Study to Evaluate the Long-term Efficacy of Opioid Analgesic Therapy in Chronic Pain
One proposed study

- Several studies are likely needed to address gaps in evidence on long-term efficacy of opioid analgesics for chronic pain
- This is a single proposed study to start the discussion
Objective: Primary Aim

• Primary aim: To evaluate whether opioid analgesics have long-term efficacy in patients with chronic pain

• Hypothesis - 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
Objective: Secondary Aims

• Hypothesis: mean scores during the final week of the maintenance phase are significantly worse in active placebo vs. continuation of full pre-study opioid dosage on validated measures of
  – mood,
  – pain-related interference with function, and
  – other aspects of health-related quality of life
Study Design

• Multicenter (25 U.S. sites), outpatient, double-blind, active placebo-controlled study

• Equal-sized strata based on:
  – mean of 2nd baseline week daily diary pain intensity ratings (≤ 4 vs. > 4 - ≤ 7.5) and
  – on pre-study opioid dosage (≥ 60 - ≤ 100 mg morphine equivalent vs. > 100 - ≤ 300 mg morphine equivalent).

• Randomized to:
  – (1) continued opioid at Full pre-study dosage
  – (2) continued opioid analgesic at approximately Half pre-study dosage
  – (3) matching active Placebo.
Study Design

Patients with chronic musculoskeletal or neuropathic pain on daily opioid analgesics for 1-4 years

Open Label Transition to ER oxycodone or ER morphine
No opioid rescue

Double-blind baseline phase (2 weeks)

Randomization (n=1200)

Continue Full Opioid Dose
Opioid Tapered to Half Dose
Opioid Tapered to Active Placebo

Primary Outcome Measure: 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 IVRS
Study Duration

Overall Duration (weeks)
- Pain score for stratification:
  - Overall Duration:
    - 0 weeks
    - 2 weeks
    - 4 weeks
    - 12 weeks
    - 20 weeks
    - 24 weeks

Primary Endpoint:
- 20 weeks
- 24 weeks

Treatment Duration (weeks)
- 0 weeks
- 2 weeks
- 10 weeks
- 18 weeks

Open Label Transition:
- Double-blind baseline
- Double-blind active placebo controlled continuation/taper phase
- Double-blind active placebo controlled maintenance phase
- Follow-up to assess safety and determine if previous opioid treatment has resumed
## Planned Trial Duration

<table>
<thead>
<tr>
<th>Activity</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start-up activities</td>
<td>6 months</td>
</tr>
<tr>
<td>Enrollment duration (25 U.S. sites expected to enroll approximately 4 patients/month)</td>
<td>12 months</td>
</tr>
<tr>
<td>Subject study duration (open label through follow-up)</td>
<td>6 months</td>
</tr>
<tr>
<td>Data analysis and top-line results summary</td>
<td>2 months</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26 months</strong></td>
</tr>
</tbody>
</table>
Study Population: Inclusion Criteria

Men or women meeting specific diagnostic criteria* for:

- Chronic musculoskeletal pain
  - painful osteoarthritis (OA) or
  - musculoskeletal lower back pain (LBP)

- Chronic neuropathic pain
  - painful diabetic peripheral neuropathy (DPN) or
  - postherpetic neuralgia (PHN)

*based on recent Phase 3 trials of duloxetine in OA and LBP and of duloxetine and pregabalin in DPN and PHN
Inclusion Criteria

• Treated continuously with 1 or more opioid analgesics at 1 or more doses per day for 1-4 years
• Stable (fluctuation of less than +/- 20%) daily dosage of either oxycodone or morphine for the past 2 months
• Age ≥ 21
• Mean of 2nd baseline week daily diary pain intensity ratings ≤ 7.5
• Pre-study opioid dosage ≤ 300 mg morphine equivalent (ME)
Exclusion Criteria

At initial Screening, patients who report:

• average pain intensity in the past week was “severe”
  – verbal pain rating scale of “none,” “mild,” “moderate,” or “severe”

• receiving no benefit from their opioid analgesic and are interested in participating in the trial as a means of discontinuing their opioid
Exclusion Criteria

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

- **refrain from initiating any new pain treatments** (pharmacologic and other) for the duration of the study
Exclusion Criteria

History of:

• substance abuse disorder within the past 2 years
• cannabis use within the past 6 months
• positive urine drug screen for any drug of abuse
• active epilepsy (i.e., \(\geq 1\) seizure) within the past 2 years
Exclusion Criteria

• History of or current psychotic disorder
• Clinically active liver, renal, or cardiovascular disease
• Major depression, panic disorder, post-traumatic stress disorder, or generalized anxiety disorder that is currently refractory to treatment
Exclusion Criteria

• Any other clinically significant medical or pain condition that would in the judgment of the investigator interfere with the subject’s ability to participate in the study. E.g.:
  – Parkinson's disease
  – cognitive impairment
  – fibromyalgia
  – complex regional pain syndrome or
  – laboratory abnormality

• Active litigation or pending workers’ compensation decision, or settled litigation or workers’ compensation within the past 6 months

• 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
  - several doses selected to permit blinded taper during the taper/withdrawal phase
- Active placebo: One-half Lomotil® tablet
  - 1.25 mg diphenoxylate hydrochloride
  - 0.0125 mg atropine sulfate
Dosage

