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

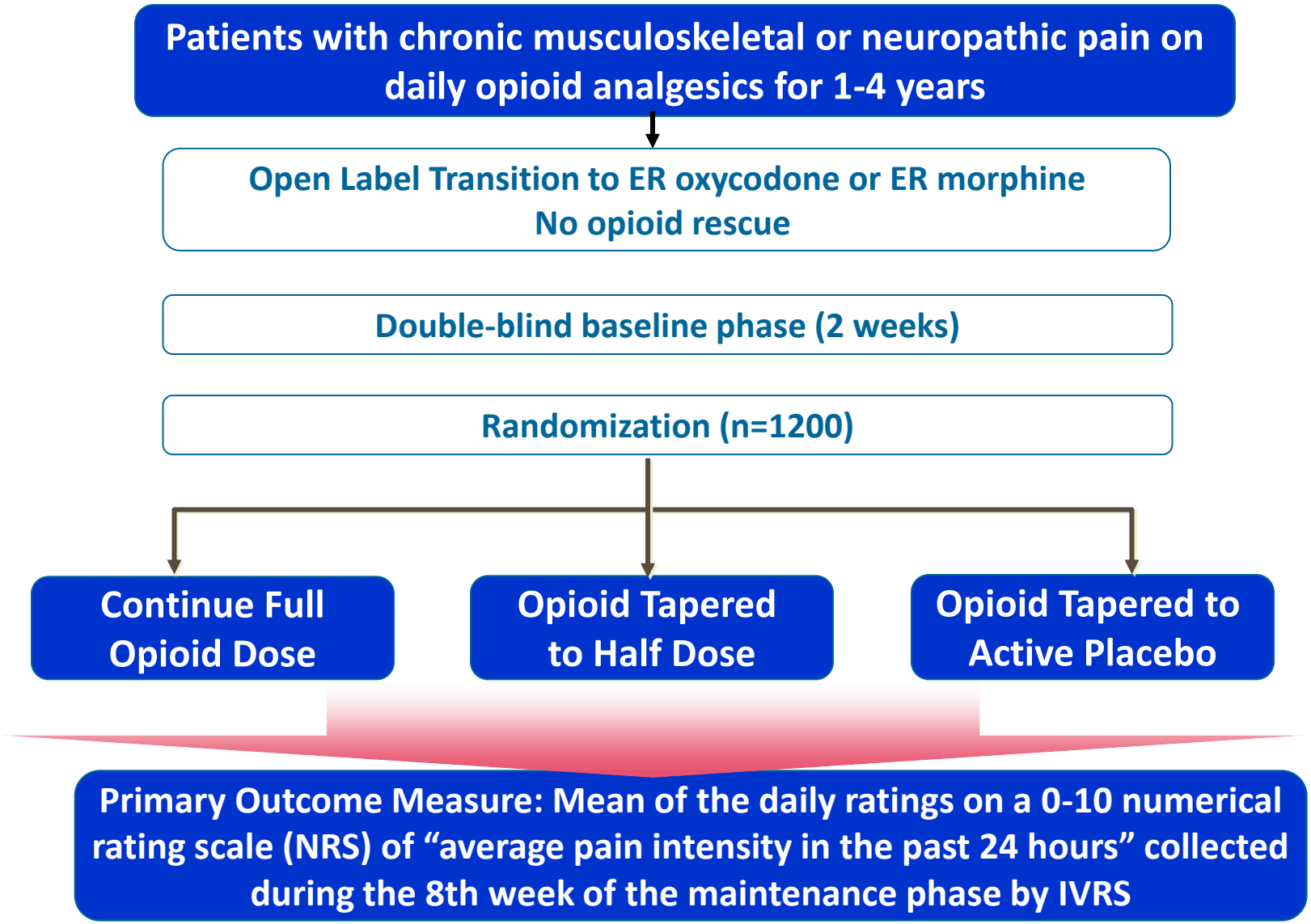
Objective: Secondary Aims

- 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

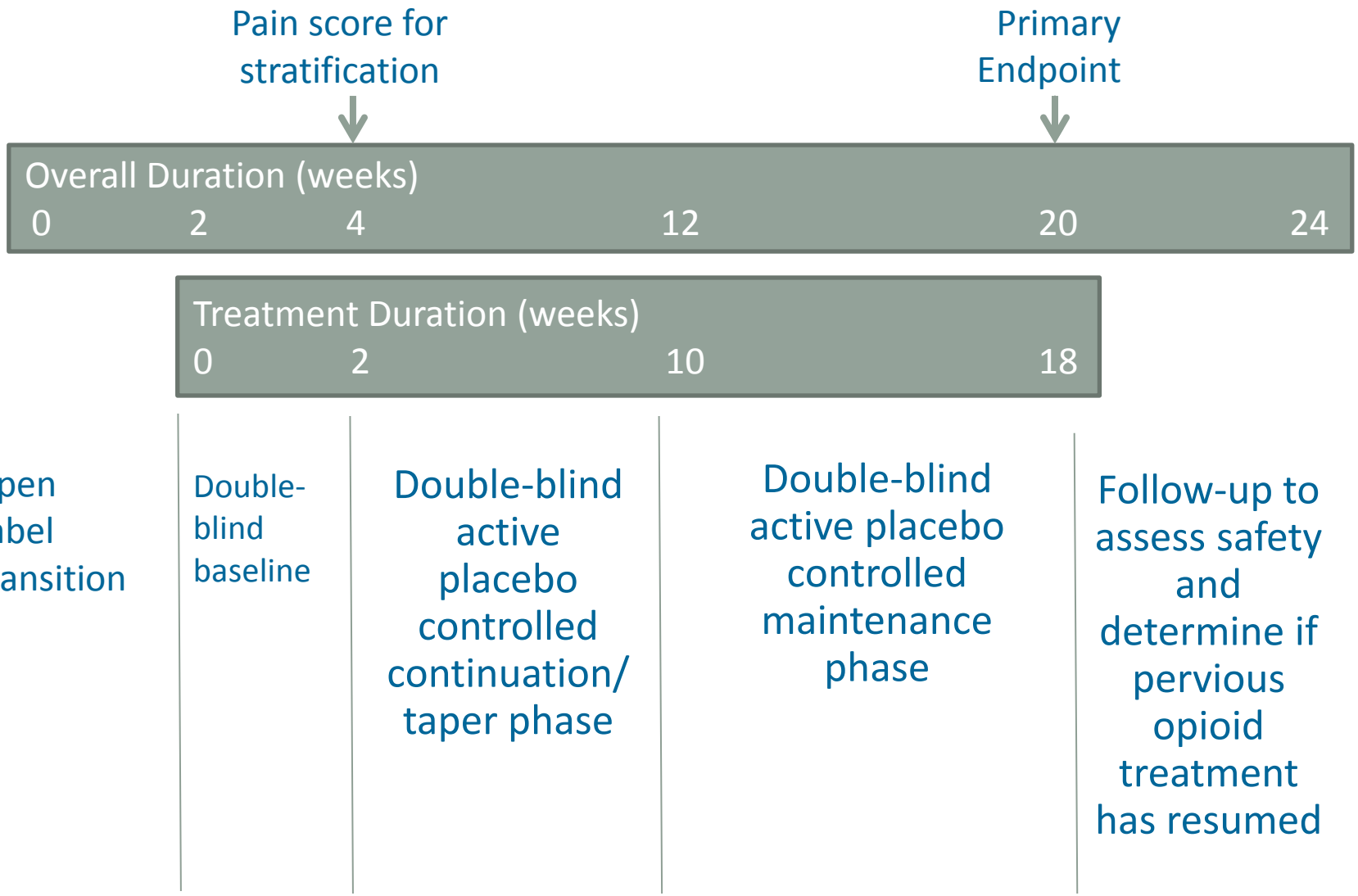
Study Design

- 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



Study Duration



Planned Trial Duration

Enrollment duration (25 U.S. sites expected to enroll approximately 4 patients/month)	12 months
Data analysis and top-line results summary	2 months
Total	**26 months**

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., ≥ 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
  - .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

	Continue Full Opioid Dose	Opioid Tapered to Half Dose	Opioid Tapered to Active Placebo
Taper Day	Morphine dose (mg)	Morphine dose (mg)	Morphine dose(mg)
0	260	260-300	260-300
1 – 5	260	260	260
6 – 10	260	220	220
11 – 15	260	180	180
16 – 20	260	150	150
21 – 25	260	120-150	120
26 – 30	260	120-150	90
31 – 35	260	120-150	70
36 – 40	260	120-150	50
41 – 45	260	120-150	40
46 – 50	260	120-150	30
51 – 56	260	120-150	20
Maintenance	260	120-150	0

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
- All investigators will be provided with a copy of Fleming T. Addressing missing data in clinical trials. Ann Intern Med 2011;154:113-117. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3319761/

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.