

# Anesthetic and Analgesic Drug Products Advisory Committee

April 19, 2023

## **Opioid Postmarketing Requirements Consortium**

### **Study 3033-11**

A 12-Month Randomized, Controlled, Double-Blind Trial Evaluating the Efficacy of Morphine Sulfate Extended-Release Tablets in the Treatment of Defined Chronic Non-Cancer Pain, with Assessment for Opioid-Induced Hyperalgesia

# Introduction

## **Charles E. Argoff, MD**

Professor of Neurology, Director Comprehensive Pain Program

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# Agenda

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## Introduction

### **Charles E. Argoff, MD**

Professor of Neurology, Director Comprehensive Pain Program  
Albany Medical Center, Albany, NY

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## Overview of Study Design – 3033-11

### **Charles E. Argoff, MD**

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## Rationale for Study Design – 3033-11

### **Nathaniel Katz, MD**

President  
Ein Sof Innovation, Wellesley, MA

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## Overview of OIH and Its Evaluation

### **Martin Angst, MD**

Professor, Anesthesiology, Perioperative and Pain Medicine  
Department Vice Chair, Strategy and Initiatives  
Stanford University Medical School, Stanford, CA

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## Protocol Considerations

### **Sandra Comer, PhD**

Professor of Neurobiology (in Psychiatry)  
Columbia University, New York, NY

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## Conclusions

### **Charles E. Argoff, MD**

# 11 Postmarketing Requirement Studies

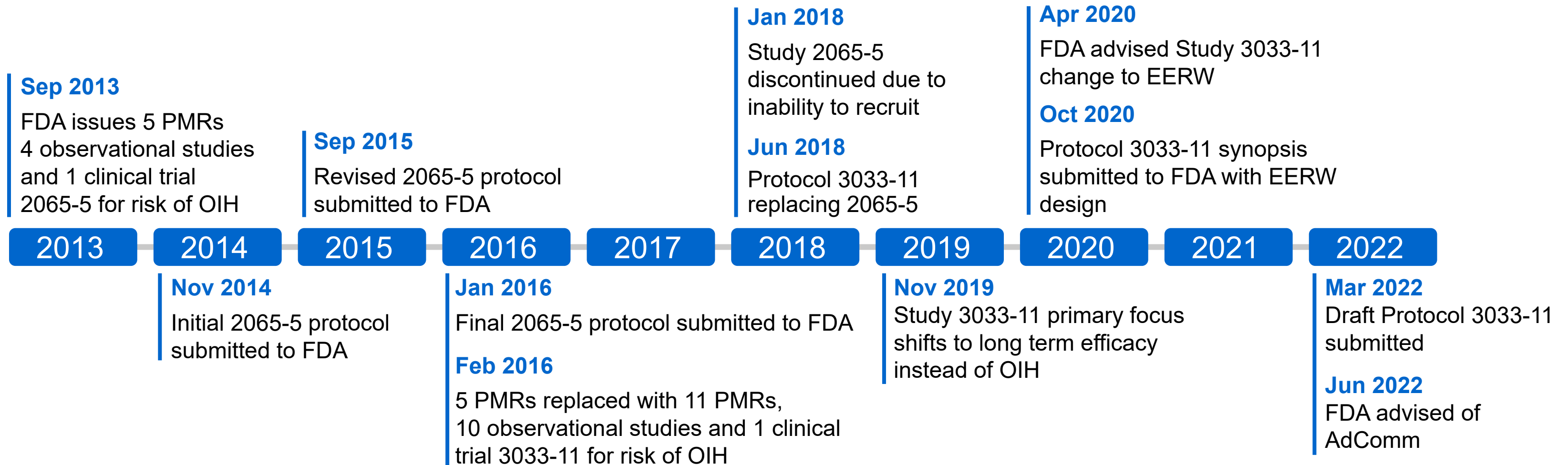
PMR #	Study Description	Study Purpose
3033-1 <sup>†</sup>	Prospective cohort study of behaviors in questionnaires and EHRs	Assess incidence and predictors of misuse, abuse, addiction, overdose, and death among participants prescribed ER/LA opioid products
3033-2 <sup>†</sup>	Retrospective study using health records, insurance claims, and death records	
3033-3	Validation studies of POMAQ instrument to measure misuse and abuse through self reporting: Qualitative	Develop and validate measures of misuse, abuse, addiction, overdose, and death
3033-4	Validation studies of POMAQ instrument to measure misuse and abuse through self reporting: Quantitative	
3033-5	Validation study of PRISM instrument to measure addiction and substance use disorder through self report	
3033-6 <sup>†</sup>	Validation of coded medical terminologies used to identify opioid-related overdose in the postmarketing databases employed in Study 1B	Validate coded medical terminologies to identify misuse, abuse, addiction, overdose, and death in databases used for studies
3033-7	Validation of diagnostic algorithm to measure abuse/addiction based on administrative claims data	
3033-8	Cross-sectional study of doctor/pharmacy shopping in a prescription database vs a claims-based diagnostic algorithm for abuse/addiction	Define and validate “doctor/pharmacy shopping” as outcomes suggestive of misuse, abuse, and addiction
3033-9	Survey study of doctor/pharmacy shopping in a prescription database vs self-reported misuse and abuse in interviews	
3033-10	Retrospective cohort study of doctor/pharmacy shopping using medical record review for misuse, abuse, and/or addiction	
3033-11	A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial of Structured Opioid Discontinuation versus Continued Opioid Therapy in Suboptimal and Optimal Responders to High-Dose Long-Term Opioid Analgesic Therapy for Chronic Pain	Evaluate long-term efficacy of ER opioids in management of CNCP, including exploring potential predictors of response and non-response, while also assessing risks of developing OIH in participants with CNCP on long-term ER opioid therapy

■ Study Completed    ■ Study Not Completed

<sup>†</sup> PMR pending fulfillment.

EHR=electronic health record; ER=extended release; LA=long acting; POMAQ=Prescription Opioid Misuse and Abuse Questionnaire; PRISM=Psychiatric Research Interview for Substance and Mental Disorders; CNCP=chronic non-cancer pain; OIH=opioid-induced hyperalgesia.

# PMR Timeline



# Evolution of the Clinical Trial PMR

## Clinical Trial PMR<sup>†</sup>

"Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy."

<sup>†</sup> <https://www.fda.gov/media/95546/download>.  
PMR=postmarketing requirement; ER=extended release; LA=long acting.

# Evolution of the Clinical Trial PMR: Study 2065-5

## Clinical Trial PMR<sup>†</sup>

"Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy."

## Study 2065-5 Objective

Better characterize contribution of OIH to suboptimal responses to opioid therapy

<sup>†</sup> <https://www.fda.gov/media/95546/download>.  
PMR=postmarketing requirement; ER=extended release; LA=long acting; OIH=opioid-induced hyperalgesia.

# Original Protocol: Study 2065-5

- Randomized withdrawal design
  - Participants already on around the clock (IR or ER) opioids  $\geq 1$  year
  - Participants must be on ER/LA opioids  $\geq 3$  months prior to entry
- 820 participants intended to be randomized into blinded structured opioid discontinuation
  - Only 32 participants (4%) randomized
- After 16 months, study terminated early due to lack of enrollment



# Evolution of the Clinical Trial PMR: Study 3033-11

## Clinical Trial PMR<sup>†</sup>

"Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy."

## Study 2065-5 Objective

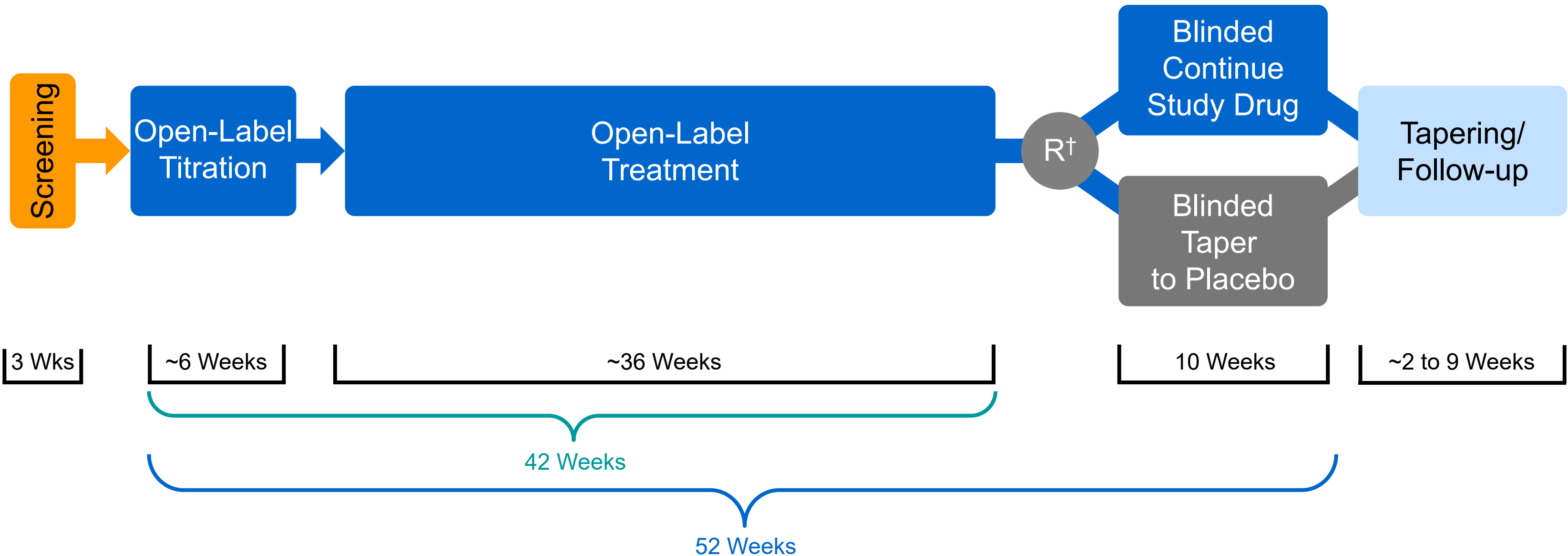
Better characterize contribution of OIH to suboptimal responses to opioid therapy

## Study 3033-11 Objective

To evaluate the persistence of analgesic efficacy of an ER opioid in patients with chronic non-cancer pain who demonstrate initial analgesic efficacy and tolerability

<sup>†</sup> <https://www.fda.gov/media/95546/download>. .  
PMR=postmarketing requirement; ER=extended release; LA=long acting; OIH=opioid-induced hyperalgesia; CNCP=chronic non-cancer pain.

