Opioid Postmarketing Requirements Consortium (OPC)

Briefing Document for:

Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

Meeting Date: April 19, 2023

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

TABLES

FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
AE	adverse event
AESI	adverse event of special interest
APAP	acetaminophen
BID	twice daily
BPI-SF	Brief Pain Inventory – Short Form
CBD	cannabidiol
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CLBP	chronic lower back pain
CNCP	chronic non-cancer pain
CNS	central nervous system
COWS	Clinical Opiate Withdrawal Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
DPN	diabetic peripheral neuropathy
ECG	electrocardiogram
EQ-5D-5L	EuroQol, 5-dimension, 5-level descriptive system
EERW	enriched enrollment randomized withdrawal
ER	extended-release
FDA	Food and Drug Administration
HCP	health care practitioner
HP50%	half-maximum heat pain
HPDIF	heat pain differential
HPTHR	heat pain threshold
HPTOL	heat pain tolerance
HYD	hydrocodone ER

IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IR	immediate-release
LA	long-acting
MME	milligram morphine equivalents
NDA	New Drug Application
NRS	numerical rating scale
OA	osteoarthritis
OIH	opioid-induced hyperalgesia
oMED	oral morphine equivalent dose
OPC	Opioid Postmarketing Requirements Consortium
PF-SF-8b	Item Bank v2.0 – Physical Function – Short Form 8b
PGIC	Patient Global Impression of Change
PI	pain intensity
PMR	postmarketing requirement
POMAQ	Prescription Opioid Misuse and Abuse Questionnaire
PPN	painful peripheral neuropathy
PPQ	Pain Profile Questionnaire
PRN	as needed
PROMIS®	Patient-Reported Outcomes Measurement Information System
PTRQ	Pain Treatment Response Questionnaire
q12h	every 12 hours
QHS	once in the evening
QST	Quantitative Sensory Testing
SAE	serious adverse event
SAO	short-acting opioid
SOWS	Subjective Opiate Withdrawal Scale
TC	teleconference

THC	9-delta-tetrahydrocannabinol
UDT	urine drug testing
US	United States
VA/DoD	Veteran's Affairs/Department of Defense
WPI	Widespread Pain Index

EXECUTIVE SUMMARY

Background and Overview

The member companies of the Opioid Postmarketing Requirements Consortium (OPC) have been asked by the US Food and Drug Administration (FDA) to participate in a meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). The purpose of the Advisory Committee meeting is to discuss the study designed to address postmarketing requirement (PMR) 3033-11, issued to application holders of New Drug Applications (NDAs) for extended-release (ER)/long-acting (LA) opioid analgesics to evaluate the long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia. The discussion will focus on a clinical trial designed to address these objectives. FDA required the holders of NDAs for ER/LA opioids to develop and complete multiple postmarketing studies to gather evidence on the use and misuse of ER/LA opioid analgesics for the management of chronic pain. ER/LA opioid manufacturers formed the OPC to design and execute these PMRs.

In September 2013, FDA sent a letter to all companies with approved NDAs for ER/LA opioid analgesics that outlined the requirement for five PMRs (to be addressed by four observational studies and one prospective clinical trial) to be conducted as individual companies or as a consortium of companies. The initial 2013 PMR letter included PMR 2065-5, a clinical trial to estimate the risk of opioid-induced hyperalgesia (OIH) following ER/LA opioid therapy for at least 1 year and to assess risk relative to efficacy over that same period.

In 2016, following multiple OPC and FDA interactions, including a public meeting, FDA replaced the prior five PMRs with 11 PMRs, which delineated several sub-studies to clarify the goals and methodology of the observational studies. As a result, the clinical trial PMR number changed from 2065-5 to 3033-11. The 11 required postmarketing studies include 10 observational studies to gather evidence on the incidence of opioid misuse, abuse, addiction, overdose, and death associated with long-term use of ER/LA opioids for the treatment of chronic pain and one randomized clinical trial, namely PMR 3033-11. While all 10 observational studies have been completed, this meeting is to discuss the draft protocol designed to fulfill PMR 3033-11. The PMR 3033-11 states:

> *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.*

Following the initial 2013 PMR letter, the OPC, in consultation with FDA, initially designed a randomized, controlled clinical trial to assess the impact of either continued treatment with, or structured discontinuation of, ER/LA opioids on OIH and pain intensity (PI) in patients receiving high-dose, long-term opioid analgesic therapy for chronic pain. This trial was known as Study 2065-5, after the original PMR number it was designed to fulfill. OPC submitted the initial design in November 2015, and after further discussion with FDA and consultation with experts, the final design was submitted in January 2016.

The resulting study design was a 26-week multicenter, randomized, double-blind, placebo-controlled study consisting of four phases: a Screening Period (1 week); a Baseline Period (1 week); a Blinded Structured Opioid Discontinuation Period (12 weeks); and a Follow-up Period (12 weeks). The study sought to enroll patients already taking high doses of around-the-clock

opioids for at least 12 months prior to enrollment and who have been on ER/LA opioids for at least the 3 months prior to study enrollment. The study population was patients with chronic lower back pain (CLBP). The study drugs were three different ER/LA opioid pain medications: oxycodone ER, morphine sulfate ER, and oxymorphone ER. The study was initiated in September 2016 but was ultimately terminated based on a mutual decision by OPC and FDA after 16 months in January 2018 due to an inability to recruit and complete a sufficient number of patients in a reasonable amount of time.

Recruitment challenges in Study 2065-5 may have been related to concurrent changes in clinical practice associated with the diagnosis and management of chronic pain and the use of ER/LA opioids. The release of clinical practice guidelines and associated state and organizational limitations on the use of opioids for the management of chronic pain has continued a downward trend in the use of opioid analgesics in general and the use of higher doses of opioids and ER/LA opioid analgesics in particular. As such, the number of investigators, sites, and patients available to participate in Study 2065-5 declined, as the trial required patients to be using relatively high doses of opioid analgesics at Screening. Some patients indicated reluctance to participate in a trial requiring them to taper off medication on which they were stabilized. Patients were also concerned about losing access to opioid analgesic medications after trial completion.

Since the termination of Study 2065-5, the OPC, in consultation with FDA and multiple external experts, has developed a new clinical trial design to meet the requirements of PMR 3033-11. While many potential trial designs have been considered, this new protocol is intended to overcome some of the challenges that led to the termination of Study 2065-5.

Several aspects of the study have changed relative to Study 2065-5, including the overall trial design, intended study population, study treatments, endpoints, and statistical approach, all of which are intended to provide the 3033-11 trial with a higher likelihood of enrolling patients and successful completion. The resulting design also reflects ongoing efforts to develop an approach that meets the PMR while attempting to address current clinical pain management practice to the extent feasible in a clinical trial setting.

Finally, in further communications regarding PMR 3033-11, FDA has clarified to OPC that its interest in this PMR has shifted to focus on the long-term efficacy over 1 year of ER/LA opioids and determining the characteristics of patient populations that would benefit from long-term opioid treatment to help prescribers determine whether long-term opioid use is appropriate for a prospective patient. These factors have all contributed to the design of the current draft protocol. The current draft protocol was submitted to FDA in March 2022. When the protocol is deemed final by FDA, OPC intends to conduct a feasibility analysis of the protocol prior to initiating the full 52-week trial and to perform a pilot quantitative sensory testing (QST) study to evaluate and refine this OIH assessment prior to its use in the trial.

Summary of Strengths and Challenges of the 3033-11 Trial Design

The planned Study 3033-11 (protocol version 0.8, dated March 01, 2022) is designed as a 12-month, multicenter, randomized, placebo-controlled, double-blind clinical trial with an enriched enrollment randomized withdrawal (EERW) design.

The primary objective of the 3033-11 trial is to evaluate the persistence of analgesic efficacy of a representative ER opioid (morphine sulfate ER) in patients with defined chronic non-cancer pain

(CNCP) who demonstrate initial analgesic efficacy and tolerability of the ER opioid. Beyond this primary objective, the trial has a wide range of secondary objectives. These include exploration of the incidence of OIH and opioid tolerance, identification of potential predictors and patient characteristics related to opioid response and non-response, evaluations of physical function, anxiety, and depression, as well as the safety of titrated doses of morphine sulfate ER.

The trial will include five phases: A Screening Phase (up to 3 weeks), an Open-Label Titration Phase (~ 6 weeks), an Open-Label Treatment Phase (~ 36 weeks), a Double-Blind Phase (10 weeks), and a Tapering and Follow-up Phase (~ 2 to 9 weeks). The current novel EERW design includes the same phases used in multiple approval studies for ER/LA opioids; however, the duration and sequence of phases have been modified to more closely resemble clinical practice in that it includes 42 weeks of open-label treatment (Open-Label Titration Phase and Open-Label Treatment Phase) prior to the 10-week randomized withdrawal (Double-Blind Phase). Thus, the design is intended to evaluate the persistence of efficacy and potential risk for OIH after 42 weeks of treatment. An overview of the trial design is provided in Figure 5. A more detailed summary of the trial design is provided in Section 4.

As with any research study, there are strengths and challenges associated with the current draft 3033-11 trial protocol. To assist the Advisory Committee in its analysis of the 3033-11 trial design, Table 1 summarizes the strengths and challenges of the trial design.

Table 1: Summary of Strengths and Challenges of the Proposed Trial Design to Address PMR 3033-11

Trial Design	Strengths	Challenges
Overall Trial Design		
Proposed Trial Design (42 weeks open-label enrichment period; 10 weeks double-blind, randomized withdrawal period)	**Duration** May allow for a demonstration of sustained efficacy.	**Duration** May lead to the inability to enroll and retain a sufficient number of patients to assess the trial endpoints, including variability among pain conditions. May result in a burden of trial participation, with total number of assessments and study visits; OIH substudy participants will undergo additional testing.
	EERW design: Used in pivotal analgesic efficacy trials for many years. Accepted by FDA as evidence of efficacy for the 12-week exposure and trial duration. Consistent with guidelines for clinical assessment of chronic pain. Greater sensitivity than alternative trial designs. Suitable for conditions where a large placebo effect exists, such as chronic pain. Decreases risk of discontinuations due to lack of tolerability. Minimizes duration of placebo exposure, which may support trial enrollment.	**EERW design:** The trial design of 42 weeks open-label and 10 weeks double-blind is untested; many unknown factors may lead to the inability to complete the trial and/or failure of trial endpoints. Risk for bias due to potential unblinding of patients in the placebo group during tapering. Limitations of generalizability of findings to a larger population of patients with CNCP. Poses significant recruitment/retention concerns: – Patients may not want to risk randomization to placebo once stabilized on a long-term ER opioid. – Patients may drop out prior to the Double-Blind Phase, and replacements may require 9 – 11 months to be eligible for randomization, therefore prolonging the duration of the trial. The incidence of OIH may not be accurately assessed in this EERW design because it is difficult to establish a baseline. Patients' prior opioid treatment history may influence the likelihood of the development of OIH during the trial.

Trial Design	Strengths	Challenges
Trial Population		
Diagnoses (CLBP, OA, PPN, DPN, post-cancer treatment pain)	Relatively well-characterized conditions. Generally associated with continuous pain as appropriate for ER/LA indication. Relatively high levels of physical dysfunction allow the evaluation of physical function as a secondary endpoint. Ambulatory patients who can operationally be evaluated in a trial setting.	Results may not be generalizable to all CNCP diagnoses. Limiting diagnoses decreases the available pool of potential participants for enrollment. Evaluating patients with different pain types may increase variability and confound efficacy evaluations.
Other Main Criteria for Inclusion (e.g., PI scores, failure of SAOs, and other therapy)	Randomization criteria for PI are consistent with established clinically important differences. Other eligibility and enrollment requirements based on ER/LA labeling/indication, i.e., pain severe enough to require daily, around-the-clock, long-term opioid treatment.	Additional criteria (e.g., Worst PI threshold and SAO use) may limit enrollment. Additional criteria may limit the generalizability of results.
Trial Restrictions	Trial restrictions consistent with labeling; intended to increase patient safety and avoid confounding efficacy.	Trial restrictions may limit enrollment and may result in premature discontinuations, e.g., exclusion of cannabis and alcohol use.
Treatment Regimen and Rescue Medications		
Treatment Regimen (morphine sulfate ER titrated to ≤ 240 mg/day)	Morphine ER is the most commonly prescribed ER/LA opioid in US. Relatively selective full mu-opioid receptor agonist. Attempts to mimic clinical practice by allowing flexible dosing. Some individual patients may require higher doses.[1] Individualized dosing increases the probability of showing efficacy.	Using morphine ER as a single entity may limit generalizability to other opioid products. High doses of opioids[1] are no longer commonly used and may be more associated with negative outcomes. The use of doses up to 240 mg/day requires a longer tapering period.
Rescue Medications and Permitted Therapies (up to	The use of rescue medications and other therapies mimics clinical practice.	Some patients may discontinue if additional rescue medications are needed.

[1] This trial defines “high doses” as those ≥ 90 MME/day.

Trial Design	Strengths	Challenges
30 mg IR morphine/APAP 3000 mg/day; use of other therapies permitted if stable)	The use of rescue may mitigate withdrawal symptoms during taper, thereby preserving the blind.	The use of rescue medications and other pain therapies may confound efficacy endpoints.
Trial Endpoints		
Primary Endpoint (time to loss of efficacy based on Worst PI, lack of efficacy, or new pharmacotherapy)	NRSs for Worst and Average PI are used in many previous studies of CNCP, as recommended in guidelines. Time to loss of efficacy endpoint more sensitive/greater power than responder rate or comparison of means. Handling missing data/discontinued patients is more straightforward with time to loss of efficacy endpoint.	Worst PI is not as commonly used compared to Average PI; the time to loss of efficacy endpoint is used in fewer clinical trials. There is no standardized approach to define “loss of efficacy”; criteria for failure are untested and may result in incorrect allocation. Initiating new therapy relies on patient self-report and does not take into account non-pharmacologic therapies that may affect efficacy outcomes.
Secondary Efficacy Endpoints (time to treatment failure, time to loss of efficacy/treatment failure using Average PI, changes in PI over time, BPI-SF, EQ-5D-5L, PGIC, PROMIS PF-SF8b)	Secondary efficacy measures are extensively validated and used in clinical trials. Secondary endpoints are captured during open-label and placebo-controlled phases to maximize data generation even in patients who discontinue early. Additional endpoints enable a more robust characterization of patient characteristics related to analgesic response, including predictors.	Differential results for secondary efficacy endpoints may complicate the interpretation of trial results. Extensive evaluations to be performed at each site visit may lead to patient fatigue and errors and omissions by site staff.
Secondary OIH/tolerance Endpoints (Worst PI [same/higher dose], sensitivity on QST, pain spread)	The protocol definition of OIH incorporates the main clinical features of OIH. QST methods based on literature review; allow for serial assessment of patient-specific pain sensitivity metrics. QST can provide reliable results in a multicenter setting with appropriate training and standardized procedures.	The protocol definition of OIH is untested. Not definitive if QST is a reliable marker of OIH, and patient variability is unknown. Other factors may affect QST, such as stress or genetic factors. The trial may not be sufficiently powered to detect the occurrence of OIH.

Trial Design	Strengths	Challenges
Safety Endpoints (standard assessments, emotional function, sleep, sexual and endocrine function, abuse/misuse)	Assessment of standard measures and domains that may be impacted by long-term opioid use, including potential for abuse/misuse.	Additional evaluations may lead to patient fatigue and errors and omissions by site staff.
End-of-Trial		
Continuity of care (unblinding of HCP to provide continuity of care)	A patient-centered approach that attempts to minimize interruptions to a patient's treatment course.	Potential for unblinding due to patient or HCP disclosure. Requires that all patients taper off the medication and restart with HCP, as needed.
Tapering Schedule (1 to 8 weeks, depending on the dose at randomization/ discontinuation)	The proposed tapering scheme is longer than most EERW trials (up to 8 weeks vs. <2 – 3 weeks). Considers dose of ER morphine, as well as dosing regimen (BID) and availability of dosage strengths. Allows patients randomized to placebo to be completely tapered off ER medication during the 10-week Double-Blind Phase.	Tapering duration shorter than those recommended in clinical practice guidelines (e.g., CDC, VA/DoD). Tapering used in shorter EERW trials may not predict the withdrawal effects seen in this trial. Potential for unblinding due to opioid withdrawal effects. The potential for withdrawal symptoms may confound efficacy outcomes.
Statistical Considerations		
Statistical Analysis (Kaplan-Meier for primary)	Uses established methods for time-to-event data. A non-parametric analysis is free from many distributional assumptions.	Potential issues in ensuring events are captured; Kaplan-Meier estimation accounts for censoring, but missed events reduce its power to detect differences among groups of interest.
Sample Size/Power	Power calculation based on established methods.	Endpoint and trial design have limited prior data available for estimating power and attrition rates over the course of the trial. A large sample size is required for Open-Label and Double-Blind Phases

APAP = acetaminophen; BID = twice daily; BPI-SF = Brief Pain Inventory-Short Form; CDC = Centers for Disease Control and Prevention; CLBP = chronic lower back pain; CNCP = chronic non-cancer pain; DPN = diabetic peripheral neuropathy; EQ-5D-5L = EuroQol, 5-dimension, 5-level descriptive system; EERW = enriched enrollment randomized withdrawal; ER = extended-release; FDA = Food and Drug Administration; HCP = health care practitioner; IR = immediate-release; LA = long-acting; NRS = numerical rating scale; OA = osteoarthritis; OIH = opioid inducted hyperalgesia; PI = pain intensity; PPN = painful peripheral neuropathy; PGIC = Patient Global Impression of Change; PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS PF-SF8b = PROMIS® Item Bank v2.0 – Physical Function – Short Form 8b; QST = quantitative sensory testing; SAO = short-acting opioid; US = United States; VA=Veteran's Affairs/DoD. that can be used across indications.

Summary of Discussion

As explained more fully in the body of this briefing document, the proposed 3033-11 protocol leverages designs and data from prior studies and incorporates lessons learned from the terminated predecessor Study 2065-5. The collaboration between and among OPC, external experts, and FDA has resulted in a trial designed to fulfill the PMR, while also considering changes in clinical pain management practice.

The EERW design was chosen because, on balance, the strengths of this trial design outweigh the potential challenges. The EERW approach provides greater sensitivity over alternative trial designs. It is, therefore, suitable for conditions like chronic pain, where efficacy and tolerability are expected in a subset of patients and where a large placebo effect exists. The EERW design minimizes the length of time patients may be required to use placebo or an ineffective pain treatment. The EERW design is well-established, has been used in pivotal analgesic efficacy trials for many years, and is accepted by FDA to provide evidence of efficacy for 12-week randomized placebo-controlled duration.

The potential for variability in efficacy outcomes exists across CNCP diagnoses, demographic and psychosocial factors, comorbidities, and the use of multiple concurrent pharmacologic and non-pharmacologic therapies. While the protocol incorporates features intended to address some of these factors, it may be impossible to control for all potential confounders in a 52-week trial.

The duration of the trial may allow for a demonstration of sustained efficacy but may also lead to enrollment and retention issues. The trial duration could also increase the risk of failing to detect a long-term benefit of ER/LA opioids when it does exist (Type 2 error). An error of this kind that incorrectly points to a lack of efficacy could have broader consequences for the treatment of patients suffering from moderate-to-severe CNCP who may have no other effective treatment options. As in all chronic pain studies, individual differences in efficacy in different sub-groups could be interpreted to mean that different patients may or may not benefit from treatment with ER/LA opioid medications; this could potentially lead to inappropriate clinical decisions.

Finally, a single trial can only contribute a defined set of data to the existing knowledge base, and results would need to be interpreted cautiously in the absence of replication; this is especially true where the interpretation of a single trial could potentially negatively impact patient care.

Changes in the understanding of OIH have occurred in parallel with trial-related activities. As discussed below, accurately determining the incidence of OIH continues to be a challenge due to the lack of consensus on methods to detect OIH in chronic pain patients and uncertainty in power calculations supporting its detection in this trial. While OPC is planning a pilot study to refine the QST assessments used to measure the incidence of OIH, this pilot trial will not determine whether the protocol definition of OIH is valid. Despite these potential challenges, data obtained from the 3033-11 trial may help further refine the understanding of possible risks of OIH and methods for its detection.

Features intended to improve the feasibility and mimic clinical practice have been incorporated into the protocol, such as flexibility in dosing and allowance for the use of concurrent pain therapies and rescue medications. However, changes in clinical practice may continue to impact patient recruitment. For example, the decreased use of ER/LA opioids and limitations on dosing

and duration may decrease the number of investigators and patients who are avaiable to participate in the trial. To address this, OPC has planned a feasibility analysis to further refine the protocol to maximize the probability of successfully completing the trial in the current treatment climate.

Summary of Conclusion

The 3033-11 trial has been designed to systematically assess the long-term efficacy of morphine sulfate ER in patients with CNCP and to contribute to the scientific understanding of OIH. The importance of designing a scientifically and operationally robust protocol is underscored by the potential impact that the trial results may have on clinical practice and the lives of individual patients suffering from chronic pain.

OPC remains committed to working with FDA to gather data that will fulfill the important goals of the PMR intended to inform the appropriate long-term use of ER/LA opioids in the interest of patient well-being and public health.

OPC also welcomes discussion with the Committee to inform the draft protocol for the 3033-11 trial.

1. INTRODUCTION

The member companies of the OPC have been asked by the US Food and Drug Administration (FDA) to participate in a meeting of the AADPAC. The purpose of the Advisory Committee meeting is to discuss the study designed to address PMR 3033-11, issued to application holders of NDAs for ER/LA opioid analgesics to evaluate the long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia. The discussion will focus on a clinical trial designed to address these objectives.

In preparation for the April 19, 2023 meeting to discuss the draft protocol for PMR 3033-11, this document focuses on the evolution of the trial design against a backdrop of changes in clinical practice and the use of ER/LA opioid analgesics, along with a detailed discussion of the strengths and challenges of the currently proposed trial design.

We look forward to a discussion with AADPAC on the design of the proposed trial to answer the questions posed by the PMR.

1.1. PMR Issuance and Formation of OPC

In September 2013, following a meeting convened by FDA, the Agency sent a letter to all companies with approved NDAs for ER/LA opioid analgesics, which outlined the requirement for five PMRs (four observational studies and one prospective clinical trial) to be conducted as individual companies or as a consortium of companies.

The initial 2013 PMR letter included PMR 2065-5, a clinical trial to estimate the risk of OIH following ER/LA opioid therapy for at least 1 year and to assess risk relative to efficacy over that same time period, as follows:

> *Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain. We strongly encourage you to use the same trial to assess the development of tolerance following use of ER/LA opioid analgesics. Include an assessment of risk relative to efficacy.*

In October 2013, OPC was formed to conduct the studies required by the PMRs. OPC initially included nine member companies (Allergan, Inc., Endo Pharmaceuticals, Inc., Hikma Pharmaceuticals, P.L.C., Janssen Pharmaceuticals, Inc., Mallinckrodt Pharmaceuticals, P.L.C., Pfizer Inc, Purdue Pharma L.P., Zogenix Inc., and Rhodes Pharmaceuticals, L.P.), eventually increasing its membership to 13 companies by the end of 2018 as FDA approved new ER/LA opioid analgesic products (with the addition of Persion Pharmaceuticals, L.L.C., Assertio Therapeutics, Inc., Collegium Pharmaceutical, Inc., BioDelivery Sciences International, Inc., Daiichi Sankyo Limited, and Egalet Corporation – along with the departure of a couple of the original companies). As companies have discontinued or divested their ER/LA opioid products, the number of member companies has steadily decreased. Currently, OPC comprises four member companies: Allergan, Inc. (now AbbVie Inc.), Collegium Pharmaceutical, Inc., Endo Pharmaceuticals, Inc., and Purdue Pharma, L.P.

As discussed in Section 3, between 2013 and 2016, there were a number of activities related to addressing the PMRs outlined in the 2013 letter, including a public meeting convened by FDA and ongoing discussions between OPC and FDA on methodology and study design.

In February 2016, the five original PMRs were expanded to 11 separate studies to address FDA's study requirements adequately. The 11 PMRs included 10 observational studies and one prospective clinical trial.

Collectively, the 10 observational studies were intended to develop and validate measures for, and assess the incidence and predictors of, misuse, abuse, addiction, overdose, and death among patients prescribed ER/LA opioid products (Appendix A: Section 9.1). To date, OPC has completed all 10 observational studies; seven have been determined by FDA to fulfill their PMR requirements, and three have been submitted and are under FDA review for PMR fulfillment (Appendix A: Section 9.1).

The clinical trial PMR, 3033-11 (formerly 2065-5), currently reads as follows:

> *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.*

In further communications regarding PMR 3033-11, and as described in Section 3 below, FDA has clarified to OPC that its interest in this PMR has shifted to focus on the long-term efficacy of ER/LA opioids and determining the characteristics of patient populations that would benefit from long-term opioid treatment to help prescribers determine whether long-term opioid use is appropriate for a prospective patient. While the assessment of OIH was maintained as a secondary endpoint, the primary focus of the trial was amended to evaluate the long-term efficacy of ER/LA opioids in the management of CNCP. Thus, the current protocol drafted for PMR 3033-11 is a 12-month, randomized, controlled, double-blind trial evaluating the efficacy of morphine sulfate ER tablets in the treatment of patients with defined CNCP, with an assessment for OIH.

In addition to the contributions of OPC member companies and external advisors with expertise in pain management, OIH, statistics, and clinical trial design, communications with FDA have been integral to the design of the protocol for PMR 3033-11 and its 2065-5 predecessor. As described in more detail in Section 3, FDA has reviewed a number of synopses and protocols for the trial, has provided written comments, and has participated in numerous teleconferences (TCs) over the years to discuss and provide input on design and analysis plans. Thus, FDA's contribution has been essential in the development of the current PMR 3033-11 draft protocol.

2. CLINICAL MANAGEMENT OF CHRONIC PAIN AND USE OF ER/LA OPIOIDS

2.1. Treatment of Chronic Pain

As defined in the 11th revision of the International Statistical Classification of Diseases and Related Health Problems, chronic pain is persistent or recurrent pain lasting longer than

3 months (Treede et al., 2015). Chronic pain is a prevalent condition; a recent analysis of data from the 2019 National Health Interview Survey found that 20.5% of adults (50.2 million) in the United States (US) reported pain on "most days or every day" (Yong et al., 2022). Chronic pain is associated with clinical, psychological, and social consequences that may result in reduced quality of life due to limited participation in complex activities, lost work productivity, and stigmatization; chronic or persistent pain is among the leading global causes of disability and reduced quality of life (Dahlhamer et al., 2018; Global Burden of Disease Study, 2015).

Non-steroidal anti-inflammatory drugs and opioids are among the most common treatments for chronic pain. Randomized controlled trials have demonstrated the efficacy of opioids in the treatment of CNCP for up to 3 – 4 months (Caldwell et al., 1999; Hale et al., 2007; Jamison et al., 1998; Meske et al., 2018; Petzke et al., 2020). Meske (2018) analyzed the EERW phases (of up to 3 months in duration) of 15 different opioid studies, including a total of 6,774 adults with varying types of CNCP. This meta-analysis found that all these randomized, placebo-controlled trials showed that opioids were efficacious relative to placebo. Specifically, the analysis demonstrated that ER/LA opioids are efficacious in decreasing pain levels for patients diagnosed with CLBP, diabetic peripheral neuropathy (DPN), and osteoarthritis (OA).

Long-term effects of opioid analgesics (i.e., ≥ 1 year) in the treatment of chronic pain have also been evaluated in multiple studies. A meta-analysis of long-term opioid treatment evaluated data from opioids administered for at least 6 months (Noble et al., 2010). The majority of studies included in the review were from open-label, long-term extensions of pivotal efficacy studies or case series, with one trial that evaluated a randomized, head-to-head comparison of two opioids (Allan et al., 2005). The authors concluded that while many patients discontinue long-term opioid therapy due to adverse events (AEs) or insufficient pain relief, weak evidence suggested that patients who were able to continue opioids long-term experience clinically significant pain relief.

A more recent open-label, single-arm study demonstrated the long-term safety and efficacy of a novel buprenorphine formulation in the treatment of moderate-to-severe chronic pain requiring around-the-clock opioids (Hale et al., 2017). One active-controlled randomized, parallel-group pragmatic trial compared the use of opioid and non-opioid medications over 1 year in the management of moderate-to-severe CLBP or hip or knee OA pain in the Veteran's Affairs (VA) system (Krebs et al., 2018). However, several important issues limit the interpretation of this trial (Covington et al., 2018). First, while 40 mg oxycodone per day (60 mg morphine equivalents [MME]/day) had previously been established as an effective dose, most patients in the opioid group received less than 50 MMEs/day, and their lack of response may have resulted from undertreatment. Second, the interpretation of the non-opioid response is complicated by the fact that 11% of the group was taking tramadol at 12 months, whose major metabolite is a mu-opioid receptor agonist. Third, despite potential underdosing in the opioid arm and use of tramadol in the non-opioid arm, both treatment groups demonstrated analgesia and improved function, thereby confirming the efficacy of oxycodone in patients with chronic pain.

A more recently published review evaluated the long-term use of ER formulations of oxycodone and hydrocodone with properties intended to deter abuse using patient-level data from FDA's Document Archiving, Reporting, and Regulatory Tracking System (Farrar et al., 2022). Farrar et al. (2022) assessed patient-level data from eight 12-month open-label treatment studies (total N=3,192); most patients in this analysis had previously completed a clinical trial with a short

titration phase prior to a 12-week randomized phase. In this analysis, 44.5% of patients who successfully titrated on ER/LA opioids to treat CNCP demonstrated continued benefit for up to 12 months at a stable or lower opioid dose, while 22.6% of patients had stable or reduced pain but increased their opioid dose, 20.8% had increased pain while receiving a stable or reduced dose of opioid, and 9.5% of patients had both increased pain and increased dose of ER opioid. Mean PI remained similar at the end of the 12-month studies, while the mean ER opioid dose rose from 54.9 MME per day at enrollment to 69.3 MME per day post-titration. Over the subsequent 52 weeks, the mean dose further increased by 7.4 MME per day. The authors concluded, "*The existence of a successful group demonstrates the potential benefit of chronic opioid therapy and supports the consideration of such therapy in a carefully selected and monitored chronic pain population who do not achieve adequate pain control with other approaches*." (Farrar et al., 2022).

While these studies collectively provide evidence of the sustained efficacy of long-term opioids in a subset of patients, the data is generally derived from open-label studies, with most randomized, placebo-controlled data obtained from withdrawal or treatment phases of up to 12 weeks. Thus, the evaluation of chronic pain beyond 12 weeks remains open for further study.

2.2. Opioid-Induced Hyperalgesia

Therapeutic use of opioid analgesics presents unique challenges in that they provide clinically significant analgesic benefits in many patients, including the treatment of pain for which other analgesics are inadequate, while also carrying the potential for serious risks of sedation, respiratory depression, overdose, abuse, misuse, and dependence (e.g., Dahan et al., 2013; Jantarada et al., 2021; Miller et al., 2015). It has also been postulated that some patients may experience loss of pain control due to OIH, a paradoxical hypersensitivity to pain.

OIH has been described as a state of nociceptive sensitization caused by exposure to opioids. Clinically, OIH has been characterized as involving three primary symptoms: increases in PI over time, pain spreading to location(s) other than the initial painful site, and an increase in pain sensitivity to external stimuli (Katz et al., 2015a). OIH has been documented in preclinical studies, human experimental pain models, and perioperative pain patients; however, the relevance of these models to patients with chronic pain on long-term opioid therapy is unclear.

Some studies have evaluated OIH in pain patients and patients with opioid use disorders with inconsistent results. However, OIH appears to be more evident in the latter group (for a review, refer to Higgens et al., 2019).

- A study in patients with CLBP who were opioid naïve at study entry found that after 1 month of morphine treatment, patients developed significant hyperalgesia assessed using a cold model but not a heat pain model (Chu et al., 2006).
- A cross-sectional study compared pain threshold, tolerance, and temporal summation (a measure of central sensitization) among patients with chronic pain on opioid therapy, patients with chronic pain without opioid therapy, and healthy control patients (Chen et al., 2009). In this study, individuals with chronic pain on opioid therapy significantly differed from the other two groups by displaying decreased heat pain thresholds and

enhanced temporal summation responses, with opioid dose correlating with these responses.

- Finally, a recent systematic search of case reports and case series of OIH in patients with chronic pain (both cancer- and non-cancer-related) found 41 articles, with a total of 72 individual cases of OIH reported (Guichard et al., 2022). This analysis found that OIH was observed in patients of both sexes, all ages, and with various types of pain. In addition, many of these cases involved treatment with very high daily doses of opioids, with an overall median oral morphine equivalent dose (oMED) of 850 mg among suspected OIH cases, with significant differences between cancer and non-cancer cases (median oMED of 1200 mg vs. 340 mg). The opioids used in these cases were morphine (33.8%), fentanyl (29.2%), oxycodone (27.7%), hydromorphone (26.2%), and methadone (14%), and in 44.6% of cases, patients consumed at least two different opioids.

Although collectively these findings suggest that OIH may occur in chronic pain patients, most of these studies have been cross-sectional, based on case reports/series, and/or with relatively small sample sizes.

More recent studies have evaluated the potential for the development of OIH in clinical practice. Briefly, Vargas-Schaffer et al. (2020) used a physician survey and found a perceived OIH prevalence of 0.002% per patient per physician practice year for acute pain and 0.01% per patient per physician practice year for chronic pain. Another survey of physicians found that 25% of respondents had not observed OIH in their practice and a further 43% had suspected cases of OIH in ≤ 5% of their patients on long-term opioid therapy, making it likely to be a relatively rare phenomenon in clinical practice (Kum et al., 2020). However, there are limitations to the above survey studies, including relatively low response rates and a lack of objective measurement.

A recent randomized, double-blind trial in CNCP patients evaluated the potential for the development of analgesic tolerance and/or OIH using an experimental model. Rowbotham and Wallace (2020) found that 3 of 17 patients who completed the 6-month trial with levorphanol demonstrated some signs of both tolerance and OIH; however, no patients met all study-defined criteria for the development of combined OIH and tolerance. Further, the analysis of Farrar et al. (2022) suggests that there is a group of patients who experience sustained pain relief without dose escalation, arguing against the formation of OIH in patients who are appropriate candidates for long-term opioid therapy.

Finally, in a search of the literature using the Medical Subject Headings (MeSH) terms “opioid-induced hyperalgesia”, “OIH”, “secondary opioid-induced hyperalgesia”, “opioid tolerance”, “allodynia”, and “opioid withdrawal-associated hyperalgesia” in PubMed from 1990 – present, no scientific evidence was found that ER/LA opioids are more likely to cause OIH than immediate-release (IR) opioids or short-acting opioids (SAOs).

Thus, while there is general agreement on the characteristics of OIH, there are not currently agreed-upon approaches to detect or diagnose OIH in practice. Related to this, the incidence of OIH in clinical practice remains unclear, and a growing body of evidence suggests that it may be relatively low. Overall, there are minimal data describing the risk of development of OIH during long-term therapy with opioids, particularly using a prospective, randomized, controlled approach.

2.3. Evolution in Clinical Practice

There have been many changes in clinical practice associated with the diagnosis and management of chronic pain and the use of ER/LA opioids since the initial PMR 2065-5 was issued almost a decade ago. These changes have occurred parallel to the evolution of the two clinical trials, the initial Study 2065-5 and the current Study 3033-11.

Changes in pain management practice largely relate to the release of guidelines, most importantly the *Centers for Disease Control and Prevention* (*CDC) Guideline for Prescribing Opioids for Chronic Pain — United States, 2016* (Dowell et al., 2016). The guidelines provide recommendations for primary care clinicians prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The recommendations advise that ER/LA opioids should not be used as the initial treatment for pain and should be reserved only for severe, continuous pain. Secondly, the recommendations state that clinicians should carefully assess individual benefits and risks when prescribing opioid doses ≥ 50 MME/day and should generally avoid or carefully justify increasing doses to ≥ 90 MME/day.

In 2017, the VA/Department of Defense (VA/DoD, 2017) issued updated guidelines on the use of opioid therapy, which included a recommendation to avoid long-term opioid use entirely and advising the use of non-pharmacological approaches to pain management over pharmacological approaches. Other federal agencies, such as the Bureau of Prisons and the Indian Health Service, have implemented similar policies and guidelines.

According to a report submitted to congress by the Department of Health and Human Services, as of April 2020, 40 states have passed laws that address the prescribing of opioid analgesic medications (*Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act Section 7024: Report to Congress on Opioid Prescribing Limits*; https://www.fda.gov/media/147152/download,https://www.fda.gov/media/147152/download, accessed 05-Dec-2022). State-specific legislation, medical and pharmacy boards, Medicaid programs, department of workforce services, and worker's compensation programs have adopted policies, guidelines, and regulations that place limits on prescribing opioid analgesic medications and/or require monitoring of opioid prescriptions. Many insurance companies and managed healthcare organizations have also implemented policies related to limitations on opioid analgesic prescriptions; this has led to a general downward trend in total daily doses of opioids used, use of ER/LA opioid analgesics, and use of high-dose opioids. This trend began even before the release of the CDC guidelines in 2016. The use of ER/LA opioid analgesics for chronic pain continues to decline year-over-year. In recent years ≥ 90% of opioid prescriptions have been for IR opioids or SAOs (Schieber et al., 2019; IQVIA® data). As a result of the guidelines and changes in state laws and medical boards, institutional rules, and payor coverage, millions of patients lost partial or full access to the opioids on which they were stable, with numerous studies demonstrating the harms associated with these involuntary dose reductions or discontinuations (Agnoli et al., 2021; Binswanger et al., 2020; Coffin et al., 2020; Fenton et al., 2019; Glanz et al., 2019; James et al., 2019; Mackey et al., 2019; Mark and Parish, 2019; Nataraj et al., 2022; Neprash et al., 2021; Oliva et al., 2020; Quinn et al., 2022; Stein et al., 2022).

In 2022, CDC released an update to its guidelines, *CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022,* at least partly due to concerns over the misapplication of the initial 2016 guidelines (Dowell et al., 2022). The updated guidelines state:

> "*Although some laws, regulations, and policies that appear to support recommendations in the 2016 CDC Opioid Prescribing Guideline might have had positive results for some patients, they are inconsistent with a central tenet of the guideline: that the recommendations are voluntary and intended to be flexible to support, not supplant, individualized, patient-centered care*."

The CDC's updated 2022 guidelines include the preference for non-pharmacologic and non-opioid pharmacologic therapy for chronic pain as appropriate for the specific patient and the use of opioid therapy only if the benefits are expected to outweigh the risks to the patient. Further, when initiating opioid therapy for acute, subacute, or chronic pain, clinicians are advised to prescribe IR opioids instead of ER/LA opioids and to reserve ER/LA opioids only for severe, continuous pain, avoiding intermittent or as-needed (PRN) use. Clinicians are also advised to prescribe the lowest effective dose of opioids for opioid-naïve patients. If continued therapy is required for subacute or chronic pain, individual benefits and risks should be evaluated when considering dose increases. The guidelines recommend a similar approach for dose changes in patients already receiving opioid therapy. Finally, if the benefits do not outweigh the risks of continuing with opioid therapy, clinicians are advised to optimize other therapies and work closely with patients to gradually taper to lower opioid doses or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. As noted by the CDC, these recommendations do not preclude the use of ER/LA opioids as an effective treatment in appropriate patients.

Due to these changes in the clinical pain management landscape since the initial issuance of the clinical trial PMR in 2013, the number of investigators, sites, and patients available to participate in a long-term ER/LA opioid trial has declined. These factors contributed to the inability to complete the OPC trial initiated in 2016 and have also influenced the evolution of the current draft protocol that is the topic of the Committee's discussion, as discussed further in Section 5 (Rationale for the current design) and Section 6 (Challenges associated with the current design).

3. REGULATORY, OPERATIONAL, AND STUDY DESIGN HISTORY OF STUDY 2065-5 AND STUDY 3033-11[1]

This section outlines how the designs of the initial Study 2065-5 and the current Study 3033-11 have evolved over the years. Although there have been many updates and versions of synopses and protocols over the years, only high-level summaries of the main design features are discussed herein.

Throughout this section, study components are described as in the original documents (synopses or protocols), which may differ from the terminology used in the current draft protocol (e.g., patient vs. subject and trial vs. study). In addition, the objectives are described as written in the

[1] Appendix B (Section 9.2) contains a full detailed timeline of activities related to PMR 2065-5/3033-11.

various documents (i.e., primary, secondary, or exploratory), which may not necessarily correspond between different documents or the current PMR.

For further clarification, when FDA released OPC from the prior five PMRs in February 2016 and replaced them with 11 PMRs (10 observational studies and one clinical trial), it changed the clinical trial PMR number from 2065-5 to 3033-11. When OPC initiated its original trial to address the PMR in September 2016, FDA advised that it had no concerns with OPC continuing to use "2065-5" on the protocol and study-related documents to avoid delays due to revising the documents with a new PMR number.

Consistent with this approach, and to avoid confusion with the current draft protocol to address PMR 3033-11, the initial study will be referred to as "Study 2065-5" within this document, while any synopses or protocols prepared following the termination of Study 2065-5 will be referred to as Study 3033-11.

3.1. Study 2065-5

In September 2016, OPC initiated Study 2065-5, which followed multiple rounds of discussion between OPC and FDA, including a public meeting in May 2014, as well as synopsis and protocol development (as detailed in Appendix B, Section 9.2). Protocols were submitted for FDA review in November 2014 and September 2015, with the final original protocol submitted in January 2016 and amendments occurring in July 2016 (Amendment 1) and February 2017 (Amendment 2).

In the February 2017 protocol (Amendment 2), the primary objective of Study 2065-5 was to evaluate the therapeutic effect of structured discontinuation of long-term opioid therapy compared to continuation of opioid therapy in the management of poor responders to high-dose, long-term opioid analgesic therapy. The secondary objective was to define the patient characteristics that predict the benefit of removal from opioid therapy compared to continued opioid therapy. An additional exploratory objective was to determine whether a poor response to high-dose opioids could be explained by OIH, by comparing the effect of opioid discontinuation to continued opioid therapy on experimental pain sensitivity.

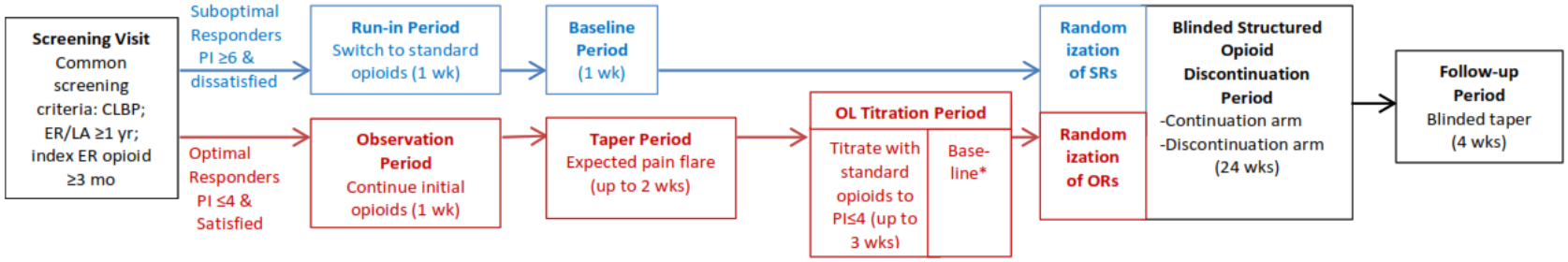
The 2065-5 study was designed as a 26-week multicenter, randomized, double-blind, placebo-controlled study using oxycodone ER (OxyContin®), morphine sulfate ER (MS Contin®), and oxymorphone ER (Opana® ER) as the investigational products in patients who were using around-the-clock opioids for non-radicular CLBP. An overview of the study design is provided in Figure 1. The design also included a QST substudy to assess pain sensitivity.

At the Screening Visit, a broad range of patients on long-term opioid analgesic therapy for CLBP were evaluated for entry into the study. Subjects were required to have been taking ER/LA opioids (or IR opioids at least four times a day) for at least 12 months for their CLBP and to have been taking high daily doses of morphine sulfate ER (120 – 540 mg), oxycodone ER (80 – 360 mg), or oxymorphone ER (40 – 180 mg) for at least the 3 consecutive months prior to Screening. Subjects were classified as Suboptimal Responders or Optimal Responders at Screening based on PI, as follows: Suboptimal Responders were those with a daily Average PI score ≥ 6 and who were dissatisfied with their pain and physical function, while Optimal

Responders were those with a daily Average PI score ≤ 4 and who was satisfied with their pain and physical function.

Suboptimal Responders participated in a 1-week Run-In period during which they were switched to fixed doses of ER opioid study medications plus matching IR opioid (≤ twice daily [BID] PRN oxycodone 10 mg, morphine sulfate 15 mg, or oxymorphone 5 mg), with acetaminophen (APAP) as a rescue medication. Subjects then entered a 1-week Baseline Period to record the subjects' 7-day daily PI scores to be averaged and used as the subject's baseline assessment. Optimal Responders participated in a 1-week Observation Period on their current medications during which they were confirmed to be Optimal Responders. The Optimal Responders then participated in a Taper Period of up to 2 weeks (+ 3 days), followed by an up to 3-week Open-Label Titration Period, during which they were titrated back onto the ER opioid study medications. Both groups of subjects were then randomized in the Blinded Structured Opioid Discontinuation Period (24 weeks) to either continue (active treatment) or discontinue (placebo) opioid therapy in a double-blinded manner. All randomized patients were provided with IR opioid rescue medication and APAP. The goal of this period was to taper subjects in the discontinuation arms of both the Suboptimal Responder and Optimal Responder groups off their opioid treatment onto placebo over approximately 3 – 4 weeks while subjects in the continuation arms were maintained on a fixed regimen of ER opioid, followed by a 4-week Follow-up Period.

Figure 1: Overview of 2065-5 Trial Design



Abbreviations: CLBP = chronic low back pain, ER = extended release, LA = long-acting, mo = month, OL = open label, OR = Optimal Responder, PI = pain intensity, SR = Suboptimal Responder, wk = week

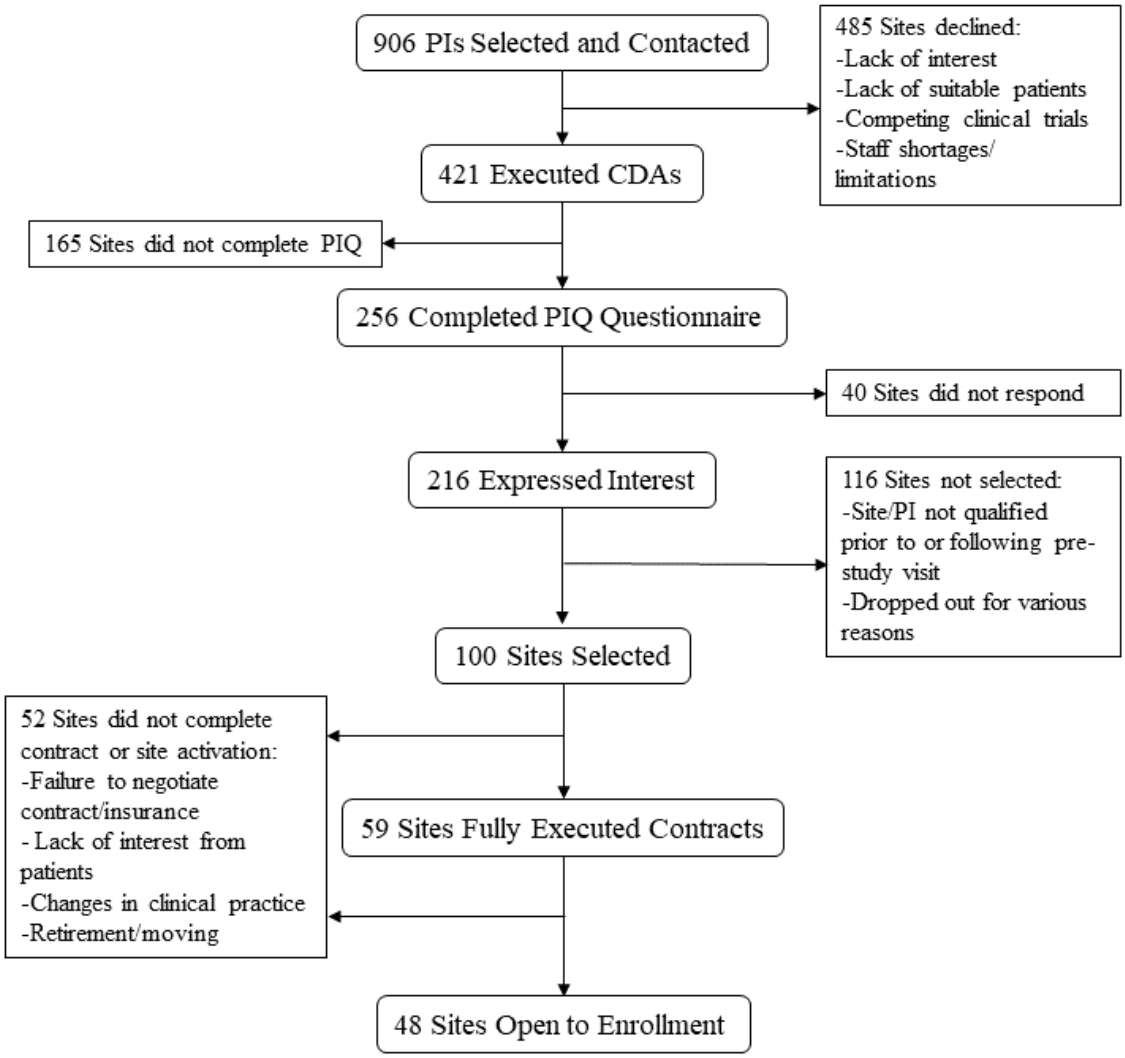
Note:

- Additional footnote in Amendment 2: ER/LA requirement could have been satisfied by use of immediate-release opioid at least 4 times a day for at least 1 year.
- Baseline PI scores = mean Average PI score including the Average PI scores during the Titration Period that met the qualification criteria (Average PI score ≤5 [≤4 in Amendment 1] for 3 consecutive non-missing values) plus any scores between the final qualification day and the Randomization Visit.

