Once Daily Controlled-Release Pregabalin In Fibromyalgia Patients: A Phase 3 Double-Blind, Randomized Withdrawal, Placebo-Controlled Study

Lesley M. Arnold MD1, Pierre Arsenault PhD, MD2, Cynthia Huffman, MD3, Jeffrey L Patrick, MBA4, Michael Messig, PhD5, Marci L Chew, PhD5, Luis Sanin, MD6, Lynne Pauer, MS7, Andrew Clair, PhD8

1University of Cincinnati College of Medicine
2Université de Sherbrooke
3Meridian Research
4Pfizer Inc

This study was sponsored by Pfizer Inc

Men or women (non-pregnant, non-lactating), aged ≥18 years who met 1990 ACR criteria for fibromyalgia who initially showed improvement with pregabalin CR compared with placebo in terms of the durability of treatment effect among patients with fibromyalgia who initially showed improvement with pregabalin CR

Secondary objectives included:

- To evaluate the efficacy of pregabalin CR compared with placebo in terms of the durability of treatment effect among patients with fibromyalgia who initially showed improvement with pregabalin CR

The primary objective was to evaluate the efficacy of pregabalin CR compared with placebo in terms of the durability of treatment effect among patients with fibromyalgia who initially showed improvement with pregabalin CR

Secondary objectives included:

- To evaluate the efficacy of pregabalin CR compared with placebo in terms of the durability of treatment effect among patients with fibromyalgia who initially showed improvement with pregabalin CR

- To assess the patient’s perception of pregabalin CR on relative benefit, satisfaction and willingness to continue

- To assess safety and tolerability

Introduction

- Pregabalin is currently approved for the treatment of fibromyalgia for twice daily dosing over a recommended range of 300–450 mg/day.

- Evidence suggests that treatment adherence and therapeutic outcome is improved with once daily dosing compared with multiple dosing regimens.

- With the goal of enhancing treatment convenience and adherence, a pregabalin controlled-release (CR) formulation was developed to evaluate once daily dosing

Methodology: Study Design

- A randomized withdrawal design consisting of 4 phases: baseline (1 week), single-blind treatment (6 weeks), double-blind treatment (13 weeks), and a double-blind taper period (1 week)

Methodology: Patient Eligibility

Major Inclusion Criteria

- Men or women (non-pregnant, non-lactating), aged ≥18 years who met 1990 ACR criteria for fibromyalgia

- Score on the numeric rating scale (NRS) for pain (1-week recall period) at screening (Visit 1) and enrollment (Visit 2)

- Average score of ≥4 on daily NRS pain diaries completed satisfactorily within the last 7 days prior to enrollment

Major Exclusion Criteria

- Failed pregabalin treatment due to lack of efficacy, hypersensitivity or intolerance to pregabalin or other α2δ ligands, or participated in a pregabalin clinical trial

- Use of prohibited medications that might affect pain or sleep in the absence of appropriate washouts

- Widespread inflammatory musculoskeletal disorders or rheumatic diseases; or any severe acute or chronic medical or psychiatric condition (including severe depression and substance abuse/dependence)

- Abnormal laboratory findings

Disclosures

- This study was sponsored by Pfizer Inc

- L. M. Arnold has received research funding and/or consulting fees from Pfizer, Eli Lilly and Company, Takeda, AstraZeneca, Forest Laboratories, Theravance, Daiichi Sankyo, Purdue

- P. Arsenaault has received research funding from and/or participated on an advisory board or speakers bureau for Pfizer, Janssen, Diex Research, Purdue, Valeant, Eli Lilly and Company

- C. Huffman has received research funding from Meriden Research

- J. L. Patrick, M. Messig, M. L. Chew, L. Sanin, L. Pauer, A Clair are full-time employees of Pfizer Inc and have stock options with Pfizer Inc

- Medical writing support for the production of this presentation was provided by Diane Hoffman, PhD, of Engage Scientific Solutions, and was funded by Pfizer Inc
Methodology: Study Medication

- Study medication was administered once daily following the evening meal.
- During the first week of single-blind phase, patients were treated with pregabalin CR 165 mg. Subsequently, the dose was increased to 330 mg or 495 mg, based on efficacy and tolerability (increases were made in 165-mg increments).
- Clinical pharmacology studies demonstrated the total daily exposure of pregabalin CR (165–495 mg/day) is equivalent to the corresponding pregabalin IR dose (150–450 mg/day) when administered with food.
- Patients were required to be taking ≥330 mg at end of dose optimization (first 3 weeks of single-blind phase) to continue in study.
- Patients randomized to placebo underwent a blinded taper from 6.8 at baseline to 4.3 at Week 6.