# Current Protocol: Study 3033-11



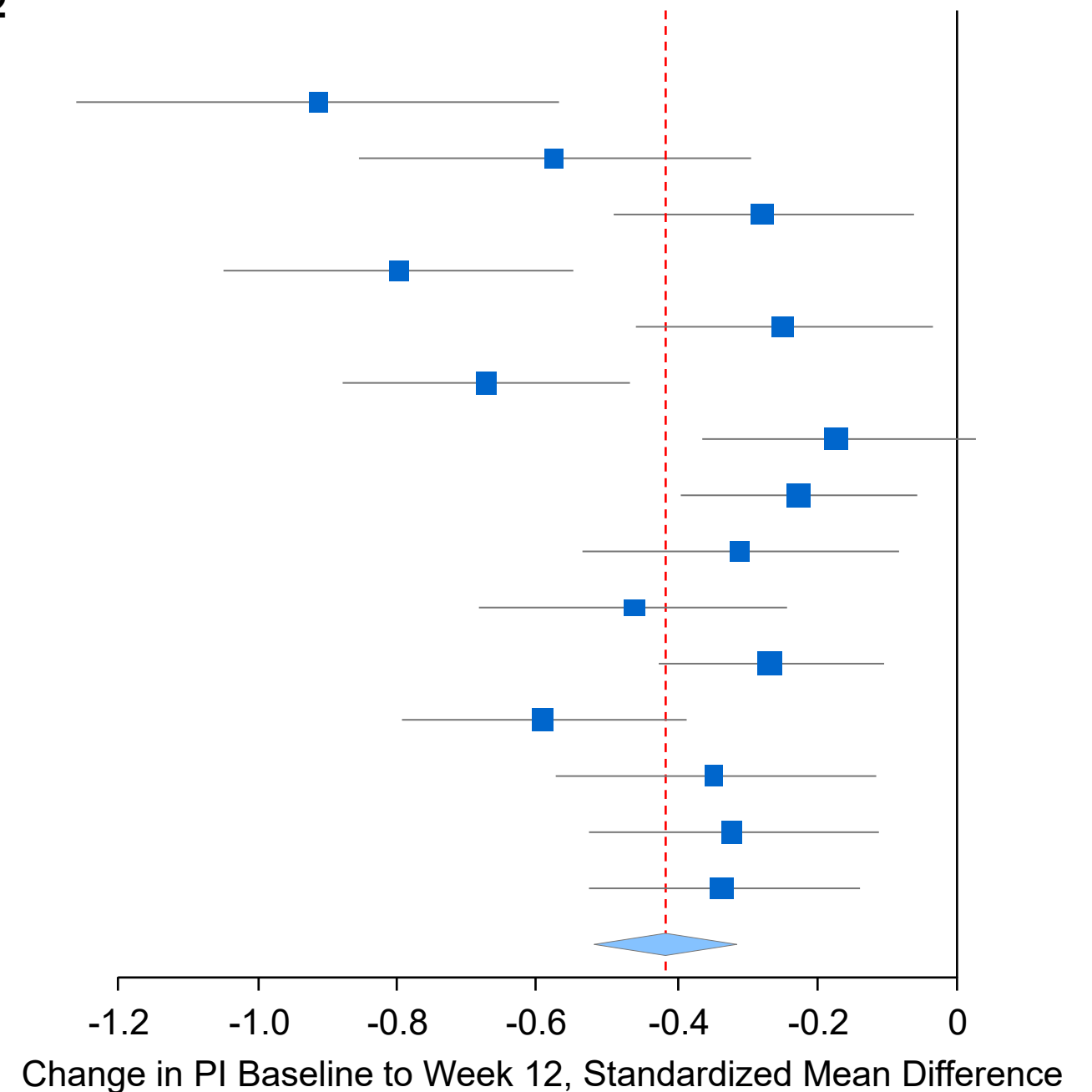
<sup>†</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Evidence Base for the Efficacy of Opioids

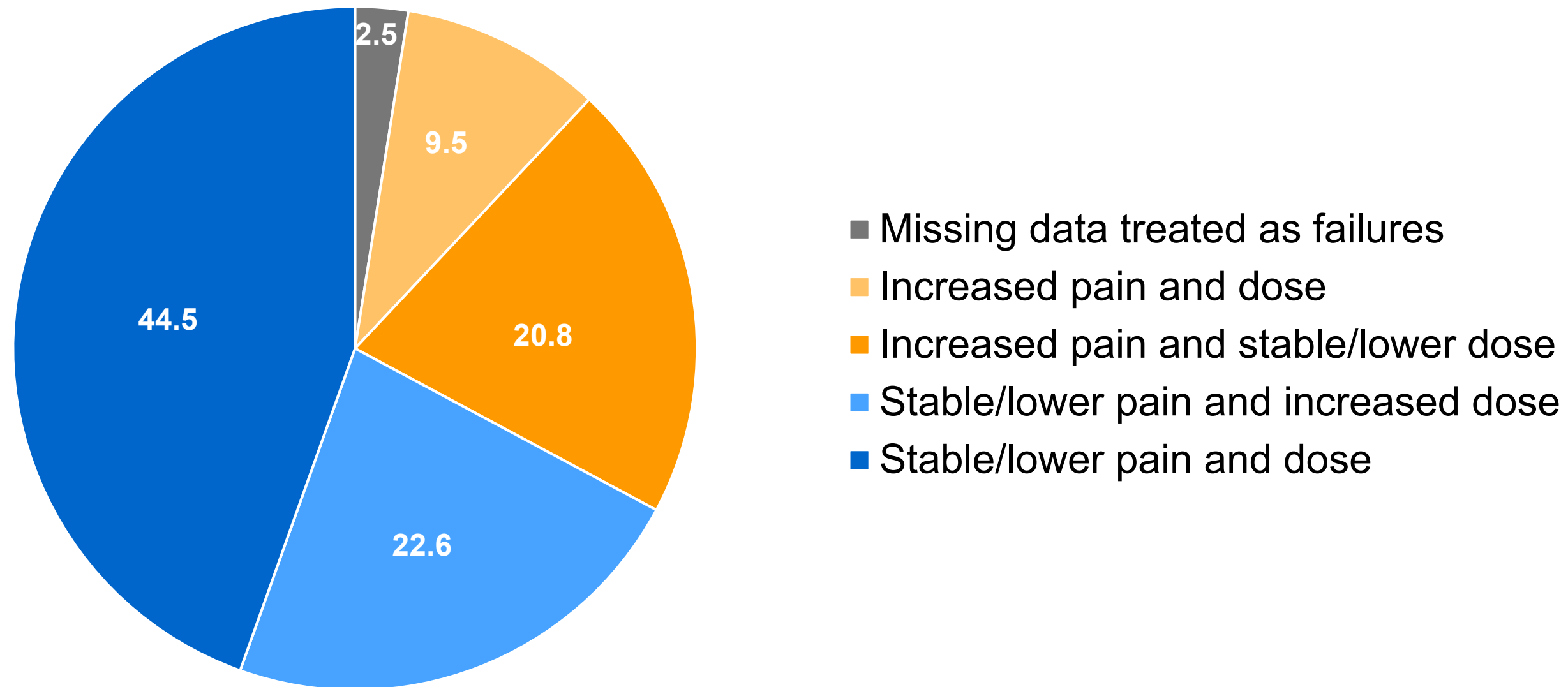
- Meske, et al. 2018<sup>1</sup>
  - A meta-analysis identified 15 randomized, double-blind, placebo-controlled EERW trials of opioids for chronic pain performed to support product approval
  - Studies were of up to 3 months in length
  - Opioid treatment was associated with statistically-significant improvements in pain intensity
- Farrar, et al. 2022<sup>2</sup>
  - Evaluated the stability of opioid efficacy over 12 months in 8 studies of chronic non-cancer pain
  - 12-month open-label studies of ER/LA opioids from FDA database
  - 3192 participants assessed for response to opioids for up to 1 year
  - There is a cohort of participants who have stable pain relief up to 1 year

# Meske 2018: Randomized, Placebo-Controlled EERW 12-Week Studies

Participants Enrolled in the OLP, n	Studies	Change in PI, Baseline to Week 12 Point Estimate
251	Hale, et al. 2007	-0.913
326	Katz, et al. 2007	-0.574
619	Vorsanger, et al. 2008	-0.276
459	Hale, et al. 2010	-0.799
547	Katz, et al. 2010	-0.249
588	Schwartz, et al. 2011	-0.672
558	Friedman, et al. 2011	-0.173
1024	Steiner, et al. 2011	-0.225
510	Rauck, et al. 2014	-0.308
459	Vinik, et al. 2014	-0.462
905	Wen, et al. 2015	-0.267
740	Katz, et al. 2015	-0.592
389	Hale, et al. 2015a	-0.347
625	Hale, et al. 2015b	-0.319
749	Rauck, et al. 2016	-0.333
6774	Overall ( $I^2=72.09%$ , $P<0.001$ )	-0.416



# Farrar 2022: Primary Outcome: Stable/Lower Pain and Dose After 12 Months of ER/LA Opioids



- 44.5% of participants who successfully titrated (N=3192) achieved the primary outcome of stable or lower pain with a stable or lower dose of opioid after 12 months of treatment

# Overview of Study Design – 3033-11

## **Charles E. Argoff, MD**

Professor of Neurology, Director Comprehensive Pain Program

Albany Medical Center

Albany, New York

# 3033-11 Study Objectives

- Primary objective
  - To evaluate the persistence of analgesic efficacy of an ER opioid in patients with chronic non-cancer pain who demonstrate initial analgesic efficacy and tolerability
- Secondary objectives include to:
  - Explore the incidences of OIH and opioid tolerance
  - Evaluate changes in pain sensitivity over time
  - Identify potential predictors of the opioid analgesic response and non-response
  - Evaluate changes in physical function and in levels of anxiety and depression
  - Evaluate the safety of titrated doses of an ER opioid
  - Evaluate all endpoints in patients who are titrated to a high dose of ER opioid

# 3033-11: Study Overview

- Placebo-controlled double-blind enriched-enrollment randomized withdrawal (EERW) design
- Study medication: Morphine sulfate ER (15-240 mg/day)
- Planned number of participants
  - Open label titration: 1100
  - Open label treatment: 666
  - Randomized: 400 (1:1, morphine ER or placebo tapering)
  - OIH Substudy: 200
- Interim analysis
  - Potential to increase enrollment if needed
- Participants can discontinue at any time
  - Participants who have received  $\geq 1$  dose of study drug will be tapered
  - Reasonable efforts to assure continuity of care
  - Participants who do not attain adequate pain control will be followed for the full 52 weeks



# Trial Population

- Participants with daily chronic pain, not receiving ER/LA opioids, and with inadequate pain control despite IR opioid treatment
  - Received IR opioids  $\geq 3$  consecutive months out of the 6 months prior to enrollment
  - Worst Pain Intensity score over the prior 7 days of  $\geq 5$  and  $\leq 9$
- Unsuccessful with non-opioid approaches to manage chronic pain
- Clinical diagnosis of chronic non-cancer pain
  - Chronic low-back pain
  - Osteoarthritis of the hip/knee
  - Painful peripheral neuropathy, including diabetic peripheral neuropathy
  - Post-cancer-treatment-related pain in participants without active cancer

# Patient Treatment Response Questionnaire

- Goal: enroll participants for whom alternative treatment options are inadequate
  - And are appropriate candidates for ER/LA opioid therapy<sup>1</sup>
- Novel tool to identify participants who have attempted other pain management modalities
- Assesses treatment history for main chronic pain condition
  - Opioid and non-opioid analgesics
  - Adjuvant therapies
  - Physical therapy
  - Behavioral therapy
  - Surgical procedures
  - Medical devices

<sup>1</sup> Dowell, et al. *MMWR Recomm Rep*. 2022.