February 2017, Amendment 2 protocol version.

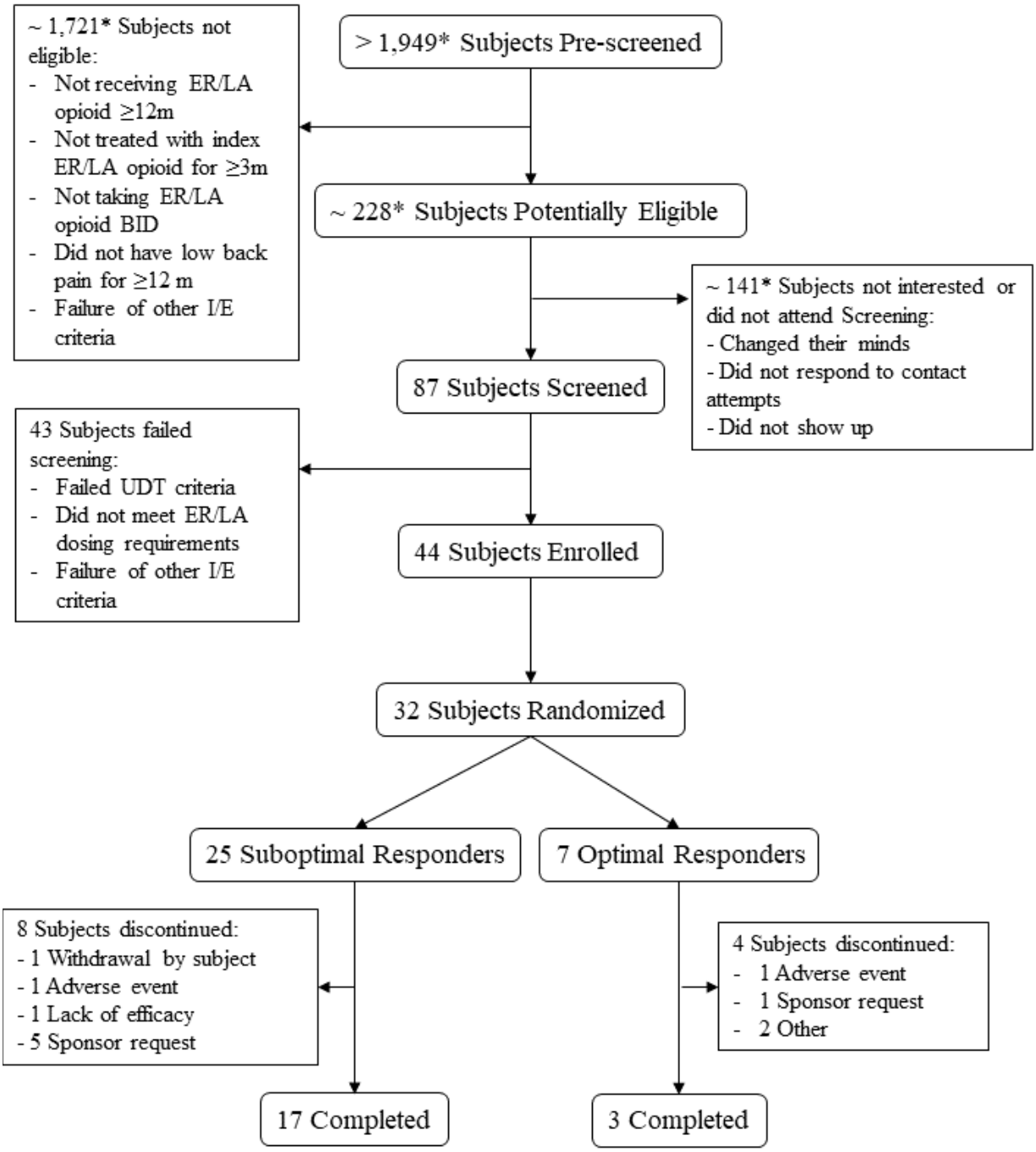
Summaries of the site selection process and subject disposition for Study 2065-5 are provided in Figure 1 and Figure 2, respectively. Approximately 820 subjects were planned to be enrolled in Study 2065-5. Despite the best efforts of the investigators, OPC, and FDA, this study was unable to recruit an adequate number of subjects. It was initiated in September 2016 and prematurely terminated in January 2018. In the 16 months after study initiation, only 32 subjects reached the randomized phase. In the QST substudy, 44 sites were initially selected, but 24 sites dropped out either before or after contract distribution, resulting in 20 sites opening for enrollment. Collectively, these sites enrolled only eight subjects.

Figure 2: Site Selection Process for Study 2065-5



Source: Status assessment dated September 06, 2017, Appendix 16.1.4 of the abbreviated clinical study report.
CDA = Confidential Disclosure Agreement; PI = Principal Investigator; PIQ = Principal Investigator Questionnaire.

Figure 3: Subject Disposition for Study 2065-5



* Based on a January 26, 2018 status memo, which represents the last estimates for subject disposition available prior to closure of study enrollment in January 2018. Other data cited in this figure are based on data listings from the abbreviated study report.
BID = twice daily; ER = extended-release; I/E = inclusion/exclusion; LA = long-acting; m = month; UDT = urine drug testing.

As noted in the above figures, the study faced significant enrollment and recruitment challenges. Enrollment of study sites was hampered by staffing issues and changes in clinical practice. Other

sites cited enrollment concerns or could not identify any patients who met entry criteria and were willing to participate in the study. Based on a survey of sites with no prescreening activity, the three primary reasons for the enrollment issues were:

- Because of changes in the opioid landscape, the pool of patients receiving high-dose ER/LA opioids had decreased, which became more acute after the issuance of the CDC guidelines in 2016.
- Patients were afraid that in the current climate of anti-opioid sentiment, they would not have access to opioid pain medications after they completed the trial should they need them. Some patients were told by their practitioners not to come back if they needed opioid medications after participating in the trial.
- Patients were afraid of experiencing withdrawal symptoms or worsening pain if they were randomized to the placebo arm of the study; even those individuals classified as Suboptimal Responders stated that they would prefer to live with what relief they were getting from their medications rather than with no opioid medication at all.

OPC and FDA attempted to address these issues with protocol amendments, but site recruitment and subject enrollment never sufficiently increased. There were also significant delays in site start-up and vendor-related issues, including drug supply, packaging, and contract negotiations.

In January 2018, OPC and FDA, agreed to terminate the study due to the inability to recruit a sufficient number of subjects over an acceptable period of time

On January 8, 2019, an abbreviated Study 2065-5 clinical study report was submitted to FDA (ClinicalTrials.Gov 2065-5 Posting: https://clinicaltrials.gov/ct2/show/NCT02741076).

3.2. Evolution in Design of the 3033-11 Protocol

The design of the 3033-11 protocol incorporates lessons learned from the initiation and early termination of Study 2065-5 and ongoing efforts to develop an approach that meets the PMR and attempts to address challenges resulting from changes in the opioid treatment landscape.

In January 2018, the same month Study 2065-5 was terminated, OPC study leads engaged with FDA to discuss changes to the trial design to address PMR 3033-11 and the recruitment/retention challenges experienced with the previous design.

In May 2018, OPC submitted a protocol synopsis to FDA for Study 3033-11, a new trial to address the PMR, along with written responses to FDA's questions.

In June 2018, OPC submitted a full protocol.

In September 2018, FDA and OPC met to discuss the Agency's significant concerns with the proposed protocol design, including that it would not address the PMR. FDA's concerns included the proposed titration schedule, evaluations for OIH, the rationale for the statistical power calculation and sample size, dropout rates, and overall design.

In May 2019, OPC provided FDA with a protocol synopsis for a revised trial design based on a two-arm open-label study and a rationale for key study design elements. As required by the

PMR, the trial was designed to address the primary objective of measuring the incidence of OIH, with secondary objectives to address the long-term efficacy of ER/LA opioids.

The May 2019 synopsis outlined a multicenter, prospective, randomized, controlled, parallel-group, open-label clinical trial to evaluate the incidence of OIH, with a randomized, controlled extension to evaluate efficacy. Subjects were eligible for the study if they had an eligible chronic pain condition (duration ≥ 12 months), received any SAO therapy (taken ≥ 2 times per day, average ≥ 6 days per week, ≤ 40 MME daily dose) for ≥ 3 consecutive months in the 12 months prior to Screening, and experienced an inadequate analgesic response.

After a 2-week Baseline Period, subjects were to be randomized (1:1) to a low-dose SAO arm (≤ 60 MME daily dose, PRN) or a titrated-dose ER opioid arm for a Dose Stabilization Period of up to 6 weeks. Subjects were to receive either hydrocodone or oxycodone per an algorithm provided to the clinical site investigator. In the SAO arm, the total daily dose of SAO medication was not to exceed 60 MME; in the ER opioid arm, subjects were to be allowed to titrate their dose to achieve efficacy using a titration structure resembling clinical practice. After Dose Stabilization, subjects who achieved an adequate analgesic response were to enter a 48-week Maintenance Period. At the end of the study, subjects were to be transitioned to the care of a physician or tapered off the study drug over a 4-week Follow-up Period.

In October 2019, based on FDA feedback (FDA Responses to Study 3033-11 Protocol Synopsis Questions, dated July 19, 2019), the design was modified to a double-blind, parallel-group design with similar eligibility criteria as the May 2019 synopsis. In this synopsis, after a Baseline Period during which subjects were to be tapered off all opioids and undergo baseline assessments, subjects were to be randomized (1:1) to receive titrated-dose BID ER opioid or BID placebo (matching the ER opioids) for a Dose Responsiveness Period of up to 8 weeks. Subjects could also receive open-label, low-dose PRN SAO (≤ 40 MME daily dose).

Like the previous design, subjects were to receive either hydrocodone or oxycodone. In both arms, BID doses were to be titrated to achieve efficacy, using a titration structure that resembles clinical practice. Investigators were to be provided with guidance for titrating the blinded BID and open-label SAO doses. After the Dose Responsiveness Period, subjects who achieved an adequate analgesic response were to enter a 48-week Continued Treatment Period (i.e., maintenance phase), followed by a 4-week Follow-up Period.

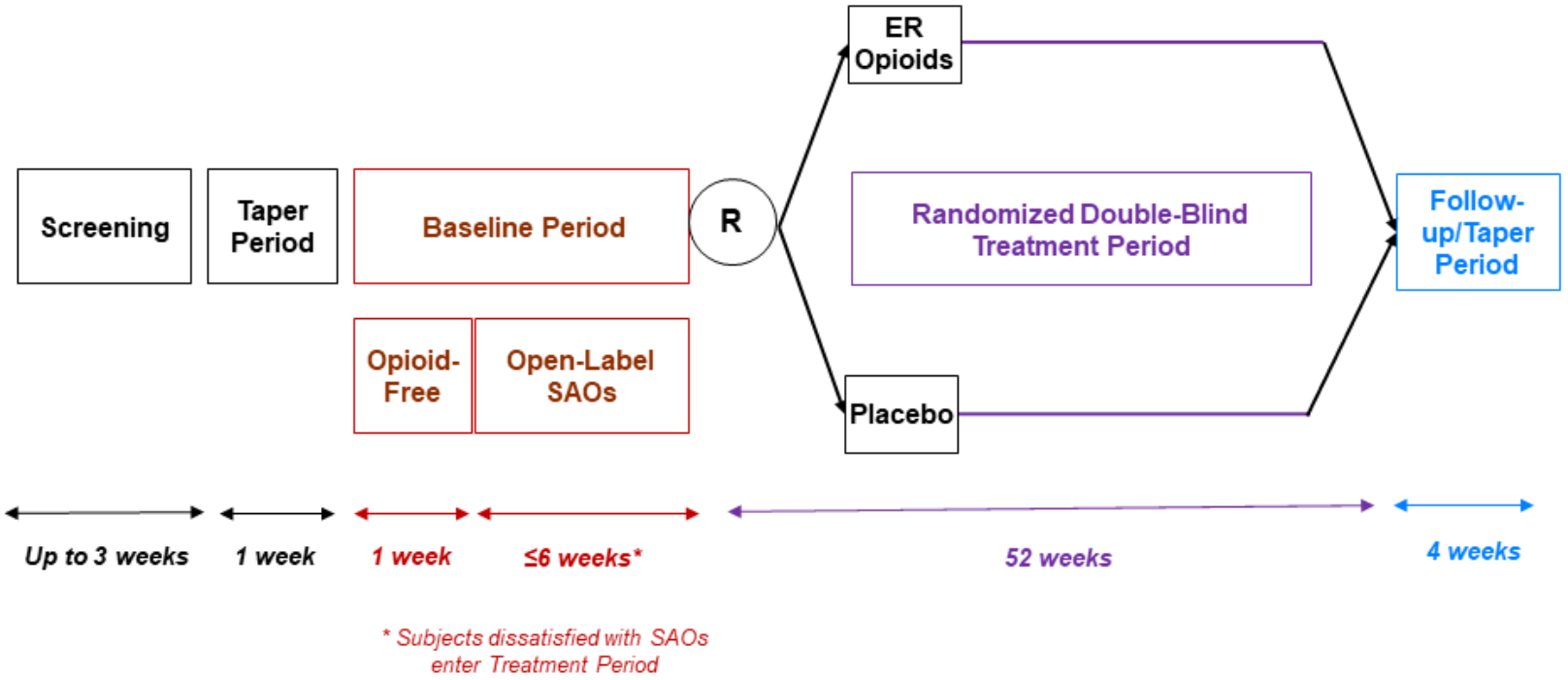
In November 2019, during a follow-up TC, FDA indicated that while it was still interested in evaluating the risks of OIH, its primary interest had shifted to assessing the long-term efficacy of ER/LA opioids and the characteristics of patient populations that would benefit from opioid treatment to help prescribers determine whether long-term opioid use is appropriate for a prospective patient.

In January 2020, OPC submitted a revised draft full protocol addressing the change in the primary objective. The protocol proposed a 12-month, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial to evaluate the long-term efficacy of titrated doses of ER opioids, in the presence of rescue medications, in subjects with CNCP (Figure 4). The protocol also included an exploratory evaluation of OIH.

In this design, subjects were to participate in a 1-week Taper Period, during which they would be tapered off all opioids (subjects were to be on relatively low doses of SAOs at study entry, up to

40 MME/day). Following taper, subjects were to enter an open-label Baseline Period with a 1-week opioid-free period and up to 6 weeks of treatment with SAOs (up to 40 MME per day), administered PRN. Subjects who remained dissatisfied with SAOs (Worst PI score ≥ 5 to ≤ 9) and who were considered appropriate candidates for ER opioid treatment according to the clinical judgment of the investigator (informed by the use of the Pain Profile Questionnaire [PPQ]), were to be eligible for randomization into the Treatment Period. Following the Baseline Period, eligible subjects were to be randomized (1:1) to receive a titrated-dose BID ER opioid (either oxycodone ER or hydrocodone ER) or BID placebo (matching the respective ER opioid) for a 52-week Treatment Period. BID doses were to be titrated to achieve efficacy and preserve tolerability, using a titration structure that resembled clinical practice. The dose levels of ER opioids or matching placebos could be increased in 10 mg increments up to 320 mg/day as indicated by a mean past 7-day Worst PI score ≥ 5 and based on the judgment of the clinical site investigator. During the Treatment Period, subjects could also receive SAOs PRN (≤ 40 MME daily dose) and other rescue medications (i.e., celecoxib, naproxen). At the end of the study, subjects were to transition to the care of a physician for continuation of their stable opioid doses, or they were to be tapered off study medication.

Figure 4: Overview of Previously Considered 3033-11 Trial Design from January 2020



ER = extended-release; R = randomization; SAO = short-acting opioid.

In April 2020, FDA expressed concern with the parallel-group design and, among other comments, recommended the use of an EERW design. FDA commented as follows:

> *After careful review, we believe it is unlikely that the protocol dated January 23, 2020 will successfully address the scientific questions under current consideration, namely the risk of hyperalgesia in long-term users of opioids and whether there is efficacy of chronic opioid therapy over a period of one year.*

(Comments for OPC Protocol 3033-11 Submitted January 2020_final, dated April 14, 2020).

In May 2020, following several rounds of written communications and TCs, OPC and FDA agreed to use an EERW design for the 3033-11 trial that would include a 42-week Open-Label Phase and a 10-week Double-Blind Phase.

In October 2020, OPC submitted a revised protocol synopsis to FDA. The October 2020 synopsis included the proposed EERW design, i.e., a 12-month multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the persistence of analgesic efficacy and tolerability of ER opioids in the Double-Blind Phase in patients with CNCP who demonstrated initial benefit and tolerability of ER opioids during the Open-Label Treatment Phase. The study was also to include an evaluation of OIH.

The overall design and methodology in the October 2020 synopsis were similar to those proposed in the current draft protocol (dated March 1, 2022), described in more detail in Section 4. However, the October 2020 synopsis included two proposed study drugs, oxycodone ER and hydrocodone ER. This was later amended to one study drug (oxycodone ER) for several reasons, including that the proposed trial was not designed to provide an analysis of two study arms separately vs. placebo, to reduce the required sample size and enrollment timeline given the potential recruitment and retention challenges with this trial, and to include an ER study drug that had been formulated with properties intended to deter abuse.

Throughout 2021, OPC and FDA continued to discuss the trial design by reviewing protocol synopses, TCs, and written communications. The specific interactions between FDA and OPC are detailed in Appendix B (Section 9.2).

In May 2021, FDA requested that the trial include morphine sulfate ER as it "*is considered the prototype opioid, is a pure-mu agonist (oxycodone has activity at kappa), and morphine ER is more widely prescribed than oxycodone ER*" (FDA Information Request, 18-May-2021). FDA also requested a rationale for using oxycodone as a single representative opioid to be used in the trial. After receipt of OPC's rationale, although FDA continued to state its preference for including two study drugs, it reiterated that morphine, not oxycodone, should be included in the study if feasibility concerns precluded the use of two opioids (FDA email, sent on 12-Aug-2021). Given the concerns with using the two study drugs outlined above, the study drug was amended to morphine sulfate ER. There were also changes to eligibility criteria, restrictions and concomitant medications, continuation of care, and other methodological issues, as outlined in Section 4.

In March 2022, OPC submitted the current draft full protocol for 3033-11.

In June 2022, FDA informed OPC of its intent to hold a public Advisory Committee meeting on the 3033-11 protocol.

4. SUMMARY OF CURRENT DRAFT 3033-11 PROTOCOL DESIGN

The draft protocol and its appendices (version 0.8, dated March 1, 2022) are attached in Appendix D (Section 9.4).

4.1. Trial 3033-11 Objectives

The primary and secondary objectives are summarized below, and the endpoints corresponding to these objectives are detailed in Section 4.5.

4.1.1. Primary Objective

The primary objective of the trial is:

- To evaluate the persistence of analgesic efficacy of an ER opioid in the Double-Blind Phase in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase.

The primary hypothesis of the trial is that there are patients with CNCP who will achieve clinically meaningful, long-term pain relief in a well-tolerated manner with morphine sulfate ER during the 12 months of this trial.

4.1.2. Secondary Objectives

The secondary objectives of the trial are:

- To explore the incidences of OIH and opioid tolerance.
- To evaluate changes in pain sensitivity over time.
- To identify potential predictors of the opioid analgesic response and non-response.
- To evaluate changes in physical function and levels of anxiety and depression.
- To evaluate the safety of titrated doses of an ER opioid.
- To evaluate all endpoints in patients who are titrated to a high dose of ER opioid.

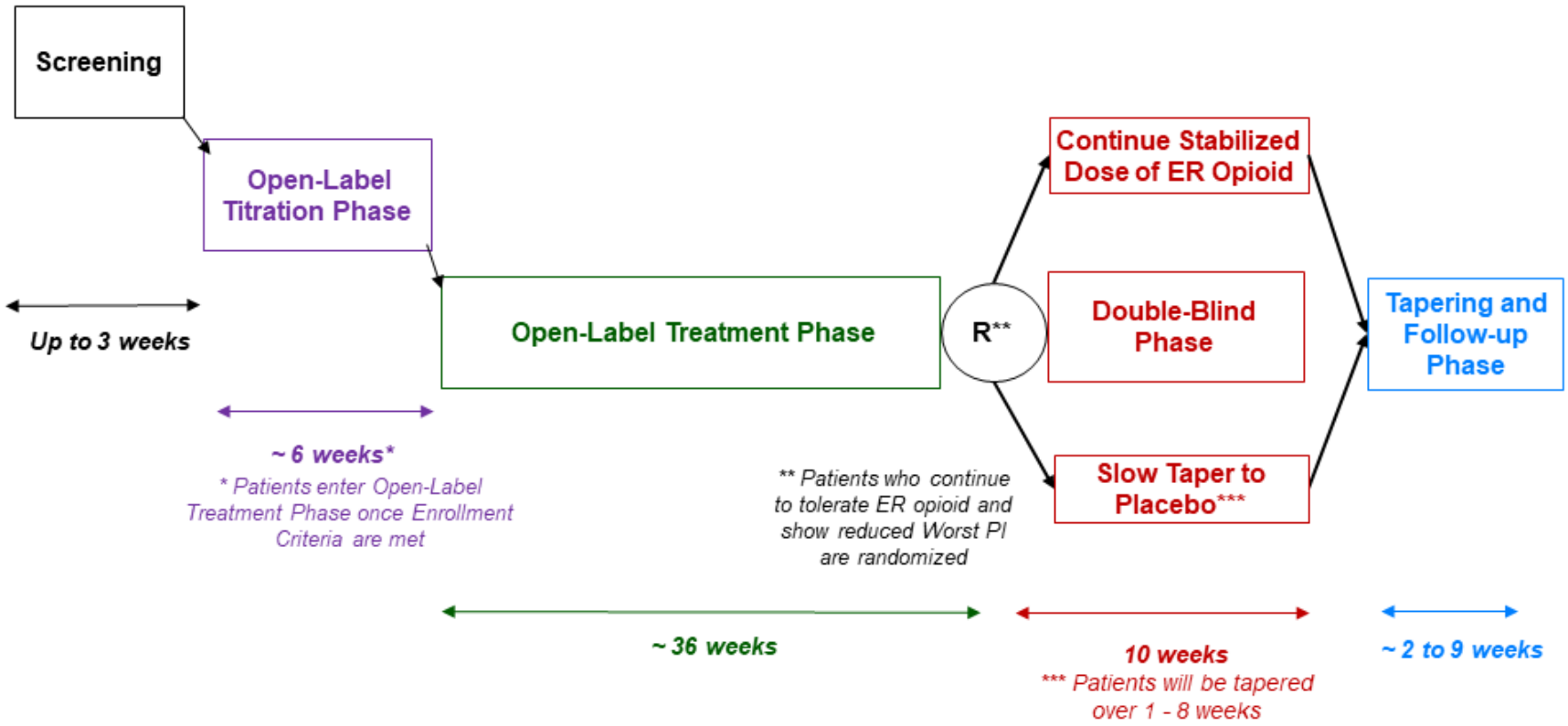
4.2. Summary of the Overall Trial Design

The planned trial will be a 12-month, multicenter, randomized, placebo-controlled, double-blind clinical trial with an EERW design to evaluate the persistence of analgesic efficacy and tolerability of a representative ER opioid (morphine sulfate ER) in the Double-Blind Phase in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase. The trial will also include an evaluation for OIH.

The trial will include five phases: A Screening Phase (up to 3 weeks), an Open-Label Titration Phase (~ 6 weeks), an Open-Label Treatment Phase (~ 36 weeks), a Double-Blind Phase

(10 weeks), and a Tapering and Follow-up Phase (~ 2 to 9 weeks). An overview of the trial design is provided in Figure 5.

Figure 5: Overview of Current 3033-11 Trial Design



ER = extended-release; PI = pain intensity; R = randomization.
Notes: The figure is not shown to scale.
The durations of the Open-Label Titration and Treatment Phases may vary; however, the total duration of the 2 phases will be 42 weeks.
All patients (including those who discontinue the trial early) will have their medications tapered over the course of 1 to 8 weeks at the end of their active treatments. This taper will occur in the Tapering and Follow-up Phase, except for patients randomized to placebo. Patients randomized to placebo will begin tapering during the Double-Blind Phase and will take placebo in a double-blinded manner during the tapering period of the Tapering and Follow-up Phase to maintain the blind (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case tapering will be completed in the Tapering and Follow-up Phase). Each patient will be asked to attend a final follow-up visit within 5 days of their last dose of ER trial medication.

At Screening, patients will be asked to provide informed consent and will then be evaluated for entry into the trial. To be eligible at Screening, each patient must report a Worst PI score over the prior 7 days of ≥ 5 and ≤ 9 on a 0 to 10 numerical rating scale (NRS) and must express dissatisfaction with SAO therapy, as determined by agreement between the clinician (i.e., research site investigator) and patient and informed by the use of the patient-reported PPQ.

Following confirmation of eligibility during the Screening Phase, patients will enter the ~ 6-week Open-Label Titration Phase, during which they will attend weekly visits. The total daily dose of morphine sulfate ER will be titrated to achieve efficacy as tolerated, using a titration structure that resembles clinical practice. The dose levels of morphine sulfate ER will be subject to increase when the mean Worst PI score is ≥ 5 in the prior 7 days; any increase will also be based on the judgment of the investigator. Rescue medications will not be permitted during the Open-Label Titration Phase.

Patients who meet enrollment criteria during the Open-Label Titration Phase will enter the ~ 36-week Open-Label Treatment Phase. The duration of the Open-Label Titration Phase will be flexible, such that patients who meet enrollment criteria may begin the Open-Label Treatment Phase prior to completing the full 6 weeks of titration or may remain in the Open-Label Titration Phase for longer if needed. The duration of the Open-Label Treatment Phase will be adapted for these patients, such that the total duration of the two phases (Open-Label Titration and Treatment) will be 42 weeks.

During the Open-Label Treatment Phase, patients will return to the clinic every 4 weeks for trial assessments, with remote contact in-between visits. Morphine sulfate ER doses may be adjusted when necessary (up to 240 mg/day), but doses must be stable for the 7 days prior to randomization. During the Open-Label Treatment Phase, patients may also receive an SAO and/or APAP PRN up to the maximum permitted doses.

Consistent with current clinical practice, patients may be offered the opportunity to taper off morphine sulfate ER during the Open-label Titration or Open-Label Treatment Phases (see Section 4.6.2). Patients who choose to be tapered off morphine sulfate ER prior to randomization in the Double-Blind Phase will be asked to complete the end-of-trial assessments planned for the Week 52 visit and then begin their taper in an unblinded fashion in the Tapering and Follow-up Phase.

After the ~ 36-week Open-Label Treatment Phase, patients who meet randomization criteria will be randomized (1:1) into the 10-week Double-Blind Phase to continue their current doses of morphine sulfate ER or to undergo a slow taper to placebo. To reduce confounding of the primary endpoint (time to loss of efficacy), randomization will be stratified by stable dose of morphine sulfate ER prior to randomization, since this will affect the required duration of tapering for those in the placebo group (i.e., eight strata of placebo patients who are opioid-free by the end of Week 1, 2, 3, 4, 5, 6, 7, or 8 or equivalent active ER doses in the ER opioid treatment group).

Patients in the placebo group will be tapered gradually in a double-blinded manner over the course of 1 to 8 weeks to minimize the likelihood of opioid withdrawal and unblinding. Note that a 1-week taper will be used only for patients receiving the lowest dosage strength of morphine sulfate ER (15 mg BID). The 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. Patients will attend clinic visits every 2 weeks during the Double-Blind Phase with remote contact every week when a visit is not scheduled. There will be no dosage adjustments during the Double-Blind Phase; however, SAO and APAP rescue medication may be administered at the discretion of the investigator.

During the Open-Label and Double-Blind Phases, PI scores (Average and Worst) in the prior 24 hours will be captured once daily before bedtime. Patients will attend monthly or biweekly visits during which other pain and quality of life measures will be assessed (Brief Pain Inventory-Short Form [BPI-SF] and EuroQol, 5-dimension, 5-level descriptive system [EQ-5D-5L]), as well as a validated assessment of physical function (Patient-Reported Outcomes Measurement Information System [PROMIS®] Item Bank v2.0 – Physical Function – Short Form 8b [PROMIS PF-SF8b]) that can be used across indications. Patient Global Impression of Change (PGIC) will be assessed at the end of each treatment phase.

Standard safety measures will be included to assess the long-term safety of ER opioids relative to placebo, including AEs, clinical laboratory tests, electrocardiogram (ECG), physical examinations, vital signs, concomitant medications, and Columbia-Suicide Severity Rating Scale (C-SSRS). Additional measures will include assessments of emotional function, sleep, sexual and endocrine function, and abuse or misuse, including the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), abuse-related AEs of special interest (AESIs), and review of urine drug testing (UDT) results.

QST assessments will be performed to evaluate the potential for hyperalgesia in a subset of patients (OIH Population) from selected trial sites. QST will be performed twice during Screening (to obtain between-session variability data), twice during the Open-Label Treatment Phase (Week 10 and Week 26), once prior to randomization into the Double-Blind Phase (Week 42), and once at the end of the Double-Blind Phase (Week 52).

Measures and endpoints, including those related to efficacy, OIH, and safety, are discussed further in Section 4.5.

Patients will enter the Tapering and Follow-up Phase at the end of the Double-Blind Phase (Week 52) or early discontinuation. ER trial medication will be tapered down over the course of 1 to 8 weeks, depending on the ER trial medication dose. Patients will be asked to attend a final safety follow-up visit within 5 days of the last dose of ER trial medication so that the Tapering and Follow-up Phase will comprise ~ 2 to 9 weeks. Reasonable efforts will be made to provide continuity of patient care, as outlined in Section 4.6.

4.3. Summary of Trial Population

4.3.1. Main Criteria for Inclusion

The proposed trial population includes generally healthy adult male and female patients with CNCP without clinically significant medical conditions or contraindications to ER/LA opioid use that would interfere with the scientific integrity of the trial or present a safety risk to the patient.

Patients must have a clinical diagnosis of CNCP, including CLBP, OA of the hip or knee, DPN, painful peripheral neuropathy (PPN), or post-cancer-treatment–related pain (i.e.,

post-thoracotomy pain, radiation plexopathy, post-chemotherapy pain) for at least 12 months that occurs daily.

Patients must have a Worst PI score of ≥ 5 and ≤ 9 over the 7 days prior to Screening for the index pain condition/site(s) and must be taking daily SAO therapy ≥ 2 times per day for ≥ 5 days per week for any ≥ 3 consecutive months in the 6 months prior to Screening, with an inadequate analgesic response to SAO therapy, and total daily dose ≥ 30 MME. Patients not currently on SAOs are considered eligible if they would have met the above criteria had they not discontinued SAO use within the prior 6 months due to tolerability issues, lack of efficacy, or loss of access. In addition to Worst PI scores, inadequate analgesic response is defined as dissatisfaction with their pain control while taking SAOs, as determined by agreement between the investigator and patient and informed by responses on the PPQ.

In addition, patients must show prior failure of non-opioid pharmacologic and non-pharmacologic treatments, defined as having not responded to, or having contraindications to, at least two non-pharmacologic and two pharmacologic treatments for pain for the index pain condition(s), according to the investigator's judgment, following review of the patient's Pain Treatment Response Questionnaire (PTRQ) responses, as well as external documentation, if available. Patients must also be considered an appropriate candidate for ER opioid therapy, according to the investigator's clinical judgment.

Additional inclusion/exclusion criteria and a brief rationale for their use are outlined in Appendix C (Section 9.3).

4.3.2. Summary of Criteria for Entry into the Open-Label Treatment Phase and for Randomization into the Double-Blind Phase

In addition to meeting the inclusion/exclusion criteria, patients must meet the following criteria for clinical stability during the Open-Label Titration Phase for enrollment into the Open-Label Treatment Phase:

- ≥ 30% reduction in past 7-day Worst PI compared to Screening, AND
- The patient and investigator agree that the patient has had meaningful improvement, guided by the PPQ, AND
- Morphine sulfate ER was tolerated, per patient and investigator judgment.

Patients must also be considered clinically stable and on a stable dose of morphine sulfate ER for at least 7 days to be randomized into the Double-Blind Phase.

These randomization criteria correspond to the patient population defined in the primary trial objective (i.e., "in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase").

In addition to inclusion/exclusion and enrollment/randomization criteria, patients will be asked to abide by certain restrictions throughout the trial, including abstinence from consuming alcohol and illicit drugs (including, for the purposes of this trial, cannabis) and non-medical use of therapeutic drugs, as well as abstinence from taking prohibited medications (barbiturates, monoamine oxidase inhibitors, opioid antagonists, non-trial investigational drugs, non-trial ER/LA opioid analgesics, opioid agonist-antagonists, central-acting alpha-agonists, medication-

assisted drug therapy for substance use disorder, and kratom). Other concomitant medications can be used with appropriate cautionary steps, including other central nervous system (CNS) depressants, serotonergic drugs, p-glycoprotein inhibitors/inducers, diuretics, and anticholinergic drugs. Patients will also be asked to avoid engaging in hazardous activities until they are sure that the medication is not impairing their judgment or performance.

4.4. Summary of the Clinical Trial Medications

4.4.1. Treatment Scheme

The trial will include an Open-Label Titration Phase, during which oral doses of morphine sulfate ER will be titrated for ~ 6 weeks. Patients who are not currently on SAOs at the time of trial entry will be initiated at morphine sulfate ER 30 mg per day (i.e., the lowest available dosage strength of 15 mg BID every 12 hours [q12h]). Patients who are currently receiving oral morphine IR formulations may be converted to morphine sulfate ER tablets by administering one-half of the patient's 24-hour requirement on a q12h schedule. For patients who are currently using other SAOs, the medication will be discontinued prior to initiating ER morphine therapy. There are no established conversion ratios for conversion from other opioids to morphine sulfate ER tablets; thus, these patients will be initiated using 15 mg tablets, administered orally q12h.

Single doses > 60 mg or total daily doses > 120 mg are only for use in patients for whom opioid tolerance has been established. Patients are considered opioid tolerant if they have taken at least 60 MME per day for ≥ 1 week.

During the Open-Label Treatment Phase, open-label, oral titrated doses of morphine sulfate ER will be administered BID to a maximum dose of 240 mg/day for ~ 36 weeks.

During both the Open-Label Titration and Open-Label Treatment Phases, the dose levels of morphine sulfate ER will be subject to increase as indicated by the mean Worst PI score in the prior 7 days (if ≥ 5) and based on the judgment of the investigator. The dose may be increased in 15 mg BID increments, up to a maximum total daily dose of 240 mg.

ER trial medication doses must be stable for 7 days prior to randomization.

Double-blind fixed oral doses of morphine sulfate ER (i.e., stabilized dose at the end of the Open-Label Treatment Phase) will be administered BID for 10 weeks in patients randomized to continue active ER opioid. Patients randomized to the placebo group will receive double-blind tapering doses of morphine sulfate ER for 1 to 8 weeks and placebo for 2 to 9 weeks, respectively, administered BID. No dosage adjustments will be permitted during the Double-Blind Phase.

4.4.2. Rescue Medications and Other Permitted Medications/Therapy

No rescue medications will be allowed during the Open-Label Titration Phase. During the Open-Label Treatment and Double-Blind Phases, daily doses of up to 30 mg IR morphine (no more than two 15 mg IR tablets per day) and APAP 3000 mg (no more than six 500 mg tablets per day) will be permitted PRN. To avoid confounding the results of the primary efficacy endpoint, additional rescue medications will not be utilized during the trial. Patients will be instructed on the proper use of rescue medications (i.e., only when the pain is worsening).

As concomitant therapies are often used in clinical practice, patients will be permitted to continue with pre-existing pharmacologic therapies, such as non-steroidal anti-inflammatory drugs, gabapentin, antidepressants, etc., provided medications remain at stable doses/regimens 1 month prior to and throughout the Double-Blind Phase of the trial. If there is any question on the definition of stability or changes in stability, the medical monitor can be consulted on a case-by-case basis. Patients using APAP will be instructed not to exceed the daily limits specified above, including rescue medications (i.e., no more than 3000 mg per day in total). In addition to pre-existing pharmacologic therapies, patients may continue using non-pharmacologic therapies during the trial.

As dosage adjustments of morphine sulfate ER are permitted during the Open-Label Treatment Phase, initiation or discontinuation of new pain therapies is permitted during this phase (i.e., doses of morphine sulfate ER may be adjusted during this phase to accommodate changes in concomitant therapies); however, any such modifications should be avoided 1 month prior to and for the duration of the Double-Blind Phase. Patients will be asked to disclose if they have initiated any new analgesic therapies, including prescription, over-the-counter, or non-pharmacologic therapies. This information will be recorded and used in the statistical analysis of trial outcomes.

On a case-by-case basis, the investigator is permitted to allow the use of non-analgesic concomitant medications as long as the medications are not restricted, and the investigator determines that the medication will not affect the patient's safety or trial integrity.

Intranasal naloxone, and instructions for its use, will be provided to all patients at the start of the Open-Label Titration Phase; naloxone will be used if a suspected overdose occurs during the trial.

4.5. Summary of Trial Endpoints

4.5.1. Efficacy and Safety Endpoints

The primary endpoint of this trial is the time to loss of efficacy (during the Double-Blind Phase), where the loss of efficacy is defined as:

- ≥ 30% increase in the past 7-day moving average of the daily Worst PI compared to the 7 days prior to randomization and past 7-day moving average of the daily Worst PI ≥ 5, OR;
- The patient initiates new pharmacologic therapy for the index chronic pain condition, OR;
- The trial drug is discontinued due to a lack of efficacy.

Secondary efficacy endpoints include time to treatment failure (loss of efficacy or discontinuation due to tolerability), time to loss of efficacy defined using Average PI, responder rates by week, changed in mean past 7-day Worst PI and Average PI by week, change in physical function, as measured by PROMIS® PF-SF-8b, as well as change in BPI-SF, PGIC, and EQ-5D-5L scores.

Exploratory efficacy endpoints include the use of SAO rescue medication and initiation of new analgesic therapy (pharmacologic and non-pharmacologic) for index chronic pain condition(s).

As per FDA's request to evaluate the characteristics of patient populations that would benefit from opioid analgesic therapy, potential predictors of opioid response and non-response will be explored, including demographics, chronic overlapping pain conditions, fibromyalgianess, personal/family history of mental illness and substance use disorders, anxiety/depression, pain catastrophizing, pain profile, physical function, AEs, QST, sleep/insomnia, and COWS results. Finally, patient responses to the unblinding questionnaire will be assessed as an exploratory endpoint.

The general safety of ER opioid therapy will be assessed by evaluating spontaneously reported AEs, serious AEs (SAEs), standard clinical laboratory test results, vital signs measurements, physical examination findings, ECG findings, and use of concomitant medications.

Safety assessments related to the evaluation of potential abuse, misuse, dependence, or withdrawal include assessment of AESIs, as well as the POMAQ, UDT results for illicit drugs or non-prescribed controlled substances, the COWS, and SOWS.

Endocrine and sexual function will be evaluated through a series of clinical laboratory tests (i.e., testosterone, luteinizing hormone, follicle-stimulating hormone, estradiol, insulin growth factor 1, cortisol, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, and thyroid-stimulating hormone), as well as the Arizona Sexual Experience Scale.

Other endpoints include changes in anxiety and depression (Hospital Anxiety and Depression Scale), sleep (Insomnia Severity Index), and suicidality and suicidal ideation (Columbia-Suicide Severity Rating Scale [C-SSRS]).

All endpoints listed above will also be assessed in a subgroup analysis of patients who achieve a high dose of morphine sulfate ER (≥ 90 mg per day).

4.5.2. Assessment for OIH and Tolerance

Secondary OIH endpoints include assessment for the incidence of patients who develop protocol-defined OIH during the entire trial and during the Open-Label Treatment Phase, as assessed by Worst PI and QST assessments. Changes in Worst PI and QST parameters will also be evaluated over time during the Open-Label Treatment Phase and by treatment group during the Double-Blind Phase, and pain spread will be assessed using the Widespread Pain Index (WPI) subscale of the Fibromyalgianess Scale. A cluster analysis of putative components of an OIH syndrome, if observed, will be evaluated as an exploratory OIH endpoint.

Opioid tolerance will similarly be assessed over the duration of the trial and during the Open-Label Treatment Phase using Worst PI and QST parameters.

Measured QST parameters intended to assess changes in pain sensitivity and potential for hyperalgesia will include heat pain threshold (HPTHR), half-maximum heat pain (HP50%), heat pain tolerance (HPTOL), and sustained heat pain ratings. Additional parameters will also be calculated, including heat pain differential (HPDIF; calculated as HPTOL-HPTHR), heat pain differential 50% (HPDIF-50%; calculated as HP50%-HPTHR), and heat pain summation (equivalent to the area under the curve depicting pain ratings over time).

The QST sessions will consist of a familiarization/training phase, followed by an assessment phase. Patients will be trained and tested for satisfactory QST performance to qualify for inclusion into the OIH Population. Between-session variability data will be obtained from two assessments performed at Screening to allow the construction of a distribution-based criterion to infer the presence or absence of OIH (e.g., value outside the 95% confidence interval [CI]). A standardized language will be used for instructing patients and performing QST assessments. A pilot or interim assessment will be conducted after testing 20 patients to evaluate the QST algorithm's feasibility and utility.

4.6. Summary of End-of-Treatment and End-of-Trial Considerations

All patients who receive at least one dose of ER trial mediation will enter the Tapering and Follow-up Phase, either at the end of the Double-Blind Phase (Week 52) or at early discontinuation. Patients will attend weekly visits (± 3 days) during the tapering period of this phase. The number of visits will depend on the duration of the individual patient's tapering period. All patients will be asked to attend a final safety follow-up visit within 5 days of receiving the last dose of ER trial medication so that the Tapering and Follow-up Phase will comprise approximately 2 to 9 weeks. For patients who are randomized to active treatment in the Double-Blind Phase, ER trial medications will be tapered in the Tapering and Follow-up Phase as described in Section 4.6.2.

4.6.1. Continuity of Care

Reasonable efforts will be made to provide continuity of care for patients. At Screening, patients will be asked to provide the investigator with contact information for their primary care or other qualified health care practitioner (HCP) involved in their pain management. The consenting process will ask that patients provide authorization to release information to the HCP regarding their participation in the trial. The Clinical Research Organization or designee will verify all HCP licenses/Drug Enforcement Agency registrations. The investigator will communicate with the HCP, using Institutional Review Board-approved letter templates, at the time of trial entry and end-of-trial. At trial entry, HCPs will be provided with the investigator's contact information to communicate concerns to the research site.

A patient profile document will be provided directly to a patient's designated HCP at end-of-trial. It will include sufficient information to enable HCPs to appropriately manage the patient's pain. Unblinding information about the patient's treatment assignment will be provided to HCPs, either through direct, one-time access to the interactive voice response system or interactive web response system or through an unblinded 3rd-party designee. During the consenting process, patients will be asked to agree that they will not communicate their treatment assignment back to the investigator or any research site personnel should they become aware of the assignment (through their HCP) after their last trial visit.

For patients who do not have an appropriately licensed HCP, the investigator will provide a referral to locally available medical and social services at the time of trial exit.

4.6.2. Tapering Methods

The proposed tapering plan is provided in Appendix 16.1 of the full protocol (Appendix D, Section 9.4). For patients who discontinue in the Open-label Titration or Open-Label Treatment Phases and for those patients who are randomized to active treatment in the Double-Blind Phase, ER trial medications will be tapered slowly to 0 mg over the course of 1 to 8 weeks in the Tapering and Follow-up Phase, depending on the dose of ER medication at the time of discontinuation/completion. The 1-week taper will only be used for patients receiving the lowest dosage strength of morphine sulfate ER (15 mg BID). These patients will receive a week of asymmetric dosing (i.e., 15 mg once in the evening [QHS]) prior to discontinuing. Patients who discontinue during the Open-Label Titration or Open-Label Treatment Phases will have their ER medications tapered in an unblinded manner.

Patients randomized to active treatment in the Double-Blind Phase will have their ER medications tapered in a double-blinded manner. Patients randomized to placebo will begin tapering following randomization in the Double-Blind Phase and will be tapered to 0 mg in a double-blinded manner over the course of 1 to 8 weeks using the same tapering plan proposed for the Tapering and Follow-up Phase. These patients randomized to placebo will continue to take placebo in a double-blinded manner during the tapering period of the Tapering and Follow-up Phase to maintain the blind (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case the taper will be completed during the end-of-trial procedures).

4.7. Summary of Statistical Considerations

The planned sample size of 200 patients per group is targeted to provide 90% power to detect a difference between treatment groups in time to loss of efficacy. A review of prior EERW studies revealed that very few studies allowed the level of rescue medication planned in the current protocol. Because this level is a key component of determining loss of efficacy and encouraging patient retention in the trial, the amount of rescue medication available was determined to be a critical factor for choosing which trial should be used as the basis of the power calculation. A single study was identified that allowed up to 30 mg oxycodone IR rescue per day (45 mg MME/day) (Wen et al., 2015). The amount available to each patient was determined by the patient's double-blind daily dose level of hydrocodone ER (referred to as HYD) (or matching placebo); this was 10 mg for patients receiving HYD 20 or 40 mg, 15 mg for patients receiving HYD 60 mg, 20 mg for patients receiving HYD 80 mg, and 30 mg for patients receiving HYD 120 mg. While neither the double-blind dose levels nor the algorithm for determining the dose of SAO rescue medication is a perfect match to the current protocol, this study was determined to be the best proxy.

A post-hoc analysis revealed a 15% rate of discontinuation for "lack of therapeutic effect" in the placebo group and a 5% rate in the active group with a 0.346 hazard ratio ($p = 0.0003$). These assumptions yield a sample size of 187 patients per group for 90% power. Adding an assumption of 17% discontinuation due to other reasons for the active group and a 13% dropout for the placebo group yields 212 patients per group. However, the software applies this assessment uniformly of the period and may overstate the early discontinuation rate, giving a more conservative sample size estimate. The planned interim analysis to re-estimate sample size will

identify if an increase is necessary due to deviations from these assumptions. A large oxycodone ER registry study with multi-year follow-up yielded 60% retention over the first year (Portenoy et al., 2007). Applied to the current trial, this retention rate would require approximately 666 patients enrolled and successfully titrated into the Open-Label Treatment Phase to randomize 400 patients into the Double-Blind Phase. The retention rate will be actively monitored throughout the trial, and enrollment will be adjusted to target the Double-Blind Phase sample size efficiently.

