LYRICA® (pregabalin) Ⓥ eLearning System

LYRICA® (pregabalin) capsules Ⓥ
Clinical Data in pDPN and PHN

Pfizer Inc

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Introduction

The information contained in this training module is for your educational purposes only. This training piece is designed to provide you with information you need on the product, the disease, and the competitive environment. It is not to be used in detailing or distributed to any third parties.

As described in previous modules of this learning system, **painful diabetic peripheral neuropathy (pDPN)** and **postherpetic neuralgia (PHN)** are 2 of the most common types of **neuropathic pain**.

Approximately 23.6 million people in the United States have diabetes. It is estimated that 60% to 70% of this population has diabetic neuropathy. One in 4 of these patients are affected by pDPN, and 9 out of 10 patients with pDPN report moderate or severe pain.

The 12-month prevalence of shingles or herpes zoster in the United States is approximately 1 million people. Of that number, an estimated 10% to 20% will develop PHN. Although the number of people who continue to experience pain decreases steadily over the 12-month period after the initial outbreak, 4% to 22% of all PHN patients will continue to feel pain more than 1 year after the incident.

Management of pDPN and PHN can be difficult, and there are few FDA-approved treatments for these conditions — for example, Cymbalta® (duloxetine) for pDPN and NEURONTIN® (gabapentin) for PHN. These disorders often respond poorly to conventional **analgesics** and other adjuvant therapies, such as anticonvulsants and tricyclic antidepressants (TCAs). Because there are similarities in the pathophysiologic and biochemical mechanisms underlying neuropathic pain and epilepsy, anticonvulsant agents have become key agents in treating pDPN and PHN. Although a number of anticonvulsants are available, many patients still continue to experience pDPN, and the product profiles of many existing agents are often problematic in terms of **pharmacokinetics**, lengthy titration schedules, drug-drug interactions, and adverse reactions.

LYRICA® (pregabalin) ©, an **alpha$_2$-delta (a_2-δ)** protein with analgesic properties, is an anticonvulsant that is FDA-approved for:

- management of neuropathic pain associated with **diabetic peripheral neuropathy (DPN)**
- management of PHN
- management of fibromyalgia
- adjunctive therapy for adult patients with **partial seizures**

* Cymbalta® is a registered trademark of Eli Lilly and Co.

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This module will focus on the clinical efficacy data for the use of LYRICA in pDPN and PHN. The key features of LYRICA include its powerful and sustained efficacy, well-studied safety profile and tolerability profile, linear pharmacokinetics, high **bioavailability**, and low potential for pharmacokinetic drug interactions. Information on these other characteristics of LYRICA can be found elsewhere in the *LYRICA® eLearning System*.

This module provides the clinical information that you will need in order to effectively discuss LYRICA with healthcare professionals:

- Section 1 provides an overview the clinical trial program in neuropathic pain
- Section 2 presents information on the key clinical trials in pDPN
- Section 3 describes the key clinical trials in PHN

The module concludes with a summary, glossary of medical terms, and bibliography.

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Section 1: Overview of Clinical Trials in Neuropathic Pain

Objectives

- Identify the studies in the pDPN and PHN clinical trial program for LYRICA
- Describe the study design used in the pDPN and PHN clinical trial program for LYRICA
- Describe the primary and secondary efficacy measures used in the pDPN and PHN clinical trial program for LYRICA
- State the difference between the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) analysis for interpreting clinical trial results
- Explain how to read a continuous responder graph
- Describe the patient selection criteria for the key clinical trials in pDPN and PHN

The efficacy of LYRICA for the management of neuropathic pain associated with DPN and PHN was established in 6 double-blind, placebo-controlled, multicenter clinical trials, 5 of which evaluated the recommended (and maximum) doses of LYRICA and are listed in the LYRICA product labeling.

This section provides an overview of the studies that were conducted in the pDPN and PHN clinical trial program for LYRICA, including the list of studies that appear in the LYRICA product labeling, the study design used in the pDPN and PHN clinical trial program, the primary and secondary efficacy measures that were used, and the patient selection criteria for these key clinical trials.

In addition, this section will discuss the difference between the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) analysis for interpreting clinical trial results and explain how to read a continuous responder graph.

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Identify the studies in the pDPN and PHN clinical trial program for LYRICA®

Studies in the Clinical Trial Program

The efficacy of LYRICA for the management of neuropathic pain associated with DPN and PHN was established in 6 double-blind, placebo-controlled, multicenter clinical trials. As noted in the LYRICA package insert:

- 3 studies with **TID** dosing established efficacy in pDPN
  - 2 of these studies (Lesser et al and Rosenstock et al) studied the maximum recommended dose
- 3 studies with **BID** and TID dosing established efficacy in PHN (studies Van Seventer et al, Dworkin et al, and Sabatowski et al)

Table 1A provides information on the patients enrolled in these trials.

Table 1A: **Supportive Neuropathic Pain Trials in Package Insert: Enrolled Patients**

Clinical Studies in the Package Insert	*Study Information*
• Lesser et al (DPN1) • Rosenstock et al (DPN2)	• 483 patients with **type 1 diabetes** or **type 2 diabetes** who had painful **distal symmetrical sensorimotor polyneuropathy** for 1 to 5 years
• Van Seventer et al (PHN1) • Dworkin et al (PHN2) • Sabatowski et al (PHN3)	• 779 patients with PHN who continued (after healing of the herpes zoster skin rash) to have pain for at least 3 months

* *Richter et al (Study 014): (n = 246) also established the efficacy of LYRICA in pDPN; however, this study did not evaluate the maximum recommended dose of LYRICA for pDPN (300 mg/day).*

Table 1B lists key features of the neuropathic pain studies described in the package insert. The table and the subsequent text identify these studies by both their designation in the package insert (for example, Lesser et al) and their designation during the clinical trial program (for example, study 029). Note that study Richter et al is mentioned in the LYRICA package insert as having established the efficacy of LYRICA in pDPN; however, it is not described further in the labeling, as this study did not evaluate the maximum recommended dose of LYRICA for pDPN (300 mg/day).

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More detailed discussions of key studies are provided in Sections 2 and 3.

Table 1B: Key Supportive Clinical Trials of LYRICA for Neuropathic Pain Associated With DPN and PHN

Study	Description	Dose Groups
Diabetic Peripheral Neuropathy		
Lesser et al. *Neurology.* 2004;63:2104-2110. DPN1: Study 029	• 5-week, randomized, double-blind, placebo-controlled trial, including 1-week dose escalation phase for 600 mg/day group • 337 patients	• LYRICA 75 mg/day (25 mg TID) • LYRICA 300 mg/day (100 mg TID) • LYRICA 600 mg/day (200 mg TID)* • placebo
Rosenstock et al. *Pain.* 2004;110:628-638. DPN2: Study 131	• 8-week, randomized, double-blind, placebo-controlled trial • 146 patients	• LYRICA 300 mg/day (100 mg TID) • placebo
Richter et al. *Pain.* 2005;6:253-260. Study 014**	• 6-week, randomized, double-blind, placebo-controlled trial • 246 patients	• LYRICA 150 mg/day (50 mg TID) • LYRICA 600 mg/day (200 mg TID)* • placebo
Postherpetic Neuralgia		
Van Seventer et al. *Curr Med Res Opin.* 2006;22(2):375-384. PHN1: Study 196	• 13-week, randomized, double-blind, placebo-controlled trial, including 1-week dose escalation phase • 368 patients	• LYRICA 150 mg/day (75 mg BID) • LYRICA 300 mg/day (150 mg BID) • LYRICA 300 mg or 600 mg/day*** (150 mg BID or 300 mg BID) • placebo
Dworkin et al. *Neurology.* 2003;60:1274-1283. PHN2: Study 127	• 8-week, randomized, double-blind, placebo-controlled trial, including 1-week dose escalation phase • 173 patients	• LYRICA 300 mg/day or 600 mg/day*** (100 mg TID or 200 mg TID) • placebo
Sabatowski et al. *Pain.* 2004;109:26-35. PHN3: Study 045	• 8-week, randomized, double-blind, placebo-controlled trial, including 1 week dose escalation phase • 238 patients	• LYRICA 150 mg/day (50 mg TID) • LYRICA 300 mg/day (100 mg TID) • placebo

** LYRICA 600 mg/day efficacy data are not to be detailed.*

*** This study is mentioned in the LYRICA package insert as 1 of the 3 double-blind, placebo-controlled, multicenter studies having established the efficacy of LYRICA in pDPN. Although this third study is referenced in the LYRICA label as having contributed to the overall efficacy of LYRICA in pDPN, the details of Richter et al are not included in the LYRICA label in any level of detail.*

**** Based on creatinine clearance*

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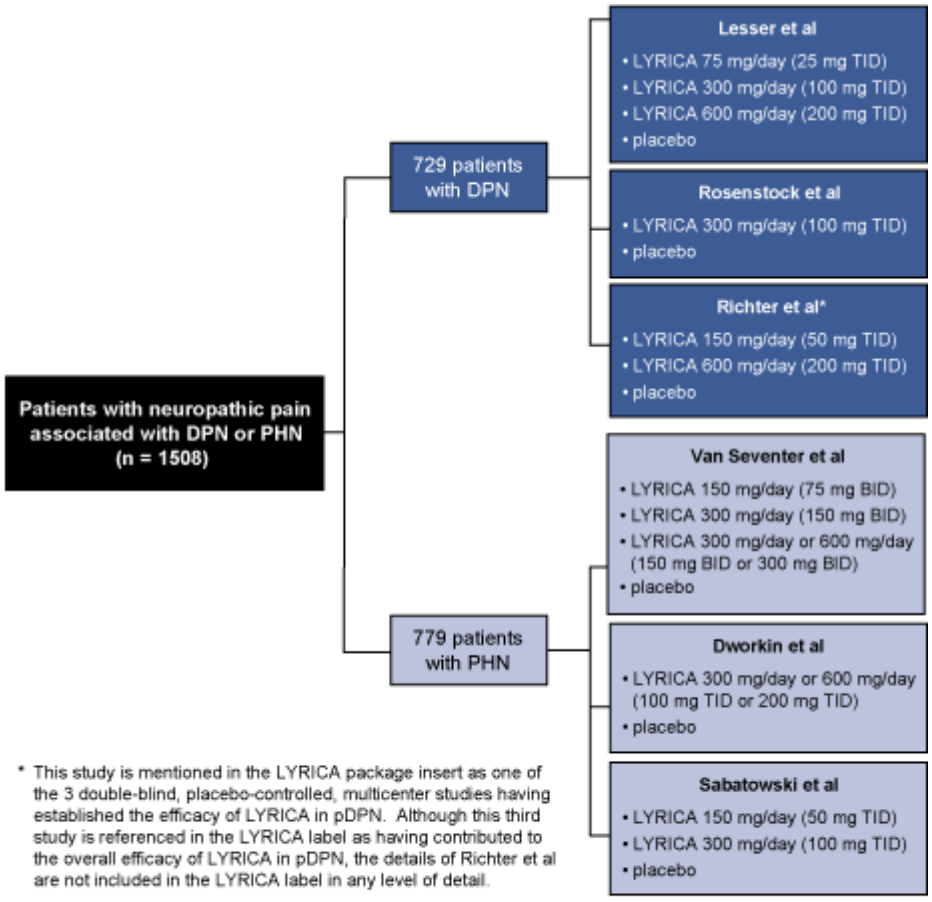
Figure 1A shows an overview of the clinical trial program in neuropathic pain for LYRICA, as described in the LYRICA package insert.

Figure 1A: Neuropathic Pain Studies Included in LYRICA Package Insert



Adapted from the LYRICA package insert, 2009

Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.

Progress Check

There may be **more than one** correct answer to each question.

1. Which of the following statements about the studies in pDPN is (are) **true**?
   - ***A*** ***In both key studies (Lesser et al and Rosenstock et al), LYRICA was administered 3 times daily.***
   - B Patients in the studies with pDPN had painful distal symmetrical sensorimotor polyneuropathy for ≥5 years.
   - ***C*** ***Lesser et al and Rosenstock et al enrolled a total of 483 patients.***

2. In some studies in PHN, the dose of LYRICA was adjusted to 300 mg/day or 600 mg/day based on:
   - A patient weight.
   - B baseline pain score.
   - ***C*** ***creatinine clearance.***

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Describe the study design used in the pDPN and PHN clinical trial program for LYRICA®

Study Designs Used in the Clinical Trial Program

The clinical trials of LYRICA for peripheral neuropathic pain associated with DPN and PHN consisted of a baseline phase and a double-blind phase, as illustrated in Table 1C and Figure 1B. Patients who completed or withdrew from the double-blind phase could elect to continue in open-label follow-on studies, or discontinue treatment.

