FDA's Perspective on the Proposed Protocol Intended To Fulfill Postmarketing Requirement (PMR) 3033-11

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

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Outline

- Purpose of this meeting
- Scope of the PMR
- Study design considerations
  - Chronic pain study design
  - Specifics of the study currently proposed
- Summary

Purpose of the AC Meeting

- The FDA is convening this Advisory Committee meeting to discuss postmarketing requirement (PMR) 3033-11, issued to application holders of new drug applications (NDAs) for extended-release and long-acting (ER/LA) opioid analgesics.
- The objectives of the PMR were to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia.
- The discussion at this meeting will be to focus on the design of a clinical trial to address these PMR objectives.
- The objective of this meeting is to stimulate robust scientific discussion to form a basis for consideration in determining the clinical trial design(s) most likely to be able to meet the stated objectives of the PMR.

Scope of This PMR

- The Agency acknowledges that available data indicate that safety/efficacy concerns of prescription opioids are not limited to extended-release/long-acting products (ER/LA).
- However, as a result of public discussion, stakeholder comments, and issue-specific literature reviews on the risks of ER/LA opioid analgesics, in 2013 FDA issued PMRs for this sub-class of products.
- Among the issues voiced were hyperalgesia, misuse, abuse, addiction, overdose, and death, but also dosage and duration of treatment for ER/LA opioid analgesics.
- The focus of this PMR is to assess the long-term efficacy of these products in the context of the serious risks they pose.

Research Question To Be Addressed

- The Agency has found that several opioid moieties were shown to be effective in adequate and well-controlled studies of 12 weeks duration.
- There are limited controlled study data evaluating effectiveness of opioids studies >12 weeks.
- Historically, the Agency extrapolates efficacy findings in 12-week efficacy studies to >12 weeks of efficacy.
- However, given that some opioid-related adverse events are related to dose and duration on drug, information on long-term opioid efficacy are in the interest of public health.
- The key public health question is whether opioids remain effective in patients >3 months to better inform the benefit-risk assessment.