Up to 30 research sites will perform QST and contribute to the OIH Population, with at least 200 patients to be included. Assuming an OIH rate of 5%, the precision of the OIH rate will be ± 2.53% with a sample size of 200 patients and ± 4% with 100 patients. For continuous QST measures, the sample size of 200 patients would be powered at 80% for comparisons between arms, assuming an effect size of approximately 0.4.

For an interim analysis, the population will be divided into two cohorts: the first 50% randomized and those after the first 50% have been randomized. Once all patients in the first 50% have exited the Double-Blind Phase of the trial (either completed or discontinued), a sample size reevaluation will be performed; this will be based on the time to loss of efficacy analysis. The conditional power will be calculated based on the data observed in the first cohort and assuming that the difference in arms in the second cohort will be identical to the observed difference in the first cohort. The sample size may be increased by up to 50% of the originally planned sample size (200 additional patients) with the goal of maintaining 90% power.

This analysis will be performed by an unblinded independent interim data monitoring committee; the only information they will convey to the blinded trial staff is a recommended increase in sample size. The recommendation will be the smallest increase in blocks of 10 patients that will raise the conditional power over 90% if the interim assessment should reveal that the power is below 90%. If the conditional power at the interim is < 30% or > 90%, the recommendation will be to maintain the current sample size.

The primary efficacy endpoint of time to loss of efficacy will be analyzed using the Kaplan-Meier methodology with stratification for the titrated dose levels. Quantiles for 25%, median, and 75% will be presented, as well as 95% CIs, if estimable. The treatment arms will be compared using a stratified log-rank test against the hypothesis that there is no difference in the time to loss of efficacy in the trial arms. The titration dose level strata may be pooled among adjacent doses in the case of small counts and/or sparse events in a given strata. Sensitivity analyses will investigate varying the threshold of SAO and APAP rescue medication use to qualify as a loss of efficacy, absolute pain (past 7-day moving average of the daily Worst PI ≥ 5) to qualify as a loss of efficacy, and including additional ambiguous reasons for early discontinuation (such as “other,” “lost to follow-up,” and “unknown,”) as a loss of efficacy.

The opioid response will be defined as ≥ 30% reduction from Screening in Worst PI and an end-of-trial PGIC score of 6 or 7 (better or much better) (or both); opioid non-response will be defined as < 30% reduction in Worst PI or a PGIC score ≤ 5 (or both). For each definition of opioid response, a logistic model will be fit, including effects for treatment arm, the predictor of interest, and an interaction between treatment arm and the predictor of interest. For each definition of opioid response, the odds ratio for the predictor in each treatment arm will be reported, as will the overall odds ratio for the predictor. Predictors to be examined include:

demographics, personal/family history of mental illness and substance use disorders, medical history, including chronic overlapping pain conditions, fibromyalgianess, anxiety/depression, pain catastrophizing, physical function, AEs, QST, and sleep/insomnia.

The OIH incidence for each endpoint will be reported as the number and percentage of patients and associated 95% CI of the percentage. For the Double-Blind Phase, the numbers and percentages will be reported by trial arm, and the differences in percentages will be reported, as well as 95% CIs. The arms will be compared using a difference in proportions Z test; if there are < 5 patients expected in a cell, a Fisher's exact test will be used instead. The primary analysis for rates of OIH will use the following approach for missing and partial data. Patients who discontinue the trial due to loss of efficacy will be treated as satisfying the pain criterion for OIH; each discontinued patient's last available dosing information and QST battery results will then be evaluated to determine whether they represent a case of OIH. All other patients with missing data will be evaluated to decide whether or not they met the OIH criteria at any earlier time point, and they will be counted as such if this occurs; otherwise, these patients will be assumed not to be cases of OIH.

Additionally, the number and proportion of patients missing each component of the OIH outcome, the proportion of patients with complete assessments, and the proportion of patients determined to exhibit OIH among those with complete assessments will be reported. Sensitivity analyses will be performed to test the robustness of the results and statistical assumptions. For patients with missing data who do not have results precluding the presence of OIH, values will be imputed and analyzed via multiple imputation.

5. RATIONALE FOR AND STRENGTHS OF THE CURRENT DRAFT 3033-11 PROTOCOL DESIGN

5.1. Rationale for, and Strengths of, the Overall Design

5.1.1. EERW Design

Enriched enrollment is not a new concept and has been contemplated and discussed in the context of clinical trial design for many decades (Amery and Dony, 1975; Kopec et al., 1993; Leber and Davis, 1998; Temple, 1994; Temple, 2010). Enrichment methods have been in use for many indications, including, but not limited to, Parkinson's disease, erectile dysfunction, spasticity in multiple sclerosis, and bipolar disorder (Moore et al., 2005; Notcutt et al., 2012; Peball et al., 2019; Tsai et al., 2011).

In analgesia clinical trials, EERW is a type of enriched enrollment whereby all randomized patients are required to demonstrate both an appropriate analgesic response and tolerability to the investigational drug. The use of an EERW design is consistent with previous studies of opioids and other analgesic therapies in the treatment of chronic pain (e.g., Binder et al., 2009; Bradford et al., 2017; Cording et al., 2015; Derry et al., 2014; Hale et al., 2015; Huffman et al., 2017; Katz et al., 2015; Rauck et al., 2014; Toth et al., 2012; Wen et al., 2015, and as reviewed in Kopsky et al., 2022; Meske et al., 2018; Moore et al., 2015; Petzke et al., 2020).

This design has been used for many years in chronic pain pivotal efficacy trials and is accepted by FDA as a design for demonstrating the efficacy of analgesic pain medications. The EERW design is also consistent with guidelines for the assessment of chronic pain, including recommendations from IMMPACT – Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (e.g., Dworkin et al., 2010; Dworkin et al., 2012; Edwards et al., 2016; Gewandter et al., 2020). The randomized withdrawal approach is an enrichment strategy that enhances the probability of including "responders" and minimizes early discontinuations due to AEs (Katz, 2009; Lemmens et al., 2006).

The current design includes the same phases used in the approval studies for ER/LA opioids, but the duration and sequence of phases have been modified. The current protocol may more closely resemble clinical practice because, after the Open-Label Titration Phase, it includes 42 weeks of open-label treatment prior to the 10-week randomized withdrawal Double-Blind Phase, for a total of 52 weeks of treatment with an ER opioid. The design is intended to enable the assessment of the persistence of efficacy after 42 weeks of treatment.

One of the initial motivations for employing the randomized withdrawal design was ethical, i.e., to minimize the time that patients spend on ineffective or harmful treatments after randomization, including undue exposure to placebo (Amery and Dony, 1975, Katz, 2009; Katz, 2021). This is particularly relevant given the trial population of patients with moderate-to-severe, continuous chronic pain and the current trial requirement to demonstrate sustained efficacy for up to 12 months. It would be very difficult to maintain patients randomized to placebo over the course of a parallel-group trial. EERW trials also address the issue of patient discontinuation and missing data since premature withdrawal due to treatment failure is informative (Dworkin et al., 2010; Katz, 2021; Katz, 2009), particularly with respect to the time to loss of efficacy primary endpoint proposed for this trial.

EERW studies may have greater sensitivity than alternative study designs, allowing statistical significance to be achieved with fewer patients, as parallel designs include both responders and non-responders in the analysis (Katz, 2009). In addition to statistical implications, measuring the average effect in a parallel-group design ignores individual benefits.

EERW studies concentrate on patients with a useful degree of pain relief and tolerance of AEs (Katz, 2009; Katz, 2021; Moore, 2013). Parallel-group designs may falsely conclude that there is a lack of efficacy when it may exist in a subset of patients for whom there may be a clinical need. That is, the treatment effect in an EERW trial is evaluated in a subset of patients who would be most likely to receive continued treatment of an ER/LA opioid in clinical practice rather than reducing the strength of the effect by incorporating results for patients who would likely be switched to an alternative therapy. For these reasons, EERW designs are thought to be more sensitive for evaluating efficacy in the subset of chronic pain patients who may benefit from opioid therapy, thereby providing information that is more relevant to clinical practice (Katz, 2021).

In addition, CNCP is a long-term condition but may not necessarily show linear progression during the course of a trial, unlike more progressive diseases like Alzheimer's disease. While other factors may influence the experience of pain, patients are more likely to return to baseline when randomized to placebo compared to more progressive diseases, making this type of condition more suitable to evaluate in an EERW design. The relatively short duration of the

Double-Blind Phase may also limit the impacts of confounding factors during the randomized withdrawal period.

Further, in conditions where there exists a relatively large placebo effect, such as pain, an EERW design may have additional advantages over a parallel design. In the context of chronic pain, placebo responses are both variable and appear to be increasing over time (Quessy and Rowbotham, 2008; Tuttle et al., 2015). The increasing placebo response over time may make it difficult to discern a treatment effect in a parallel-group design.

Analgesic clinical trials of opioids can have a large number of nonrandom early discontinuations. The active group generally has more early discontinuations due to AEs, and the placebo group due to lack of efficacy. It is important to minimize missing data in clinical trials by focusing "on two critical elements: (1) careful design and conduct to limit the amount and impact of missing data and (2) analysis that makes full use of information on all randomized participants and is based on careful attention to the assumptions about the nature of the missing data underlying estimates of treatment effects" (National Research Council, 2010). The EERW design utilized in the protocol for Study 3033-11 incorporates these principles by permitting titration of the morphine dose during the 36-week open-label period and using the time to loss of effect outcome during the final 12-week randomized period. Further, premature withdrawal due to treatment failure is informative (Dworkin et al., 2010; Katz, 2009), particularly with respect to the time to loss of efficacy primary endpoint proposed for this trial.

Finally, the trial is expected to provide information on whether pain and hyperalgesia increase, remain stable, or decrease during and after tapering in the Double-Blind Phase following long-term use of morphine sulfate ER in the Open-Label Treatment Phase; this may provide information on whether some patients may continue to use and escalate opioid doses due to OIH rather than continued efficacy. Thus, the 3033-11 trial can potentially add to our understanding of the possible features and risks for developing OIH in defined CNCP patients.

5.1.2. Duration of the Trial

The 3033-11 trial will include 52 weeks of treatment to address the long-term efficacy and safety of ER/LA opioids, including a 42-week Open-Label Titration and Treatment Phase and a 10-week Double-Blind Phase. The long duration of the trial is intended to demonstrate clinically meaningful, long-term pain relief with morphine sulfate ER in patients with defined CNCP. The extended duration of the Open-Label Phase is required to evaluate the effects of long-term ER opioid therapy while minimizing the duration of time that patients who are randomized to the placebo group may be required to use placebo. The extended duration of this phase may also provide more informative data that more closely align with clinical practice. In addition, the enrichment phase (Open-Label Treatment Phase) includes regular assessments of efficacy, OIH, and safety, using multiple measures (Section 4.5). This phase itself will provide important data on what may occur in clinical practice and will allow for the evaluation of predictors of opioid response and non-response to help practitioners decide which patients may benefit from ER/LA opioid treatment.

The duration of 10 weeks for the Double-Blind Phase, including up to 8 weeks of tapering for the placebo group, should be sufficient to evaluate the primary endpoint of time to loss of efficacy. Separation between arms for outcomes such as treatment failure typically occurs within a few weeks of transition to placebo or earlier (i.e., during down-titration) (Hale et al., 2010; Hale et

al., 2015; Katz et al., 2015b; Rauck et al., 2014; Rauck et al., 2015; Wen et al., 2015). An analysis of EERW trials in chronic pain has found that the median time to exit due to lack of efficacy in placebo groups ranged from 3.8 to 16 days for five of the trials that included detailed information on discontinuations, and > 90% of discontinuations due to lack of efficacy in these five trials occurred within 15 days of randomization (Katz, 2009).

Due to the long duration of the trial, the protocol has additional provisions to help increase the retention of patients, such as minimizing the number of trial visits and burdensome procedures (e.g., by limiting QST to a subpopulation as guided by a power analysis), frequent phone calls from research site staff for general check-ins and tolerability assessments, use of an online patient support tool, and proactive prevention and treatment of opioid-related side effects.

5.2. Rationale for and Strengths of the Trial Population

5.2.1. Main Criteria for Inclusion

The selection of patients with specific CNCP diagnoses, rather than opening the trial to all possible patients with CNCP conditions, was intended to balance generalizability to the broader population of patients with CNCP against the necessity, in a clinical trial, to evaluate a sufficiently homogeneous population to provide conclusive evidence of efficacy on the primary endpoint. The patient populations associated with these diagnoses have also been relatively well characterized and are expected to show the efficacy of ER/LA opioids based on prior studies and medical literature (e.g., Hale et al., 2015, Katz et al., 2015a; Rauck et al., 2015; Vinik et al., 2014). The inclusion of multiple types of CNCP is also intended to improve recruitment and generalizability compared to Study 2065-5, which included only patients with CLBP.

In addition, CNCP conditions have been selected where patients are more likely to be ambulatory to allow for the accommodation of trial visits and assessments in a clinical trial setting. These CNCP conditions are also known to be associated with relatively high levels of physical dysfunction, which is an important secondary objective and endpoint, given that physical function may have a significant impact on quality of life (Davies et al., 2006; Ge et al., 2022; Gonçalves et al., 2022; Atukorala and Hunter, 2023).

Finally, these diagnoses are generally associated with persistent or continuous pain for which ER/LA opioids may be needed, in contrast to conditions associated with intermittent pain that would not be considered appropriate for long-term ER opioid therapy (Dowell et al. 2022).

Patients must also have a Worst PI score of ≥ 5 and ≤ 9 over the 7 days prior to Screening for the index pain condition/site(s). Although it may vary between different pain populations and underlying patient characteristics, scores of 1 to 3, 4 to 6, and 7 to 10 on an 11-point NRS are often considered to represent mild, moderate, and severe pain, respectively. Because ER/LA opioids are indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment, PI scores indicating moderate-to-severe pain were selected (Boonstra et al., 2016). This is particularly relevant since the primary endpoint is Worst PI rather than Average PI; a Worst PI score of 5 rather than 4 has been selected as the lower threshold to represent the population of patients who may be suitable for ER opioid therapy.

Given that ER/LA opioids are indicated for patients for whom alternative treatment options are inadequate (Dowell et al. 2022), patients selected for this trial are required to be currently taking or have relatively recently taken SAOs. This is also consistent with CDC and other guidelines advising initiation of treatment with IR opioids or SAOs rather than ER/LA opioids and with current medical practice whereby ER opioids are generally only used for patients after failure of SAOs (Dowell et al., 2016; Dowell et al. 2022).

Eligible patients must be dissatisfied with their current or past SAO regimens as informed by the PPQ at Screening. Patients may also be appropriate candidates for ER/LA opioid therapy if they can benefit from reduced adverse effects associated with peak blood levels, and less fluctuation in blood levels across the course of the day or night, as well as end-of-dose failure, mild symptoms of withdrawal upon awakening, or sleep disturbance due to pain returning during the night (Andrade, 2015; Keith, 2006; Nicholson, 2009). The requirement for experience with SAOs, with some flexibility in dosing and duration/timing of use, may also increase recruitment efficiency compared to Study 2065-5, where subjects were required to have been taking high doses of morphine sulfate ER (120 – 540 mg), oxycodone ER (80 – 360 mg), or oxymorphone ER (40 – 180 mg) for at least 3 consecutive months prior to Screening – a factor which led to many sites opting out of participating in the study due to a lack of patients meeting this criterion.

The trial will allow enrollment of patients who are not currently on SAOs at the time of Screening. However, rather than allowing patients with any lifetime SAO use, the discontinuation of SAOs must be relatively recent (i.e., within 6 months of Screening) to increase the likelihood that the patient's chronic pain condition has remained relatively stable. In addition, these patients will be started at the lowest available dose of ER opioids due to a potential loss of tolerance. The minimum SAO requirement of 30 MME/day at Screening is intended to exclude patients who may be dissatisfied with SAOs due to underdosing and whose pain symptoms could potentially be managed simply by increasing the SAO dose.

Consistent with current clinical practice (Dowell et al. 2022), a careful assessment of the patients' therapeutic and medication history will be performed to confirm that patients have failed prior therapies and are suitable candidates for ER/LA opioid therapy. The protocol-defined threshold of failure (i.e., the patient has not responded to therapy or has contraindications) is at least two pharmacologic and two non-pharmacologic therapies, as informed by the PTRQ and external documentation (where available). Consistent with ER/LA opioid prescribing information, the intention is to enroll only patients for whom alternative treatment options are inadequate. Failure of 2 pharmacologic and two non-pharmacologic therapies will provide clear guidance to the investigators and is a reasonable threshold for defining failure of prior therapies without patients being required to fail all possible alternative therapies.

To accurately document previous treatment responses/failures, OPC has developed a measure of past treatment experience (PTRQ) similar to one that has been used in patients with treatment-resistant depression, the Massachusetts General Hospital Antidepressant Response Questionnaire (Chandler et al., 2010). The questionnaire will include a list of non-opioid pharmacologic and non-pharmacologic treatments for pain and will capture information such as the duration of treatment and reason(s) for discontinuation. The responses on the PTRQ will be reviewed by the investigators to confirm that patients have appropriately trialed alternative treatments (Protocol Appendix 16.3).

5.2.2. Enrollment and Randomization Criteria

The requirement for an improvement of ≥ 30% on the Worst PI (based on an average of the past 7 days of daily scores) has been established as a standard threshold for determining a clinically meaningful individual effect on an 11-point PI NRS (Dworkin et al., 2008). Although absolute numeric changes were considered, a percentage-based change was selected as it is considered valid across ranges of PI, i.e., a patient's score changing from 6 to 8 may represent a different clinical outcome compared to, for example, a change from 3 to 5. Therefore, the use of percentage-based change is consistent with current design recommendations for chronic pain trials and will more appropriately reflect clinical benefit across a range of scores.

To further increase the probability that treatment effects are clinically relevant, enrollment and randomization criteria will also require the investigator's and patient's subjective assessment that they have achieved meaningful improvement in the pain associated with the CNCP condition. Finally, consistent with clinical practice, the medication should be tolerated, according to the patient and investigator.

Seven days has been selected as the period for defining clinical stability prior to randomization, as it has been used in prior published EERW studies for ER/LA opioids that FDA has accepted (e.g., Katz et al., 2015a; Rauck et al., 2014; Rauck et al., 2015; Wen et al. 2015).

5.2.3. Trial Restrictions

The trial restrictions, particularly around the use of concomitant medications and other substances (i.e., alcohol), are largely based on warnings and precautions provided in the prescribing information for ER/LA opioids as required to help increase safety for patients in the trial. Specifically, drugs or substances that are known respiratory or CNS depressants are restricted or must be used with appropriate cautionary steps due to the potential for additive or synergistic respiratory depression. Other medications or substances may have pharmacokinetic or other types of pharmacodynamic interactions with opioids (e.g., p-glycoprotein inhibitors/inducers, serotonergic drugs), which may interfere with the assessments of efficacy and/or present a safety risk to patients. Finally, medications or substances like opioid antagonists or non-trial opioid medications have been restricted to mitigate potential impacts on the evaluation of efficacy.

Cannabis use will be restricted in this trial due to potential safety concerns regarding additive CNS depression, as well as potential interference in the assessments of efficacy, as some types of cannabinoids (i.e., high 9-delta-tetrahydrocannabinol [THC] to cannabidiol [CBD] ratio and comparable THC to CBD ratio products) have been associated with small-to-moderate improvements in pain severity in patients with chronic pain (McDonagh et al., 2021).

As opioids may be associated with sedative-like side effects and there is a potential for cognitive or motor impairment with their use (Kamboj et al., 2005), patients will be warned to avoid engaging in potentially hazardous activities until they are reasonably sure that the medications are not impairing their performance; this advice is consistent with standard warnings/precautions included in ER/LA opioid prescribing information.

5.3. Rationale for, and Strengths of, the Proposed Clinical Trial Medications

5.3.1. Treatment Scheme

Morphine sulfate ER has been proposed as an appropriate opioid product for assessment of efficacy and OIH. A meta-analysis of opioid trials in patients with CNCP found no significant differences in pain reduction, patient global impression, physical function, SAEs, or mortality in head-to-head comparisons of hydromorphone, morphine, oxymorphone, and tapentadol to oxycodone. However, the evidence was considered low-to-moderate quality (Lauche et al., 2015). Morphine sulfate ER was selected, following communications with FDA, as a pharmacologically generalizable opioid given its relatively selective mu-opioid receptor agonist profile. In addition, generic morphine sulfate ER is the most commonly prescribed ER/LA opioid in US clinical practice, accounting for approximately half of all ER/LA opioid prescriptions in 2022 (IQVIA® data). Therefore, findings with morphine sulfate ER may have the most practical relevance to patients with CNCP in the current opioid prescribing climate.

The Open-Label Titration Phase will permit patients to titrate to effect slowly and safely; this is typical in clinical practice due to the wide interpatient variability in optimal doses and a relatively narrow therapeutic index associated with opioids. This approach has been used successfully in prior opioid efficacy studies (e.g., Hale et al., 2015; Katz et al., 2015b), in prior studies of CNS-active analgesics (Freynhagen et al., 2005), and is generally considered to work better than fixed-dose designs for CNS-active analgesics (Katz, 2005). The use of flexible, patient-centered doses is consistent with standard clinical practice and will enable a more accurate assessment of the efficacy of morphine sulfate ER, as patients will be receiving the dose that is most appropriate to their medical situation. To increase patient retention, dose adjustments will also be permitted during the 36-week Open-Label Treatment Phase given the long duration of this phase. However, to avoid confounding the efficacy endpoints, no dosage adjustments of the ER medications will be permitted during the Double-Blind Phase, and doses of morphine sulfate ER must be stable for at least 7 days prior to randomization. This is to help ensure that patients are not randomized to the Double-Blind Phase at a time when their pain situation is in flux, which would compromise the assessments of efficacy.

To accurately assess the efficacy of ER opioids, the 3033-11 design allows patients to increase their doses up to a maximum MME of 240 per day since, despite decreasing trends in the use of high-dose opioids, some patients may continue to require these higher doses in clinical practice (Salas et al., 2021). While current guidelines recommend using lower doses where possible (i.e., ≤ 90 MME/day), they do not preclude the use of higher doses where it may be clinically necessary for an individual patient and instead advise carefully assessing the risks to the individual patient of increasing the doses against diminishing returns in benefits (Dowell et al. 2022).

Accordingly, the trial will use a structured, step-wise approach to dose escalation to assist research site investigators with dosing decisions and provide a more consistent approach across patients and research sites. Dose escalation levels were selected based on an algorithm consistent with clinical practice that considers PI, tolerability, and meaningful pain relief with the current dose. In addition, dose escalation will use the smallest possible increment in the context of available dosage strengths of morphine sulfate ER (i.e., 15 mg BID). This approach is designed

to protect the safety of patients while still allowing a relatively high maximum MME that will accurately reflect what may be used by individual patients in clinical practice (Salas et al., 2021). The allowance of higher ER opioid doses may also help contribute to trial feasibility by enabling the recruitment and retention of a broader patient population, particularly during the relatively long Open-Label Treatment Phase. Finally, allowing the use of higher doses, as needed by individual patients, will enable a more rigorous evaluation of OIH, which remains an important secondary objective of the trial.

The definition of "high-dose" ER opioids used in a secondary objective and analysis is based on the definition identified in the initial *CDC Guideline for Prescribing Opioids for Chronic Pain* (Dowell et al., 2016), i.e., a daily dose of ≥ 90 MME. As needed, additional subgroup analyses of patients who achieve various dosing levels may be performed, as appropriate.

5.3.2. Rescue Medications and Other Permitted Medications/Therapy

Patients will be permitted to use SAO rescue medication and APAP during the trial's Open-Label Treatment and Double-Blind Phases. The use of rescue medication is common in clinical trials of CNCP (Kopsky et al., 2022; Meske et al., 2018). However, to avoid confounding the primary endpoint of time to loss of efficacy, the daily SAO and APAP doses will be limited, as specified above. In addition to attempting to mimic clinical practice to the extent feasible in a clinical trial setting, rescue medication is a critical factor for patient retention over the relatively long duration of the trial. The use of SAO rescue medication may also help mitigate the emergence of withdrawal symptoms in patients in the placebo group, thereby decreasing the potential for the confounding effects of withdrawal symptoms associated with tapering in some patients.

Further, patients on pre-existing, stable pharmacologic or non-pharmacologic therapies (except those identified as restricted medications) will be permitted to continue using the therapies during the trial. This is consistent with guidelines (e.g., CDC; Dowell et al. 2022) and current practice in pain management, allowing for a more realistic assessment of efficacy. To avoid confounding the primary efficacy endpoint, doses/regimens of concomitant medications must remain stable within 1 month of and during the Double-Blind Phase, and therapies that may affect the efficacy outcomes should not be initiated or discontinued within 1 month of and during the Double-Blind Phase. Although in clinical practice, therapies and doses of medications may be modified during treatment, allowing patients to initiate or discontinue additional therapies during the Double-Blind Phase would make it difficult to establish the effect of ER opioids on the primary endpoint (time to loss of efficacy), thereby compromising the scientific validity of the trial.

5.4. Rationale for, and Strengths of, the Proposed Trial Endpoints

5.4.1. Efficacy Endpoints

NRSs for Worst and Average PI have been used as primary outcome measures in many previous studies of CNCP (Meske et al., 2018; Kopsky et al., 2022), and the use of these unidimensional pain scales has been recommended for the assessment of PI in patients with chronic pain (Ferreira-Valente et al., 2011; Hjermstad et al., 2011). Worst PI, rather than Average PI, has been included in the primary endpoint definition of this trial to capture breakthrough pain in the context of the rescue medication available to patients. Time to loss of efficacy has been proposed

as the primary derived endpoint as endpoints of this kind have been found to be more statistically powerful than mean PI (Katz, 2009).

In addition to the potential for greater statistical power with a time to loss of efficacy analysis, the handling of missing data and discontinued patients is more straightforward. In the trials using NRS as the primary endpoint, the handling of drop-outs can significantly influence the effect size (Kopsky et al., 2022). For continuous outcomes at specific timepoints, one must either assume that they are missing at random (rarely the case) or make some distributional assumptions about the missing values and impute values based on these assumptions. However, because these missing data are never observed, it is impossible to know the accuracy of the assumptions. Sensitivity analyses can test various assumptions to see whether it changes the conclusions; however, where trial conclusions are impacted by assumptions, it typically remains unclear which set of assumptions is accurate. Even when patients provide data up to a point, assumptions must still be made for outcomes after that point.

With the use of a Kaplan-Meier analysis (refer to Section 4.7), many of the reasons for discontinuation serve as an event, allowing these patients to contribute to the estimation. Likewise, censored patients contribute information throughout the period where they are known not to have experienced an event. Without imputation, an analysis of PI at a given timepoint will have no information contributed by patients that discontinue prior to that timepoint. The markedly longer duration of this trial compared to previous EERW trials may result in more patient discontinuations, making considerations around missing data particularly important for this trial.

Changes in Worst PI over time, responder rates, and similar endpoints using Average PI will be included as secondary efficacy endpoints, as well as other measures of the efficacy of ER opioids, including BPI-SF, EQ-5D-5L, and PGIC. These measures have been extensively validated and used in clinical trials of ER/LA opioids, and the additional endpoints will enable a more robust characterization of the analgesic response (Cleeland and Ryan, 1994; Daut et al., 1983; EuroQOL Group, 1990; Ferreira-Valente et al., 2011; Hjermstad et al., 2011, Keller et al., 2004; Obradovic et al., 2013; Meske, 2018; Chou, 2014), which will contribute to FDA's goal of providing additional important information for prescribers. These secondary endpoints are also assessed during both the Open-Label and Double-Blind Phases, which may capture important efficacy data even from patients who discontinue prior to randomization. A validated assessment of physical function (PROMIS PF-SF-8b; Chiarotto et al., 2020; Feng et al., 2020) that can be used across CNCP diagnoses has been selected to increase the power of statistical analyses of this domain by allowing the pooling of patients with different diagnoses, rather than attempting subgroup analyses using condition-specific measures.

To address FDA's request to evaluate the characteristics of patient populations that would benefit from opioid treatment, selected measures will be evaluated as potential predictors of opioid response and non-response, including demographics, chronic overlapping pain conditions, fibromyalgianess (based on the Fibromyalgianess Scale), personal/family history of mental illness and substance use disorders, anxiety/depression, pain catastrophizing, pain quality, pain profile, physical function, AEs, QST, and sleep/insomnia. Many of these characteristics have been previously assessed as potential predictors or have been recommended for use in chronic pain phenotyping (Edwards et al., 2016; Grosen et al., 2017). As outlined in Section 4.7, an opioid response will be defined as a ≥ 30% reduction in Worst PI and a PGIC score of 6 or 7

("better" or "much better"). A ≥ 30% reduction is considered a clinically important difference in Worst PI (Farrar et al., 2010; Marcus et al., 2018). The inclusion of the PGIC score allows for consideration of the patient's perception of their overall improvement in the response, as a single measure of PI may not fully capture the patient's therapeutic outcome.

5.4.2. OIH Assessments

OIH has been characterized clinically as involving increases in PI over time, pain spreading to location(s), and increases in pain sensitivity to external stimuli (Katz et al., 2015a). The protocol definition for OIH includes assessments for all three of these components by assessing changes in PI in the context of an equivalent or higher ER opioid dose, as well as hypersensitivity using QST. At the same time, the WPI (pain map) will also be used to assess for pain spread. QST is a method to quantitatively measure pain sensitivity in response to noxious and non-noxious stimuli of different modalities.

The QST methods to evaluate the potential development of OIH were selected based on systematic literature reviews, including one supported by OPC (Grosen et al., 2013; Katz, 2015a). The reviews determined that, while the literature was limited and mixed, heat pain appeared to be the most promising stimulus type for detecting OIH. QST allows for the reliable and serial assessment of patient-specific pain sensitivity metrics as the intensity of the painful stimulus is known and can be safely controlled (e.g., the maximum temperature of the probe in contact with skin). In addition, QST can provide reliable results in multicenter settings with appropriate training and standardized procedures. To confirm the reliability, feasibility, and utility of the proposed QST algorithm and assist in developing standardized procedures, a pilot or interim assessment will be conducted after testing 20 patients. Finally, to minimize investigator and patient burden, the QST assessments will be limited to up to 30 research sites and a subset of at least 200 patients who enter the Open-Label Titration Phase.

5.4.3. Safety Measures

Standard safety measures will be included to assess the long-term safety of ER opioids during the Open-Label Phases and relative to placebo in the Double-Blind Phase. Additional measures will include assessments of emotional function, sleep, sexual and endocrine function, as these domains may be potentially impacted by long-term opioid use (Edwards et al., 2016). As all opioids may carry risks of abuse, misuse, or dependence, the POMAQ (Coyne et al., 2021a; Coyne et al., 2021b; Coyne et al., 2021c) will be included to assess these risks in the trial population and actual cases of potential abuse, misuse, dependence, diversion, etc., related to the trial medications (morphine sulfate ER or SAO rescue medications) will be captured as abuse-related AESIs. Periodic UDT results will be reviewed for potential abuse of other drugs, including illicit drugs.

5.5. Rationale for, and Strengths of, the Proposed End-of-Treatment and End-of-Trial Procedures

5.5.1. Continuity of Care

This trial includes measures to provide for continuity of care at the trial exit, including communicating the treatment assignment and other information to their HCP. This will help

minimize interruptions to the patient's treatment course to the extent feasible. Patients without an HCP at trial exit will be given a referral for local services. Steps will be taken to minimize the potential for unblinding of the site investigator or staff due to disclosure of the treatment assignment. These additional steps that address continuity of care may be an important factor for recruitment of this trial, as many patients declined to participate in Study 2065-5 due to fears over the loss of access to their opioid medications after study completion.

5.5.2. Tapering Methods

During the Double-Blind Phase, patients in the placebo group will taper slowly to placebo in a double-blinded manner over the course of 1 to 8 weeks. Previously published EERW trials using designs and doses similar to those in the current trial have typically included tapering durations ranging from 3 to 20 days, with 14 days being the most commonly used tapering period (Hale et al., 2010; Hale et al., 2015; Katz et al., 2015b; Rauck et al., 2014; Rauck et al., 2015; Vinik et al., 2014; Wen et al., 2015).

Although many tapering guidelines recommend slower tapering schedules in clinical practice, a review of clinical trials with EERW design found that patient withdrawal symptoms are minimal in a double-blinded setting, even with shorter tapering durations (i.e., most commonly 2 weeks) (Meske at al., 2018). Based on a review of EERW studies of ER opioids in the literature that used tapering periods ranging from 3 to 20 days, differences in the incidence of opioid withdrawal in the placebo groups compared to active ER opioid groups ranged from –3.4% to +5.3% (defined using COWS or AEs). These data demonstrate that withdrawal effects that are common in clinical practice, where patients are not blinded, may be at least partly related to expectancy effects (i.e., the anticipation of and anxiety related to tapering the opioid doses). Thus, the 1- to 8-week tapering period (depending on the patient's dose at randomization) is considered adequate to control withdrawal symptoms in the double-blind setting.

The proposed tapering plan also considers the dose of ER morphine that the patient is currently taking, as well as the dosing regimen (BID) and the availability of dosage strengths of morphine sulfate ER (i.e., 15 mg is the smallest available strength). The tapering period must also allow sufficient time for patients randomized to placebo to be completely tapered off the ER trial medication and to fail treatment if they do so (i.e., Double-Blind Phase is only 10 weeks). The 1-week taper will only be used for patients who are receiving the lowest dosage strength of morphine sulfate ER (i.e., 15 mg tablets, administered BID) as a longer taper is not considered medically necessary for these patients. These low-dose patients will receive a week of asymmetric dosing (i.e., 15 mg QHS) prior to receiving 0 mg (placebo) for blinded patients or discontinuing the use of morphine sulfate ER for unblinded patients.

SAOs and APAP will continue to be permitted during the tapering period to alleviate any severe withdrawal symptoms. To evaluate potential unblinding due to opioid withdrawal effects in the placebo group, an unblinding questionnaire will be administered at the end of the Double-Blind Phase to evaluate patients' assessments of which treatment groups they believed they were assigned to and the reason(s) for their selections.

5.6. Rationale for, and Strengths of, the Proposed Statistical Approach

The proposed statistical analysis is standard for time-to-event data and, as it is non-parametric, it is free from many distributional assumptions. Kaplan and Meier also demonstrated that their estimator is the non-parametric maximum likelihood estimator of survival, giving this approach a solid theoretical justification. In this particular case, the circumstances that would commonly result in a patient withdrawing from a trial (resulting in missing or censored data) are among the items that qualify as an event: Increase in pain, lack of efficacy, and initiating new therapies. In this way, missing and censored data will be held to a minimum. A Cox proportional hazards model is a reasonable alternative analysis; however, the proportional hazards assumption may not be met; patients randomized to placebo may be more prone to events shortly after they have tapered from their open-label dose, whereas patients randomized to active treatment are more likely to have a uniform distribution of events over time. Additionally, there are no clearcut covariates to be included in the Cox model that would require its use or provide an advantage in estimation over the Kaplan-Meier methodology.

6. POTENTIAL CHALLENGES ASSOCIATED WITH THE CURRENT DRAFT 3033-11 PROTOCOL DESIGN

6.1. Potential Challenges with the Overall Trial Design

6.1.1. Novel EERW Design

An EERW design for opioid analgesics of this type and duration (i.e., 42-week Open-Label Phase and 10-week Double-Blind Phase) has never been tested due to the potential challenges in enrollment, early discontinuation, and duration. A few previous trials of up to 12 months duration did not include placebo controls (active-controlled or open-label) and/or were conducted in a managed care setting (e.g., Hale et al., 2017; Krebs et al., 2018).

The long duration of the trial may lead to the inability to complete the trial and/or failure of trial endpoints for reasons that cannot necessarily be predicted. A major challenge in the previous study was enrollment and patients remaining in the trial until completion. As with Study 2065-5, the placebo-controlled design may present recruitment concerns, as patients may not want to participate in a trial where they have a 50% probability of being withdrawn from the ER opioid on which they have been stabilized, particularly in a trial where the therapy is already available on the market. This has been somewhat mitigated in the current design by the relatively short duration of the Double-Blind Phase (10 weeks); however, it is still conceivable that some patients may choose not to participate in the trial or may drop out at the end of the Open-Label Phase rather than risk being randomized to placebo, even for a relatively short duration. Based on meta-analyses of EERW trials with shorter open-label/enrichment phases, the response rate is expected to be ~ 60 to 65%, with the majority of drop-outs being related to AEs (Katz, 2009; Kopsky et al., 2022). For the current design, the responder rate and attrition rate are unknown as no EERW trial in CNCP has yet evaluated such a long enrichment phase.

While EERW trials are thought to have greater statistical power and assay sensitivity compared to the parallel-group design for assessing the efficacy of opioid analgesics, a systematic review

comparing 8 EERW pain trials with 39 non-EERW pain trials examining opioids did not find a statistically significant difference in effect size (Furlan et al., 2011). However, there was a relatively small number of EERW trials included, which may have affected the statistical power to detect a significant difference in effect size, in addition to differences in endpoints, patient populations, and other methodologies between the trials. In addition, none of the trials included in the review were more than 6 months.

The current design presents a risk for bias due to the potential unblinding of patients in the placebo group during tapering due to the emergence of opioid withdrawal symptoms or other factors. Although the proposed tapering plan is expected to limit the emergence of withdrawal signs in a blinded clinical trial environment (as discussed further in Section 5.5.2), it is possible that some patients may still experience symptoms. The unblinding questionnaire will be administered at the end of the trial to explore this possibility. The emergence of withdrawal symptoms may also confound the measurement of the primary endpoint, Worst PI. Specifically, it may be difficult to distinguish opioid-withdrawal-related pain from a return of their original non-opioid-related chronic pain. However, SOWS and COWS measures will be included during the Double-Blind Phase to explore this possibility.

While an EERW design enables an evaluation of a cohort of patients who respond to and tolerate a medication, one of its key advantages, this may limit the generalizability of the results. In this particular protocol with an extended open-label phase prior to randomization, this effect may be exaggerated. However, information regarding response rates and predictors in the larger population of patients with these CNCP diagnoses will be collected in the Open-Label Phases and may further inform clinical practice regarding which patients may be appropriate candidates for ER/LA opioid analgesic therapy. In addition, the use of ER/LA opioids only in patients who show efficacy and acceptable tolerability is reflective of clinical practice.

6.1.2. Duration of the Trial

The 52-week duration of the trial may also lead to retention problems. Patients may drop out of the trial prior to the Double-Blind Phase, thereby requiring more patients to be screened and enrolled to increase the probability that a sufficient number of patients are available for randomization. Also, if patients drop out relatively close to randomization, potentially due to concerns about being randomized to placebo, it will take 10 – 11 months for replacement patients to complete Screening and the Open-Label Phases to be eligible for randomization. While flexibility in dosing, allowance for the use of concomitant and rescue therapies, and patient support are intended to promote the retention of patients over the duration of the trial, it is unknown whether these measures will be sufficient.

6.1.3. Evaluation for OIH

An additional limitation of the current trial design is that, in addition to limitations in the potential OIH assessments themselves (as described in Section 6.4.2), the emergence of OIH may not be accurately evaluated because baseline assessments are difficult with patients recently or currently on opioids. While a prospective parallel-group trial could allow for evaluation of how responses change over time compared to placebo in the absence of additional variables such as tapering/withdrawal, such a design may also include patients for whom ER/LA opioids are not appropriate for long-term use, thereby compromising the validity of the estimates. In the current design, the incidence of OIH over time will be derived primarily from the Open-Label Treatment

Phase in a subset of patients who initially respond to ER opioids in the Open-Label Titration Phase. In addition, the Double-Blind Phase will determine whether PI and hyperalgesia increase, remains stable, or decrease in the context of long-term opioid discontinuation.

6.2. Potential Challenges with the Proposed Trial Population

6.2.1. Main Criteria for Inclusion

A limitation of the proposed CNCP pain diagnoses is that the trial results may not be generalizable to all CNCP diagnoses. In addition, allowing enrollment of only patients with certain specific diagnoses may limit potential recruitment for the trial by decreasing the available pool of participants.

Using a Worst PI threshold that encompasses both moderate and severe pain as a group, rather than separately, could confound results as severe pain can be more difficult to control.

The requirement for a specific threshold of SAO use prior to the trial, although necessary for the selection of appropriate candidates for ER opioid therapy, may also limit the generalizability of the results and place additional limitations on the recruitment of trial participants.

The use of the PTRQ, an investigator-guided assessment of the patient's therapeutic history, relies on patient self-report, which may result in recall bias, and/or patients failing to disclose medications or therapies that they have used in the past. In addition, patients may not necessarily be able to recognize or name medications they have used in the past; this may lead to errors in reporting their prior pain therapy history.

An alternative option for documenting the failure of previous treatments would be to require clinical sites to obtain patients' medical records. However, this option would result in significant challenges for the investigators as these records are often unavailable or may contain errors and omissions. The possibility of performing the trial in a managed care setting was also considered since prior treatments are typically well-documented within these settings. However, moving the trial into such a setting may result in at least a 1-year delay in trial initiation for the establishment of relationships, contracts, etc. For example, OPC made several approaches to regional Veterans Health Administration institutions beginning in October 2016 but was met with a general lack of interest.

6.2.2. Enrollment and Randomization Criteria

The use of percentage reduction in PI may be more difficult to operationalize for investigational sites compared to specific numeric cut-offs; however, the change in PI will be based on a 7-day average; therefore, it is unlikely that the changes would occur in exact numeric integers. In addition, the use of the judgment of both the patient and investigator in terms of meaningful efficacy and tolerability may increase the variability in the types of enrolled or randomized patients due to the subjective nature of the assessments. Finally, the use of composite criteria, whereby the patient must meet all three criteria, may lead to the exclusion of patients who may otherwise be appropriate candidates to continue ER opioid therapy, compared to a strictly quantitative criterion or a strictly subjective judgment.

The use of 7 days to show clinical stability may lead to delay or exclusion of patients from randomization if some patients require changes in dose or have unrelated changes to or progression in their CNCP condition prior to randomization. Conversely, a longer period may provide additional evidence that patients have demonstrated clinical stability prior to randomization.

6.2.3. Trial Restrictions

Restrictions in the use of concomitant medications and substances may lead to a decrease in the generalizability of the trial results to a broader CNCP population, where the use of concomitant medications or substances is common due to comorbidities, particularly in older patients (Schneider et al., 2021). It may also limit the potential pool of trial participants available to participate in the trial. In addition, restrictions on the use of concomitant medications or substances during the trial may increase patient attrition due to early discontinuations. Alcohol or cannabis use is common in the general population and in patients with chronic pain (Ferrie et al., 2022), and cannabinoids are widely used by the general public as analgesics, which may present specific challenges to the recruitment and retention of trial participants.

6.3. Potential Challenges with the Proposed Clinical Trial Medications

6.3.1. Treatment Approach

Although morphine sulfate ER is an appropriate representative candidate for ER/LA opioids, it is possible that not all findings related to the efficacy or OIH with morphine sulfate ER may be generalizable to other ER/LA opioid products with differing pharmacodynamic or pharmacokinetic profiles. Response to different opioid medications varies, potentially limiting the interpretation of the efficacy results for ER morphine as related to other products. This is particularly true of the evaluation for OIH, as it may be influenced by the specific receptor pharmacology of the molecule, as well as pharmacokinetic factors such as time and concentration at the receptor (Chu et al., 2008), which may differ between different ER/LA opioid products given that opioid rotation is an accepted approach to the treatment of OIH (Angst and Clark, 2006; Guichard et al., 2022; Mercadante et al., 2019; Yi and Pryzbylkowski 2015).

Flexible, individualized dosing may make it more difficult to assess any dose-response relationships of the ER opioid. In addition, the use of fixed dosing may permit a more robust exploration of the possible risk for OIH. However, dose-response relationships of ER opioids and assessment for OIH are not the primary goals of this trial.

The use of fixed doses in the Double-Blind Phase (i.e., the dose the patient was stabilized on prior to randomization) is a departure from clinical practice. It is possible that some patients may fail treatment during this phase simply due to changes in their progression or clinical condition that may have been ameliorated by changes in dosing. However, this is necessary to have an accurate representation of the efficacy of ER opioids relative to placebo. The relatively short 10-week duration of the Double-Blind Phase may minimize the influence of progression or other changes in the patient's condition during that timeframe.

A potential criticism of the maximum proposed MME of 240 mg/day is that these dose levels are no longer as commonly used in the current opioid prescribing climate. The use of higher doses may be associated with a greater risk of negative outcomes, such as dependence, overdose, or other serious safety concerns (Coyle et al., 2018; Liang and Turner, 2015). However, the controlled, step-wise approach to any dosing changes may help mitigate such effects. In addition, patients will have naloxone dispensed throughout the trial in case of any accidental overdoses.

The availability of additional doses of morphine sulfate ER tablets may possibly increase the risk of misuse, abuse, or diversion (Coyle et al., 2018). Drug accountability will be monitored throughout the trial, and any aberrant events or behaviors suggesting misuse, abuse, or diversion will be recorded as AESIs, along with a careful evaluation of the patient's suitability to continue in the trial.

Finally, the use of higher morphine sulfate ER doses up to 240 mg/day will require a longer tapering period in patients randomized to placebo, thereby shortening the duration of the off-medication period to 2 weeks. Further, patients using higher doses of morphine sulfate ER may be more likely to experience withdrawal symptoms during tapering, which may confound the primary efficacy endpoint or lead to unblinding in these patients.

6.3.2. Rescue Medications and Other Permitted Medications/Therapy

While SAO and APAP up to the per-protocol maximum permitted quantities should be sufficient in the context of morphine sulfate ER use, it is possible that some patients may need additional rescue medications and, therefore, may discontinue from the trial due to lack of efficacy.

Conversely, it is possible that even this level of rescue medication use, along with the continued use of other analgesic medications and therapies, may confound the primary efficacy endpoint of time to loss of efficacy by allowing some patients on placebo to continue in the trial without the ER opioid medications or by delaying the time to loss of efficacy.

6.4. Potential Challenges with the Proposed Trial Endpoints

6.4.1. Efficacy Endpoints

One limitation of the selected primary measure (Worst PI) is that it has not been as commonly used as a primary endpoint in clinical trials of ER/LA opioids compared to Average PI; therefore, there is less experience with which to predict and compare outcomes.

Although the time to loss of efficacy or treatment failure may be considered to have more statistical power than other endpoints, a meta-analysis of EERW trials in chronic pain found that while some trials failed to show statistical significance with NRS but did with time to loss of efficacy/treatment failure, the reverse was also true (Kopsky et al., 2022). However, in the EERW chronic pain trials examined, there were many different composite definitions for time to loss of efficacy/treatment failure, which makes a comparison between trials on this endpoint difficult.

Currently, there is no consensus on the definition of loss of efficacy or treatment failure. Most trials using these endpoints defined them differently (Kopsky et al., 2022). The use of time to loss of efficacy rather than responder rates or mean PI values is limited by the fewer clinical

trials in CNCP that have used this endpoint, each with different definitions of loss of efficacy/treatment failure. This makes hypothesizing about the trial results more uncertain, leading to potential difficulties in estimating power and sample size (as discussed further in Section 6.6).

In the current protocol, several different criteria are used to define "loss of efficacy" rather than relying only on changes in PI. Requiring that patients meet all three criteria may result in the incorrect allocation of some patients who might otherwise be appropriate candidates to continue morphine sulfate ER therapy. Further, the requirement related to initiating a new therapy does not consider non-pharmacologic therapies that may affect efficacy outcomes and relies on patient self-report, which may lead to underreporting. The criterion related to discontinuation due to lack of efficacy is based on the subjective judgment of the investigator, which may lead to variability and bias in the outcome.

While multiple endpoints and measures evaluating efficacy have been included to provide a more robust evaluation of efficacy and predictors of response and non-response, if discordant results across endpoints are observed, it will make the interpretation of results difficult.

To assess physical function, a scale that can be used across CNCP conditions has been selected. This may lead to less accurate assessments of physical function than scales that have been developed and are more widely used for specific conditions, such as the Roland-Morris Disability Questionnaire, Knee Injury and Osteoarthritis Outcome Score, etc.

6.4.2. OIH Assessments

The protocol definition for the development of OIH in this trial is based on changes in Worst PI and hyperalgesia based on QST assessments. It is unknown if the definition will accurately estimate the incidence of OIH as there is no widespread consensus on assessments for OIH, and it has not been previously tested.