# Use of Prohibited Substances

- Use of illicit drugs (including cannabis), non-prescribed controlled substances (opioid and non-opioid), and alcohol are not allowed during the trial
- POMAQ will be administered at screening and during the trial to identify behaviors related to misuse and abuse
- Quantitative UDTs will be performed at screening and during the trial
  - Tests will be performed for illicit drugs, non-prescribed controlled substances, and alcohol
    - At a minimum, tests will be performed at screening and the beginning and end of the randomized phase
    - Additional tests may be performed at the investigators' discretion
  - Positive test results at screening will result in exclusion
  - Positive test results during the trial will be investigated per protocol and may result in participant discontinuation

# Continuity of Care

## At screening and trial entry:

- Participants identify HCP(s) who manage their pain
- Participants consent to HCP being informed of trial participation
- Investigator communicates with the HCP using IRB-approved letter templates

## At end of trial participation:

- All participants will taper off study drug
- Investigator communicates with HCP(s) using IRB-approved letter templates
- A participant profile document, including treatment assignment, will be provided directly to HCP(s) to support management of the participant's pain
- Participants with no appropriately licensed HCP referred to locally available medical and social services

# Primary Endpoint: Time to Loss of Efficacy in the Double-Blind Phase

## Loss of efficacy

- $\geq 30\%$  increase from baseline in recent Worst Pain Intensity and be in at least moderate pain
- Initiation of a new (non-study) medication for chronic pain
- Discontinuation for lack of efficacy

## Worst Pain Intensity

- 0-10 Numerical Rating Scale
- Extensively validated in this population
- Use in prior clinical trials of ER/LA opioids for chronic pain

# Selected Secondary Endpoints

- Secondary efficacy endpoints
  - Time to treatment failure (loss of efficacy or discontinuation for adverse events)
  - Time to loss of efficacy as defined by Average Pain Intensity
  - Proportion of participants with loss of efficacy or treatment failure by week
  - Multiple endpoints based on changes in pain scores
  - Changes in physical function
  - Changes in Brief Pain Inventory Short Form 8b, Change in Patient Global Impression of Change
  - Change in health-related quality of life
- Secondary OIH incidence endpoints
  - Use of QST to assess changes in pain sensitivity
  - Use of the FS-WPI to assess spread of pain sensitivity
- Safety endpoints assess outcomes such as AEs, withdrawal symptoms, signs of misuse or abuse, and insomnia
- Assessment of participants receiving study drug doses  $\geq 90$  mg/day (all endpoints)

# Evaluation of Selected Endpoints

Endpoint/Assessment		Open-Label Titration Phase	Open-Label Treatment Phase	Double-Blind Phase
<b>Primary endpoint</b>	<b>Time to loss of efficacy</b>			
Secondary efficacy endpoints	Time to treatment failure			
	Change in worst PI and average PI			
	Change in BPI-SF			
	PGIC, EQ-5D-5L scores			
	Change in PROMIS®			
Secondary OIH endpoints	Incidence of OIH development during OL Treatment			
	Incidence of OIH development during trial			
	Pain spread			
Safety and wellbeing endpoints	Adverse events and other safety assessments			
	Change in anxiety/depression scores (HADS)			
	Change in sleep (ISI)			
	Change in sexual (ASEX) and endocrine function			
	Change in suicidal behavior/ideation			
	Opioid withdrawal (COWS)			

# Predictors of Opioid Response

- Opioid response will be defined as  $\geq 30\%$  reduction from Screening in Worst PI and an end-of-trial PGIC score of 6 or 7 (better or much better)
- A logistic model for predictors of opioid response will be fit that includes:
  - Effects for treatment arm
  - Predictors of interest
  - Interaction between treatment arm and predictors of interest

## Predictors of opioid response to be examined

### Demographics

Personal/family history of mental illness or substance use disorders

Medical history, including chronic overlapping pain conditions

Fibromyalgia score

Anxiety/depression

Pain catastrophizing

Physical function

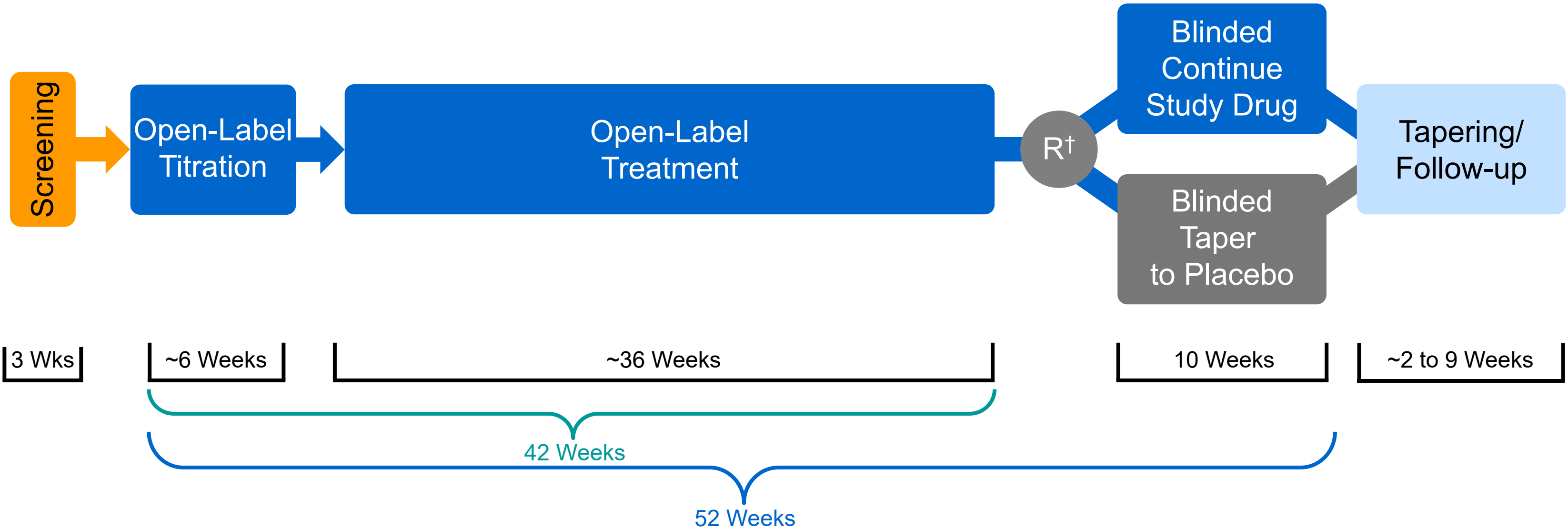
### AEs

QST outcomes

Sleep/insomnia



# 3033-11: Study Schematic



<sup>†</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Open-Label Titration Phase

- Dose titrated to achieve efficacy
  - Maximum daily dose 240 mg/day



<sup>†</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

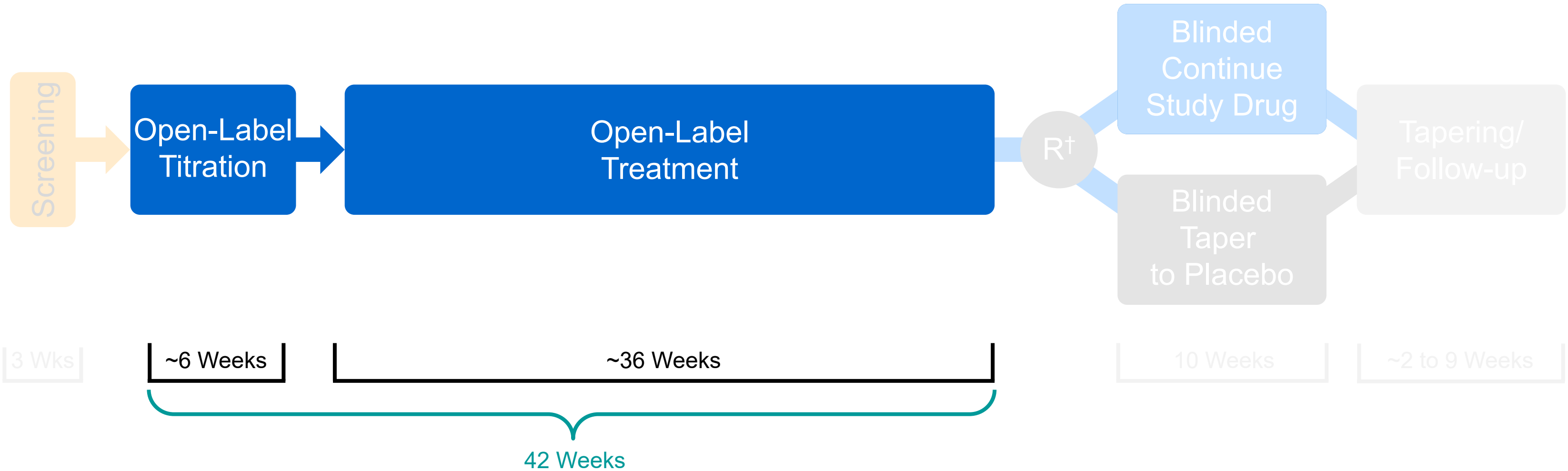
# Open-Label Treatment Phase

- Participants who tolerate and respond to study drug receive open-label treatment<sup>†</sup>
- HCPs may continue to adjust dose based on participant response



<sup>†</sup> All criteria must be met for a participant to enter into the Open-Label Treatment phase:  $\geq 30\%$  reduction in past 7-day Worst PI compared to Screening; participant and investigator agree that the participant has had meaningful improvement, guided by the Pain Profile Questionnaire; and morphine sulfate ER was tolerated, as per participant and investigator judgment. <sup>‡</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).  
HCP=health care professional.

