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mexiletine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levodopa, dopamine agonists or other agents for Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tramadol</td>
<td>At least 2 days prior to V1</td>
</tr>
<tr>
<td></td>
<td>Dextromethorphan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NSAIDs/COXIBs</td>
<td></td>
</tr>
<tr>
<td>Tender Point injections</td>
<td></td>
<td>Last injection must be at least 1 month prior to V1</td>
</tr>
<tr>
<td>Medications Used for Relief of Insomnia</td>
<td>Benzodiazepines (e.g., Xanax)</td>
<td>At least 7 days prior to V1</td>
</tr>
<tr>
<td></td>
<td>Zolpidem (Ambien)</td>
<td>At least 1 day prior to V1</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine (Benadryl)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Melatonin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eszopiclone (Lunesta)</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Thioridazine, vigabatrin, hydroxychloroquine, Deferoxamine</td>
<td>Patients who have ever taken these medications are not eligible for this study.</td>
</tr>
</tbody>
</table>

\(^a\) Not a comprehensive list
\(^b\) Fluoxetine requires a 30-day washout.

Source: Final Protocol Amendment 2 Study 1245, p. 147]
defined as the mean of the last 7 observations prior to the start of the SB treatment. SB baseline pain score was to have been compared to the 7 day rolling average of daily pain responses in the DB treatment phase.

- Primary Efficacy Parameter: Daily Pain Diary
  - The primary efficacy endpoint was derived from information collected in the daily pain diary. The daily pain diary was to have been completed by subjects daily upon awakening using an IVRS. Subjects are asked to rate their pain during the previous 24 hours using a pain rating scale that consists of 11 points ranging from 0 (no pain) to 10 (worst possible pain). Daily pain diaries were to have been administered from Visit 1 (Baseline) through Visit 10 (End of DB Phase) or Early Termination.

Secondary Efficacy Endpoints
The secondary efficacy endpoints were to have been the following:

- Daily Tiredness Diary (Tiredness NRS)
  - The daily tiredness diary was to have been completed by subjects daily upon awakening from Visit 1 (screening) through Visit 9 (End of DB Phase) or Early Termination using an IVRS. Subjects are asked to rate their tiredness due to FM during the previous 24 hours using a rating scale that consists of 11 points ranging from 0 (not tired) to 10 (extremely tired).

- Daily Sleep Diary – Subjective Sleep Questionnaire (SSQ)
  - The SSQ is designed to look at subjective behavior in those with disrupted sleep. Subjects are asked to report latency to sleep onset (estimate of time to fall asleep), total sleep time, number of awakenings after sleep onset and sleep quality using a rating scale that consists of 11 points ranging from 0 (very poor) to 10 (excellent).

- Fibromyalgia Impact Questionnaire (FIQ)
  - A 20-item, self-administered questionnaire used to assess functioning, pain, fatigue and psychological distress in patients with FM. The questionnaire contains 10 subscales which are combined to yield a total score. The scoring range is 0 to 100 with higher scores indicating more impairment.

- Multidimensional Fatigue Instrument (MFI)
  - A 20-item self-report questionnaire used to measure general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Items are summed to yield subscale scores – no total score is collected. Higher scores indicate more dysfunction.

- Work Productivity and Activity Impairment (WPAI)
  - A 6-item, subject rated questionnaire used to qualitatively and quantitatively assess work productivity and impairment. Subjects answer questions regarding current employment, hours missed and actually worked and degree to which a specific health problem impacted work productivity and regular activities over
the past 7 days. Each subscale score is expressed as an impairment percentage on a scale from 0 to 100 with higher numbers indicating more impairment and less productivity.

- Pain NRS – 1 week recall period
  - Same as Study 1224
- Medical Outcomes Study – Sleep Scale (MOS-SS)
  - Same as Study 1224
- Patient Global Impression of Change (PGIC)
  - Same as Study 1224
- Short Form 36 Health Survey (SF-36)
  - Same as Study 1224
- Hospital Anxiety and Depression Scale (HADS)
  - Same as Study 1224
- Benefit, Satisfaction, Willingness to Continue Measure (BSW)
  - Same as Study 1224

**Exploratory Efficacy Endpoint**
The exploratory efficacy endpoint was to have been the following:

- Actigraphy Functional/Sleep Assessment
  - An accelerometer which was worn on the wrist like a watch was used to record subjects' movements over predetermined intervals of time. The information collected was used to calculate several endpoints including total sleep time, minutes awake after sleep onset, sleep fragmentation index, total daytime activity and percentage of daytime spent in sedentary activity.

**Safety Endpoints:**
The safety endpoints were to have been the following:

- Laboratory assessments at Visit 1, Visit 6/Termination and Visit 9/Termination
  - Additional testing at screening for Study 1245 included the following:
    - Rheumatoid Factor (RF)
    - Westergren Erythrocyte Sedimentation Rate
    - Antinuclear Antibody (ANA)
- Physical and neurological examinations to include weight assessment, edema assessment and vital signs at Visit 1, Visit 6/Termination and Visit 9/Termination
- ECGs at Visit 1 and Visit 9 or upon early termination
- Suicidality Assessment
  - PHQ-8 and C-SSRS – same as Study 1224
  - STS (for subjects enrolled prior to approval of protocol amendment 2)

**Pharmacokinetic Endpoints:**
Pharmacokinetic (PK) samples were to have been collected at Visits 5, 6, and 7 for Study 1245. Additional PK sampling was to have been required at any early termination visit. The blood samples were to have been collected from subjects at random times post-study drug dosing in order to provide a wide distribution of PK sample collection times post-dose. The time of the blood sample collection, the time of the last dose of study drug administration and the time of the meal prior to the last dose of study drug were to have been recorded. Additionally, de-identified pharmacogenomic sampling was to have been performed in Study 1245 at Visit 0 or Visit 1. Pharmacogenomic sampling was an optional aspect of the study that was to have required completion of a separate informed consent form for subjects who agree to participate.

**Statistical Analysis Plan**

[The null hypothesis for Study 1245 assumed that there was no difference between pregabalin ER and placebo. The alternative hypothesis assumed that there was a difference between pregabalin ER and placebo. The weight of treatment effects was to be estimated by use of adjusted means and associated 95% CIs (ANCOVA). For survival analyses, the weight of treatment effects was to be estimated by use of median time to event and associated 95% CIs if estimable. Descriptive statistics were to be performed on the single-blind analysis set (SBAS) for the SB Phase of the study. The primary and secondary efficacy analyses were to be performed on the full analysis set (FAS) for the DB Phase of the study.

Centers with a low number of subjects (fewer than four subjects) were to be combined with other centers based on geographical location before breaking the blind. In any model that included center as a factor, the pooled centers were to be used in analyses in place of center. Analyses that used the pooled site variable were required to have both treatments represented in each pooled site. The primary efficacy analysis and the secondary endpoints of PGIC, pain responders, and BSW were not to have used the pooled site variable. An error in the calculation of the pooled site variable was identified on May 3, 2016 (after completion of the original CSR and the first CSR amendment). The corrected implementation of the pooled site variable was recalculated for the final version of the CSR. The corrected implementation of the pooled site variable was to have been based on the FAS.

The Applicant selected a sample size in order to achieve 90% power to detect a difference in the primary endpoint, LTR, defined as <30% pain response relative to the SB baseline or subject discontinuation due to lack of efficacy or AEs during the DB Phase of the study. Data from a previous randomized withdrawal design study of pregabalin IR (Study A0081059) were used to estimate sample size for Study 1245. The Applicant originally estimated that a total of 74 LTR events would need to be observed in the DB Phase of the study. Therefore, the Applicant estimated that approximately 145 subjects would need to participate in the DB Phase of the study in order to yield 74 LTR events. It was further estimated that about 50% of the subjects who entered the SB Phase of the study would be eligible for randomization into the DB Phase of the study.]

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the study. Therefore, the Applicant estimated that 290 subjects would need to participate in the SB Phase of the study.

The Applicant tracked the total number of LTR events in both treatment arms during the DB Phase of the study in a blinded manner. Given that a lower number of events than expected occurred during the tracking period, the number of subjects enrolled and randomized was increased in order to obtain the required number of LTR events. The Applicant stated that the number of LTR events was not discussed with investigators or investigational site personnel and that the tracking of LTR events remained blinded with no reference to treatment arms. The Applicant concluded that this interim look at the data had no impact on Type I error rate.

Interim Analysis, Final Analyses, and Unblinding
No interim analysis was to have been conducted for Study 1245. However, since the study duration extended beyond one year, an interim safety data review by the internal review committee (IRC) was conducted within three months of the one year time point. Safety data was initially presented to the IRC and study team members were blinded and reviewed in an open session. Unblinded safety data was reviewed by the IRC only in a closed session. Final analyses were to be conducted after requirements for final release of the randomization codes were met and the official database was released. Study 1245 did not use a Data Monitoring Committee.

Statistical Decision Rules
Survival analyses were to have been estimated using median time to event and associated 95% confidence intervals. The magnitude of treatment effects was to have been estimated using adjusted means and associated 95% confidence intervals. A two-sided 0.05 level was to have been applied when significance testing was to be used. No adjustments for multiplicity of tests were to have been made.

Analysis Sets:
Full Analysis Set
The full analysis set (FAS) is the primary efficacy analysis set. The FAS consists of all subjects randomized to the double blind Phase of the study who received at least one dose of study medication. Subjects were to have been reported under the treatment to which they were randomized.

Single-Blind Analysis Set
The single-blind analysis set (SBAS) consists of all subjects enrolled into the single-blind Phase of the study who received at least one dose of study medication.

Safety Analysis Set
The safety analysis set consists of all subjects who received at least one dose of study medication.
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Subjects were to have been reported under the treatment which they received.

Treatment Misallocations:
Treatment misallocations were to be handled in the following manner:

- Subjects who were treated in the SB Phase and randomized but not treated in the DB Phase were to have been excluded from the FAS as they did not take at least one dose of study medication in the DB Phase. They were to have been included in the SBAS and in the safety analysis.
- Subjects who were randomized but not treated in either the SB or DB phases were to have been excluded from the efficacy analyses (SBAS, FAS) and the safety analyses as they did not take any study medication.
- Subjects who were randomized but took the incorrect treatment in the DB Phase were to have been reported under their randomized treatment group for all efficacy analyses based on the FAS. These subjects were to have been included in the SBAS as well.

Primary Efficacy Analysis:
The primary efficacy analysis (time to LTR) was to have been performed on the FAS population using survival techniques to compare time to LTR between the pregabalin ER treatment group and the placebo treatment group. LTR was defined as any of the following in the DB Phase of the study:

- Less than 30% pain response relative to the SB baseline pain score
- Patient discontinuation due to lack of efficacy
- Patient discontinuation due to adverse events

Subjects who did not experience an LTR event were to have been analyzed as censored observations. Kaplan-Meier estimates were to have been calculated and the log-rank test was to have been used to compare the treatment groups. P-values, median times to LTR and 95% CIs were to have been presented if estimable. Missing values were not to have been replaced.

Sensitivity Analyses of the Primary Endpoint:
Four sensitivity analyses of the primary endpoint were to have been performed to assess the robustness of the primary analysis by altering assumptions with regard to the censoring mechanism.

Kaplan-Meier estimates were to have been performed on the following modified FAS populations:

- All subjects who withdrew from the study for any reason were assumed to have experienced LTR;
- Subjects who withdrew due to lack of efficacy prior to LTR but did not also experience LTR based on the daily pain diaries were defined as having experienced LTR. All other withdrawals (including AEs) were counted as censored;
- All subjects who withdrew within the first week of DB treatment were assumed to be censored, regardless of reason for withdrawal;
Subjects who withdrew based on lack of efficacy (worsening of symptoms based on investigator judgment), but did not also experience LTR based on the daily pain diaries were defined as censored rather than having experienced LTR.

Secondary Efficacy Analyses:
All secondary endpoints were to have been analyzed using analysis of covariance (ANCOVA) to compare changes from the relevant baseline score between the pregabalin ER treatment group and the placebo treatment group for the DB Phase of the study using the FAS population. Analyses of secondary endpoints were to have been performed separately for data collected during the SB and DB Phases. Terms for the relevant baseline score, center, and treatment were to have been fitted in the model. This model was to have been used to estimate and present treatment differences, with associated 95% 2-sided CI’s and p-values. Adjusted means and 95% CI’s for each treatment group were to have been presented as well. Study 1245 had the following secondary endpoints that were not included in Study 1224:

- Change from baseline to endpoint in each of the five domains of the SSQ, derived from the daily sleep diary
- Change from baseline to endpoint in average of week daily tiredness severity, determined from the daily tiredness diary
- Change from baseline to endpoint in the FIQ, for both total score and each sub-domain
- Change from baseline to endpoint in each of the subscales of the MFI
- For the WPAI, descriptive statistics by treatment were to have been provided for actual values and change from baseline (if appropriate) for each time point for the four subscales

Exploratory Analyses:
The analysis of Actigraphy data was considered exploratory and was to have been documented in the SAP.

Handling of Missing Values:
For the primary efficacy analysis (time to LTR), the Applicant was to have handled dropouts in the following manner:

- Subjects who completed the DB Phase of the study or who withdrew not due to AEs or lack of efficacy prior to LTR were right-censored
- Subjects with no post-baseline observations were right-censored at DB Day 1
- Right-censoring is defined as a subject having no events up to a certain time point after which there are no additional data

For the primary efficacy analysis (time to LTR), the Applicant was to have handled missing data in the following manner:

- The method of last observation carried forward (LOCF) was to have been used for all endpoint analyses that occurred at more than 1 visit
- For diary measures, the last 7 diary entries while on study drug were used to calculate
the endpoint mean pain score and the endpoint mean sleep interference score. If less than 4 diary entries were present in the last 7 days, then the entries for the previous days were included until there were 4 non-missing pain entries.

Safety Analysis:
The safety analysis was to have included summaries of the following information:
- All AEs
- Repeated physical and neurological examinations
- Weight assessments
- Vital signs
- C-SSRS or S-STS results
- 12-lead ECG results
- Laboratory test results

Safety data was to have been presented separately for the SB (SBAS population) and DB (FAS population) phases of the study and as a combined analysis for the safety analysis set.

Protocol Amendments

[Original Protocol, February 26, 2010]
No subjects were enrolled under the original protocol.

Amendment 1, October 19, 2010
Amendment 1 was issued prior to enrolling any subjects in the trial. The following changes were made in this amendment:
- The daily diary (consisting of the daily pain/tiredness/sleep diaries) was now referred to as the “daily IVRS diary” to clarify that it was completed by the subject using an Interactive Voice Recognition System (IVRS).
- The NRS-Pain scale completed by subjects at clinic visits 1, 2, 6 and 9 was referred to as the “weekly NRS-Pain” to clarify that it was based on a 1-wk recall period and to differentiate it from the daily NRS-Pain.
- Clarification was provided that changes in pain response criteria were based on the daily pain diary (Section 2.2, primary efficacy endpoint; Section 4.3 randomization).
- Visits 3 and 4 were designated as clinic visits (previously, investigator sites had the option of conducting these visits by telephone) and suicidality assessment (STS) was added to these visits.
- The primary endpoint analysis set was changed to include those subjects who discontinue due to an adverse event in the DB Phase (Sections 3 and 9.3).
- The sleep disturbance sub-domain of the MOS-SS was changed from a “key” secondary endpoint to a standard secondary endpoint.
Sample size increased to 290 subjects in order to provide the necessary 74 events required to analyze the primary endpoint (previous sample size 260 subjects to yield 54 events).

The sensitivity analyses were updated to reflect changes to the primary endpoint.

The daily fatigue severity NRS which was part of the daily IVRS diary was substituted with the daily tiredness NRS.

The WPAI assessment was added to the study as a secondary endpoint.

Amendment 2, July 24, 2011
The following changes were made in this amendment:

- The suicidality assessment was changed from the STS to the S-CCRS for all subjects screened after approval and initiation of protocol amendment 2; subjects already using the STS continued to use that questionnaire.
- Procedures which allowed monitoring for hepatotoxicity were added.
- Procedures for the washout visit (Visit 0) and the screening visit (Visit 1) were outlined for situations where Visit 0 has been conducted.
- The timing for the screening visit was changed from 7 days prior to enrollment to 7-14 days prior to enrollment.
- Pharmacogenomic sampling at Visits 0 or 1 was added.
- A guideline for an appropriate washout of prohibited medications – “a minimum of 7 days or 5 half-lives, whichever is greater” was added.
- Maximum total daily dose of acetaminophen as rescue medication was lowered from 4 grams to 3 grams.
- Postmenopausal definition was added.
- Procedures for rescreening of eligible subjects were outlined.
- Additional information regarding pharmacokinetic sampling was added.
- Requirements were added with regard to the use of non-drug treatments.
- Requirement of subject withdrawal due to pregnancy was added.