Table 1C: **Clinical Trial Phases**

Clinical Study Phases	*Description*
Baseline phase	• 1-week period in which patients were screened for eligibility to enter the double-blind phase
Double-blind phase	• 5-week to 13-week treatment period during which time patients received LYRICA or placebo

In the majority of the trials, doses of LYRICA were escalated over a period of 2 to 12 days; schedules varied from study to study. Patients then remained at a fixed dose for the remainder of the double-blind phase (4 to 12 weeks).

Figure 1B depicts the design of these trials.

Figure 1B: Study Design of Neuropathic Pain Trials

The design of the neuropathic pain trials included a 1-week baseline phase followed by a double-blind treatment phase lasting from 5 to 13 weeks. Patients then had the option of continuing treatment in open-label follow-on studies.

Adapted from Pfizer Research Report, Summary of Clinical Efficacy

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Progress Check

There may be **more than one** correct answer to each question.

1. A patient who completed or withdrew from the double-blind phase of a clinical trial of LYRICA could elect to:
   - A enroll in a different double-blind trial of LYRICA.
   - ***B continue in open-label follow-on studies.***
   - C re-enroll in the same double-blind trial of LYRICA.
   - ***D discontinue treatment.***

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Describe the primary and secondary efficacy measures used in the pDPN and PHN clinical trial program for LYRICA®

Primary and Secondary Efficacy Study Endpoints

Pain is recognized as a highly subjective and personal experience, which can present a challenge when evaluating pain relief in clinical trials. While many trials have shown statistically significant changes in pain on many different measurement tools in patients who have been administered an agent, the clinical importance of these differences has not been clear. Physicians need to know what changes on a pain intensity scale actually mean for patients. This information is necessary not only for treatment decisions for individual patients, but also in terms of establishing a common definition of clinically meaningful pain relief that can be used for different agents and across different trials. The uniform design of the clinical trials of LYRICA has provided an opportunity to analyze the concept of clinically meaningful pain relief in a pool of patients large enough (>2700 patients) to provide **statistical power**.

The following paragraphs first describe the key measurement tools in the LYRICA clinical trial program, and then describe how the results of these trials have identified a correlation with patient perception of significant pain relief.

Primary Efficacy Measure

The primary efficacy measure in the **intent-to-treat (ITT) population** was the endpoint mean pain score, which was derived from a daily pain diary recorded by patients using an 11-point scale called the Pain Intensity Numeric Rating Scale (PI-NRS). Upon awakening, patients evaluated their pain for the previous 24 hours by circling the number on the scale that best described the pain they experienced. The PI-NRS rates pain from 0 (no pain) to 10 (worst possible pain), as shown in Figure 1C.

To enter the trials, patients had to have moderate to severe pain, which translates to a score of ≥4. The baseline mean pain scores ranged from:

- 6.1 to 6.7 across Lesser et al and Rosenstock et al
- 6.0 to 7.0 across Van Seventer et al, Dworkin et al, and Sabatowski et al

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In addition, supplemental analyses of the primary efficacy measure were conducted and include:

- the proportion of ≥50% responders (patients who had their pain cut in half) from baseline to endpoint mean scores
- weekly analysis of pain scores

Figure 1C: Pain Intensity Numeric Rating Scale (PI-NRS)

The primary efficacy measure for neuropathic pain, mean pain score at endpoint, was derived from the 11-point Pain Intensity Numeric Rating Scale (PI-NRS). Each morning upon awakening, patients evaluated their pain over the previous 24 hours by circling a number from 0 to 10 on the PI-NRS.

Adapted from Farrar et al, 2003

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Secondary Efficacy Measures

A number of secondary efficacy measures were used to evaluate changes in pain experience, pain-related sleep interference, mood, and other patient-reported outcomes during treatment.

These secondary measures are not described in the package insert, but are discussed in this module as background information only. The majority of these instruments were self-administered by the patient and are described in Table 1D. Please note that not all instruments were used for every study.

Table 1D: Secondary Efficacy Measures

Secondary Efficacy Parameter	Description
Pain	
• Short-Form McGill Pain Questionnaire (SF-MPQ)	• patients use descriptors to characterize their pain in terms of sensory and affective parameters • consists of 3 sections: total score, 100 mm visual analog scale (VAS); present pain intensity (PPI) • administered at each visit
Global Measure	
• Patient and Clinician Global Impression of Change (PGIC and CGIC)	• PGIC: patients rate on a 7-point scale their change in pain since beginning of study from 1 (very much improved) to 7 (very much worse); administered at termination • CGIC: physicians rate on the same 7-point scale the observed change in pain in patients since beginning of study; administered at termination
Sleep	
• Pain-related sleep interference	• patients assess pain interference with sleep during past 24 hours; rated from 0 (did not interfere) to 10 (unable to sleep); self-assessment performed daily upon awakening
• Medical Outcomes Study-Sleep (MOS-Sleep) Scale	• patients rate their sleep using 12-item assessment, 7 subscales, and 9-item overall sleep problems index; completed at randomization and termination
Mood (Depression and Anxiety Disturbances)	
• Zung Self-Rating Depression Scale (Zung SDS)	• patient-administered 20-item test that assesses severity of depression symptoms; completed at randomization and termination
• Hospital Anxiety and Depression Scale (HADS)	• patient-rated instrument containing two 7-item subscales for anxiety and depression rated on 4-point scales; completed at randomization and termination
Patient-Reported Outcomes	
• Short-Form-36 Health Questionnaire (SF-36)	• patient-rated, 36-item, quality-of-life scale that assesses 8 health domains; completed at randomization and termination

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Significant Pain Relief

PHN and pDPN are difficult chronic pain conditions to treat. Two standard measures that physicians use to assess pain and pain relief are the:

- Pain Intensity Numeric Rating Scale (PI-NRS)
- Patient's Global Impression of Change (PGIC)

An analysis by Farrar et al of the data from the LYRICA trials compared the results for these 2 rating scales, which were used in the trials. The results of the analysis showed a close correlation between changes on the PI-NRS and the PGIC that was highly consistent over multiple trials, regardless of the type of neuropathic pain, whether the patient received active treatment or placebo, the trial outcome, or patient factors such as age and gender. Most patients who considered themselves "much improved" or "very much improved" on the PGIC had a decrease of 30% or greater in pain on the PI-NRS from baseline to endpoint.

These data mean that patients feel that at least a 30% decrease in their pain level — no matter what their starting pain level was — provides meaningful pain relief.

Note that in order to meet regulatory guidelines, the higher hurdle of at least a 50% decrease in pain level (ie, pain cut in half) was used in these clinical studies of LYRICA (as in any trial evaluating an agent for pain) to define meaningful pain relief.

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Progress Check

There may be **more than one** correct answer to each question.

1. The Pain Intensity Numeric Rating Scale (PI-NRS):
   - ***A was used to evaluate pain on a daily basis in the LYRICA clinical trial program.***
   - B was used only at the end of the LYRICA clinical trial program, to provide the endpoint mean pain score.
   - C is a 5-point scale.
   - D rates pain on a scale from 1 (no pain) to 10 (worst possible pain).

2. _____ was a secondary efficacy measure administered only at termination in the LYRICA clinical trial program.
   - A Pain-related sleep interference
   - B The Short-Form McGill Pain Questionnaire
   - C The Short-Form-36 Health Questionnaire
   - ***D The Patient Global Impression of Change***

3. Analysis of data from the LYRICA trials showed that patients feel that _____ in their pain level provides meaningful relief, regardless of their starting pain level.
   - ***A at least a 30% decrease***
   - B at least a 50% decrease

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State the difference between the last observation carried forward (LOCF) and baseline observation carried forward (BOCF) analysis for interpreting clinical trial results

Data Analysis and Presentation

As you learn about and then discuss the data from the clinical trials of LYRICA in pDPN and PHN, it is important that you understand how these data were obtained. One consideration is how data are handled from patients who drop out part way through the trial. Two key points are:

- Are data from patients who dropped out included at all? This question refers to the use of intent-to-treat (ITT) versus observed cases analysis.
- If data from patients who dropped out are included, how are they handled? This question refers to the use of last observation carried forward (LOCF) versus baseline observation carried forward (BOCF) analysis.

Intent-to-Treat Versus Observed Cases

The analysis for these studies was conducted on an intent-to-treat (ITT) basis. The ITT population was defined as all randomized patients who took at least one dose of study medication. Observed cases usually refer to the patients who actually completed a trial. Analyzing data on an ITT basis is a more rigorous method of analysis.

In the LYRICA program:

- 89% of all patients who received LYRICA completed Lesser et al and Rosenstock et al
- 73% of all patients who received LYRICA completed Van Seventer et al, Dworkin et al, and Sabatowski et al

LOCF versus BOCF

The second question is what to report for the data points for a subject after that subject has dropped out of the trial. For example, if a patient dropped out after week 4 in a trial that has weekly measurements for 8 weeks, data exist for that patient for weeks 1, 2, 3, and 4, but do not exist for weeks 5, 6, 7, and 8.

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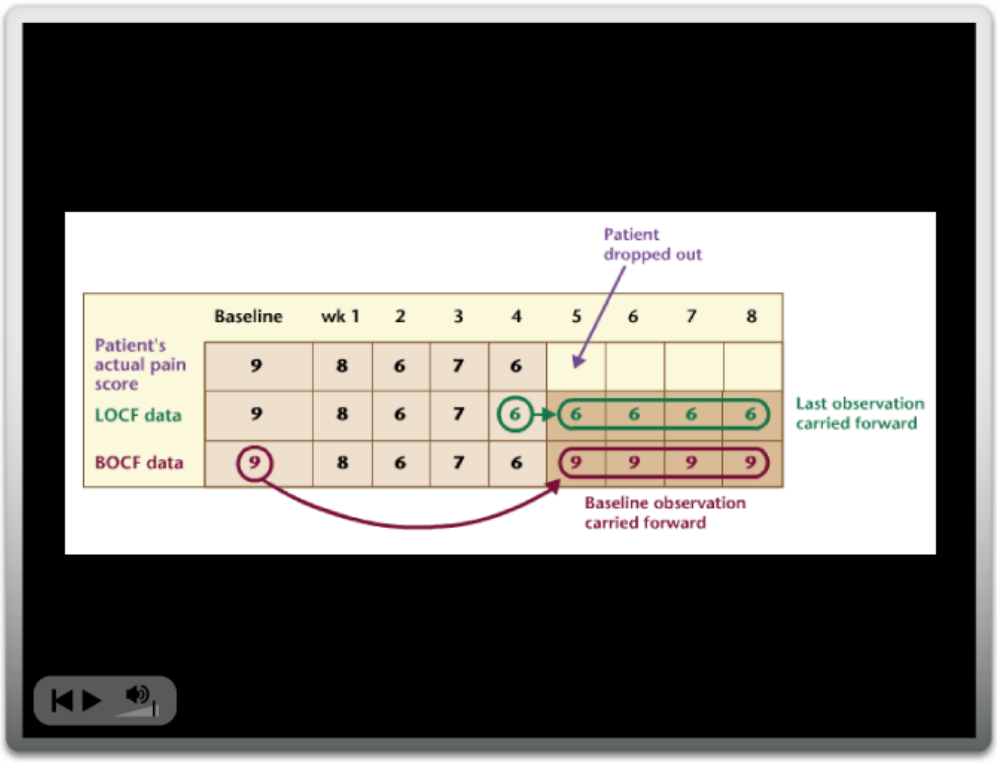
The traditional method of reporting these data has been last observation carried forward (LOCF). ***In general terms, LOCF means that the last data measurement for a patient who dropped out is also used for the value at all subsequent measurement times.*** In our example, the value reported by the patient at week 4 would also be used at weeks 5, 6, 7, and 8, as well as for week 4. This definition is sometimes modified, based on the particular efficacy measures used in a trial. In the LYRICA trials in pDPN and PHN, LOCF was defined as:

- for pain and sleep diary data: the average of the last 7 diary scores during treatment; this value was then used for all subsequent diary scores
- for all other measures in these trials: the last measurement taken during treatment was then used for all subsequent measurements (that is, the standard definition of LOCF)

The FDA division that evaluates analgesics — that is, the group evaluating LYRICA for pDPN and PHN — recently changed its requirements on how data for patients who drop out should be handled. The new requirement is to use baseline observation carried forward (BOCF) analysis. ***With BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment.*** Using our previous example of a patient who drops out after week 4 of an 8-week trial, instead of using the data from week 4 for all subsequent measurement points, the data from baseline (week 0) would be used for all subsequent measurement points.