# Open-Label Titration and Treatment Phases



<sup>†</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Double-Blind Randomized Withdrawal Phase

- Participants who tolerate and respond to study drug are randomized to:
  - Continued ER morphine
  - Structured taper to placebo over 1 to 8 weeks



† Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Blinded Taper Arm

- Randomization will be stratified by participants' stable pre-randomization dose of study drug
- Participants randomized to the placebo arm will be tapered in a structured double-blind manner over 1 to 8 weeks

<b>Stable Daily Dose of Study Drug Before Randomization to Placebo</b>	<b>Duration of Structured Double-Blind Taper</b>
30 mg	1 week
60 mg	2 weeks
90 mg	4 weeks
120 mg	5 weeks
150 mg	6 weeks
180 mg	6 weeks
200 mg	7 weeks
230 mg	8 weeks
240 mg (maximum allowed)	8 weeks

# Tapering and Follow-Up Phase

- All participants who receive  $\geq 1$  dose of trial medication will enter the Tapering and Follow-up phase
- Reasonable efforts will be made to ensure continuity of care for participants on exiting the trial

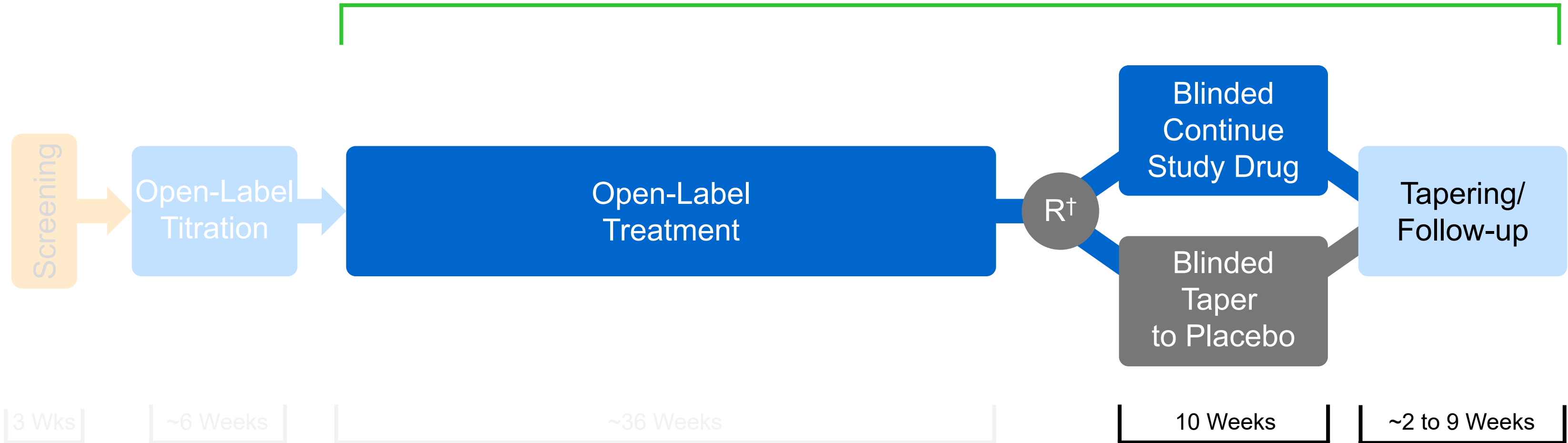


† Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Rescue Medications

## Rescue medications allowed

(acetaminophen up to 3000 mg daily, IR morphine up to 30 mg daily)



† Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).



# Opioid-Induced Hyperalgesia (OIH) Substudy

- OIH incidence will be explored as a change in pain sensitivity
- OIH Population: 200 participants
- Quantitative sensory testing (QST) with thermal pain
- Widespread Pain Index will be used to assess pain spread

## 3033-11 Trial Design: Summary

- Designed to evaluate the persistence of analgesic efficacy of ER morphine for chronic pain in participants who demonstrate initial analgesic efficacy and tolerability
  - Secondary objectives include evaluation of the incidence of OIH and opioid tolerance
  - Additional objectives include identification of predictors of response
  - Extensive data will be collected on all study participants; all followed for the full 52 weeks
- Reflects current clinical practice and guidelines
- Addresses some of the challenges encountered in Study 2065-5

# Rationale for Study Design – 3033-11

**Nathaniel Katz, MD**

President

Ein Sof Innovation, Wellesley, MA

# Study 3033-11 Design Goals

## Fulfill Clinical Trial Study Objectives<sup>†</sup>

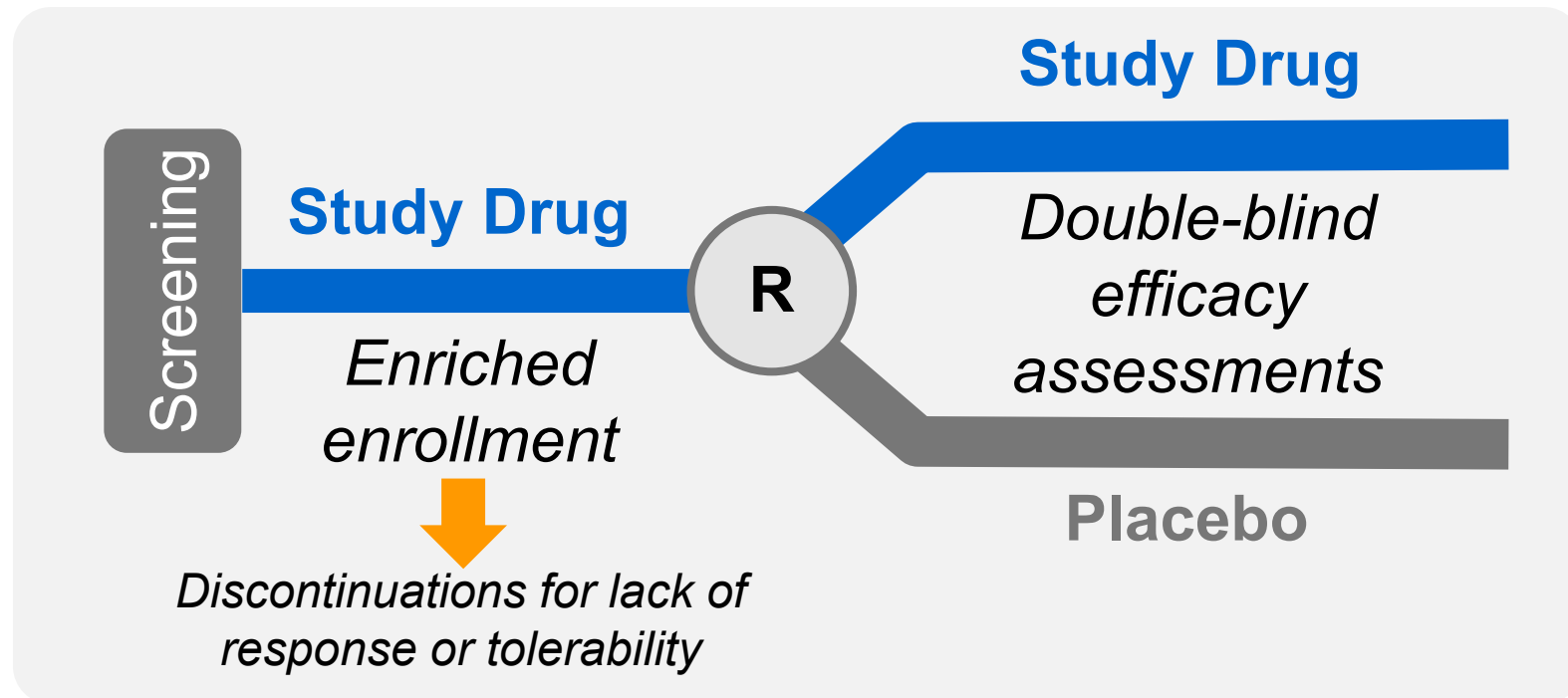
- Assess persistence of efficacy of ER/LA opioids
- Evaluate the risks of OIH
- Identify predictors of response/non-response

## Overcome Enrollment Challenges (2065-5)

- Participation to be viewed favorably by:
  - Potential study investigators
  - Appropriate participants with chronic pain