The patients’ pre-study daily dosage of morphine or oxycodone will either be:

1. continued at the Full pre-study dosage
2. tapered to approximately Half of the pre-study opioid dosage*
3. complete discontinuation*

*over 8 weeks in tandem with substitution with active placebo
## Dosage: 8 Week Taper Phase Example

<table>
<thead>
<tr>
<th>Taper Day</th>
<th>Continue Full Opioid Dose</th>
<th>Opioid Tapered to Half Dose</th>
<th>Opioid Tapered to Active Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>260</td>
<td>260-300</td>
<td>260-300</td>
</tr>
<tr>
<td>1 – 5</td>
<td>260</td>
<td>260</td>
<td>260</td>
</tr>
<tr>
<td>6 – 10</td>
<td>260</td>
<td>220</td>
<td>220</td>
</tr>
<tr>
<td>11 – 15</td>
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<tr>
<td>16 – 20</td>
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<td>150</td>
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<td>21 – 25</td>
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<td>120-150</td>
<td>120</td>
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<tr>
<td>26 – 30</td>
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<td>36 – 40</td>
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<td>41 – 45</td>
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<td>120-150</td>
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<td>46 – 50</td>
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</tr>
<tr>
<td>Maintenance</td>
<td>260</td>
<td>120-150</td>
<td>0</td>
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</table>
Taper Phase: Drop-Out Reduction

- During weeks 1, 3, 5, and 7
- All subjects will receive a standardized, brief, psychoeducational intervention
- Designed to reduce the number who drop out
- Delivered either during study visits or by telephone, whichever will be most convenient for subjects
Weekly Follow Up

• Major strategy to minimize missing data for the primary outcome measure
• 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
• 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
Minimize missing data

• All patients will be provided with educational materials describing the adverse effects that missing data have on the scientific value of clinical trials

3-tier Rescue Medication Protocol

• Throughout the trial, subjects with unacceptable pain will be treated according to a 3-tier rescue medication protocol

• Patients with pain 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
  – referred to a physician with expertise in pain treatment
3-tier Rescue Medication Protocol

Tier 1

• Available at beginning of taper phase
• Open-label acetaminophen 325 mg
• titrated as needed to a maximum of 8 tablets (2,600 mg) daily (2 tablets qid)
• Lack of satisfactory response – replaced by Tier 2
3-tier Rescue Medication Protocol

Tier 2

- Available, if necessary, at subsequent scheduled or unscheduled study visits.
- Open-label ibuprofen 200 mg, titrated as needed to a maximum 8 tablets (1600 mg) daily (2 tablets qid).
- Skipped in subjects
  - taking any prescription or OTC NSAID medication (other than a cardioprotective dosage of aspirin) on a regular basis for comorbid conditions, or
  - history of a GI disorder that in the investigator’s judgment is a contraindication for NSAID
- Lack satisfactory response - replaced by Tier 3.
3-tier Rescue Medication Protocol

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.

• 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.
Bowel Regimen

- Encouraged to continue their pre-study bowel regimen
  - including laxatives and stool softeners
  - adjusted if considered necessary by the investigator
  - 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 IVRS
Secondary Efficacy 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.
Secondary Efficacy Outcome Measures

• Types and total dosages of rescue medications assessed by daily IVRS.
• Brief Pain Inventory (BPI) physical functioning, emotional functioning, and sleep scores at the end of the baseline, taper, and maintenance phases.
• Hospital Anxiety and Depression Scale (HADS) measures of anxiety and depression at the end of the baseline, taper, and maintenance phases.
• SF-12 scales of health-related quality of life collected at the end of the baseline, taper, and maintenance phases.
• Patient Global Impression of Change (PGIC) scores at the end of the maintenance phase.
Secondary Safety Outcome Measures

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

Additional assessments

• Success of double-blind assessed by subject guesses of which treatment group they were in and primary reason for their guess.

• At screening, patient ratings of perceived benefit from pre-study opioid treatment using a modified PGIC scale.

• After signing consent, subject reasons for participation in the trial, for example, desire to taper off their opioid analgesic.
Sample Size

• Assumption that both of the 2 stratification factors are treatment effect moderators for the Full current dosage vs. Placebo comparison.
  – baseline pain intensity (i.e., high vs. low pain intensity) and
  – pre-study opioid dosage (i.e., high vs. low pre-study opioid dosage)

• Low pain intensity (≤ 4) at baseline and high pre-study opioid dosage (>100 - ≤ 300mg ME)
  – considered the most informative with respect to the long-term efficacy of opioid analgesics and
  – having the greatest assay sensitivity
Sample Size

• Low pain intensity (≤ 4) at baseline and high pre-study opioid dosage (>100 - ≤ 300mg ME)

• 120 subjects per arm provides:
  – 90% power
  – Detect a treatment difference of 1.25 points (SD = 2.5) on the NRS
  – Using a test statistic having (one-sided) 0.005 false positive error rate
Sample Size

• Each of the 3 additional statistical comparisons of the Full current dosage vs. Placebo arms that will be conducted in the other 3 subgroups

• Sample size of 93 subjects per arm provides:
  – 80% power to
  – Detect a treatment difference of 1.25 points (SD = 2.5) on the NRS
  – Using a test statistic having (one-sided) 0.005 false positive error rate
Sample Size

- 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.
Sample Size

- 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.
Sample Size

- 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.