The animation illustrates the difference between LOCF and BOCF analysis for the data from an individual patient.



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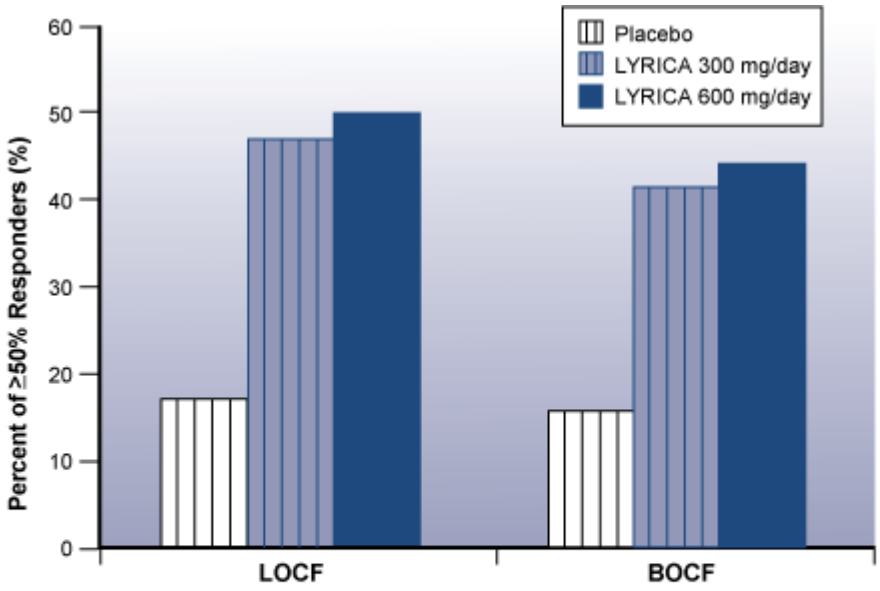
Because the *baseline* values (before any treatment) are reported for patients who drop out, BOCF data usually result in lower response rates and other results compared to LOCF data.

Figure 1D compares the ≥50% response rates from Lesser et al using both LOCF and BOCF analysis. As you can see, the bars in the BOCF set are lower than the bars in the LOCF set.

Figure 1D: LOCF versus BOCF Analysis for Lesser et al*



Because BOCF analysis assigns patients who drop out to their baseline score, BOCF results are lower than LOCF results. This graph compares LOCF ≥50% responder rates (on the left) with BOCF 50% responder rates (on the right) from Lesser et al in patients with DPN.

** Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.*

The switch to BOCF analysis has several key implications for the promotion of LYRICA, and it is important that you be prepared to address these in your discussions.

Incorrect Impressions of Efficacy Compared to Other Agents

Because using BOCF data is a recent regulatory change, the data for LYRICA as reported in the package insert cannot be compared to the data from studies of other agents that were previously reported, since those studies used LOCF analysis. While it is never appropriate to directly compare results for agents that are not from direct comparative trials, it is particularly important that physicians do not get the impression, just from looking at overall response rates, that LYRICA is less effective. In fact, LYRICA has excellent response rates, and you will need to show and explain this to physicians.

- For example, data for gabapentin in PHN were calculated using LOCF data, so these response rates cannot be compared with the BOCF response rates for LYRICA in the package insert.

Please note that how BOCF is described can also color a physician's perception of efficacy. For example, the package insert defines patients as not completing the study as being assigned to "0% improvement." As noted previously, however, another way to describe these patients is that they were assigned to their "baseline measurement."

Data in the Package Insert Versus Published Articles

The LYRICA package insert reports BOCF data for pDPN and PHN, and the published articles of the studies report LOCF data. For pDPN and PHN, only BOCF data from the package insert can be discussed with physicians.

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Progress Check

There may be **more than one** correct answer to each question.

1. Since BOCF data analysis involves reporting baseline values for patients who drop out, BOCF data generate _____ response rates compared to LOCF.

   A higher

   B lower

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Explain how to read a continuous responder graph

Presentation of Results: Continuous Responder Graph

In order to effectively present LYRICA to healthcare providers, you will need to be able to confidently explain the way that the data in the package insert are visually presented. The data displayed in the package insert are termed continuous responder graphs. For a range of degrees of improvement in pain from baseline to study endpoint, a continuous responder graph shows the fraction of patients achieving that degree of improvement. A continuous responder graph is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. Patients who did not complete a study were assigned 0% improvement. Some patients experienced a decrease in pain as early as Week 1, which persisted throughout a given study.

In other words, a continuous responder graph shows the relative benefit of a dose across the entire range of response:

- the horizontal axis shows the percent of improvement in pain from baseline to endpoint for each dose
- the vertical axis shows the corresponding percent of patients achieving that level of pain reduction or greater

For example, as illustrated in Figure 1E, in order to find out what percentage of patients achieved ≥50% reduction in pain:

- (1) find 50% on the horizontal axis
- (2) draw a line vertically that intersects the line for the dose you are interested in
- (3) then draw a horizontal line to the vertical axis
- (4) where it intersects the vertical axis, that is the percentage of patients who had ≥50% of pain relief; note that this percentage is cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%

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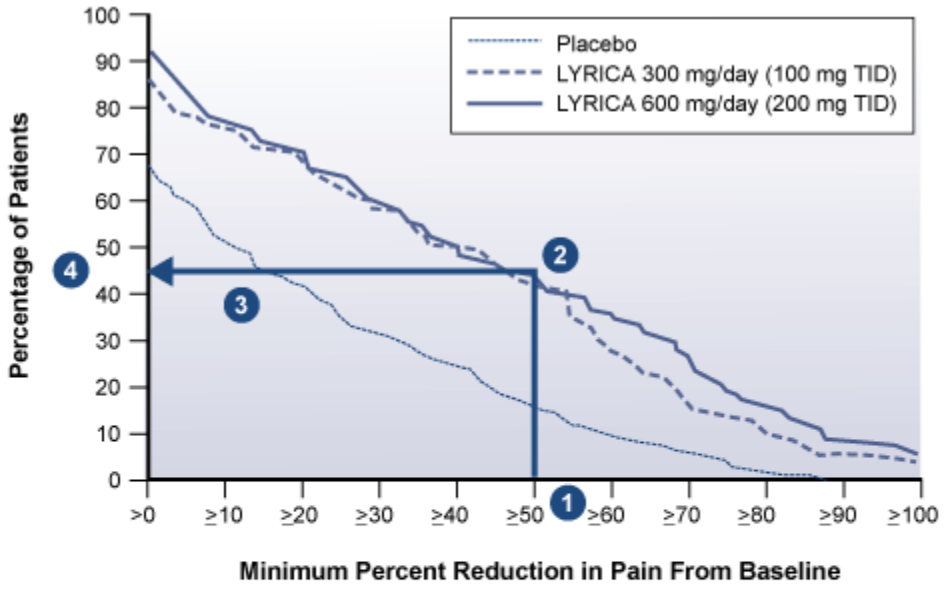
In the example in Figure 1E, approximately 45% of patients with pDPN in Lesser et al who received LYRICA 600 mg/day (administered TID) had ≥50% of pain relief compared with baseline.

Figure 1E: Reading a Continuous Responder Graph*



A responder profile shows the relative benefit of a dose across the entire range of response:

- (1) find 50% on the horizontal axis
- (2) draw a line vertically that intersects the line for the dose you are interested in
- (3) then draw a horizontal line to the vertical axis
- (4) where it intersects the vertical axis, that is the percentage of patients who had ≥50% of pain relief—in this example, approximately 45%

** Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.*

Adapted from the LYRICA package insert, 2009

Click on the icon to reinforce what you have learned about reading a continuous responder graph.

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Progress Check

There may be **more than one** correct answer to each question.

1. A continuous responder graph shows the:
   - A percent median reduction of pain experienced by 50% or more patients.
   - ***B relative benefit of a dose across the entire range of response.***
   - C mean number of patients who experienced pain relief of 30% or less during the trial midpoint.
   - D all of the above

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Describe the patient selection criteria for the key clinical trials in pDPN and PHN

Patient Selection Criteria

Eligible patients were males or nonpregnant, nonlactating females of any race who were ≥18 years of age. To be randomized for treatment, patients had to meet the following inclusion criteria:

- completed at least 4 daily pain diary entries during the baseline phase
- rated their pain both at screening and at randomization at ≥40 mm on the 0 mm to 100 mm visual analog pain scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ)
- had a mean pain score ≥4 over the 7-day baseline phase (moderate to severe pain)

Inclusion and exclusion criteria with regard to prior use of gabapentin evolved during the clinical trials program. Because gabapentin and pregabalin share the same mechanism of action, it was thought that inclusion of patients refractory to gabapentin treatment might bias the patient sample with those who would not respond to LYRICA treatment.

- In most studies, patients who had failed to respond to gabapentin ≥1200 mg/day for pDPN were excluded.
- Later in the clinical trial program — for example, Van Seventer et al — patients who had previously taken gabapentin, irrespective of dose, were included in the trials.

In general, patients in the pDPN studies were required to discontinue all analgesic medications except acetaminophen up to prespecified levels prior to baseline. Patients in the PHN studies were allowed to remain on a stable analgesic regimen, with the exception of concomitant anticonvulsants.

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Progress Check

There may be **more than one** correct answer to each question.

1. Patients were only randomized for treatment if they:
   - ***A*** ***had a mean pain score ≥4 over the 7-day baseline phase (moderate to severe pain).***
   - ***B*** ***completed at least 4 daily pain entries during the baseline phase.***
   - ***C*** ***were ≥18 years of age.***

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Section 2: Key Clinical Trials in pDPN

Objectives

- Describe the study design of Lesser et al
- Discuss the results of Lesser et al and their significance
- Describe the study design of Rosenstock et al
- Discuss the results of Rosenstock et al and their significance
- Discuss the study design and results of Richter et al

The efficacy of LYRICA for the management of neuropathic pain associated with diabetic peripheral **neuropathy** was established in 3 randomized, double-blind, placebo-controlled studies, 2 of which studied the maximum recommended dose of 300 mg/day (100 mg TID) — Lesser et al and Rosenstock et al.

This section discusses the study designs, results, and impact of Lesser et al and Rosenstock et al, which are summarized in the LYRICA package insert, as well as the results of Richter et al, which helped the efficacy of TID dosing in pDPN.

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Describe the study design of Lesser et al

Lesser et al Design

Lesser et al (study DPN1 in the LYRICA prescribing information) was a 5-week, double-blind, placebo-controlled trial in 337 patients with pDPN, conducted at 45 sites in the United States. This study has been reported by Lesser et al in *Neurology*, 2004. The study consisted of a 1-week baseline phase, after which, qualified patients were randomized to treatment or placebo, and a 5-week double-blind treatment phase.

The ITT population consisted of 337 patients who were randomized to 1 of the following 4 treatment groups (TID regimen):

- placebo (n = 97)
- LYRICA 75 mg/day (25 mg TID) (n = 77)
- LYRICA 300 mg/day (100 mg TID) (n = 81)
- LYRICA 600 mg/day (200 mg TID) (n = 82)

Patients in the placebo, LYRICA 75 mg/day (25 mg TID), and LYRICA 300 mg/day (100 mg TID)groups started treatment at their fixed dose on day 1 of the 5-week treatment phase. Patients in the LYRICA 600 mg/day (200 mg TID)group had their medication increased during week 1, after which time dosage was maintained at the fixed dose for the remainder of the study. At the end of the 5-week double-blind phase, patients had the option of entering an open-label follow-on study.

Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.

Most patients (91%) in the study had type 2 diabetes, while 9% had type 1 diabetes. The percentages of patients with type 2 diabetes by treatment group were:

- 86% in the placebo group
- 92% in the LYRICA 75 mg/day (25 mg TID) group
- 94% in the LYRICA 300 mg/day (100 mg TID) group
- 93% in the LYRICA 600 mg/day (300 mg TID) group

Acetaminophen was the only analgesic allowed during the study in a dosage of up to six 500 mg tablets per day.

The primary efficacy variable was pain, as recorded by patients in a daily diary and rated on an 11-point scale, as described previously.

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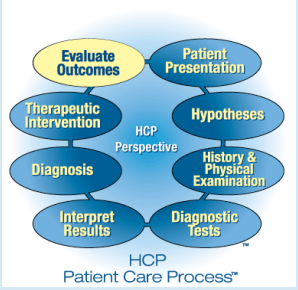
Secondary efficacy variables included pain-related sleep interference, SF-MPQ, CGIC, PGIC, and SF-36 Health Questionnaire. The CGIC and PGIC were administered at the termination visit at the end of week 5; the SF-36 Health Questionnaire was administered both at randomization and termination; and the SF-MPQ was administered to patients at each visit.

These secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed (except for PGIC LOCF data). If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to read about the results of treatment for Rodney, a patient with pDPN.

CASE STUDY

Rodney — A Patient with pDPN



Dr. Holmes has prescribed LYRICA 50 mg TID (150 mg/day) to 66-year-old Rodney to manage the neuropathic pain associated with his pDPN. He further tells Rodney to come back for a follow-up appointment after taking the LYRICA for 2 weeks so he can evaluate treatment effectiveness and any adverse events Rodney might experience related to treatment.

When Rodney returns for his follow-up appointment 2 weeks later, he tells Dr. Holmes that he believes treatment with LYRICA has helped. He describes the pain in his feet and calves as "tolerable". Rather than a "stabbing" pain, he says the pain feels closer to a "dull burn". Although he is getting more sleep, Rodney describes it as "interrupted", and that he continues to use a cane if he expects to do a lot of walking. Rodney adds that he experienced one bout of dizziness after starting treatment, but he's not sure if it's related to his diabetes or to LYRICA.

Dr. Holmes believes that Rodney's pain could be further reduced and decides to increase his LYRICA dose to 100 mg TID (300 mg/day). Dr. Holmes tells Rodney to return for a re-evaluation of the new treatment regimen in 3 weeks. He stresses that if Rodney experiences any serious side effects before his scheduled appointment, Rodney should immediately contact him.

Rodney returns for his second scheduled follow-up appointment. Rodney tells Dr. Holmes that his pain has continued to decrease with the increase in dose. He says that the pain in his calves and feet "comes and goes" and feels more like a "tingling" sensation "like my foot's fallen asleep". Rodney says that he's more likely to feel these tingling sensations when he exerts himself, spends too much time on his feet, and in the evening.

As for adverse events, Rodney tells Dr. Holmes that for the first week after reaching 300 mg/day in divided doses, he felt sleepy and light-headed, but that those feelings have mostly faded over the past few days.

Rodney tells Dr. Holmes that he feels better due to his reduction in pain.

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Progress Check

There may be **more than one** correct answer to each question.

1. Lesser et al evaluated LYRICA:
   - ***A 75 mg/day (25 mg TID).***
   - B 150 mg/day (50 mg TID).
   - ***C 300 mg/day (100 mg TID).***
   - ***D 600 mg/day (200 mg TID).***
   - E 1200 mg/day (400 mg TID).

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Discuss the results of Lesser et al and their significance

Lesser et al Results and Significance

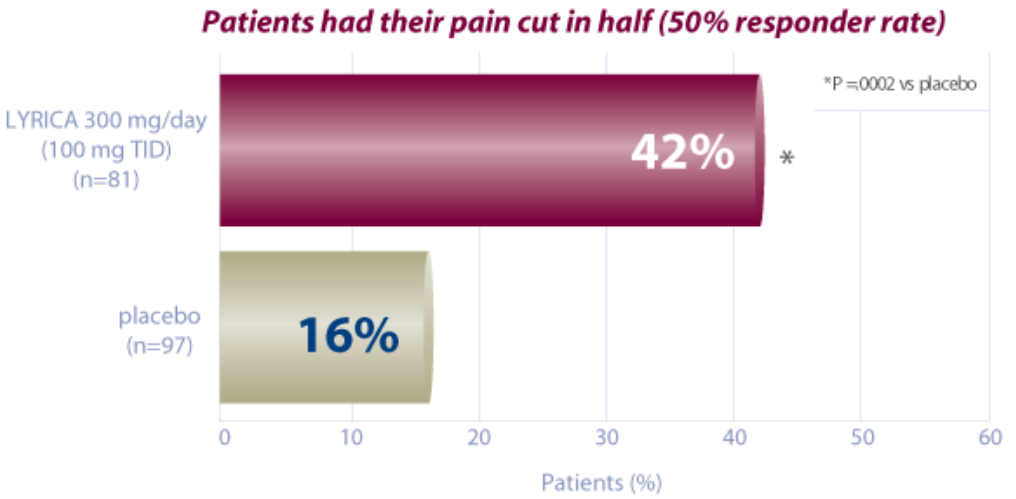
Primary Efficacy Measure: Mean Pain Score at Endpoint

Mean pain score at endpoint data were reported by Lesser et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. Only BOCF data from Lesser et al are included in this section.

A supplemental analysis of the primary efficacy variable was the proportion of responders (percent of patients with ≥50% decrease in mean pain scores from baseline to endpoint). As shown in Figure 2A, according to the BOCF data, the proportion of ≥50% responders (patients who had their pain cut in half) was significantly greater in the LYRICA 300 mg/day (100 mg TID) treatment group compared to placebo.

Figure 2A also shows that LYRICA cut pain in half (50% responder rate) in more than 40% of patients.

Figure 2A: Percentage of ≥50% Responders (Patients Who Had Their Pain Cut in Half) in Lesser et al at 5 Weeks (BOCF)



According to BOCF analysis, the proportion of ≥50% responders (patients who had their pain cut in half) in Lesser et al were significantly greater in the LYRICA 300 mg/day (100 mg TID) treatment group compared to placebo (P =.0002).

Adapted from Lesser et al and Study Report 029

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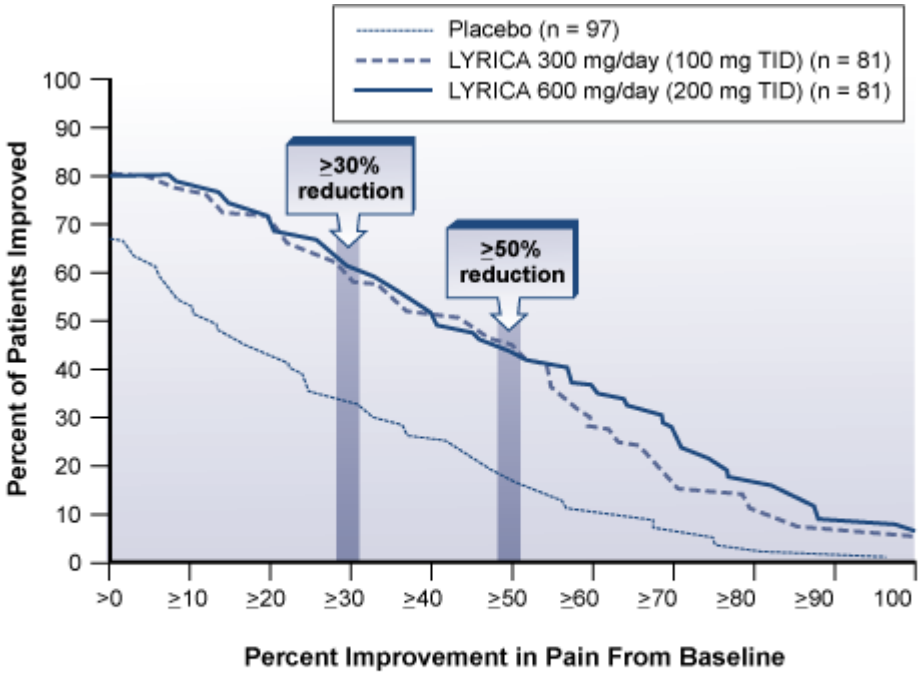
A significantly greater percentage of patients in the LYRICA 300 mg/day (100 mg TID) treatment group also experienced a ≥30% decrease in mean pain scores from baseline to endpoint compared to placebo. Recall that most patients consider themselves "much improved" or "very much improved" if they experience a 30% or greater decrease in pain.

Figure 2B illustrates the proportion of patients experiencing varying degrees of pain relief in the LYRICA and placebo groups. This figure, which is from the package insert, shows BOCF data. As noted earlier, BOCF data usually result in lower response rates compared to LOCF data.

Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 2B: Continuous Responder Graph from Lesser et al at 5 Weeks (BOCF)*



This figure (BOCF data) displays the relative benefit of various doses of LYRICA across the entire range of response in Lesser et al. A 75 mg/day (25 mg TID) dose was also evaluated.

Adapted from the LYRICA package insert, 2009

** Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.*

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As noted in Section 1, with BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment. Because the *baseline* values (before any treatment) are reported for patients who drop out, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

Click on the icon to reinforce what you have learned about the primary efficacy measure for Lesser et al.

Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed (except for PGIC LOCF data). If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information. This section presents LOCF data for PGIC only.

PGIC LOCF data are the only secondary endpoint data for pDPN included in the LYRICA package insert. These secondary endpoint data are included because a concomitant general trend for a positive effect on PGIC was observed across the 3 pivotal pDPN trials when pain reduction was considered across the approved LYRICA dose range. In other words, when patients were observed to have a reduction in their level of pain following LYRICA administration, they tended to say they felt better (as reported on the PGIC). Also, it is important to note that these PGIC data are LOCF because the PGIC assessment was done at the end of the study and therefore does not have any *baseline* values. As there are no baseline values for PGIC, there can be no BOCF analysis.

Figure 2C illustrates the LOCF data from the PGIC for the LYRICA 300 mg/day (100 mg TID) group. These data show a statistically significant effect of LYRICA 300 mg/day (100 mg TID) on PGIC.

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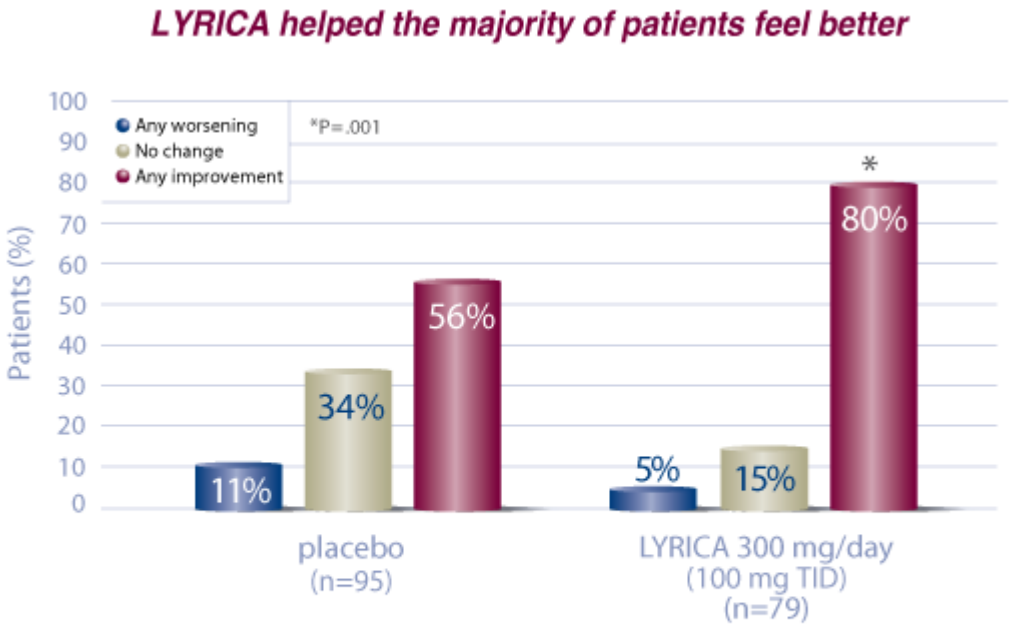
Figure 2C: Change in PGIC from Baseline to Endpoint in Lesser et al (LOCF)



In Lesser et al, the percentage of patients with improved PGIC scores was significantly greater for the LYRICA 300 mg/day (100 mg TID) group than for placebo (P = .001, LOCF data).

Adapted from Study Report 029

Click on the icon to view important information about what can and cannot be said when the Lesser et al reprint with a healthcare provider.

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Progress Check

There may be **more than one** correct answer to each question.

1. In Lesser et al, _____ of patients in the 300 mg/day (100 mg TID) group had a ≥50% reduction in mean pain scores, compared to _____ of patients in the placebo group.
   - A 22%; 21%
   - ***B 42%; 16%***
   - C 60%; 45%
   - D 83%; 52%

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Describe the study design of Rosenstock et al

Rosenstock at al Design

Rosenstock et al (study DPN2 in the LYRICA prescribing information) was an 8-week, randomized, double-blind, placebo-controlled trial in 146 patients with painful diabetic neuropathy, conducted at 25 centers in the United States. This study has been reported by Rosenstock et al in *Pain*, 2004. After a 1-week baseline phase, patients were randomized to 8 weeks of treatment (TID regimen) with either:

- LYRICA 300 mg/day (100 mg TID from day 1, no titration) (n = 76)
- placebo (n = 70)

At the end of the double-blind phase, patients could discontinue treatment or continue in an open-label follow-on study with a starting dose of LYRICA 300 mg/day (100 mg TID).