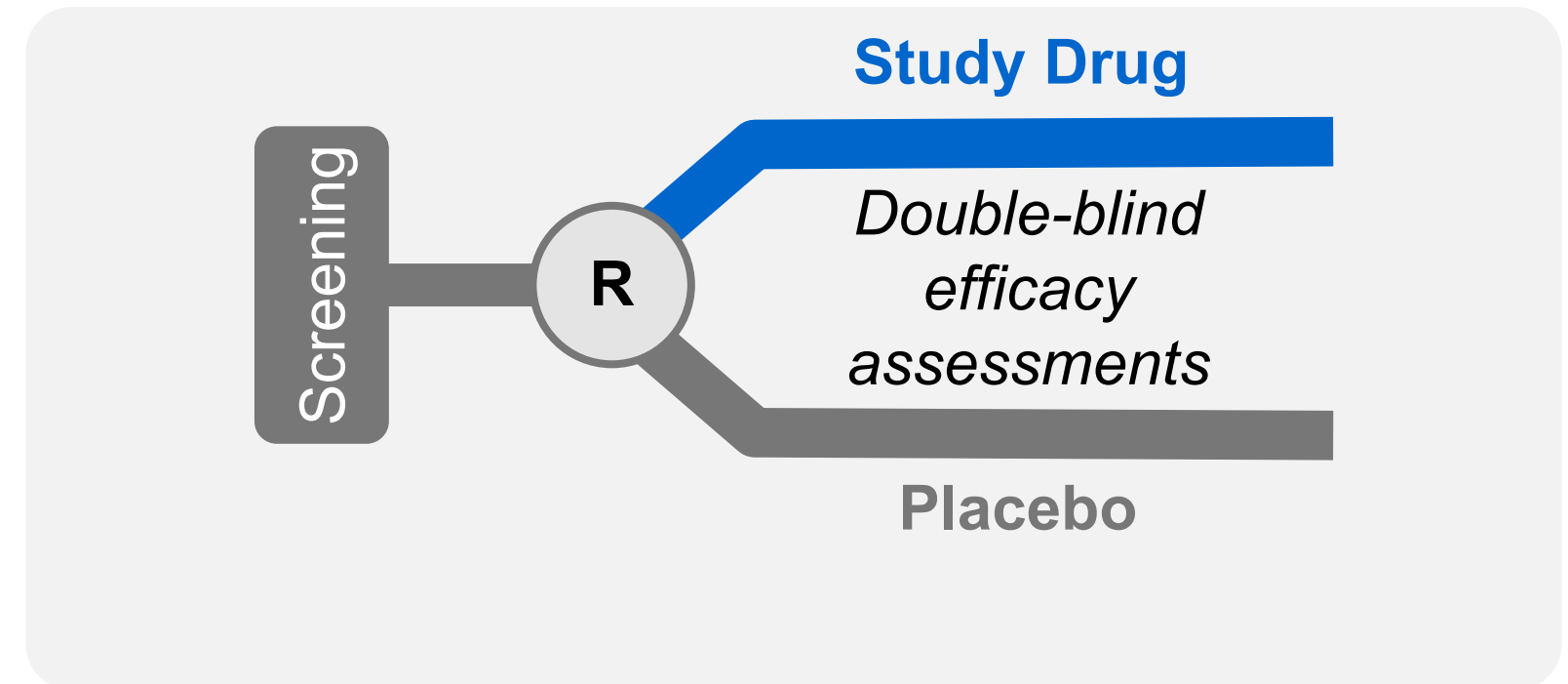
# Enriched Enrollment Randomized Withdrawal versus Non-Enriched Prospective Treatment Designs

## Enriched Enrollment Randomized Withdrawal



Among participants who have been on a study treatment for a period of time, is the treatment more efficacious than placebo?

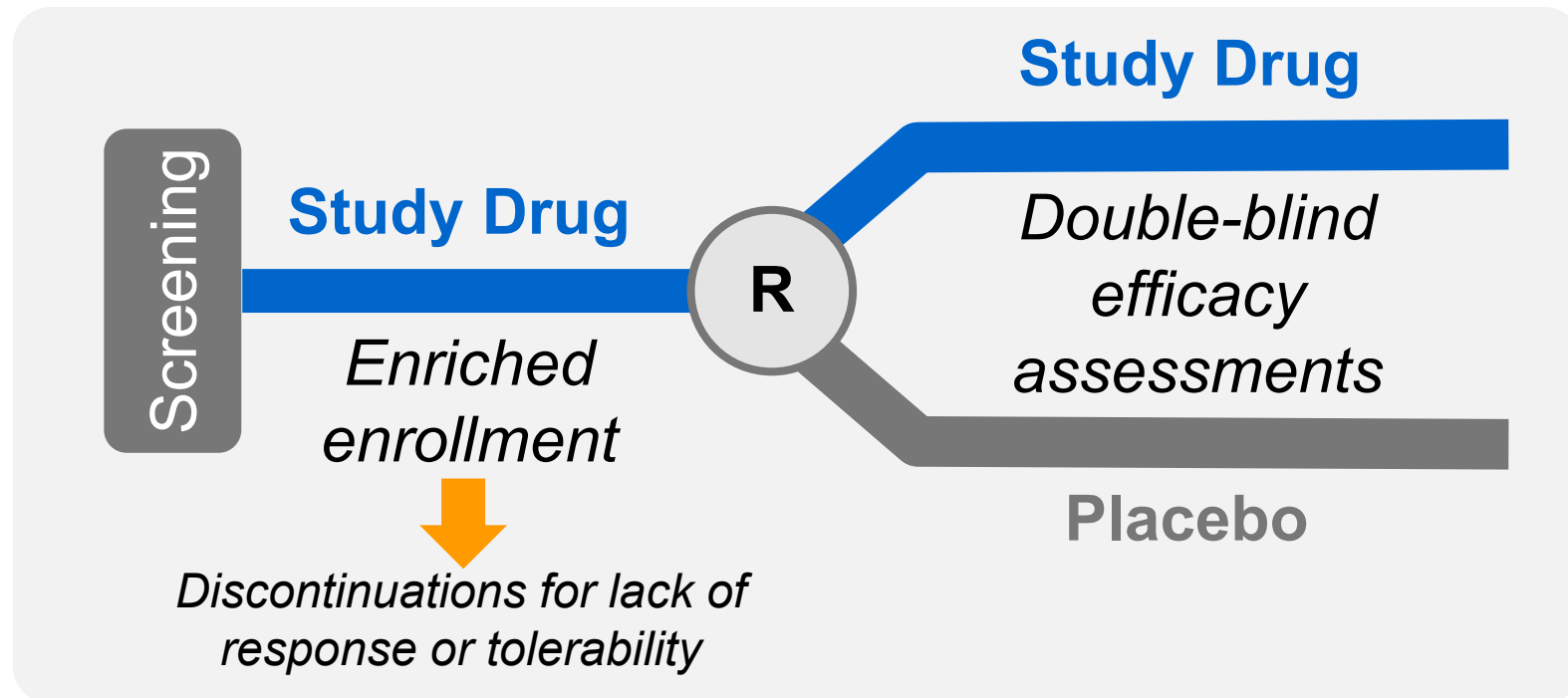
## Non-Enriched Prospective Treatment



Among participants not currently on study treatment, how efficacious is the treatment compared to placebo?

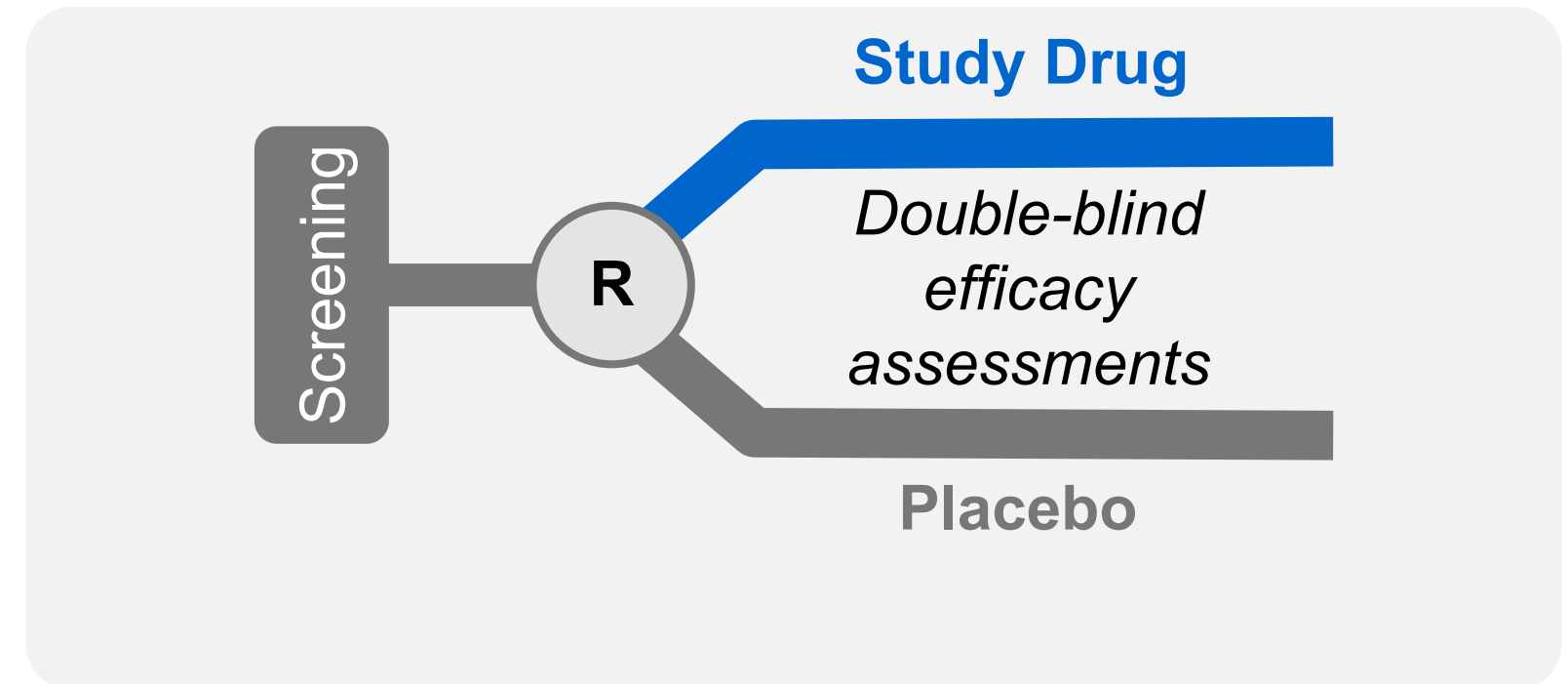
# Enriched Enrollment Randomized Withdrawal versus Non-Enriched Prospective Treatment Designs<sup>1-3</sup>

## Enriched Enrollment Randomized Withdrawal



- All participants begin on treatment
- Population enriched for responders
- Randomized to continued treatment or placebo
- Efficacy demonstrated by relative loss of response in Placebo group

## Non-Enriched Prospective Treatment



- Participants begin symptomatic and without treatment
- Randomized to de-novo treatment or placebo
- Efficacy demonstrated by relative response in Study Drug group

# Time to Loss of Efficacy Endpoints

- Various types of time to loss of efficacy endpoints can be constructed

## Strengths

- More statistically efficient
- Fewer participants required to achieve study objectives
- Less need for imputation of missing data
- Secondary endpoints available to aid in interpretation

## Limitations

- Unclear clinical interpretation of differences in time to loss of efficacy
- Challenges in constructing optimal definitions of loss of efficacy

# 3033-11: Recruitment and Retention

## Enriched Enrollment Randomized Withdrawal

- Participants more likely to enroll and continue participation for a year with access to a treatment they are not currently receiving
- Shorter duration of potential exposure to placebo is likely to be more appealing to participants

