PROTOCOL SYNOPSIS – *Evaluation of long-term opioid efficacy for chronic pain*

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Centers</strong></td>
<td>25 U.S. sites identified and reviewed by the Steering Committee and Contract Research Organization (CRO) with appropriate experience that can be expected to enroll approximately 4 patients/month</td>
</tr>
</tbody>
</table>
| **Study Period** | 19-20 weeks: (1) open-label transition to extended-release oxycodone without opioid rescue (for oxycodone-treated patients) or extended-release morphine without opioid rescue (for morphine-treated patients) with dosage stabilization (1-2 weeks); (2) double-blind baseline phase (2 weeks); (3) double-blind active placebo-controlled taper/discontinuation phase (8 weeks); and (4) double-blind active placebo-controlled maintenance phase (8 weeks).  
Planned trial duration: 26 months  
- Start-up activities: 6 months  
- Enrollment duration: 12 months  
- Subject study duration: 6 months  
- Data analysis and top-line results summary: 2 months |
| **Study Objective** | Primary aim: To evaluate whether opioid analgesics have long-term efficacy in patients with chronic pain by testing the hypothesis that mean daily pain intensity during the final week of the maintenance phase is significantly higher in patients randomized to active placebo than in patients randomized to continuation of Full pre-study opioid dosage.  
Secondary aims: To test the hypothesis that mean scores on validated measures of mood, pain-related interference with function, and other aspects of health-related quality of life during the final week of the maintenance phase are significantly worse in patients randomized to active placebo than in patients randomized to continuation of Full pre-study opioid dosage. |
<p>| <strong>Study Population</strong> | Patients with chronic musculoskeletal pain (i.e., painful osteoarthritis [OA] or musculoskeletal low back pain [LBP]) or chronic neuropathic pain (i.e., painful diabetic peripheral neuropathy [DPN] or postherpetic neuralgia [PHN]) who have been treated continuously for their pain condition with 1 or more opioid analgesics at 1 or more doses per day for 1-4 years and who have been on a stable (fluctuation of less than +/- 20%) daily dosage of either oxycodone or morphine for the past 2 months. |
| <strong>Study Design</strong> | Multicenter, outpatient, double-blind, active placebo-controlled study with equal-sized strata based on mean of 2nd baseline week daily diary pain intensity ratings (≤ 4 vs. &gt; 4 - ≤ 7.5) and on pre-study opioid dosage (≥ 60 - ≤ 100 mg morphine equivalent vs. &gt; 100 - ≤ 300 mg morphine equivalent). Patients will be randomized to 1 of 3 treatment groups: (1) continued opioid at Full pre-study dosage; (2) continued opioid analgesic at approximately Half pre-study dosage; or (3) matching active placebo. |</p>
<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Approximately 1,200 randomized</th>
</tr>
</thead>
</table>
| **Inclusion Criteria** | 1. Men and women with painful OA, musculoskeletal LBP, painful DPN, or PHN who have been treated continuously for their pain condition with 1 or more opioid analgesics at 1 or more doses per day for 1-4 years and who have been on a stable (fluctuation of less than +/- 20%) daily dosage of either oxycodone or morphine for the past 2 months.  
2. Patients must meet specific diagnostic criteria for painful OA, musculoskeletal LBP, painful DPN, or PHN provided in a protocol appendix (based on recent Phase 3 trials of duloxetine in OA and LBP and of duloxetine and pregabalin in DPN and PHN).  
3. Age ≥ 21.  
4. Mean of 2nd baseline week daily diary pain intensity ratings ≤ 7.5 and on pre-study opioid dosage ≤ 300 mg morphine equivalent. |
| **Exclusion Criteria** | 1. At initial Screening contact, patients who report that their average pain intensity in the past week was “severe” on a verbal pain rating scale of “none,” “mild,” “moderate,” or “severe.”  
2. At initial Screening, patients who report that they are receiving no benefit from their opioid analgesic and are interested in participating in the trial as a means of discontinuing their opioid.  
3. Patients who do not agree to maintain all pre-study pain treatments (pharmacologic and other, for example, physical therapy) at pre-study dosages for the duration of the study and who do not agree to refrain from initiating any new pain treatments (pharmacologic and other) for the duration of the study.  
4. History of substance abuse disorder within the past 2 years.  
5. History of cannabis use within the past 6 months.  
7. History of active epilepsy (i.e., ≥ 1 seizure) within the past 2 years.  
8. Clinically active liver, renal, or cardiovascular disease.  
9. History of or current psychotic disorder.  
10. Major depression, panic disorder, post-traumatic stress disorder, or generalized anxiety disorder that is currently refractory to treatment.  
11. Any other clinically significant medical or pain condition (e.g., Parkinson’s disease, cognitive impairment, fibromyalgia, complex regional pain syndrome) or laboratory abnormality that would in the judgment of the investigator interfere with the subject’s ability to participate in the study.  
12. Active litigation or pending workers’ compensation decision, or settled litigation or workers’ compensation within the past 6 months.  
13. Participation in other treatment studies or receiving other investigational drugs within 30 days prior to screening. |
| **Route and Dosage Form** | Oral, encapsulated, extended-release oxycodone or extended-release morphine in several doses selected to permit blinded taper during the taper/withdrawal phase, and active placebo (one-half Lomotil® tablet; 1.25 mg diphenoxylate hydrochloride and .0125 mg atropine sulfate). |
Dosage