The majority of patients (87%) had type 2 diabetes. Patients were allowed to take up to 4 g per day of acetaminophen concurrently with study medication, and were also allowed up to 325 mg of aspirin per day for the prophylaxis of stroke and myocardial infarction. The use of certain medications for anxiety or depression was permitted as long as the patient had been on a stable regimen for ≥30 days prior to enrolling in the trial.

The primary efficacy variable was pain, as recorded in a daily diary and rated on an 11-point scale.

Secondary efficacy variables were pain-related sleep interference, SF-MPQ, PGIC, CGIC, and the SF-36 Health Questionnaire. The PGIC and CGIC were administered at the termination visit at the end of week 8, the SF-36 Health Questionnaire was administered at randomization and termination, and the SF-MPQ was administered to patients at each visit.

These secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

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Progress Check

There may be **more than one** correct answer to each question.

1. Rosenstock et al evaluated LYRICA:
   - A 150 mg/day (50 mg TID).
   - ***B 300 mg/day (100 mg TID).***
   - C 600 mg/day (200 mg TID).

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Discuss the results of Rosenstock et al and their significance

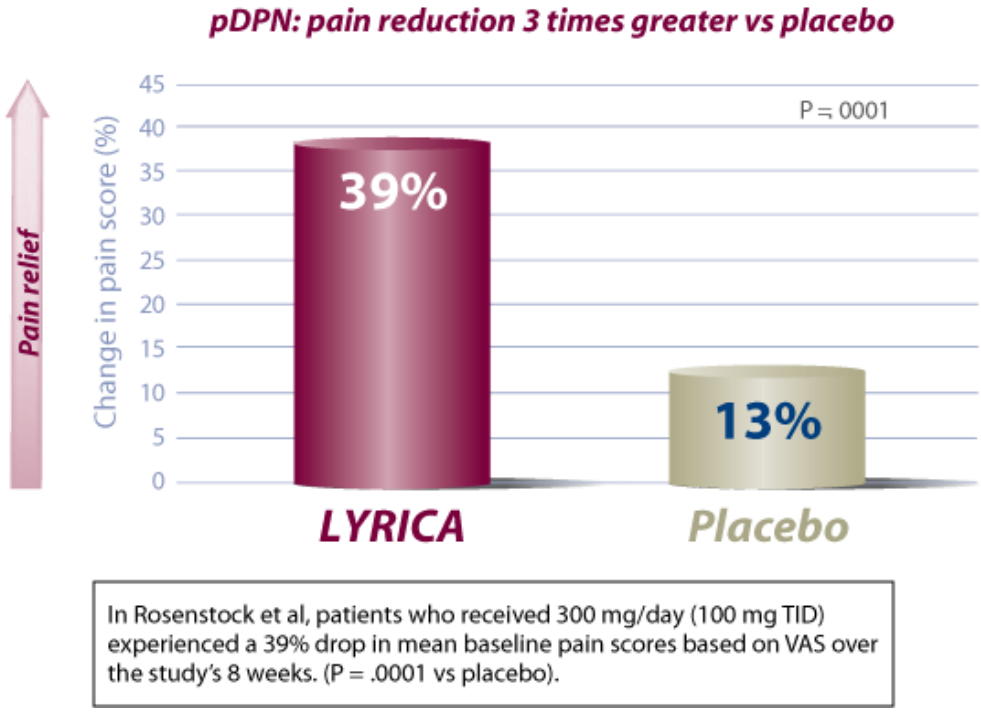
Rosenstock at al Results and Significance

Primary Efficacy Measure: Mean Pain Score at Endpoint

Mean pain score at endpoint data were reported by Rosenstock et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. Only BOCF data from Rosenstock et al are included in this section.

Figure 2D shows the total (BOCF) mean reduction from baseline pain scores that occurred in the LYRICA treatment group vs placebo during the study's 8-week period.

Figure 2D: Total (BOCF) Mean Percentage Reduction in Pain Scores in Rosenstock et al



In Rosenstock et al, patients who received 300 mg/day (100 mg TID) experienced a 39% drop in mean baseline pain scores based on VAS over the study's 8 weeks. (P = .0001 vs placebo).

Adapted from Rosenstock et al

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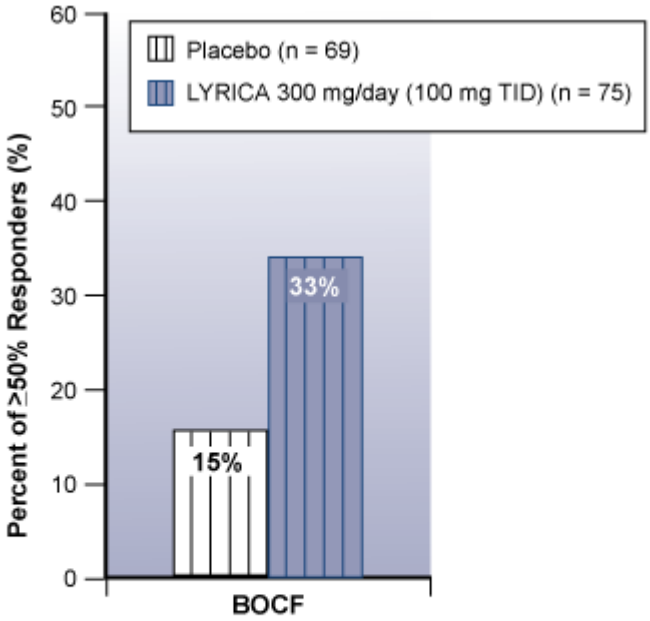
As shown in Figure 2E, according to BOCF data, significantly more patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders (patients who had their pain cut in half) compared to patients who received placebo (33% versus 15%, *P* = .01). As you recall, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

Figure 2E: Percentage of ≥50% Responders (Patients Who Had Their Pain Cut in Half) in Rosenstock et al at 8 Weeks (BOCF)



P=.01 versus placebo

In Rosenstock et al, according to BOCF data, significantly more patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders at 8 weeks compared to patients who received placebo (*P*=.01).

Adapted from Study Report 131

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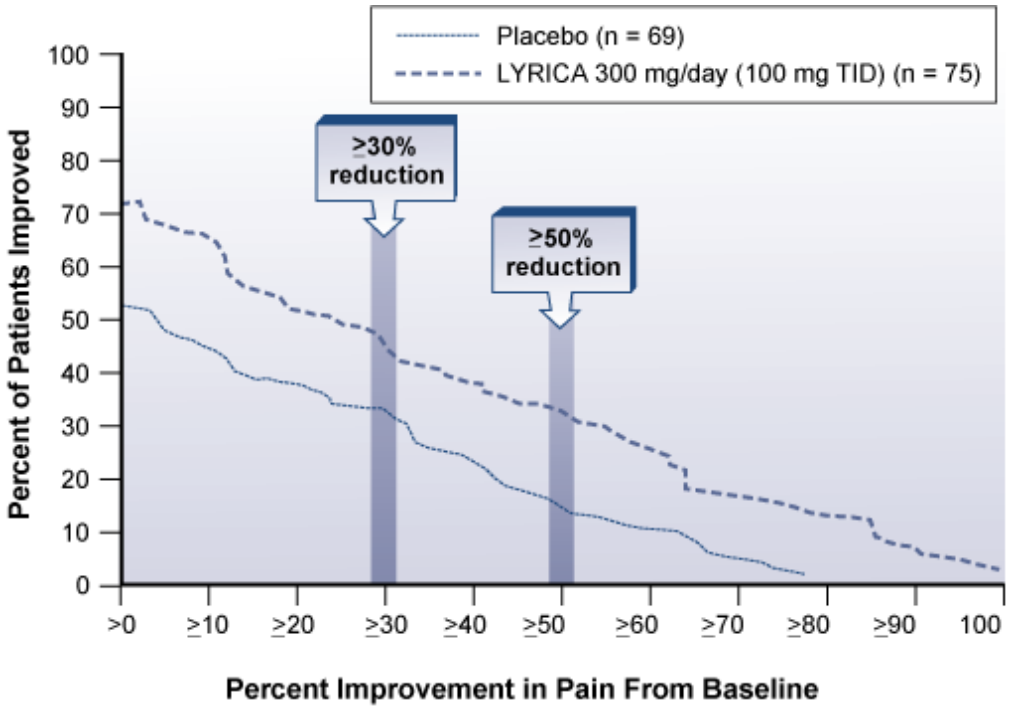
Figure 2F illustrates the proportion of patients experiencing varying degrees of pain relief in the LYRICA and placebo groups. This figure, which is from the package insert, shows BOCF data.

Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 2F: Continuous Responder Graph from Rosenstock et al at 8 Weeks (BOCF)



This figure (BOCF data) displays the relative benefit of LYRICA 300 mg/day (100 mg TID) across the entire range of response in Rosenstock et al.

Adapted from Study Report 131

Click on the icon to reinforce what you have learned about the percentage of ≥50% responders (patients who had their pain cut in half) in Rosenstock et al.

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Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to view important information about what can and cannot be said when the Rosenstock et al reprint with a healthcare provider.

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Progress Check

There may be **more than one** correct answer to each question.

1. According to Rosenstock et al BOCF data, _____ of patients who received LYRICA 300 mg/day were ≥50% responders (patients who had their pain cut in half) compared to _____ of patients who received placebo.

   A 12%; 8%

   B 33%; 15%

   C 54%; 31%

   D 71%; 58%

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Discuss the study design and results of Richter et al

Richter at al Design and Results

Richter et al (Study 014) was a 6-week, randomized, double-blind, multiple-dose, placebo-controlled, parallel-group trial in 246 patients with pDPN, conducted at 29 centers in the United States and Canada. This study has been reported by Richter et al in the *Journal of Pain* in 2005. Patients received one of the following treatment regimens (TID regimen):

- placebo (n = 85)
- LYRICA 150 mg/day (50 mg TID) (n = 79)
- LYRICA 600 mg/day (200 mg TID) (n = 82)

Please note that:

- LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.
- This study is mentioned in the LYRICA package insert as 1 of the 3 double-blind, placebo-controlled, multicenter studies having established the efficacy of LYRICA in pDPN. Although this third study is referenced in the LYRICA label as having contributed to the overall efficacy of LYRICA in pDPN, the details of Richter et al are not included in the LYRICA label in any level of detail.

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Section 3: Key Clinical Trials in PHN

Objectives

- Describe the study design of Van Seventer et al
- Discuss the results of Van Seventer et al and their significance
- Describe the study design of Dworkin et al
- Discuss the results of Dworkin et al and their significance
- Describe the study design of Sabatowski et al
- Discuss the results of Sabatowski et al and their significance

The efficacy of LYRICA for the management of neuropathic pain associated with PHN was established in 3 randomized, double-blind, placebo-controlled studies involving a total of 779 patients. This section describes the efficacy results from each of these 3 key trials:

- Van Seventer et al, a 13-week study with a BID regimen of LYRICA 150 mg/day (75 mg BID), 300 mg/day (150 mg BID), and 600 mg/day (150 mg BID or 300 mg BID, based on creatinine clearance) versus placebo
- Dworkin et al, an 8-week study with a TID regimen of LYRICA 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID), based on creatinine clearance, versus placebo
- Sabatowski et al, an 8-week study with a TID regimen of LYRICA 150 mg/day and 300 mg/day versus placebo

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Describe the study design of Van Seventer et al

Van Seventer at al Design

Van Seventer et al (study PHN1 in the LYRICA prescribing information) was a 13-week, randomized, double-blind, placebo-controlled trial in 368 patients with PHN, conducted at 76 centers in Europe and Australia. This study has been reported by Van Seventer et al in *Current Medical Research and Opinion* in 2006. Following a 1-week baseline phase, patients were randomized to (BID regimen):

- placebo (n = 93)
- LYRICA 150 mg/day (75 mg BID) (n = 87)
- LYRICA 300 mg/day (150 mg BID) (n = 98)
- LYRICA 600 mg/day (150 mg BID or 300 mg BID, based on creatinine clearance) (n = 90)

Patients with low CL_{cr} (>30 and ≤60 mL/min) randomized to the LYRICA 600 mg/day group received LYRICA 300 mg/day, while patients with normal CL_{cr} (>60 mL/min) received LYRICA 600 mg/day. Pharmacokinetic studies of pregabalin have shown that a dose of LYRICA 300 mg/day in patients with a CL_{cr} of 30 mL/min to 60 mL/min is basically equivalent to a 600 mg/day dose in patients with CL_{cr} >60 mL/min. Therefore, patients randomized to the LYRICA 600 mg/day group who received either 300 mg/day or 600 mg/day were analyzed as a single treatment group. Patients randomized to the LYRICA 600 mg/day group had a 1-week escalation phase, followed by a 12-week fixed-dose treatment phase.