Data Quality and Integrity: Sponsor’s Assurance

[The Applicant has stated that periodic monitoring visits were conducted to ensure that the protocol and GCPs were followed. During these monitoring visits, the clinical sites provided the Applicant’s monitors with direct access to source documents. The monitors used these source documents to authenticate that the data recorded on CRFs were veracious. The clinical sites were also subject to inspection by regulatory authorities, to quality assurance audits by the Applicant and to review by the IRB or IEC. Study and site level oversight was provided by compliance oversight leads in order to ensure that the study met high quality standards. Compliance oversight leads conducted oversight both on-site and remotely to evaluate monitoring effectiveness and to ensure compliance with the study protocol by investigational sites according to local regulation, applicable standard operating procedures and ICH/GCP.]
6.2.2. Study Results

Compliance with Good Clinical Practices

[The Applicant has provided attestation that Study 1224 was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidance for Good Clinical Practice (GCP) (International Conference on Harmonisation [ICH] 1996), and the Declaration of Helsinki (World Medical Association 2008).]

Financial Disclosure

[The Applicant has submitted financial disclosure information on Study 1245 for the time period from the start of the study through one year after completion of the study. The Applicant has submitted Debarment Certification and FDA form 3454 certifying that none of the financial interests or arrangements described in 21 CFR Part 54 exists for 204 of 209 clinical investigators who participated in the covered study listed above. The Applicant was unable to obtain a completed Financial Disclosure Form, despite multiple attempts, for the following two clinical investigators who participated in Study 1245: Dr. Jonathan M. Mosley and Terri Higbee. For those clinical investigators no longer at the institution where the study was conducted, the Applicant has certified that reasonable attempts were made to contact the clinical investigator to obtain disclosable financial information. The Applicant has identified no clinical investigators who were full-time or part-time employees of the sponsor of the covered studies. The Applicant has identified three clinical investigators from [REDACTED] who 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.

See the completed Clinical Investigator Financial Disclosure Review Form below.

Covered Clinical Study (Name and/or Number): Study 1245

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes ☒</th>
<th>No ☐ (Request list from Applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are Sponsor employees (including both full-time and part-time employees):</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>If there are investigators with disclosable financial interests/arrangements, identify the</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDER Clinical Review Template 2015 Edition

Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)

Reference ID: 4150575
number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payments of other sorts: 3
- Proprietary interest in the product tested held by investigator: 0
- Significant equity interest held by investigator in Sponsor of covered study: 0

| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☑  | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☑  | No ☐ (Request information from Applicant) |

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2

| Is an attachment provided with the reason: | Yes ☑  | No ☐ (Request explanation from Applicant) |

The Applicant has adequately disclosed financial interests with clinical investigators. Three investigators, received payments from the Applicant exceeding $25,000 for consulting and as honorarium. enrolled 4 patients (1% of the study population), Site enrolled patients % of the study population), and Site enrolled patients % of the study population) in the DB Phase of Study 1245. Each clinical investigator with a financial interest in excess of $25,000 provided a minimal contribution to the study data when the data are considered as a whole. Therefore, the clinical investigators with significant financial interests did not favorably influence the efficacy findings for this study.

**Patient Disposition**

[The disposition of subjects and the primary reasons for subject discontinuation in both the SB and DB phases of Study 1245 are summarized in the outline below.

**Subject disposition during the single-blind/enrichment phase of the study:**

| Number of subjects screened for inclusion | 770 |
| Number of subjects who received at least 1 dose of pregabalin ER in SB Phase | 441 |
| Number of subjects who discontinued from the study during the SB Phase | 121 (27.4%) |
| Number of subjects who completed SB treatment | 320 (72.6%) |
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Reasons for discontinuations during the SB Phase of the study:
- Study drug related adverse event 48 (10.9%)
- Insufficient clinical response 37 (8.4%)
- No longer willing to participate 15 (3.4%)
- Lost to follow-up 10 (2.3%)
- Unrelated adverse event 4 (1%)
- Other 4 (1%)
- Protocol violation 3 (0.7%)

Subject disposition during the double-blind Phase of the study:
Number of subjects screened for inclusion in DB Phase 320 (72.6%)
Number of subjects discontinued from study before randomization 198 (44.9%)
Number of subjects randomized 122 (27.7%)
Number of subjects randomized but discontinued before receiving treatment 1

Number of subjects who received at least 1 dose of pregabalin ER in DB Phase 121 (27.4%)
- pregabalin ER treatment group 63 (14.3%)
- placebo treatment group 58 (13.2%)

Number of subjects who discontinued from the study during the DB Phase 28 (23.1%)
- pregabalin ER treatment group 17 (27%)
- placebo treatment group 11 (19%)

Number of subjects who completed DB treatment 93 (76.9%)
- pregabalin ER treatment group 46 (73%)
- placebo treatment group 47 (81%)

Reasons for discontinuation from DB Phase of study for pregabalin ER treatment group:
- Insufficient clinical response
- No longer willing to participate
- Study drug related AE
- Lost to follow-up
- Unrelated AE
- Other

Reasons for discontinuation from DB Phase of study for placebo treatment group:
- Insufficient clinical response
- Lost to follow-up
- No longer willing to participate
Reviewer Comment: The primary reason for subject discontinuation in the DB Phase of Study 1245 for both the pregabalin ER treatment group and the placebo treatment group was Protocol Violations/Deviations

Overall, 107 subjects (24.3%) had one major protocol deviation and 114 subjects (25.9%) had one minor protocol deviation during the course of Study 1245. With the exclusion of the protocol deviations labeled as “other”, the most frequent major protocol deviations in the SB Phase of the study were in the categories of disallowed medications and inclusion/exclusion criteria. For the DB Phase of the study, the most frequent major protocol deviations were in the categories of disallowed medications and “other” for the pregabalin ER treatment group and in the categories of disallowed medications and informed consent for the placebo treatment group. Review of the line listing of protocol deviations showed that ibuprofen, distantly followed by hydroxyzine and duloxetine were the medications most frequently cited as cause for a major protocol violation during Study 1245.

Table 28   Major Protocol Violations by Category and Treatment Arm for Study 1245
Reviewer Comment: “Disallowed medications” is the most prevalent category after “other” for major protocol violations in both the SB and DB Phases of Study 1245. On more detailed review of the line listing of major protocol violations, I determined that subjects most frequently violated protocol by self-treating with the non-steroidal anti-inflammatory, ibuprofen. The propensity of subjects to default to use of disallowed pain medications, such as ibuprofen, during the study likely indicates inadequate pain management with pregabalin ER in this population.

Table of Demographic Characteristics

[The demographic characteristics for the pregabalin ER and placebo treatment groups in the DB Phase of Study 1245 were similar with respect to age, gender and race. The mean age was 50.3 in the pregabalin ER group and 49.3 in the placebo group. The majority of subjects were female in both groups – 92.1% in the pregabalin ER group and 89.7% in the placebo group. The majority of subjects were white for both groups – 90.5% in the pregabalin ER group and 89.7% in the placebo group. The mean weight for subjects was 78.4 kg in the pregabalin ER group and 85.8 in the placebo group. See the table below for details.]

[Table 29 Demographic Characteristics for Each Treatment Arm in the DB Phase of Study 1245]
Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

[Other relevant baseline characteristics for the pregabalin ER treatment group and the placebo treatment group in the DB Phase of Study 1245 are presented in the table below. The pregabalin ER treatment group and the placebo treatment group were fairly comparable with respect to duration since diagnosis of FM in years and other diseases present at screening. Subjects with impaired renal function (estimated CLcr <60 mL/min) were to have been excluded from Study 1245; therefore, the pregabalin ER treatment group and the placebo treatment group were comparable with respect to renal function.]

Table 30 Other Baseline Characteristics for Each Treatment Arm in the DB Phase of Study 1245

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Pregabalin ER (N=63) (100%)</th>
<th>Placebo (N=58) (100%)</th>
<th>Total (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration since diagnosis of PHN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mean years  |  5.8  |  6.4  |  6.1  
Min, max (years)  |  0, 28.3  |  0, 26  |  0, 28.3  

**Another disease present at screening**

<table>
<thead>
<tr>
<th>Category</th>
<th>Treatment Group 1</th>
<th>Treatment Group 2</th>
<th>Treatment Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI disorder</td>
<td>30 (47.6%)</td>
<td>27 (46.6%)</td>
<td>57 (47.1%)</td>
</tr>
<tr>
<td>GE reflux disease</td>
<td>15 (23.8%)</td>
<td>8 (13.8%)</td>
<td>23 (18.8%)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>30 (47.6%)</td>
<td>24 (41.4%)</td>
<td>54 (44.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (14.3%)</td>
<td>9 (15.5%)</td>
<td>18 (14.9%)</td>
</tr>
<tr>
<td>MS and connective tissue disorders</td>
<td>30 (47.6%)</td>
<td>24 (41.4%)</td>
<td>54 (44.5%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>26 (41.3%)</td>
<td>20 (34.5%)</td>
<td>46 (37.9%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14 (22.2%)</td>
<td>4 (6.9%)</td>
<td>18 (14.6%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>26 (41.3%)</td>
<td>26 (44.8%)</td>
<td>52 (43%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20 (31.7%)</td>
<td>20 (34.5%)</td>
<td>40 (33%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>22 (34.9%)</td>
<td>16 (27.6%)</td>
<td>38 (31.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (27%)</td>
<td>13 (22.4%)</td>
<td>30 (24.8%)</td>
</tr>
</tbody>
</table>

Source: Study 1245 CSR, pp. 78-79

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Treatment compliance, concomitant medications, and rescue medication use were comparable between the pregabalin ER treatment group and the placebo treatment group for the DB Phase of Study 1245. In the pregabalin ER treatment group, 59 subjects (93.7%) were on prior medications before the start of the study. In the placebo treatment group, 58 subjects (100%) were on prior medications before the start of the study. The more common medications used prior to the start of Stud 1245 were as follows: paracetamol, ibuprofen, multivitamins, ergocalciferol, pregabalin, duloxetine hydrochloride, acetylsalicylic acid, and amitriptyline. The washout period for most prohibited medications was 7 days or 5 half-lives (whichever was greater) prior to Visit 1. The washout period for pregabalin was 30 days prior to Visit 1.

The proportion of subjects having any concomitant medications was also comparable between treatment groups in the DB Phase. In the pregabalin ER treatment group, 57 subjects (90.5%) were using concomitant medications during the study. In the placebo treatment group, 52 subjects (89.7%) were using concomitant medications during the study. The more common concomitant medications used during Study 1245 included the following: paracetamol, multivitamins, ergocalciferol, levothyroxine sodium, acetylsalicylic acid, calcium, and hydrochlorothiazide.

Subjects were generally compliant with study treatment during both phases of the study. In the SB Phase, 383 subjects (86.8%) had >90% overall compliance. In the DB Phase, 61 subjects...
(96.8%) in the pregabalin ER treatment group and 59 subjects (100%) in the placebo arm had >90% overall compliance.

Table 31  Study Medication Compliance Overall

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Number (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin CR SB 165 - 495 mg/day (N=441)</td>
</tr>
<tr>
<td>Overall Compliance</td>
<td></td>
</tr>
<tr>
<td>&lt; 80%</td>
<td>30 (6.8)</td>
</tr>
<tr>
<td>80% to 90%</td>
<td>28 (6.3)</td>
</tr>
<tr>
<td>&gt; 90%</td>
<td>383 (86.8)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>95.0 (13.24)</td>
</tr>
<tr>
<td>Range</td>
<td>7.7 to 116.7</td>
</tr>
</tbody>
</table>

Source: Section 14, Table 14.4.1.4.1
Abbreviations: CR=controlled release; DB=double-blind; N=number of subjects in treatment group; SB=single-blind; SD=standard deviation.
Source: CSR Study 1245, p. 83

With regard to medication compliance within one hour of any meal, 364 subjects (82.5%) had >90% compliance during the SB Phase. In the pregabalin ER treatment group, 59 subjects (93.7%) had >90% compliance during the DB Phase. In the placebo treatment group, 59 subjects (100%) had >90% compliance during the DB Phase. The medication compliance rate when study medication was dosed within one hour of any meal remained fairly comparable between treatment groups in the DB Phase of Study 1245.

Table 32  Study Medication Compliance within One Hour of Any Meal
With regard to medication compliance within one hour of the evening meal, 283 subjects (64.2%) had >90% compliance during the SB Phase. In the pregabalin ER treatment group, 44 subjects (69.8%) had >90% compliance during the DB Phase. In the placebo treatment group, 50 subjects (84.7%) had >90% compliance during the DB Phase. Consequently, the medication compliance rate when study medication was dosed within one hour of the evening meal was much higher in the placebo treatment group as compared to the pregabalin ER treatment group.

Table 33  Study Medication Compliance within One Hour of the Evening Meal

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Number (% of Subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregabalin CR SB 165 - 495 mg/day (N=441)</td>
</tr>
<tr>
<td>Study Medication Compliance</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td></td>
<td>80% to 90%</td>
</tr>
<tr>
<td></td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>88.3 (16.81)</td>
</tr>
<tr>
<td>Range</td>
<td>7.1 to 102.4</td>
</tr>
</tbody>
</table>

Source: Section 14, Table 14.4.1.4.2  
Abbreviations: CR=controlled release; DB=double-blind; FAS=full analysis set; N=number of subjects in treatment group; SB=single-blind; SBAS=single-blind analysis set; SD=standard deviation.

Source: CSR Study 1245, p. 84
Reviewer Comment: There is a notable difference in the medication compliance rate between treatment groups in the DB Phase of Study 1245 when assessing compliance with medication administration within one hour of the evening meal. About 70% of subjects in the pregabalin ER treatment group as compared to about 85% of subjects in the placebo treatment group complied with study medication administration within one hour of the evening meal. The Applicant’s clinical pharmacology studies showed that pregabalin ER is less bioavailable when administered one hour after breakfast or lunch; therefore, I would argue that this difference in medication compliance between treatment groups likely negatively impacted the efficacy results for Study 1245. Those in the pregabalin ER treatment group who took the study medication one hour after breakfast rather than dinner may have had suboptimal systemic exposure to pregabalin ER and, hence, insufficient treatment effect.

Efficacy Results - Primary Endpoint

[The Applicant selected time to LTR as the primary endpoint for Study 1224. However, DAAAP recognizes the landmark endpoint of change in pain from baseline to end-of-therapy as more clinically meaningful than time to LTR and, therefore, most applicable when determining drug efficacy. The Applicant was informed of the importance of the landmark endpoint in an FDA advice letter dated August 2010 and again at the pre-NDA meeting in April 2016. Consequently, I will present the Applicant’s efficacy results on change in pain as the primary endpoint and the Applicant’s results on time to LTR as the secondary endpoint.]
7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

[As previously described in this review, the Applicant selected “time to LTR” as the primary endpoint to be analyzed using a Kaplan-Meier estimate for both efficacy trials. While the Agency did not insist on the use of a landmark analysis of change in pain intensity from BL to EOT as the primary endpoint, the Division did emphasize the importance of conducting an analysis of change in pain from BL to EOT during presubmission regulatory activity. We also emphasized that our review of the efficacy results for Studies 1224 and 1245 would focus on the consistency of the results across the analyses of both change in pain intensity and time to LTR.]

7.1.2. Secondary and Other Endpoints

[Typical secondary endpoints for analgesic clinical studies were assessed and generally supported the primary endpoint in Study 1224. Though Study 1245 failed to demonstrate efficacy...

7.1.3. Subpopulations

[As is typical in analgesic clinical studies, the demographics for both studies were restricted and had a substantial plurality of Caucasians. Within the limitations of the spectrum of the demographics, I did not identify any demographic trends for safety or efficacy.]
7.1.4. **Dose and Dose-Response**

In both studies, patients were titrated to an optimal dose, within specified lower and upper bounds, based on a balance between efficacy and tolerability. In Study 1224, 660 of the 801 patients (82.4%) who started the SB phase of the study met randomization criteria. The mean and median doses for patient who entered the DB phase of the study were 368 and 330 mg. This suggests that the dose range selected for marketing is likely to meet the needs of most patients with peripheral neuropathic pain.

7.1.5. **Onset, Duration, and Durability of Efficacy Effects**

The Applicant did not conduct any analyses that inform the onset of action. What can be inferred is that a large proportion of PHN patients exposed to LYRICA CR had clinically meaningful analgesia within four weeks (the dose optimization portion of the SB phase). Additionally, as inferred from the Kaplan-Meier estimates, efficacy appears preserved for the 13-week period following randomization.

7.2. **Additional Efficacy Considerations**

7.2.1. **Considerations on Benefit in the Postmarket Setting**

Pregabalin does not require any particular skill or knowledge on the part of the healthcare provider to be used successfully. The expectation of benefit in the postmarketing setting is no different than what was observed in the clinical trial.

7.2.2. **Other Relevant Benefits**

The benefits of the pregabalin moiety are well characterized.

7.3. **Integrated Assessment of Effectiveness**

Please see Section 1.2 of this review for my assessment of effectiveness for the neuropathic pain indications.

8 **Review of Safety**

The Applicant evaluated the safety of pregabalin ER tablets for the management of neuropathic pain associated with DPN, the management of PHN, and the management of FM in...
twelve Phase 1 clinical pharmacology studies and three Phase 3 clinical trials. See Tables 29 and 30 below.