## Non-Enriched Prospective Treatment

- Participants less likely to commit to a year of potential exposure to placebo, regardless of assurances of rescue medication
- Approximately half of participants will drop out of the study after 1 year based on open-label studies



# 3033-11: Challenges Associated with the Opioid Taper During the Randomized Phase

- Following randomization in the EERW study, half the participants gradually taper to placebo
- In theory, this could result in an acute opioid abstinence syndrome (opioid withdrawal)
  - Often associated with increased pain
  - Could compromise the interpretation of the study
- In practice, acute opioid abstinence syndrome rarely occurs in EERW studies
  - Despite rapid tapers
  - Even when opioid withdrawal symptoms measured daily with comprehensive questionnaires
- In this study, concerns about opioid withdrawal will be addressed by:
  - More gradual taper than past studies
  - Clinical guidance for management of withdrawal symptoms
  - Repeated assessments of opioid withdrawal following randomization

# Enriched Enrollment Randomized Withdrawal versus Non-Enriched Prospective Treatment Designs for Assessment of Analgesics

	Enriched Enrollment Randomized Withdrawal	Non-Enriched Prospective Treatment
Ability to detect efficacy	✓✓✓	✓✓
Persuasiveness of efficacy finding	✓✓	✓✓✓
Interpretability	✓✓	✓✓✓
Handling of missing data	✓✓	✓
Recruitment and retention	✓✓	✓

# Study 3033-11: Study Drug: Morphine Sulfate ER

## Strengths

- Assessment of a single ER/LA reduces operational complexity and the required study sample size
  - FDA recommended the trial include morphine sulphate ER as it is the original prototype full mu opioid agonist and is widely prescribed

## Limitations

- Generalizability of study outcomes to other opioid molecules is unknown
- Not an abuse-deterrent formulation

# Potential Advantages of 3033-11 Design Over 2065-5

	Study 2065-5	Study 3033-11
<b>Study population</b>	Participants receiving ER/LA opioids Randomized to lose their ER/LA opioid	Participants receiving IR opioids with inadequate pain control Randomized to receive an ER/LA opioid
<b>Timing of randomized withdrawal phase</b>	After $\leq 6$ weeks of open-label treatment	After 42 weeks of open-label treatment
<b>Length of randomized withdrawal phase</b>	24 weeks	10 weeks

# Study 3033-11: Summary

- Designed to fulfill clinical trial objective and overcome potential enrollment challenges
  - Reflects lessons learned from the prior 2065-5 trial
- Assess tolerability and effectiveness during 42 weeks of open-label treatment
- Assess efficacy in participants who tolerated and responded to long-term treatment
- Minimize the potential period of placebo treatment
- Enroll appropriate participants for ER/LA opioid treatment under current clinical guidelines

# Overview of OIH and its Evaluation

## **Martin Angst, MD**

Professor of Anesthesiology, Perioperative and Pain Medicine

Department Vice Chair, Strategy and Initiatives

Stanford University School of Medicine

# Opioid-Induced Hyperalgesia (OIH)

- Opioid-induced hyperalgesia (OIH) has been described as a state of nociceptive sensitization caused by exposure to opioids
- Clinical OIH is characterized by:<sup>1</sup>
  - An increase in pain intensity over time
  - Spread of pain from the index site to other locations
  - An increase in pain sensation in response to external stimuli
- OIH is established as a concept, has been demonstrated in animal models, and there are published reports of OIH<sup>2-5</sup>
- There are not currently agreed-upon approaches to detect or diagnose OIH<sup>1-4</sup>
- The incidence and prevalence of OIH in patients receiving opioids is unclear and may be low<sup>2-5</sup>

# Perioperative OIH

- OIH has been demonstrated in perioperative settings<sup>1-6</sup>
  - A meta-analysis of 27 studies and 1494 patients found higher intra-operative remifentanil doses are associated with increased post-surgical acute pain and increased post-operative opioid requirements<sup>1</sup>
- Characteristics of perioperative OIH include:<sup>1-6</sup>
  - Expanded area near wound with hyperalgesia
  - Higher pain scores
  - Increased use of opioids
- Most associated with the short-term use of high-dose opioids<sup>1-7</sup>
  - For example, cumulative doses of remifentanil IV  $\geq 50 \mu\text{g}/\text{kg}$

<sup>1</sup> Fletcher and Martinez. *Br J Anaesth*. 2014. <sup>2</sup> Kim, et al. *Front Pharmacol*. 2014. <sup>3</sup> Guignard, et al. *Anesthesiology*. 2000. <sup>4</sup> Wilson, et al. *Pain Manag*. 2021. <sup>5</sup> Comelon, et al. *Br J Anaesth*. 2016. <sup>6</sup> Yu, et al. *Anesthesiology*. 2016. <sup>7</sup> Angst. *J Cardiothorac Vasc Anesth*. 2015.



# Pain Management Physicians Believe OIH to be Uncommon

- A survey of Canadian pain management HCPs (462 responses) found:<sup>1</sup>
  - Prevalence of symptoms and signs consistent with OIH was estimated to be <1%
- A survey of HCPs who manage chronic pain with opioid therapy (318 responses) found:<sup>2</sup>
  - Most HCPs suspected OIH in  $\leq 5\%$  of their patients receiving long-term opioid therapy

# OIH Assessment: Quantitative Sensory Testing (QST)

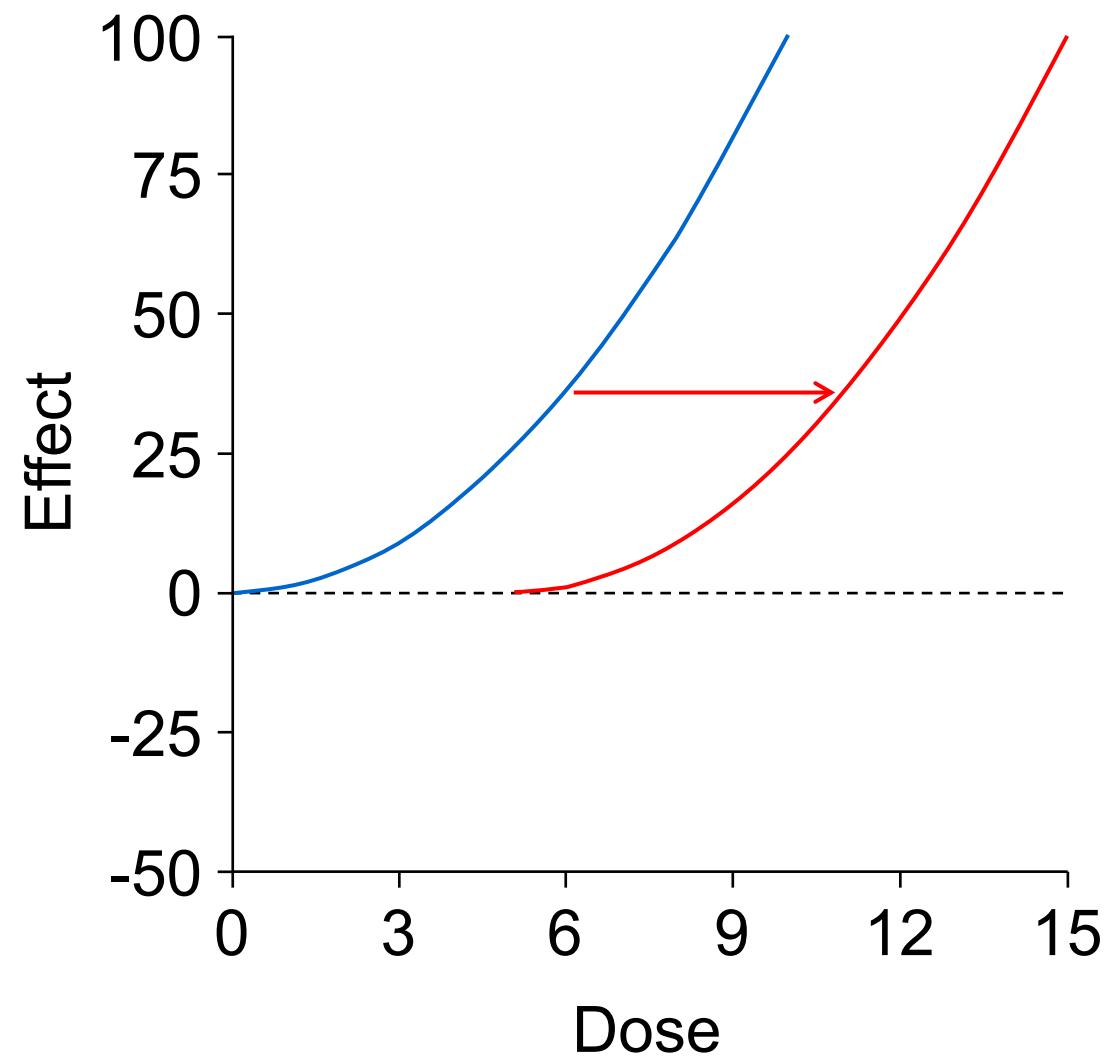
- QST is a laboratory pain assessment technique to quantitate sensory function
  - Different types of noxious stimuli, including mechanical and thermal, are applied at a controlled intensity to measure the participant's pain sensitivity
- Different QST stimuli have been used in investigation of OIH<sup>1,2</sup>
- A systematic review found that, based on limited evidence from 14 studies<sup>†</sup>, heat pain sensitivity may be the most promising QST assessment for OIH<sup>1</sup>

<sup>†</sup>In patients with chronic pain receiving long-term opioid treatment.