In order to enter the study, patients had to have had PHN for at least 3 months following healing of their herpes zoster lesions. However, the median duration of PHN pain was 27 months. PHN pain most commonly affected the thoracic dermatomal region in this trial (46% of patients). Analgesics could be taken concurrently with study medication as long as patients were on a stable dose prior to enrollment (≥30 days for narcotics). Patients could take acetaminophen up to 4 g per day for pain, and aspirin up to 325 mg per day for the prevention of stroke and myocardial infarction.

The primary efficacy measure was the endpoint mean pain score, which was rated on an 11-point scale. Secondary efficacy parameters included endpoint and weekly sleep interference.

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

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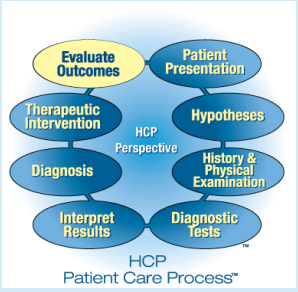
Click on the icon to read the results of treatment for Jennifer, a patient with PHN.

CASE STUDY

Jennifer — A Patient with PHN



Dr. Wagner has prescribed LYRICA 50 mg TID (150 mg/day) to 68-year-old Jennifer to manage the neuropathic pain associated with her PHN. She further tells Jennifer to come back for a follow-up appointment after taking LYRICA for 2 weeks so she can evaluate treatment effectiveness and any adverse events that Jennifer might experience related to treatment.

When Jennifer returns for her follow-up appointment 2 weeks later, she tells Dr. Wagner that she believes her treatment with LYRICA has helped. She says that the pain in her right chest wall that extends from her back to the nipple line has been reduced "by half". The pain feels more like a "tingling sensation" that seems to come and go. She's able to wear blouses and nightgowns, and can wear a brassiere for most of the day without too much pain.

Although Jennifer is pleased with the reduction in pain, she tells Dr. Wagner that she has experienced some minor dizzy spells since beginning treatment. She adds that when she experiences dizziness, she sits down and the spell usually passes "within 5 or 10 minutes." She adds that she often feels sleepy late in the day, and that she has more than once needed to take a nap.

Jennifer tells Dr. Wagner that she feels like her life has "much improved" due to the reduction in pain. Although Dr. Wagner thinks that an increase in dose could further reduce Jennifer's pain, she wants to further monitor Jennifer for treatment-related adverse effects.
Dr. Wagner decides to keep Jennifer on LYRICA 50 mg TID (150 mg/day) and continue monitoring her progress.

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Progress Check

There may be **more than one** correct answer to each question.

1. Van Seventer et al was a _____ trial that involved _____ patients.
   - A 12-week; 173
   - B 8-week; 238
   - ***C 13-week; 368***
   - D 7-week; 427

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Discuss the results of Van Seventer et al and their significance

Van Seventer at al Results and Significance

Two key features of Van Seventer et al are:

- the use of a BID regimen
- inclusion of patients who had previously received gabapentin, regardless of dose

The other 2 studies that established the efficacy of LYRICA in PHN involved TID regimens and excluded patients who had received gabapentin doses >1200 mg/day. Of the 368 patients in Van Seventer et al, 66% completed the study.

Primary Efficacy Measure: Mean Pain Score at Endpoint

Mean pain score at endpoint data were reported by Van Seventer et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. Only BOCF data from Van Seventer et al are included in this section.

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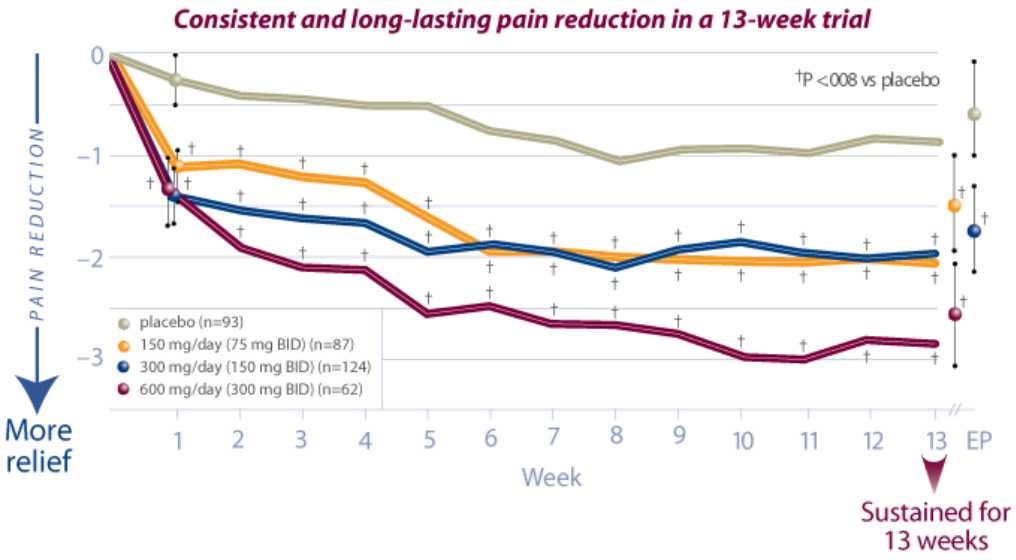
As shown in Figure 3A, weekly mean pain scores from baseline (BOCF) were significantly better for all 3 LYRICA treatment groups versus placebo starting at week 1.

Figure 3A: Weekly Mean Pain Reduction Scores from Baseline (BOCF) in Van Seventer et al



In Van Seventer et al, in patients with moderate to severe PHN for ≥3 months, mean pain scores for all LYRICA treatment groups (BID regimen) were significantly better than placebo beginning at week 1 and continuing through week 13 ($P < .008$ vs placebo).

Adapted from Van Seventer et al

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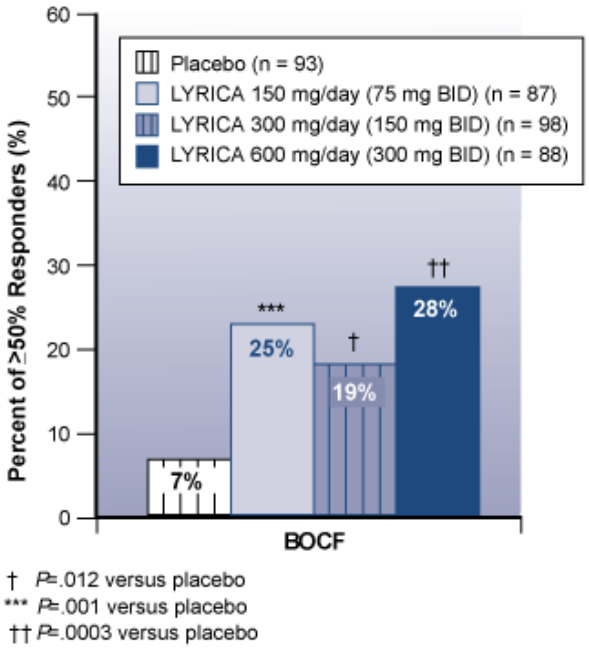
As shown in Figure 3B, according to BOCF data, all 3 LYRICA treatment groups had a significantly greater proportion of ≥50% responders. As noted previously, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

As noted in Section 1, with BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment. Because the *baseline* values (before any treatment) are reported for patients who drop out, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

Figure 3B: Percentage of ≥50% Responders (Patients Who Had Their Pain Cut in Half) in Van Seventer et al (BOCF)



† P=.012 versus placebo
*** P=.001 versus placebo
†† P=.0003 versus placebo

According to BOCF data, in Van Seventer et al, treatment with LYRICA 150 mg/day (75 mg BID), 300 mg/day (150 mg BID), and 600 mg/day (300 mg BID) all resulted in a significantly greater proportion of ≥50% responders compared with placebo.

Adapted from Study Report 196; Data on File

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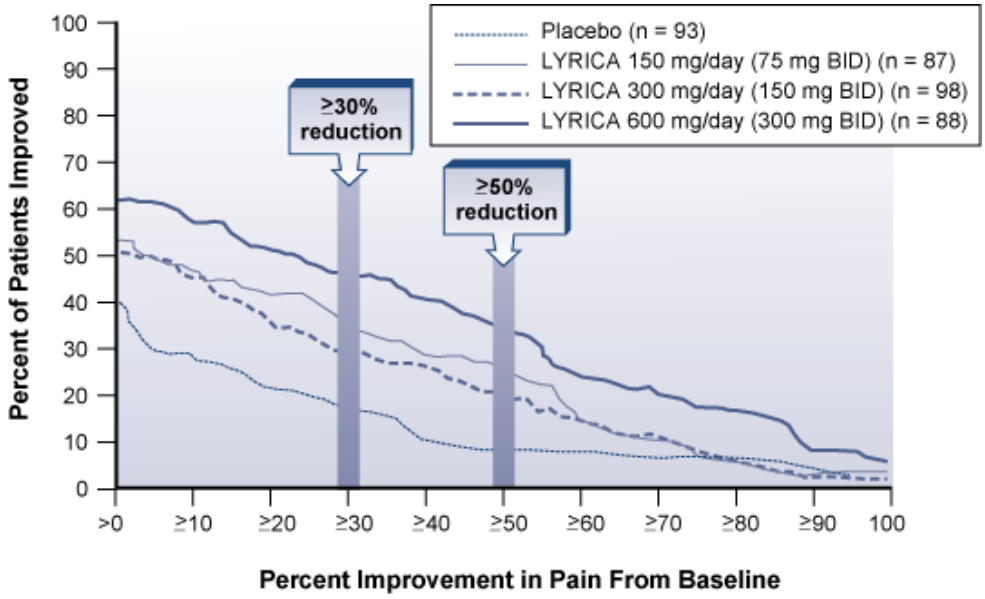
Figure 3C illustrates the proportion of patients experiencing varying degrees of pain relief in the LYRICA and placebo groups. This figure, which is from the package insert, shows BOCF data.

Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 3C: Continuous Responder Graph from Van Seventer et al (BOCF)



This figure (BOCF data) displays the relative benefit of LYRICA doses (BID regimen) across the entire range of response in Van Seventer et al.

Adapted from the LYRICA package insert, 2009

Click on the icon to reinforce what you have learned about results from Van Seventer et al.

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Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to view important information about what can and cannot be said when the Van Seventer et al reprint with a healthcare provider.

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Progress Check

There may be **more than one** correct answer to each question.

1. According to Van Seventer et al BOCF data, _____ of patients who received LYRICA 150 mg/day, _____ of patients who received LYRICA 300 mg/day, and _____ of patients who received LYRICA 600 mg/day were ≥50% responders (patients who had their pain cut in half).

   A ***25%; 19%; 28%***

   B 35%; 29%; 38%

   C 45%; 39%; 48%

   D 55%; 49%; 58%

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Describe the study design of Dworkin et al

Dworkin at al Design

Dworkin et al (study PHN2 in the LYRICA prescribing information) was an 8-week, double-blind, placebo-controlled, parallel-group trial in 173 patients with PHN conducted at 29 centers in the United States and Canada. This study was reported by Dworkin et al in *Neurology*, 2003. Following a 1-week baseline phase, patients were randomized to (TID regimen):

- placebo (n = 84)
- LYRICA 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID) (n = 88) (as noted previously, patients with CL_{cr} >30 mL/min but ≤60 mL/min received 300 mg/day, and patients with CL_{cr} >60 mL/min received 600 mg/day)

All patients randomized to LYRICA — 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID), based on creatinine clearance — were analyzed as a single LYRICA treatment group. Study medication was increased to the target dose during the first week of the double-blind phase, after which time, patients received a fixed dose for the remaining 7 weeks.

In order to enter the study, patients needed to have had PHN for at least 3 months. However, the median duration of PHN pain in this study was 19 months. Almost half of all patients randomized had pain predominantly in the thoracic dermatomal region. Patients were allowed to take analgesics and antidepressants concurrently with study medication as long as they were on a stable regimen prior to enrollment. Acetaminophen was allowed as rescue medication in dosages up to 4 g per day; up to 325 mg of aspirin per day was allowed for the prevention of stroke and myocardial infarction.

The primary efficacy measure was the endpoint mean pain score, which was rated on an 11-point scale.

Secondary efficacy parameters were sleep interference, SF-MPQ, PGIC, CGIC, SF-36 Health Questionnaire, and the MOS-Sleep Scale.

These secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to reinforce what you have learned about percentage of ≥50% responders in Dworkin et al.

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Progress Check

There may be **more than one** correct answer to each question.

1. In Dworkin et al, patients:
   - A were not allowed to take analgesics or antidepressants concurrently with study medication.
   - ***B were allowed to take analgesics or antidepressants concurrently with study medication as long as they were on a stable regimen prior to enrollment.***

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Discuss the results of Dworkin et al and their significance

Dworkin et al Results and Significance

Of the 173 patients in Dworkin et al, 65% of those who received LYRICA and 88% of those who received placebo completed the trial. The 65% completion rate was the lowest completion rate for a LYRICA treatment group among the clinical trials. Please keep in mind that in this study, the dose of LYRICA was titrated to 600 mg/day (the highest approved dose) over only 1 week, which is not the recommended titration schedule.

Primary Efficacy Measure: Mean Pain Scores at Endpoint

Mean pain score at endpoint data were reported by Dworkin et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. Only BOCF data from Dworkin et al are included in this section.

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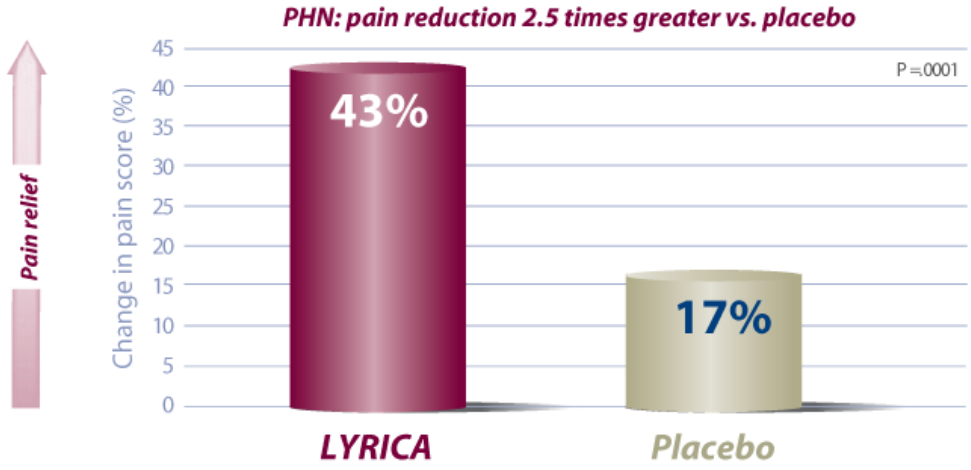
Figure 3D shows the total (BOCF) mean reduction from baseline pain scores that occurred in the LYRICA treatment group vs placebo during the study's 8-week period.

Figure 3D: Total (BOCF) Mean Percentage Reduction in Pain Scores in Dworkin et al



In Dworkin et al, patients with PHN ≥3 months who received 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID) based on creatinine clearance experienced a 43% drop in mean baseline pain scores based on VAS over the study's 8 weeks. Mean scores for the pregabalin treatment group decreased from a baseline mean pain score of 6.3 to a mean pain score of 3.6 at endpoint vs the placebo group, which decreased from a baseline mean pain score of 6.4 to a mean pain score of 5.29 at endpoint (P = .0001 vs placebo).

Adapted from Dworkin et al

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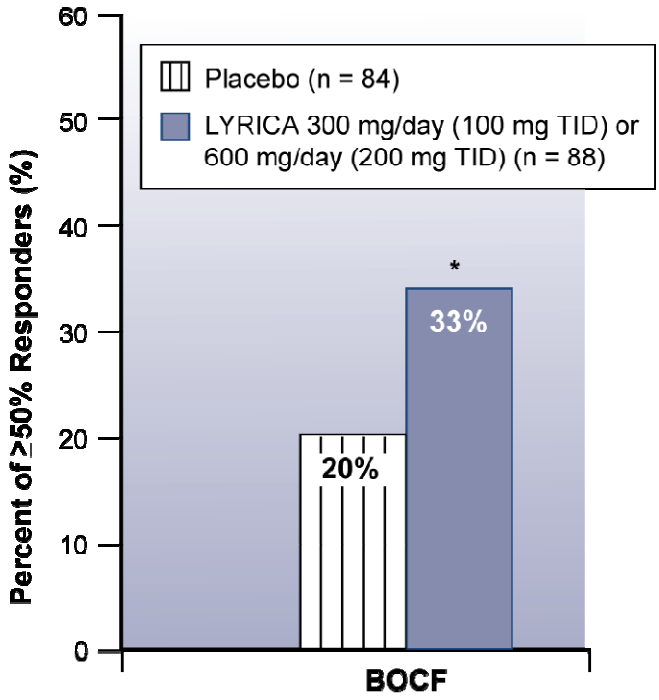
As shown in Figure 3E, according to BOCF data, significantly more patients who received LYRICA rather than placebo were considered ≥50% responders (patients who had their pain cut in half). As you recall, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

Figure 3E: Percentage of ≥50% Responders (Patients Who Had Their Pain Cut in Half) in Dworkin et al at 8 Weeks (BOCF)



* *P*=.05 versus placebo

According to BOCF data, the LYRICA 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID) group in Dworkin et al had a significantly higher proportion of ≥50% responders at 8 weeks compared with placebo (*P*=.05, BOCF data).

Adapted from Study Report 127

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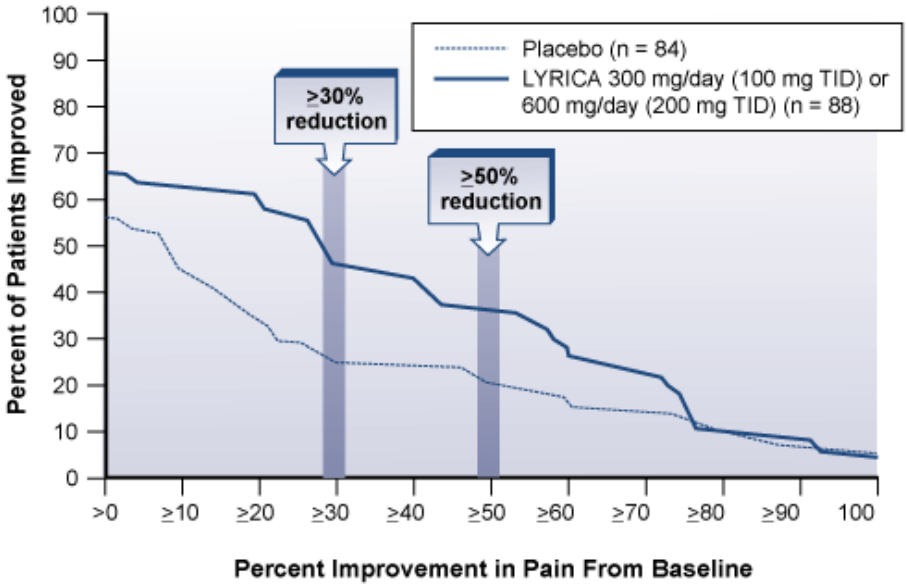
Figure 3F illustrates the proportion of patients experiencing varying degrees of pain relief in the LYRICA and placebo groups. This figure shows BOCF data.

Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 3F: Continuous Responder Graph from Dworkin et al at 8 Weeks (BOCF)



This figure (BOCF data) displays the relative benefit of LYRICA 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID) across the entire range of response in Dworkin et al.

Adapted from the LYRICA package insert, 2009

Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Click on the icon to view important information about what can and cannot be said when the Dworkin et al reprint with a healthcare provider.

Progress Check

There may be **more than one** correct answer to each question.

1. In Dworkin et al, _____ of patients who received LYRICA were considered ≥50% responders (patients who had their pain cut in half) according to BOCF analysis (compared to 20% with placebo).

   A 33%

   B 44%

   C 50%

   D 65%

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Describe the study design of Sabatowski et al

Sabatowski at al Design

Sabatowski et al (study PHN3 in the LYRICA prescribing information) was an 8-week, randomized, double-blind, placebo-controlled, parallel-group trial in 238 patients with PHN, conducted at 53 international centers. This study was published by Sabatowski et al in *Pain*, 2004. Following a 1-week baseline phase, the patients were randomized to 8 weeks of (TID regimen) treatment (including a 1-week titration phase) with:

- placebo (n = 81)
- LYRICA 150 mg/day (50 mg TID) (n = 81)
- LYRICA 300 mg/day (100 mg TID) (n = 76)

Patients in the trial had to have experienced PHN for at least 3 months after healing of their herpes zoster rash. However, most patients in this study had experienced PHN for >2 years, predominately of the thoracic (50%) and trigeminal (25%) dermatomal regions. Patients were allowed to take analgesics concurrently with study medication if the dosage remained within the stated restrictions of the study; use of opioids, NSAIDs, non-opioid analgesics, and antidepressants were allowed as long as treatment was stable and initiated prior to enrollment. Acetaminophen of up to 3 g per day was allowed, as was up to 325 mg of aspirin per day for the prevention of stroke and myocardial infarction.

The primary efficacy variable was pain, as recorded by patients in a daily pain diary and rated on an 11-point scale.

Secondary efficacy variables were sleep interference, SF-MPQ, CGIC, PGIC, SF-36 Health Questionnaire, and the Zung Self-Rating Depression Scale (SDS).

These secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

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Progress Check

There may be **more than one** correct answer to each question.

1. Most patients in Sabatowski et al had experienced PHN for >2 years, predominately of the thoracic and trigeminal dermatomal regions.

   A ***true***

   B false

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Discuss the results of Sabatowski et al and their significance

Sabatowski at al Results and Significance

Of the 238 patients, 81% completed Sabatowski et al.

Primary Efficacy Measure: Mean Pain Score at Endpoint

Mean pain score at endpoint data were reported by Sabatowski et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. Only BOCF data from Sabatowski et al are included in this section.

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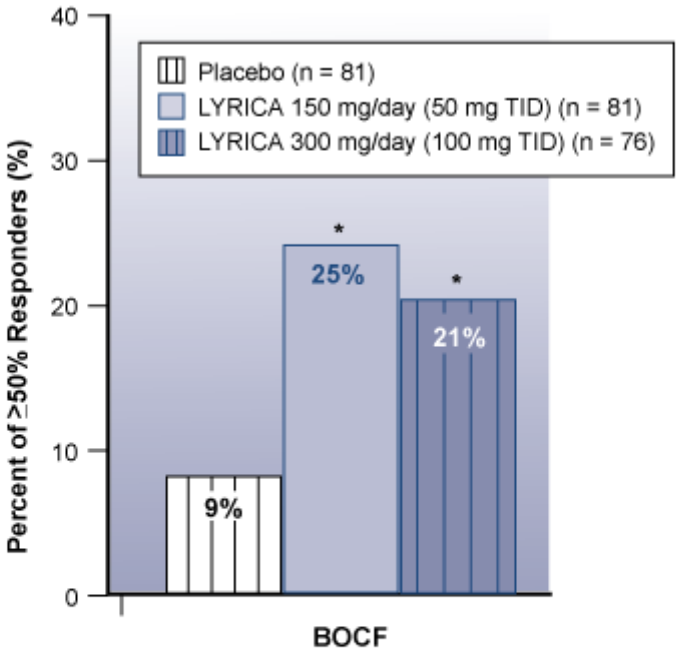
According to BOCF data, there was also a significantly higher proportion of ≥50% responders in both the LYRICA 150 mg/day (50 mg TID) and 300 mg/day (100 mg TID) treatment groups compared with placebo, as shown in Figure 3G. As you recall, BOCF data usually result in lower response rates (and other results) compared to LOCF data.

Figure 3G: Percentage of ≥50% Responders in Sabatowski et al at 8 Weeks (BOCF)



*P<.05 versus placebo

According to BOCF data, the LYRICA 150 mg/day (50 mg TID) and LYRICA 300 mg/day (100 mg TID) treatment groups in Sabatowski et al both had a significantly higher proportion of responders at 8 weeks compared with placebo (*P*<.05).

Adapted from Study Report 045

Click on the icon to reinforce what you have learned about the results from Sabatowski et al.