### Table 39 Overview of Phase 1 Clinical Studies Using Pregabalin ER Tablets

<table>
<thead>
<tr>
<th>Study Number (No. of Treated Subjects)</th>
<th>Objective</th>
<th>Pregabalin Treatment and No. of subjects who received at least one dose of study medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single Dose Clinical Pharmacology Studies Evaluating Pregabalin ER Tablets: Open-label, randomized, crossover studies in healthy volunteers</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| A0081188 (28)                        | To evaluate the PK and BA of the 330 mg ER tablet administered following a 400-500, 600-750 and 800-1000 kcal medium-fat lunch relative to the pregabalin 300 mg IR capsule administered fasted in mid-afternoon. | 330 mg ER  
25 subjects 400-500 kcal  
26 subjects 600-750 kcal  
28 subjects 800-1000 kcal (medium-fat lunch)  
300 mg IR  
27 subjects (fasted) |
| A0081227 (28)                        | To evaluate the PK and BA of the 330 mg ER tablet administered following an 800-1000 kcal low-, medium-, or high-fat evening meal relative to the pregabalin 300 mg IR capsule administered following an 800-1000 kcal medium-fat evening meal. | 330 mg ER  
28 subjects low-fat  
28 subjects medium-fat  
27 subjects high-fat (evening meal)  
300 mg IR  
27 subjects medium-fat (evening meal)  |
| A0081228 (24)                        | To evaluate the PK and BA of the 330 mg ER tablet administered in the fasted state and following a 600-750 kcal medium-fat evening meal relative to the pregabalin 300 mg IR capsule administered fasted in the evening. In addition, to evaluate the PK and BA of the 330 mg ER tablet administered fed relative to the 330 mg ER tablet administered fasted. | 330 mg ER  
24 subjects medium-fat meal  
23 subjects fasted  
300 mg IR  
23 subjects fasted |
| A0081238 (24)                        | To evaluate the PK and BA of the 330 mg ER tablet administered fasted at bedtime and following a 400-500 and 600-750 kcal medium-fat evening meal relative to the pregabalin 300 mg IR capsule administered fasted in the evening. In addition, to evaluate the PK and BA of the 330 mg ER tablet administered fed relative to the 330 mg ER tablet administered fasted. | 330 mg ER  
23 subjects immediately after 400-500 kcal  
24 subjects immediately after 600-750 kcal  
22 subjects 4 hours following 600-750 kcal (medium-fat evening meal)  
300 mg IR  
22 subjects (evening, fasted) |
| A0081239 (24)                        | To evaluate the PK and BA of the 330 mg ER tablet administered following a 400-500, 600-750, and 800-1000 kcal medium-fat breakfast relative to the pregabalin 300 mg IR capsule administered fasted in the morning. | 330 mg ER  
23 subjects immediately after 400-500 kcal  
23 subjects immediately after 600-750 kcal |
<table>
<thead>
<tr>
<th>Study Number (No. of Treated Subjects)</th>
<th>Objective</th>
<th>Pregabalin Treatment and No. of subjects who received at least one dose of study medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0081197 (18)</td>
<td>To evaluate the effect of the gastrointestinal prokinetic medication erythromycin on the PK and BA of the 330 mg ER tablet administered following a 600-750 kcal, medium-fat evening meal.</td>
<td>330 mg ER alone 18 subjects 330 mg ER plus erythromycin 500 mg q6 for 3 doses 17 subjects</td>
</tr>
</tbody>
</table>

### Multiple Dose Clinical Pharmacology Studies Evaluating Pregabalin ER Tablets: Open-label, randomized, crossover studies in healthy volunteers

<table>
<thead>
<tr>
<th>Study Number (No. of Treated Subjects)</th>
<th>Objective</th>
<th>Pregabalin Treatment and No. of subjects who received at least one dose of study medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0081225 (20)</td>
<td>To evaluate the steady-state PK, extent of absorption, and tolerability of the 330 mg ER tablet administered following a 600-750 kcal medium-fat evening meal as compared to the pregabalin 150 mg IR capsule administered fasted BID.</td>
<td>330 mg ER, QD 20 subjects 150 mg IR, q12 20 subjects</td>
</tr>
<tr>
<td>A0081198 (24)</td>
<td>To evaluate the steady-state PK, extent of absorption, and tolerability of the 330 mg ER tablet and 2 x 165 mg ER tablets administered following a 600-750 kcal medium-fat evening meal as compared to the pregabalin 150 mg IR capsule administered fasted BID. In addition, to evaluate PK and extent of absorption of 2 x 165 mg ER relative to 1 x 330 mg ER.</td>
<td>330 mg ER, QD 24 subjects 2 x 165 mg ER, QD 23 subjects 150 mg IR, q12 24 subjects</td>
</tr>
<tr>
<td>A0081215 (18)</td>
<td>To evaluate the steady-state PK, extent of absorption, and tolerability of the 82.5 mg ER tablet administered following a 600-750 kcal medium-fat evening meal relative to the pregabalin 25 mg IR capsule administered fasted TID.</td>
<td>82.5 mg ER, QD 18 subjects 25 mg IR, TID 17 subjects</td>
</tr>
<tr>
<td>A0081216 (18)</td>
<td>To evaluate the PK, extent of absorption, and tolerability of 2 x 330 mg ER tablets administered following a 600-750 kcal medium-fat evening meal relative to the pregabalin 300 mg IR capsule administered fasted BID.</td>
<td>2 x 330 mg ER, QD 18 subjects 300 mg IR, q12 18 subjects</td>
</tr>
<tr>
<td>A0081226 (24)</td>
<td>To evaluate the PK, extent of absorption, and tolerability of the 165 mg ER tablet and 2 x 82.5</td>
<td>165 mg ER, QD 24 subjects</td>
</tr>
</tbody>
</table>
Clinical Review
Lisa Wiltrout
NDA 209501
Lyrica CR (pregabalin ER)

<table>
<thead>
<tr>
<th>Study Number (No. of Treated Subjects)</th>
<th>Objective</th>
<th>Pregabalin Treatment and No. of subjects who received at least one dose of study medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg ER tablets administered following a 600-750 kcal medium-fat evening meal as compared to the pregabalin 75 mg IR capsule administered fasted BID.</td>
<td>2 × 82.5 mg ER, QD 23 subjects 75 mg IR, q12 24 subjects</td>
</tr>
</tbody>
</table>

Source: Summary of Clinical Safety, Table 1, pp. 14-17; No. = number; *2 subjects discontinued from the study and did not receive pregabalin ER

Table 40 Overview of Phase 3 Clinical Studies Using Pregabalin ER Tablets

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Study Design</th>
<th>No. of Treated Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SB Phase</td>
<td>DB Phase</td>
</tr>
<tr>
<td></td>
<td>Pregabalin ER</td>
<td>Pregabalin ER</td>
</tr>
</tbody>
</table>

Placebo-Controlled Phase 3 Efficacy and Safety Studies

A0081224 6-week SB; 13-week DB, RWD, PHN study; primary efficacy endpoint was time to LTR; pregabalin ER dose administered 82.5-660 mg QD following the evening meal (4 weeks flexible during dose-optimization phase and then dose maintained) 801 (82.5-330mg/day for subjects with CLcr >30 to <60 ml/min OR 165-660mg/day for subjects with CLcr ≥60 ml/min) 208 (165-660 mg/day) 205

A0081245 6-week SB; 13-week DB, RWD, FM study; primary efficacy endpoint was time to LTR; pregabalin ER dose administered 165-495 mg QD following the evening meal (3 weeks flexible during dose-optimization phase and then dose maintained) 441 (165-495mg/day) 63 (330-495 mg/day) 58

A0081194 14-week randomized, DB, parallel group epilepsy study; primary efficacy endpoint was log-transformed 28-day seizure rate for all partial onset seizures collected during the DB treatment phase; 2-week dose escalation phase and 12-week maintenance phase with fixed pregabalin ER dose administered 165 mg or 330 mg QD following the evening meal NA 100 (165mg/day) 113 (330mg/day) 110

Source: Summary of Clinical Safety, Table 2, p. 18

The Applicant integrated safety data across all Phase 1 multiple dose studies (Studies 1198, 1215, 1216, 1226, and 1225 [330 mg arm only]) for the Summary of Clinical Safety and the Integrated Summary of Safety but did not integrate safety data from the Phase 1 single dose studies. The Applicant integrated safety data from the two Phase 3 pain studies (Studies 1224 and 1245) for the Summary of Clinical Safety and the Integrated Summary of Safety. These
studies had the same study design and the same primary endpoint. The Phase 3 epilepsy study (Study 1194) utilized a different study design than the Phase 3 pain studies. Therefore, the safety data from the Phase 3 epilepsy study was not integrated with the safety data from the two Phase 3 pain studies.

8.1. Safety Review Approach

[I reviewed the integrated safety data for the multiple dose Phase 1 studies, the integrated safety data for the two Phase 3 pain studies (Study 1224 and 1245), and the individual study safety data from Studies 1224, 1245, and 1194 to assess the Applicant’s safety submission. I focused on the well-known adverse reactions seen in controlled trials and post-marketing with pregabalin IR – dizziness, somnolence, edema, and weight gain. I reviewed the gastrointestinal adverse events associated with pregabalin ER given its purported longer residence time in the stomach to enhance absorption. And I closely reviewed the central nervous system AEs of special interest as presented by the Applicant – euphoric effects and suicide assessment. I did not identify any new safety concerns for pregabalin ER. The adverse reaction profile of pregabalin ER is comparable to that of Lyrica.]

8.2. Review of the Safety Database

8.2.1. Overall Exposure

[Overall, 1728 subjects received at least one dose of pregabalin ER and were included in the safety analyses – 273 subjects in the Phase 1 studies and 1455 subjects in the Phase 3 studies. Of the 1455 subjects in the Phase 3 studies, 801 subjects were in Study 1224, 441 subjects were in Study 1245, and 213 subjects were in Study 1194.]

[Table 41 Safety Database for Pregabalin ER]

<table>
<thead>
<tr>
<th>Clinical Trial Groups</th>
<th>Pregabalin ER (n= 1728)</th>
<th>Pregabalin IR (n= 103)</th>
<th>Placebo (n= 638)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 single dose studies</td>
<td>169</td>
<td>103</td>
<td>265</td>
</tr>
<tr>
<td>Phase 1 multiple dose studies</td>
<td>104</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled trials conducted for pain indications</td>
<td>1242</td>
<td>0</td>
<td>263</td>
</tr>
<tr>
<td>PHN 801</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM 441</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled trials</td>
<td>213</td>
<td>0</td>
<td>110</td>
</tr>
</tbody>
</table>
A total of 1455 subjects were exposed to pregabalin ER in the Phase 3 studies. The most frequently received pregabalin ER dosage for less than one week was 82.5 mg daily in 217 subjects. Those subjects with impaired renal function received pregabalin ER 82.5 mg daily as a starting dose in Study 1224. Additionally, all subjects received pregabalin ER 82.5 mg during the 2 week dose escalation phase in Study 1194. Given that most subjects had normal renal function, the majority of subjects (1377 out of 1455 or 95%) received pregabalin 165 mg daily for greater than or equal to one week as this is the recommended starting dose in the setting of normal renal function. The most frequently received pregabalin ER dosage for greater than or equal to three weeks was 330 mg daily in 401 subjects. The 165 mg and 330 mg doses of pregabalin ER were each received daily for greater than or equal to six weeks in 179 and 175 subjects respectively. One hundred sixty-two (162) subjects received pregabalin ER 330 mg daily for ≥ 11 weeks. The 330 mg, 495 mg, and 660 mg doses of pregabalin ER were each received daily for ≥ 15 weeks in 56, 53, and 58 subjects respectively. The most frequently received pregabalin ER dosage for ≥ 19 weeks was 165 mg daily in 26 subjects.

<table>
<thead>
<tr>
<th>Exposure Category</th>
<th>Total Daily Dose of Pregabalin ER (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>82.5</td>
</tr>
<tr>
<td>No. of Subjectsb</td>
<td>1455</td>
</tr>
<tr>
<td>Weeks</td>
<td></td>
</tr>
<tr>
<td>&lt;1 week</td>
<td>217</td>
</tr>
<tr>
<td>≥1 weeks</td>
<td>159</td>
</tr>
<tr>
<td>≥3 weeks</td>
<td>29</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>16</td>
</tr>
<tr>
<td>≥11 weeks</td>
<td>3</td>
</tr>
<tr>
<td>≥15 weeks</td>
<td>3</td>
</tr>
<tr>
<td>≥19 weeks</td>
<td>3</td>
</tr>
<tr>
<td>Total subject-days</td>
<td>3491</td>
</tr>
<tr>
<td>Total subject-weeks</td>
<td>498.71</td>
</tr>
<tr>
<td>Total subject-years</td>
<td>9.56</td>
</tr>
</tbody>
</table>

Source: SCS, Table 7, p.31

aIndicates days on all specified pregabalin ER doses. Does not include days off drug and days when dose as unknown. Includes 5 subjects from Study 1224 for whom the dose was not known.
bEach subject could be counted in more than one row within a column. Subjects who received more than one dose level of pregabalin ER appear in multiple columns.

Disposition
For the Phase 3 pain studies, 980 subjects out of 1242 pregabalin ER treated subjects completed the SB Phase. Of the 980 subjects who were screened for the DB Phase, 540
subjects were randomized – 274 subjects to pregabalin ER and 266 subjects to placebo. Two hundred twenty-eight (228) subjects out of 271 pregabalin ER treated subjects completed the DB Phase. Two hundred seven (207) subjects out of 263 placebo treated subjects completed the DB Phase. Therefore, a total of 435 subjects completed both the SB and DB Phases of the Phase 3 pain studies with 228 subjects having exposure to a fixed dose of pregabalin ER for twelve weeks.

For the Phase 3 epilepsy study, 325 subjects out of 400 screened subjects were assigned to treatment arms – 101 subjects to pregabalin ER 165 mg, 114 subjects to pregabalin ER 330 mg, and 110 subjects to placebo. Ninety-one (91) subjects out of 100 pregabalin ER 165 mg treated subjects completed the study. Ninety-eight (98) subjects out of 113 pregabalin ER 330 mg treated subjects completed the study. Ninety-eight (98) subjects out of 110 placebo treated subjects completed the study. Therefore, a total of 287 subjects completed the Phase 3 epilepsy study with 189 subjects having exposure to a fixed dose of pregabalin ER for twelve weeks.

For all Phase 3 studies combined, the Applicant had 417 subjects total (228 subjects from the Phase 3 pain studies and 189 subjects from the Phase 3 epilepsy study) who were exposed to fixed doses of pregabalin ER, ranging from 165 mg daily to 660 mg daily, for a three month period of time.

Table 43 Subject Disposition for the Phase 3 Studies

| Source: SCS, Table 6, p. 29 |

<table>
<thead>
<tr>
<th></th>
<th>Phase 3 Pain Studies 1224 and 1245 Combined</th>
<th>Phase 3 Epilepsy Study 1194</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SB</td>
<td>DB</td>
</tr>
<tr>
<td>No. (%) of Subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screened</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed SB but not randomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Treated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: SCS, Table 6, p. 29

a. Completed SB phase and evaluated for DB phase.
b. A total of 440 subjects completed the SB phase but were not randomized into the DB phase.
c. Denominator for all percentages in Study 1194 is the number of subjects assigned to study treatment. Denominator for all percentages in the combined Studies 1224 and 1245 is the number of treated subjects.
d. Subjects were enrolled or randomized, but did not receive treatment.

8.2.2. Relevant characteristics of the safety population:

[The Phase 1 multiple dose studies safety population consisted of healthy volunteers who were...
primarily Caucasian males. The mean age and mean weight of this population was 36.5 years and 75 kg, respectively. The duration of exposure to study drug was ≤ 8 days.

The Phase 3 studies safety population consisted of subjects from the Phase 3 pain studies (Studies 1224 and 1245 combined) and subjects from the Phase 3 epilepsy study (Study 1194). For the Phase 3 pain studies, more women (approximately 70%) than men (approximately 30%) were treated with pregabalin ER, more than half of the subjects were Caucasian, over 80% of the subjects had at least one disease or syndrome at screening, ≥ 78% of subjects had prior medication use at screening, ≥ 80% had concomitant medication use during the study, and the mean age was 57.9 years for pregabalin ER treated subjects during the SB Phase and 59.2 and 59.4 years for pregabalin ER treated subjects and placebo treated subjects, respectively, during the DB Phase. Approximately 20% of subjects in Study 1224 had renal impairment as compared to no subjects in Study 1245 or Study 1194. Additionally, the average age for subjects in Study 1224 was about 10 years and 20 years older than the average age of subjects in Study 1245 and Study 1194, respectively. For the Phase 3 epilepsy study, women and men were equally represented, more than half of the subjects were Caucasian, about 50% of subjects had at least one disease or syndrome at screening, about 50% of subjects were taking two antiepileptic drugs at screening, all except one subject treated with placebo had concomitant medication use during the study, and the mean age was 37.9, 39.6, and 38.7 for subjects treated with pregabalin ER 165 mg daily, pregabalin ER 330 mg daily, and placebo daily, respectively.