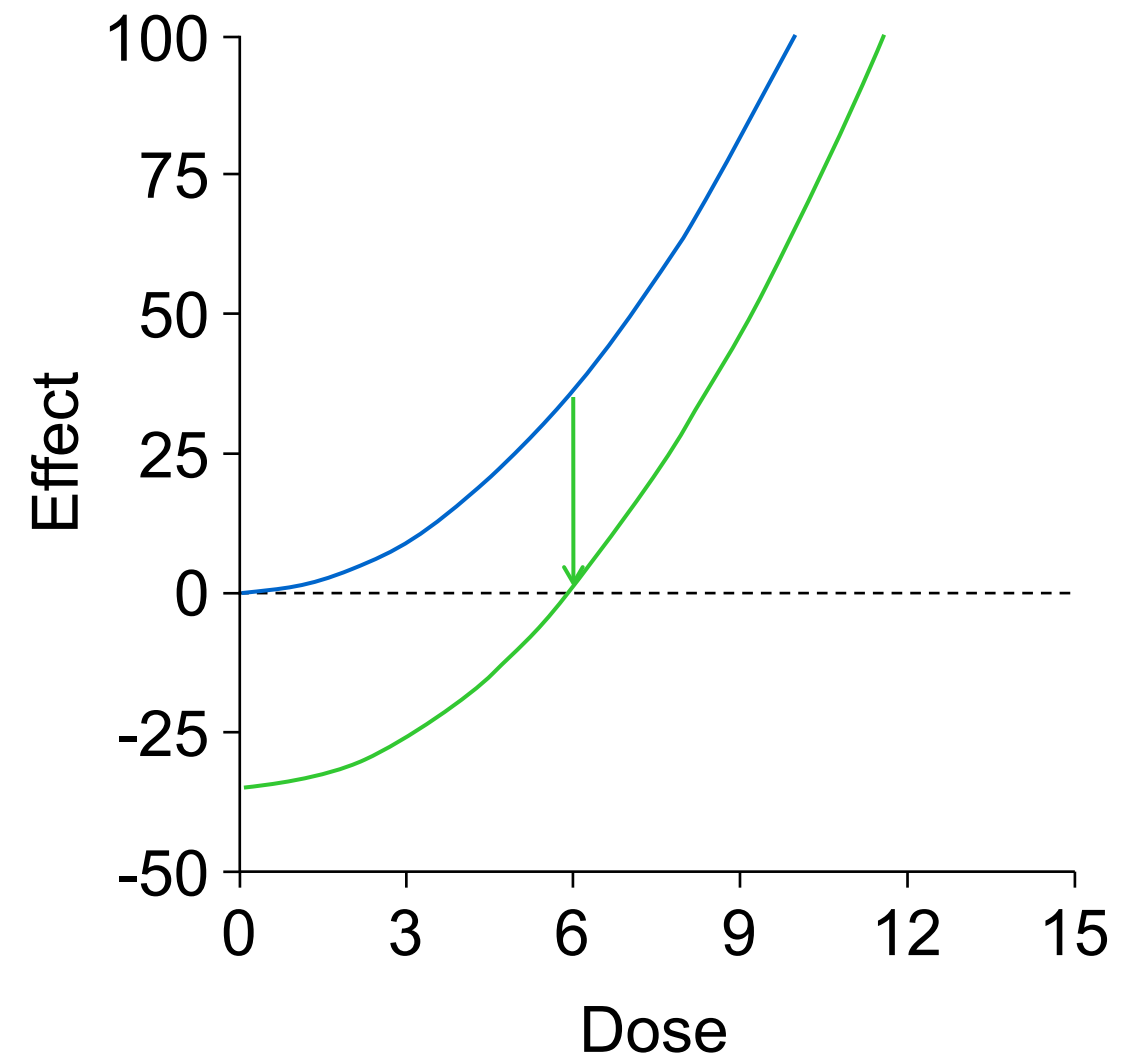
<sup>1</sup>Katz, et al. *Anesthesiol Rev.* 2015. <sup>2</sup>Higgins, et al. *Br J Anaesth.* 2019.

# Dose Effect Curves: Tolerance and OIH

**Tolerance  
(right-shift)**



**OIH  
(down-shift)**



# Incidences of Development of OIH and Opioid Tolerance†

## Incidence of OIH

- Worst PI at the final assessment  $\geq$  screening, when participant is receiving an ER opioid dose  $\geq$  screening dose

*AND*

- QST batteries at the final assessment show increased pain sensitivity compared to screening

## Incidence of opioid tolerance

- Worst PI at the final assessment  $\geq$  screening, when participant is receiving an ER opioid dose  $\geq$  screening dose

*AND*

- QST batteries at the final assessment show no increase in pain sensitivity compared to screening

† The incidence of OIH and tolerance will be assessed in the OIH subpopulation after completion of the trial..

# OIH Assessments in Study 3033-11

## Characteristics of OIH<sup>1,2</sup>

### Attribute

Increase in pain intensity over time

Spread of pain from index site

Increase in pain sensation in response to external stimuli

### Assessment in 3033-11 study

Change in Worst Pain Intensity

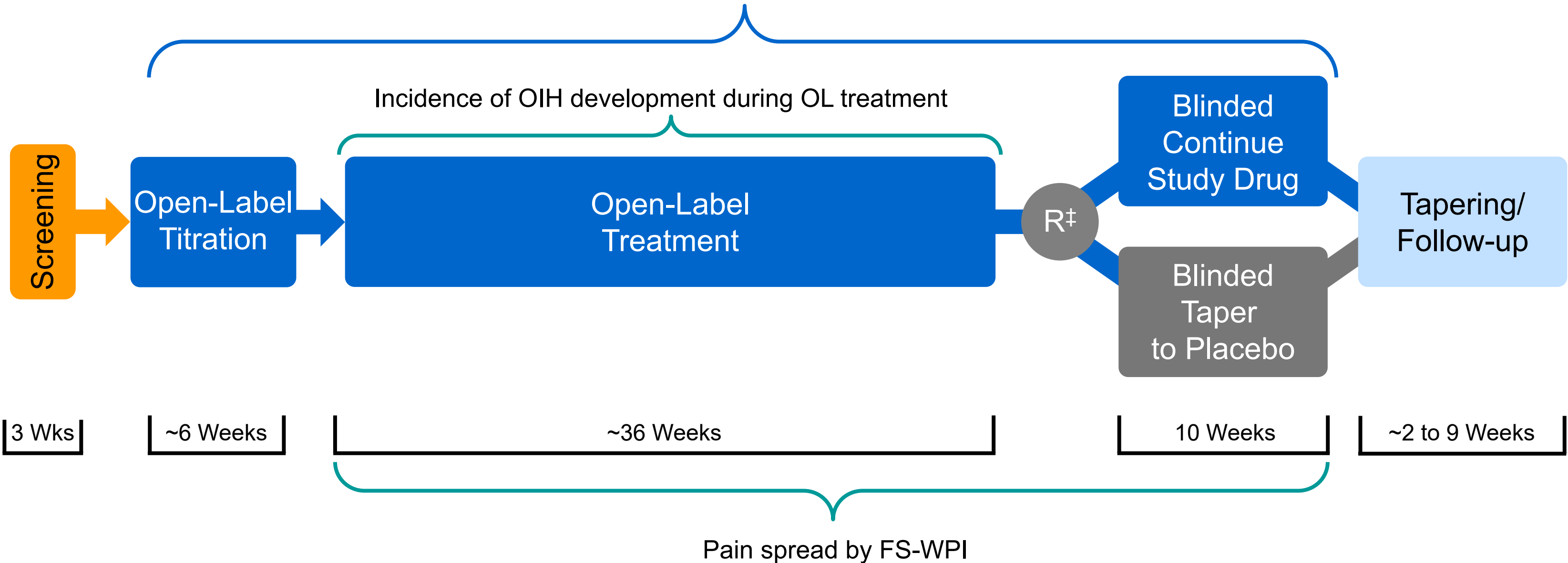
Spread of pain documented by Fibromyalgia Scale – Widespread Pain Index

Change in pain sensitivity to heat pain by QST

<sup>1</sup> Lee, et al. *Pain Physic*. 2011. <sup>2</sup> Katz, et al. *Anesthesiol Rev*. 2015.  
QST=quantitative sensory testing.

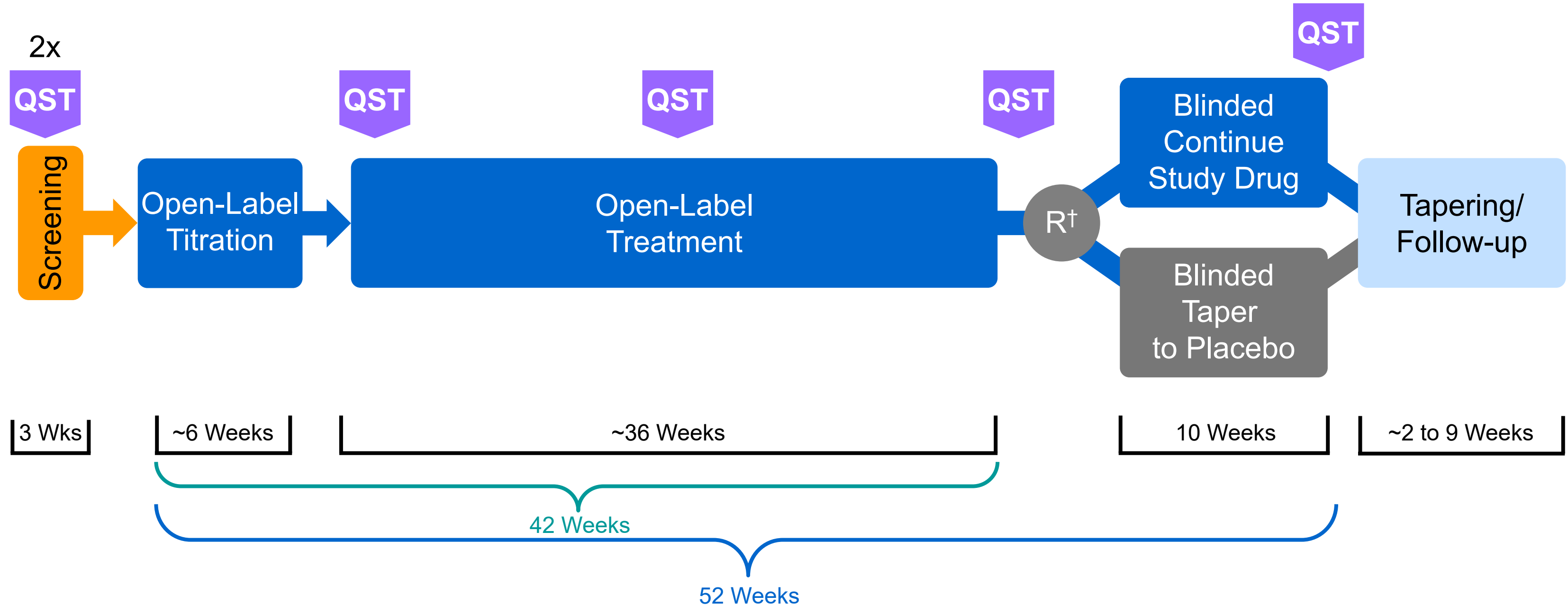
# OIH Endpoints and Assessments†

Incidence of OIH development during trial, Changes in Worst Pain Intensity by NRS, Changes in pain sensitivity by QST



†OIH population is all participants who enter the Open-Label Titration phase and have  $\geq 1$  post-trial treatment QST evaluation.  
 ‡ Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).  
 NRS=numerical rating scale; FS-WPI=Fibromyalgia Scale widespread pain index; OL=open label; QST=quantitative sensory testing.