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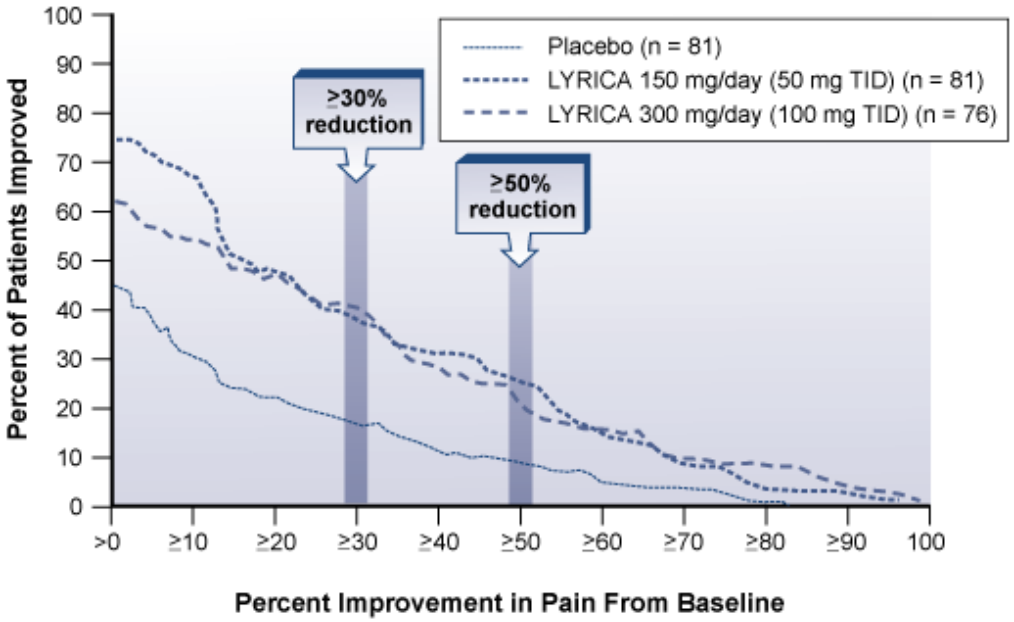
Figure 3H illustrates the proportion of patients experiencing varying degrees of pain relief in the LYRICA and placebo groups. This figure, which is in the package insert, shows BOCF data.

Some patients experienced a decrease in pain as early as week 1, which persisted throughout the study.

Figure 3H: Continuous Responder Graph from Sabatowski et al at 8 Weeks (BOCF)



This figure (BOCF data) displays the relative benefit of LYRICA (TID regimen) across the entire range of response in Sabatowski et al.

Adapted from the LYRICA package insert, 2009

Secondary Efficacy Measures

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed and are not presented here. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Progress Check

There may be **more than one** correct answer to each question.

1. In Sabatowski et al, _____ of patients who received LYRICA 150 mg/day (50 mg TID), and _____ of patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders (BOCF data).

   A 12%; 8%

   B 25%; 21%

   C 37%; 33%

   D 61%; 57%

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Module Summary

(1) **Overview of the neuropathic pain clinical trial program:** The efficacy of LYRICA for the management of neuropathic pain associated with DPN and PHN was established in double-blind, placebo-controlled, multicenter clinical trials. As noted in the LYRICA package insert:

- 3 studies with TID dosing established efficacy in pDPN
  - 2 of these studies — Lesser et al (DPN1) and Rosenstock et al (DPN2), which are in the package insert — studied the maximum recommended dose (n = 483)
- 3 studies with BID and TID dosing established efficacy in PHN — Van Seventer et al, Dworkin et al, and Sabatowski et al are in the package insert (n = 779)

Study design: The clinical trials in pDPN and PHN consisted of a baseline phase and a double-blind phase. In the majority of trials, doses of LYRICA were escalated over a period of 2 to 12 days, after which patients remained at a fixed dose for the remainder of the double-blind phase (5 to 13 weeks). Patients who completed or withdrew from the double-blind phase could elect to continue in open-label follow-on studies, or discontinue treatment.

Study endpoints: The primary efficacy measure in the intent-to-treat (ITT) population was the endpoint mean pain score, which was derived from a daily pain diary recorded by patients using the Pain Intensity Numeric Rating Scale (PI-NRS). Supplemental analysis of the primary efficacy measure included the proportion of ≥50% responders (patients who had their pain cut in half) and weekly analysis of pain scores.

Secondary efficacy measures included:

- the Short-Form McGill Pain Questionnaire (SF-MPQ)
- the patient and clinician global impression of change (PGIC and CGIC)
- pain-related sleep interference
- Medical Outcomes Study-Sleep (MOS-Sleep)
- Zung Self-rating Depression Scale (Zung SDS)
- Hospital Anxiety and Depression Scale (HADS)
- Short-Form-36 Health Questionnaire (SF-36)

A separate analysis by Farrar et al showed a close correlation between changes on the PI-NRS and the PGIC that was highly consistent over multiple trials. This analysis also showed that patients feel that at least a 30% decrease in their pain level — no matter what their starting pain level — provides meaningful relief. In order to meet regulatory guidelines, the higher hurdle of at least a 50% decrease in pain level was used in clinical studies of LYRICA to define meaningful pain relief.

Data analysis and presentation: All clinical studies listed in the LYRICA product labeling were analyzed on an intent-to-treat (ITT) basis using the baseline observation carried forward (BOCF).

Intent-to-treat means the entire population of study subjects who were randomized and took at least one dose of study medication was included in the analysis of the study. In a BOCF analysis, if patients drop out of the trial, instead of using their last measurement while on treatment and carrying it forward (LOCF), their original baseline measurement is carried forward — eliminating any measurements they reported during the time they did receive treatment.

Responder profile presentation: In the LYRICA product labeling, responder profiles are presented as a continuous responder graph with a horizontal axis that shows the percent of improvement in pain from baseline to endpoint for each dose, and a vertical axis that shows the corresponding percentage of patients who achieve certain levels of pain reduction.

Patient selection criteria: Eligible patients were males or nonpregnant, nonlactating females of any race who were ≥18 years of age. To be randomized for treatment, patients had to meet the following inclusion criteria:

- completed at least 4 daily pain diary entries during the baseline phase
- ≥40 mm on the visual analog pain scale (VAS) of the SF-MPQ
- had a mean pain score ≥4 (moderate to severe pain) over the 7-day baseline phase

(2) **Key clinical trials in pDPN:** The efficacy of LYRICA for the management of neuropathic pain associated with DPN was established in 2 trials that evaluated the maximum recommended dose of LYRICA for pDPN at 300 mg/day (100 mg TID).

Lesser et al (**Study DPN1):** Lesser et al was a 5-week double-blind trial in which 337 patients with pDPN were randomized to placebo, LYRICA 75 mg/day (25 mg TID), LYRICA 300 mg/day (100 mg TID), or LYRICA 600 mg/day (200 mg TID).

Mean pain score at endpoint data were reported by Lesser et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed.

42% (P = .0002) of patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders (patients who had their pain cut in half) compared to 16% of patients who received placebo (BOCF analysis).

In terms of secondary efficacy measures, patients who received LYRICA 300 mg/day (100 mg TID) or LYRICA 600 mg/day (200 mg TID) had significantly improved PGIC scores. Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed (except for PGIC LOCF data). If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Please note that LYRICA 600 mg/day is not an approved dose for pDPN, and the 600 mg/day efficacy data are not to be detailed. Although LYRICA was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended for pDPN.

Rosenstock et al (Study DPN2): Rosenstock et al was an 8-week trial in which 146 patients with pDPN were randomized to placebo or LYRICA 300 mg/day (100 mg TID) (100 mg/day, from day 1 — no titration).

Mean pain score at endpoint data were reported by Rosenstock et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed.

Patients who received 300 mg/day (100 mg TID) experienced a 39% drop (P = .0001) in mean baseline pain scores based on VAS over the study's 8 weeks, compared to 13% for patients treated with placebo (BOCF analysis).

33% (P=.01) of patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders (patients who had their pain cut in half) compared to 15% of patients who received placebo (BOCF analysis).

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Richter et al (Study 014): This 6-week, randomized, double-blind, multiple dose, placebo-controlled, parallel group clinical trial is mentioned in the LYRICA product labeling, but its results are not included because it did not evaluate the maximum recommended dose for pDPN.

(3) **Key clinical trials in PHN:** The efficacy of LYRICA for the management of neuropathic pain associated with PHN was established in 3 studies.

Van Seventer et al (Study PHN1): Van Seventer et al was a 13-week trial in which 368 patients with PHN were randomized to placebo, LYRICA 150 mg/day (75 mg BID), LYRICA 300 mg/day (150 mg BID), or LYRICA 600 mg/day (150 mg BID or 300 mg BID, based on creatinine clearance).

Mean pain score at endpoint data were reported by Van Seventer et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed.

25% (P = .001) of patients who received LYRICA 150 mg/day, 19% (P = .012) of patients who received LYRICA 300 mg/day (150 mg BID), and 28% (P = .0003) of patients who received LYRICA 600 mg/day (300 mg BID) were ≥50% responders (patients who had their pain cut in half) compared to 7% of patients who received placebo (BOCF analysis).

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Dworkin et al (Study PHN2): Dworkin et al was an 8-week trial in which 173 patients with PHN were randomized to placebo, LYRICA 300 mg/day (100 mg TID), or LYRICA 600 mg/day (200 mg TID), based on creatinine clearance.

Mean pain score at endpoint data were reported by Dworkin et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed.

Patients who received 300 mg/day (100 mg TID) or 600 mg/day (200 mg TID) experienced a 43% drop (P = .0001) in mean baseline pain scores based on VAS over the study's 8 weeks, compared to 17% for patients treated with placebo (BOCF analysis).

33% (P = .05) of patients who received LYRICA 600 mg/day were ≥50% responders (patients who had their pain cut in half) compared to 20% of patients who received placebo (BOCF analysis).

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Sabatowski et al (Study PHN3): Sabatowski et al was an 8-week trial in which 238 patients with PHN were randomized to placebo, LYRICA 150 mg/day (50 mg TID), or LYRICA 300 mg/day (100 mg TID).

Mean pain score at endpoint data were reported by Sabatowski et al using LOCF analysis and are not included in the LYRICA product labeling; therefore, the results cannot be detailed.

25% (P < .05) of patients who received LYRICA 150 mg/day (50 mg TID), and 21% (P < .05) of patients who received LYRICA 300 mg/day (100 mg TID) were ≥50% responders (patients who had their pain cut in half) compared to 9% of patients who received placebo (BOCF analysis).

Secondary endpoints are not included in the LYRICA product labeling; therefore, the results cannot be detailed. If a request is made by a customer for information on these secondary endpoints, you should refer him or her to Pfizer Medical Information.

Glossary

alpha$_2$-delta (α_2-δ)
an auxiliary subunit of voltage-gated calcium channels in central nervous system tissues that can be involved in the treatment of epilepsy and neuropathic pain

analgesic
a compound capable of relieving pain by altering perception of nociceptive stimuli without producing anesthesia or loss of consciousness

BID
twice a day; abbreviation for the Latin *bis in die*

bioavailability
the physiologic availability of a given amount of a drug; proportion of the administered dose that is absorbed into the bloodstream

diabetic peripheral neuropathy (DPN)
diabetes mellitus-related damage of the peripheral nervous system; can result in neuropathic pain

distal symmetrical sensorimotor polyneuropathy
neuropathy that features loss of sensation in the feet and sometimes the hands before progressing to a "stocking-glove" distribution of sensory loss; the signs and symptoms may vary depending of the classes of nerve fibers involved

intent-to-treat (ITT) population
the population of patients, including all those randomized to receive treatment, whether or not they completed the trial

neuropathic pain
pain that is initiated or caused by a primary lesion or dysfunction in the nervous system; has no protective function; pain is generally chronic and does not respond to standard analgesic treatment

neuropathy
inflammation or degeneration of the peripheral nerves

painful diabetic peripheral neuropathy (pDPN)
diabetes mellitus-related damage of the peripheral nervous system; can result in neuropathic pain

partial seizure
a seizure characterized by localized cerebral ictal onset, also called focal or localization-related seizure

pharmacokinetics
movements of drugs within biologic systems, as affected by uptake, distribution, binding, elimination, and biotransformation; particularly the rates of such movements

postherpetic neuralgia (PHN)
chronic severe, stabbing, or throbbing pain that continues after the visible evidence of an episode of shingles (herpes zoster) has resolved

statistical power
the probability of rejecting the null hypothesis (the statistical hypothesis that one variable has no association with another variable or set of variables) when it is false

TID
3 times a day; abbreviation for the Latin *ter in die*

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type 1 diabetes
formerly known as insulin-dependent diabetes mellitus (IDDM); usually develops abruptly before the age of 20; an autoimmune disease characterized by a complete failure of insulin production

type 2 diabetes
formerly known as non-insulin-dependent diabetes mellitus (NIDDM); often of gradual onset, usually in obese individuals over age 40; characterized by a relative lack of insulin production and a decreased tissue response to insulin

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