8.2.3. Adequacy of the safety database:

[The Applicant’s safety database of 1455 subjects exposed to pregabalin ER during the pregabalin ER drug development program is adequate. The pregabalin ER treatment interval of 12 weeks is shorter than the treatment interval recommended in the ICH guidelines. For chronically administered drugs, the ICH guidelines propose treatment of 300 to 600 patients for six months and 100 patients for one year at the dose range believed to be efficacious. However, we have safety data from controlled trials with Lyrica (NDA 21446, NDA 21446/S-010, and NDA 21466/S-028) as well as postmarketing experience with Lyrica that can be extrapolated to support the safety of pregabalin ER.

Given the demographics of typical analgesic clinical study participants, the Applicant has provided a reasonable demographic composition for the safety population. In general, the FM and epilepsy populations are younger and the PHN and DPN populations are older. There is limited racial diversity though not unusual for controlled clinical trials. There is female predominance – not unusual for FM, but PHN, DPN, and epilepsy affect both genders equally. There is some renal impairment representation.]

8.3. Adequacy of Applicant’s Clinical Safety Assessments
8.3.1. Issues Regarding Data Integrity and Submission Quality

[Some mathematical errors, poor quality safety narratives, missing information in CRFs; but all small issues that do not impact the overall approvability of pregabalin ER; speaks more to the attention to detail, editorial process of the Applicant’s drug development program]

8.3.2. Categorization of Adverse Events

[All adverse events were coded by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) with Version 14.1 used for Study 1194, Version 16.0 used for Study 1245, and Version 18.1 used for Study 1224. The integrated adverse events analyses were performed by the Applicant using preferred terms from MedDRA Version 18.0 or higher.]

8.3.3. Routine Clinical Tests

[Clinical laboratory testing was performed at the screening visit (Visit 1 for Studies 1224, 1245, and 1194), at the end of treatment (Visit 8) for Study 1194, at the end of SB treatment (Visit 7 for Study 1224 and Visit 6 for 1245), and at the end of DB treatment (Visit 10 for Study 1224 and Visit 9 for 1245). Laboratory testing at any of these visits included the following:

- Hematology: hemoglobin, hematocrit, WBC count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, and platelet count
- Chemistry: amylase, AST, ALT, albumin, alkaline phosphatase (ALK), blood urea nitrogen, creatinine, electrolytes (sodium, potassium, chloride, calcium), glucose, total protein, total bilirubin, uric acid
- Urinalysis: pH, specific gravity, glucose, blood/hemoglobin, and microscopic sediment examination (additional testing for Study 1194 – protein, nitrate, ketones)

Laboratory testing at Visit 1 (Study 1224) only used to determine eligibility included the following:

- Thyroxin (T4)/thyroid-stimulating hormone and vitamin B12 (folate)
- Serum pregnancy test (all females of child bearing potential)

Laboratory testing at Visit 0 or 1 (Study 1245) required to determine eligibility included the following:

- Thyroid-stimulating hormone and vitamin B12/folate
- Rheumatoid Factor
- Westergren ESR
- Antinuclear Antibody
- Serum pregnancy test (all females regardless of childbearing potential)

Laboratory testing at Visit 1 (Study 1194) required to determine eligibility included the
following:

- T4/TSH
- Vitamin B12/folate
- Creatinine clearance
- Urine pregnancy test (with serum test confirmation if urine positive); also required at Visits 3 and 8

8.4. Safety Results

8.4.1. Deaths

[Three subjects died in the Phase 3 pregabalin ER studies. Two deaths occurred during Study 1224 – one subject receiving pregabalin ER 165 mg daily during the SB Phase and one subject randomized to placebo during the DB Phase. One death occurred during Study 1194 - subject died prior to randomization. There were no deaths in Study 1245. Summaries of the deaths with inclusion of my assessment of causality are provided below.

Individual Summaries of Deaths

Subject Number: [Redacted]
Study Number: 1224 (pregabalin ER, SB Phase)
PT at death: Acute respiratory failure

Subject [Redacted] was a 28 year old, HIV+, African-American male who died, reportedly of respiratory failure, during the study. He was a non-smoker with no history of respiratory disease. His HIV diagnosis was poorly documented. The Applicant reported an HIV diagnosis date of [Redacted] yet the subject’s CD4 count on [Redacted] was significantly low at 184. The subject likely had advanced HIV disease at screening on [Redacted]. His baseline weight was 62 kg and height was 167 cm – BMI 21.9. His baseline labs were notable for the following: low WBC count (3.8 x 10^9/L), low H/H (10.6 g/dl/31 %), low ALC (0.51 x 10^3/mm^3), low albumin (2.7 g/dl), elevated amylase (148 IU/L), and elevated AST (56 U/L). He was started on oral anti-retroviral medication (lamivudine, efavirenz, and tenofovir) on [Redacted].

The subject received pregabalin ER from [Redacted]. He completed the SB Phase of the study, did not meet randomization criteria for the DB Phase, and then completed a one week taper off pregabalin ER. Pertinent to the SAE that led to his death, he had an upper respiratory infection (URI) approximately six weeks prior to his death that was considered mild by the investigator, was treated with an oral antibiotic, an oral expectorant and an oral bronchodilator for 5 days, and resolved within one week.

His last study visit was conducted on [Redacted] – 12 days before his death. His laboratory results were significant for the following: elevated LFTs (ALT 127 U/L/AST 269 U/L), elevated
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alkaline phosphatase (838 U/L), elevated glucose (139 mg/dl), elevated serum uric acid (256), decreased H/H (6.4 g/dl/18 %), decreased serum sodium (129 mEq/L), decreased albumin (2.3 g/dl), and decreased serum calcium (7.9 mg/dl). The CRF mentioned concern for “liver failure” though the evidence for liver dysfunction in the available documentation was limited to elevated transaminases.

There is little detail around the terminal event. Apparently, the subject was short of breath and was taken to the hospital where he was pronounced dead on arrival with cause of death documented as acute respiratory failure. No autopsy was performed. The Applicant was unable to produce any other information about this case.

Impression

Subject was a young man with advanced HIV disease at screening who died after seven weeks of treatment with pregabalin ER. He had no history of pulmonary disease but apparently experienced sudden respiratory failure and death. His labs at baseline showed anemia, leukopenia, transaminitis, and hypoalbuminemia. His labs two weeks prior to his death showed worsening anemia, transaminitis, hypoalbuminemia, and other non-specific metabolic abnormalities consistent with poor nutritional status. The Applicant considered this subject’s death not related to pregabalin ER and suggested that efavirenz could not be ruled out. Efavirenz is not associated with respiratory failure. While this subject’s death is likely due to advanced HIV disease, the contribution of pregabalin ER cannot be excluded.

Subject Number: 
Study Number: 1224 (pregabalin ER, SB Phase; placebo, DB Phase)
PT at death: Cerebrovascular disorder

Subject was a 78 year old, Caucasian, male who died from cerebrovascular disorder during the study. He was a cigarette smoker with a history of Type 2 DM and chronic bronchitis. He received pregabalin ER from . He completed the SB Phase of the study, met randomization criteria, and was randomized on to placebo for the DB Phase of the study. He completed a one week taper off pregabalin ER and took placebo from . Relevant to the SAE that led to his death, the subject experienced gait disturbance 11 days prior to his death (on ) while taking pregabalin ER. This adverse event was considered mild and resolved within one week. His last study visit was conducted on – 17 days before his death. His physical examination remained unchanged from his baseline at screening and his laboratory results were only notable for an elevated glucose level (160 mg/dl).

There is really no information around the terminal event. Apparently, an ambulance was called
for unknown reasons, unknown medications were administered via injections, and the subject
died on the same day with a diagnosis of cerebrovascular disorder. The subject was not
hospitalized and no autopsy was performed.

**Impression**
Subject was an elderly man with underlying diabetes and smoking history who died
as a result of cerebrovascular disease after two months of treatment with pregabalin ER and 11
days of treatment with placebo. The Applicant considered this subject’s fatal event not related
to pregabalin ER and suggested that his underlying medical condition contributed to his death.
The subject’s older age, underlying diabetes, and smoking history placed him at increased risk
for cerebrovascular disease. The adverse event of gait disturbance 11 days prior to his death
was likely the consequence of cerebrovascular disease as well. It is not uncommon for patients
with cerebrovascular disease to have smaller, less consequential, ischemic events preceding a
larger, more debilitating, or potentially fatal, ischemic event. Additionally, the subject was on
placebo at the time of his cerebrovascular event. This SAE is not related to pregabalin ER.

**Subject Number:**  
**Study Number:** 1194 (Screening Phase)  
**PT at death:** Status epilepticus

Subject was a 46 year old, Hispanic female who died as a result of status epilepticus
during the screening phase of the study. She had a screening visit on but
was not randomized into the study because of her death. She did not receive pregabalin ER.

The subject had ongoing complex partial and generalized seizures, as well as somnolence and
lack of coordination, while taking oral magnesium valproate and oral phenytoin during the
screening phase. On , seven days before her death, she had a fall because of her incoordination that resulted in a head injury. In the four days preceding her death, she
stopped taking her oral anti-epileptic medication, and had less somnolence, but resumed
having partial seizures. On the day of her death, she was restarted on both oral magnesium
valproate and oral phenytoin.

There is minimal information regarding her terminal event. The subject had a fall as a result of
pain, numbness, and loss of sensation in her legs. She was taken to a hospital, was discharged,
and then was taken to another hospital where she arrived in cardiac arrest. The medical team
attempted resuscitation unsuccessfully. The subject died as a result of status epilepticus.

**Impression**
Subject was a middle aged woman with a long-standing history of epilepsy who died
from status epilepticus while in the screening phase of the study. The Applicant did not
consider causality as the fatal event occurred prior to randomization and was related to the
subject’s underlying medical condition. In my opinion, this subject’s death had no relatedness to pregabalin ER as the subject died from status epilepticus, before randomization into the study, and before initiation of any study medication. ]

8.4.2. Serious Adverse Events

[One SAE was reported during the Phase 1 single dose studies – Subject \( (b) (6) \) in Study 1239 had drug exposure in utero. This SAE was identified after the subject completed the study and reported having an elective abortion. No SAEs occurred in the Phase 1 multiple dose studies.

A total of 41 pregabalin ER treated subjects reported SAEs during the Phase 3 studies. Twenty-four subjects in Study 1224 reported SAEs – one SAE that resulted in death (Subject \( (b) (6) \)) has already been described in Section 8.4.1. Seven subjects in Study 1245 and 10 subjects in Study 1194 also reported SAEs.

I reviewed the line listings for all SAEs and for all AEs leading to discontinuation that occurred in the Phase 3 clinical studies. I conducted a complete review of 32 SAEs. Summaries of the selected SAEs with inclusion of my assessment of causality are provided below.

Individual Summaries of Serious Adverse Events NOT Leading to Permanent Study Discontinuation

Subject Number: \( (b) (6) \)
Study Number: 1224 (pregabalin ER, SB Phase)
PT: Pharyngitis/Dehydration

Subject \( (b) (6) \) is a 45 year old, HIV+, African-American, female who had pharyngitis and dehydration warranting hospitalization during the study. The subject reported her HIV status as negative during screening; however, she was diagnosed with HIV when hospitalized during the study. She received pregabalin ER from \( (b) (6) \). She completed the SB Phase of the study and was randomized on \( (b) (6) \) to pregabalin ER for the DB Phase of the study. She completed the DB Phase of the study as well and tapered off pregabalin ER from \( (b) (6) \).

On \( (b) (6) \), two days before starting pregabalin ER and three days before her hospitalization, the subject experienced pharyngitis that was considered moderate in severity and was treated with one dose of IM antibiotics and a five-day course of oral antibiotics. By \( (b) (6) \), she was unable to eat or drink because of worsening pharyngitis. She consulted a specialist who had her hospitalized for pharyngitis and dehydration. Blood work done during the hospitalization revealed the following abnormalities: low CD4 count (371 x \( 10^3 \)/mm\(^3\)), low Hgb (10.5 g/dl; unchanged from baseline), high viral load (655,047 IU/ml), and...
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elevated CRP (19.2 mg/L). She was treated fairly aggressively with an IV antiviral, an IV antibiotic, and an oral antifungal. After discharge from the hospital on [b (6)], she resumed participation in the study and restarted pregabalin ER daily.

**Impression**
Subject [b (6)] is a middle aged woman with previously undiagnosed HIV disease who experienced pharyngitis and dehydration during the study. The Applicant considered these adverse events not related to pregabalin ER but rather to the subject’s intercurrent conditions. Her underlying HIV disease resulted in leukopenia and immunosuppression that left her vulnerable to infection. Additionally, her pharyngitis started two days before she initiated daily intake of pregabalin ER. This subject’s adverse events of pharyngitis and dehydration are not related to pregabalin ER.

**Subject Number:** [b (6)]
**Study Number:** 1224 (pregabalin ER, SB Phase)

**PT:** Cerebrovascular accident

Subject [b (6)] is a 49 year old, African-American male, with a reported history of HIV and hypertension that is poorly documented in the submission, who experienced a left-sided cerebrovascular accident (CVA) during the study. He received pregabalin ER from [b (6)] to [b (6)]. He completed the SB Phase of the study, was randomized on [b (6)] to placebo for the DB Phase of the study but never received any placebo as he was no longer willing to participate in the study. On [b (6)], the subject had a left-sided CVA that resulted in hospitalization. He continued on pregabalin ER daily. The left-sided CVA was documented as still present but recovering as of [b (6)] after which time the subject was lost to follow up. He was withdrawn from the study on [b (6)] as he was no longer willing to participate.

**Impression**
Subject [b (6)] is a middle aged man with HIV and hypertension who experienced a left-sided CVA after approximately one month of treatment with pregabalin ER. The Applicant considered the CVA not related to pregabalin ER but rather to the subject’s underlying or intercurrent condition. Both of this subject’s underlying medical problems, hypertension and HIV, place him at increased risk for a cerebrovascular event. The SAE of left-sided CVA is not related to pregabalin ER.

**Subject Number:** [b (6)]
**Study Number:** 1224 (pregabalin ER, SB Phase)

**PT:** Chronic Obstructive Pulmonary Disease

Subject [b (6)] is a 64 year old, Asian, male with a history of pulmonary TB s/p right upper
lobectomy, COPD, and bronchiectasis who experienced two episodes of chronic obstructive pulmonary disease (COPD) exacerbation both resulting in hospitalization during the study. He is an ex-smoker who typically has a COPD exacerbation once a month requiring hospitalization. He received pregabalin ER from [redacted] [redacted]. He completed the SB Phase of the study on [redacted] [redacted] but did not meet randomization criteria for the DB Phase. He experienced a COPD exacerbation on [redacted] [redacted] with hospitalization for two days and again on [redacted] [redacted] with hospitalization for six days. Each time, he was treated with oral antibiotics, oral steroids, inhaled steroids, an inhaled beta-agonist, and several other inhaled medications. He was discharged from the hospital after both events with resolution of the COPD exacerbation. He withdrew from the study on [redacted] [redacted] because of insufficient clinical response.

Impression
Subject is an elderly man with significant underlying pulmonary disease who had two COPD exacerbations during the study. One COPD exacerbation occurred six days after starting pregabalin ER and the other occurred one month into treatment with pregabalin ER. The Applicant considered these COPD events not related to pregabalin ER but rather natural progression of the subject’s pre-existing COPD. This subject has multiple pulmonary conditions, including a prior lobectomy, bronchiectasis, and COPD, as well as a smoking history that place him at considerably increased risk for respiratory infection and respiratory compromise. He also has a known history of monthly hospitalization for COPD exacerbation. The SAEs of COPD exacerbation are not related to pregabalin ER.

Subject Number: [redacted] [redacted]
Study Number: 1224 (pregabalin ER, SB Phase)
PT: Syncope

Subject is an 83 year old, Caucasian, male with coronary artery disease s/p quadruple bypass surgery, hypercholesterolemia, HTN, and anemia who had a syncopal event during the study. He received pregabalin ER from [redacted] [redacted]. On [redacted] [redacted], he had a syncopal event that resulted in hospitalization for 8 days. He had no preceding complaints of dizziness or lightheadedness at the time of the SAE. An evaluation for myocardial infarction was negative. A cardiac catheterization revealed triple vessel coronary artery disease. The subject no longer wanted to participate in the study or return for an early termination visit; therefore, he was permanently discontinued from the study on [redacted] [redacted].

Impression
Subject is an elderly man with known cardiac disease who had a syncopal event, likely caused by coronary insufficiency, after two weeks of treatment with pregabalin ER. The Applicant considered the SAE of syncope not related to pregabalin ER. This subject’s past medical history of coronary artery disease, hypercholesterolemia, and HTN places him at
significant risk for coronary artery disease and coronary insufficiency. Coronary insufficiency leads to decreased cardiac and cerebral perfusion and, potentially, syncope. The SAE of syncope is not related to pregabalin ER.