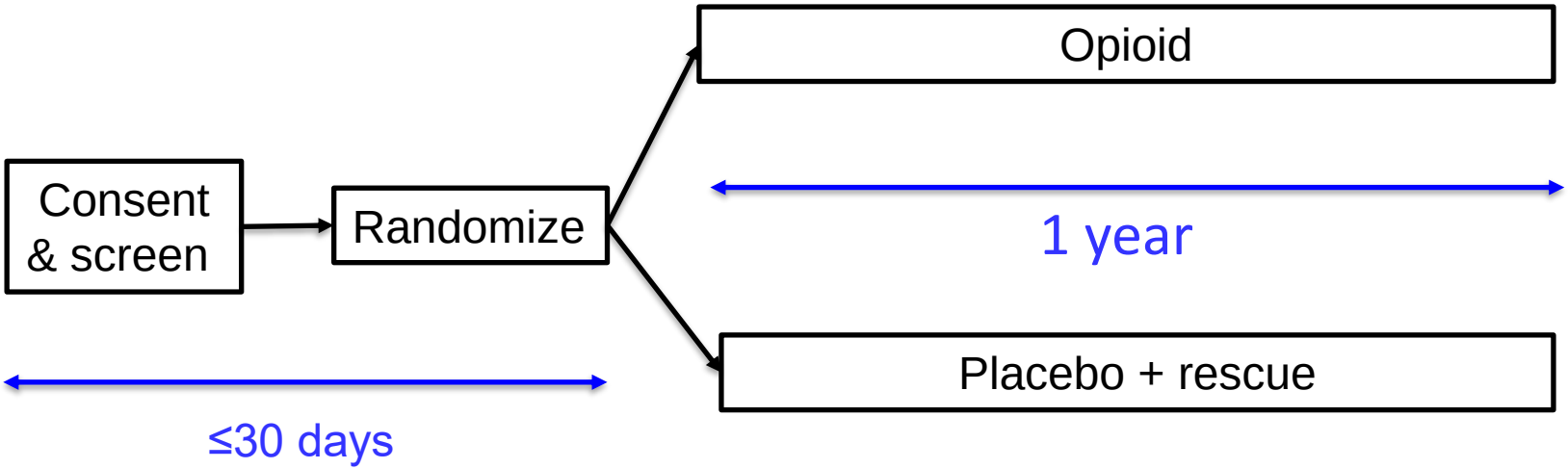
Study Design Considerations

Chronic Pain Study Designs

Challenges of Trials in Chronic Pain

- Comparators
- Population
- Endpoints
- Discontinuation rate

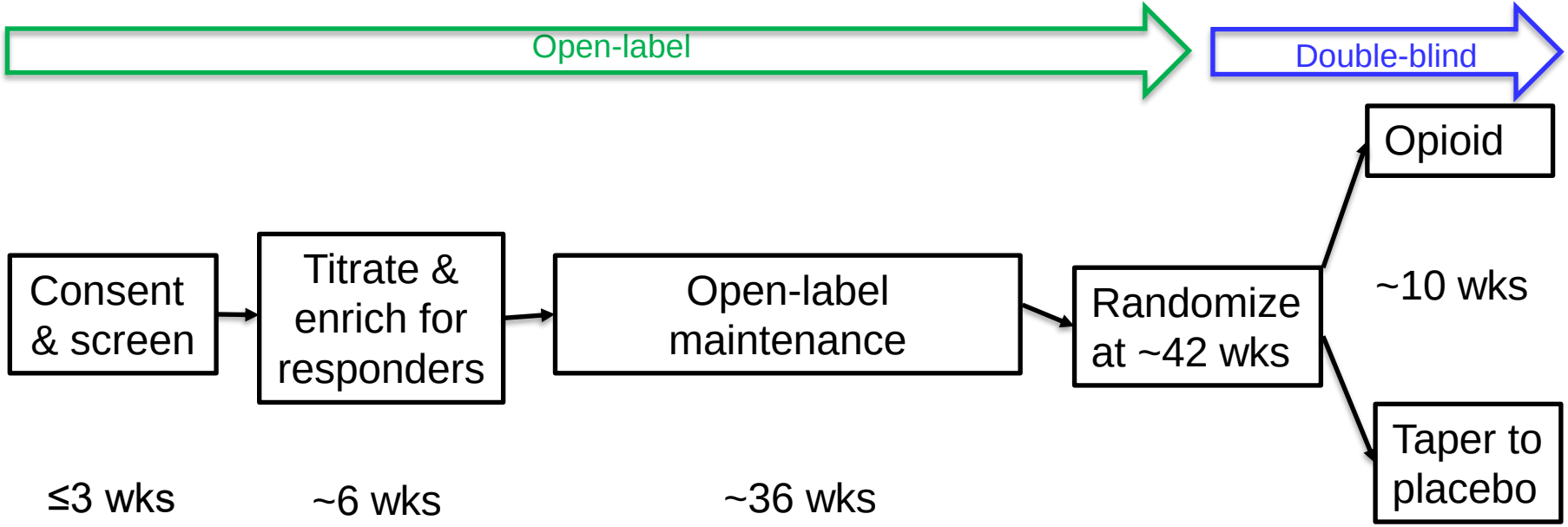
Placebo-controlled, Parallel-group Schematic



Placebo-controlled, Parallel-group (Flexible Dose Opioid Versus Placebo + ≤40 Morphine Milligram Equivalents Short-Acting Opioid)

- Advantages
  - "Gold standard" clinical trial design
  - Risk of unblinding likely lower than enriched enrollment randomized withdrawal (EERW)
- Disadvantages
  - Expected to be difficult to recruit due to ceiling for rescue opioid in placebo arm
  - Dropout rate in the both arms, but especially the placebo arm, could be very high and compromise interpretability
  - Study design envisioned (up to 40 morphine milligram equivalents (MME) of short-acting opioid (SAO) for rescue in placebo) may not represent true placebo.

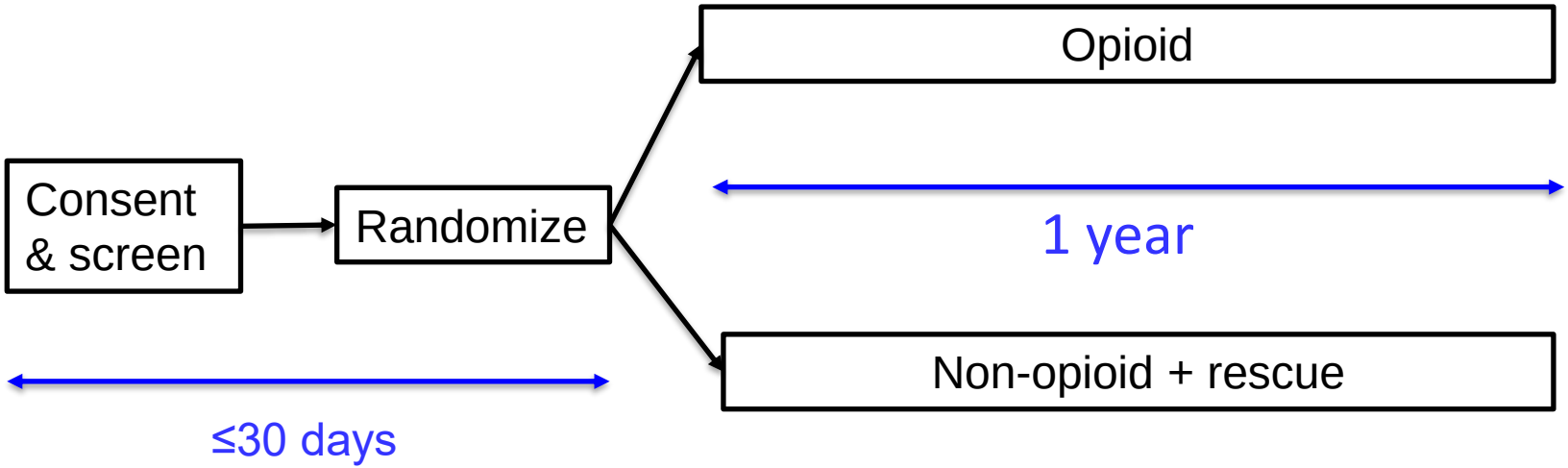
Enriched Enrollment Randomized Withdrawal Schematic