Further, although it appears to be promising, it is not known if QST will be a reliable marker of OIH, and within-patient variability is unknown. A pilot or interim analysis has been proposed; however, pilot/preliminary data will be assessed for logistic feasibility and reliability and will not be able to confirm that QST is a valid assessment for OIH. Additional limitations associated with QST assessments include the need to perform the assessments in a controlled environment to increase the reliability of the testing, i.e., quiet room, controlled for temperature, and including comfortable seating or semi-seating options for trial participants; this may preclude testing at some research sites.

The development of standardized QST protocols can be quite complex and require specific expertise to govern interactions between operators and trial participants, which may increase variability across research sites. The successful implementation of QST protocols requires training and supervision of QST operators by QST experts with a proven track record for producing high-quality QST data. These assessments can be burdensome for research investigators and patients; therefore, protocols must consider time requirements and frequency of test procedures to ascertain the feasibility and limit participant fatigue. The latter is a critical consideration, as QST is a psycho-physical task requiring attentive trial participants. As such, QST protocols must include performance metrics for potential trial participants (e.g., test-retest reliability). Finally, QST devices require regular evaluation of performance and calibration, and

data would need to be reviewed regularly by a qualified QST expert to ensure the continued accuracy of the assessments.

6.4.3. General Limitations

Despite attempts to limit the number and length of the scales and assessments (as outlined in Section 4.5), there remains an extensive list of questionnaires and evaluations to be performed at each site visit, which may lead to patient fatigue and/or errors and omissions by the investigational site staff.

6.5. Potential Challenges with End-of-Treatment and End-of-Trial Procedures

6.5.1. Continuity of Care

Even though the protocol includes steps to help provide continuity of care for patients after the end of the trial, changes in the prescribing landscape may make it difficult to find physicians available to patients should they need to continue their opioid medication. Although steps will be taken to minimize the potential unblinding of the site investigator or staff, it remains a possibility that the patient or patient's HCP may disclose the treatment assignment to the site investigator or staff. However, as the patient will have completed the treatment course and all trial assessments, the risk for bias to the efficacy or safety outcomes, should this occur, is relatively low and does not outweigh the need to take these reasonable measures related to the continuity of care.

6.5.2. Tapering Methods

Although the tapering schedule is expected to adequately minimize the occurrence of withdrawal in most patients, it is possible that some patients may experience withdrawal symptoms, which could lead to unblinding of the treatment assignment and bias to the trial endpoints. In addition, it is possible that withdrawal symptoms in some patients may confound the efficacy outcomes, including the primary endpoint of time to loss of efficacy. The enrichment phases of the published EERW trials discussed in the previous section were of a shorter duration than the currently proposed 42-week period, which may result in an underestimation of the potential for withdrawal effects in the current trial. However, many of these trials did enroll opioid-experienced patients.

6.6. Statistical Approach

The key challenges to the proposed statistical approach are powering and ensuring events are captured. This endpoint/design has limited data available for estimating power, particularly with the availability of SAOs in the quantities allowed to the patients randomized to placebo in the Double-Blind Phase. As described above, only a single study was identified that allowed up to 30 mg oxycodone IR rescue per day (45 mg MME/day) (Wen et al., 2015), and this study was not a perfect match to the current protocol.

To mitigate the risk of underpowering the trial, an interim analysis will be performed after the first 50% of subjects have been randomized and exit the Double-Blind Phase of the trial. The interim analysis will evaluate the conditional power of the trial based on this first cohort and may

add up to 200 additional participants to cover any shortfall in power at that time. In addition to calculating power for the Double-Blind Phase, there are also limited data to predict attrition across the Open-Label Phases due to their long duration. The need to over-enroll the Open-Label Phases to account for attrition will put additional strain on recruitment and enrollment efforts.

In addition, the trial, including the interim analysis, has been powered for the primary efficacy endpoint, with no expectation of statistical inferences for secondary efficacy endpoints. As noted above, differential results between different efficacy endpoints may complicate the interpretation of the trial. Although a power analysis was performed for the OIH assessment, this assumed an OIH incidence of 5%. Given recent estimates of possible OIH being as low as 0.01% per patient per physician practice year, determining between-arm differences may not be possible.

The second key challenge of the statistical analysis approach is ensuring that events are captured. Kaplan-Meier estimation accounts for censoring; however, missed events reduce its power to detect differences among the groups of interest. Patients lost to follow-up may have experienced a treatment failure event, and the long duration of the trial may result in a greater number of subjects exiting the trial without discontinuation and evaluation for events. This is mitigated by the short Double-Blind Phase relative to the Open-Label Phases and clear instructions to the sites on contacting patients lost to follow-up.

7. DISCUSSION

Placebo-controlled clinical trials have demonstrated the efficacy of opioids in the treatment of CNCP over durations of approximately 3 – 4 months (Meske et al., 2018; Petzke et al., 2020). EERW designs have been used successfully to assess response during the initial months of treatment but, to date, have not been used to demonstrate the persistence of benefit through 52 weeks. Multiple open-label observational studies have followed patients for 12 months, but these were not placebo-controlled. Still, patient-level data from these studies have identified a subpopulation of patients who maintained stable pain, reduction in PI, and physical function while using stable doses of ER oxycodone or ER hydrocodone for 12 months (Farrar et al., 2022). The current 3033-11 trial would complement existing data by assessing long-term efficacy in a randomized, controlled design beyond the 12 weeks that have traditionally been evaluated.

The primary objective of the 3033-11 trial is to evaluate the persistence of analgesic efficacy of morphine ER for defined CNCP in patients who demonstrate initial analgesic efficacy and tolerability. Key secondary endpoints include evaluations for OIH and opioid tolerance, while additional objectives include identification of predictors of opioid response, evaluation for changes in physical function, anxiety, and depression, and evaluation of the safety of titrated doses of an ER opioid. The protocol design addresses some of the challenges encountered in Study 2065-5 and includes extensive evaluation and data collection on all patients to better evaluate the long-term efficacy and safety of ER opioids. Finally, the trial is expected to provide information regarding the possible risk for OIH and whether it is a factor involved in sustained use and dose escalation of opioids.

7.1. Interpretation of Trial Results

There are strengths and limitations associated with the current draft 3033-11 protocol, as summarized in Table 1; however, there may be challenges associated with any 52-week trial of ER/LA opioids for the treatment of chronic pain in the current clinical practice and prescribing climate, as discussed in Section 2.3. If completed successfully, the trial could provide evidence of sustained, long-term efficacy in patients who initially respond to morphine sulfate ER during the Open-Label Phase. While it is expected that this trial will contribute to the science on the clinical use of ER/LA opioid analgesics, there are potential limitations on the interpretation of the results of this trial that should be acknowledged.

For subjective pain endpoints, there is the potential for multiple confounders to affect outcomes, such as differential changes in the underlying pain condition of each patient that could vary over time differently across pain types.

The protocol has attempted to control for such variability over time by requiring patients to have a stable diagnosis of CNCP for at least 12 months, limiting the duration of the randomized withdrawal (double-blind) phase, and requiring that patients demonstrate a degree of clinical stability prior to randomization. In addition, it is difficult to control for other factors that may influence the experience of pain, such as concurrent depression or anxiety. As such, the protocol proposes an exploratory analysis of a broad range of potential predictors of opioid response and non-response, including demographic, psychological, behavioral, and familial factors and comorbidities (Section 5.4.1).

Finally, in addition to other factors that may increase variability in efficacy outcomes, the need to mimic current clinical practice, where management of chronic pain is multimodal and may include multiple pharmacologic and non-pharmacologic therapies, may make it more difficult to discern an effect of the morphine sulfate ER trial medication. Thus, despite protocol features intended to control for variability, it may not be possible to control for all potential confounders during a trial of such a long duration.

In all studies, there is a risk of Type 2 error. In the current study, the error would be failing to detect a long-term benefit of ER/LA opioids when it does, in fact, exist. The novel design and the extended duration of the trial may increase the risk of a Type 2 error. A false negative result that incorrectly points to a lack of efficacy could have broader consequences in general for the treatment of patients suffering from moderate-to-severe CNCP who may have no other effective treatment options. As such, the results of this trial may have a disproportionate effect on clinical practice in this area.

Because there are no other randomized, placebo-controlled trials of this duration, there is a risk that the results may be overinterpreted. For example, an ambiguous or mixed trial outcome could lead to further restrictions on the responsible use of opioid pain medications, even in appropriate patients for whom the benefits outweigh the risks.

The trial design also seeks to include a mixture of different patients with varying pain conditions, which could increase variability in the results. As the trial is not powered for subgroup comparisons, it is possible that there may appear to be differential responses for different pain conditions or patients of different ages or other demographic factors. These differences could be interpreted to mean that different patients or pain conditions may or may not benefit from

treatment with ER/LA opioid medications, leading to inappropriate clinical decisions for individual patients.

Further, when PMR 2065-5 was issued in 2013, and even when PMR-3033-11 was re-issued in 2016, relatively little was known about OIH, which remains the primary goal of PMR 3033-11 as currently written. However, it is now a secondary endpoint in the protocol. Several studies have evaluated the potential prevalence of OIH in pain management practice according to practicing physicians and have found that OIH may not be as prevalent in clinical settings as was once thought (Kum et al., 2020; Vargas-Schaffer et al., 2020). These surveys, combined with data from Farrar et al. (2022) demonstrating a population of patients receiving long-term opioid treatment at generally stable doses, suggest that OIH may not be a frequent driver of dose escalation in patients on long-term opioid analgesic therapy. In addition, given that OIH has been postulated to be associated with higher opioid doses, it is less likely to occur with the changing practices related to high-dose opioid prescribing.

Given the uncertainty regarding the potential prevalence of OIH in clinical practice, the OIH Population of the trial (a subset of 200 patients) may not be powered to detect a sufficient number of events of OIH to make any definitive conclusions about the occurrence of OIH or its risk factors or predictors, complicating fulfillment of this aspect of the PMR. Nonetheless, due to limitations in the currently available data regarding OIH, the 3033-11 trial has been designed to assess the potential for OIH as a contributing factor in continued opioid use and/or dose escalation. Although the data may not definitively identify the incidence of OIH in this defined set of CNCP patients, it is expected to provide complementary data to those already collected using other study types.

Finally, a single trial can only contribute a defined set of data to the existing knowledge base, as is the case for any clinical trial or research study. Therefore, results would need to be interpreted cautiously in the absence of replication using similar and alternative study types. While limitations are expected in a clinical trial setting, regardless of design, care must be taken so that the potential impact of the trial results on patient care does not exceed what the trial can support.

7.2. Summary of Factors Affecting Feasibility of the 3033-11 Trial

Trial Duration

The long trial duration, irrespective of the overall trial design, may affect its feasibility by limiting the number of investigators/sites and patients willing to participate. In addition, retention of patients over the > 52 weeks of this trial will pose significant challenges, particularly in the context of restrictions required for patient safety, as observed in Study 2065-5. When FDA advised OPC that an Advisory Committee would be convened to discuss the 3033-11 trial, an analysis was already planned to assess the feasibility of conducting and completing the study. The feasibility analysis intends to further inform OPC on potential modifications to the trial design that may increase the probability that the trial can be successfully recruited and completed.

EERW Design

Recruitment challenges may be encountered in this design because patients may not want to risk randomization to placebo once stabilized on a long-term ER opioid over 42 weeks or may drop out prior to the Double-Blind Phase to avoid randomization to placebo. However, recruitment challenges can be expected with any design that requires the use of a placebo control in this patient population. This design is a significant improvement over the previous design used for Study 2065-5 as it limits the duration of time that patients are required to stay on placebo. In addition, it is an improvement over the parallel-group design, where it may be very difficult to maintain patients with continuous, moderate-to-severe pain in the placebo arm.

Eligibility and Restrictions

The many eligibility and trial restrictions required for the selection of appropriate candidates for ER/LA opioid therapy and to increase patient safety, as per ER/LA opioid labeling, may further limit the enrollment and retention of patients over the extended duration of the trial. Although some restrictions are unavoidable, the protocol allows individual investigator judgment in the use of concomitant medications, and concurrent therapies are permitted over the longest portion of the trial, namely the Open-Label Treatment Phase.

Treatment Regimen and Rescue

Flexibility in morphine sulfate ER dosing during the Open-Label Phase and the allowance for the use of concurrent pain therapies may increase the feasibility of the trial and patient retention. However, as noted above, this may confound the interpretation of long-term ER opioid efficacy results. Allowance for the use of rescue medications during the Open-Label Treatment and Double-Blind Phases may help increase patient retention over the relatively long duration of the trial, though with the same data concerns.

Changes in Clinical Practice

In parallel with 2065-5/3033-11 trial-related activities, fundamental changes in the clinical practice of chronic pain management and the use of opioid analgesics have occurred over the past 9 – 10 years. Irrespective of the overall trial design (i.e., EERW or alternative), these changes may affect the feasibility of the 3033-11 trial. For example, decreased use of ER/LA opioids and fewer HCPs prescribing opioids may mean fewer investigators and patients to participate in the trial.

Although potential recruitment and retention challenges for this trial remain, the difference in patient population and trial design from Study 2065-5, which required patients on high doses of ER opioids to relatively rapidly taper off, may increase the potential recruitment of this trial compared to that study. As noted above, a planned feasibility analysis will help to determine the probability of successfully completing the trial.

7.3. Overall Conclusions

The conclusions of the Farrar, et al. publication, which analyzed studies that supported FDA approval of multiple ER/LA opioids, suggest that a meaningful subset of patients on chronic ER/LA opioid therapy do well for up to a year (Farrar et al., 2022). The current protocol is

designed to add to the evidence base for individualizing the care of patients with chronic pain. Still, a single trial can only contribute a defined set of data to the existing knowledge base, as is the case for any clinical trial or research study. Therefore, results will need to be interpreted cautiously in the absence of replication using similar and alternative study types. While limitations are expected in a clinical trial setting, regardless of design, care must be taken so that the potential impact of the trial results on patient care does not exceed what the trial can support.

The 3033-11 trial has been designed to systematically assess the long-term efficacy of morphine sulfate ER in patients with CNCP and to contribute to the scientific understanding of OIH. The importance of designing a scientifically and operationally robust protocol is underscored by the potential impact that the trial results may have on clinical practice and the lives of individual patients suffering from chronic pain.

Accordingly, OPC remains committed to working through the challenges of this clinical trial requirement to gather data that will inform the appropriate long-term use of ER/LA opioids in the interests of patients' well-being and public health and to fulfill the important goals of the PMR.

OPC welcomes discussion with the Committee about the protocol design for this trial.

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9. APPENDICES

9.1. Appendix A: ER/LA Opioid PMRs and Current Status

Study #	PMR #	Study Description	Status	Publications
1A	3033-1	Prospective cohort study of behaviors in questionnaires and EHRs	Completed	
1B	3033-2	Retrospective study using health records, insurance claims, and death records	Completed	Manuscript in preparation
2A - Qualitative	3033-3	Validation studies of POMAQ instrument to measure misuse and abuse through self-reporting	Fulfilled	Coyne et al. Curr Med Res Opin. 2021;37(3):505–14. doi:10.1080/03007995.2020.1865891. PMID: 33331184. Coyne et al. Curr Med Res Opin. 2023;39(3):441–50. doi:10.1080/03007995.2023.2174343. PMID: 36715144
2A - Quantitative	3033-4		Fulfilled	Coyne et al. Curr Med Res Opin. 2021;37(3):483–92. doi:10.1080/03007995.2020.1865889. PMID: 33331191 Coyne et al. Curr Med Res Opin. 2021;37(3):493–503. doi:10.1080/03007995.2020.1865890. PMID: 33327799. Coyne et al. Curr Med Res Opin. 2022;38(6):971–80. doi:10.1080/03007995.2022.2065139. PMID: 35437075
2B	3033-5	Validation study of Psychiatric Research Interview for Substance and Mental Disorders instrument to measure addiction and substance use disorder through self-report	Fulfilled	
3A	3033-6*	Validation of coded medical terminologies used to identify opioid-	Completed	Green et al. Pharmacoepidemiol Drug Saf. 2019;28(8):1138–42.

Study #	PMR #	Study Description	Status	Publications
		related overdose in the postmarketing databases employed in Study 1B		doi: 10.1002/pds.4797. PMID: 31095831. Green et al. Pharmacoepidemiol Drug Saf. 2019;28(8):1127–37. doi: 10.1002/pds.4772. PMID: 31020755. Hazlehurst et al. Pharmacoepidemiol Drug Saf. 2019;28(8):1143–51. doi: 10.1002/pds.4810. PMID: 31218780
3B	3033-7	Validation of a diagnostic algorithm to measure abuse/addiction based on administrative claims data	Fulfilled	Carrell et al. J Drug Assess. 2020;9(1):97–105. doi:10.1080/21556660.2020.1750419. PMID: 32489718
4A	3033-8	Cross-sectional study of doctor/pharmacy shopping in a prescription database vs. a claims-based diagnostic algorithm for abuse/addiction	Fulfilled	Walker et al. Clin J Pain. 2017;33(11):976–82. doi:10.1097/AJP.0000000000000483. PMID: 28145912 Walker et al. Subst Abuse Rehabil. 2019;10:47–55. doi: 10.2147/SAR.S201725. PMID: 31534380
4B	3033-9	Survey study of doctor/pharmacy shopping in a prescription database vs. self-reported misuse and abuse in interviews	Fulfilled	Stephenson et al., J Pain Res. 2020;13:689–701. doi: 10.2147/JPR.S232409. PMID: 32308468
4C	3033-10	Retrospective cohort study of doctor/pharmacy shopping using medical record review for misuse, abuse, and/or addiction	Fulfilled	Esposito et al., J Pain Res. 2019;12:2291–303. doi: 10.2147/JPR.S203350 PMID: 31413626

EHR = electronic health record; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire.
* PMR 3033-6 will not be fulfilled until the fulfillment of Study 1B.

9.2. Appendix B: Detailed Timeline of Study Activities

Summary of key interactions in the timeline of the development of the study to address PMR 2065-5 and the revised study to address PMR 3033-11.

Date	Activity
2014	OPC / FDA participated in bi-monthly TCs to discuss potential study design, endpoints, dosage, sample size, titration, and next steps for draft protocol submissions.
09-Apr-2014	OPC submitted draft synopses for all PMRs, including 2065-5, for discussion in May 2014 public meeting.
15-May-2014	During quarterly SC TC, FDA requested OPC provide a draft SAE reporting document; OPC provided on 20-May-2014.
19-May-2014 to 20-May-2014	FDA held a public meeting to discuss PMRs.
26-Jun-2014	OPC and FDA held TC to discuss public meeting feedback, and OPC proposed conducting a QST pilot study and patient focus group to assess recruitment/retention. OPC noted that the overall design of PMR 5 was acceptable to participants and considered panelist comments for the protocol.
14-Aug-2014	OPC provided a list of pros/cons for study design options and potential “poor responders”-only draft 2065-5 protocol for FDA’s review.
23-Sep-2014	OPC and FDA had TC to discuss responses to FDA’s questions/recommendations related to 2065-5 protocol development.
30-Sep-2014	OPC provided draft 2065-5 protocol to FDA for review.
Nov-2014	OPC submitted a revised draft 2065-5 protocol incorporating several FDA comments.
21-Nov-2014	During quarterly SC TC, OPC requested IND exemption for 2065-5.
08-Dec-2014	OPC selected CRO for 2065-5.
2015	OPC began CRO kickoff activities, identified study vendors, and began study drug manufacturing.
06-Feb-2015	FDA advised 2065-5 IND was exempt.
12-Aug-2015	During quarterly SC TC, OPC informed FDA of 2065-5 study start-up delays due to CRO contracting and drug supply challenges. OPC also informed FDA of poor results from a 2065-5 protocol feasibility study that examined factors related to recruitment/retention.
09-Sep-2015	OPC provided the final 2065-5 protocol for FDA review.
2016	OPC continued study kickoff activities and began enrollment for study 2065-5.
20-Jan-2016	OPC submitted the final original 2065-5 protocol (10-Jan-2016).
04-Feb-2016	FDA released OPC from the five PMRs issued Sept 2013 and replaced them with 11 PMRs (10 observation studies and one clinical trial), thus changing 2065-5 to 3033-11. For administrative ease, study number 2065-5 continued to be used.
26-Feb-2016	During quarterly SC TC, OPC provided FDA an update on the status of vendor agreements and challenges experienced with site contracting for 2065-5.
14-Apr-2016	OPC finalized the QST protocol that was included in the 2065-5 protocol.

Date	Activity
May-2016	OPC held the first investigators meeting for protocol 2065-5 with 31 sites.
18-Jul-2016 to 22-Jul-2016	OPC submitted 2065-5 amendment 1 (07-Jul-2016): – Adjusted Screening procedure to no more than 14 days apart – Clarified discontinuance of suboptimal responders – Clarified study discontinuation assessments – Clarified reporting of adverse events – Clarified open-label taper and titration schedule – Clarified questionnaires.
14-Sep-2016	OPC received notice of the first subject screened in 2065-5.
Oct-2016	OPC held second investigators meeting for protocol 2065-5 with 34 sites.
03-Nov-2016	During quarterly SC TC, OPC provided 2065-5 study updates, noted site selection challenges, enrollment issues, and the limited number of eligible patients. FDA expressed concern regarding enrollment issues.
2017	OPC continued 2065-5 enrollment efforts and discussed challenges/difficulties with FDA.
08-Feb-2017	During quarterly SC TC, OPC provided 2065-5 study updates and provided FDA with additional context regarding primary reasons for pre-screen and screen failure during enrollment.
24-Feb-2017	OPC submitted 2065-5 protocol amendment 2 (08-Feb-2017): – Adjusted Screening procedure to no more than 21 days apart – Further defined CLBP – Expanded Observation Period – Inclusion criteria expanded to also allow the use of IR opioids for at least 12 months – Broadened depression and weight exclusion criteria – Added to prohibited prior medications and procedures – Adjusted suboptimal responder discontinuation criteria
22-May-2017	During quarterly SC TC, OPC summarized its efforts to increase 2065-5 site and patient enrollment.
Sep-2017	OPC consultants completed a status assessment of the issues faced in 2065-5 to be taken into account for 3033-11, including: – Increased legislative, regulatory, and insurance company efforts to control opioid prescribing, which resulted in significant patient and site scarcity. – Decreased use and reduced doses of opioids for chronic pain management. – Scientific question as to whether a hyperalgesia study is still clinically relevant to long-term opioid use.
19-Sep-2017	During quarterly SC TC, OPC presented 2065-5 status assessment indicating concerns and study challenges. FDA requested OPC provide alternatives to address the scientific question of hyperalgesia.
Jan-2018	FDA agreed to premature 2065-5 study termination due to the inability to recruit a sufficient number of subjects over an acceptable period of time. Study 3033-11 design was initiated.

Date	Activity
	A partial abbreviated clinical study report for 2065-5 was submitted to FDA.
11-Jan-2018	FDA had a TC with consultants of OPC to discuss study progression and potential changes to the 3033-11 protocol and study design.
2018 to 2019	OPC continued development and revisions related to PMR 3033-11 protocol.
11-May-2018	OPC submitted to FDA 3033-11 protocol synopsis and questions to FDA regarding the study.
29-May-2018	FDA and OPC had a TC to discuss FDA concerns regarding the 3033-11 titration schedule, OIH, and rationale for statistical power calculation, sample size, and dropout rates.
28-Jun-2018	OPC submitted to FDA 3033-11 protocol and responses to FDA questions from the meeting on 29-May-2018.
28-Sep-2018	FDA and OPC had TC to discuss the FDA's significant concerns with the proposed 3033-11 design, including that the design would not address the PMR.
24-Oct-2018	The SUPPORT Act was passed, allowing FDA to require post-market efficacy studies in certain circumstances.
31-Oct-2018	OPC provided the FDA with a concept for a two-arm open-label study (3033-11).
08-Jan-2019	FDA and OPC met to discuss the FDA feedback on 3033-11 study concept.
28-May-2019	OPC provided to FDA a 3033-11 protocol synopsis and rationale of key study design elements with questions to FDA.
09-Jul-2019	FDA provided responses to OPC 3033-11 questions on the synopsis and rationale submitted 28-May-2019.
19-Jul-2019	OPC provided a response to FDA comments of 9-Jul-2019.
08-Nov-2019	FDA and OPC had TC to discuss the FDA recommendations on 3033-11 protocol. FDA requested a change of the primary objective to efficacy.
2020	OPC submitted draft 3033-11 protocol and addressed FDA feedback.
24-Jan-2020	OPC submitted draft 3033-11 protocol to FDA.
10-Feb-2020	OPC provided 3033-11 FAQ memo and a response to FDA's 03-Feb-2020 IR. FAQ memo recapped previous responses to FDA from May and July 2019 and updated responses and questions based on the primary objective change.
15-Apr-2020	FDA provided comments on draft 3033-11 protocol dated 23-Jan-2020.
17-Apr-2020	FDA and OPC had TC to discuss FDA feedback on the proposed 3033-11 study design.
20-May-2020	OPC submitted a written response to FDA comments of 15-Apr-2020 and from request during FDA/OPC TC of 17-Apr-2020.
21-Jul-2020	FDA provided feedback on 3033-11 study design options during quarterly FDA SC TC.
03-Sep-2020	FDA and OPC had TC to discuss the FDA feedback on the proposed 3033-11 study design.
11-Sep-2020	OPC informed FDA of the 3033-11 synopsis timeline.
30-Oct-2020	OPC submitted draft 3033-11 synopsis to FDA updated based on a discussion held on 03-Sep-2020.

Date	Activity
2021	OPC continued addressing FDA feedback on draft 3033-11 synopsis for incorporation into the revised 3033-11 protocol.
10-Feb-2021	OPC informed FDA of potential study drug change, including the use of a single representative ER opioid product.
19-Mar-2021	FDA provided a review of draft 3033-11 synopsis.
07-Apr-2021	OPC approved the use of oxycodone ER as an investigational study drug in the 3033-11 trial.
30-Apr-2021	OPC informed FDA of 3033-11 study drug changes, referencing oxycodone ER as an investigational study drug.
12-May-2021	OPC provided responses to FDA's review of draft 3033-11 synopsis of 19-Mar-2021.
18-May-2021	FDA provided IR for draft 3033-11 synopsis requesting a rationale for the use of oxycodone ER as the sole investigational drug and inclusion criteria regarding use of SAOs.
19-May-2021	OPC provided a draft PTRQ to FDA.
24-May-2021	OPC provided a response to FDA IR of 18-May-2021 with a rationale for the study drug and inclusion criteria regarding SAOs.
27-May-2021	FDA and OPC had TC to discuss FDA comments on draft 3033-11 synopsis and 18-May-2018 IR.
04-Jun-2021	FDA/OPC quarterly SC TC where discussions of draft 3033-11 protocol and alignment on investigational study drug continued.
10-Jun-2021	OPC provided FDA with outcomes summary of 27-May-2021 TC.
18-Jun-2021	OPC provided FDA with additional rationale supporting the use of oxycodone ER as the sole investigational drug in 3033-11.
12-Aug-2021	FDA provided comment on 3033-11 OIH items and study drug selection, recommending the use of morphine sulfate ER and oxycodone ER or only morphine sulfate ER if feasibility issues prevented the use of two investigational drugs.
16-Sep-2021	OPC agreed to the use of morphine sulfate ER in 3033-11 and provided additional rationale regarding the OIH approach.
21-Oct-2021	FDA confirmed an agreement with the proposed OIH approach and the use of morphine sulfate ER.
01-Dec-2021	FDA OPC quarterly TC further summary discussions of 3033-11 and timing for the next draft protocol submission.
2022	OPC submitted the draft 3033-11 protocol for FDA review.
01-Mar-2022 and 09-Mar-2022	OPC submitted the draft 3033-11 protocol.
09-Jun-2022	During quarterly SC TC, FDA informed OPC of their intent to hold a public Advisory Committee meeting on the 3033-11 protocol in Q1 2023.
21-Jul-2022	FDA informed OPC that it may provide feedback on the 3033-11 protocol by late Summer or early Fall 2022.
17-Aug-2022	FDA informed OPC of its intent to hold the public Advisory Committee meeting on the 3033-11 protocol in April / May 2023.

Date	Activity
20-Sep-2022	FDA/OPC quarterly SC TC advising Advisory Committee will focus on EERW study design, and OPC could assist by providing background and historical perspective.
07-Dec-2022	FDA/OPC quarterly SC TC advising planning for Advisory Committee ongoing. Further detail to be provided at the 22-Dec-2022 meeting.
16-Dec-2022	OPC submitted discussion topics for FDA OPC TC re: Advisory Committee.
22-Dec-2022	FDA/OPC SC TC to review plans for Advisory Committee meeting scheduled for 19-Apr-2023.

CLBP = chronic lower back pain; CRO = Clinical Research Organization; EERW = enriched enrollment randomized withdrawal; ER = extended-release; FAQ = frequently asked questions; FDA = Food and Drug Administration; IND = Investigational New Drug application; IR = Information Request; OIH = opioid-induced hyperalgesia; OPC = Opioid Postmarketing Requirements Consortium; PMR = postmarketing requirement; PTRQ=Patient Treatment Response Questionnaire; QST = quantitative sensory testing; SAE = serious adverse event; SAOs = short-acting opioids; SC = sub-committee; SUPPORT = Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities; TC = teleconference.

9.3. Appendix C: Rationale for Inclusion/Exclusion Criteria

Criteria	Rationale
Inclusion Criteria	
1. Is male or a non-pregnant (confirmed by pregnancy test), non-lactating female, aged 18 years or older.	Restricted to adults of either sex as this is not a pediatric study.
2. Has had clinical diagnosis of CNCP for a minimum of 12 months that: – Occurs daily, and – Includes CLBP, OA of the hip or knee, DPN, PPN, or post-cancer-treatment–related pain (i.e., post-thoracotomy pain, radiation plexopathy, post-chemotherapy pain) Note: Patients with overlapping CNCP conditions are permitted to enroll in the trial, provided that the patient reports that pain associated with the non-index pain condition(s)/site(s) is mild.	Diagnoses are restricted to patients expected to benefit from, who are appropriate candidates for ER/LA opioids, and who are generally ambulatory.
3. Has a Worst PI score of ≥ 5 and ≤ 9 over the 7 days prior to Screening for the index pain condition/site(s).	Moderate-to-severe pain consistent with appropriate use of ER/LA opioids.
4. Is taking daily SAO therapy, defined as any SAO drug product: – Taken ≥ 2 times per day ≥ 5 days per week for any ≥ 3 consecutive months in the 6 months prior to Screening, with an inadequate analgesic response, as determined below, and – Total daily dose is ≥ 30 MME Note: Patients not currently on SAOs are considered eligible if they would have met the above criteria had they not discontinued SAO use within the prior 6 months due to tolerability issues, lack of efficacy, or loss of access.	Consistent with clinical guidance recommending the use of SAOs prior to initiating the use of ER/LA opioids. MME threshold to confirm that patient dissatisfaction is not related to inadequate SAO dosing.
5. Is dissatisfied with his or her pain control while taking SAOs, as determined by agreement between the investigator and patient and informed by responses on the PPQ.	Consistent with clinical guidance recommending the use of SAOs prior to initiating the use of ER/LA opioids.
6. Has not responded or has contraindications to ≥ 2 non-pharmacologic classes and ≥ 2 non-pharmacologic therapies for the index pain condition(s), according to the investigator's judgement, following review of the patient's PTRQ responses, as well as external documentation, if available.	Consistent with clinical guidance recommending the use of non-pharmacologic or pharmacologic therapies prior to the use of opioids.
7. Is an appropriate candidate for ER opioid therapy, according to the investigator's clinical judgement.	Allows other factors that may impact the appropriateness of ER/LA opioid use in an individual patient to be considered by the investigator.
8. Is considered, in the opinion of the investigator, to be generally healthy, based on the results of medical history, physical examination, 12-lead ECG, and laboratory profile.	For safety reasons, patients should be considered healthy enough to receive ER/LA opioid therapy safely.
9. Female patient of non-childbearing potential must be surgically sterile or postmenopausal (postmenopausal is defined as at least 1 year without menses and confirmed by serum FSH ≥ 50 mIU/mL). A female patient is considered to be surgically	Intended to decrease the risk of unplanned pregnancies.

Criteria	Rationale
sterile if she has had a tubal ligation, hysterectomy, bilateral salpingo-oophorectomy or bilateral oophorectomy, or hysterectomy with bilateral salpingo-oophorectomy	
10. Female patient of childbearing potential must be using a medically accepted method of contraception (minimum required use 30 days prior to the first dose of ER trial medication, if not otherwise specified) and agree to continued use of this method for the duration of the trial and for 30 days after the last dose of ER trial medication. Acceptable methods of contraception include abstinence from heterosexual intercourse, intrauterine device (with or without hormones), hormonal contraceptives (i.e., birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch [at least 90 days prior]), partner vasectomy (at least 6 months prior), or double-barrier method of contraception (e.g., male condom in addition to a diaphragm, contraceptive sponge, or spermicide).	
11. Is able to speak, read, write, and understand English, understand the consent form, has the capacity to provide informed consent, and can effectively communicate with the trial staff.	Ethical reasons, as well as to enable patients to complete assessments required for the trial.
12. Is voluntarily willing to give informed consent in signed and dated writing prior to participation in the performance of the trial procedures.	Ethical requirement.
13. Is willing and able to participate in all trial procedures and requirements, as described in the informed consent form.	Ethical reasons and to increase the probability that patients will complete the trial.
Exclusion Criteria	
1. Has any clinically significant medical or psychiatric condition that would, in the opinion of the investigator, preclude trial participation or interfere with the assessment of pain or other symptoms or would increase the risk of opioid-related AEs, including opioid use disorder.	To increase patient safety.
2. Has a primary diagnosis of fibromyalgia, complex regional pain syndrome, peripheral or central neuropathic pain, somatoform pain syndromes, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, discitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm that is not currently in remission.	Exclusion of diagnoses where ER/LA opioids are not expected to have a benefit or conditions where it would be difficult for the patient to attend visits and complete assessments.
3. Has experienced myocardial infarction or coronary artery bypass graft surgery within 12 months prior to Screening.	To increase patient safety.
4. Has known allergies or hypersensitivity to naloxone, morphine, or other opioids.	To increase patient safety.
5. Has known or suspected gastrointestinal obstruction, including paralytic ileus.	To increase patient safety and allow for absorption of oral study medications.

Criteria	Rationale
6. Has a current diagnosis of irritable bowel syndrome or other visceral pain syndrome causing moderate-to-severe pain.	To increase patient safety and avoid confounding efficacy endpoints.
7. Has any sensory loss in the arms that, in the opinion of the clinician, is likely to interfere with QST (OIH Population only).	To allow for QST measurements.
8. Has undergone a surgical procedure for the primary cause of pain within 6 months prior to Screening.	To avoid confounding efficacy endpoints.
9. Has had an intra-articular injection of any medication or a nerve or plexus block, including epidural steroid injections or facet blocks, within 6 weeks prior to Screening, or has had botulinum toxin injection in the lower back region or high-dose topical capsaicin within 3 months prior to Screening.	To avoid confounding efficacy endpoints.
10. Has had confirmed malignancy within 6 months of Screening, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin.	To increase patient safety and avoid confounding efficacy endpoints.
11. Has uncontrolled blood pressure defined by a sitting systolic blood pressure > 180 mmHg or < 90 mmHg or a sitting diastolic blood pressure > 110 mmHg or < 40 mmHg at Screening.	To increase patient safety.
12. Has a clinically significant abnormality in clinical chemistry, hematology, or urinalysis, including serum glutamic-oxaloacetic transaminase/aspartate aminotransferase or serum glutamic pyruvic transaminase/alanine aminotransferase ≥ 3-fold the upper limit of the reference range, or serum creatinine > 2 mg/dL at Screening.	To increase patient safety.
13. Has a body mass index ≥ 40 kg/m^2 or is considered by the investigator to be at high risk for development of respiratory depression, including a STOP-Bang Questionnaire score ≥ 5, or has severe, uncontrolled bronchial asthma.	To increase patient safety.
14. Has clinically significant depression or anxiety based on a score of ≥ 14 on either subscale of the HADS at Screening or suicidal ideation associated with actual intent and a method or plan (“Yes” answers on items 4 or 5 of the C-SSRS, Screening Version) or a previous history of suicidal behaviors (“Yes” answer to any of the suicidal behavior items of C-SSRS Screening), in the past 5 years).	To increase patient safety.
15. Has a diagnosis, per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), of any substance use disorder (except for nicotine or caffeine), or has a positive UDT for illicit drugs (including cannabis), non-prescribed controlled substances (opioid or non-opioid), or alcohol at Screening.	To increase patient safety and avoid confounding study assessments.
16. Has ever experienced an opioid overdose, which, according to the investigator’s review and judgment, may present a future safety risk to the patient when using short-acting or ER opioid therapy in this trial.	To increase patient safety.
17. Has ongoing or past litigation or compensation associated with pain, has pending applications for workers compensation or disability, or plans to file litigation or claims within the next 12 months.	To avoid potential bias in reporting of pain.

Criteria	Rationale
18. Has used a monoamine oxidase inhibitor within 14 days prior to Screening.	To increase patient safety.
19. Has taken ER/LA opioids in the past and discontinued for lack of tolerability or effectiveness or has recently taken ER/LA opioids (currently and/or within 1 month of Screening).	To increase patient safety and to avoid confounding efficacy endpoints.
20. Has taken opioid agonist-antagonists (pentazocine, butorphanol, or nalbuphine), central-acting alpha-agonists, barbiturates, medication-assisted drug therapy for substance use disorder, kratom, or more than 1 type of benzodiazepine drug within 1 month prior to Screening.	To increase patient safety.
21. Has taken any investigational drug within 1 month prior to Screening or is currently enrolled in another investigational drug trial.	To increase patient safety.

CLBP = chronic lower back pain; CNCP = chronic non-cancer pain; C-SSRS = Columbia-Suicide Severity Rating Scale; DPN = diabetic peripheral neuropathy; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG = electrocardiogram; ER/LA = extended-release/long-acting; FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; MME = milligram morphine equivalents; OA = osteoarthritis; OIH = opioid-induced hyperalgesia; PI = pain intensity; PPN = painful peripheral neuropathy; PPQ = Pain Profile Questionnaire; PTRQ = Pain Treatment Response Questionnaire; QST = quantitative sensory testing; SAO = short-acting opioid; UDT = urine drug testing.

9.4. Appendix D: Draft Protocol and Appendices, Dated March 01, 2022

Clinical Trial Protocol
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

PRODUCT: MORPHINE SULFATE EXTENDED-RELEASE (ER) TABLETS

Original Protocol: 0.8, 01-Mar-2022

1. SPONSOR AND KEY PERSONNEL CONTACT INFORMATION

Contact information will be provided in a separate document.

2. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)	
Name of Investigational Product: morphine sulfate extended-release tablets	
Name of Active Ingredient: morphine sulfate	
Study Title: 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	
Principal Investigator: TBD	
Trial Centers: TBD	
Trial Period: Estimated date first patient enrolled: TBD Estimated date last patient completed: TBD	**Phase of Development:** 4

Objectives:

Primary Objective:

- To evaluate the persistence of analgesic efficacy of an extended-release (ER) opioid in the Double-Blind Phase, in patients with defined chronic non-cancer pain (CNCP) who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase.

Secondary Objectives:

- To explore the incidences of opioid-induced hyperalgesia (OIH) and opioid tolerance.
- To evaluate changes in pain sensitivity over time.
- To identify potential predictors of the opioid analgesic response and non-response.
- To evaluate changes in physical function and in levels of anxiety and depression.
- To evaluate the safety of titrated doses of an ER opioid.
- To evaluate all endpoints in patients who are titrated to a high dose of ER opioid.

Methodology:

Note: this synopsis provides an overview of the trial; refer to the body of the protocol below for additional details.

The planned trial is a 12-month multicenter, randomized, placebo-controlled, double-blind clinical trial with an enriched-enrollment randomized withdrawal (EERW) design to evaluate the persistence of analgesic efficacy and tolerability of a representative ER opioid (morphine sulfate ER) in the Double-Blind Phase, in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase. The trial will also include an evaluation for OIH.

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate
The trial will include 5 phases: A Screening Phase (up to 3 weeks), an Open-Label Titration Phase (~ 6 weeks), an Open-Label Treatment Phase (~ 36 weeks), a Double-Blind Phase (10 weeks), and a Tapering and Follow-up Phase (~ 2 to 9 weeks). At Screening, patients will be asked to provide informed consent and will subsequently be evaluated for entry into the trial. To be eligible at Screening, each patient must report a Worst Pain Intensity (PI) score over the prior 7 days of ≥ 5 and ≤ 9 on a 0 to 10 numerical rating scale (NRS) and must express dissatisfaction with short-acting opioid (SAO) therapy, as determined by agreement between the clinician (i.e., research site investigator) and patient, and informed by use of the patient-reported Pain Profile Questionnaire (PPQ). Following confirmation of eligibility during the Screening Phase, patients will enter the ~ 6-week Open-Label Titration Phase, during which they will attend weekly visits. The total daily dose of morphine sulfate ER will be titrated to achieve efficacy as tolerated, using a titration structure that resembles clinical practice. The dose levels of morphine sulfate ER will be subject to increase when the mean Worst PI score is ≥ 5 in the prior 7 days; increase will also be based on the judgment of the investigator. Rescue medications will not be permitted during the Open-Label Titration Phase. Patients who meet enrollment criteria during the Open-Label Titration Phase will enter the ~ 36-week Open-Label Treatment Phase. The duration of the Open-Label Titration Phase will be flexible, such that patients who meet enrollment criteria may begin the Open-Label Treatment Phase prior to completing the full 6 weeks of titration or may remain in the Titration Phase for longer if needed. However, the duration of the Open-Label Treatment Phase will be adapted for these patients, such that the total duration of the 2 phases (Open-Label Titration and Treatment) will be 42 weeks. During the Open-Label Treatment Phase, patients will return to the clinic every 4 weeks for trial assessments, with remote contact in between visits. Morphine sulfate ER may be adjusted, when necessary (up to 240 mg/day), but doses must be stable for the 7 days prior to randomization. During the Open-Label Treatment Phase, patients may also receive an SAO and/or acetaminophen (APAP) as needed (PRN) up to the maximum permitted doses. Consistent with current clinical practice, patients may be offered the opportunity to taper off morphine sulfate ER during the Open-label Titration or Open-Label Treatment Phases. Patients who are tapered off morphine sulfate ER prior to randomization in the Double-Blind Phase will be discontinued from that phase, complete the Week 52 assessments, and then begin their taper in an unblinded fashion in the Tapering and Follow-up Phase. After the ~ 36-week Open-Label Treatment Phase, patients who meet randomization criteria will be randomized (1:1) into the 10-week Double-Blind Phase to continue their current doses of morphine sulfate ER, or to undergo a slow taper to placebo. Patients in the placebo group will be tapered gradually in a double-blinded manner over the course of 1 to 8 weeks to minimize the likelihood of opioid withdrawal and unblinding. Note that a 1-week taper will be used only for patients receiving the lowest dosage strength of morphine sulfate ER (15 mg twice daily [BID]). The 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. Patients will

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate
attend clinic visits every 2 weeks during the Double-Blind Phase with remote contact every week when a visit is not scheduled. There will be no dosage adjustments during the Double-Blind Phase; however, SAO and APAP rescue medication may be administered at the discretion of the investigator. At the end of the Double-Blind Phase (Week 52) or early discontinuation, patients will enter the Tapering and Follow-up Phase. ER trial medication will be tapered down over the course of 1 to 8 weeks, depending on the ER trial medication dose. Patients will be asked to attend a final safety follow-up visit within 5 days of the last dose of ER trial medication, so that the Tapering and Follow-up Phase will comprise ~ 2 to 9 weeks. Reasonable efforts will be made to ensure continuity of care for patients, as outlined in Section 7.1.5 of the protocol. Quantitative Sensory Testing (QST) assessments will be performed in a subset of patients (OIH Population). QST will be performed twice during Screening (to obtain between-session variability data), during the Open-Label Treatment Phase (Week 10 and Week 26), prior to randomization into the Double-Blind Phase (Week 42), and at the end of the Double-Blind Phase (Week 52).
Number of Patients (Planned): The planned sample size is 200 patients randomized into each treatment group in the Double-Blind Phase (400 patients in total). An interim analysis of efficacy will be performed, and the sample size may be increased, as needed. Based on an assumption of 60% retention, 666 patients will be enrolled into the Open-Label Treatment Phase to randomize 400 patients in the Double-Blind Phase. It is estimated that approximately 1,100 patients will need to be enrolled in the Open-Label Titration Phase to achieve the targeted number of patients for the Open-Label Treatment Phase. Up to 30 research sites will perform QST and contribute to the OIH Population, which will comprise at least 200 patients who enter the Open-Label Titration Phase and have at least 1 post-treatment QST evaluation. The retention rate will be actively monitored throughout the trial and enrollment adjusted to efficiently target the Double-Blind sample size, as well as the OIH population goal.
Diagnosis and Main Criteria for Inclusion: Generally healthy adult (≥ 18 years of age) males, or non-pregnant, non-lactating females, with a clinical diagnosis of daily CNCP (chronic pain that is not directly cancer related, including chronic low back pain [CLBP], osteoarthritis [OA] of the hip/knee, diabetic peripheral neuropathy [DPN], painful peripheral neuropathy [PPN], or post-cancer-treatment–related pain in patients without active cancer), who have been taking SAO therapy ≥ 2 times per day (≥ 30 milligram morphine equivalents [MME]/day) at least 5 days/week for any ≥ 3 consecutive months in the 6 months prior to Screening and are dissatisfied with their pain control.
Investigational Product, Dosage, and Mode of Administration: ***Open-Label Titration Phase:*** Open-label, oral titrated doses of morphine sulfate ER, administered BID to a maximum dose of 240 mg per day for ~ 6 weeks.

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate
Open-Label Treatment Phase: Open-label, oral titrated doses of morphine sulfate ER, administered BID to a maximum dose of 240 mg per day for ~ 36 weeks. Morphine sulfate ER doses must be stable for the 7 days prior to randomization. ***Double-Blind Phase:*** Double-blind fixed oral doses of morphine sulfate ER (i.e., stabilized dose at the end of the Open-Label Treatment Phase), administered BID, for 10 weeks, in patients randomized to continue active ER opioid. No dosage adjustments will be permitted during the Double-Blind Phase.
Reference Therapy, Dosage, and Mode of Administration: ***Double-Blind Phase:*** Double-blind tapering doses of morphine sulfate ER for 1 to 8 weeks, and placebo for 9 to 2 weeks, respectively, administered BID, in patients randomized to the placebo group. Tapering schedules will vary depending on the stabilized dose at randomization. ***Rescue Medications:*** No rescue medications will be allowed during the Open-Label Titration Phase. During the Open-Label Treatment and Double-Blind Phases, oral SAO up to 2 × 15 mg immediate-release (IR) morphine tablets per day and APAP up to 3000 mg per day will be permitted PRN. To avoid confounding the results of the primary endpoint, additional rescue medications (such as NSAIDs) will not be permitted during the trial. Intranasal naloxone, and instructions for its use, will be provided to all patients during the trial.
Duration of Trial: Patients may participate in the trial for up to 64 weeks: up to 3 weeks for Screening, ~ 6 weeks for the Open-Label Titration Phase, ~ 36 weeks for the Open-Label Treatment Phase (duration of the Open-Label Titration Phase may vary, but the actual duration will combine with that of the Open-Label Treatment Phase to be 42 weeks), 10 weeks for the Double-Blind Phase, and ~ 2 to 9 weeks for the Tapering and Follow-up Phase. The maximum exposure to titrated doses of morphine sulfate ER in this trial will be 53 to 60 weeks for patients randomized to ER opioid (including 42 weeks in Open-Label Titration/Treatment Phases; 10 weeks in Double-Blind Phase; and 1-8 weeks of taper in Tapering and Follow-up Phase) and 43 to 50 weeks for patients randomized to placebo (including 42 weeks in Open-Label Titration/Treatment Phases and 1-8 weeks of tapering in Double-Blind Phase).
Criteria for Evaluation: ***Trial Endpoints:*** ***Primary Endpoint*** ▪ Time to loss of efficacy (during the Double-Blind Phase), where loss of efficacy is defined as: o ≥ 30% increase in past 7-day moving average of the daily Worst PI compared to the 7 days prior to randomization and past 7-day moving average of the daily Worst PI ≥ 5, OR o Patient initiates new pharmacologic therapy for the index chronic pain condition, OR o Trial drug is discontinued due to lack of efficacy.