Subject Number: [blank]
Study Number: 1224 (pregabalin ER, SB Phase)
PT: Pneumonia

Subject [blank] is a 77 year old, Caucasian, female with significant cardiac disease (coronary artery disease s/p bypass surgery, atrial fibrillation (Afib), congestive heart failure, and aortic valve disease), pulmonary disease (COPD and asthma), chronic renal disease, and Type 2 DM who reportedly had pneumonia during the study. She received pregabalin ER from [blank] She was incorrectly dosed with pregabalin ER 330 mg daily instead of pregabalin ER 247.5 mg daily (appropriate for renal impairment) from [blank] After one month of treatment with pregabalin ER, the subject presented to the hospital with altered mental status, an elevated WBC count (13.9 x 10^9/L), an elevated BNP (486 pg/ml), a normal troponin level, normal oxygenation, and chest x-ray findings of moderate pulmonary congestion with diffuse worsened interstitial markings and cardiomegaly. She was diagnosed with pneumonia and hospitalized for 4 days. Her ECG showed atrial fibrillation with a rapid ventricular response (RVR) rate of 130, her head CT was unremarkable, and her blood cultures were negative. She was treated with IV antibiotics, oral antibiotics, and an oral beta-blocker. The pneumonia was documented as resolved by [blank] at which time the subject withdrew from the study as she was no longer willing to participate.

Impression
Subject [blank] is an elderly female with known cardiopulmonary disease and renal disease who, I conclude, had a CHF exacerbation rather than pneumonia after one month of treatment with pregabalin ER. Her clinical presentation of altered mental status with no fever is more consistent with CHF exacerbation than pneumonia. Her laboratory finding of an elevated BNP, x-ray findings of worsening interstitial infiltrates and cardiomegaly, and ECG findings of Afib with RVR all are consistent with CHF exacerbation as well. Additionally, pneumonia is much less common in the summer months. The Applicant considered the SAE of pneumonia not related to pregabalin ER but rather to the subject’s history of COPD. From my perspective, the SAE of CHF exacerbation is a consequence of this subject’s underlying cardiopulmonary disease and not related to pregabalin ER.

Subject Number: [blank]
Study Number: 1224 (pregabalin ER, SB Phase)
PT: Urinary Tract Infection/Septic Shock

Subject [blank] is a 58 year old, Asian, female with likely poorly-controlled DM (baseline
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serum glucose of 431 mg/dl on ), bladder disorder, and diabetic retinopathy who had a urinary tract infection (UTI) and septic shock while tapering off pregabalin ER. She received pregabalin ER from , was discontinued from the study on as required by the medical monitor due to patient safety concerns (retinopathy), and tapered off pregabalin ER from . Three days into her pregabalin ER taper, the subject had fever and was seen in the ED. During her ED visit, she had hypotension and was diagnosed with septic shock secondary to a UTI. She was hospitalized for five days and was treated with dopamine, fluids, and oral antibiotics. She was discharged from the hospital on at which time her septic shock had resolved. Her UTI resolved by

Impression
Subject is a middle aged woman with DM who had a UTI and septic shock after six weeks of treatment with pregabalin ER. The Applicant considered both SAEs not related to pregabalin ER but rather caused by an intercurrent infectious condition. Patients with diabetes are at increased risk for UTIs because of high urine glucose content and defective host immunity. Localized infection, when not recognized and treated appropriately with antibiotics, can then spread systemically leading to bacteremia and septic shock. This subject’s diabetes left her immunocompromised and susceptible to infection. The SAEs of UTI and septic shock are not related to pregabalin ER.

Subject Number:
Study Number: 1224 (pregabalin ER, SB Phase)
PT: Vertebrobasilar insufficiency

Subject is a 71 year old, Russian, female with osteochondrosis and autoimmune thyroiditis who experienced vertebrobasilar insufficiency during the study. She received pregabalin ER from . She completed the SB Phase of the study, was randomized on to pregabalin ER for the DB Phase, completed the DB Phase of the study, and then tapered off pregabalin ER from . On after one month on pregabalin ER, the subject experienced dizziness and diplopia and was diagnosed with vertebrobasilar insufficiency. Her symptoms worsened over several days with development of an abnormal neurological examination - bilateral nystagmus, a positive Romberg, and an intention tremor with finger nose finger testing. She was hospitalized, treated with medication, and evaluated for possible basilar stroke. Her work-up was negative except for cervical x-rays that showed kyphosis. She was discharged from the hospital after resolution of her neurological symptoms with a final diagnosis of vertebrobasilar insufficiency. Additionally, the subject had two other non-serious AEs surrounding the SAE that were mild in intensity - headache on that resolved in five days and vertigo on that did not resolve by the end of the study.
Impression
Subject is an elderly woman with no significant past medical history who experienced vertebrobasilar insufficiency after one month of treatment with pregabalin ER. The Applicant considered this SAE not related to pregabalin ER but rather the result of an intercurrent medical condition; however, the Applicant considered the surrounding AEs of headache and vertigo related to pregabalin ER. I would argue that the contribution of pregabalin ER to the SAE of vertebrobasilar insufficiency as well as the AEs of headache and vertigo cannot be excluded.

The subject’s older age, post-menopausal status, and hypoactive thyroid place her at increased risk for vertebrobasilar insufficiency, yet all of her symptomatology consists of known adverse reactions with Lyrica. She initially complained of headache followed by dizziness and diplopia - known adverse reactions with Lyrica. Her neurological abnormalities of nystagmus, a positive Romberg (which can occur when one has dizziness or ataxia), and tremor are also known adverse reactions with Lyrica. Lastly, she had vertigo – another known adverse reaction with Lyrica - during the DB Phase of the study that remained through completion of the study.

Subject Number:  
Study Number: 1224 (pregabalin ER, SB Phase)  
PT: Gastroesophageal Reflux Disease (GERD)/WBC count increased

Subject is a 54 year old, Caucasian, female with GERD and hiatal hernia who experienced an event of nausea, vomiting, chest pain, pain radiating to the left shoulder, dizziness, and disorientation that resulted in an ED visit during the study. She received pregabalin ER from . She completed the SB Phase of the study, was randomized to pregabalin ER on for the DB Phase of the study, and then completed the DB Phase of the study. After about three weeks on pregabalin ER, she had the above-listed symptoms, was seen in the ED, was treated with IV fluids, an antiemetic, and an H2 blocker, and was diagnosed with GERD exacerbation and leukocytosis (WBC count 13,600). Pregabalin ER was stopped for one day but was restarted on when all of her symptoms had resolved. The pregabalin ER dosage was then decreased on . The subject had no recurrence of her symptomatology throughout the rest of the study.

Impression
Subject is a middle aged woman with known gastrointestinal issues who apparently experienced either a viral gastritis or a GERD exacerbation and leukocytosis after three weeks on pregabalin ER. Her symptoms resolved within one day after IV hydration and medication. There is no documentation of any causality for the subject’s leukocytosis. The Applicant considered the events of GERD exacerbation and leukocytosis not related to pregabalin ER. I agree with this conclusion as the subject’s symptoms did not recur once pregabalin ER was restarted.
Subject
Study 1224 SB Phase
PT: Haematuria

Subject is an 82 year old, Caucasian male with a 9 year history of PHN. His past medical history was significant for nephropathy stage III, bladder cancer stage III, non-Hodgkin’s lymphoma, COPD, HTN, coronary artery disease s/p coronary artery bypass and heart valve operation, anemia, and dyslipidemia. He was enrolled in Study 1224 on . He took pregabalin ER from . He started on the lowest dose of pregabalin ER due to decreased renal function (CLcr 37 ml/min). On , while taking pregabalin ER 247.5 mg, he developed hematuria. He was seen in the ED on and had CT of abdomen and pelvis and bladder irrigation. Study drug was interrupted from . The AE of hematuria resolved on without intervention. The subject withdrew from the study for unknown reasons on . The Applicant considered the AE related to the subject’s underlying cancer and renal condition, not study drug.

Impression

I agree that the AE of hematuria is likely related to the subject’s underlying medical problems and is unrelated to pregabalin ER.

Subject
Study 1224 SB Phase
PT: Acute myocardial infarction

Subject is an 80 year old, Caucasian male with a 1 year history of PHN. His past medical history is significant for the following: HTN, hyperlipidemia, arrhythmia, CAD s/p CABG. He was enrolled in Study 1224 on . He took pregabalin ER from . He completed the SB phase and was randomized to placebo for the DB Phase from . On while taking pregabalin 165 mg daily, the subject presented to the ED with chest pain and was hospitalized with the diagnosis of acute myocardial infarction. He did not take medication on the day of the event. Labs showed elevated troponin levels. Other testing showed restenosis of previously placed stents. His medications were modified and he was discharged on . He underwent CABG on and the AE of AMI was considered resolved. The subject discontinued from the study on for other reasons. The Applicant considered the AE of acute myocardial infarction not related to study drug.

Impression
I agree that the SAE of acute myocardial infarction is not related to pregabalin ER as the subject had a significant past medical history of coronary artery disease and prior CABG with evidence of blocked coronary arteries during his hospitalization.

Subject

Study 1224 DB Phase
PT Anaemia of chronic disease

Subject is a 59 year old, African-American female with a 14 month history of PHN. Her past medical history is significant for HIV infection and HTN. She was enrolled in Study 1224 on  followed by a one week taper of study medication. On while taking pregabalin 660 mg daily, the subject was diagnosed with anemia of chronic disease (anemia in chronic infection) with a Hgb 6.6/Hct 22 and was treated with a blood transfusion. On repeat Hgb 5.2/Hct 17, ANC 1.59 x 10³/mm³, WBC count 3 x 10⁹/L, and decreased platelet count. She was then referred to the hospital.

On, the subject was admitted to the hospital for anemia of chronic disease and respiratory distress on exertion. The subject had pancytopenia secondary to HIV infection. She was treated with IV fluids and oral ferrous sulfate, ascorbic acid and multivitamins. She was discharged on .

On , the subject received a blood transfusion (2 units). Her anemia was resolved on . The subject also had increased LFTs, increased amylase, increased glucose. H/H improved to 9.8/30 by . The investigator the AE of anemia of chronic disease not related to study drug.

Impression

I agree that the SAE of anemia is not related to pregabalin ER. The subject had an underlying chronic infection (HIV) that caused anemia.

Subject

Study 1224 DB Phase
PT: Acute sinusitis

Subject is a 63 year old, Caucasian female with a ten month history of PHN. Her past medical history is notable for the following: autoimmune thyroiditis, asthma, essential HTN, chronic cerebral ischemia, and papillomatosis of the cervix s/p hysterectomy. She was enrolled in Study 1224 on took pregabalin ER from . She completed the SB Phase and was randomized to receive pregabalin 165

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mg daily in the DB Phase from [blurred].

On [blurred] while taking pregabalin 165 mg daily, the subject was diagnosed with acute right maxillary sinusitis that necessitated hospitalization and drainage of the right maxillary sinus. She was treated with oral clarithromycin and oral anti-histamine. The AE of acute sinusitis resolved and the subject was discharged from the hospital on [blurred]. The Applicant considered the AE of acute sinusitis not related to study drug but rather due to an intercurrent or underlying condition.

Impression

I agree that the AE of acute sinusitis is not related to pregabalin ER.

Subject [blurred]
Study 1224 DB Phase
PT: Back pain

Subject [blurred] is a 52 year old, Caucasian male ex-smoker with an almost two year history of PHN. His past medical history is significant for the following: hiatal hernia, HTN, GERD, Barrett’s esophagus, hypertriglyceridemia, and Vitamin B complex deficiency. He was enrolled in Study 1224 on [blurred]. He took pregabalin ER from [blurred]. He completed the SB Phase and was randomized to pregabalin ER 660 mg daily for the DB Phase from [blurred].

On [blurred] while taking pregabalin 660 mg daily, the subject experienced back pain, was seen in the ED and was hospitalized. His work up for renal stones, cholelithiasis, and radiculopathy was negative. His CT of the chest, abdomen and pelvis was negative. His chest x-ray showed elevation of the right diaphragm and patchy right lower lobe infiltrate likely from atelectasis. He was treated with pain medications. On [blurred], he was discharged home on Flexeril and Vicodin. The AE of back pain resolved on [blurred]. The subject discontinued from the study on [blurred] at the request of the Sponsor because he had missed more than four doses of study medication during his hospitalization. The Applicant considered the AE of back pain not related to study drug, but rather an intercurrent condition.

Impression

I agree that the AE of back pain is not related to pregabalin ER.

Subject [blurred]
Study 1224 DB Phase
PT: Perirectal abscess
Subject is a 76 year old, Caucasian male with a three year history of PHN. His past medical history was notable for the following: Parkinson’s disease, Type 2 DM, hyperlipidemia, and HTN. He was enrolled in Study 1224 on . He took pregabalin ER daily from . He completed the SB phase and was randomized to pregabalin 330 mg daily for the DB phase from .

On while taking pregabalin 330 mg daily, the subject developed a perirectal abscess and was started on oral antibiotics. On he visited the ED and was admitted to the hospital for perirectal abscess. He underwent an incision and drainage on and was started on IV antibiotics. He was discharged from the hospital on . The perirectal abscess resolved on . The subject discontinued from the study on for other reasons. The Applicant considered the AE of perirectal abscess not related to study drug.

Impression

I agree that the AE of perirectal abscess is not related to study drug.

Subject Study 1245 SB Phase
PT: pneumonia

Subject is a 39 year old Caucasian, non-smoking female with a five month h/o FM. Her past medical history is significant for depression. She enrolled in Study 1245 on and took pregabalin ER from . On , the subject returned for Visit 6 but was then lost to follow up. The subject was permanently discontinued from the study on because she was lost to follow up. On , reportedly 12 days after the subject’s last dose of pregabalin ER, the subject was hospitalized with pneumonia. There is no additional information about the hospitalization or the subject’s treatment. On , the subject was discharged from the hospital. The Applicant considerer the SAE of pneumonia unrelated to pregabalin ER and, instead, related to acute infection.

Impression

The data provided are insufficient to confidently conclude that the subject’s diagnosis of pneumonia was correct - no physical examination, no x-ray results, no lab findings. is an uncommon time of the year in the United States for exposure to community acquired pneumonia, especially in a young, otherwise healthy individual. The role of pregabalin ER in this AE of pneumonia cannot be excluded.
Subject: (b) (6)

Study 1245 DB Phase

PT: Breast cancer

Subject is a 55 year old Caucasian, non-smoking, postmenopausal female with a 15 year h/o FM. Her past medical history included the following: migraines, uterine enlargement, uterine prolapse and OA. She was enrolled in Study 1245 on , took pregabalin ER from , and then was randomized to receive pregabalin ER 330 mg from . She tapered off pregabalin ER from . The subject received the last dose of study drug on . She was no longer willing to participate and discontinued from the study on .

On while taking pregabalin ER 330 mg, the subject had a mammogram with biopsy. A diagnosis of Stage 2 breast cancer (infiltrating ductal carcinoma of the right breast) was made necessitating further medical treatment. The investigator considered the event to be severe and serious. On she had a right breast lumpectomy. She started the first cycle of chemotherapy on and the second cycle on . The investigator considered the AE of breast cancer to be unrelated to study drug.

Impression

I agree that the AE of breast cancer is unrelated to study drug.

Individual Summaries of Serious Adverse Events Leading to Permanent Study Discontinuation

Subject Number: (b) (6)

Study Number: 1224 (pregabalin ER, SB Phase)

PT: Liver function test abnormal

Subject is a 78 year old, Caucasian, male with multiple known drug hypersensitivities, hyperlipidemia, treated with lovastatin for two years, and PHN treated with paracetamol who had elevated liver function tests during the study. He received pregabalin ER from . His LFTs at screening were normal. Of relevance to this SAE, he developed a pruritic, papular rash on his forearms after 19 days on pregabalin ER that resulted in permanent discontinuation of the study drug. Nine days later and one day after taking his last dose of pregabalin ER, on the subject had hyperbilirubinemia and transaminitis with an elevated total bilirubin, AST, ALT, and alkaline phosphatase. He was hospitalized for further evaluation. Lovastatin and paracetamol were discontinued. His labs did not meet Hy’s law criteria. Reactive hepatitis, viral hepatitis, and biliary obstruction were ruled out. His total bilirubin peaked at 3.9 mg/dl, his AST and ALT peaked at 75 IU/L and 225 IU/L, and his alkaline phosphatase peaked at 297 IU/L with slow resolution of his labs to normal by

Reference ID: 4150575
He developed pruritus of the lower legs and then severe, generalized pruritus that improved but was ongoing by the end of his participation in the study.

**Impression**
Subject is an elderly man who developed transaminitis after one month of treatment with pregabalin ER. The Applicant considered the SAE of transaminitis related to pregabalin ER; however, the contributory role of the subject’s other medications, lovastatin and paracetamol, could not be ruled out. I agree with this conclusion as the subject’s lab abnormalities, pruritic rash, and generalized pruritus slowly resolved with elimination of the study drug. The SAE of transaminitis is related to pregabalin ER yet the potential role of lovastatin and paracetamol cannot be excluded.