The patients’ pre-study daily dosage of morphine or oxycodone will either be continued at the full pre-study dosage, or be tapered over 8 weeks in tandem with substitution with active placebo to either approximately Half of the pre-study opioid dosage or to complete discontinuation.

Taper Phase

For a patient taking 260-300 mg morphine equivalent at enrollment (similar schedules would be used for patients taking other dosages at enrollment):

<table>
<thead>
<tr>
<th>Study day</th>
<th>Morphine dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>enrollment</td>
<td>260-300</td>
</tr>
<tr>
<td>1-5</td>
<td>260</td>
</tr>
<tr>
<td>6-10</td>
<td>220</td>
</tr>
<tr>
<td>11-15</td>
<td>180</td>
</tr>
<tr>
<td>16-20</td>
<td>150</td>
</tr>
<tr>
<td>21-25</td>
<td>120</td>
</tr>
<tr>
<td>26-30</td>
<td>90</td>
</tr>
<tr>
<td>31-35</td>
<td>70</td>
</tr>
<tr>
<td>36-40</td>
<td>50</td>
</tr>
<tr>
<td>41-45</td>
<td>40</td>
</tr>
<tr>
<td>46-50</td>
<td>30</td>
</tr>
<tr>
<td>51-56</td>
<td>20</td>
</tr>
</tbody>
</table>

During weeks 1, 3, 5, and 7 of the taper phase, all subjects will receive a standardized, brief, psychoeducational intervention designed to reduce the number who drop out during this phase. The intervention will be developed to have minimal impact on subject burden, and could be delivered either during study visits or by telephone, whichever will be most convenient for subjects.

Duration of Treatment and Follow Up

The total duration of treatment with double-blind opioid and/or active placebo will be 18 weeks. In addition, an in-person follow-up visit will be scheduled 4 weeks after the final dose of blinded medication to provide additional safety data and to assess whether subjects have resumed their pre-study opioid treatment.

The major strategy that will be used to minimize missing data for the primary outcome measure will be the use of weekly contacts with subjects that will consist of either in-person study visits or telephone interviews to ensure that sites remain in ongoing contact with all subjects. Subjects who withdraw from blinded treatment or do not adhere to the protocol will be asked to continue all weekly contacts throughout the duration of the trial (the importance of continued participation will be described in the consent form). Subjects who refuse to continue such participation will be asked for permission to be contacted for a single telephone interview at the appropriate time to collect the primary endpoint and key secondary endpoint measures.

To further minimize missing data, all investigators will be provided with a copy of the following article and encouraged to read it carefully: Fleming T. Addressing missing data in clinical trials. Ann Intern Med 2011;154:113-
As emphasized in this article, all patients will also be provided with educational materials describing the adverse effects that missing data have on the scientific value of clinical trials.

**Rescue Medication**

Throughout the trial, subjects with unacceptable pain will be treated according to a 3-tier rescue medication protocol for unacceptable pain. All subjects may be provided the 1st tier of the rescue medication at the beginning of the taper/withdrawal phase. The 2nd and 3rd tiers of rescue medication will be provided, if necessary, at subsequent scheduled or unscheduled study visits. To reduce the likelihood of gastrointestinal adverse events, subjects taking any prescription or over-the-counter NSAID medication (other than a cardioprotective dosage of aspirin) on a regular basis for comorbid conditions, or having a history of a gastrointestinal disorder that in the investigator’s judgment is a contraindication for NSAID treatment, will skip Tier 2 of the rescue medication protocol.

**Tier 1:** Open-label acetaminophen 325 mg, titrated as needed to a maximum of 8 tablets (2,600 mg) daily (2 tablets qid). If a subject fails to obtain a satisfactory response with this treatment, their acetaminophen will be replaced by Tier 2.

**Tier 2:** Open-label ibuprofen 200 mg, titrated as needed to a maximum 8 tablets (1600 mg) daily (2 tablets qid). If a subject fails to obtain a satisfactory response with this treatment, their ibuprofen will be replaced by Tier 3.

**Tier 3:** Double-blind morphine 5 mg or matching placebo, titrated as needed to a maximum of 2 tablets (10 mg) daily (1 tablet bid). Subjects in the active placebo arm will receive blinded morphine and subjects in the Full- and Half-dosage arms will receive blinded matching placebo so that there will be no increase in opioid dosages due to rescue medication in subjects receiving opioids.