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)

Name of Investigational Product: morphine sulfate extended-release tablets

Name of Active Ingredient: morphine sulfate

Secondary Efficacy Endpoints

- Time to treatment failure (loss of efficacy or tolerability), including for patients who meet the above composite definition of loss of efficacy OR patients who discontinue due to adverse events (AEs).
- Time to loss of efficacy defined using Average PI (≥ 30% increase in past 7-day moving average of the daily Average PI compared to the 7 days prior to randomization and past 7-day moving average of the daily Average PI ≥ 4).
- Proportion of patients who meet the criteria for loss of efficacy and treatment failure (as defined above) by week.
- Change in mean past 7-day Worst PI and Average PI.
- Change in physical function, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS®) Item Bank v2.0 – Physical Function – Short Form 8b (PROMIS PF-SF-8b).
- Change in Brief Pain Inventory–Short Form (BPI-SF) scores.
- Patient Global Impression of Change (PGIC) scores.
- Change in health-related quality of life, as measured using the EuroQOl, 5-dimension, 5-level descriptive system (EQ-5D-5L).

Secondary OIH Endpoints

- Incidence of patients who develop OIH associated with ER opioid during the trial, defined for the purposes of this analysis 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
  - QST batteries at the final assessment show increased pain sensitivity compared to QST results obtained at Screening.
- Incidence of patients who develop OIH during the Open-Label Treatment Phase, defined for the purposes of this analysis as:
  - Worst PI prior to randomization is the same or higher than at Screening, when the patient is receiving an ER opioid at an equivalent or higher dose

    AND
  - QST batteries prior to randomization show increased pain sensitivity compared to QST results obtained at Screening.
- Pain sensitivity changes (QST) over time during the Open-Label Treatment Phase and by treatment group during the Double-Blind Phase.
- Pain spread, as assessed by the Widespread Pain Index (WPI) subscale of the Fibromyalgianess Scale (FS)

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate

Other Secondary Endpoints

- Incidence of patients who develop opioid tolerance during the trial, 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
  - QST batteries at the final assessment show no increase in pain sensitivity compared to QST results obtained at Screening.
- Incidence of patients who develop opioid tolerance during the Open-Label Treatment Phase, defined for the purposes of this analysis as:
  - Worst PI prior to randomization is the same or higher than at Screening, when the patient is receiving an ER opioid at an equivalent or higher dose

    AND
  - QST batteries prior to randomization show no increase in pain sensitivity compared to QST results obtained at Screening.
- Incidence of patients who experience a loss of effect of opioid over time, including patients who develop OIH and patients who develop tolerance, as defined above.

Exploratory Endpoints

- Mean total mg of IR morphine (SAO) and APAP rescue medications used for each treatment group during the Double-Blind Phase.
- Proportion of patients who initiated new analgesic therapy (pharmacologic and non-pharmacologic) for index chronic pain condition(s) by trial phase.
- Fibromyalgianess, as measured by the FS (analyzed only as a predictor).
- Predictors of opioid analgesic response and non-response, such as demographics, chronic overlapping pain conditions, fibromyalgianess, personal/family history of mental illness and substance use disorders, anxiety/depression, pain catastrophizing, pain profile, physical function, AEs, QST, sleep/insomnia, and COWS results.
- Cluster analysis of putative components of the OIH syndrome.
- Patient responses on the unblinding questionnaire.

Safety Endpoints

General Safety Endpoints:

- Safety of ER opioid therapy, as assessed by spontaneously reported AEs, clinical laboratory test results, vital signs measurements, physical examination findings, electrocardiogram (ECG) findings, and use of concomitant medications.
- Proportion of patients who discontinue due to AEs or who experience serious AEs (SAEs).
- Proportion of patients with abuse-related AEs of special interest (AESIs).
- Proportion of patients who meet criteria for prescription opioid abuse, misuse, or both, according to the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ).

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate

- Proportion of patients with positive urine drug test (UDT) results for illicit drugs or non-prescribed controlled substances.
- COWS and SOWS scores over time.
- Proportion of patients who meet criteria for opioid withdrawal (COWS ≥ 5).

Endocrine and Sexual Function:

- Change in endocrine function tests (i.e., free and total testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol [women only], insulin growth factor–1 [IGF 1], cortisol, adrenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEAS], and thyroid-stimulating hormone [TSH]) from Screening to the final assessment.
- Proportion of male patients with total testosterone < 250 ng/dL at the final assessment.
- Change in sexual function scores (Arizona Sexual Experience Scale [ASEX]) from Screening to the final assessment.

Psychological Assessments, Sleep, and Other Endpoints:

- Change in levels of anxiety and depression symptoms, as measured by the Hospital Anxiety and Depression Scale (HADS) from Screening to the final assessment.
- Pain catastrophizing, as measured by the Pain Catastrophizing Scale (PCS; analyzed only as a predictor).
- Change in sleep, as measured by the Insomnia Severity Index (ISI), from Screening to the final assessment.
- Positive reports of suicidality and suicidal ideation, as per the Columbia Suicide Severity Rating Scale (C-SSRS).

High Dose ER Opioid Endpoints

- All endpoints listed above also assessed in a subgroup analysis of patients who achieve a high dose of ER opioid (≥ 90 mg per day).

Statistical Methods (Data Analysis):

Trial Populations:

Full Analysis Set (FAS): The FAS will include all patients randomized into the Double-Blind Phase. This population will be used for efficacy reporting.

OIH Population: The OIH Population will include all patients who enter the Open-Label Titration Phase and have at least 1 post-treatment QST evaluation.

Full Safety Population: The Full Safety Population will include all patients dosed with morphine sulfate ER at any point in the trial.

Open-Label Treatment Safety Population: The Open-Label Treatment Safety Population will include all patients who are successfully titrated and dosed in the Open-Label Treatment Phase.

Double-Blind Safety Population: The Double-Blind Safety Population will include all patients who are randomized and dosed in the Double-Blind Phase.

Name of Sponsor/Company: Opioid Postmarketing Requirements Consortium (OPC)
Name of Investigational Product: morphine sulfate extended-release tablets
Name of Active Ingredient: morphine sulfate
Analyses: The primary efficacy endpoint of time to loss of efficacy will be analyzed using Kaplan-Meier methodology with stratification for the titrated dose levels. Quantiles for 25%, median, and 75% will be presented, as well as 95% confidence intervals (CIs), if estimable. The treatment arms will be compared using a stratified log-rank test against the hypothesis that there is no difference in the time to loss of efficacy in the trial arms. Sensitivity analyses will investigate varying the threshold of SAO and APAP rescue medication use to qualify as a loss of efficacy and including additional ambiguous reasons for early discontinuation (such as "other," "lost to follow-up," and "unknown,") as loss of efficacy. The OIH incidence for each endpoint will be reported with the number and percentage of patients and associated 95% CI of the percentage. For the Double-Blind Phase, the numbers and percentages will be reported by trial arm and the differences in percentages will be reported as well as 95% CIs. The arms will be compared using a difference in proportions Z test; if there are less than 5 patients expected in a cell, a Fisher's exact test will be used instead. The primary analysis for rates of OIH will use the following approach for missing and partial data. Patients who discontinue the trial due to loss of efficacy will be treated as satisfying the pain criterion for OIH; each discontinued patient's last available dosing information and QST battery results will then be evaluated to determine whether he or she represents a case of OIH. All other patients with missing data will be evaluated to determine whether they met the OIH criteria at any earlier time point, and they will be counted as such if this occurs; otherwise, these patients will be assumed not to be cases of OIH. Additionally, the number and proportion of patients missing each component of the OIH outcome, the proportion of patients with complete assessments, and the proportion of patients determined to exhibit OIH among those with complete assessments will be reported. Sensitivity analyses will be performed to test the robustness of the results and statistical assumptions. For patients with missing data who do not have results precluding the presence of OIH, values will be imputed and analyzed via multiple imputation in 2 different ways: (1) A multiple imputation approach will be applied, assigning each patient as having an event with the same probability as the observed rate in his or her treatment arm. (2) A multiple imputation approach will be applied, assigning each patient as having an event with the same probability as the overall observed rate across both treatment arms.

3. TABLE OF CONTENTS

Table of Tables

Table of Figures

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks
AE	Adverse event
AESI	Adverse event of special interest
APAP	Acetaminophen
ASEX	Arizona Sexual Experience Scale
BID	Twice daily
BPI-SF	Brief Pain Inventory – Short Form
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLBP	Chronic low back pain
CNCP	Chronic non-cancer pain
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form (may include electronic data capture systems or paper forms)
CRO	Contract Research Organization
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
DEA	Drug Enforcement Agency
DHEAS	Dehydroepiandrosterone sulfate
DPN	Diabetic peripheral neuropathy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	Electrocardiogram
EDC	Electronic data capture

EERW	Enriched-enrollment randomized withdrawal
EQ-5D-5L	EuroQOL, 5-dimension, 5-level descriptive system
ER	Extended-release
FAS	Full Analysis Set
FDA	Food and Drug Administration
FS	Fibromyalgianess Scale
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
IGF 1	Insulin growth factor–1
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare provider
HP50%	Half-maximum heat pain
HPDIF	Heat pain differential
HPRAT	Sustained heat pain ratings
HPSUM	Heat pain summation
HPTHR	Heat pain threshold
HPTOL	Heat pain tolerance
ICD-11	11th revision of the International Statistical Classification of Diseases and Related Health Problems
ICF	Informed consent form
ICH	International Council on Harmonisation
IR	Immediate-release
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LA	Long-acting
LH	Luteinizing hormone

LtFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MME	Morphine milligram equivalent
NRS	Numerical rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OIH	Opioid-induced hyperalgesia
OPC	Opioid Postmarketing Requirements Consortium
PCS	Pain Catastrophizing Scale
PF-SF-8b	Physical Function – Short Form 8b
PGIC	Patient Global Impression of Change
PgP	P-glycoprotein
PI	Pain Intensity
PMR	Postmarketing requirement
POMAQ	Prescription Opioid Misuse and Abuse Questionnaire
PPN	Painful peripheral neuropathy
PPQ	Pain Profile Questionnaire
PRN	As needed
PROMIS	Patient-Reported Outcomes Measurement Information System
PTRQ	Pain Treatment-Response Questionnaire
Q12H	Every 12 hours
QHS	Once in the evening
QST	Quantitative Sensory Testing
SAE	Serious adverse event
SAO	Short-acting opioid
SAP	Statistical analysis plan

SOC	System organ class
SOWS	Subjective Opiate Withdrawal Scale
SSS	Symptom Severity Score
STOP-Bang	Snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference and gender questionnaire
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
UDT	Urine drug test
USP	United States Pharmacopeia
WHO-DDE	World Health Organization – Drug Dictionary Enhanced
WPI	Widespread Pain Index

5. INTRODUCTION

5.1. Background

The Food and Drug Administration (FDA) released 5 postmarketing requirements (PMRs) on September 13, 2013; these were subsequently replaced with 11 PMRs in February, 2016 (10 postmarketing studies and 1 clinical trial). PMR 3033-11 consists of the requirement to "*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*." Within this PMR was a further mandate to "*include an assessment of risk relative to efficacy*." Further communications have clarified FDA's expressed interest in the characteristics of patient populations that would benefit from opioid treatment, in order to help prescribers determine whether long-term opioid use is appropriate for a prospective patient (November 8, 2019, FDA–Opioid Postmarketing Requirements Consortium [OPC] meeting minutes).

Although definitions of chronic pain vary, the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) defines chronic pain as persistent or recurrent pain lasting longer than 3 months (Treede et al., 2015). Chronic pain may result from underlying medical diseases or conditions, injury, medical treatment, inflammation, or unknown causes. Chronic pain is a prevalent condition, affecting an estimated 20% of people worldwide (Breivik et al., 2006; Goldberg & McGee, 2011; Gureje et al., 2008). The 2012 National Health Interview Survey found that 11.2% of adults reported having daily pain (Nahin, 2015), while the Global Burden of Disease Study estimated that persistent pain affects over 100 million adults in the United States (US) at any given time (2015). Clinical, psychological and social consequences of chronic pain may limit participation in complex activities, result in lost work productivity, and lead to stigmatization; chronic or persistent pain is among the leading global causes of reduced quality of life (Dahlhamer et al., 2018; Global Burden of Disease Study, 2015).

Patients with chronic pain are treated with a wide range of interventions, with analgesic medications, such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, among the most common treatments. Extended-release and long-acting (ER/LA) opioids provide an important treatment option for patients suffering from chronic pain conditions. In 2018, approximately 52 million patients were dispensed prescriptions for oral or transmucosal opioid analgesics from US outpatient retail pharmacies; 0.2% of these patients received higher dosage strength product prescriptions (≥ 90 morphine milligram equivalents [MME] per unit; FDA, 2019). Of note, the number of patients with dispensed prescriptions for ER/LA opioid analgesics from US outpatient retail pharmacies decreased from 21,446,004 in 2013 to 17,461,720 in 2017 (FDA, 2018a).

Opioids have been shown to be efficacious in the treatment of chronic non-cancer pain (CNCP) for up to 3–4 months in randomized controlled trials (Caldwell et al., 1999; Hale et al., 2007; Jamison et al., 1998; Meske et al., 2018). However, only a few studies have been conducted to rigorously assess the long-term benefits of opioids (i.e., for at least 1 year) for chronic pain (Chou et al., 2014; Farrar et al., 2022). In addition, long-term administration of opioids may

involve risks of serious side effects, such as sedation, respiratory depression, overdose, and in some cases, drug misuse, abuse, or dependence.

Further, a proportion of patients on long-term opioid therapy experience the loss of initial pain control despite dose escalation. This recurrence of pain can potentially occur as a result of opioid tolerance or opioid-induced hyperalgesia (OIH) (Katz et al., 2015b). In the case of opioid tolerance, the effect of opioid therapy is lost over time, while pain sensitivity remains unchanged. With OIH, it is postulated that opioid therapy causes a paradoxical hypersensitivity to pain that effectively neutralizes the analgesic effects of the drug. Both phenomena manifest as an apparent loss of drug effect over time and are expressed as a rebound of pain intensity, the need for dose escalation to maintain pain control, or both.

Thus, opioid analgesics present unique challenges in clinical practice and public health, in that they provide clinically significant analgesic benefits, including for pain for which other analgesics are inadequate, while also carrying serious risks, including the potential for development of opioid tolerance or OIH, especially when used for an extended duration.

5.1.1. Potential Benefits of Investigational Product

Morphine sulfate ER will be included in the current trial as a representative of the ER/LA opioid class. ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Product labels and studies published in the literature demonstrate the efficacy of these ER opioids in the management of CNCP for periods of up to 3 months (Meske et al., 2018; Nicholson et al., 2006; Rauck et al., 2006).

5.1.2. Risks Associated with Investigational Product

Information about the risks associated with morphine sulfate ER tablets can be found in the product label. Briefly, as with all opioids, ER opioids may expose users to the risks of opioid use disorder and misuse. Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended, although the risk is greatest during dose initiation or following a dose increase. Cases of adrenal insufficiency have been reported with opioid use; these occur more frequently following treatment > 1 month in duration. ER opioids may increase the risk of seizures or increase their frequency in patients with seizure disorders or in clinical settings associated with seizures. ER opioids may impair the mental or physical capabilities needed to perform potentially hazardous activities, such as driving a car or operating machinery. Common adverse events (AEs) observed with ER opioids include constipation, nausea, vomiting, somnolence, dizziness, and pruritus.

5.2. Trial Rationale

It has long been recognized that inter-patient variability in analgesic outcomes, even for efficacious treatments, is marked. This variability has been found to be greater between patients than between different pain syndromes, suggesting that the variability may be based at the level of the individual rather than at the level of the disease (Edwards et al., 2016). Such findings also highlight the importance of generating data to help direct specific treatments to those patients

who will demonstrate the most favorable risk-benefit profiles (i.e., those who are most likely to demonstrate analgesia and improvement in function, and least likely to experience serious side effects).

In addition, the majority of registration-focused clinical trials with ER opioids have had durations of 3 months (Meske et al., 2018), highlighting the need to examine longer-term benefits of these products in the management of chronic pain (i.e., for at least 1 year).

Finally, while a number of studies have evaluated OIH in pain patients and patients with opioid use disorders, the majority have been cross-sectional and/or with relatively small sample sizes. There remains a need to evaluate the risks of OIH in a large prospective randomized controlled trial (Chen et al., 2009; Chu et al., 2006; Higgins et al., 2019).

The purpose of this clinical trial is to address PMR 3033-11 by evaluating the long-term efficacy of a representative ER opioid in the management of defined CNCP, including exploring potential predictors of response and non-response, while also assessing the risks of developing OIH in patients with CNCP on long-term ER opioid therapy.

6. TRIAL OBJECTIVES, HYPOTHESIS, AND ENDPOINTS

6.1. Trial Objectives

6.1.1. Primary Objective

The primary objective of the trial is:

- To evaluate the persistence of analgesic efficacy of an ER opioid in the Double-Blind Phase, in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase.

6.1.2. Secondary Objectives

The secondary objectives of the trial are:

- To explore the incidences of OIH and opioid tolerance.
- To evaluate changes in pain sensitivity over time.
- To identify potential predictors of the opioid analgesic response and non-response.
- To evaluate changes in physical function and in levels of anxiety and depression.
- To evaluate the safety of titrated doses of an ER opioid.
- To evaluate all endpoints in patients who are titrated to a high dose of ER opioid.

6.2. Primary Hypothesis

There are patients with CNCP who will achieve clinically meaningful, long-term pain relief in a well-tolerated manner with morphine sulfate ER during the 12 months of this trial.

6.3. Trial Endpoints

6.3.1. Primary Endpoint

The primary endpoint of this trial is as follows:

- Time to loss of efficacy (during the Double-Blind Phase), where loss of efficacy is defined as:
    - ≥ 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
    - Trial drug is discontinued due to lack of efficacy.

6.3.2. Secondary Endpoints

6.3.2.1. Secondary Efficacy Endpoints

- Time to treatment failure (loss of efficacy or tolerability), including for patients who meet the above composite definition of loss of efficacy OR patients who discontinue due to AEs.
- Time to loss of efficacy defined using Average PI (≥ 30% increase in past 7-day moving average of the daily Average PI compared to the 7 days prior to randomization and past 7-day moving average of the daily Average PI ≥ 4).
- Proportion of patients who meet the criteria for loss of efficacy and treatment failure (as defined above) by week.
- Change in mean past 7-day Worst PI and Average PI.
- Change in physical function, as measured by Patient-Reported Outcomes Measurement Information System (PROMIS®) Item Bank v2.0 – Physical Function – Short Form 8b (PF-SF-8b).
- Change in Brief Pain Inventory – Short Form (BPI-SF) scores.
- Patient Global Impression of Change (PGIC) scores.
- Change in health-related quality of life, as measured using the EuroQOL, 5-dimension, 5-level descriptive system (EQ-5D-5L).

6.3.2.2. Secondary OIH Endpoints

- Incidence of patients who develop OIH associated with ER opioid during the trial, defined for the purposes of this analysis 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.
- Incidence of patients who develop OIH during the Open-Label Treatment Phase, defined for the purposes of this analysis as:
    - Worst PI prior to randomization is the same or higher than at Screening, when the patient is receiving an ER opioid at an equivalent or higher dose

      AND

    - QST batteries prior to randomization show increased pain sensitivity compared to QST results obtained at Screening.
- Pain sensitivity changes (QST) over time during the Open-Label Treatment Phase and by treatment group during the Double-Blind Phase.

- Pain spread, as assessed by the Widespread Pain Index (WPI) subscale of the Fibromyalgianess Scale (FS)

6.3.2.3. Other Secondary Endpoints

- Incidence of patients who develop opioid tolerance during the trial, 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

    - QST batteries at the final assessment show no increase in pain sensitivity compared to QST results obtained at Screening.
- Incidence of patients who develop opioid tolerance during the Open-Label Treatment Phase, defined for the purposes of this analysis as:
    - Worst PI prior to randomization is the same or higher than at Screening, when the patient is receiving an ER opioid at an equivalent or higher dose

      AND

    - QST batteries prior to randomization show no increase in pain sensitivity compared to QST results obtained at Screening.
- Incidence of patients who experience a loss of effect of opioid over time, including patients who develop OIH and patients who develop tolerance, as defined above.

6.3.2.4. Exploratory Endpoints

- Mean total mg of immediate-release (IR) morphine (short-acting opioid [SAO]) and acetaminophen (APAP) rescue medication used for each treatment group during the Double-Blind Phase.
- Proportion of patients who initiated new analgesic therapy (pharmacologic and non-pharmacologic) for index chronic pain condition(s) by trial phase.
- Fibromyalgianess, as measured by the FS (analyzed only as a predictor).
- Predictors of opioid analgesic response and non-response, including demographics, chronic overlapping pain conditions, fibromyalgianess, personal/family history of mental illness and substance use disorders, anxiety/depression, pain catastrophizing, pain profile, physical function, AEs, QST, sleep/insomnia, and Clinical Opiate Withdrawal Scale (COWS) results.
- Cluster analysis of putative components of the OIH syndrome.
- Patient responses on the unblinding questionnaire.

6.3.2.5. Safety Endpoints

6.3.2.5.1. General Safety Endpoints

- Safety of ER opioid therapy, as assessed by spontaneously reported AEs, clinical laboratory test results, vital signs measurements, physical examination findings, electrocardiogram (ECG) findings, and use of concomitant medications.
- Proportion of patients who discontinue due to AEs or experience serious AEs (SAEs).
- Proportion of patients with abuse-related AEs of special interest (AESIs).
- Proportion of patients who meet criteria for prescription opioid abuse, misuse, or both, according to the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ).
- Proportion of patients with positive urine drug test (UDT) results for illicit drugs or non-prescribed controlled substances.
- COWS and Subjective Opiate Withdrawal Scale (SOWS) scores over time.
- Proportion of patients who meet criteria for opioid withdrawal (COWS $\geq$ 5).

6.3.2.5.2. Endocrine and Sexual Function

- Change in endocrine function tests (i.e., free and total testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH], estradiol [women only], insulin growth factor-1 [IGF-1], cortisol, adrenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEAS], and thyroid-stimulating hormone [TSH]) from Screening to the final assessment.
- Proportion of male patients with total testosterone < 250 ng/dL at the final assessment.
- Change in sexual function scores (Arizona Sexual Experience Scale [ASEX]) from Screening to the final assessment.

6.3.2.5.3. Psychological Assessments, Sleep, and Other Endpoints

- Change in levels of anxiety and depression symptoms, as measured by the Hospital Anxiety and Depression Scale (HADS) from Screening to the final assessment.
- Pain catastrophizing, as measured by the Pain Catastrophizing Scale (PCS; analyzed only as a predictor).
- Change in sleep, as measured by the Insomnia Severity Index (ISI), from Screening to the final assessment.
- Positive reports of suicidality and suicidal ideation, as per the Colombia-Suicide Severity Rating Scale (C-SSRS).

6.3.2.6. High Dose ER Opioid Endpoints

- All endpoints listed above also assessed in a subgroup analysis of patients who achieve a high dose of ER opioid (≥ 90 mg per day).

7. INVESTIGATIONAL PLAN

7.1. Overall Trial Design and Plan

The planned trial is a 12-month multicenter, randomized, placebo-controlled, double-blind clinical trial with an enriched-enrollment randomized withdrawal (EERW) design to evaluate the persistence of analgesic efficacy and tolerability of a representative ER opioid (morphine sulfate ER) in the Double-Blind Phase, in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase. The trial will also include an evaluation for OIH. An overview of the trial design is provided in Figure 1.

The trial will include 5 phases: a Screening Phase, an Open-Label Titration Phase, an Open-Label Treatment Phase, a Double-Blind Phase, and a Tapering and Follow-up Phase. Patients may participate in the trial for up to 64 weeks: up to 3 weeks for Screening, approximately 6 weeks for the Open-Label Titration Phase, approximately 36 weeks for the Open-Label Treatment Phase (duration of the Open-Label Titration Phase may vary, but the actual duration will combine with that of the Open-Label Treatment Phase to be 42 weeks), 10 weeks for the Double-Blind Phase, and approximately 2 to 9 weeks for the Tapering and Follow-up Phase.

Trial assessments and procedures will be performed at the visits and time points outlined in the Schedule of Assessments (Table 1). More detailed information on trial procedures and assessments is provided in Section 10.

7.1.1. Screening Period

At Screening, patients will be asked to provide informed consent and will subsequently be evaluated for entry into the trial based on medical history, physical examination results, clinical laboratory testing, vital signs, ECG, Worst PI score over the prior 7 days, UDT, and other assessments, as outlined in Table 1. To be eligible at Screening, each patient must report a Worst PI score over the prior 7 days of ≥ 5 and ≤ 9 on a 0 to 10 numerical rating scale (NRS) and must express dissatisfaction with SAO therapy, as determined by agreement between the investigator (i.e., research site investigator) and patient, and informed by use of the patient-reported Pain Profile Questionnaire (PPQ). Prior history of pharmacologic and non-pharmacologic treatments will be confirmed using the guided Pain Treatment-Response Questionnaire (PTRQ). Research sites will be required to make reasonable efforts to obtain external documentation of prior medications, to the extent available, to corroborate the PTRQ. Patients who do not have external documentation may be enrolled at the investigator's discretion, on a case-by-case basis, following approval of the medical monitor. For the OIH Population, Screening will be separated into 2 visits, at least 3 days apart, to accommodate 2 separate QST assessments for evaluation of between-session variability.

7.1.2. Open-Label Titration Phase

Following confirmation of eligibility during the Screening Phase, patients will enter the approximately 6-week Open-Label Titration Phase, during which they will attend weekly visits (± 3 days). The total daily dose of morphine sulfate ER will be titrated to achieve efficacy as

tolerated, using a titration structure that resembles clinical practice, as outlined in Section 9.1. The dose levels of ER opioids will be subject to increase when the mean Worst PI score is ≥ 5 in the prior 7 days; increase will also be based on the judgment of the investigator (dose may be increased in 30 mg daily increments [15 mg twice daily (BID)] per week, up to 240 mg per day). Rescue medications will not be permitted during the Open-Label Titration Phase.

Consistent with current clinical practice, patients who have begun the titration may be offered the opportunity to taper off morphine sulfate ER during this phase. Patients who discontinue prior to entering the Open-Label Treatment Phase will complete the Week 52 assessments and then begin tapering (as appropriate based on the dose at discontinuation). Such patients will begin the Tapering and Follow-up Phase in an unblinded fashion.

7.1.3. Open-Label Treatment Phase

Patients who meet enrollment criteria during the Open-Label Titration Phase (Section 8.3) will enter the ~ 36-week Open-Label Treatment Phase. The duration of the Open-Label Titration Phase will be flexible, such that patients who meet enrollment criteria may begin the Open-Label Treatment Phase prior to completing the full 6 weeks of titration or may remain in the Titration Phase for longer if needed. However, the duration of the Open-Label Treatment Phase will be adapted for these patients, such that the total duration of the 2 phases (Open-Label Titration and Treatment) will be 42 weeks.

During the Open-Label Treatment Phase, patients will return to the clinic every 4 weeks (± 5 days) for trial assessments, as outlined in Table 1. Remote contact will be performed approximately midway between visits. Morphine sulfate ER may be adjusted, when necessary (up to 240 mg/day), but doses must be stable for the 7 days prior to randomization. Patients will be permitted SAO and APAP rescue medication, as outlined in Section 9.7.2.1.

Consistent with current clinical practice, patients may be offered the opportunity to taper off morphine sulfate ER during this phase. Patients who discontinue prior to randomization in the Double-Blind Phase will complete the Week 52 assessments and then begin tapering (as appropriate based on the dose at discontinuation). Such patients will begin the Tapering and Follow-up Phase in an unblinded fashion.

7.1.4. Double-Blind Phase

After the ~ 36-week Open-Label Treatment Phase, patients who meet randomization criteria (Section 8.4) will be randomized (1:1) into the 10-week Double-Blind Phase to continue their current doses of morphine sulfate ER, or to undergo a slow taper to placebo.

To reduce confounding of the primary endpoint (time to loss of efficacy), randomization will be stratified by stable dose of morphine sulfate ER prior to randomization, since this will affect the required duration of tapering for those in the placebo group (i.e., 8 strata of placebo patients who are opioid free by Weeks 2, 3, 4, 5, 6, 7, 8, or 9 or equivalent active ER doses in the ER opioid treatment group). Patients in the placebo group will be tapered gradually in a double-blinded manner over the course of 1 to 8 weeks to minimize the likelihood of opioid withdrawal and unblinding (Appendix 16.1). Note that the 1-week taper will only be used for patients receiving the lowest dosage strength of morphine sulfate ER (15 mg BID). The COWS and SOWS will be

administered regularly to monitor for the potential emergence of withdrawal signs and symptoms.

Patients will attend clinic visits every 2 weeks (± 3 days) during the Double-Blind Phase; a remote contact will be performed every week (± 3 days) when a visit is not scheduled. There will be no dosage adjustments during the Double-Blind Phase; however, SAO and APAP rescue medication may be administered at the discretion of the investigator (Section 9.7.2.1). Patients will be reminded only to take rescue medications when needed (i.e., pain is worsening).

QST assessments will be performed in a subset of patients (OIH Population). QST will be performed twice during Screening (to obtain between-session variability data), during the Open-Label Treatment Phase (Week 10 and Week 26), prior to randomization into the Double-Blind Phase (Week 42), and at the end of the Double-Blind Phase (Week 52).

Additional procedures to be performed during the Double-Blind Phase are outlined in Table 1.

7.1.5. Tapering and Follow-up Phase

All patients who receive at least 1 dose of ER trial mediation will enter the Tapering and Follow-up Phase, either at the end of the Double-Blind Phase (Week 52) or at early discontinuation.

For patients who discontinue in the Open-label Titration or Open-Label Treatment Phases and for those patients who are randomized to active treatment in the Double-Blind Phase, ER trial medications will be tapered slowly to 0 mg over the course of 1 to 8 weeks in the Tapering and Follow-up Phase, depending on the dose of ER medication at the time of discontinuation/completion (refer to Appendix 16.1). Patients who discontinue during the Open-Label Titration or Open-Label Treatment Phases will have their ER medications tapered in an unblinded manner. Patients randomized to active treatment in the Double-Blind Phase will have their ER medications tapered in a double-blinded manner. Patients randomized to placebo will begin tapering during the Double-Blind Phase and will take placebo in a double-blinded manner during the tapering period of the Tapering and Follow-up Phase, to maintain the blind (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case the taper will be completed in the Tapering and Follow-up Phase).

Patients will attend weekly visits (± 3 days) during the tapering period of this phase. The number of visits will depend on the duration of the individual patient's tapering period. Guidelines for tapering are provided in Appendix 16.1.

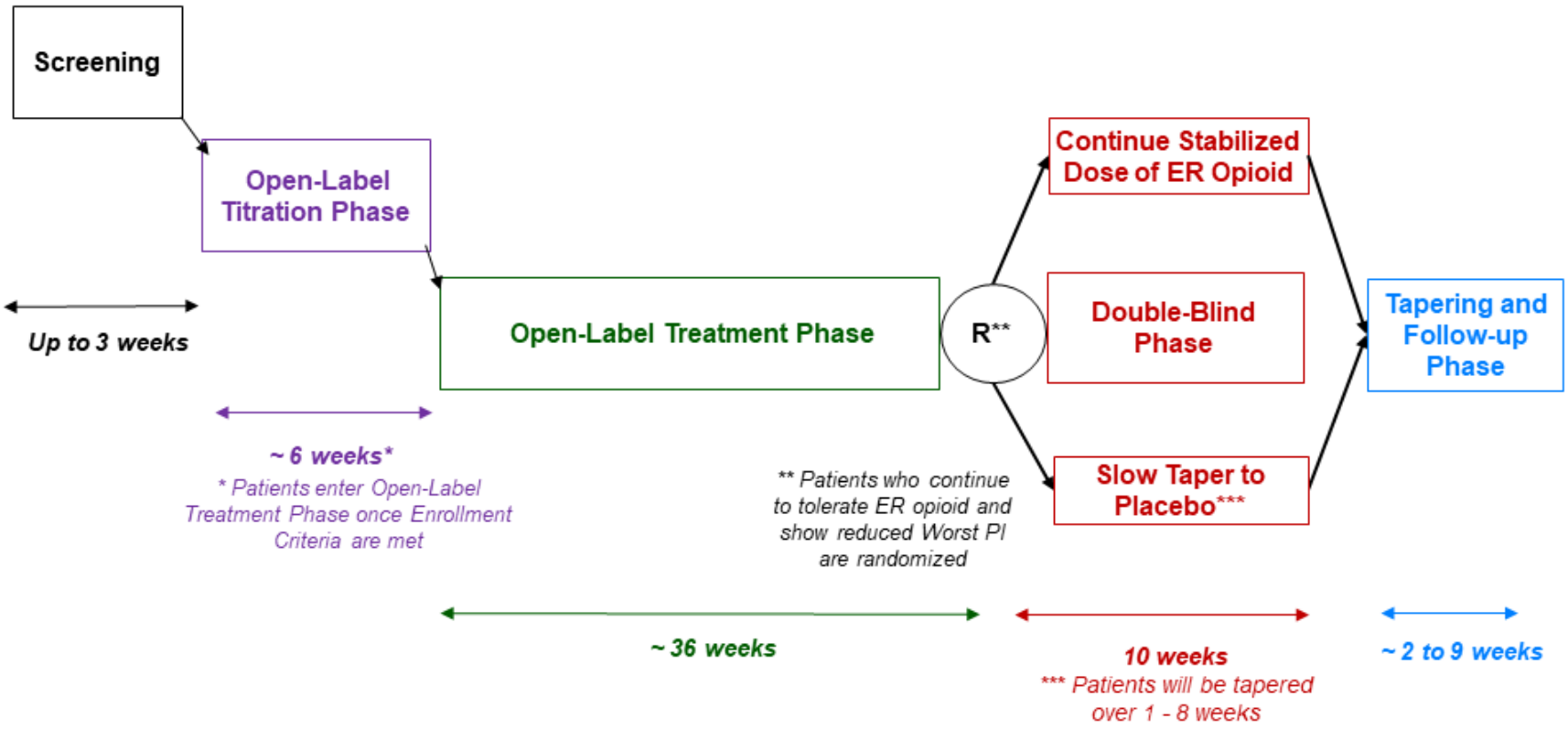
Reasonable efforts will be made to ensure continuity of care for patients. At Screening, patients will be asked to provide the investigator with contact information for their primary care or other qualified healthcare provider (HCP) involved in their pain management. The consenting process will ensure that patients provide authorization to release information to the HCP regarding their participation in the trial. All HCP licenses/Drug Enforcement Agency (DEA) registrations will be verified by the Clinical Research Organization or designee. The investigator will communicate with the HCP, using Institutional Review Board (IRB)-approved letter templates, at the time of trial entry and at end-of-trial. At trial entry, HCPs will be provided with the investigator's contact information to communicate any concerns to the research site.

A patient profile document will be provided directly to HCPs at end-of-trial and will include sufficient information to enable the HCPs to appropriately manage the patient's pain. Unblinding information about the patient's treatment assignment will be provided to HCPs to ensure appropriate continuation of care (refer to Section 9.6 for processes related to HCP unblinding and steps taken to ensure continuation of blinding for research sites and other trial personnel). During the consenting process, patients will be asked to agree that they will not communicate their treatment assignment back to the investigator or any research site personnel, should they become aware of the assignment (through their HCP) after their last trial visit.

For patients who do not have an appropriately licensed HCP, the investigator will provide a referral to locally available medical and social services at the time of trial exit.

All patients will be asked to attend a final safety follow-up visit within 5 days of receiving the last dose of ER trial medication, so that the Tapering and Follow-up Phase will comprise approximately 2 to 9 weeks. Assessments to be performed during the Tapering and Follow-up Phase are outlined in Table 1.

Figure 1: Overview of Trial Design



ER = extended-release; PI = Pain Intensity; R = Randomization.
Notes: Figure is not shown to scale.
The durations of the Open-Label Titration and Treatment Phases may vary; however, the total duration of the 2 phases will be 42 weeks.
All patients (including those who discontinue the trial early) will have their medications tapered over the course of 1 to 8 weeks at the end of their active treatments. This taper will occur in the Tapering and Follow-up Phase, except for those patients who are randomized to placebo. Patients randomized to placebo will begin tapering during the Double-Blind Phase and will take placebo in a double-blinded manner during the tapering period of the Tapering and Follow-up Phase in order to maintain the blind (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case tapering will be completed in the Tapering and Follow-up Phase). Each patient will be asked to attend a final follow-up visit within 5 days of his or her last dose of ER trial medication.

Table 1: Schedule of Assessments

Trial Phase:	Screening[1]	Open-Label Titration[2]	Open-Label Treatment[3]																Double-Blind[4]											Tapering/ Follow-up[5]	
																														Taper visits	Follow-up visit
Week:	-3 to -1	1 to 6	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	43	44	45	46	47	48	49	50	51	52[5]	53+	54+
Visit:	1-2	3.1 to 3.X	4	-	5	-	6	-	7	-	8	-	9	-	10	-	11	-	**12**	-	13	-	14	-	15	-	16	-	17	18+	
Remote contact[6]:			-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	
Informed consent[7]	X																														
Demographics	X																														
Medical history	X																														

[1]. Screening will be separated into 2 visits, at least 3 days apart, to accommodate screening assessments, including 2 separate QST assessments for evaluation of between-session variability (OIH Population only).

[2]. Patients will attend weekly visits (± 3 days) during the Open-Label Titration Phase. Patients who meet enrollment criteria may enter the Open-Label Treatment Phase prior to 6 weeks or may take longer for titration; however, the duration of the Open-Label Treatment Phase will be adjusted accordingly such that the duration of the 2 phases is 42 weeks.

[3]. Patients will return to the clinic every 4 weeks (± 5 days) in the Open-Label Treatment Phase for trial assessments and adjustment of the trial medication when necessary. Dose levels of morphine sulfate ER will be subject to increase/decrease based on the clinical judgment of the investigator. Remote contact will be performed approximately midway between visits.

[4]. Patients will return to the clinic for visits every 2 weeks (± 3 days) during the Double-Blind Phase, with remote contact performed every week in between research site visits (± 3 days).

[5]. Following completion of the Double-Blind Phase (Week 52) or at early discontinuation, patients will attend a final visit with Week 52 assessments and begin a ~ 2- to 9-week Tapering and Follow-up Phase, where all patients (including those who discontinue the trial early) will slowly taper to 0 mg over the course of 1 to 8 weeks (depending on dose of ER medication). Tapering will begin at the Week 52 visit or at the time of discontinuation, except those randomized to placebo. Patients randomized to placebo will begin tapering during the Double-Blind Phase and will take placebo in a double-blinded manner during the tapering period of the Tapering and Follow-up Phase to maintain the blind (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case tapering will be completed in the Tapering and Follow-up Phase). Patients who complete the Double-Blind Phase or discontinue during the Double-Blind Phase will have their medications tapered in a double-blinded manner. Patients who discontinue during the Open-Label Titration or Open Label Treatment Phases will have their medications tapered in an unblinded manner. Patients will attend weekly visits (± 3 days) during tapering; the total number of visits will depend on the duration of tapering needed. Patients will attend a final safety Follow-up Visit within 5 days of the last dose of ER trial medication.

[6]. Remote contact may occur via telephone, email, text messaging, or video conferencing, according to the research site and patient's preferences.

[7]. Patients must sign the informed consent form prior to conducting any trial procedures.

Trial Phase:	Screening[1]	Open-Label Titration[2]	Open-Label Treatment[3]																Double-Blind[4]											Tapering/ Follow-up[5]	
																														Taper visits	Follow-up visit
Week:	-3 to -1	1 to 6	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	43	44	45	46	47	48	49	50	51	52[5]	53+	54+
Visit:	1-2	3.1 to 3.X	4	-	5	-	6	-	7	-	8	-	9	-	10	-	11	-	**12**	-	13	-	14	-	15	-	16	-	17	18+	
Remote contact[6]:			-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	
Prior medications/PTRQ[8]	X																														
Concomitant medications[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[10]	X		X																X									X		X
Vital signs[11]	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X
12-lead ECG	X																														X
Clinical laboratory tests	X		X								X								X									X		X
Serum pregnancy test[12]	X		X								X								X									X		
Urine pregnancy test[12]		X			X		X		X				X		X		X				X		X		X		X			X	X
STOP-Bang	X																														
COWS/SOWS[13]																			X		X		X		X		X		X	X	
Online support tool introduction/reminder[14]	X	X	X																X												
PCS	X																														

[8]. Research sites will be required to make reasonable efforts to obtain external documentation, to the extent available, to corroborate the PTRQ. Patients who don't have either medical records or other data may be enrolled at the investigator's discretion following approval of the medical monitor.
[9]. Patients will be questioned on use of concomitant medications at each visit/remote contact.
[10]. Full physical examination at Screening and brief physical examinations (examination of heart, lungs, abdomen, and legs) thereafter.
[11]. At Screening: Height, weight, pulse rate, respiratory rate, blood pressure, and body mass index. At subsequent visits: pulse rate, respiratory rate, and blood pressure only.
[12]. Women of childbearing potential only. Serum pregnancy tests will coincide with clinical laboratory tests. A urine pregnancy test will be performed once at the beginning of the Titration Phase, and once monthly during the other phases (excluding Screening), at visits where serum pregnancy tests are not performed.
[13]. To be performed during the Double-Blind Phase to assess opioid withdrawal.
[14]. Patients will be introduced to the online support tool at the Screening Visit to aid in the management of the patients' chronic pain. Patients will be reminded of the tool's availability at the beginning of each phase.

Trial Phase:	Screening[1]	Open-Label Titration[2]	Open-Label Treatment[3]																Double-Blind[4]											Tapering/ Follow-up[5]	
																														Taper visits	Follow-up visit
Week:	-3 to -1	1 to 6	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	43	44	45	46	47	48	49	50	51	52[5]	53+	54+
Visit:	1-2	3.1 to 3.X	4	-	5	-	6	-	7	-	8	-	9	-	10	-	11	-	**12**	-	13	-	14	-	15	-	16	-	17	18+	
Remote contact[6]:			-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	
PPQ[15]	X	X	X								X								X										X		
Full FS (WPI and SSS)	X																														
WPI only			X								X								X										X		
PROMIS PF-SF-8b	X		X								X								X										X		
Daily 24-hr Average/Worst PI score on NRS[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
UDT[17]	X																		X										X		
Enrollment[18]		X																													
Randomization[19]																			X												
Scheduled QST[20]	X		X								X								X										X		
Daily morphine sulfate ER or placebo administration			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[15]. Dissatisfaction with pain control on SAO therapy is defined as mean Worst PI score of ≥ 5 and ≤ 9 over the prior 7 days; the PPQ will also be used to help identify appropriate candidates for extended-release opioid therapy.
[16]. PI scores (Average and Worst) in the prior 24 hours will be captured once daily before bedtime.
[17]. Quantitative UDT for illicit drugs, non-prescribed controlled substances (opioid and non-opioid), and alcohol. Unscheduled or repeat UDTs may be performed at the investigator's discretion. Note, data for morphine and its metabolites obtained during the Double-Blind Phase will NOT be shared by the laboratory until after completion of the trial to avoid unblinding of the patients or the investigator.
[18]. Patients will be entered into the Open-Label Treatment Phase once they meet enrollment criteria in the Open-Label Titration Phase.
[19]. Patients who meet randomization criteria at the end of 42 weeks (including Open-Label Titration and Treatment Phases) will be randomized to continue their stable doses of morphine sulfate ER or to be tapered to placebo over the course of a 1- to 8-week period (depending on the morphine sulfate ER dose prior to randomization) followed by a 2- to 9-week opioid-free period.
[20]. QST will be performed on the OIH Population twice during Screening (to obtain between-session variability data), at Week 10 and Week 26 during the Open-Label Treatment Phase, and at the start (prior to randomization) and end of the Double-Blind Phase.

Trial Phase:	Screening[1]	Open-Label Titration[2]	Open-Label Treatment[3]																Double-Blind[4]											Tapering/ Follow-up[5]	
																														Taper visits	Follow-up visit
Week:	-3 to -1	1 to 6	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	43	44	45	46	47	48	49	50	51	52[5]	53+	54+
Visit:	1-2	3.1 to 3.X	4	-	5	-	6	-	7	-	8	-	9	-	10	-	11	-	**12**	-	13	-	14	-	15	-	16	-	17	18+	
Remote contact[6]:			-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	
Adjustment of daily ER dose, as needed.		X	X		X		X		X		X		X		X		X														
Dispensing of morphine sulfate ER or placebo		X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Dispensing of SAO and APAP rescue medications[21]			X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	
Dispensing of naloxone[22]		X																													
Collect trial and rescue drugs/assess drug accountability		X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X
C-SSRS[23]	X		X								X								X										X		X
HADS	X		X								X								X										X		
ISI	X		X								X								X										X		
Endocrine and sexual function	X		X								X								X										X		
POMAQ[24]	X										X																		X		
BPI-SF	X		X								X								X										X		
EQ-5D-5L	X		X								X								X										X		
PGIC																			X										X		
Unblinding questionnaire																													X		

[21]. SAO and APAP rescue medication will be permitted during the Open-Label Treatment Phase and Double-Blind Phases, if needed.
[22]. If a patient uses naloxone themselves to medicate a suspected overdose, they will be removed from the trial and the overdose recorded as an SAE. If the patient loses the naloxone or it is used by a non-trial participant, it may be re-dispensed.
[23]. The "Screening" version will be administered at Screening. The "Since Last Visit" version will be administered at subsequent visits.
[24]. Administered approximately every 6 months.

Trial Phase:	Screening[1]	Open-Label Titration[2]	Open-Label Treatment[3]															Double-Blind[4]											Tapering/ Follow-up[5]	
																													Taper visits	Follow-up visit
Week:	-3 to -1	1 to 6	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	43	44	45	46	47	48	49	50	51	52[5]	53+	54+
Visit:	1-2	3.1 to 3.X	4	-	5	-	6	-	7	-	8	-	9	-	10	-	11	-	**12**	-	13	-	14	-	15	-	16	-	17	18+	
Remote contact[6]:			-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	X	-	-	
AEs[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Early Discontinuation Assessment[26]																													X		

Abbreviations: AE = adverse event; APAP = acetaminophen; BPI-SF = Brief Pain Inventory–Short Form; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; EQ-5D-5L = EuroQOl, 5-dimension, 5-level descriptive system; ER = extended-release; FS = Fibromyalgianess Scale; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; NRS = numerical rating scale; OIH = opioid-induced hyperalgesia; PCS = Pain Catastrophizing Scale; PF-SF-8b = PROMIS® Item Bank v2.0 – Physical Function – Short Form 8b; PGIC = Patient Global Impression of Change; PI = pain intensity; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PPQ = Pain Profile Questionnaire; PTRQ = Pain Treatment-Response Questionnaire; QST = Quantitative Sensory Testing; SAE = serious adverse event; SAO = short-acting opioid; SOWS = Subjective Opiate Withdrawal Scale; SSS = Symptom Severity Score; STOP-Bang = snoring, tiredness, observed apnea, blood pressure, body mass index, age, neck circumference and gender questionnaire; UDT = urine drug test; WPI = Widespread Pain Index.

[25]. Patients will be questioned about adverse events using a non-leading question at each visit and phone call.

[26]. The Early Discontinuation Assessment will be completed for patients who were administered at least 1 ER trial medication dose and who withdraw consent from the trial (i.e., subject decision). This assessment will be used to evaluate the patient's reason(s) for withdrawal (Appendix 16.5). Patients who discontinue early will advance to the Week 52 visit/assessments.