**Subject**
Study 1224 SB Phase
PT: cardiac failure

Subject is a 71 year old, Caucasian female with an almost 10 year h/o PHN. Her past medical history is notable for mitral valve incompetence, aortic valve stenosis, coronary artery arteriosclerosis, migraines, and depression. She enrolled in Study 1224 on , took pregabalin ER from , randomized to pregabalin 165 mg daily for the DB phase of the study, and took pregabalin ER 165 mg daily from .

On while on pregabalin 165 mg daily, the subject had cardiac failure that resulted in hospitalization. She was diagnosed with calcification of the aortic valve. On a transesophageal echocardiogram and a cardiac catheterization revealed aortic valve stenosis and mitral insufficiency. A carotid duplex ultrasound showed no clinically significant findings. On , the subject underwent aortic valve replacement. On , her cardiac failure was documented as resolved. The subject was permanently discontinued from the study on . The investigator considered the SAE of cardiac failure not related to pregabalin ER.

**Impression**
I agree that the SAE of cardiac failure is not related to the study drug. The subject had an underlying medical condition which led to aortic valve stenosis and subsequently cardiac failure.

**Subject**
Study 1224 SB Phase
PT: Thrombocytopenia

Subject is a 77 year old, Caucasian female with a four year history of PHN. Her past medical history...
medical history is significant for the following: obesity, hyperlipidemia, thrombocytopenia, and leukopenia. She was enrolled in Study 1224 on [ ]. She took pregabalin ER daily from [ ]. She completed the SB Phase and was randomized to placebo daily on [ ].

On [ ], the subject had a platelet count of 96 x 10^3/mm^3. On [ ], while taking pregabalin 330 mg daily, the subject had a platelet count of 24 x 10^3/mm^3 that was considered severe and serious by the investigator. On [ ], her platelet count was 26 x 10^3/mm^3. The study drug was discontinued after the subject completed her tapering phase due to the AE of worsening thrombocytopenia. The last dose of study medication was taken on [ ].

The subject discontinued from the study on [ ]. The subject had a bone marrow biopsy on [ ] to rule out leukemia and lymphoma. The subject’s platelet count reached a low of 15 x 10^3/mm^3 on [ ] and then improved to 27 x 10^3/mm^3 on [ ]. The AE of worsening thrombocytopenia resolved with sequelae on [ ].

Per the investigator and sponsor, the AE of worsening thrombocytopenia was not related to study drug. The investigator stated there was a reasonable possibility that the worsening thrombocytopenia was related to the subject’s concomitant medications – ezetimibe and atorvastatin. The sponsor stated that the worsening thrombocytopenia was likely due to underlying medical conditions.

Impression

I agree that the AE of worsening thrombocytopenia is not related to pregabalin ER. I suspect that the worsening thrombocytopenia was likely a consequence of the subject’s underlying medical history. I do not agree that the AE was related to the subject’s concomitant medications given her longstanding use for approximately 10 years of both ezetimibe and atorvastatin.

Subject [ ]
Study 1224 SB Phase
PT: Sexual Abuse

Subject [ ] is a 68 year old, Hispanic male with a brief history of PHN. His past medical history is remarkable for the following: radical prostatectomy, DM, and urinary tract infection. He was enrolled in Study 1224 on [ ]. He took pregabalin ER daily from [ ].

On [ ], while taking pregabalin ER 660 mg daily, the subject reported that he
attempted to sexually assault a minor aged child, his granddaughter. This event was considered
severe by the investigator. The subject admitted to playing with and touching the lower private
parts of his granddaughter but did not anything further as he is impotent. He passed by her
bed in the early morning hours and sat on her bed while feeling drowsy and somnolent. He
used drowsiness as a possible explanation for his behavior. The study drug was permanently
discontinued due to this AE. The subject discontinued from the study on (b) (6) A
psychiatric evaluation was performed at discontinuation visit – no underlying psychiatric
pathology identified but mild cognitive impairment (expected for his age). The investigator,
considered the AE of sexual abuse related to the study drug; however, the Applicant did not
consider the AE of sexual abuse related to the study drug.

Impression

I agree with the Applicant that the AE of sexual abuse is not related to the study drug (b) (6).

Subject (b) (6)
Study 1224 SB Phase
PT: Hyponatremia

Subject (b) (6) is a 73 year old, Caucasian male with a four and one-half year history of PHN.
His past medical history is significant for the following: HTN, gout, and osteoarthritis. She was
enrolled in Study 1224 on (b) (6). He took pregabalin ER daily from (b) (6). On (b) (6) before taking pregabalin ER, the subject’s serum sodium was normal at
140 mEq/L and the CLCR was normal at 66 mL/min. On (b) (6) while taking
pregabalin 165 mg daily, the subject was diagnosed with hyponatremia (serum sodium 128
mmol/L and estimated GFR 56ml/min). He was seen in the ED and administered IV fluids. The
study drug was discontinued because of this event. The subject discontinued from the study on (b) (6) due to diagnoses from his PCP of acute hyponatremia, acute renal
insufficiency, and depression. On (b) (6) his GFR improved to 83 ml/min and his
hyponatremia resolved with a serum sodium of 140 mmol/L. Both the investigator and the
considered the AE of hyponatremia not related to study drug.

Impression

I disagree with the Applicant. I conclude that the potential role of pregabalin ER in the SAE of
hyponatremia cannot be excluded.
Subject Study 1245 SB Phase PT: Glossitis

Subject is a 39 year old Caucasian female with a three month h/o FM and known food allergies. She enrolled in Study 1245 on and took pregabalin ER from while on pregabalin 330 mg, the subject experienced glossitis of the tongue a few hours after eating garlic sausage. The event was considered severe and medically significant. She was seen in the ED and received diphenhydramine 50 mg IV BID and oral acetaminophen 1000 mg PRN. Her physical examination was notable for edema of tongue and lower limbs. She was discharged from the ED after a few hours and told to discontinue pregabalin ER. Her glossitis was downgraded from severe to mild on. The subject discontinued from the study on. Her glossitis was documented as resolved on. The investigator considered the AE of glossitis possibly related to pregabalin ER.

Impression

I agree that the AE of glossitis is possibly related to the study drug. From the provided clinical data, the subject likely experienced an anaphylactic reaction while taking pregabalin ER.

Subject Study 1245 SB Phase PT: Chest Pain/Hypertension

Subject is a 52 year old, cigarette smoking, Caucasian, post-menopausal female with a 6 year h/o FM. The subject’s PMH is notable for the following: obesity, cholelithiasis and cholecystectomy, hypertriglyceridemia, asthma, and seasonal allergies. Her screening physical examination was notable for being overweight and having faint rhonchi on lung exam. She had mildly elevated LFTs and glucose at screening. She was enrolled in Study 1245 on and took pregabalin ER from.

On during a screening visit, the subject had an elevated BP measurement of 133/85. On during another study visit, the subject again had an elevated BP measurement of 131/87 and also complained of chest pain. The study drug was permanently discontinued as a result of the event of chest pain. The subject discontinued from the study during the SB Phase on.

The subject went to the ED for further evaluation of her chest pain on and was admitted to the hospital. Her BP varied from 105/63 to 186/117 during the hospitalization. She was evaluated for cardiac ischemia with monitoring of cardiac enzymes, a chest x-ray, and multiple ECGs. The subject’s hypertension and chest pain were documented as resolved on.
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The subject had a negative Lexiscan pharmacologic stress test on [b][6]. Phone follow-up on [b][6] revealed that the subject had no further episodes of chest pain or elevated BP.

The investigator and sponsor considered the events of hypertension and chest pain related to the subject’s underlying medical conditions and not the study drug. The site listed possible coronary artery disease as the most likely cause of the subject’s chest pain and essential HTN as the most likely cause of the subject’s elevated blood pressure.

**Impression**

I agree that the AEs of hypertension and chest pain are most likely related to the subject’s h/o obesity, hypertriglyceridemia, menopausal status and possible ongoing hyperglycemia and not related to pregabalin ER.

**Subject** [b][6]

**Study 1245 SB Phase**

**PT:** Post-traumatic stress disorder (PTSD)

Subject [b][6] is a 39 year old Caucasian, premenopausal female with a 17 year h/o FM. She was enrolled in Study 1245 on [b][6]. Her screening physical examination was unremarkable. Her PMH was notable for the following: cryptosporidiosis infection [b][6], colorectal cancer (full remission following gene therapy), PTSD [b][6].

She took the following dosages of pregabalin ER: 165 mg daily from [b][6], 330 mg daily from [b][6], 495 mg daily from [b][6], 165 mg daily from [b][6], 330 mg daily from [b][6], 165 mg daily from [b][6], 330 mg daily on [b][6], 165 mg daily from [b][6], and 165 mg daily from [b][6].

On [b][6] while on pregabalin ER 495 mg daily, the subject experienced re-emergence of post-traumatic stress disorder symptoms to include daily nightmares, flashbacks, poor sleeping and eating patterns, avoidant behavior, and weight loss. She started attending group therapy 3 times per week.

On [b][6] while on pregabalin ER 495 mg daily, the subject reported an increase in anxiety since [b][6] that was considered an exacerbation of her PTSD by the investigator. The AE was considered severe and serious. The subject’s pregabalin ER dose was decreased to 330 mg daily. The subject was also seen in the ED and treated on [b][6] – no details provided. On [b][6] the study drug was decreased to 165 mg daily.

On [b][6] while on pregabalin ER 165 mg daily, the subject had a convulsion which was...
considered to be moderate in severity and resolved the same day. The subject also reported an incident while driving where she crossed over into several lanes of oncoming traffic and remembered her head shaking and feeling tremulous. The subject attributed the driving incident to PTSD. The study drug was discontinued due to the SAE of PTSD. The investigator felt that the subject’s psychiatric co-morbidities and concomitant medications made her a poor candidate for continuation in the study.

The last dose of pregabalin ER 165 mg daily was taken on [blank] The subject was discontinued from the study on [blank].

On [blank], the subject began taking clonazepam 0.5 mg TID and paroxetine 20 mg daily for recurrent PTSD. The event of PTSD was ongoing at the time of discontinuation.

The investigator and sponsor considered the AE of PTSD unrelated to the study drug.

**Impression**

The role of pregabalin ER in the AE of recurrent PTSD is uncertain particularly given the known adverse event of increased suicidal thoughts or behavior associated with antiepileptic drugs. I am also concerned about the possibility of new onset seizures in this subject.

**Subject**

**Study 1194**

**PT: Somnolence**

Subject [blank] is a 40 year old Caucasian, non-smoking female with an almost 20 year history of epilepsy with partial onset seizures. Her past medical history is significant for the following: pneumococcal meningitis [blank], epilepsy (since [blank] mixed anxiety and depressive disorder [blank]), skull fracture as a result of a bicycle accident (date unknown).

She was screened for Study 1194 on [blank]. Her physical examination was unremarkable and her ECG was normal.

She was randomized to pregabalin 330 mg daily from [blank]. Her concomitant medications were as follows: oxcarbazepine BID and etipro BID.

On [blank] while taking pregabalin 330 mg daily, the subject experienced dizziness, weakness and somnolence in the morning and could not go to work. The event was considered mild in severity, serious and medically significant by the investigator. The study drug was permanently discontinued due to the event. The adverse event of somnolence resolved on [blank]. The subject discontinued from the study on [blank] due to the adverse event of somnolence. The
investigator and the Applicant considered the AE of somnolence related to the study drug.

Impression

I agree that SAE of somnolence is likely related to pregabalin ER given the known side effect profile of pregabalin IR, the sudden onset of symptoms three days after starting study drug, and rapid resolution of symptoms one day after stopping study drug.]

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effect

[Two subjects discontinued due to AEs during the Phase 1 single dose studies – one subject with elevated BP in Study 1188 and one subject with scrotal pain in Study 1239

A total of 141 pregabalin-treated subjects experienced AEs that resulted in permanent study discontinuation: 73 subjects (9.1%) in Study 1224 (PHN), 57 subjects (12.9%) in Study 1245 (FM) and 11 subjects in Study 1194 (Epilepsy).

I reviewed the line listings for all AES leading to discontinuation that occurred in the Phase 3 clinical studies. Clinical summaries of selected cases are provided below.

Subject

Study 1224
PT: dizziness

Subject is a 74 year old, Caucasian female with a 6 year history of PHN. Her past medical history is notable for the following: CVA, amnesia, hypercholesterolemia, hypertension, arrhythmia, fatigue, Type 2 DM, obesity, insomnia and dizziness.

She was enrolled in Study 1224 on . She took pregabalin ER 165 mg daily from . Her concomitant medications were as follows: nebivolol hydrochloride, spironolactone, hydralazine, amlodipine, furosemide, atorvastatin, ezetimibe, glipizide, insulin, doxylamine succinate, and paracetamol PRN.

On while taking pregabalin 330 mg daily, the subject experienced worsening of intermittent fatigue that was considered mild in severity by the investigator. This event resolved on .

On while taking pregabalin 660 mg daily, the subject experienced worsening of intermittent fatigue, worsening of intermittent dizziness and amnesia. All of these events were considered severe in severity by the investigator. Other adverse events noted at this time included vomiting and lower extremity edema. The study drug was temporarily discontinued on because of the event of worsening intermittent dizziness and was resumed on.
The event of worsening intermittent fatigue resolved on [b][6] The study drug was permanently discontinued because of the events of worsening intermittent dizziness and amnesia. The last dose of pregabalin ER 165 mg daily was taken on [b][6]

On [b][6], the events of worsening intermittent dizziness and amnesia improved to mild in severity. The subject permanently discontinued from the study on [b][6]. The events of worsening intermittent dizziness and amnesia were ongoing at the time of study discontinuation. All of the events were considered to be related to study drug.

**Impression**

I agree that the events of worsening intermittent fatigue, worsening intermittent dizziness and amnesia are likely related to pregabalin ER.

**Subject** [b][6]

**Study 1224 SB Phase**

**PT:** Dizziness

Subject [b][6] is a 68 year old Caucasian female with a 6 year history of PHN. Her past medical history is remarkable for the following: depression, GERD, dizziness, migraines, anemia and asthma. She was enrolled in Study 1224 on [b][6] She took pregabalin ER 165 mg daily from [b][6]. Her only concomitant medication was salbutamol sulfate.

On [b][6] while taking pregabalin ER 165 mg daily, the subject experienced worsening dizziness that was considered moderate in severity by the investigator. The study drug was permanently discontinued on [b][6] because of the event of worsening dizziness. The last dose of pregabalin ER 165 mg daily was taken on [b][6].

The subject permanently discontinued from the study on [b][6].

The investigator considered the event of worsening dizziness to be related to study drug.

**Impression**

I agree that the AE of worsening dizziness is likely related to pregabalin ER given the known safety profile of pregabalin IR, the rapid onset of symptoms one day after initiating medication, and the rapid resolution of symptoms two days after stopping medication.

**Subject** [b][6]

**Study 1224**

**PT:** Headache/Somnolence
Subject is a 23 year old African-American female with a 7 year history of PHN. Her past medical history is notable for the following: HIV infection, herpes zoster, and pulmonary TB. She was enrolled in Study 1224 on . She was administered pregabalin ER daily from . Her concomitant medications were as follows: lamivudine, efavirenz, tenofovir and paracetamol.

On , two days after initiating treatment with pregabalin ER 165 mg daily, the subject complained of headache that was considered mild in severity and somnolence that was considered moderate in severity by the investigator. These events resolved without treatment on . The study drug was discontinued and the subject was discontinued from the study due to the events of headache and somnolence. The subject started a taper period on and took the last dose of pregabalin ER 165 mg on .

The investigator considered the events of headache and somnolence to be related to study drug.

Impression

I agree that the events of headache and somnolence are likely related to pregabalin ER.

Subject
Study 1224 SB Phase
PT: Somnolence

Subject is an 84 year old Caucasian, male with a 9 year history of PHN. His past medical history is significant for the following: congestive heart failure, pulmonary embolism, Type II DM, hepatic cirrhosis, hypertension and GERD. He was enrolled in Study 1224 on . His screening labs were notable for hyperglycemia and thrombocytopenia. He took pregabalin ER daily from . His concomitant medications were as follows: metformin, metoprolol, warfarin, and omeprazole.

On while taking pregabalin ER 82.5 mg, the subject experienced dizziness that was considered mild in severity by the investigator. On while taking pregabalin ER 82.5 mg, the subject experienced somnolence that was considered moderate in severity by the investigator. On while taking pregabalin ER 82.5 mg, the subject had vivid dreams that were considered moderate in severity by the investigator. On the study drug was permanently discontinued due to the event of somnolence. The last dose of pregabalin ER 82.5 mg was taken on . On the events of somnolence and abnormal dreams resolved. The subject permanently discontinued from the study on .
The investigator considered the events of somnolence, dizziness and vivid dreams to be related to study drug.

**Impression**

I agree that the events of somnolence, dizziness and vivid dreams are likely related to pregabalin ER given the fairly rapid onset of symptoms after pregabalin ER initiation and rapid resolution after pregabalin ER discontinuation.