Any subjects who cannot tolerate pain that has remained intractable to the blinded study medication and treatment with the 3 tiers of the rescue medication will be reminded of their right to exit the trial and be referred to a physician with expertise in pain treatment.

**Bowel Regimen**

All patients will be encouraged to continue their pre-study bowel regimen, including laxatives and stool softeners, and will have their bowel regimen adjusted if considered necessary by the investigator. These medications will not be provided by the sites.

**Primary Outcome Measure**

The mean of the daily ratings on a 0-10 numerical rating scale (NRS) of “average pain intensity in the past 24 hours” collected during the 8th week of the maintenance phase by interactive voice recording system (IVRS).

**Secondary Outcome Measures**

- Time to treatment discontinuation due to inadequate pain relief.
- Time to Tier 2 rescue medication.
- Time to Tier 3 rescue medication.
- Weekly means of daily IVRS ratings on 0-10 NRSs for “average” and
“worst” pain intensity in the past 24 hours for the last week of the taper phase and weeks 1-8 of the maintenance phase.
5. Types and total dosages of rescue medications assessed by daily IVRS.
6. Brief Pain Inventory (BPI) physical functioning, emotional functioning, and sleep scores at the end of the baseline, taper, and maintenance phases.
7. Hospital Anxiety and Depression Scale (HADS) measures of anxiety and depression at the end of the baseline, taper, and maintenance phases.
8. SF-12 scales of health-related quality of life collected at the end of the baseline, taper, and maintenance phases.
9. Patient Global Impression of Change (PGIC) scores at the end of the maintenance phase.

Safety
1. Incidence, severity, duration, and relatedness of all AEs and SAEs.
2. Incidence, severity, duration, and relatedness of pre-specified opioid-associated AEs.
3. Current Opioid Misuse Measure (COMM) scores at the end of the baseline, taper, and maintenance phases.
4. Clinical Opiate Withdrawal Scale (COWS) scores at the end of the baseline, taper, and maintenance phases.
5. Urine drug testing at screening and at the end of the taper and maintenance phases.

Additional assessments
1. Success of double-blind assessed by subject guesses of which treatment group they were in and primary reason for their guess.
2. At screening, patient ratings of perceived benefit from pre-study opioid treatment using a modified PGIC scale.
3. After signing consent, subject reasons for participation in the trial, for example, desire to taper off their opioid analgesic.

### Sample Size Considerations
Sample size estimation has been based on the assumption that both of the 2 stratification factors – baseline pain intensity (i.e., high vs. low pain intensity) and pre-study opioid dosage (i.e., high vs. low pre-study opioid dosage) – are treatment effect moderators for the Full current dosage vs. Placebo comparison. For the 4 Full current dosage vs. Placebo comparisons that will be conducted separately in each of the 4 “pain intensity by opioid dosage” subgroups, the analysis considered the most informative with respect to the long-term efficacy of opioid analgesics and having the greatest assay sensitivity is in the subjects with low pain intensity at baseline and high pre-study opioid dosage. In this subgroup, a sample size of 120 subjects per arm provides 90% power to detect a treatment difference of 1.25 points (SD = 2.5) on the NRS when using a test statistic having (one-sided) 0.005 false positive error rate. For each of the 3 additional statistical comparisons of the Full current dosage vs. Placebo arms that will be conducted in the other 3 subgroups, a sample size of 93 subjects per arm provides 80% power to detect a difference of 1.25 points (SD = 2.5) on the NRS between these 2 treatment groups.
when using a test statistic having (one-sided) 0.005 false positive error rate.

A 5th primary analysis for the comparison of Full current dosage vs. Placebo arms will be conducted using the data pooled across the 4 subgroups. In this analysis, the sample size of 399 subjects per arm provides 90% power to detect a difference of 0.80 points (SD = 2.5) on the NRS between these 2 groups when using a test statistic having (one-sided) 0.0005 false positive error rate.

As with the Full current dosage and Placebo arms, the Half current dosage arm will have 120 subjects with low pain intensity at baseline and high pre-study opioid dosage, and 93 subjects in each of the other 3 “pain intensity by opioid dosage” subgroups. A 6th primary analysis in the trial will be conducted to assess the Half current dosage vs. Placebo comparison using the data pooled across the 4 subgroups. In this analysis, the sample size of 399 subjects per arm provides 95% power to detect a difference of 0.75 points (SD = 2.5) on the NRS scale between these 2 groups when using a test statistic having (one-sided) 0.005 false positive error rate.

When considering the 4 patient subgroups and 3 treatment arms, multiple other tests of hypotheses are possible in addition to the 6 pre-specified primary analyses described above. To address multiplicity, a hierarchical procedure will be pre-specified for these additional analyses and will provide the statistical basis that will guide interpretation of those additional trial results.