7.2. Discussion of Trial Design

The planned trial is a 12-month, multicenter, randomized, placebo-controlled, double-blind clinical trial with an EERW design. The overall EERW design is consistent with previous studies of ER opioids (e.g., Hale et al., 2015; Katz et al., 2015a; Rauck et al., 2014; Wen et al., 2015) and IMMPACT recommendations (e.g., Dworkin et al., 2010; Dworkin et al., 2012; Edwards et al., 2016; Gewandter et al., 2020). The trial will utilize a randomized withdrawal approach as an enrichment strategy to enhance the probability of including "responders" and to minimize early discontinuations due to AEs (Katz, 2009; Lemmens et al., 2006). The Open-Label Titration Phase will permit patients to slowly and safely be titrated to effect, as would be conducted in clinical practice. This approach has been used successfully in prior opioid efficacy studies (e.g., Hale et al., 2015; Katz et al., 2015a). The use of fixed opioid doses may permit a more rigorous assessment of dose response, however, the limited number of doses may reduce success as they are not optimized to meet the patients' needs.

Randomization, to remain on active ER opioid or to slowly taper to placebo, will be used during the Double-Blind Phase to avoid bias in the assignment of patients to treatment, to increase the likelihood that known and unknown patient attributes are evenly balanced across treatment groups (e.g., demographics and baseline characteristics), and to enhance the validity of statistical comparisons across treatment groups. A placebo control will be used during the Double-Blind Phase to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment, as well as to minimize patient and investigator bias.

The trial will include 52 weeks of treatment in order to address the long-term efficacy and safety of ER/LA opioids, including a 42-week Open-Label Titration and Treatment Phase, and a 10-week Double-Blind Phase. The extended duration of the Open-Label Phase is required to evaluate the effects of long-term ER opioid therapy, while minimizing the duration of time that patients in the placebo group may be required to use placebo. The duration of 10 weeks for the Double-Blind Phase (including up to 8 weeks of tapering for the placebo group) should be sufficient to evaluate the primary endpoint of time to treatment failure, given that for most patients who fail treatment in such trials, failure typically occurs within a few weeks of transition to placebo or earlier (i.e., during down-titration) (Hale et al., 2010; Hale et al., 2015; Katz et al., 2015a; Rauck et al., 2014; Rauck et al., 2015; Wen et al., 2015). The long duration of the trial will have additional provisions to help ensure retention of patients, such as minimizing the number of trial visits and burdensome procedures (e.g., by limiting QST to a subpopulation as guided by a power analysis), frequent phone calls from research site staff for general check-ins and tolerability assessments, use of an online patient support tool, and proactive prevention and treatment of opioid-related side effects.

The trial will include patients with common CNCP conditions that are known to be associated with relatively high levels of physical dysfunction, such as chronic low back pain (CLBP), osteoarthritis (OA) of the hip and knee, diabetic peripheral neuropathy (DPN), and painful peripheral neuropathy (PPN). The selection of these CNCP pain conditions was intended to balance generalizability with a need for a relatively homogeneous population in which to evaluate efficacy on the primary endpoint, as well as on measures of physical function. In addition, the patient populations associated with these diagnoses have been relatively well-characterized, and the feasibility of the trial may be improved as these patients are more likely to

be sufficiently ambulatory to allow for clinic visits and procedures. Finally, these diagnoses are associated with an appropriate temporal profile of pain (i.e., persistent/continuous pain for which ER/LA opioids may be needed), in contrast to conditions associated with intermittent pain that would not be considered appropriate for long-term ER opioid therapy. Patients with post-cancer-treatment pain (who do not have active cancer) have also been included to allow more full generalization to potential patients who may require ER/LA opioid therapy in clinical practice, while maintaining the power and integrity of the trial. For ethical reasons, patients with conditions for which ER/LA opioids are not expected to show a benefit and/or who would be difficult to accommodate in a clinical trial will not be included (e.g., complex regional pain syndrome).

Rescue medication is a critical element of the proposed trial design, as it is likely to have an important influence on patient retention over the long duration of the trial, and because its use is consistent with clinical practice. Thus, during all phases of the trial, with the exception of the Open-Label Titration Phase, patients will be permitted to use SAO rescue medication (up to a maximum of 30 mg IR morphine per day), as well as APAP up to 3000 mg per day, as needed (PRN). Also, patients on pre-existing, stable therapies will be allowed to continue using these therapies for the duration of the trial; however, to avoid confounding the primary efficacy endpoint, therapies that, in the opinion of the investigator, may affect the efficacy outcomes, should not be initiated or discontinued, and doses/regimens of concomitant analgesic medications should remain stable within 1 month of and for the duration of the Double-Blind Phase. Although changes in therapies and doses of medication may occur in clinical practice, allowing patients to initiate or discontinue additional therapies during the Double-Blind Phase of the trial would make it difficult to ascertain the effect of ER opioids on the primary endpoint (time to treatment failure), thereby compromising the scientific integrity of the trial.

ER/LA opioids are indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Given that patients randomized in the proposed trial will be placed on ER opioid medications and allowed to titrate their doses, the trial will include only patients who are currently on SAOs or those who have been using SAOs but have recently (within 6 months) discontinued due to tolerability issues, lack of efficacy, or loss of access. This SAO-use criterion is important given that ER opioids are generally only indicated for patients after the failure of SAOs. Eligible patients must be dissatisfied with their current or past SAO regimens as informed by the PPQ at Screening. In addition to inadequate effectiveness or poor tolerability, patients may be dissatisfied with their SAO therapies for other reasons, such as end-of-dose failure, mild symptoms of withdrawal upon awakening, or sleep disturbance by pain returning during the night. Such patients would be appropriate candidates for ER/LA opioid therapy due to dissatisfaction with their responses. Any discontinuation of SAOs or interruption in their access must occur within 6 months prior to Screening, to provide reassurance that the patient's biological state has not evolved appreciably since having discontinued SAOs. However, any patients who are not currently using SAOs will be started at the lowest available doses of ER opioid due to a potential loss of tolerance. The minimum SAO requirement of 30 MME/day at Screening is required to exclude patients who may be dissatisfied with SAOs simply because of underdosing, or whose symptoms may be effectively ameliorated by a modest dose increase.

Patients must also have not responded or have contraindications to at least 2 pharmacologic and 2 non-pharmacologic therapies, as informed by the PTRQ and external documentation, where available. Consistent with ER/LA opioid labels, the intention is to enroll only patients for whom alternative treatment options are inadequate. Failure of 2 pharmacologic and 2 non-pharmacologic therapies provides a reasonable threshold and clear guidance for investigators, while affording some degree of consistency among patients, as is necessary in a clinical trial setting.

During the Double-Blind Phase, patients in the placebo group will taper slowly to placebo in a double-blinded manner over the course of 1 to 8 weeks. Previously published EERW trials using designs and doses similar to those in the current trial have typically included tapering durations ranging from 3 to 20 days, with 14 days being the most commonly used tapering period (Hale et al., 2010; Hale et al., 2015; Katz et al., 2015a; Rauck et al., 2014; Rauck et al., 2015; Wen et al., 2015; Vinik et al., 2014). Based on these studies, there were no clear differences in incidence of opioid withdrawal in the active ER opioid groups compared to placebo groups (defined using COWS or AEs; differences ranging from -3.4% to +5.3%). These data demonstrate that withdrawal effects that are common in clinical practice, where patients are not blinded, may be at least partly related to expectancy effects (i.e., anticipation of and anxiety related to tapering the opioid doses). Thus, the 1- to 8-week tapering period (depending on the patient's dose at randomization) is considered adequate to control withdrawal symptoms in the double-blinded setting. The 1-week taper will be used only for patients who are receiving the lowest dosage strength of morphine sulfate ER (i.e., 15 mg tablets, administered BID) as a longer taper is not considered medically necessary for these patients. These low-dose patients will receive a week of asymmetric dosing (i.e., 15 mg once in the evening [QHS]), prior to receiving 0 mg (placebo) for blinded patients or discontinuing use of morphine sulfate ER for unblinded patients. These durations of tapering will also be used for patients at the end of the trial (end of Double-Blind Phase or early discontinuation). SAOs and APAP will continue to be permitted during the tapering period to alleviate any severe withdrawal symptoms. To evaluate potential unblinding due to opioid withdrawal effects in the placebo group, an unblinding questionnaire will be administered at the end of the Double-Blind Phase that will evaluate patients' assessments of which treatment groups they believed they were assigned to and the reason(s) for their selections.

A rationale for the selection of doses in this trial is provided in Section 9.4.

Rationales for the selection of measures/endpoints are provided in Section 10.5.

8. SELECTION OF TRIAL POPULATION

The planned sample size is 200 patients randomized into each treatment group in the Double-Blind Phase (400 patients in total). An interim analysis of efficacy will be performed, and the sample size may be increased, as needed.

Based on an assumption of 60% retention, 666 patients will be enrolled into the Open-Label Treatment Phase to randomize 400 patients in the Double-Blind Phase. It is estimated that approximately 1,100 patients will need to be enrolled in the Open-Label Titration Phase to achieve the targeted number of patients for the Open-Label Treatment Phase. Up to 30 research sites will perform QST and contribute to the OIH Population, which will comprise at least

200 patients who enter the Open-Label Titration Phase and have at least 1 post-treatment QST evaluation. The retention rate will be actively monitored throughout the trial and enrollment adjusted to efficiently target the Double-Blind Phase sample size, as well as the OIH population goal.

The sample size may be increased based on the interim analysis as needed for evaluation of efficacy (Section 12.4.2).

8.1. Inclusion Criteria

Each patient must meet the following inclusion criteria to be eligible for participation in the trial:

1. Is male or a non-pregnant (confirmed by pregnancy test), non-lactating female, aged 18 years or older.
2. Has had clinical diagnosis of CNCP for a minimum of 12 months that:
    - Occurs daily, and
    - Includes CLBP, OA of the hip or knee, DPN, PPN, or post-cancer-treatment–related pain (i.e., post-thoracotomy pain, radiation plexopathy, post-chemotherapy pain)

    Note: Patients with overlapping CNCP conditions are permitted to enroll in the trial, provided that the patient reports that pain associated with the non-index pain condition(s)/site(s) is mild.
3. Has a Worst PI score of ≥ 5 and ≤ 9 over the 7 days prior to Screening for the index pain condition/site(s).
4. Is taking daily SAO therapy, defined as any SAO drug product:
    - Taken ≥ 2 times per day ≥ 5 days per week for any ≥ 3 consecutive months in the 6 months prior to Screening, with an inadequate analgesic response, as determined below, and
    - Total daily dose is ≥ 30 MME (refer to Appendix 16.2 opioid conversion chart)

    Note: Patients not currently on SAOs are considered eligible if they would have met the above criteria had they not discontinued SAO use within the prior 6 months due to tolerability issues, lack of efficacy, or loss of access.
5. Is dissatisfied with his or her pain control while taking SAOs, as determined by agreement between the investigator and patient, and informed by responses on the PPQ.
6. Has not responded or has contraindications to ≥ 2 non-pharmacologic classes and ≥ 2 non-pharmacologic therapies for the index pain condition(s), according to the investigator's judgement, following review of the patient's PTRQ responses, as well as external documentation, if available.

    Note: Guidance regarding appropriate trials of prior therapies is provided in Appendix 16.3.

7. Is an appropriate candidate for ER opioid therapy, according to the investigator's clinical judgement.
8. Is considered, in the opinion of the investigator, to be generally healthy, based on the results of medical history, physical examination, 12-lead ECG, and laboratory profile.
9. Female patient of non-childbearing potential must be surgically sterile or postmenopausal (postmenopausal is defined as at least 1 year without menses and confirmed by serum FSH ≥ 50 mIU/mL). A female patient is considered to be surgically sterile if she has had a tubal ligation, hysterectomy, bilateral salpingo-oophorectomy or bilateral oophorectomy, or hysterectomy with bilateral salpingo-oophorectomy.
10. Female patient of childbearing potential must be using a medically accepted method of contraception (minimum required use 30 days prior to the first dose of ER trial medication, if not otherwise specified) and agree to continued use of this method for the duration of the trial and for 30 days after the last dose of ER trial medication. Acceptable methods of contraception include abstinence from heterosexual intercourse, intrauterine device (with or without hormones), hormonal contraceptives (i.e., birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch [at least 90 days prior]), partner vasectomy (at least 6 months prior), or double-barrier method of contraception (e.g., male condom in addition to a diaphragm, contraceptive sponge, or spermicide).
11. Is able to speak, read, write, and understand English, understand the consent form, has the capacity to provide informed consent, and can effectively communicate with the trial staff.
12. Is voluntarily willing to give informed consent in signed and dated writing prior to participation in the performance of the trial procedures.
13. Is willing and able to participate in all trial procedures and requirements, as described in the informed consent form.

8.2. Exclusion Criteria

A patient will not be eligible to participate in this trial if any one of the following exclusion criteria is met:

1. Has any clinically significant medical or psychiatric condition that would, in the opinion of the investigator, preclude trial participation or interfere with the assessment of pain or other symptoms, or would increase the risk of opioid-related AEs, including opioid use disorder.
2. Has a primary diagnosis of fibromyalgia, complex regional pain syndrome, peripheral or central neuropathic pain, somatoform pain syndromes, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, discitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm that is not currently in remission.

3. Has experienced myocardial infarction or coronary artery bypass graft surgery within 12 months prior to Screening.
4. Has known allergies or hypersensitivity to naloxone, morphine, or other opioids.
5. Has known or suspected gastrointestinal obstruction, including paralytic ileus.
6. Has a current diagnosis of irritable bowel syndrome or other visceral pain syndrome causing moderate to severe pain.
7. Has any sensory loss in the arms that, in the opinion of the clinician, is likely to interfere with QST (OIH Population only).
8. Has undergone a surgical procedure for the primary cause of pain within 6 months prior to Screening.
9. Has had an intra-articular injection of any medication or a nerve or plexus block, including epidural steroid injections or facet blocks, within 6 weeks prior to Screening, or has had botulinum toxin injection in the lower back region or high-dose topical capsaicin within 3 months prior to Screening.
10. Has had confirmed malignancy within 6 months of Screening, with the exception of successfully treated basal cell or squamous cell carcinoma of the skin.
11. Has uncontrolled blood pressure defined by a sitting systolic blood pressure > 180 mmHg or < 90 mmHg, or a sitting diastolic blood pressure > 110 mmHg or < 40 mmHg at Screening.
12. Has a clinically significant abnormality in clinical chemistry, hematology, or urinalysis, including serum glutamic-oxaloacetic transaminase/aspartate aminotransferase or serum glutamic pyruvic transaminase/alanine aminotransferase ≥ 3-fold the upper limit of the reference range, or serum creatinine > 2 mg/dL at Screening.
13. Has a body mass index ≥ 40 kg/m^2 or is considered by the investigator to be at high risk for development of respiratory depression, including a STOP-Bang Questionnaire score ≥ 5, or has severe, uncontrolled bronchial asthma.
14. Has clinically significant depression or anxiety based on a score of ≥ 14 on either subscale of the HADS at Screening, or suicidal ideation associated with actual intent and a method or plan (“Yes” answers on items 4 or 5 of the C-SSRS, Screening Version) or a previous history of suicidal behaviors (“Yes” answer to any of the suicidal behavior items of C-SSRS Screening), in the past 5 years.
15. Has a diagnosis, per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), of any substance use disorder (except for nicotine or caffeine), or has a positive UDT for illicit drugs (including cannabis), non-prescribed controlled substances (opioid or non-opioid), or alcohol at Screening (refer to Appendix 16.4 for analytes and instructions on management of positive results).
16. Has ever experienced an opioid overdose, which, according to the investigator’s review and judgment, may present a future safety risk to the patient when using short-acting or ER opioid therapy in this trial.
17. Has ongoing or past litigation or compensation associated with pain, has pending applications for workers compensation or disability, or plans to file litigation or claims within the next 12 months.

18. Has used a monoamine oxidase inhibitor within 14 days prior to Screening.
19. Has taken ER/LA opioids in the past and discontinued for lack of tolerability or effectiveness, or has recently taken ER/LA opioids (currently and/or within 1 month of Screening).
20. Has taken opioid agonist-antagonists (pentazocine, butorphanol, or nalbuphine), central-acting alpha-agonists, barbiturates, medication-assisted drug therapy for substance use disorder, kratom, or more than 1 type of benzodiazepine drug within 1 month prior to Screening.
21. Has taken any investigational drug within 1 month prior to Screening or is currently enrolled in another investigational drug trial.

8.3. Criteria for Entry into the Open-Label Treatment Phase

Each patient must meet the following criteria for enrollment into the Open-Label Treatment Phase:

- ≥ 30% reduction in past 7-day Worst PI compared to Screening, AND
- Patient and investigator agree that the patient has had meaningful improvement, guided by the PPQ, AND
- Morphine sulfate ER was tolerated, as per patient and investigator judgment.

8.4. Criteria for Randomization into the Double-Blind Phase

Each patient must meet the following criteria for clinical stability prior to randomization in the Double-Blind Phase, following a stable dose of morphine sulfate ER for at least 7 days:

- ≥ 30% reduction in past 7-day Worst PI compared to Screening, AND
- Patient and investigator agree that the patient has had meaningful improvement, guided by the PPQ, AND
- Morphine sulfate ER was tolerated, as per patient and investigator judgment.

Seven days has been selected as a standard time period for defining clinical stability prior to randomization, based on published EERW studies for ER/LA opioids that have been accepted by FDA (e.g., Katz et al., 2015a; Rauck et al., 2014; Rauck et al., 2015; Wen et al. 2015).

8.5. Removal of Patients from Therapy or Assessment

A patient is free to withdraw his or her consent and discontinue participation in the trial at any time for any reason.

A patient must be discontinued from the trial for any of the following reasons:

- Safety reasons, including AEs or significant concomitant illness, injury, suicidality, unexpected positive UDT result(s), or urgent surgeries/procedures that would, in the judgment of the investigator, present an unacceptable risk to the patient, affect

assessments of clinical status to a significant extent, and/or require discontinuation of ER trial medication
- Opioid overdose, including use of naloxone by the patient
- Discontinuation is requested by the sponsor or designee, regulatory agency, or IRB
- Patient is lost to follow-up
- Patient treatment allocation is unblinded (i.e., individual code break during the patient's participation in the trial)
- Death of patient

A patient may also be discontinued from the trial, at the discretion of the investigator and/or sponsor (or designee), for any of the following reasons:

- Lack of efficacy
- Refusal or inability to adhere to the trial protocol
- Major protocol violation, such as falsifying medical history or tampering with the UDT sample
- Pregnancy
- Use of unacceptable concomitant medication(s)
- Not considered in the best interest of the patient to continue
- Administrative reasons (e.g., termination of enrollment or trial)

Patients who provide written informed consent but do not enter the Open-Label Titration Phase will be considered screen failures.

Any patient who discontinues from the trial for any of the reasons above (excluding screen failures) will be asked to return to the clinic for end-of-treatment procedures (i.e., those listed for Week 52 in Table 1) and to enter the Tapering and Follow-up Phase. During this phase, ER trial medications will be tapered slowly to 0 mg over the course of 1 to 8 weeks, depending on the dose of ER medication at the time of discontinuation, excluding patients randomized to placebo, who will be tapered to 0 mg during the Double-Blind Phase; these patients will receive placebo during the taper period in the Tapering and Follow-up Phase, unless the patient discontinued prior to completing the taper in the Double-Blind Phase, in which case tapering will be completed in the Tapering and Follow-up Phase. Patients who discontinue during the Open-Label Titration or Treatment Phases will have their ER medications tapered in an unblinded manner. Patients who discontinue during the Double-Blind Phase will have their ER medications tapered in a double-blinded manner, as applicable.

If a patient chooses to withdraw consent from the trial, the investigator will provide safety counselling to these patients, including informing them of the risks of abrupt discontinuation of opioids and reminding them to return unused trial medication to the research site.

The investigator must maintain a record of all patients who discontinue from the trial prior to completion. If a patient withdraws consent from the trial (i.e., subject decision), the patient's reason(s) for trial discontinuation will be documented using the Early Discontinuation Assessment (Appendix 16.5). The investigator should make a reasonable attempt to obtain and

record these reason(s) for withdrawal, if possible, although the patient is not obligated to provide such a reason. If a patient declines to provide a reason for withdrawal or complete the Early Discontinuation Assessment, this information will be recorded. If a patient does not return for trial visits, the investigator will attempt to contact the patient a minimum of twice by telephone; if the investigator is unable to contact the patient after 2 attempts, a final letter will be sent by registered US Mail. If the patient does not respond after these 3 attempts, they will be considered lost to follow-up (LtFU).

8.6. Trial Restrictions

In addition to the inclusion/exclusion criteria described in Section 8, patients must agree to abide by the following trial restrictions during the consent process:

- Patients will be asked to abstain from consuming alcohol throughout the trial.
- Patients will be asked to abstain from illicit drug use (including, for the purposes of this trial, cannabis), or non-medical use of therapeutic drugs throughout the trial.
- Patients will be required to abstain from taking the prohibited medications described in Section 9.7.2.4 throughout the trial.
- Morphine sulfate ER may impair the mental or physical abilities needed to perform potentially hazardous activities, such as driving a car or operating machinery. Patients will be warned to refrain from driving, operating machinery, or engaging in hazardous activities until they are sure the ER trial medication is not impairing their judgment and/or ability to perform skilled tasks.

9. TREATMENTS

9.1. Treatment Administration

9.1.1. Open-Label Titration Phase

Oral doses of morphine sulfate ER will be titrated for ~ 6 weeks. Patients can be enrolled in the Open-Label Treatment Phase once criteria are met (Section 8.3), which may occur before or after 6 weeks of titration; however, the duration of the Open-Label Treatment Phase will be adjusted accordingly so that the total duration of the 2 phases is equal to 42 weeks. Patients who are not currently on SAOs at the time of trial entry will be initiated at morphine sulfate ER 30 mg per day (15 mg BID every 12 hours [q12h]).

Patients who are currently receiving oral morphine IR formulations may be converted to morphine sulfate ER tablets by administering one-half of the patient's 24-hour requirement on a q12h schedule.

For patients who are currently using other SAOs, the medication will be discontinued prior to initiating ER morphine therapy. There are no established conversion ratios for conversion from other opioids to morphine sulfate ER tablets; thus, patients should be initiated using 15 mg tablets, administered orally q12h. It is safer to underestimate than to overestimate a patient’s 24-

hour oral morphine dosage and manage an adverse reaction due to overdose. While tables of opioid equivalents are readily available, there is inter-patient variability in the potency of opioid drugs and opioid formulations.

The dose levels of morphine sulfate ER tablets will be subject to increase, as tolerated and indicated by the mean Worst PI score in the prior 7 days (if ≥ 5), and based on the judgment of the investigator. The dose may be increased in 15 mg BID increments, up to a maximum of 240 mg per day, as outlined in Table 2. Close observation and frequent titration are warranted until pain management is stable on the morphine sulfate ER tablets.

Table 2: Guidelines for Titration of Morphine Sulfate ER Tablets

Total Daily Morphine Sulfate ER Dose	Morphine Sulfate ER BID q12h Dose	Suggested BID Tablet Combination
30 mg	15 mg	1 × 15 mg
60 mg	30 mg	1 × 30 mg
90 mg	45 mg	1 × 15 mg 1 × 30 mg
120 mg	60 mg	1 × 60 mg
150 mg	75 mg	1 × 15 mg 1 × 60 mg
180 mg	90 mg	1 × 30 mg 1 × 60 mg
200 mg	100 mg	1 × 100 mg
230 mg	115 mg	1 × 15 mg 1 × 100 mg
240 mg	120 mg	2 × 60 mg

Abbreviations: BID=twice daily; ER = extended-release; q12h = every 12 hours.
Titration schedule assumes morphine sulfate ER tablet dosage strengths of 15, 30, 60, and 100 mg. (Actual schedule may be updated pending confirmation of clinical supplies.)

Single doses greater than 60 mg or total daily doses greater than 120 mg are only for use in patients for whom opioid tolerance has been established. Patients are considered opioid tolerant if they have taken at least 60 MME per day for ≥ 1 week.

Rescue medications are not permitted during this phase.

Intranasal naloxone will be provided to all patients at the beginning of the Open-Label Titration Phase, as outlined in Section 9.7.2.3.

9.1.2. Open-Label Treatment Phase

During the Open-Label Treatment Phase, open-label, oral titrated doses of morphine sulfate ER will be administered BID to a maximum dose of 240 mg per day for ~ 36 weeks.

The dose levels of morphine sulfate ER will be subject to increase as indicated by the mean Worst PI score in the prior 7 days (if ≥ 5) and based on the judgment of the investigator. The dose may be increased in 15 mg BID increments, up to a maximum total daily dose of 240 mg.

ER trial medication doses must be stable for the 7 days prior to randomization.

Rescue medications are permitted in this phase, as outlined in Section 9.7.2.1.

9.1.3. Double-Blind Phase

Double-blind fixed oral doses of morphine sulfate ER (i.e., stabilized dose at the end of the Open-Label Treatment Phase) will be administered BID for 10 weeks in patients randomized to continue active ER opioid. Patients randomized to the placebo group will received double-blind tapering doses of morphine sulfate ER for 1 to 8 weeks, and placebo for 9 to 2 weeks, respectively, administered BID. Tapering schedules will vary depending on the stabilized dose at randomization (Appendix 16.1).

No dosage adjustments will be permitted during the Double-Blind Phase.

Rescue medications are permitted in this phase, as outlined in Section 9.7.2.1.

9.1.4. Tapering and Follow-up Phase

Patients randomized to morphine sulfate ER will begin tapering in a double-blinded manner in the Tapering and Follow-up Phase; patients randomized to placebo will receive placebo in a double-blinded manner during this phase (unless the patient discontinues the trial during tapering in the Double-Blind Phase, in which case tapering will be completed in the Tapering and Follow-up Phase). Patients who discontinue during the Open-Label Titration or Treatment Phases will be tapered in an unblinded manner, also during the Tapering and Follow-up Phase. Refer to Appendix 16.1 for guidelines on tapering the ER trial medications.

Rescue medications are permitted in this phase, as outlined in Section 9.7.2.1.

9.2. Identity of Investigational Product(s) and Other Trial Medications

The trial medications are FDA approved and will be provided by the sponsor or designee. Each container of trial medication will be clearly labeled with trial-specific information meeting all applicable regulatory requirements.

Non-opioid medications that patients continue to use and take (e.g., NSAIDs, gabapentin, antidepressants) will not be supplied by the sponsor or designee (refer to Section 9.7.2.2).

9.2.1. Investigational Product

Morphine sulfate ER is the investigational product and will be supplied as 15, 30, 60, and 100 mg tablets.

Placebo is the reference therapy and will be provided by the manufacturer of the active ER medication. Placebo tablets will be identical to the respective strengths of morphine sulfate ER tablets in aspect, size, and color.

For purposes of this document, “ER trial medication” refers to morphine sulfate ER and placebo.

9.2.2. Rescue Medications

Rescue medications are commercially available and will be provided by the sponsor or designee in an open-label fashion as trial prescribed medications. SAO rescue medication will be supplied to patients as morphine IR tablets (e.g., 15 mg) for oral administration. Patients will also be supplied with APAP (500 mg) tablets.

9.2.3. Naloxone

An intranasal naloxone formulation will be provided to all patients, to be used if there is a suspected overdose during the trial. Instructions for use are provided in the product label (Appendix 16.6). Naloxone will be commercially sourced and re-labeled for trial use.

9.2.4. Handling, Storage, and Accountability

All trial medications (including rescue medication) will be transported, received, stored, and handled strictly in accordance with the container or product labels, with instructions provided to the research site in compliance with all applicable regulations.

ER trial medications and SAOs must be handled and stored strictly in accordance with the restrictions related to controlled substances. All opioid trial medications must be kept securely locked with access limited to appropriate trial personnel, according to applicable regulations. Morphine sulfate ER is a controlled substance under Schedule II of the Controlled Substances Act. Like all opioids, the ER trial medications and SAOs are at risk of diversion and misuse and should be handled accordingly. Note that discrepancies in drug accountability records may be indicative of diversion; investigators should thoroughly investigate and report any cases of suspected diversion as outlined in Section 10.3.1.3.

Morphine sulfate ER tablets and double-blinded medication for the Double-Blind and Tapering and Follow-up Phases should be stored at 25°C (77°F), with excursions permitted between 15° to 30°C (59° to 86°F) (see United States Pharmacopeia [USP] Controlled Room Temperature). Morphine IR tablets should be stored at 20° to 25°C (68° to 77°F) (see USP Controlled Room Temperature) and protected from moisture. APAP tablets and naloxone should be stored as specified in the labels.

The investigator is required to maintain current medication accountability logs and all medications must be accounted for throughout the trial. All unused supplies will be checked against the medication accountability records during and at the end of the trial. Patients will be instructed to return all unused trial medications to the research site. All unused trial medication must be disposed of in accordance with applicable requirements; at the end of the trial, the sponsor or designee will provide additional instruction regarding the disposition of unused trial medications. Until instructions have been provided, each research site must store unused materials on site.

9.2.5. Dispensing and Administration

Only eligible patients participating in the trial will receive the trial medications. Only authorized research site staff may dispense the trial medications. Once dispensed, trial medication may not be relabeled or reassigned for use by other patients.

[[Further descriptions will be added to the protocol once clinical supplies are confirmed]]

Patients should be provided with FDA-approved patient labeling and counseled according to Section 17 (Patient Counseling Information) of the approved product labels.

Patients will be instructed to swallow morphine sulfate ER tablets whole. Crushing, chewing, or dissolving morphine sulfate ER tablets will result in uncontrolled delivery of morphine and can lead to overdose or death.

9.3. Method of Assigning Patients to Treatment Groups

Randomization will be used to avoid bias in the assignment of patients to treatments, to increase the likelihood that known and unknown patient attributes (e.g., demographics, baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Patients who provide written informed consent will be assigned a unique number in the screening process. This number will be used to identify the patient throughout the trial.

In the Double-Blind Phase, patients who meet randomization criteria (Section 8.4) will be randomized in a 1:1 ratio to either continue their stable doses of morphine sulfate ER or to taper slowly to placebo. To reduce confounding of the primary endpoint (time to loss of efficacy), randomization will be stratified by stable dose of morphine sulfate ER prior to randomization, because this dose will affect the required duration of tapering for those in the placebo group (i.e., 8 strata of placebo patients who are opioid free by Weeks 2, 3, 4, 5, 6, 7, 8, or 9, or equivalent active ER doses in the ER opioid treatment group).

Randomization will be accomplished using central randomization (Interactive Voice or Web Response Systems [IVRS or IWRS]) managed by the sponsor or designee.

Once any patient number or randomization number has been assigned, it cannot be reassigned to any other patient.

9.4. Selection of Doses

Consistent with clinical practice, dosing will be flexible in this trial. The structured, step-wise approach to dose escalation will assist research site investigators with dose decision-making, provide a more consistent dose escalation approach across patients and research sites, and support patient safety. Dose escalation levels were selected based on an algorithm consistent with clinical practice that considers pain intensity, tolerability, and meaningful pain relief with the current dose. The maximum dosing of ER morphine in this trial will be 240 mg per day.

The definition of high-dose ER opioids used in secondary analyses is aligned with the Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain (Dowell et al., 2016), which defines high-dose opioid use as a daily dose of ≥ 90 MME. This threshold can be supported through additional subgroup analyses of patients who achieve various dosing levels as appropriate.

Patients may be permitted to increase their doses during the Open-Label Titration or Open-Label Treatment Phases up to a maximum permitted dose of 240 mg per day, as some patients may require these higher doses in clinical practice. While guidelines, such as CDC's, recommend using lower doses where possible, they do not preclude use of higher doses where it may be clinically necessary for an individual patient (i.e., "*Most experts also agreed that opioid dosages should not be increased to ≥90 MME/day without careful justification based on diagnosis and on individualized assessment of benefits and risks*.") In addition to ensuring that the trial reflects the range of doses potentially required by individual patients, use of higher doses will enable evaluation of the incidence of OIH, which remains an important secondary objective of the trial, to evaluate the safety signal identified in PMR 3033-11. To avoid confounding the efficacy endpoints, no dosage adjustments of the ER medications will be permitted during the Double-Blind Phase, and doses of morphine sulfate ER must be stable for at least 7 days prior to randomization.

Use of rescue medication is consistent with clinical practice and is common in the clinical trial setting; however, to avoid confounding the primary endpoint of time to treatment failure, daily SAO doses have been capped at 30 mg IR morphine/day, along with up to 3000 mg APAP per day.

9.5. Selection and Timing of Dose

Patients will receive morphine sulfate ER (or placebo during the Double-Blind Phase) at individualized (titrated) doses. During the Open-Label Titration, Open-Label Treatment, and Double-Blind Phases of the trial, morphine sulfate ER (or placebo) will be administered BID, with approximately 12 hours between doses. Asymmetric dosing (e.g., 15 mg QHS) will be implemented during tapering, as outlined in Appendix 16.1. No fasting or special dietary requirements are required for the trial, with the exception of alcohol restrictions, described in Section 8.6. Patients will be advised not to abruptly discontinue their ER trial medications.

9.6. Blinding

This is a double-blind, placebo-controlled EERW trial. The patient, investigator, research site personnel, Contract Research Organization (CRO) personnel, and sponsor or designee (with the exception of, where applicable, designated unblinded personnel who manage trial medications, compliance auditor[s], and statistician[s] who generate the code) will not know which treatment is being administered during the Double-Blind Phase.

Placebo matching morphine sulfate ER tablets will be supplied by the manufacturer and will be identical in appearance, size, color, and other attributes to the respective dosage strengths of morphine sulfate ER. Rescue medications will be administered in an unblinded manner.

Under normal circumstances, the investigators and any trial personnel, including research site personnel, CRO personnel, or any other individuals involved in the documentation, management, analysis, or reporting of trial data (i.e., external consultants or vendors), will remain blinded until all patients have completed treatment. Patients will remain blinded for the duration of their participation in the trial. In case of emergency, and only if the information is required by the investigator to manage a patient's medical condition, the treatment may be unblinded at the research site using the IVRS/IWRS. If possible, the investigator should contact the sponsor or designee prior to unblinding. Whenever a research site prematurely unblinds a treatment, the reason, date, and time of the unblinding, and the name of the individual who broke the blind, must be documented. An individual code break will result in withdrawal of the patient from the trial.

If the patient has a qualified HCP at the end of the trial or early discontinuation, to support continuity of care, the HCP will receive access to the patient's treatment assignment, either through direct, one-time access to the IVRS or IWRS system, or through an unblinded 3rd party designee. During the registration process for unblinding access, the HCP must agree not to disclose the treatment assignment back to the investigator or research site personnel. The patient must agree during the consenting process that, if he or she should become aware of the treatment assignment through the HCP after trial participation, he or she will not disclose this information to the investigator or trial personnel.

9.7. Prior and Concomitant Therapy

All non-trial medications reported by the patient, including prescription, over-the-counter, or herbal therapies, will be documented for the 30 days prior to Screening and throughout the trial. Medications prior to this must be recorded if relevant to the protocol (e.g., date of last contraceptive patch). The investigator will determine if the prior/concomitant medication(s) have affected the patient's eligibility to participate or to continue to participate in the trial.

Specific collection requirements for histories of analgesic therapy, as required by inclusion criteria, are outlined in Section 9.7.1.

9.7.1. Prior Therapy

Prior history of pharmacologic and non-pharmacologic treatments will be evaluated using the guided PTRQ, a copy of which is provide in Appendix 16.3. Guidance on appropriate trials of prior analgesic therapies is also provided in Appendix 16.3. Research sites will be required to make reasonable efforts to obtain external documentation (e.g., medical records and/or surveillance or claims data), to the extent available, to corroborate the PTRQ. Patients who do not have either medical records or other external data may be enrolled based on the investigator's clinical judgement, on a case-by-case basis, following approval of the medical monitor.

[[A description of monitoring or claims data will be added to the protocol, once available]]

9.7.2. Concomitant Therapy

9.7.2.1. Analgesic Rescue Medications

No rescue medications will be allowed during the Open-Label Titration Phase.

During the Open-Label Treatment and Double-Blind Phases, daily doses of up to 30 mg IR morphine (i.e., no more than two 15 mg IR tablets per day) and APAP 3000 mg (i.e., no more than six 500 mg tablets per day), will be permitted PRN. To avoid confounding the results of the primary endpoint, additional rescue medications will not be utilized during the trial.

Patients will be instructed on the proper use of rescue medications (i.e., only when the pain is worsening).

9.7.2.2. Other Permitted Medications/Therapy

As concomitant therapies are often used in clinical practice, patients will be permitted to continue with pre-existing pharmacologic therapies, such as NSAIDs, gabapentin, antidepressants, etc., provided medications remain at stable doses/regimens 1 month prior to and throughout the Double-Blind Phase of the trial. If there is any question on the definition of stability or changes in stability, the medical monitor can be consulted on a case-by-case basis. Patients using APAP will be instructed not to exceed the daily limits specified above, including rescue medications (i.e., no more than 3000 mg per day in total).

Patients may continue to use non-pharmacologic therapies during the trial. As dosage adjustments of morphine sulfate ER are permitted during the Open-Label Treatment Phase, initiation or discontinuation of new pain therapies is permitted during this phase (i.e., doses of morphine sulfate ER may be adjusted during this phase to accommodate changes in concomitant therapies); however, any such modifications should be avoided 1 month prior to and for the duration of the Double-Blind Phase. Patients will be asked to disclose if they have initiated any new analgesic therapies, including prescription, over-the-counter, or non-pharmacologic therapies. This information will be recorded and used in the statistical analysis of trial outcomes.

On a case-by-case basis, the investigator is permitted to allow the use non-analgesic concomitant medications, as long as the medications are not listed below under restricted medications (Section 9.7.2.4), and the investigator determines that the medication will not affect the patient's safety or trial integrity. The investigator, if desired, can choose to discuss the appropriateness of the concomitant medication(s) with the medical monitor.

9.7.2.3. Naloxone

Intranasal naloxone, and instructions for its use, will be provided to all patients at the start of the Open-Label Titration Phase; naloxone will be used if a suspected overdose occurs during the trial. Patients will be questioned on use of their naloxone at each visit and additional naloxone may be provided if a patient loses the medication or if the naloxone is used by a non-trial person. Patients who used the naloxone themselves to medicate a suspected overdose will be discontinued from the trial, and the overdose will be recorded and managed as an SAE.

Instructions for naloxone use (i.e., patient instructions provided in the product label) are provided in Appendix 16.6.

9.7.2.4. Restricted Medications

The following medications are not permitted during the trial:

- Barbiturates will be prohibited throughout the trial. Patients using barbiturates within 1 month prior to Screening will be excluded from the trial (Section 8.2).
- Monoamine oxidase inhibitors will be prohibited throughout the trial. Patients using monoamine oxidase inhibitors within 14 days prior to Screening will be excluded from the trial (Section 8.2).

Wherever possible, the investigator should obtain approval from the medical monitor prior to the patient using the following medications:

- Concomitant use of benzodiazepines and other sedative hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, or other central nervous system (CNS) depressants (including alcohol) may cause respiratory and CNS depression. Use of cimetidine may potentiate the effects of morphine, including respiratory depression. Use of these substances should be minimized during the trial (i.e., these substances should only be used in patients for whom alternative treatment options are inadequate, and dosages and durations of use should be limited to the minimum required). If these medications are required, the medical monitor must be consulted prior to initiating treatment. Patients should be monitored for signs of respiratory depression and doses of morphine sulfate ER and/or the interacting agent should be decreased as needed. Patients should be advised of the danger of concomitant use of sedatives while participating in the trial. Patients taking more than 1 type of benzodiazepine within 1 month prior to Screening will be excluded from the trial (Section 8.2).
- If concomitant use of serotonergic drugs is warranted, the medical monitor should be consulted prior to initiating treatment. The patient should be carefully observed during treatment initiation and dose adjustment for signs of serotonin syndrome. Examples of serotonergic drugs include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, triptans, 5-HT_3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and certain muscle relaxants (i.e., cyclobenzaprine, metaxalone).
- Patients should not initiate or discontinue use of p-glycoprotein (PgP) inhibitors/inducers during the trial. Stable, chronic doses of PgP inhibitors/inducers that are ongoing at trial entry and expected to continue for the duration of the trial may be permitted at the discretion of the investigator and medical monitor. If initiation or discontinuation of these medications is warranted after the patient has entered the trial, the doses of morphine sulfate ER and/or PgP inhibitor/inducer may need to be decreased, as necessary.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Patients requiring concomitant diuretics should be monitored for signs of diminished diuresis and/or effects on blood pressure, and the diuretic dose should be increased, as needed.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Patients should be monitored for signs of urinary retention or reduced gastric motility if concomitant use of anticholinergic drugs is required.

- Non-trial ER/LA opioid analgesics, opioid agonist-antagonists (pentazocine, butorphanol buprenorphine, or nalbuphine), central-acting alpha-agonists, medication-assisted drug therapy for substance use disorder, and kratom will be prohibited throughout the trial. Patients taking these drugs/substances within 1 month prior to Screening will be excluded from the trial (Section 8.2).
- Opioid antagonists will not be permitted during the trial. Patients taking opioid antagonists will be required to discontinue their use after the Screening visit for the duration of the trial.
- Non-trial investigational drugs or investigational trial participation other than the current trial will be prohibited throughout the trial; patients taking any other investigational drug within 30 days prior to Screening will be excluded from the trial (Section 8.2).

9.8. Treatment Compliance

Doses of trial medication intake will be captured by the patients once daily. Treatment compliance will be monitored and recorded by reconciling the number of tablets of morphine sulfate ER/placebo and SAO/APAP rescue medications dispensed against the number of tablets/capsules returned at each visit and diary entries.

10. TRIAL PROCEDURES AND ASSESSMENTS

All trial assessments will be performed at the visits and time points outlined in the Schedule of Assessments (Table 1); the following sections outline the details and procedures associated with the assessments. Further information is provided in the protocol appendices, as noted in the sections below.

10.1. Demographics and Other Baseline Characteristics

10.1.1. Informed Consent

The nature of the trial and its potential risks and benefits will be explained to the patient by the investigator or designated trial personnel. The patient must provide written informed consent on an IRB-approved informed consent form (ICF) prior to performing any trial-related procedures.

10.1.2. Demographics

The following demographics will be recorded: age, sex, race, and ethnicity.

10.1.3. Medical History

The complete medical history will include histories of acute, chronic, or infectious disease; surgical or oncologic histories; and any reported conditions affecting major body systems. Medical history will include personal and family history of psychiatric illness and substance use disorders. All findings on medical history will be evaluated by the investigator for clinical significance. The WPI of the FS will be used for evaluation of chronic overlapping pain conditions at Screening; a copy of the FS (including the WPI) is provided in Appendix 16.7.

10.1.4. Pain Catastrophizing Scale

The PCS is a widely used and validated instrument for the assessment of pain catastrophizing, which has been shown to be associated with responses to opioids in chronic pain patients (Grosen et al., 2017; Sullivan et al., 1995). The PCS instructions ask patients to reflect on past painful experiences, and to indicate the degree to which they have experienced each of 13 thoughts or feelings when experiencing pain, on 5-point scales from (0) not at all to (4) all the time. The PCS yields total scores ranging from 0 to 52, with 3 subscale scores assessing rumination, magnification, and helplessness. The PCS has been recommended for patient phenotyping in clinical trials assessing chronic pain (Edwards et al., 2016). A copy of the PCS is provided in Appendix 16.8.

10.1.5. Pain Profile Questionnaire

The PPQ was developed to guide investigators in determining satisfaction with SAO treatment and appropriateness of ER opioid use. A copy of the PPQ is provided in Appendix 16.9.

10.1.6. STOP-Bang

The STOP-Bang Questionnaire consists of 8 dichotomous (yes/no) items related to the clinical features of obstructive sleep apnea (Chung et al., 2016). The total score ranges from 0 to 8. Patients with a STOP-Bang score of 5 to 8 can be classified as high risk for moderate to severe sleep apnea. A copy of the STOP-Bang questionnaire is provided in Appendix 16.10.

10.1.7. Pain Treatment-Response Questionnaire and External Documentation of Prior Therapies

The guided PTRQ was developed to document prior pharmacologic and non-pharmacologic therapies used by patients for treatment of their primary chronic pain conditions. A copy of the PTRQ is provided in Appendix 16.3. The PTRQ will be reviewed by the investigator in conjunction with other external documentation, such as medical records, monitoring data, or claims data (as available), to confirm that patients are appropriate candidates for ER/LA opioid therapy. Investigator-completed forms associated with the PTRQ will provide investigators with guidance on definitions of prior treatment failures for each indication. This information will be based on available indication-specific treatment guidelines.

[[A description of “other data”, i.e., monitoring or claims data, will be added to the protocol once confirmed]]

10.2. Efficacy and Other Assessments

10.2.1. Pain Intensity Numerical Rating Scale

The NRS is an 11-point scale to assess PI with anchors at 0 (no pain) and 10 (worst pain imaginable). Patients will record their Average and Worst PI once daily before bedtime. Worst PI will be assessed for the index site/condition as the primary endpoint. Trial personnel and patients will undergo training on how to complete this assessment. A copy of the PI NRS is provided in Appendix 16.11.

10.2.2. Brief Pain Inventory – Short Form

The BPI-SF is a 9-item, self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of the pain on the patient's daily functioning (Cleeland & Ryan, 1994; Daut et al., 1983). A copy of the BPI-SF is provided in Appendix 16.12.

10.2.3. Patient Global Impression of Change

The PGIC is a 7-point scale that requires the patient to assess how much his or her pain has improved or worsened relative to a baseline state at the beginning of the intervention. Pain is rated as: 1 – much worse; 2 – worse; 3 – a little worse; 4 – no change; 5 – a little better; 6 – better; or 7 – much better. A copy of the PGIC is provided in Appendix 16.13.

10.2.4. EuroQOL Group, 5-Dimension, 5-Level Descriptive System

The EQ-5D-5L descriptive system is a generic, multidimensional, health-related, quality-of-life instrument. The profile allows patients to rate their health states in 5 health domains: mobility, self-care, usual activities, pain/discomfort, and mood, using a 5-level scale. These combinations of attributes are converted into a weighted health-state Index Score according to the US-population-based algorithm, with higher scores indicating better quality of life. A copy of the EQ-5D-5L is provided in Appendix 16.14.

10.2.5. PROMIS v2 – Physical Function Short Form 8b

The National Institutes of Health have established the PROMIS to assess health across various chronic illnesses. The PROMIS PF-SF-8b has been validated to assess physical function across a wide range of patients with chronic illnesses, including chronic pain conditions, and has been cross-validated against other measures of physical function, such as the Oswestry Disability Index and the Roland-Morris Disability Questionnaire (Chiarotto et al., 2020; Feng et al., 2020; Orlando Edelen et al., 2021). Given the number of indications that are eligible for this trial, the use of a general physical function scale that can be applied across indications, rather than separate indications-specific scales, will increase the statistical power to assess the effects of long-term ER opioids on physical function. A copy of the PROMIS PF-SF-8b is provided in Appendix 16.15.

10.2.6. Fibromyalgianess Scale

Diagnostic criteria were developed in a longitudinal trial of patients of the National Data Bank for Rheumatic Diseases, resulting in a self-reported questionnaire assessing the number of pain sites and somatic symptom severity with fibromyalgia. The diagnostic criteria include 2 subscales, the WPI and the Symptom Severity Score (SSS), which together constitute the FS. FS scores will be assessed as a potential predictor of opioid response; however, the WPI subscale will also be used to identify the location of pain sites at Screening and to identify potential spread of pain as a part of the assessment for OIH. A copy of the FS (WPI and SSS) is provided in Appendix 16.7.

10.2.7. Quantitative Sensory Testing

QST is a method to quantitatively measure pain sensitivity in response to noxious and non-noxious stimuli of different modalities. These dynamic tests are aimed to assess distinct pro- and/or anti-nociceptive mechanisms.

Measured QST parameters will include heat pain threshold (HPTHR), half-maximum heat pain (HP50%), heat pain tolerance (HPTOL), and sustained heat pain ratings (HPRAT). Additional parameters will also be calculated, including heat pain differential (HPDIF; calculated as HPTOL-HPTHR), heat pain differential 50% (HPDIF-50%; calculated as HP50%-HPTHR), and heat pain summation (HPSUM; equivalent to the area under the curve depicting pain ratings over time).

The QST sessions will consist of a familiarization/training phase, followed by an assessment phase. Patients will be trained and tested for satisfactory QST performance to qualify for inclusion into the OIH Population. Between-session variability data will be obtained from the 2 assessments performed at Screening, to allow construction of a distribution-based criterion to infer presence or absence of OIH (e.g., value outside the 95% confidence interval). Standardized language will be used for instructing patients and performing QST assessments.