**Subject**

**Study 1224 SB Phase**

PT: Oedema peripheral

Subject is a 52 year old Asian, post-menopausal female with a 4 month history of PHN. Her past medical history is notable for the following: Type II DM, essential hypertension, and obesity. She was enrolled in Study 1224 on . Her screening labs were notable for mild hyperglycemia. She took pregabalin ER daily from . Her concomitant medications were as follows: enalapril, hydrochlorothiazide, metformin, acetylsalicylic acid, amlodipine, indomethacin, potassium chloride and paracetamol.

On while taking pregabalin ER 330 mg daily, the subject complained of bipedal pitting edema that was considered to be mild in severity by the investigator. The subject was treated with furosemide from . On while taking pregabalin ER 330 mg daily, the subject had GERD and acute sinusitis that were both considered moderate in severity by the investigator. The study drug was temporarily interrupted from . The subject was treated with amoxicillin from and Gastron from .

On , the study drug was permanently discontinued and the subject discontinued from the study because of the event of peripheral edema. The subject had a taper period from and took her last dose of pregabalin ER 165 mg daily on .

The event of GERD resolved on and the event of acute sinusitis resolved on . The event of peripheral edema resolved on – 27 days after completion of pregabalin ER. The investigator considered the events of peripheral edema, GERD and acute sinusitis to be unrelated to study drug.

**Impression**

I suspect that the AE of peripheral edema is possibly related to pregabalin ER given the known safety profile of Lyrica IR and the onset of symptoms within two days of a pregabalin ER dosage increase from 165 mg daily to 330 mg daily. However, I cannot explain the prolonged time to...
resolution of peripheral edema symptoms – almost four weeks as compared to more typical resolution of symptomatology in days. I agree that the AEs of GERD and acute sinusitis are unlikely to be related to pregabalin ER.

Subject
Study 1224 SB Phase
PT: Oedema peripheral

Subject is an 88 year old Caucasian, post-menopausal female with a 1 year and 3 month history of PHN. Her past medical history is significant for depression, hypothyroidism, hypercholesterolemia, and hypertension. She was enrolled in Study 1224 on . Her labs were notable for mildly elevated BUN at screening.

She took pregabalin ER from . The study drug was temporarily discontinued from due to the event of blurred vision. Her concomitant medications were as follows: simvastatin, levothyroxine, losartan, duloxetine and paracetamol.

On while taking pregabalin ER 165 mg, the subject had bilateral leg edema that was considered moderate in severity by the investigator. The study drug was permanently discontinued because of the event of bilateral leg edema. The subject completed a taper period and took the last dose of pregabalin ER on . The event of bilateral leg edema resolved on . The subject permanently discontinued from the study on .

The investigator considered the event of bilateral leg edema to be related to study drug.

Impression

I suspect that both the event of blurred vision and the event of bilateral leg edema are likely related to pregabalin ER given the known safety profile of Lyrica IR, the onset of blurred vision 3 days after dosage increase from 165 mg daily to 330 mg daily and the rapid resolution of bilateral leg edema after pregabalin ER discontinuation.

Subject
Study 1224 SB Phase
PT: Left bundle branch block (LBBB)

Subject is a 75 year old, Caucasian, female with a 10 month history of PHN. Her past medical history is significant for the following: sinus arrhythmia, GERD, and insomnia. She was enrolled in Study 1224 on and took pregabalin ER daily from . Her screening ECG on showed sinus rhythm with sinus arrhythmia, left axis deviation, left ventricular hypertrophy with repolarization abnormality; septal infarct (age undetermined), and
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prolonged QT (no numerical criteria documented). These ECG findings were considered abnormal but not clinically significant.

On [b/d], while on pregabalin 82.5 mg daily, the subject had tachycardia that was considered moderate in severity. On [b/d] (Study Day 42), while on pregabalin 82.5 mg daily, an ECG showed LBBB with a heart rate of 85 beats per minute, RR interval of 706 msec, PR interval of 166 msec, QRS complex of 140 msec, QT interval of 404 msec, QTcB (Bazett’s correction) interval of 480 msec, and QTcF (Fridericia’s correction) interval of 454 msec. This ECG finding was considered severe by the investigator; consequently, the study drug was discontinued and the subject was discontinued from the study due to the event of LBBB. The LBBB resolved on the same day [b/d] without treatment. The event of tachycardia resolved on [b/d]. The subject tapered off pregabalin ER from [b/d]. The investigator considered the AE of LBBB related to pregabalin ER. The Applicant did not provide an opinion about causality.

**Impression**

In my opinion, the contributory role of pregabalin ER in this AE of LBBB is uncertain. The subject had a history of sinus arrhythmia. The subject had documentation of an abnormal ECG prior to initiation of pregabalin ER. Additionally, the finding of LBBB resolved spontaneously, on the same day that it was noted, before the subject had discontinued taking pregabalin ER. Therefore, relatedness of this subject’s AE of LBBB to pregabalin ER cannot be determined.

8.4.4. **Significant Adverse Events**

[As noted throughout this review, the pregabalin moiety has a well-characterized safety profile and no new significant AEs were identified in my review of the submitted data.]

8.4.5. **Treatment Emergent Adverse Events and Adverse Reactions**

[After a complete review of the safety data generated in this clinical development program, LYRICA CR is associated with the following most common adverse events: dizziness, somnolence, headache, fatigue, peripheral edema, nausea, blurred vision, dry mouth, and weight gain. See the table below for a full listing of treatment emergent AEs in ≥ 1% of all pregabalin ER-treated subjects in the Phase 3 clinical studies.]

| Table 44 | Incidence and Severity of AEs in ≥ 1% of Subjects by PT in Decreasing Order of Frequency – All Pregabalin ER-treated Subjects in Studies 1224, 1245, and 1194 |

CDER Clinical Review Template 2015 Edition

*Version date: November 5, 2015 for initial rollout (NME/original BLA reviews)*

Reference ID: 4150575
When looking at AEs by daily dose, the distribution of AEs is fairly equitable across all dosages with no definite evidence that higher doses are associated with an increased incidence of AEs. See the table below for details.

### Table 45

<table>
<thead>
<tr>
<th>MedDRA (v18.0) PT</th>
<th>Pregabalin ER (N=1455)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Severity n (%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>326 (22.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>207 (14.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>86 (5.9)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>82 (5.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>81 (5.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>80 (5.5)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>68 (4.7)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>68 (4.7)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>59 (4.1)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>43 (3.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (2.8)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>39 (2.7)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>39 (2.7)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>33 (2.3)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>31 (2.1)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>31 (2.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>29 (2.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25 (1.7)</td>
</tr>
<tr>
<td>Back pain</td>
<td>24 (1.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>23 (1.6)</td>
</tr>
<tr>
<td>Feeling abnormal</td>
<td>22 (1.5)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (1.4)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>19 (1.3)</td>
</tr>
<tr>
<td>Rash</td>
<td>18 (1.2)</td>
</tr>
<tr>
<td>Peripheral swelling</td>
<td>17 (1.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16 (1.1)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16 (1.1)</td>
</tr>
<tr>
<td>Sedation</td>
<td>15 (1.0)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>14 (1.0)</td>
</tr>
</tbody>
</table>

Source: SCS, Table 8, p. 32
I also scrutinized AEs between pregabalin formulations (ER versus IR), across approved indications (DPN, PHN, FM, SCI, and epilepsy), and in the postmarketing setting for pregabalin IR. The most common AEs are comparable between the pregabalin ER and IR formulations and across all indications with the exception of some population-dependent findings. See the table below for a detailed AE comparison by pregabalin formulation and by approved indication.

**Table 46  Comparison of AEs by Pregabalin Formulation and by Approved Indication**

<table>
<thead>
<tr>
<th>MedDRA (v18.0) PT</th>
<th>No. (%) of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PGB ER 82.5 mg QD (N=34)</td>
</tr>
<tr>
<td></td>
<td>PGB ER 165 mg QD (N=354)</td>
</tr>
<tr>
<td></td>
<td>PGB ER 247.5 mg QD (N=31)</td>
</tr>
<tr>
<td></td>
<td>PGB ER 330 mg QD (N=451)</td>
</tr>
<tr>
<td></td>
<td>PGB ER 495 mg QD (N=343)</td>
</tr>
<tr>
<td></td>
<td>PGB ER 660 mg QD (N=237)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td></td>
<td>71 (20.1)</td>
</tr>
<tr>
<td></td>
<td>8 (25.8)</td>
</tr>
<tr>
<td></td>
<td>113 (25.1)</td>
</tr>
<tr>
<td></td>
<td>96 (28.0)</td>
</tr>
<tr>
<td></td>
<td>27 (11.4)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (14.7)</td>
</tr>
<tr>
<td></td>
<td>43 (12.1)</td>
</tr>
<tr>
<td></td>
<td>4 (12.9)</td>
</tr>
<tr>
<td></td>
<td>76 (16.9)</td>
</tr>
<tr>
<td></td>
<td>60 (17.5)</td>
</tr>
<tr>
<td></td>
<td>18 (7.6)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>3 (8.8)</td>
</tr>
<tr>
<td></td>
<td>10 (2.8)</td>
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<td></td>
<td>3 (9.7)</td>
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<td>9 (2.0)</td>
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<td>5 (1.5)</td>
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<td>9 (3.8)</td>
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<tr>
<td>Balance disorder</td>
<td>2 (5.9)</td>
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<td></td>
<td>11 (3.1)</td>
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<td></td>
<td>1 (3.2)</td>
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<td></td>
<td>15 (3.3)</td>
</tr>
<tr>
<td></td>
<td>9 (2.6)</td>
</tr>
<tr>
<td></td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td></td>
<td>4 (1.1)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>2 (0.4)</td>
</tr>
<tr>
<td></td>
<td>1 (0.3)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Haemiatoma</td>
<td>2 (5.9)</td>
</tr>
<tr>
<td></td>
<td>0 (0.0)</td>
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<tr>
<td></td>
<td>0 (0.0)</td>
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<td>0 (0.0)</td>
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Source: SCS, Table 9, p. 33
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<th>Indication</th>
<th>LYRICA (pregabalin ER)</th>
<th>LYRICA CR (pregabalin ER)</th>
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<tr>
<td><strong>All indications</strong></td>
<td>Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, thinking abnormal</td>
<td>Dizziness, somnolence, peripheral edema, fatigue, HA, nausea, blurred vision, weight gain, dry mouth</td>
</tr>
<tr>
<td>Most common AEs</td>
<td>Dizziness, somnolence, ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, peripheral edema</td>
<td>Dizziness, somnolence, peripheral edema, blurred vision, increased weight</td>
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<tr>
<td>AEs leading to D/C</td>
<td>Dizziness, somnolence, ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, peripheral edema</td>
<td>Dizziness, somnolence, edema</td>
</tr>
<tr>
<td><strong>PHN</strong></td>
<td>Dizziness, somnolence, peripheral edema, dry mouth, headache, infection, pain, constipation, ataxia, blurry vision,</td>
<td>Dizziness, somnolence, peripheral edema, fatigue, vertigo, blurred vision, dry mouth, HA, nausea, constipation, weight increased, balance disorder</td>
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<tr>
<td>Most common AEs</td>
<td>Dizziness, somnolence, confusion, peripheral edema, asthenia, ataxia, abnormal gait</td>
<td>N/A</td>
</tr>
<tr>
<td>AEs leading to D/C</td>
<td>Dizziness, somnolence, asthenia, confusion, peripheral edema</td>
<td>N/A</td>
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<tr>
<td><strong>DPN</strong></td>
<td>Dizziness, somnolence, peripheral edema, asthenia, dry mouth, weight gain, blurry vision, accidental injury, constipation, neuropathy</td>
<td>N/A</td>
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<tr>
<td>Most common AEs</td>
<td>Dizziness, somnolence, confusion, peripheral edema, asthenia, ataxia, abnormal gait</td>
<td>N/A</td>
</tr>
<tr>
<td>AEs leading to D/C</td>
<td>Dizziness, somnolence, fatigue, headache, balance disorder, weight increased</td>
<td>Dizziness, somnolence, peripheral edema, fatigue</td>
</tr>
<tr>
<td><strong>FM</strong></td>
<td>Dizziness, somnolence, HA, weight increased, dry mouth, blurred vision, constipation, fatigue, euphoric mood, peripheral edema</td>
<td>Dizziness, somnolence, HA, fatigue, weight increased, blurred vision, peripheral edema, dry mouth, disturbance in attention, insomnia, increased appetite, balance disorder, constipation, feeling abnormal, UTI, URI</td>
</tr>
<tr>
<td>Most common AEs</td>
<td>Dizziness, somnolence, fatigue, headache, balance disorder, weight increased</td>
<td>Dizziness, somnolence, peripheral edema, fatigue</td>
</tr>
<tr>
<td>AEs leading to D/C</td>
<td>Dizziness, somnolence, fatigue, diplopia, accidental injury, tremor, thinking abnormal</td>
<td>Peripheral edema, weight increased, somnolence, fatigue, anxiety, depression, disturbance in attention, myoclonus, ataxia, vomiting</td>
</tr>
<tr>
<td><strong>Epilepsy</strong></td>
<td>Dizziness, somnolence, ataxia, weight gain, blurred vision, diplopia, accidental injury, tremor, thinking abnormal</td>
<td>Dizziness, somnolence, weight increased, fatigue, blurred vision, dry mouth</td>
</tr>
<tr>
<td>Most common AEs</td>
<td>Dizziness, ataxia, somnolence, asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, confusion</td>
<td>Peripheral edema, weight increased, somnolence, fatigue, anxiety, depression, disturbance in attention, myoclonus, ataxia, vomiting</td>
</tr>
<tr>
<td>AEs leading to D/C</td>
<td>Dizziness, ataxia, somnolence, asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, confusion</td>
<td>Peripheral edema, weight increased, somnolence, fatigue, anxiety, depression, disturbance in attention, myoclonus, ataxia, vomiting</td>
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<tr>
<td><strong>SCI</strong></td>
<td>Dizziness, somnolence, fatigue, dry mouth, peripheral edema, constipation, edema, nasopharyngitis, blurred vision, nausea, muscular weakness</td>
<td>N/A</td>
</tr>
<tr>
<td>Most common AEs</td>
<td>Somnolence, edema, fatigue, balance disorder</td>
<td>N/A</td>
</tr>
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**Other AEs in controlled trials**
Clinical Review  
Lisa Wiltrout  
NDA 209501  
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<table>
<thead>
<tr>
<th>Indication</th>
<th>LYRICA (pregabalin IR)</th>
<th>LYRICA CR (pregabalin ER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent (≥ 1/100)</td>
<td>Abdominal pain, fever, GE, increased appetite, ecchymosis, arthralgia, myalgia, myasthenia, anxiety, hypertonia, nystagmus, libido decreased, sedation, twitching, pruritus, conjunctivitis, diplopia, otitis media, tinnitus, anorgasmia, impotence, urinary frequency, urinary incontinence</td>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Infrequent (1/100 to 1/1000)</td>
<td>Abscess, cellulitis, malaise, heart failure, hypotension, cholecystitis, dysphagia, esophagitis, GI hemorrhage, melena, anemia, eosinophilia, leukocytosis, leukopenia, thrombocytopenia, arthrosis, abnormal dreams, agitation, apathy, aphasia, dysarthria, hallucinations, alopecia, hirsutism, urticarial, blepharitis, dry eyes, hyperacusis, photophobia, albuminuria, dysuria, urinary retention</td>
<td>Palpitations, diplopia, visual impairment, periorbital edema, visual acuity decreased, flatulence, GERD, toothache, abdominal distension, gait disturbance, chest pain, face edema, generalized edema, bronchitis, sinusitis, pneumonia, blood CK increase, coordination abnormal, amnesia, dysgeusia, sciatia, irritability, oropharyngeal pain</td>
</tr>
<tr>
<td>Rare (&lt;1/1000)</td>
<td>Ascites, hangover effect, shock, ST depressed, V-fib, myelofibrosis, purpura, aphthous stomatitis, esophageal ulcer, glucose tolerance decreased, urate crystalluria, generalized spasm, addiction, cerebellar syndrome, coma, delirium, delusions, intracranial HTN, manic reaction, personality disorder, torticollis, trismus, apnea, lung edema, nail disorder, SJS, skin atrophy, anisocoria, blindness, optic atrophy, ptosis, uveitis, papilledema, ophthalmoplegia, acute kidney failure, pyelonephritis</td>
<td>Cardiac failure, tachycardia, hearing impaired, abnormal feces, Barrett’s esophagus, facial pain, hepatic steatosis, GI infection, dermatitis infected, heat stroke, glucose urine present, lipase increased, neutrophil count increased, proteinuria, coccycdynia, myokymia, depressed level of consciousness, bradykinesia, TIA, vertebrobasilar insufficiency, Bipolar II disorder, dysphonia, post-menopausal hemorrhage, onychalgia</td>
</tr>
<tr>
<td>Post-marketing AEs</td>
<td>HA, nausea, diarrhea, gynecomastia, breast enlargement, reduced lower GI tract function when Lyrica co-administered with opioid analgesics</td>
<td>N/A</td>
</tr>
</tbody>
</table>