# QST Assessments in 3033-11



† Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).  
QST=quantitative sensory testing.

# Summary

- Our understanding of OIH in individuals with chronic pain is currently limited<sup>1,2</sup>
  - The perceived incidence of OIH in routine practice appears to be low<sup>3,4</sup>
- Heat pain sensitivity by QST may be the most promising assessment of OIH<sup>1</sup>
- The 3033-11 study will assess the 3 cardinal symptoms associated with OIH<sup>1</sup>
  - Increase in Worst Pain Intensity NRS
  - Spread of pain by FS-WPI
  - Increase in pain sensation in response to thermal QST stimuli
- 3033-11 has the potential to meaningfully add to our understanding of the features and development of OIH in individuals with chronic pain



# Protocol Considerations

## **Sandra Comer, PhD**

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# Levels of Evidence<sup>1</sup> for ER/LA Opioid Efficacy

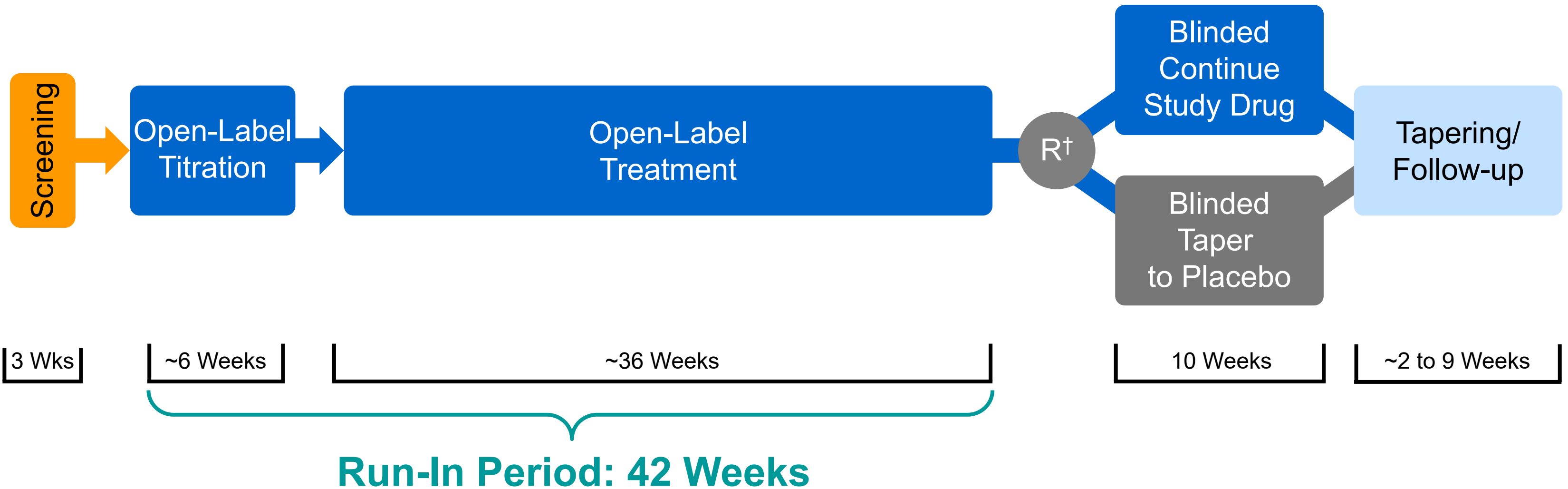
- Level I Evidence: Systematic Review of Multiple RCTs
  - ER/LA opioid efficacy through 12 weeks
  - Example: Meske et al, 2018<sup>2</sup>
- Level II Evidence: Evidence from at Least One Well-Designed RCT
  - ER/LA opioid efficacy through 52 weeks
  - May be provided by Study 3033-11
- Level III Evidence: Evidence from Multiple Non-Randomized Cohort Studies
  - ER/LA opioid effectiveness through 52 weeks
  - Example: Farrar et al, 2022<sup>3</sup>

<sup>1</sup> Sackett. *Chest*. 1986. <sup>2</sup> Meske, et al. *J Pain Res*. 2018. <sup>3</sup> Farrar, et al. *Pain*. 2022.  
RCT=randomized controlled trial.

# Novel Study Design

- Contribution of new placebo-controlled data on long-term efficacy through 52 weeks
- Proposed study is unique
  - Outcomes should be interpreted cautiously without replication
- Risk of overinterpretation may impact patient care

# Study 3033-11: Novel Design with Extended Run-In Period



<sup>†</sup> Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Risk of Failing to Detect a Signal of Benefit (Type 2 Error)

- Extended trial duration
  - May increase risk of confounding
- Novel design
  - No precedent for sample size calculation
- A false negative result may incorrectly suggest lack of efficacy
  - Potentially broad implications for patients with severe chronic non-cancer pain

# Extensive Assessment of Efficacy

- Multiple efficacy endpoints
  - Time to loss of efficacy
  - Time to treatment failure
  - Change in mean past 7-day worst pain intensity and average pain intensity
  - Change in physical function
  - Change in brief pain inventory
- Positive secondary endpoint results can strengthen primary and enhance interpretation
- Varied or discordant results would be difficult to interpret

# Study Includes Participants with Multiple Pain Conditions

- Expands eligible population compared to a study of a single condition
- Enhances generalizability of results across pain conditions
- There may be differential changes in the underlying pain conditions for each participant
  - Pain reporting is subject to multiple potential confounders
- Exogenous factors may influence a participant's experience of pain
  - eg, concurrent depression or anxiety

# Study Allows Multimodal Pain Treatments

- Participants may continue on concomitant therapies for pain
- Pre-existing permitted pharmacologic pain therapies
  - Adjuvant therapies: eg, anticonvulsants, antidepressants
  - OTC pain medications: eg, NSAIDs
- Pre-existing non-pharmacologic pain therapies
  - Eg, behavioral therapy, physical therapy, electric stimulation, yoga
- Advantages
  - Expands eligible participants
  - Reflects real-world clinical practice
- Disadvantages
  - May increase variability in efficacy outcomes
  - May be more difficult to discern an effect of the ER/LA opioid



# Protocol Considerations Summary

- Opportunity to generate Level II evidence<sup>1</sup> of 52-week efficacy of ER/LA opioids
  - Randomized, double blind, placebo-controlled trial
- Scientifically and operationally robust approach
- Novel study design
  - Enables evaluation of persistence of efficacy
  - Will lack replication
- Multiple efficacy endpoints
  - Consistent results may enhance robustness and interpretability
  - Divergent results may be difficult to interpret
- Multiple pain conditions
  - Enhance recruitment and generalizability
  - May increase variability that could bias toward Type 2 Error
- Multimodal pain therapies
  - Enhance recruitment and retention; reflect real-world care
  - May increase variability that could bias toward Type 2 Error

<sup>1</sup> Sackett. *Chest*. 1986.

# Conclusions

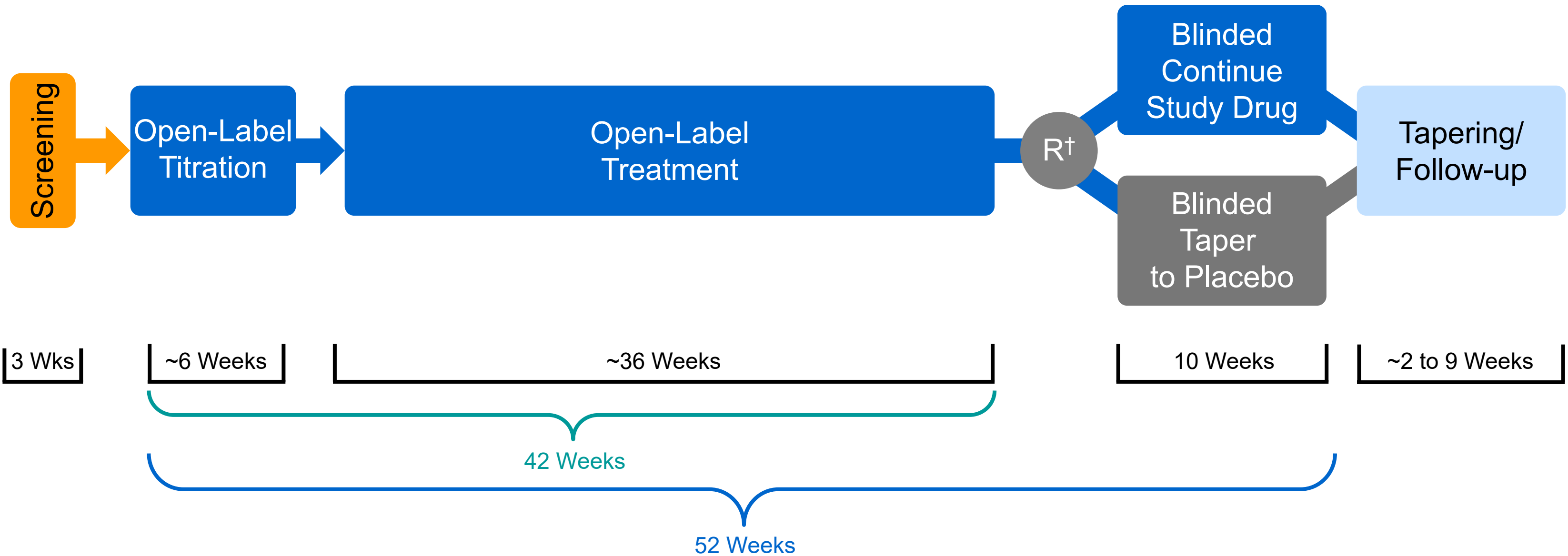
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# Study 3033-11



† Participants who continue to tolerate ER opioid and show reduced worst pain intensity are randomized (R).

# Opioid Postmarketing Requirements Consortium

The Opioid Postmarketing Requirements Consortium (OPC) is dedicated to collaborating with FDA to gather data that will inform the appropriate long-term use of ER/LA opioids in the interests of patients' well-being and the public health. The study before us today has been created with this in mind. We would appreciate the insights of the Committee on the proposed protocol.

# Additional Experts Available to Answer Questions

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