Results: Secondary Endpoints

- In the single-blind phase (n=441), mean daily pain score decreased from 6.8 at baseline to 4.3 at Week 6.
- In the double-blind phase, the pregabalin CR group (n=63) tended to show better daily pain scores over the course of treatment vs placebo group (n=58).
- Treatment groups were not significantly different at endpoint (secondary endpoint).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Single-blind, Mean (SD), n=441</th>
<th>Double-blind</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Daily Pain Score</td>
<td>6.8 (1.3)</td>
<td>4.3 (2.2)</td>
</tr>
<tr>
<td>FGQ Total</td>
<td>57.0 (13.6)</td>
<td>43.5 (16.5)</td>
</tr>
<tr>
<td>SSG Sleep Quality</td>
<td>4.8 (1.5)</td>
<td>6.3 (1.8)</td>
</tr>
</tbody>
</table>

Percentage of patients:

- PGIC:
  - 34.9% vs 36.7%: 0.4585
- BSQ:
  - Benefit: 83.8% vs 93.3%: 0.0236
  - Satisfaction: 75.3% vs 78.7%: 0.0491
  - Willingness: 75.4% vs 78.8%: 0.2577

Results: Primary Endpoint

- Median time from randomization to LTR (Kaplan-Meier analysis; p=0.021) - Pregabalin CR: 58 days
  - Placebo: 22 days

- During double-blind phase, 34/63 (54.0%) pregabalin CR and 41/58 (70.7%) placebo patients met LTR.

- Four sensitivity analyses were conducted using different assumptions related to LTR (e.g., all patients who withdrew from the study for any reason were assumed to have experienced LTR).

Methodology: Assessments

- Measures of pain severity, global assessment, functional status, tiredness, and sleep.
- Patient perception of treatment benefit, satisfaction and willingness to continue.
- Analyzed using an endpoint mean score analysis.

AE, adverse event; ECG, electrocardiogram

- Physical and neurologic examinations.
- Clinical laboratory tests.
- ECG.
- Suicidality assessments.
- AEs.
Results: Secondary Endpoints Summary

- In the single-blind phase, patients treated with pregabalin CR showed improvement on secondary endpoints related to pain, sleep, tiredness, and functional status
- Trends continued in the double-blind phase, generally favoring pregabalin CR, but differences vs placebo were not statistically significant
- Patients treated with pregabalin CR were more likely to report a benefit from treatment during the double-blind phase compared with placebo (OR 2.29; p=0.0296)

Treatment-Emergent AEs: Discontinuation Rates

Discontinued due to an AE

- Single-blind phase: 54/441 (12.2%) patients
  - Of these, 48 were considered treatment-related; most common were dizziness, peripheral edema, somnolence, fatigue, balance disorder and disturbance in attention
- Double-blind phase: 3/63 (4.8%) patients in the pregabalin group and 0/58 (0%) in the placebo group
  - Of the 3 patients who discontinued, 2 AEs (confusional state and feeling abnormal) were considered related to pregabalin CR

Conclusions

- The primary objective of this study was met
  - The time to LTR was statistically significantly longer with pregabalin CR vs placebo (58 vs 22 days, p=0.021)
- Secondary endpoints related to pain, sleep, tiredness, and function showed improvements following single-blind pregabalin CR treatment that were maintained with pregabalin CR during the double-blind phase; however, comparisons to placebo were not statistically significant
- Patients treated with pregabalin CR were more likely to report a benefit from treatment
- Pregabalin CR was well-tolerated
  - Discontinuation rates due to AEs and safety profile were consistent with prior studies of pregabalin IR with dizziness, somnolence, and peripheral edema among the most common

Thank you

Q&A