8.4.6. Laboratory Findings

(Clinical laboratory testing was performed at the screening visit (Visit 1 for both Studies 1224 and 1245), at the end of SB treatment (Visit 7 for Study 1224 and Visit 6 for 1245), and at the end of DB treatment (Visit 10 for Study 1224 and Visit 9 for 1245). Clinical laboratory testing was performed at the screening visit (Visit 1) and at the end of treatment (Visit 8) for Study 1194. Laboratory testing at any of these visits included the following:

- Hematology: hemoglobin, hematocrit, WBC count including differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, and
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platelet count
- Chemistry: amylase, AST, ALT, albumin, alkaline phosphatase (ALK), blood urea nitrogen, creatinine, electrolytes (sodium, potassium, chloride, calcium), glucose, total protein, total bilirubin, uric acid
- Urinalysis: pH, specific gravity, glucose, blood/hemoglobin, and microscopic sediment examination (additional testing for Study 1194 – protein, nitrate, ketones)

Laboratory testing at Visit 1 (Study 1224) only used to determine eligibility included the following:
- Thyroxin (T4)/thyroid-stimulating hormone and vitamin B12 (folate)
- Serum pregnancy test (all females of child bearing potential)

Laboratory testing at Visit 0 or 1 (Study 1245) required to determine eligibility included the following:
- Thyroid-stimulating hormone and vitamin B12/folate
- Rheumatoid Factor
- Westergren ESR
- Antinuclear Antibody
- Serum pregnancy test (all females regardless of childbearing potential)

Laboratory testing at Visit 1 (Study 1194) required to determine eligibility included the following:
- T4/TSH
- Vitamin B12/folate
- Creatinine clearance
- Urine pregnancy test (with serum test confirmation if urine positive); also required at Visits 3 and 8

I reviewed the CSRs for each Phase 3 clinical trial (Studies 1224, 1245, and 1194), the line listings of individual laboratory results in each Phase 3 clinical trial, the pertinent safety narratives and CRFs for subjects with clinically significant laboratory abnormalities or with laboratory abnormalities that resulted in subject discontinuation from the study, as well as the Applicant’s discussion of laboratory result findings in the Clinical Summary of Safety and in the Integrated Summary of Safety. The Applicant states that there were no clinically meaningful changes in laboratory results for any of the Phase 3 clinical studies; however, I identified the following clinically meaningful change in laboratory results:

In Study 1224, the median change from baseline in platelet count was higher in the pregabalin ER treatment arm (-11 x 10^3/mm^3) as compared to the placebo treatment arm (-1 x 10^3/mm^3) for the DB phase of the study. In Study 1245, the median change from baseline in platelet count was also higher in the pregabalin ER treatment arm (-14 x 10^3/mm^3) as compared to the
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placebo treatment arm (-1 x 10^3/mm^3) for the DB phase of the study. There were no findings of difference in change in platelet count between the pregabalin treatment arms and the placebo treatment arm in Study 1194. This laboratory finding of decreased platelet count in association with LYRICA CR use is consistent with the known side effects of LYRICA.

There were two subjects in Study 1224 who had thrombocytopenia. On more detailed review of these cases, both subjects had abnormal platelet counts at screening. Both subjects were treated with pregabalin ER during the SB Phase and placebo during the DB Phase. Both subjects had a significant decrease in platelet count at Visits 7 and 10 during the study. Brief summaries of each subject are provided below.

Subject Study 1224
Pregabalin ER SB Phase and placebo DB Phase

Subject had a low baseline platelet count that was reported as “platelet clumping, platelet estimate decreased”. Subsequent platelet counts at Visits 7 and 10 were low and reported as 40,000 and 21,000. The contribution of pregabalin ER to this subject’s thrombocytopenia is unclear given that the subject had a decreased platelet count at baseline that worsened throughout the study after treatment with both pregabalin ER and placebo.

Subject Study 1224
Pregabalin ER SB Phase and Placebo DB Phase

Subject had a low baseline platelet count of 96,000 that should have prevented the subject from being enrolled in Study 1224 as a platelet count < 100,000 was an exclusion criterion. Nevertheless, the subject was enrolled and had a subsequent low platelet count of 24,000 at Visit 7. Follow up platelet counts prior to the subject discontinuing from the study were as follows: 26,000, 15,000, 15,000, and 27,000. The contribution of pregabalin ER to this subject’s thrombocytopenia is unclear given that the subject met an exclusion criterion with a platelet count < 100,000 at the time of screening. Her platelet count significantly worsened throughout the study after treatment with both pregabalin ER and placebo.

8.4.7. Vital Signs

[I reviewed the CSRs for each Phase 3 clinical trial (Studies 1224, 1245, and 1194) as well as the Applicant’s discussion of vital sign findings in the Clinical Summary of Safety and the Integrated Summary of Safety. There were no clinically meaningful changes in vital signs for Studies 1224, 1245, and 1194.]

8.4.8. Electrocardiograms (ECGs)
I reviewed the CSRs for each Phase 3 clinical trial (Studies 1224, 1245, and 1194) as well as the Applicant’s discussion of ECG findings in the Clinical Summary of Safety and the Integrated Summary of Safety. There were no clinically significant ECG changes for Studies 1245 and 1194; however, there were clinically significant ECG findings for subjects in Study 1224.

In the SB phase of Study 1224, two subjects had clinically significant ECG abnormalities. Brief clinical summaries are presented below.

Subject [b] had a non-serious AE of mild sinus bradycardia noted at Visit 7 (Week 6). This AE was considered unrelated to pregabalin ER. The sinus bradycardia was documented as ongoing at the time of last data collection for the Summary of Clinical Safety.

Impression

I agree that the AE of sinus bradycardia is unlikely to be related to pregabalin ER.

Subject [b] is an 84 year old African-American male with a two year history of PHN. His past medical history is significant for Type 2 DM, hypertension, hypothyroidism, COPD, lung cancer in remission since [b] and colon cancer in remission since [b]. The more pertinent concomitant medications are as follows: glibenclamide, metformin, amlodipine, levothyroxine, Vicodin, and acetylsalicylic acid. He took pregabalin ER for 42 days and then tapered off study drug as he did not meet DB phase randomization criteria. He had complete right bundle branch block (RBBB) at screening that was considered abnormal but not clinically significant. During study drug taper, he had RBBB and atrial fibrillation on an end-of-study ECG. Both findings were considered clinically significant. A repeat ECG six days later showed persistent RBBB and first degree atrioventricular (AV) block but resolution of the atrial fibrillation. The event of atrial fibrillation was considered not related to pregabalin ER but rather cardiac arrhythmia.

Impression

I agree that the ECG finding of atrial fibrillation that resolved spontaneously in the setting of underlying RBBB and new onset first degree AV block is likely related to underlying cardiac conduction abnormalities and not related to pregabalin ER.

In the DB phase of Study 1224, one subject had clinically significant ECG findings at Visit 7 (Week 6) and two subjects had clinically significant ECG findings at Visit 10 (Week 19/Early Termination). Brief clinical summaries are presented below.

Subject [b] had clinically significant left axis deviation, ST-T segment changes, and sinus bradycardia noted at Visit 7 (Week 6). This subject went on to experience cardiac failure necessitating hospitalization and aortic valve replacement. The SAE of cardiac failure was
considered not related to pregabalin ER. See my clinical summary of the SAE in Section 8.4.2 for details.

Impression

The ECG findings of left axis deviation, ST-T segment changes, and sinus bradycardia are likely related to the subject’s underlying cardiac problems of aortic valve stenosis and cardiac failure.

Subject (b) (6) had non-clinically significant left ventricular hypertrophy noted on his ECG prior to randomization. At Week 19, his ECG showed possible silent myocardial ischemia with sinus rhythm, left ventricular hypertrophy, and an inverted T wave in V5-V6. A non-serious AE of moderate myocardial ischemia was reported at that time. The subject had a known past medical history of coronary heart disease and hypertension. He was started on acetylsalicylic acid and metoprolol from Day 134 onwards.

Impression

The ECG findings of myocardial ischemia are unrelated to pregabalin ER and instead related to the subject’s underlying medical conditions of hypertension and coronary artery disease.

Subject (b) (6) was noted to have an abnormal, non-clinically significant sinus arrhythmia prior to randomization. On Study Day 42, her ECG showed clinically significant left bundle branch block (LBBB) with a heart rate of 85 bpm. A non-serious AE that was considered to be severe was reported. The investigator considered the ECG finding of LBBB to be related to pregabalin ER; therefore, the subject was taken off pregabalin ER and was discontinued from the study. See my clinical summary of the SAE in Section 8.4.2 for details.

Impression

The contribution of pregabalin ER to the ECG findings of LBBB cannot be excluded.

8.4.9. QT

[The pregabalin moiety is associated with PR interval prolongation. Clinical studies evaluating the potential for an increased risk of PR prolongation with use of pregabalin IR were conducted during the clinical development program for LYRICA. Subgroup analyses did not identify an increased risk of PR prolongation or in patients with baseline PR prolongation or in patients taking other PR prolonging medications. The Applicant did not conduct any additional QT studies in the clinical development program for LYRICA CR. Only one subject previously discussed in Section 8.4.2 and above in Section 8.4.8 experienced QT prolongation while on pregabalin ER; however, this subject had underlying sinus arrhythmia and an abnormal finding of prolonged QT at screening prior to taking pregabalin ER.]
8.4.10. **Immunogenicity**

[Not applicable]

8.5. **Analysis of Submission-Specific Safety Issues**

[Given that pregabalin ER tablets are designed to reside in the stomach for a longer time, the Applicant performed an analysis of gastrointestinal-related AEs for the Phase 3 clinical trials. The most common gastrointestinal-related AEs are dry mouth, nausea, vomiting, diarrhea, and constipation. There were no reports of any cases of obstruction.

Euphoria is a known central nervous system (CNS) adverse event associated with LYRICA; therefore, the Applicant performed an analysis of AEs related to euphoric mood. In the Phase 3 clinical studies, the overall incidence of euphoric mood was 0.9% (13 out of 1455 subjects with 3 subjects in the SB phase of Study 1224, 10 subjects in the SB phase of Study 1245, and no subjects in Study 1194). All events of euphoric mood were mild to moderate in intensity and resolved during the studies. No events of euphoric mood led to subject discontinuation from the studies.

Increased risk of suicidal thoughts or behavior is another known CNS adverse event associated with LYRICA; therefore, the Applicant performed suicidality assessments using the STS (and later, the C-SSRS) at each study visit for Studies 1224 and 1245 and using the STS only at each study visit for Study 1194. After review of the suicidality assessments as well as the safety data for the Phase 3 clinical studies, I conclude that LYRICA CR use is associated with increased risk of suicidal thoughts or behavior.]

8.6. **Safety Analyses by Demographic Subgroups**

[As is typical in analgesic trials, the demographics were restricted, all three trials had a substantial plurality of Caucasians, and the pain trials (Studies 1224 and 1245) had a substantial predominance of females. The age distribution was fairly equitable amongst the three trials. Within these demographic constraints, I saw no demographic subgroup trends for safety.]

8.7. **Specific Safety Studies/Clinical Trials**

[No special safety studies were conducted.]

8.8. **Additional Safety Explorations**

8.8.1. **Human Carcinogenicity or Tumor Development**

[No human carcinogenicity studies were conducted.]
8.8.2. Human Reproduction and Pregnancy

[There was one SAE of exposure in utero that occurred in a Phase 1 single dose study (Study 1239). The exposure in utero was discovered after the subject completed the study. The safety database was updated based on the subject’s verbal report that she had an elective abortion.]

8.8.3. Pediatrics and Assessment of Effects on Growth

[The PHN and DPN indications are not applicable to the pediatric population.]

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

[A total of 55 patients received over 660 mg of LYRICA CR in the clinical development program. There were no clinically significant events in those patients. Pregabalin is known to have an abstinence syndrome. For those reasons, a one-week taper was used in all studies with the ER product. No issues with withdrawal or rebound were observed using that dosing paradigm. During the Phase 3 clinical trials, some subjects abruptly or rapidly discontinued use of pregabalin ER against the recommendation of clinical investigators. The following five symptoms potentially related to rapid discontinuation were noted: anxiety, insomnia, nausea, headache, and diarrhea.]

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

[There is no postmarket experience with pregabalin ER for the treatment of neuropathic pain associated with DPN and the treatment of postherpetic neuralgia.]

8.9.2. Expectations on Safety in the Postmarket Setting

[The postmarketing experience for LYRICA CR is expected to be similar to that of the IR product.]

8.10. Additional Safety Issues From Other Disciplines

[No additional safety issues were identified from other disciplines]

8.11. Integrated Assessment of Safety

[The methods and extent of safety data collection were sufficient to define the safety profile for this new formulation of pregabalin. LYRICA CR is commonly associated with fatigue, dizziness, somnolence, weight gain, and peripheral edema. The adverse event profile is substantially identical to the IR formulation.]
9 Advisory Committee Meeting and Other External Consultations

[No Advisory Committee Meeting was held for this product.]

10 Labeling Recommendations

10.1. Prescribing Information

[I recommend the following key changes to the proposed prescribing information for LYRICA CR:

1) [B] (4)

2) Addition of any AEs identified during the LYRICA CR clinical development program that are not included in Section 5

3) [B] (4)

4) Simplification of the “Other Adverse Reactions Observed During Clinical Studies with LYRICA and LYRICA CR” portion of Section 6 given the comparable adverse event profile of LYRICA CR and LYRICA

5) [B] (4)

presentation of the continuous responder analysis instead in Section 14

6) Addition of language about the negative clinical study in the FM population and the negative clinical study in the epilepsy population in Section 14 ]

10.2. Patient Labeling

[I recommend the following key changes to the proposed medication guide for LYRICA CR:

1) Inclusion of language that, if you have epilepsy, and you stop taking LYRICA CR suddenly, you may have seizures more often

2) Inclusion of language that the efficacy of LYRICA CR as adjunctive therapy for adult patients with partial onset seizures of for management of FM has not been established ]

10.3. Nonprescription Labeling

[Not applicable]

11 Risk Evaluation and Mitigation Strategies (REMS)

[I do not recommend any REMS for LYRICA CR.]
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11.1. **Safety Issue(s) that Warrant Consideration of a REMS**

[Not applicable]

11.2. **Conditions of Use to Address Safety Issue(s)**

[Not applicable]

11.3. **Recommendations on REMS**

[Not applicable]

12 **Postmarketing Requirements and Commitments**

[At the time of finalization of this review, I do not recommend any clinical postmarketing requirement or commitments.]

13 **Appendices**

13.1. **References**


13.2. **Financial Disclosure**

[Please see Section 6.1.2 for detailed review of financial disclosure for Studies 1224 and 1245. Copies of the clinical investigator financial disclosure forms for each study are included below.]

**Covered Clinical Study (Name and/or Number): Study 1224**

<table>
<thead>
<tr>
<th>Was a list of clinical investigators provided:</th>
<th>Yes X</th>
<th>No [ ] (Request list from Applicant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of investigators identified:</td>
<td>535</td>
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<tr>
<td>Number of investigators who are Sponsor employees (including both full-time and part-time employees):</td>
<td>0</td>
<td></td>
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</table>
**Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3**

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)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payments of other sorts: 3
- Proprietary interest in the product tested held by investigator: 0
- Significant equity interest held by investigator in Sponsor of covered study: 0

| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☑ | No ☐ (Request details from Applicant) |
|ientos of the disclosable financial interests/arrangements: | Is a description of the steps taken to minimize potential bias provided: | Yes ☑ | No ☐ (Request information from Applicant) |

| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 7 |

| Is an attachment provided with the reason: | Yes ☑ | No ☐ (Request explanation from Applicant) |

**Covered Clinical Study (Name and/or Number): Study 1245**

| Was a list of clinical investigators provided: | Yes ☑ | No ☐ (Request list from Applicant) |

| Total number of investigators identified: 209 |

| 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): 3 |

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)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payments of other sorts: 3
- Proprietary interest in the product tested held by investigator: 0
<table>
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<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Notes</th>
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<tr>
<td>Significant equity interest held by investigator in Sponsor of covered</td>
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<td>study:</td>
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<tr>
<td>Is an attachment provided with details of the disclosable financial</td>
<td>Yes</td>
<td>No</td>
<td>(Request details from Applicant)</td>
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<td>interests/arrangements:</td>
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<tr>
<td>Is a description of the steps taken to minimize potential bias provided:</td>
<td>Yes</td>
<td>No</td>
<td>(Request information from Applicant)</td>
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<td>Number of investigators with certification of due diligence (Form FDA</td>
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<td>3454, box 3):</td>
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<tr>
<td>Is an attachment provided with the reason:</td>
<td>Yes</td>
<td>No</td>
<td>(Request explanation from Applicant)</td>
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</table>
Clinical Review
Lisa Wiltrout
NDA 209501
Lyrica CR (pregabalin ER)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA M WILTROUT
09/08/2017

ROBERT B SHIBUYA
09/09/2017