Enriched Enrollment Randomized Withdrawal (EERW)

- Advantages
  - May be most feasible
  - Appealing to patients because they are guaranteed to receive an adequate dose of opioid
  - Limited confounding due to dropout
- Disadvantages
  - Potential for unblinding
  - Does not assess effectiveness in all patients eligible for opioid therapy

Active-controlled, Parallel-group Schematic



Active-controlled, Parallel-group (Flexible Dose Opioid Versus Non-Opioid Treatment)

- Advantages
  - Reasonable clinical trial design if designed for superiority, not non-inferiority
  - Risk of unblinding likely lower than EERW
- Disadvantages
  - Expected to be difficult to recruit. Patients are opioid-ready but could be randomized to non-opioid therapy
  - Dropout rate in the non-opioid arm could be very high and compromise interpretability

Study Design Considerations

Specific to the Protocol Under Discussion

Study 3033-11 Key Study Design Considerations

The Agency is interested in evaluating whether opioids remain effective in patients >3 months and it appears that the EERW design may be an acceptable/feasible study design to address this question.

Key considerations for discussion:

1. Study duration and mitigation of patient dropout
2. Population
3. Endpoint
4. Blinding
5. Opioid-induced hyperalgesia (OIH) definition and surveillance

Study Duration and Dropout Risk

- Patients will be on opioids for a minimum of 42 weeks to a maximum of 52 weeks
- FDA and Opioid Postmarketing Requirements Consortium (OPC) have agreed on a 12- month duration to support long term efficacy for the proposed trial
- Dropout is to be mitigated by the use of rescue and allowing patients to exit the study for treatment failure

Population

- Determining appropriate inclusion criteria that will identify the target patient population
- Heterogeneity across patients
  - Variability in underlying chronic pain clinical entity
  - Range of baseline pain intensity ratings
  - Many patients may have multiple confounders such as comorbidities

Primary Endpoint

- Proposed primary endpoint
  - At least 30% increase in past 7-day moving average of the daily Worst pain intensity (PI) compared to the 7 days prior to randomization and past 7-day moving average of the daily Worst PI ≥5, OR
  - Patient initiates new pharmacologic therapy for the index chronic pain condition, OR
  - Study drug is discontinued due to lack of efficacy.
- Historical endpoint for ER/LA opioids
  - Difference in pain intensity from baseline (end of open-label) to end of double-blind
  - Negatively affected by dropout

Blinding

- For higher doses, rapidity of taper may risk unblinding
- Sponsor has proposed to use an Unblinding Questionnaire
- Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) will be administered regularly to monitor for the emergence of potential withdrawal signs and symptoms

Opioid-induced Hyperalgesia (OIH)

- OIH is a secondary endpoint, defined as:
  - Worst PI at the final assessment is the same or higher than at Screening, when the patient is receiving an ER opioid at an equivalent or higher dose

  AND

  - Quantitative Sensory Testing (QST) batteries at the final assessment show increased pain sensitivity compared to QST results obtained at Screening.
- The OIH population is at least 200 patients who enter the Open-Label Titration Phase
  - Must have at least one post-treatment QST
- QST done at Screening (twice) and Weeks 10, 26, 42, and 52

Summary

- While there are many valid scientific questions that would benefit public health in this realm, this PMR is intended to assess whether opioids remain effective for longer than 12 weeks.
- Designing a clinical trial to address this question is difficult and various designs have been considered.
- EERW may or may not be the best option to address the research question.
- If EERW reflects the best design compromise, concerns about some critical issues remain.
- The Agency seeks a robust discussion of this matter.

Thank you

Charge to the Committee

Discussion Question 1

Discuss the advantages and limitations of using the enriched enrollment randomized withdrawal (EERW) design to assess long-term effectiveness; discuss the advantages and limitations of using a placebo-controlled design to assess long term effectiveness.

a) Include in your discussion the likelihood of maintaining sufficient patients in the randomized treatment period in each of these study designs to assure an adequate assessment of effectiveness at the end of the double-blind treatment period.

Discussion Question 2

Discuss the proposed protocol for PMR 3033-11 (EERW). Include in your discussion the following:

a. Is 42 to 52 weeks an adequate duration to assess the long-term effectiveness of opioids?

b. What degree of dropout is expected in a study in this patient population? Will enough patients be expected to complete this study in order for the results to be interpretable?

c. Is the time-to-treatment-failure endpoint informative? If yes, should use of rescue above a prespecified threshold be added as a treatment failure criterion? If no, why not?

d. Given that the pain scores could be variable, are there measures that could be employed to assure that the threshold for increase in pain is clinically meaningful and does not represent short-term variability?

e. Does the proposed tapering scheme adequately mitigate concerns about unblinding?

f. Is the proposed definition of OIH and surveillance for development of the condition appropriate?

g. To better characterize OIH, should patients diagnosed with OIH undergo a diagnostic/therapeutic opioid taper?

Discussion Question 3

Discuss other designs that should be considered in the assessment of long-term effectiveness of opioids.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