A pilot or interim assessment will be conducted after testing 20 patients to evaluate the QST algorithm feasibility and utility.

Specific QST procedures are outlined in Appendix 16.16; an instruction manual will also be provided.

10.2.8. Unblinding Questionnaire

A questionnaire will be completed by patients at the end of the Double-Blind Phase or at early discontinuation from the Double-Blind Phase to evaluate which treatment patients believe they received during the Double-Blind Phase (morphine sulfate ER or placebo). To avoid influencing responses, the questionnaire will include an open-ended follow-up question regarding the reason(s) for the patient's response. A copy of the assessment is provided in Appendix 16.17.

10.3. Safety Assessments

10.3.1. Adverse Events and Serious Adverse Events

The investigator and research site staff are responsible for the detection, documentation, classification, reporting, and follow-up of events meeting the definition of an AE or SAE. All AEs will be recorded following informed consent (at Screening) until the end of the Tapering and Follow-up Period of the trial.

10.3.1.1. Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and may not necessarily have a causal relationship with the administered treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant laboratory abnormality), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational

product. During the trial, an AE can also occur outside the time that the investigational product(s) was given (e.g., during a washout period). Pre-existing conditions, diseases, or disorders are not considered AEs unless there is a change in intensity, frequency, or quality.

10.3.1.2. Serious Adverse Events and Serious Unexpected Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (at the time of the event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the trial patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A serious and unexpected AE is an SAE that is not identified in nature, intensity, or frequency in the risk information set out in the prescribing information of the medication.

Any SAE experienced by a trial patient—expected or unexpected, irrespective of relationship to trial treatments, including death due to any cause—will be reported to the sponsor or designee by the investigator within 24 hours of learning of the event. Information regarding the SAE will be transmitted to the sponsor or designee, according to the instructions and contact information provided in the safety management plan. The sponsor or designee assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor or designee will also report to the investigator all SAEs that are unlisted and associated with the use of the trial medication. The investigator (or sponsor/designee, where required) must report these events to the appropriate IRB that approved the protocol (unless otherwise required and documented by the IRB). Follow-up evaluations for SAEs will also be reported to the sponsor or designee.

10.3.1.3. Adverse Events of Special Interest (AESIs)

Abuse (including use by inappropriate routes), misuse, diversion, psychological dependence, overdose, physical dependence/opioid withdrawal, therapeutic errors, or suicide-related AEs will be recorded as AESIs. Product issues will be considered reportable events of interest. These events may be related to the morphine sulfate ER or to the morphine IR rescue medication (collectively referred to as the narcotic trial medications).

Note that this section contains information on the collection and categorization of these events for the purposes of regulatory reporting for this trial, based on Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks (ACTTION) recommendations (Smith et al., 2017). These terms are not intended for use during interactions

with patients. In patient interactions involving these events, investigators should take necessary steps to reduce the potential for stigma and negative bias (refer to NIDA guidelines available at https://nida.nih.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction).

Investigators and relevant research site personnel will receive training in the recognition and reporting of AESIs, including further guidance on when such events may need to be reported as SAEs. For all AESIs, additional commentary from the investigator will be required in the Case Report Form (CRF) or other study-specific document in order to construct narratives of the events.

The continued participation of patients with AESIs in the trial will be assessed on a case-by-case basis and should be discussed with the medical monitor or designee.

Drug Abuse or Psychological Dependence

As noted previously, development of drug abuse or dependence is considered a medically important event that, in addition to being considered an AESI, may also be recorded as an SAE, and subjected to the reporting requirements outlined in Section 10.3.1.2. Abuse of narcotic trial medications may involve intentionally taking more drug than indicated for a desired psychological effect (such as feeling good or "high") rather than for pain relief or may involve tampering with and using the medications by an inappropriate route, such as crushing and swallowing or "snorting" to increase the euphorigenic effects of the medications.

For the purposes of this trial, drug dependence will include only "psychological" dependence (refer to the below paragraph for physiological or physical dependence). Signs of psychological dependence, in the context of this trial, may include cravings or strong desire to take the drug for reasons other than pain relief; obsessive, intractable and distracting thoughts about the narcotic trial medications; or placing a higher priority on narcotic trial medication use than on other activities and obligations (i.e., impaired behavioral control with respect to use of narcotic trial medications).

Suicide-Related Events

An actual suicide or suicide attempt will also be considered an SAE (Section 10.3.1.2); suicidal ideation or self-harm may be recorded only as an AESI and not an SAE, subject to the investigator's clinical judgement, provided it does not meet any of the criteria for an SAE outlined in Section 10.3.1.2 (e.g., life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity).

Overdose

Accidental or intentional overdose of the narcotic trial medications resulting in severe toxicity requiring medical intervention, including the requirement for naloxone rescue (either in a clinical setting or use of the take-home naloxone nasal spray by the patient) will be recorded as an SAE and must be reported as outlined in Section 10.3.1.2.

Misuse

Misuse includes events related to intentionally using the narcotic trial medications in a manner other than that specified in the protocol or as directed by the investigator, but still within the context of therapeutic use (i.e., use for pain relief). Examples of misuse in the context of this trial include taking the narcotic trial medications using an inappropriate regimen (e.g., more than BID) or taking more doses than permitted in the context of pain relief (e.g., that do not result in an opioid overdose). Misuse will be recorded as an AESI unless the case otherwise meets criteria for an SAE (Section 10.3.1.2; e.g., life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity).

Therapeutic Errors

Therapeutic errors will be recorded as AESIs—examples of therapeutic error include unintentionally administering the wrong dose of trial medication or the wrong blinded trial medication. Therapeutic errors may be made by the patient, investigator, or research site staff involved in the dispensing of trial medications. Therapeutic errors that result in an opioid overdose, as outline above, will be recorded as SAEs and will be subject to the reporting requirements outlined in Section 10.3.1.2. Incorrect packaging or other errors in provision of clinical trial supplies to the research site will be considered a product issue.

Physical Dependence

Signs/symptoms of opioid withdrawal upon tapering will be recorded as AESIs but will not be considered SAEs, as physical dependence is an expected physiological process associated with long-term administration of morphine. If clinically significant opioid withdrawal is noted in the course of administering the COWS assessment, this will be reported as an AESI unless the case otherwise meets criteria for an SAE (Section 10.3.1.2; e.g., life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity).

Diversion

Drug accountability records will be routinely monitored for cases of potential diversion. Examples of diversion include giving or selling the narcotic trial medications for any purpose, even therapeutic, to another individual. Diversion should be suspected if a patient repeatedly fails to return trial medications for pill counts or repeatedly claims to have lost or had medications stolen. Diversion of narcotic medications (ER and IR morphine) must be recorded as an AESI and the sponsor or designee should be notified within 3 days of the research site learning of the event.

Product Issues

Product Issues may involve intentional tampering with the narcotic trial medications by patients without further evidence of abuse, diversion, or misuse. If the tampering is associated with inappropriate administration of the drug (such as crushing the medication for ingestion or administration by an inappropriate route), this will be considered an AESI associated with drug abuse. Product issues may also include errors or problems with the clinical trial supplies, such as

incorrect packaging, damaged pills or blister packs, or incorrect labelling. Although not recorded as an AE, in the event of a product issue, the sponsor or designee should be notified within 3 days of learning of the issue.

10.3.1.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Abnormal clinical laboratory findings (e.g., clinical chemistry, hematology, urinalysis, or UDT) or other abnormal assessments (e.g., from vital signs or ECG), judged as clinically significant by the investigator, will be recorded as AEs or SAEs if they meet the definitions provided previously. Abnormal laboratory or other findings present at baseline that significantly worsen following the start of the trial will be reported as AEs or SAEs.

10.3.1.5. Classification of Adverse Event Intensity and Causality

For each recorded AE or SAE, the investigator must make an assessment of intensity based on the following criteria:

Mild:	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate:	An event that is alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the patient.
Severe:	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living or significantly affects clinical status. The event poses a significant risk of harm to the patient and hospitalization may be required.

The investigator must make an assessment of causality based on the following criteria to determine the relationship between the AE/SAE and ER trial medication:

Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the patient's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational product. In case of cessation or reduction of the dose, the AE may abate or resolve, and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the investigational product.

For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

10.3.1.6. Follow-up of Adverse Events and Serious Adverse Events

All SAEs and AEs must be collected from the signing of the informed consent for trial participation through 30 days after the patient's last dose of trial medication.

All SAEs and AEs that result in discontinuation will be followed until the event resolves, stabilizes (according to the judgment of the investigator), returns to a baseline value (if a baseline value is available), or can be attributed to agents other than the trial medications or to factors unrelated to trial conduct.

When it becomes unlikely that any additional information can be obtained (e.g., patient or healthcare practitioner refuses to provide additional information, the patient is lost to follow-up), the investigator or designee will ensure that the follow-up includes any pertinent supplemental investigations (e.g., laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals) to elucidate the nature and/or causality of the AE or SAE.

Investigators are not obligated to actively seek AEs or SAEs in former trial patients that occur after the Tapering and Follow-up Period. However, if the investigator learns of any AE or SAE within 30 days of the last dose of trial medication and the event is considered reasonably related to the ER trial medication, the investigator will notify the sponsor or designee.

For each recorded AE or SAE, the investigator must make an assessment of outcome at the time of last observation, as follows:

Fatal:	The patient died
Recovered/Resolved:	The AE or SAE has ended
Recovered/Resolved with Sequelae:	The AE or SAE has ended but changes are noted from baseline
Not Recovered/Not Resolved:	The AE or SAE has not improved or recuperated
Recovering/Resolving:	The AE or SAE is improving
Unknown:	Not known, not observed, not recorded, or refused

10.3.2. Pregnancy

If a female patient becomes pregnant or suspects pregnancy while participating in the trial or within 30 days after the last dose of ER trial medication, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. All pregnancies must be followed up regarding the course and outcome, including any post-natal

sequelae in the infant. Follow-up information will be obtained where possible (with the consent of the patient or the pregnant partner).

SAEs occurring in the child (congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must be documented and reported. The investigator will report the pregnancy and pregnancy outcomes to the sponsor or designee within 24 hours of the research site learning of the event using the pregnancy reporting form.

Any patient who becomes pregnant during the trial will be immediately withdrawn from the trial and provided with a referral to appropriate local care (e.g., high risk obstetrician, if available). The investigator will be responsible for managing the patient's care during the transition process.

10.3.3. Clinical Laboratory Assessments

Blood and urine samples will be collected, processed, and shipped according to instructions from the sponsor/designee and/or central safety laboratory. All clinical laboratory data will be reviewed by the investigator for clinical significance.

All protocol-specified laboratory tests on blood and urine samples will be performed at a selected central laboratory, with the exception of urine pregnancy tests. The central lab will generate laboratory reports and forward them to the research site in a timely manner, along with flags/alerts for abnormal results and clinical significance of the abnormal results. It is the responsibility of the investigator to review and sign all lab reports expeditiously, in order to document appropriate safety monitoring of trial patients. The investigator should sign and date each lab report concurrent with her or his review. Notations indicating that a value is clinically significant (CS) should also include a brief description of the underlying disease or condition that is associated with the value (e.g., "CS/mild anemia"), if known. In general, abnormal CS laboratory values are expected to be associated with an item recorded in medical history or with an AE. CS clinical laboratory findings at Screening may affect patient eligibility for entry into the trial (refer to Section 8.2).

Additional laboratory samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure safety. Specific hematology, biochemistry, and urinalysis assessments are listed in Table 3.

Table 3: Clinical Laboratory Assessments

Hematology	Biochemistry	Urinalysis
Hematocrit Hemoglobin Red blood cell count Total and differential (absolute) white blood cell count Platelets	Sodium Potassium Glucose (random) Creatinine Total protein Blood urea nitrogen Albumin Total bilirubin Alanine transferase Aspartate transferase Lactic dehydrogenase Gamma-glutamyl transferase Alkaline phosphatase Creatine phosphokinase	Color pH Specific gravity Ketones Protein Glucose Bilirubin Nitrite Urobilinogen Occult blood Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*

In addition to the tests listed in the above table, endocrine function will be assessed using free and total testosterone, LH, FSH, estradiol (women only), IGF 1, cortisol, ACTH, DHEAS, and TSH). FSH will be reviewed at Screening for post-menopausal women (by medical history) only to confirm non-childbearing status.

Pregnancy testing for the presence of β-human chorionic gonadotropin will be performed for all women of childbearing potential. Results of pregnancy tests will be reported and determined to be negative prior to enrollment and randomization.

10.3.4. Urine Drug and Alcohol Testing

Quantitative UDTs will test for illicit drugs (including, for the purposes of this trial, cannabis), non-prescribed controlled substances (opioid and non-opioid), and alcohol (refer to Appendix 16.4 for details on the analytes to be tested). Quantitative testing will be performed at the visits outlined in Table 1.

Patients with positive UDT result(s) at Screening will be excluded from the trial, as per exclusion criteria (Section 8.2). If a patient has an unexpected positive UDT result (i.e., for non-prescribed substance[s]) after entry into the trial (post-Screening), the investigator will manage the patient according to guidance provided in Appendix 16.4. In addition, the investigator must consult the medical monitor in the event of an unexpected positive UDT result to confirm the appropriate course of action. Repeat or unscheduled UDTs may be performed at the investigator's discretion (e.g., in case of initial positive results that require follow-up or if the investigator is concerned about the patient's use of other substances). To avoid unblinding, UDT data for morphine and its metabolites obtained during the Double-Blind Phase will NOT be shared by the laboratory until after completion of the trial.

10.3.5. Vital Signs

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mmHg), pulse rate (beats per minute), and respiratory rate (breaths/min), collected while sitting, following a rest period of at least 3 minutes. The investigator will review all vital signs findings for clinical significance. Any findings meeting the investigator's or sponsor/designee's criteria for clinical significance will be recorded as AEs or SAEs as appropriate. CS vital signs findings at Screening may affect patient eligibility for entry into the trial (refer to Section 8.2).

Height, weight, and body mass index will be assessed at Screening.

10.3.6. 12-Lead Electrocardiograms

ECGs will be performed after the patient has been resting in a supine or semi-supine position for at least 3 minutes. The ECG variables will include ventricular heart rate and PR, QRS, QT, QTcB, and QTcF intervals. The investigator will review all ECG findings for clinical significance. Any findings meeting the investigator's or sponsor/designee's criteria for clinical significance will be recorded as AEs or SAEs as appropriate. CS ECG findings at Screening may affect patient eligibility for entry into the trial (refer to Section 8.2).

10.3.7. Physical Examination

A complete physical examination assessing the patient's overall health and physical condition will be performed at Screening, and a brief physical examination (examination of heart, lungs, abdomen, and legs) will be performed thereafter. The investigator will review all physical examination findings for clinical significance. Any findings meeting the investigator's or sponsor/designee's criteria for clinical significance will be recorded as AEs or SAEs as appropriate. CS physical examination findings at Screening may affect patient eligibility for entry into the trial (refer to Section 8.2).

10.3.8. Opiate Withdrawal Scales

The trial personnel will assess clinical observations indicative of withdrawal using the COWS during the Double-Blind Phase. This scale consists of 11 common opiate withdrawal signs or symptoms, which are rated on a numeric scale and based on a timed period of observation of the patient by the rater. A copy of the COWS is provided in Appendix 16.18.

Patients will complete a self-assessment of withdrawal symptoms using the SOWS during the Double-Blind Phase. This form contains 16 questions that rate the intensity of withdrawal from 0 ("not at all") to 4 ("extremely"). A copy of the SOWS is provided in Appendix 16.19.

10.3.9. Hospital Anxiety and Depression Scale

The HADS is a 14-item scale, with 7 items to assess depressive symptoms and 7 items to assess anxiety symptoms (Norton et al., 2013). Each item is rated on a scale from 0 to 3. Scores of 8 to 10 indicate borderline abnormal cases, and scores from 11 to 21 indicate abnormal cases. The HADS has been recommended for patient phenotyping in clinical trials assessing chronic pain (Edwards et al., 2016). A copy of the HADS is provided in Appendix 16.20.

10.3.9.1. Prescription Opioid Misuse and Abuse Questionnaire

The 19-item POMAQ was developed to identify behaviors related to misuse and abuse, the intention behind each behavior, and prescription opioid diversion behaviors. A behavior or combination of behaviors is classified as opioid misuse or abuse (or both) based upon how the person responded to the intent of the specific behavior. The POMAQ has been validated for use in chronic pain patients and is designed for assessment over the prior 3 months (Coyne et al., 2021a; 2021b; 2021c). A copy of the POMAQ and scoring guidelines are included in Appendix 16.21.

10.3.10. Sexual Function

The ASEX will be used to assess sexual function in both males and females (using the male and female specific questions, respectively). The ASEX is designed to assess 5 major global aspects of sexual dysfunction: drive, arousal, penile erection/vaginal lubrication, ability to reach orgasm, and satisfaction from orgasm, which are the domains most commonly impaired by psychotropic drugs (McGahuey et al., 2000). The scale measures these in a brief, relatively nonintrusive, bimodal fashion, using a 6-point Likert scale ranging from hyperfunction (1) to hypofunction (6). The concise and less explicit nature of the scale relative to other measures of sexual function is expected to contribute to patient compliance. A copy of this assessment is provided in Appendix 16.22.

10.3.11. Columbia-Suicide Severity Rating Scale

The C-SSRS tracks all suicidal events and provides a summary of suicidal ideation and behavior. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

Two versions of the C-SSRS will be used in this trial: the Baseline/Screening version (Lifetime) and the Since Last Visit version. The Screening/Lifetime version will be administered at Visit 1 (Screening), and the Since Last Visit version will be administered at all subsequent assessments.

A validated telephone or tablet/device-based C-SSRS assessment will be used in this trial. The investigator will have access to the patient's results after completion of the Screening assessment in order to determine patient eligibility (i.e., C-SSRS findings at Screening may affect patient eligibility for entry into the trial; refer to Section 8.2). The investigator will receive immediate notification of any high-risk responses and will be responsible for management of the patient (e.g., discontinuation of participation and referral to appropriate follow-up care). Copies of the C-SSRS versions used in this trial are provided in Appendix 16.23.

10.3.12. Sleep Scale

The ISI has been recommended for phenotyping in chronic pain patients (Edwards et al., 2016). The 7-item ISI assesses the severity and impact of insomnia symptoms (Bastien et al., 2001). A copy of the ISI is provided in Appendix 16.24.

10.3.13. Other Assessments and Procedures

10.3.13.1. Early Discontinuation Assessment

The Early Discontinuation Assessment is a clinician-guided assessment that will be completed for patients who withdraw consent from the trial (i.e., subject decision) to thoroughly evaluate patient-reported reasons for withdrawal. A copy is provided in Appendix 16.5.

10.3.13.2. Online Support Tool

An easy-to-use computer-based online support tool (https://painguide.com/) will be introduced at the Screening Visit-to aid in the management of the patients' chronic pain. Patients will be reminded of the tool's availability at the beginning of each phase.

10.4. Drug Concentration Measurements

Not applicable in the current trial.

10.5. Appropriateness of Measures

The use of unidimensional pain scales, such as the NRS, is recommended for the assessment of PI (Ferreira-Valente et al., 2011; Hjermstad et al., 2011); these scales have been used as primary outcome measures in previous studies evaluating efficacy of opioids. Worst PI has been included in the primary endpoint definition in this trial to capture breakthrough pain in the context of the rescue medication available to patients. Time to loss of efficacy is included as the primary derived endpoint as it has been found to be a more statistically powerful endpoint than mean PI (Katz, 2009). Average PI will be included as a secondary efficacy endpoint. In addition to PI NRS, several other measures are included to evaluate the efficacy of ER opioids, including BPI-SF and EQ-5D-5L, as well as a validated assessment of physical function (PROMIS PF-SF-8b) that can be used across indications.

The OPC supported a systematic literature review to determine which QST methods have been tested for the assessment of OIH, and whether any of these methods have been successful in detecting OIH (Grosen et al., 2013). The review determined that heat pain appeared to be the most promising stimulus type for detecting OIH. The WPI will also be used to assess for pain spread.

Standard safety measures will be included to assess the long-term safety of ER opioids relative to placebo, including AEs, clinical laboratory tests, ECG, physical examinations, vital signs, concomitant medications, and C-SSRS. Additional measures will include assessments of emotional function, sleep, sexual and endocrine function, and abuse or misuse, including the POMAQ, abuse-related AESIs, and review of UDT results.

Selected baseline, efficacy, and safety assessments will also be evaluated as potential predictors of response and non-response to ER opioids. Many of these indicators have been previously examined as potential predictors of response to opioids or have been recommended for use in chronic pain phenotyping (Edwards et al., 2016; Grosen et al., 2017).

10.6. Outcome Variables

Trial endpoints are outlined in Section 6.3. Trial endpoints relative to trial objectives are summarized further in Table 4.

Table 4: Objectives and Corresponding Assessments/Endpoints

Objective	Assessment/Endpoint	Screening	Open-Label Titration Phase	Open-Label Treatment Phase	Double-Blind Phase
PRIMARY	**PRIMARY**				
To evaluate the persistence of analgesic efficacy of an ER opioid in the Double-Blind Phase, in patients with defined CNCP who demonstrate initial analgesic efficacy and tolerability of the ER opioid during the Open-Label Treatment Phase	Time to loss of efficacy after randomization to continued ER opioid treatment or taper to placebo (composite measure: increase by ≥ 30% increase in past 7-day moving average of the daily Worst 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 analgesic therapy for index chronic pain condition(s) OR trial drug discontinuation due to lack of efficacy				X
	SECONDARY				
	Time to treatment failure (loss of efficacy or tolerability using above composite OR dropouts due to AEs)				X
	Time to loss of efficacy, defined using Average PI (≥ 30% increase in past 7-day moving average of the daily Average PI compared to the 7 days prior to randomization and past 7-day moving average of the daily Average PI ≥ 4)				X
	Proportion of patients who meet the criteria for loss of efficacy or treatment failure (as defined above) by week				X
	Change in mean Worst PI and Average PI (past 7 days)			X	X
	Change in BPI-SF scores			X	X
	PGIC scores			X	X
	Change in EQ-5D-5L scores			X	X
	EXPLORATORY				
	Mean total mg of IR morphine (SAO) and APAP rescue medications				X
	Proportion of patients who initiated new analgesic therapy (pharmacologic and non-pharmacologic) for index chronic pain condition by trial phase.			X	X
	Patient responses on the unblinding questionnaire				X

Objective	Assessment/Endpoint	Screening	Open-Label Titration Phase	Open-Label Treatment Phase	Double-Blind Phase
SECONDARY	**SECONDARY**				
To explore the incidences of OIH and opioid tolerance.	Incidence of patients who develop OIH with ER opioid during the trial (Worst PI at final assessment is same or higher than at Screening [patient is receiving same/ higher dose] AND QST at final assessment shows increased pain sensitivity vs. Screening)		X	X	X
	Incidence of patients who develop OIH during Open-Label Treatment Phase (Worst PI prior to randomization is same or higher than at Screening [patient is receiving same/ higher dose] AND QST prior to randomization shows increased pain sensitivity vs. Screening)			X	
	Incidence of patients who develop opioid tolerance during the trial (Worst PI at final assessment is same or higher than at Screening [patient is receiving same/ higher dose] AND QST at final assessment does not show increased pain sensitivity vs. Screening)		X	X	X
	Incidence of patients who develop opioid tolerance during the Open-Label Treatment Phase (Worst PI prior to randomization is same or higher than at Screening [patient is receiving same/higher dose] AND QST prior to randomization does not show increase in pain sensitivity vs. Screening)			X	
	Incidence of patients who experience loss of opioid effect over time (patients who develop tolerance or OIH, as defined above)		X	X	X
	Pain spread, as assessed by the WPI			X	X
	EXPLORATORY Cluster analysis of putative components of OIH syndrome: pain intensity (Worst PI), pain spread (WPI), dose change over time (mg/day), measured pain sensitivity (QST)		X	X	X
To evaluate changes in pain sensitivity over time	Pain sensitivity changes (by QST) over time by trial phase, and by treatment group (Double-Blind Phase)		X	X	X
To identify potential predictors of the opioid response and non-response	**EXPLORATORY** Demographics, personal/family history, including mental illness and substance use disorders, medical history, including chronic overlapping pain conditions, FS (fibromyalgianess), HADS (anxiety/depression), PCS (pain catastrophizing), pain profile,			X	X

Objective	Assessment/Endpoint	Screening	Open-Label Titration Phase	Open-Label Treatment Phase	Double-Blind Phase
	physical function, AEs, QST, ISI (sleep/insomnia), and COWS results.				
To evaluate changes in physical function and in level of anxiety and depression	Change in physical function scores (PROMIS PF-SF-8b), and anxiety/depression (HADS) scores		X	X	X
To evaluate the safety of titrated doses of an ER opioid	Evaluation of AEs, endocrine and sexual function, sleep (ISI), suicidality (C-SSRS), and other safety assessments (vital signs measurements, clinical laboratory tests, ECG findings, physical examination findings, concomitant medications)		X	X	X
	COWS/SOWS scores over time and proportion of patients with COWS $\geq$ 5				X
	Proportion of patients with abuse-related AESIs, proportion of patients who meet criteria for abuse/misuse and opioid use disorder (POMAQ), and positive results for illicit drugs or non-prescribed controlled substances (UDT results)		X	X	X
To evaluate all endpoints in patients who are titrated to a high dose of ER opioid	All endpoints listed above assessed in patients who achieve a high dose of ER opioid prior to randomization ($\geq$ 90 mg per day).		X	X	X
ELIGIBILITY/ENDPOINT EVALUATION OR BASELINE CHARACTERIZATION					
Prior pain treatments	PTRQ	X			
	External documentation (medical records, monitoring or claims report)	X			
Pain profile	PPQ	X	X	X	X
Sleep apnea	STOP-Bang	X			

Abbreviations: AEs = adverse events; AESI = adverse events of special interest; APAP = acetaminophen; BID = twice daily; BPI-SF = Brief Pain Inventory – Short Form; CNCP = chronic non-cancer pain; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EQ-5D-5L = EuroQOL, 5-dimension, 5-level descriptive system; ER = extended-release; FAS = Full Analysis Set; FS = Fibromyalgianess Scale; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; NRS = numerical rating scale; OIH = opioid-induced hypersensitivity; PCS = Pain Catastrophizing Scale; PGIC = Patient Global Impression of Change; PI = Pain Intensity; POMAQ = Prescription Opioid Misuse and Abuse Questionnaire; PPQ = Pain Profile Questionnaire; PROMIS PF-SF-8b = PROMIS v2– Physical Function Short Form 8b; PTRQ = Pain Treatment-Response Questionnaire; QST = Quantitative Sensory Testing; SAO = short-acting opioid; SOWS = Subjective Opiate Withdrawal Scale; UDT = urine drug testing; WPI = Widespread Pain Index.

11. DATA QUALITY ASSURANCE

This trial will be conducted under Good Clinical Practice (GCP) standards and all applicable regulatory requirements. To ensure compliance, the sponsor or designee may conduct a quality assurance audit, as outlined in Section 11.2.

Actions to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial centers; the review of protocol procedures with the investigator and trial personnel prior to trial start; the design of suitable source documents with appropriate instructions for use (where applicable); the internal audit of source data according to GCP and internal procedures to ensure their accuracy, completeness, and verifiability; as well as the periodic site monitoring by the sponsor or designee. Written instructions will be provided for collection, preparation, and shipment of blood, plasma, and urine samples. The sponsor or designee will review source documents for accuracy and completeness during on-site monitoring visits and after their return to the sponsor or designee; any discrepancies will be resolved with the investigator, as appropriate.

Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.

11.1. Data Collection

Source documents include, but are not limited to, original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, patient diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. This trial will use electronic data capture (EDC). At a minimum, all data required by the protocol should have supporting source documentation for entries in the EDC system, unless that data can be recorded directly in the study database using an electronic clinical outcome assessment tool.

All CRFs will be completed by the research site staff prior to review by the sponsor's monitor or designated representative. All entries, corrections, and alterations will be made by the investigator or other authorized trial personnel. Source data and/or CRF entries will be reviewed by the sponsor's monitor or designated representative according to a monitoring plan developed prior to initiation of the trial.

11.2. Trial Auditing and Monitoring

Monitoring of the research sites (including, but not limited to, reviewing CRFs for accuracy and completeness) will be performed by the sponsor's designated monitor. The extent, nature, and frequency of on-site visits will be based on such considerations as the trial objectives and/or endpoints, the purpose of the trial, trial design complexity, and enrollment rate. By signing the protocol, the investigator agrees that, within local regulatory restrictions and institutional and ethical considerations, authorized representatives of the sponsor (or designee), a regulatory

authority, and/or an IRB may visit the research sites to perform audits or inspections, including the medication storage area, trial medication stocks, medication accountability records, patient charts and source documents, and other records related to trial conduct. The purpose of the sponsor audit or inspection is to systematically and independently examine all trial-related activities and documents to determine whether the trial-related activities were conducted, and data recorded, analyzed, and accurately reported according to the protocol, the site's standard operating procedures, GCP guidelines of the International Council on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact the sponsor or designee immediately if contacted by a regulatory agency regarding an inspection.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical and Analytical Plans

Complete details of the statistical analyses to be performed will be documented in a statistical analysis plan (SAP), which will be completed prior to unblinding of the trial data. This document will include more detail of analysis populations, summary strategies, and any amendments to the proposed analyses listed here, if necessary. Any changes to the SAP will be outlined in the final clinical trial report.

12.2. Analysis Populations

The trial analysis populations will consist of:

Full Analysis Set (FAS): The FAS will include all patients randomized into the Double-Blind Treatment Phase. This population will be used for efficacy reporting.

OIH Population: The OIH Population will include all patients who enter the Open-Label Titration Phase and have at least 1 post-trial treatment QST evaluation.

Full Safety Population: The Full Safety Population will include all patients dosed with morphine sulfate ER at any point in the trial.

Open-Label Treatment Safety Population: The Open-Label Treatment Safety Population will include all patients who are successfully titrated and dosed in the Open-Label Treatment Phase.

Double-Blind Safety Population: The Double-Blind Safety Population will include all patients who are randomized and dosed in the Double-Blind Phase.

12.3. Planned Analyses

12.3.1. Reporting Groups

All efficacy and safety assessments will be presented by treatment arm (where applicable) and for the subgroup of patients who titrate to above a predetermined "high dose" threshold of ≥ 90 mg per day.

12.3.2. Demographics and Other Baseline Characteristics

Disposition for all randomized patients will be summarized by the randomized treatment group. Reasons for discontinuation will be tabulated for each treatment group and overall.

Demographic data will be summarized by analysis population.

Tabular summaries and/or listings will be provided for baseline clinical characteristics, such as medical history, inclusion/exclusion criteria, medication history, the PPQ, the COWS/SOWS, and the STOP-Bang.

Prior medications will be coded using the World Health Organization – Drug Dictionary Enhanced (WHO-DDE) and summarized using descriptive statistics.

12.3.3. Analysis of Efficacy Outcome Measures

The primary efficacy endpoint of time to loss of efficacy will be analyzed using Kaplan-Meier methodology with stratification for the titrated dose levels. Quantiles for 25%, median, and 75% will be presented, as well as 95% confidence intervals (CIs), if estimable. The treatment arms will be compared using a stratified log-rank test against the hypothesis that there is no difference in the time to loss of efficacy in the trial arms. The titration dose level strata may be pooled among adjacent doses in the case of small counts and/or sparse events in a given strata. Sensitivity analyses will investigate varying the threshold of SAO and APAP rescue medication use to qualify as a loss of efficacy, absolute pain (past 7-day moving average of the daily Worst PI ≥ 5) to qualify as loss of efficacy, and including additional ambiguous reasons for early discontinuation (such as "other," "lost to follow-up," and "unknown,") as loss of efficacy.

12.3.4. Analysis of OIH Outcome Measures

The OIH incidence for each endpoint will be reported with the number and percentage of patients and associated 95% CI of the percentage. For the Double-Blind Phase, the numbers and percentages will be reported by trial arm and the differences in percentages will be reported as well as 95% CIs. The arms will be compared using a difference in proportions Z test; if there are less than 5 patients expected in a cell, a Fisher's exact test will be used instead.

The primary analysis for rates of OIH will use the following approach for missing and partial data. Patients who discontinue the trial due to loss of efficacy will be treated as satisfying the pain criterion for OIH; each discontinued patient's last available dosing information and QST battery results will then be evaluated to determine whether he or she represents a case of OIH. All other patients with missing data will be evaluated to determine whether they met the OIH criteria at any earlier time point, and they will be counted as such if this occurs; otherwise, these patients will be assumed not to be cases of OIH. Additionally, the number and proportion of

patients missing each component of the OIH outcome, the proportion of patients with complete assessments, and the proportion of patients determined to exhibit OIH among those with complete assessments will be reported.

Sensitivity analyses will be performed to test the robustness of the results and statistical assumptions. For patients with missing data who do not have results precluding the presence of OIH, values will be imputed and analyzed via multiple imputation in 2 different ways:

1) A multiple imputation approach will be applied, assigning each patient as having an event with the same probability as the observed rate in his or her treatment arm.

2) An MI approach will be applied assigning patients as having an event with the same probability as the overall observed rate across both treatment arms.

Additional analyses related to OIH (e.g., pain sensitivity over time, pain spread, cluster analyses) will be detailed in the SAP.

12.3.5. Predictors of Opioid Response

Opioid response will be defined as ≥ 30% reduction from Screening in Worst PI and an end-of-trial PGIC score of 6 or 7 (better or much better) (or both); opioid non-response will be defined as < 30% reduction in Worst PI or a PGIC score ≤ 5 (or both).

For each definition of opioid response, a logistic model will be fit including effects for treatment arm, the predictor of interest, and an interaction between treatment arm and the predictor of interest. For each definition of opioid response, the odds ratio for the predictor in each treatment arm will be reported, as will the overall odds ratio for the predictor.

Predictors to be examined include:

- Demographics
- Personal/family history of mental illness and substance use disorders
- Medical history, including chronic overlapping pain conditions
- Fibromyalgianess (FS)
- Anxiety/depression (HADS)
- Pain catastrophizing (PCS)
- Physical function (PROMIS-PF-SF-8b)
- AEs
- QST
- Sleep/insomnia (ISI)

12.3.5.1. Drug Dose, Drug Concentration, and Relationships to Response

As described above, patients who titrate to above a predetermined “high dose” threshold of ≥ 90 mg per day will be reported separately in addition to the reporting by treatment group.

12.3.5.2. Drug-Drug and Drug-Disease Interactions

Not applicable.

12.3.6. Analysis of Safety Assessments

The Full Safety Population, Open-Label Treatment Safety Population, and Double-Blind Safety Population will be used for all safety analyses.

Exposure to ER trial medication will be summarized by period and treatment group.

AEs and treatment-emergent AEs (TEAEs) will be coded by primary system organ class (SOC) and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs will be summarized with number and percent of patients by primary SOC and preferred term. Summaries of TEAEs will be presented for relationship to trial medication, intensity, seriousness, TEAEs or SAEs leading to discontinuation, treatment-emergent AESIs, and TEAEs occurring in 5% or greater of any treatment group (by preferred term). Frequencies of deaths and hospitalizations will also be summarized by treatment group and overall. For the purposes of analysis and reporting, AESIs may be further categorized according to ACTTION recommendations (Smith et al., 2017).

Data for clinical laboratory tests, ECG, vital signs, C-SSRS, physical examinations, and other safety assessments will be summarized using standard descriptive and/or change from baseline statistics, as appropriate.

Concomitant medications will be coded using the WHO-DDE and summarized using descriptive statistics.

By-patient listings will be provided for all safety data.

12.4. Determination of Sample Size

12.4.1. Sample Size Estimation

The planned sample size of 200 patients per group is targeted to provide 90% power to detect a difference in time to loss of efficacy. A review of prior EERW studies revealed that very few studies allowed the level of rescue medication planned in the current protocol. Because this level is a key component of determining loss of efficacy and encouraging patient retention in the trial, the amount of rescue medication available was determined to be a critical factor for choosing which trial should be used as the basis of the power calculation.

A single study was identified that allowed up to 30 mg oxycodone IR rescue per day (45 mg MME/day) (Wen et al., 2015). The amount available to each patient was determined by the patient's double-blind daily dose level of ER hydrocodone (referred to as HYD) (or matching placebo); this was 10 mg for patients receiving HYD 20 or 40 mg, 15 mg for patients receiving HYD 60 mg, 20 mg for patients receiving HYD 80 mg, and 30 mg for patients receiving HYD 120 mg. While neither the double-blind dose levels nor the algorithm for determining the dose of SAO rescue medication are a perfect match to the current protocol, this study was determined to be the best proxy. A post-hoc analysis revealed a 15% rate of discontinuation for "lack of therapeutic effect" in the placebo group and a 5% rate in the active group with a 0.346 hazard

ratio (p = 0.0003). These assumptions yield a sample size of 187 patients per group for 90% power. Adding an assumption of 17% discontinuation due to other reasons for the active group and a 13% dropout for the placebo group yields 212 patients per group. However, the software applies this assessment uniformly of the period and may overstate the early discontinuation rate, giving a more conservative sample size estimate. The planned interim analysis to re-estimate sample size will identify if an increase is necessary due to deviations from these assumptions.

A large oxycodone ER registry study with multi-year follow-up yielded 60% retention over the first year (Portenoy et al., 2007). Applied to the current trial, this retention rate would require approximately 666 patients enrolled and successfully titrated into the Open-Label Treatment Phase to randomize 400 patients into the Double-Blind Phase. The retention rate will be actively monitored throughout the trial and enrollment adjusted to efficiently target the Double-Blind sample size.

Up to 30 research sites will perform QST and contribute to the OIH Population, with at least 200 patients to be included. Assuming an OIH rate of 5%, the precision of the OIH rate will be ± 2.53% with a sample size of 200 patients and ± 4% with 100 patients. For continuous QST measures, the sample size of 200 patients would be powered at 80% for comparisons between arms assuming an effect size of approximately 0.4.

12.4.2. Interim Analysis/Sample Size Re-estimation

The population will be divided into 2 cohorts: the first 50% randomized, and those after the first 50% has been randomized. Once all patients in the first 50% have exited the Double-Blind Phase of the trial (either completed or discontinued), a sample size reevaluation will be performed. This will be based on the time to loss of efficacy analysis. The conditional power will be calculated based on the data observed in the first cohort and assuming that the difference in arms in the second cohort will be identical to the observed difference in the first cohort. The sample size may be increased by up to 50% of the originally planned sample size (200 additional patients) with the goal of maintaining 90% power.

This analysis will be performed by an unblinded independent interim data monitoring committee; the only information they will convey to the blinded trial staff is a recommended increase in sample size. The recommendation will be the smallest increase in blocks of 10 patients that will raise the conditional power over 90%, if the interim assessment should reveal that the power is below 90%. If the conditional power at the interim is under 30% or over 90%, the recommendation will be to keep the current sample size.

For the primary and key secondary efficacy outcomes, the results from before and after the interim analysis will be combined using the Cui, Hung, Wang methodology (Cui et al., 1999). Full details of the interim analysis and adjustments to the final trial estimates will be given in the SAP.

13. TRIAL ADMINISTRATION AND INVESTIGATOR RESPONSIBILITIES

Additional details may be outlined in the Clinical Trial Agreement (CTA) between the sponsor or designee and the research site.

13.1. Regulatory and Ethical Considerations

13.1.1. Ethical Conduct of the Trial

The investigator will conduct the trial in accordance with GCP standards and all applicable regulations, including, where applicable, the Declaration of Helsinki. The trial will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the sponsor's designated representatives and/or regulatory authority's representatives at any time.

13.1.2. Ethics Approval

A central IRB will be selected by the trial sponsor or designee. The research site is responsible for entering into a reliance agreement with the chosen IRB that contains any remaining roles and responsibilities of the research site's IRB, if one exists. The research site's IRB must meet all relevant regulatory requirements. The trial protocol and ICF will be reviewed by the IRB prior to enrolling patients into the trial; written approval from the committee must be received by the sponsor or designee before medication will be released to the investigator. The investigator is responsible for submitting all protocol or ICF changes and SAE reports to the IRB according to local procedures. At a minimum, all SAEs requiring an investigational new medication safety report must be immediately reported.

In accordance with applicable local regulatory requirements, the investigator may be obligated to provide periodic safety updates on the conduct of the trial at his or her research site and notification of trial closure to the IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor or designee. The sponsor or designee will be provided with copies of all notifications sent to the IRB.

All relevant correspondence from the IRB will be forwarded by the respective research site to the sponsor or designee in a timely fashion.

13.1.3. Patient Informed Consent

The investigator (or authorized designee) will ensure that each patient (or the patient's legal representative) is given full and adequate oral and written information about the nature, purpose, potential and possible risks and benefits of the trial. Each prospective patient will receive an IRB-approved ICF that summarizes the pertinent trial information and will be given ample time to read the form and ask questions about the trial. All information is to be provided in a language understandable to the patient and must not include any language that waives the patient's legal rights. Prospective patients must also be informed of their right to withdraw consent without prejudice at any time during the trial. If the patient chooses to participate, he/she must sign the ICF before any trial-related procedures are performed.

Significant changes to the protocol or product safety information may require a revision of the ICF, which must be reviewed and signed by all applicable trial patients.

The time when that informed consent is obtained must be documented. The investigator must maintain the original signed and dated ICF in the patient's source documents. A copy of the signed ICF must be given to the trial patient.

13.2. Privacy and Confidentiality

The investigator is responsible for complying with applicable privacy regulations, per his or her jurisdiction. Only information identified in this protocol will be collected. The information collected will only be used for the purposes identified in this protocol.

To ensure anonymity and to limit disclosure, patients will be assigned a unique identifier at their first assessment. This identifier will be cross-referenced in the patient's chart. The identifier will not contain any potentially identifiable information. An identifier log will be maintained, linking each patient's name to the corresponding identifier. This log will be stored at the research site in a secure location.

The knowledge gained through this trial is the property of the sponsor. The sponsor, representatives, and affiliated companies of the sponsor, the IRB, and regulatory agencies (such as the FDA) may inspect medical records related to the trial to check the validity and accuracy of the data gathered in this trial. Patient medical records (with patient's initials and/or date of birth) may be copied. Confidentiality of patient records will be maintained except where release of information is required by law.

The results of this trial will be reported in such a manner that patients will not be identifiable in any way. Published reports or presentations will refer to grouped data or coded individual data and not to any identifiable individuals. Trial reports sent to the sponsor (or designee) or drug regulatory agencies will not include patient names.

By signing the ICF, the patient consents to the collection, access, use, and disclosure of his or her information as described in the ICF document. If a patient withdraws consent, some of the patient's information may still be collected, used, and disclosed by those involved in this trial, per applicable laws.

By signing this protocol, the investigator affirms that he or she will maintain in confidence information furnished to him or her by the sponsor or designee and will divulge such information to his or her respective IRB under an appropriate understanding of confidentiality with such board. All data will be considered the sole property of the sponsor. Please refer to the CTA for details.

13.3. Trial and Site Closure

Upon completion of the trial, all trial data will be provided to the sponsor or designee following review of research site trial records for completeness, and data clarifications and resolutions. Accounting, reconciliation, and final disposition of used and unused trial medications, treatment codes, and emergency code break envelopes will be performed, as applicable.

In addition, the sponsor or designee reserves the right to temporarily suspend or prematurely discontinue this trial at any time and for any reason. If such action is taken, the sponsor or designee will discuss this with the investigator at that time (including the reasons for taking such action). The sponsor or designee will promptly inform any other investigators and/or institutions conducting the trial if the trial is suspended or terminated for safety reasons, and will inform the regulatory authorities of the suspension or termination of the trial and the reason(s) for the action. If required by applicable regulations, the investigator will inform the IRB promptly and provide the trial patients with the reason for the suspension or termination. If the trial is prematurely discontinued, all trial data will be returned to the sponsor or designee.

13.4. Regulatory Documents and Records Retention

The investigator is responsible for creating and/or maintaining all trial documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 Section 8, as well as any other documentation defined in the protocol or CTA. The investigator must provide key documents to the sponsor or designee prior to the start of the trial. A complete list of required regulatory documents will be supplied by the sponsor or its representative.

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this trial for whichever of the following is the longest period of time:

- A period of 2 years following the final date of release of the PMR by FDA or other regulatory agency of the ER trial medication for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the ER trial medication that was the purpose of the investigation.

The sponsor or designee will notify investigators once one of the above 2 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained for a period of 2 years following notification by the sponsor or designee that the entire clinical investigation (not merely the investigator's portion) is completed, terminated, or discontinued or 2 years following withdrawal of the Investigational New Drug application/Clinical Trial Authorization or request for marketing approval (New Drug Application/Marketing Authorization Application).

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The sponsor or designee must be notified in writing of the name and address of the new custodian. Trial records should not be destroyed without consultation with the sponsor or designee.

13.5. Delegation of Responsibilities and Adequate Resources

The investigator should have adequate time to conduct the trial properly and should have an adequate number of qualified staff to assist with the conduct of the trial.

The term "investigator" used throughout this protocol refers to the principal investigator and/or qualified sub-investigators (i.e., research site investigators). However, the investigator/sub-investigators may delegate responsibilities to other research site personnel. The investigator shall delegate tasks only to individuals qualified by education, training, and experience to perform the delegated tasks. The investigator shall have direct oversight of all delegated activities and shall document delegation of responsibilities. The investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned trial responsibilities. A delegation log identifying all delegated duties and the individual to whom they have been delegated will be maintained at the research site.

13.6. Protocol Amendments

Approval of a protocol amendment by the investigator's IRB must be obtained before implementation of the protocol amendment, unless a change is necessary to eliminate an apparent immediate hazard to the patient or when the change involves logistical or administrative aspects of the trial. The protocol amendment must be approved by the sponsor's designated representative and signed and dated by the investigator.

13.7. Financial Disclosure

Clinical investigators are required to provide financial disclosure information for the submission of certification or disclosure statements required under 21 CFR § 54. As defined in 21 CFR § 54.2, a clinical investigator is a listed or identified investigator or sub-investigator who is directly involved in the treatment or evaluation of the people in the research population. The term also includes the spouse and each dependent child of the investigator. In addition, investigators must promptly update financial disclosure information if any relevant changes occur during the course of the investigation and for 1 year following completion of the trial.

14. INVESTIGATOR PROTOCOL AGREEMENT PAGE

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

Version: 0.8

Date: 01-Mar-2022

I agree to conduct the trial in accordance with the protocol and with all applicable government regulations and International Council on Harmonisation/Good Clinical Practice guidances.

Investigator's Name
(please print or type) _____

_____ _____

Investigator's Signature Date

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16. APPENDICES

16. APPENDICES

Note that copies of scales and questionnaires are provided for informational purposes only. Licensed versions of the assessments for use in the study will be provided in the Study Manual.

The format and appearance of the licensed assessments may differ from those presented herein, and may be based on updated versions not available at the time of protocol publication.

TABLE OF CONTENTS

16.1. Guidelines for Opioid Tapering after Treatment Completion

In the 10-week Double Blind Phase, each patient in the placebo group will be tapered to 0 mg in a double-blinded manner over the course of 1 to 8 weeks, depending on his or her ER opioid dose at randomization. Patients who discontinue during the Double-Blind Phase will also undergo double-blinded taper to 0 mg following the schedules outlined below, during the Tapering and Follow-up Phase. Patients who discontinue during Open-Label Titration and Treatment Phases may be tapered in an open-label manner.

Although many tapering guidelines recommend slower tapering schedules in clinical practice, a review of clinical trials with EERW design found that patient withdrawal symptoms are minimal in a double-blinded setting, even with shorter tapering durations (i.e., most commonly 2 weeks). Based on a review of EERW studies of ER opioids in the literature that used tapering periods ranging from 3 to 20 days, differences in incidence of opioid withdrawal in the placebo groups compared to active ER opioid groups from -3.4% to +5.3% (defined using COWS or AEs). Therefore, a tapering period of up to 8 weeks should be sufficient to mitigate risks of opioid withdrawal, while allowing sufficient time for the post-opioid evaluation period. The 1-week taper will only be used for patients receiving the lowest dosage strength of morphine sulfate ER (15 mg BID). These patients will receive a week of asymmetric dosing (i.e., 15 mg once at bedtime) prior to discontinuing.

Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. In addition, patients should be monitored for any changes in mood, emergence of suicidal thoughts, or use of other substances.

ER Morphine Tapering Schedules

Stable Total Daily Dose at Time of Discontinuation (BID Dose)	Week of Double-Blind Phase/Tapering									
	1	2	3	4	5	6	7	8	9*	10*
	Total Daily Dose (BID Dose) in Milligrams (mg)									
240 (120) mg	200 mg (100 mg)	180 mg (90 mg)	120 mg (60 mg)	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0
230 (115) mg	200 mg (100 mg)	180 mg (90 mg)	120 mg (60 mg)	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0
200 (100) mg	150 mg (75 mg)	120 mg (60 mg)	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0
180 (90) mg	120 mg (60 mg)	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0	0
150 (75) mg	120 mg (60 mg)	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0	0
120 (60) mg	90 mg (45 mg)	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0	0	0
90 (45) mg	60 mg (30 mg)	45 mg (15 mg QAM, 30 mg QHS)	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0	0	0	0
60 (30) mg	30 mg (15 mg)	15 mg (15 mg QHS)	0	0	0	0	0	0	0	0
30 (15) mg	15 mg (15 mg QHS)	0	0	0	0	0	0	0	0	0

Abbreviations: BID = twice daily; QAM = once daily in the morning; QHS = once daily at bedtime.
* For patients in the placebo group of the Double-Blind Phase only. Patients in the Tapering and Follow-up Phase will receive 1 to 8 weeks of tapering followed by a final follow-up visit within 5 days of the last dose.
Note: Tapering schedule assumes morphine ER dosage strengths of 15, 30, 60, and 100 mg. (Actual schedule may be updated pending confirmation of clinical supplies.)

16.2. Opioid Conversion Chart

The following opioid conversion chart will be used to calculate MMEs for determination of eligibility (refer to Inclusion Criterion 4; Protocol Section 8.1):

Opioid	**Conversion Factor**
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone: 1-20 mg/day	4
Methadone: 21-40 mg/day	8
Methadone: 41-60 mg/day	10
Methadone: ≥61-80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol	0.4

Reference; https://www.cdc.gov/opioids/providers/prescribing/guideline.html#anchor_1561563251 (accessed 10-Feb-2022).

16.3. Pain Treatment-Response Questionnaire (PTRQ)

The PTRQ will be administered as a guided questionnaire to assist the investigator in determining whether the patient has appropriately tried and failed at least 2 non-pharmacologic and 2 pharmacologic treatments for pain. The PTRQ will be maintained in the patient's source documents at the study site.

DRAFT

PAIN TREATMENT RESPONSE QUESTIONNAIRE (PTRQ)

[Note: The final appearance and functionality of the questionnaire may be modified following user testing, and may be implemented electronically]

Purpose of the Questionnaire

This questionnaire records any previous therapies used for your main chronic pain condition. Your main chronic pain condition is the condition for which you are seeking to enroll in the study, such as back pain, arthritis, nerve pain, or post-cancer treatment pain.

I'm going to you ask about drugs (medications) you have tried (including pills, patches, gels, creams, or injections), as well as other therapies (such as acupuncture, physiotherapy, etc.). I will give you examples of different types of therapies.

The extended-release opioid drug in this study should only be used for patients for whom other types of therapies did not work or produced undesirable effects.

The purpose of these questions is to identify therapies that you have tried, including those that were stopped because they did not provide any benefit or for other reasons.

A) Pain Relievers

1. Have you ever tried any of the following drugs for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Acetaminophen (e.g., Tylenol)	☐
Acetaminophen combination products (e.g., Exedrin)	☐
Aspirin (e.g., ASA, Bayer)	☐
Celecoxib (e.g., Celebrex)	☐
Choline magnesium trisalicylate (e.g., Trisilate)	☐

Diclofenac (e.g., Voltaren)	☐
Diclofenac/ misoprostol (e.g., Arthrotec)	☐
Diflunisal (e.g., Dolobid)	☐
Etodolac (e.g., Lodine, Lodine XL)	☐
Ibuprofen (e.g., Advil, Motrin)	☐
Ibuprofen combination products (e.g., Advil Dual Action, Advil PM)	☐
Indomethacin (e.g., Indocin, Tivorbex)	☐
Ketorolac (e.g., Toradol)	☐
Magnesium Salicylate (e.g., Doan's)	☐
Meloxicam (e.g., Mobic)	☐
Nabumetone (e.g., Relafen)	☐
Naproxen (e.g., Aleve, Naprosyn)	☐
Oxaprozin (e.g., Daypro)	☐
Piroxicam (e.g., Feldene)	☐
Sulindac (e.g., Clinoril)	☐
Tolmetin (e.g., Tolectin)	☐
None of the above	☐

2. Have you ever tried any of the following prescription antiepileptic drugs, which are sometimes used to treat pain, for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Carbamazepine (e.g., Tegretol, Carbatrol, Equetro)	☐
Divalproex (e.g., Depakote)	☐
Gabapentin (e.g., Neurontin)	☐
Gabapentin enacarbil extended-release (Gralise)	☐
Lacosamide (e.g., Vimpat)	☐
Oxcarbazepine (e.g., Trileptal, Oxtellar XR)	☐
Pregabalin (Lyrica, Lyrica CR)	☐

Valproic acid (e.g., Depakene)	☐
Valproic acid delayed release (Stavzor)	☐
Topiramate (e.g., Topomax, Qudexy XR, Trokendi XR)	☐
Zonisamide (e.g., Zonegran)	☐
None of the above	☐

3. Have you ever tried any of the following prescription antidepressant drugs, which are sometimes used to treat pain, for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Amitriptyline (e.g., Elavil)	☐
Bupropion (e.g., Wellbutrin, Wellbutrin XR, Forfivo XL, Contrave, Aplenzin)	☐
Desipramine (e.g., Norpramin)	☐
Desvenlafaxine (e.g., Khedezla, Pristiq)	☐
Doxepin (e.g., Silenor)	☐
Duloxetine (e.g., Cymbalta)	☐
Imipramine (e.g., Tofranil)	☐
Levomilnacipran (e.g., Fetzima)	☐
Milnacipran (e.g., Savella)	☐
Nortriptyline (e.g., Pamelor)	☐
Venlafaxine (e.g., Effexor, Effexor XR)	☐
None of the above	☐

4. Have you ever tried any of the following prescription steroid drugs for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Dexamethasone (e.g., Hemady)	☐
Hydrocortisone (e.g., Cortef)	☐

Methylprednisolone (e.g., Medrol)	☐
Prednisone (e.g., Rayos)	☐
Prednisolone (e.g., Orapred ODT)	☐
None of the above	☐

5. Have you ever tried any of the following prescription muscle relaxants for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Baclofen (e.g., Lioresol, Gablofen)	☐
Carisoprodol (e.g., Soma)	☐
Chlorzoxazone (e.g., Parafon Forte)	☐
Cyclobenzaprine (e.g., Amrix)	☐
Dantrolene (e.g., Dantrium)	☐
Metaxolone (e.g, Skelaxin)	☐
Methocarbamol (e.g., Robaxin)	☐
Orphenadrine (e.g., Orphengesic Forte)	☐
Tizanidine (e.g., Zanaflex)	☐
None of the above	☐

6. Have you ever tried any of the following gels, creams, or pain patches for your <u>main</u> chronic pain condition?

Name of Medication	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Capsaicin 0.25% (e.g., Zostrix, Bengay Heat)	☐
Capsaicin patch 8% (Qutenza)	☐
Diclofenac 1% gel (Voltaren Arthritis Pain)	☐
Diclofenac 1.5 or 2 % solution (Pennsaid)	☐
Diclofenac epolamine 1.3% patch (Flector)	☐

Lidocaine gel (e.g., Xylocaine, Aspercreme Lidocaine)	☐
Lidocaine/Prilocaine (e.g., Emla patch)	☐
Lidocaine 5% patch (e.g., Lidoderm)	☐
Menthol (e.g., Bengay Ice, Tiger Balm)	☐
Methyl salicylate (e.g., Bengay, Salonpas, Bengay arthritis)	☐
Trolamine salicylate (e.g., Aspercreme)	☐
None of the above	☐

7. Have you ever received any of the following injections or implanted pumps for your main chronic pain condition?

Name of Medication	**Ever used for main chronic pain condition** **Check (√) all that apply**
Steroid/cortisone injection (e.g., Depo-Medrol, Solu-Medrol, Kenalog, Celestone)	☐
Epidural (into the back) or facet (into the joints) injection of pain relievers	☐
Hylan injection (e.g., Synvisc, Synvisc-One) injection into knee or hip to cushion and lubricate the joint	☐
Hyaluronic acid injection into knee or hip (e.g., Euflexxa, Gel-One, Hyalgan, Monovisc, Orthovisc, Supartz)	☐
Botox injection	☐
Trigger point injections (injections into a muscle to relax it)	☐
Implanted medication pump, please state which medication was used in the pump	☐ _____
Other type of injection, please state which one	☐
None of the above	☐

8a. Have you ever tried any other drugs or medications (including pills, patches, gels, creams, or injections) for your main chronic pain condition that were not listed previously?

☐ YES (Patient proceeds to Question 8b)

☐ NO (Patient proceeds to the next section)

8b. Please list any other drugs or medications used for your <u>main</u> chronic pain condition.

_____

_____

_____

[For each reported medication ever used for the index chronic pain condition, the following questions will be administered]

a) Are you still taking [medication name] for your <u>main</u> chronic pain condition?

☐ YES (Patient proceeds to Question b and skips Questions c and d)

☐ NO (Patient proceeds to Question c and d)

b) How long have you been taking [medication name] for your <u>main</u> chronic pain condition?

☐ Less than 1 week

☐ Less than 1 month

☐ 1 month to 6 months

☐ 6 months to 1 year

☐ 1 to 2 years

☐ 3 to 5 years

☐ More than 5 years

c) How long did you take [medication name] for your <u>main</u> chronic pain condition?

☐ Less than 1 week

☐ Less than 1 month

☐ Less than 1 year

☐ 1 to 2 years

☐ 3 to 5 years

☐ More than 5 years

d) Why did you stop taking [medication name]? Check (√) all that apply

☐ Did not work

☐ Side effects

☐ No longer available

☐ Could not afford

☐ Other reason _____

B) Other Therapies

9. Have you ever tried any of the following physical/external therapies to treat your <u>main</u> chronic pain condition?

Name of Therapy	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Acupressure	☐
Acupuncture	☐
Exercise	☐
Hot-cold treatments	☐
Hydrotherapy	☐
Massage/therapeutic touching	☐
Resting/Movement restriction	☐
Occupational therapy	☐
Physiotherapy (PT)	☐
Positioning	☐
Transcutaneous electrical nerve stimulation (TENS)	☐
None of the above	☐

10. Have you ever tried any of the following behavioral therapies to treat your <u>main</u> chronic pain condition?

Name of Therapy	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Behavioral therapy	☐
Biofeedback	☐
Hypnosis	☐
Meditation/mindfulness	☐
Relaxation – breathing techniques	☐
Yoga	☐
None of the above	☐

11. Have you ever tried medical devices or surgical procedures to treat your <u>main</u> chronic pain condition?

Name of Therapy	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Radiofrequency ablation (RFA) of the back, neck, or hip (electrical current to heat up and remove an area of pain)	☐
Spinal cord stimulator trial or implant (electrical implant to block nerve impulses)	☐
Peripheral nerve stimulator trial or implant (electrical implant to block nerve impulses)	☐
Other type of device	☐
Other surgical procedure	☐
None of the above	☐

12. Have you ever tried other therapies to treat your <u>main</u> chronic pain condition?

Name of Therapy	**Ever used for <u>main</u> chronic pain condition Check (√) all that apply**
Aromatherapy	☐
Chiropractic	☐
Herbal treatments	☐

Musical therapy	☐
Reflexology	☐
None of the above	☐

13a. Have you ever tried any other non-drug therapies to treat your <u>main</u> chronic pain condition that were not listed previously?

☐ YES (Patient proceeds to Question 13b)

☐ NO (Patient proceeds to next section)

13b. Please list any other therapies used for your <u>main</u> chronic pain condition.

_____

_____

_____

[For each reported therapy ever used for the index chronic pain condition, the following questions will be administered]

a) Are you still using [therapy name] for your <u>main</u> chronic pain condition?

☐ YES (Patient proceeds to Question b and skips Questions c and d)

☐ NO (Patient proceeds to Question c and d)

b) How long have you been using [therapy name] for your <u>main</u> chronic pain condition?

☐ Less than 1 week

☐ Less than 1 month

☐ 1 month to 6 months

☐ 6 months to 1 year

☐ 1 to 2 years

☐ 3 to 5 years

☐ More than 5 years

c) How long did you use [therapy name] for your <u>main</u> chronic pain condition?

☐ Less than 1 week

☐ Less than 1 month

☐ 1 month to 6 months

☐ 6 months to 1 year

☐ 1 to 2 years

☐ 3 to 5 years

☐ More than 5 years

d) Why did you stop using [therapy name]? Check (√) all that apply

☐ Did not work

☐ Side effects

☐ No longer available

☐ Could not afford

☐ Other reason _____

----------End of Questionnaire----------

Investigator Guidelines for Trials of Prior Therapy

For all indications/types of chronic pain, patients must have not responded to or have had contraindications to at least 2 non-pharmacologic therapies, such as ice/heat, psych, relax, physical therapy, etc., as outlined in the PTRQ.

The following table indication outlines prior medications that are commonly prescribed for the indications included in this study. Refer to example indication-specific guidances referenced below for more detailed information.

Indication/Type of Chronic Pain	Commonly Prescribed Medications
CLBP	Acetaminophen, NSAIDs, muscle relaxants, duloxetine
OA of the knee/hip	Acetaminophen, NSAIDs, glucocorticoid injections
DPN or PPN	Pregabalin, gabapentin, duloxetine, sodium SNRIs, TCAs
Post-cancer treatment pain	NSAIDs, other drugs based on origin of pain (e.g., duloxetine, gabapentin/pregabalin, or TCAs for neuropathic origin, acetaminophen)

Abbreviations: CLBP = chronic low back pain; DPN = diabetic peripheral neuropathy; NSAID = non-steroidal anti-inflammatory; OA = osteoarthritis; PPN = painful peripheral neuropathy; SNRI = serotonin norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant.

References:

Bril V, England J, Franklin GM, et al. Evidence-based guideline: Treatment of painful diabetic neuropathy. Neurology. 2011;76(20):1758–1765.

Kolasinski SL, Neogi T, Hochberg MC, et al. Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care & Research. 2020;72(2):149–162.

Loprinzi CL, Lacchetti C, Bleeker J et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO guideline update. J Clin Oncol. 2020 Oct 1;38(28):3325–3348.

Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. Annals of Internal Medicine. 2017;166(7):514-530.

[The investigator will assess eligibility criteria following a review of data from the patient's PTRQ responses, as well as other independent documentation (e.g., medical records and/or state monitoring data or claims data, if available). Eligibility may be considered on a case-by-case basis for patients with incomplete documentation; however, approval must be obtained from the medical monitor]

[The following will be entered into the CRF:]

Failed Non-Opioid Pharmacologic Treatments

Patient reported <u>at least 2</u> failed non-opioid pharmacologic treatments.	☐ YES ☐ NO

Failed Non-Pharmacologic Treatments

Patient reported <u>at least 2</u> failed non-pharmacologic treatments.	☐ YES ☐ NO

16.4. Urine Drug Testing Procedures and Management of Unexpected Findings

General Procedure

Urine Drug Testing (UDT) will be performed according to the Schedule of Procedures of the protocol. Testing will be performed for the presence of the following drugs:

- Illegal drugs, as outlined in the table below (Listing of UDT Analytes).
- Non-prescribed controlled substances (opioid and non-opioid)
- Alcohol or cannabis

To avoid unblinding, data for morphine and its metabolites obtained during the Double-Blind Phase will NOT be shared by the laboratory until after completion of the study.

Listing of UDT Analytes

[[To be confirmed pending selection of laboratory vendor.]]

Note that all specimens will be subject to validation tests (e.g., temperature and creatinine/specific gravity). In case of out-of-range urinalysis results obtained in the context of validation testing (e.g., creatinine and/or specific gravity), investigators may repeat tests at their discretion to rule out medical causes.

Reportable Compound Name	
Note that the following list outlines only the name of the parent drug/substance—metabolites only or parent + metabolite(s) may be assessed depending on the substance in question (e.g., cocaine metabolites), pending confirmation from the laboratory vendor	
Alcohol	Lorazepam
Alprazolam	Lysergic acid diethylamide
Amphetamine	MDMA
Buprenorphine	Methadone
Butalbital	Methamphetamine
Cannabinoids	Morphine[b]
Clonazepam	Oxazepam
Cocaine	Oxycodone
Codeine	Oxymorphone
Diazepam	Phenobarbital
Ephedrine / Pseudoephedrine	Primidone
Eszopicolone	Secobarbital
Fentanyl	Tapentadol

Heroin[a]	Tramadol
Hydrocodone	Temazepam
Hydromorphone	Zolpidem

a. Metabolite specific to heroin

b. Data for morphine/metabolites obtained during the Double-Blind Phase will not be shared by the laboratory until completion of the study.

Management of Unexpected Findings

Unexpected findings (i.e., detection of non-study drugs) will be managed according to the following table:

	Unexpected Result/Report	Possible Explanation	Recommended Action
1	UDT *positive* for non-study opioid medication	If not prescribed, patient acquired opioids from other sources (doctor shopping, street)	• Report indicates detection of non-study opioid. • Investigator to determine whether result is appropriate based on patient's prescribed rescue regimen and phase of study. • If result is not explained by study medication or known concomitant medications, investigator schedules the patient for an unscheduled visit. • Investigator contacts the medical monitor and performs the "Supplemental Evaluation and Intervention" (see below). • Patient may receive counselling and continue in the study or be discontinued, according to the guidelines provided in the Supplemental Evaluation. • Manage patient according to "Patient Management" (see below). • Patients who receive counseling and remain in the study must be terminated from study upon second event. • For safety reasons, patients who test positive for fentanyl for any reason will be terminated.
2	UDT *positive* for *non-opioid* controlled medication	If not prescribed, patient acquired non-opioids from other sources (doctor shopping, street)	• Report indicates detection of non-opioid controlled substance. Identity of substance is provided. • Investigator to determine whether result is appropriate based on patient's prescribed concomitant medications. • If result is not explained by known concomitant medications, investigator schedules the patient for an unscheduled visit. • Investigator contacts the medical monitor and performs the "Supplemental Evaluation and Intervention" (see below). • Patient may receive counselling and continue in the study or be discontinued, according to the guidelines provided in the Supplemental Evaluation. • Manage patient according to "Patient Management" (see below). • Patients who receive counseling and remain in the study must be terminated from study upon second event.
3	UDT *positive* for illicit drugs (e.g., cocaine, heroin) (not cannabis; see below)	Patient is abusing the detected substance	• Report indicates detection of an illicit substance. • Since use of an illicit substance creates a patient safety issue, patient is terminated from study. • Manage patient according to "Patient Management" (see below).
4	UDT *positive* for alcohol or cannabis	Patient is abusing alcohol	• Report indicates detection of alcohol or cannabis. • Investigator schedules the patient for an unscheduled visit. • Investigator contacts the medical monitor and performs the "Alcohol and Cannabis Evaluation and Intervention" (see below).

	Unexpected Result/Report	Possible Explanation	Recommended Action
			• Patient may receive counselling and continue in the study or be discontinued, according to the guidelines provided in the Alcohol and Cannabis Evaluation and Intervention. • Manage patient according to "Patient Management" (see below). • Patients who receive counseling and remain in the study must be terminated from study upon second event.
5	Failed specimen validity test (e.g., temperature, creatinine, specific gravity)	Patient added water to sample	• Repeat testing of urinalysis results may be performed at the investigator's discretion to rule out medical causes. • Since intentionally tampering with urine samples is a serious protocol violation, patient is terminated from the study. • Manage patient according to "Patient Management" (see below).

EVALUATION AND INTERVENTIONS

Supplemental Evaluation and Intervention

- Check prescription monitoring or claims data, if available, for recent non-study pain medication prescriptions.
- Bring patient in for unscheduled visit to discuss test results in non-judgmental manner.
- Take a detailed history of the patient's medication use for the preceding 7 days (e.g., could learn that patient ran out of study medication several days prior to test or that a legitimate supplemental prescription had been provided, such as for a dental or other medical procedure).
- Ask patient if he or she took any non-prescribed medications, and if so, which ones, doses, duration, etc. Determine the reason for use of the non-prescribed or non-study medication.
- Monitor study medication compliance with pill counts.
- Repeat UDT may be performed if the patient denies use of the medication in question.
- Review results of the interview or any additional supplemental information (i.e., prescription monitoring data, repeat UDT results) with the medical monitor to determine if the patient should be discontinued (e.g., due to safety reasons, protocol violation, or lack of efficacy) or receive counseling and continue in the study.

Alcohol and Cannabis Evaluation and Intervention

- Bring patient in for unscheduled visit to discuss test results in non-judgmental manner.
- Take a detailed alcohol or cannabis exposure history for the preceding 7 days.
- Repeat testing may be performed if the patient denies use of alcohol or cannabis.
- Review results of the interview with the medical monitor to determine if the patient should be discontinued (e.g., due to patient safety reasons) or receive counseling and continue in the study.

PATIENT MANAGEMENT

For patients who are discontinued due to positive UDT results:

- Complete the Early Termination CRF page.

For patients continuing in the study:

- Counsel patient that repeated similar results (i.e., use of restricted medications or substances exceeding allowed limits) may lead to discontinuation from study.

16.5. Early Discontinuation Assessment

The Early Discontinuation Assessment will thoroughly evaluate the patient-reported reasons for discontinuation should the patient withdraw consent (i.e., subject decision) and aid the investigator in the completion of the Early Termination CRF. The Early Discontinuation Assessment will be maintained in the patient's source documents.

Reason for Discontinuation		**Please check (√) the <u>primary</u> reason that the patient is leaving the study**
1)	Too much pain	□
2)	Side effects from medications	□
3)	Feeling sick from medication withdrawal	□
4)	Anxiety or nervousness	□
5)	Trouble sleeping	□
6)	Transportation problems	□
7)	Study procedures are too uncomfortable	□
8)	Study procedures require too much of my time	□
9)	Cannot take time from work or other obligations	□
10)	Do not like not knowing what medication I am on	□
11)	Need treatment that is not allowed in this study *If yes, please state which one:*_____	□
12)	Moving too far from the research center	□
13)	Developed a new medical condition *If yes, please state condition:*_____	□
14)	Do not want to be in an experiment any longer	□
15)	Personal circumstances have changed	□
16)	Do not like the research center	□

Other reason(s) not listed above:

_____

16.6. Instructions for Naloxone Use

A copy of the Patient Information and Instructions for Use portions of the intranasal naloxone product label will be provided in the final version of the protocol.

16.7. Fibromyalgianess Scale (FS)

New Clinical Fibromyalgia Diagnostic Criteria – Part 1.

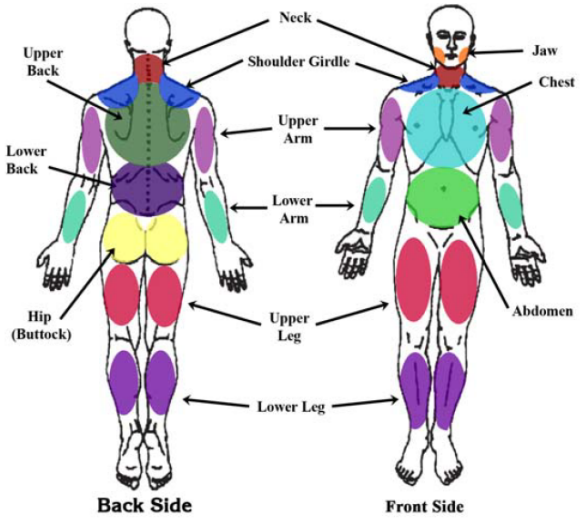
To answer the following questions, patients should take into consideration

- how you felt the **past week**,
- while taking your current therapies and treatments, and
- exclude your pain or symptoms from other known illnesses such as arthritis, Lupus, Sjogren's, etc.

Check each area you have felt pain in over the past week.

- ☐ Shoulder girdle, left
- ☐ Shoulder girdle, right
- ☐ Upper arm, left
- ☐ Upper arm, right
- ☐ Lower arm, left
- ☐ Lower arm, right
- ☐ Hip (buttock) left
- ☐ Hip (buttock) right
- ☐ Upper leg left
- ☐ Upper leg right
- ☐ Lower leg left
- ☐ Lower leg right
- ☐ Jaw left
- ☐ Jaw right
- ☐ Chest
- ☐ Abdomen
- ☐ Neck
- ☐ Upper back
- ☐ Lower back
- ☐ None of these areas

Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.



Count up the number of areas checked and enter your Widespread Pain Index or WPI score score here _____.

Symptom Severity Score (SS score) - Part 2a.

Indicate your level of symptom severity over the past week using the following scale.

Fatigue

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Waking unrefreshed

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Cognitive symptoms

- ☐ 0 = No problem
- ☐ 1 = Slight or mild problems; generally mild or intermittent
- ☐ 2 = Moderate; considerable problems; often present and/or at a moderate level
- ☐ 3 = Severe: pervasive, continuous, life disturbing problems

Tally your score for Part 2a (not the number of checkmarks) and enter it here _____.

Symptom Severity Score (SS score)- Part 2b

Check each of the following OTHER SYMPTOMS that you have experienced over the past week?

- ☐ Muscle pain
- ☐ Irritable bowel syndrome
- ☐ Fatigue/tiredness
- ☐ Thinking or remembering problem
- ☐ Muscle Weakness
- ☐ Headache
- ☐ Pain/cramps in abdomen
- ☐ Numbness/tingling
- ☐ Dizziness
- ☐ Insomnia
- ☐ Depression
- ☐ Constipation
- ☐ Pain in upper abdomen
- ☐ Nausea
- ☐ Nervousness
- ☐ Chest pain
- ☐ Blurred vision
- ☐ Fever
- ☐ Diarrhea
- ☐ Dry mouth
- ☐ Itching
- ☐ Wheezing
- ☐ Raynauld's
- ☐ Hives/welts
- ☐ Ringing in ears
- ☐ Vomiting
- ☐ Heartburn
- ☐ Oral ulcers
- ☐ Loss/change in taste
- ☐ Seizures
- ☐ Dry eyes
- ☐ Shortness of breath
- ☐ Loss of appetite
- ☐ Rash
- ☐ Sun sensitivity
- ☐ Hearing difficulties
- ☐ Easy bruising
- ☐ Hair loss
- ☐ Frequent urination
- ☐ Painful urination
- ☐ Bladder spasms

Count up the number of symptoms checked above.
*If you tallied:

0 symptoms	Give yourself a score of 0
1 to 10	Give yourself a score of 1
11 to 24	Give yourself a score of 2
25 or more	Give yourself a score of 3

Enter your score for Part 2b here _____.

Now add Part 2a AND 2b scores, and enter ____.
This is your Symptom Severity Score (SS score), which can range from 0 to 12.

What Your Scores Mean

A patient meets the diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1a. The WPI score (Part 1) is greater than or equal to 7 **AND** the SS score (Part 2a & b) is greater than or equal to 5

OR

1b. The WPI score (Part 1) is from 3 to 6 **AND** the SS score (Part 2a & b) is greater than or equal to 9.

2. Symptoms have been present at a similar level for at least 3 months.

3. You do not have a disorder that would otherwise explain the pain.

For example:
If your WPI (Part 1) was 9 and your SS score (Parts 2a & b) was 6, then you **would meet** the new FM diagnostic criteria.

If your WPI (Part 1) was 5 and your SS score (Parts 2a & b) was 7, then you **would NOT** meet the new FM diagnostic criteria.

*The new FM diagnostic criteria did not specify the number of "Other Symptoms" required to score the point rankings from 0 to 3. Therefore, we estimated the number of symptoms needed to meet the authors' descriptive categories of:

0 = No symptoms
1 = Few symptoms
2 = A moderate number
3 = A great deal of symptoms

* Wolfe F, *et al.* Arthritis Care Res 62(5):600-610, 2010.

For information about Fibromyalgia Network, call our office Monday through Friday, 9:00 a.m. to 5:00 p.m. (PST) at (800) 853-2929 or visit us online at www.fmnetnews.com.

This survey is not meant to substitute for a diagnosis by a medical professional. Patients should not diagnose themselves. Patients should always consult their medical professional for advice and treatment. This survey is intended to give you insight into research on the diagnostic criteria and measurement of symptom severity for fibromyalgia.

Reference: Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res. 2010;62(5):600–10.

16.8. Pain Catastrophizing Scale (PCS)

PCS

Client No.: _____ Age: _____ Sex: M(__) F(__) Date: _____

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

1. ☐ I worry all the time about whether the pain will end.
2. ☐ I feel I can't go on.
3. ☐ It's terrible and I think it's never going to get any better.
4. ☐ It's awful and I feel that it overwhelms me.
5. ☐ I feel I can't stand it anymore.
6. ☐ I become afraid that the pain will get worse.
7. ☐ I keep thinking of other painful events.
8. ☐ I anxiously want the pain to go away.
9. ☐ I can't seem to keep it out of my mind.
10. ☐ I keep thinking about how much it hurts.
11. ☐ I keep thinking about how badly I want the pain to stop.
12. ☐ There's nothing I can do to reduce the intensity of the pain.
13. ☐ I wonder whether something serious may happen.

… Total

Reference: Sullivan M, Bishop S, Pivik J. The Pain Catastrophizing Scale: development and validation. Psychological Assessment. 1995;7:524–532.

16.9. Pain Profile Questionnaire (PPQ)

Pain Profile Questionnaire

Please think about your pain in the <u>past week</u> when you answer the following questions.

1. Please indicate how severe your pain was <u>at its worst</u>.				
□ None	□ Mild	□ Moderate	□ Severe	□ Excruciating
2. Please indicate how severe your pain was <u>at its least</u>.				
□ None	□ Mild	□ Moderate	□ Severe	□ Excruciating
3. Please indicate how severe your pain was <u>on average.</u>				
□ None	□ Mild	□ Moderate	□ Severe	□ Excruciating
4. How often did pain interfere with your sleep?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
5. How often did you have pain when you first woke up in the morning that was bad enough to take pain medication (whether you took it or not)?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
6. How often did your pain medication last as long as you would like?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
7. How often did you have side effects <u>within the first 1-2 hours</u> after taking your pain medication?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
8. How often did you feel intoxicated (drunk, high) within the first 1-2 hours after taking a dose of pain medication?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
9. How often did you still have side effects more than 4 hours after taking a dose of pain medication?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
10. Sometimes when people stop taking opioid medications they experience symptoms like shakiness, nausea, vomiting, sweating, stomach cramps, diarrhea, nervousness, irritability, etc. How often did you feel these types of symptoms between doses of pain medication?				
□ Never	□ Rarely	□ Sometimes	□ Often	□ Always
11. Did taking a pill for your pain give you a sense of control over your pain?				

☐ Never	☐ Rarely	☐ Sometimes	☐ Often	☐ Always
12. How satisfied were you with your pain medication?				
☐ Not at all	☐ A little bit	☐ Moderately	☐ Very much	☐ Completely
13. What percent of the 24-hour day did you typically need pain medicine?				
☐ 0-20%	☐ 20-40%	☐ 40-60%	☐ 60-80%	☐ 80-100%
14. How many times in a 24-hour day was your pain bad enough to take a dose of pain medication (whether you took one or not)?				
☐ 0-1	☐ 1-2	☐ 3-4	☐ 5-6	☐ 7 or more
15. How many days last week did you have no pain, or pain mild enough that it would not be worth taking pain medication?				
☐ 0	☐ 1-2	☐ 3-4	☐ 5-6	☐ 7
15. Ideally, how many times a day would you prefer to take pain medication, to have control over your pain at all times?				
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 or more
17. On average, how many times a day did you take your pain medication?				
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 or more

16.10. STOP-Bang

Please answer the following questions to determine if you are at risk for obstructive sleep apnea (OSA):

Yes ○ No ○	**Snoring?** Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
Yes ○ No ○	**Tired?** Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving)?
Yes ○ No ○	**Observed?** Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep?
Yes ○ No ○	**Pressure?** Do you have or are being treated for **High Blood Pressure**?
Yes ○ No ○	**Body Mass Index more than 35 kg/m^2?**
Yes ○ No ○	**Age older than 50 year old?**
Yes ○ No ○	**Neck size large? (Measured around Adams apple)** For male, is your shirt collar 17 inches/43 cm or larger? For female, is your shirt collar 16 inches/41 cm or larger?
Yes ○ No ○	**Gender = Male?**

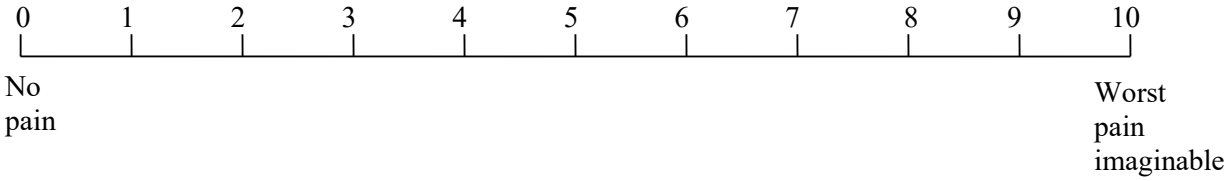
Scoring Criteria:

For general population
Low risk of OSA: Yes to 0 - 2 questions
Intermediate Risk of OSA: Yes to 3 - 4 questions
High Risk of OSA: Yes to 5 - 8 questions
or Yes to 2 or more of 4 STOP questions + male gender
or Yes to 2 or more of 4 STOP questions + BMI > 35kg/m^2
or Yes to 2 or more of 4 STOP questions + neck circumference 17 inches / 43cm in male or 16 inches / 41cm in female

Modified from Chung F et al. Anesthesiology. 2008; 108:812-21, Chung F et al. Br J Anaesth. 2012; 108:768–75, Chung F et al J Clin Sleep Med. Sept 2014.

16.11. Pain Intensity Numerical Rating Scale (NRS)

Pain Intensity on 0-10 NRS



16.12. Brief Pain Inventory – Short Form (BPI-SF)

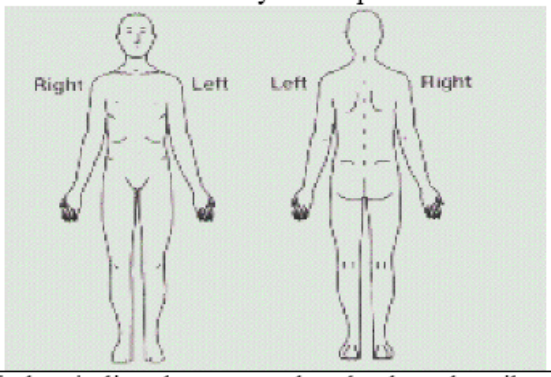
The BPI-SF is shown in its entirety. However, for this study, questions 2 and 7 are not relevant and that information will not be entered into the eCRF.

BRIEF PAIN INVENTORY (SHORT FORM)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

   ☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at it worst in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average

   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

   0 1 2 3 4 5 6 7 8 9 10
   No Pain — Pain as bad as you can imagine

7. What treatments or medications are your receiving for your pain

   _____
   _____
   _____
   _____

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

---

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Reference: Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. Pain. 1983;17:197–210.

16.13. Patient Global Impression of Change (PGIC)

√ (Check) the box you feel most closely describes any change you have experienced in your chronic pain since you entered the study. Choose only ONE response.

□ 1. Very Much Improved

□ 2. Much Improved

□ 3. Minimally Improved

□ 4. No Change

□ 5. Minimally Worse

□ 6. Much Worse

□ 7. Very Much Worse

Reference: Farrara JT, Young JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149–158.

16.14. EuroQOL Group, 5-Dimension, 5-Level Descriptive System (EQ-5D-5L)

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

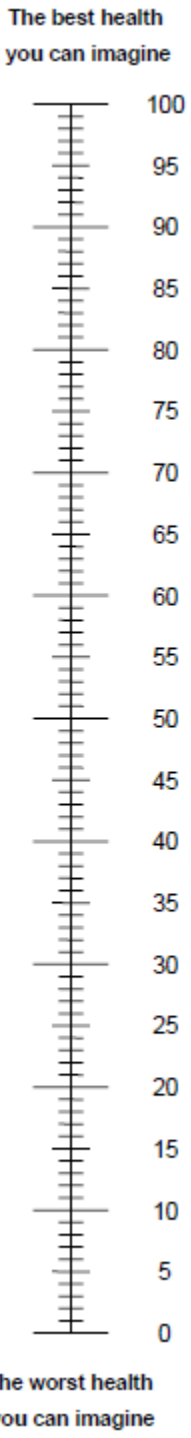
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Reference: The EuroQOL Group. EuroQOL—a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199–208.

16.15. PROMIS® Physical Function – Short Form 8b (PROMIS PF-SF-8b)

PROMIS® Item Bank v2.0 – Physical Function – Short Form 8b

Physical Function – Short Form 8b

Please respond to each question or statement by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFC12	Does your health now limit you in doing two hours of physical labor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Reference: Feng D, Laurel F, Castille D, et al. Reliability, construct validity, and measurement invariance of the PROMIS Physical Function 8b-Adult Short Form v2.0. Qual Life Res. 2020 Dec;29(12):3397–3406.

16.16. Quantitative Sensory Testing (QST) Procedures

Additional instructions regarding QST procedures will be outlined in a QST manual or protocol. The following sections outline general aspects of the QST procedures.

16.16.1. General Considerations

- Standardized language will be used for instructing patients and performing QST.
- Where possible, the same operator should perform longitudinal QST in a given patient.
- QST assessments utilized for training purposes will be conducted at the non-dominant volar forearm.
- QST assessments conducted for calculation of QST parameters will be obtained at the dominant volar forearm.
- Where possible, QST assessments should be performed when trough opioid plasma concentrations are likely, i.e., prior to the morning or evening doses.
- Patients will be trained and tested for satisfactory QST performance to qualify for inclusion into the QST study arm.
- Half-maximum heat pain will be added as an outcome measure, as some patients may tolerate a thermode temperature > 50°C.

16.16.2. QST Parameters

Direct QST Parameters

- Heat pain threshold (HPTHR)
- Heat pain tolerance (HPTOL)
- Half-maximum heat pain (HP50%)
- Sustained heat pain ratings (HPRAT)

Derived QST Parameters

- Heat pain differential (HPDIF), calculated as HPTOL-HPTHR
- Heat pain differential 50% (HPDIF-50%), calculated as HP50%-HPTHR
- Heat pain summation (HPSUM), equivalent to the area under the curve depicting pain ratings over time

16.16.3. Overview of QST Session Procedures

The QST session will consist of a familiarization/training phase, followed by an assessment phase.

A satisfactory QST performance is established when the HPTHR deviates by less than 0.7 degrees Celsius between 2 assessments. If the HPTHR deviates by more than 0.7 degrees Celsius, the HPTHR may be assessed again to determine whether the patient may pass the performance criterion with repeated exposure. A maximum of 4 repeated assessments is allowed.

Pivotal QST assessments will be performed at the volar dominant forearm. The HPTHR will be determined at the distal third of the forearm, the HP50% will be determined at the middle third of the forearm, the HPTOL will be determined at the proximal third of the forearm at the medial site, and the HPRAT will be determined at the proximal third of the forearm at the lateral site.

Order of assessments and time estimates is as follows:

1. Training/familiarization (~ 15 minutes)
2. HPTHR assessed twice with a 5-minute interval between assessments (~ 10 minutes)
3. HPTOL assessed twice with a 5-minute interval between assessments (~ 10 minutes)
4. HP50% assessed once (~ 5 minutes)
5. HPRAT assessed once (~ 5 minutes)

16.16.4. Assessment of QST Parameters

Heat Pain Threshold (HPTHR):

The thermode will be handheld by the operator and be brought into full contact with skin using gentle pressure only. Starting at a thermode temperature of 35°C, the temperature will be increased at a rate of 0.5 °C per second. The patient will push the button of a hand-held device at the onset of pain (perception changes from very hot to painful). This procedure will be repeated twice, and the average temperature eliciting pain will be recorded as the HPTHR. The inter-stimulus interval will be 30 seconds (Chu et al., 2012).

Heat Pain Tolerance (HPTOL):

The thermode will be handheld, as described for the HPTHR. Starting at a thermode temperature of 35°C, the temperature will be increased at a rate of 0.5 °C per second. The patient will push the button of a hand-held device as soon as the elicited pain is no longer tolerable. This procedure will be repeated twice, and the average temperature causing maximum tolerable pain will be recorded as the HPTOL. The inter-stimulus interval will be 30 seconds. In some participants, the maximum thermode temperature of 50 °C may be reached without inflicting intolerable pain. In this instance, HP50% will be determined using 50°C as the HPTOL value.

Half-Maximum Heat Pain (HP50%):

The target temperature causing half-maximum pain will be inferred as follows:

- 5 stimuli of increasing intensity will be applied to determine what thermode temperature causes a pain rating of 5–6 on an 11-point numerical pain rating scale.

The thermode temperature for inflicting HP50% will be determined as follows:

- Stimulus 1 = HPTHR + (0.2*[HPTOL – HPTHR]), stimulus 2 = HPTHR + (0.4*[HPTOL – HPTHR]), stimulus 3 = HPTHR + (0.5*[HPTOL – HPTHR]), stimulus 4 = HPTHR + (0.6*[HPTOL – HPTHR]), and stimulus 5 = HPTHR + (0.7*[HPTOL – HPTHR]).

The stimuli will be delivered by raising the thermode temperature at a rate of 0.5 °C per second to the target temperature, which will be held for 2 seconds. The pain evoked by the stimulus will

then be rated. Once a rating of 5–6/10 has been obtained, no further stimuli will be applied, as the temperature causing half maximum pain has been determined (Weissman-Fogel et al., 2015). If inflicted pain is rated < 5–6/10 after application of all 5 stimuli, additional stimuli will be applied until such rating has been obtained: Stimulus 6 = HPTHR + (0.8*[HPTOL – HPTHR)]), stimulus 7 = HPTHR + (0.9*[HPTOL – HPTHR]), and stimulus 8 = HPTOL.

Sustained Heat Pain Ratings (HPRAT):

The thermode will be handheld as described for the HPTHR. Starting at a thermode temperature of 35°C, the temperature will be increased at a rate of 0.5 °C per second, to a target temperature eliciting mild to moderate pain (3–4/10). This temperature will be known based on the determination of HP50%. If the temperature eliciting mild/moderate pain is > 47 °C, a temperature of 47 °C will be used for safety reasons. The target temperature will be maintained for 60 seconds. Participants will be asked to rate the intensity of pain on an 11-point numerical rating scale at 15-second intervals.

16.16.5. Interim Assessment of QST Algorithm Feasibility and Utility

A pilot or interim assessment will be conducted with 20 subjects or patients. Metrics used will include:

- Time requirements to complete assessments
- Performance metrics used to include/exclude patients
- Reasons as to why patients are not willing to undergo proposed test procedures
- Confirm if HPTOL and/or HP50% can be measured in the majority of patients (>90%)
- Confirm if HPSUM can be determined in the majority of patients (>80%), as indicated by a positive area under the curve (AUC)

Potential modifications of the QST algorithm as a result of the interim analysis include:

- Shortening the test session by eliminating repeated assessments (HPTHR, HPTOL), or by reducing the number of directly determined QST parameters (HPTHR, HPTOL, HPRAT)
- Modification of the algorithm used to determine HPSUM (e.g., modification of half-maximum pain inference)
- Modification of derived QST parameters (e.g., use the difference between the last and first pain ratings rather than the AUC to infer HPSUM)

16.16.6. Metrics for Inferring Opioid-Induced Hyperalgesia

1. Decrease in HPTHR
2. Decrease in HP50%
3. Decrease in HPTOL
4. Decrease in HPDIF
5. Decrease in HPDIF-50%
6. Increase in HPSUM

16.16.7. References

Chu LF, D'Arcy N, Brady C, et al. Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain. Pain. 2012;153(8):1583–92.

Weissman-Fogel I, Dror A, and Defrin R. Temporal and spatial aspects of experimental tonic pain: Understanding pain adaptation and intensification. Eur J Pain. 2015;19(3): 408–18.

16.17. Unblinding Questionnaire

The unblinding questionnaire will be completed by patients at the end of the Double-Blind Phase or at early termination from the Double-Blind Phase to evaluate which treatment patients believe they received during the Double-Blind Phase (morphine sulfate ER or placebo).

Question 1. To which group do you believe you were assigned during the Double-Blind Phase?

A) Active ER morphine

B) Placebo, which contains no active drug and may be called a "sugar-pill"

C) I don't know

If patient responds A) or B), they will continue to Question 2. Patients will not be permitted to change their response to Question 1 after completing Question 2.

Question 2. Please briefly describe the reason for your selection:

[Open text field]

16.18. Clinical Opiate Withdrawal Scale (COWS)

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Item	Score
Resting Pulse Rate: _____ (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	
Restlessness: *Observation during assessmen*t 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	
Pupil size: 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	
Bone or Joint aches: *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	
Runny nose or tearing: *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting	

Item	Score
Tremor: *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching	
Yawning: *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute	
Anxiety or Irritability: 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult	
Gooseflesh skin: 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
Total scores **with observer's initials**	

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
More than 36 = severe withdrawal

Reference: Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35:253–259.

16.19. Subjective Opiate Withdrawal Scale (SOWS)

Date:	Time:	Please score each of the 16 items below according to how you feel NOW (circle one number)				
	Symptom	**Not at all**	**A little**	**Moderately**	**Quite a bit**	**Extremely**
1	I feel anxious	0	1	2	3	4
2	I feel like yawning	0	1	2	3	4
3	I am perspiring	0	1	2	3	4
4	My eyes are teary	0	1	2	3	4
5	My nose is running	0	1	2	3	4
6	I have goosebumps	0	1	2	3	4
7	I am shaking	0	1	2	3	4
8	I have hot flushed	0	1	2	3	4
9	I have cold flushes	0	1	2	3	4
10	My bones and muscles ache	0	1	2	3	4
11	I feel restless	0	1	2	3	4
12	I feel nauseous	0	1	2	3	4
13	I feel like vomiting	0	1	2	3	4
14	My muscles twitch	0	1	2	3	4
15	I have stomach cramps	0	1	2	3	4
16	I feel like using now	0	1	2	3	4
				Total Score		

Reference: Handelsman L, Cochrane KJ, Aronson MJ, et al. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13:293–308.

16.20. Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Reference: Norton S, Cosco T, Doyle F, et al. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. J Psychosom Res. 2013;74(1):74–81.

16.21. Prescription Opioid Misuse and Abuse Questionnaire (POMAQ)

A copy of the POMAQ will be provided at the time of protocol finalization.

16.22. Arizona Sexual Experience Scale (ASEX)

ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-MALE

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. Can you easily get and keep an erection?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

ARIZONA SEXUAL EXPERIENCES SCALE (ASEX)-FEMALE

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How easily are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

Reference: McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther. 2000;26 (1):25–40.

16.23. Columbia-Suicide Severity Rating Scale (C-SSRS)

Baseline, Version 1/14/09

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____
© 2008 Research Foundation for Mental Hygiene, Inc. C-SSRS—Baseline (Version 1/14/09) Page 1 of 2	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

C-SSRS—Baseline (Version 1/14/09)
Page 2 of 2

Since Last Visit, Version 1/14/09

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others. (2) Mostly to get attention, revenge or a reaction from others. (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling). (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted or Self-Interrupted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted or self-interrupted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Completed Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

16.24. Insomnia Severity Index (ISI)

Insomnia Severity Index

The Insomnia Severity Index has seven questions. The seven answers are added up to get a total score. When you have your total score, look at the 'Guidelines for Scoring/Interpretation' below to see where your sleep difficulty fits.

For each question, please CIRCLE the number that best describes your answer.

Please rate the CURRENT (i.e. LAST 2 WEEKS) SEVERITY of your insomnia problem(s).

Insomnia Problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problems waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?

Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

6. How WORRIED/DISTRESSED are you about your current sleep problem?

Not at all Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

Guidelines for Scoring/Interpretation:

Add the scores for all seven items (questions 1 + 2 + 3 + 4 + 5 +6 + 7) = _____ your total score

Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Reference: Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2001; 2(4):297–307.