FDA Briefing Document

Products: Extended-Release/Long-Acting Opioid Analgesics

Industry Consortium: Opioid Postmarketing Requirements Consortium

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

April 19, 2023

Division of Anesthesiology, Addiction Medicine, and Pain Medicine

Office of Neuroscience

Office of New Drugs

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the review Division or Office. We bring the question of how best to evaluate long-term efficacy of opioid analgesics and opioid-induced hyperalgesia in a clinical trial to this AC in order to gain the AC's insights and opinions. The background package may not include all issues relevant to the final recommendation. This document is intended to focus on issues identified by the Agency for discussion by the AC. The issues to be discussed will include comparing potential study designs (such as enriched enrollment randomized withdrawal (EERW), placebo-control, and active-control trials), that will help overcome challenges with recruitment, dropout, and confounding. The FDA will not issue a final determination on the issues at hand until input from the AC process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the AC meeting.

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Glossary

AC	Advisory Committee
AE	adverse event
BID	twice daily
CNCP	chronic non-cancer pain
COWS	Clinical Opiate Withdrawal Scale
EERW	enriched enrollment randomized withdrawal
ER/LA	extended-release and long-acting
FDA	Food and Drug Administration
IR	immediate-release
MME	morphine milligram equivalents
NDA	New Drug Application
OIH	opioid-induced hyperalgesia
OPC	Opioid Postmarketing Requirements Consortium
PI	pain intensity
PMR	postmarketing requirement
prn	as-needed
QST	quantitative sensory testing
SAO	short-acting opioid

1 Executive Summary/Draft Points for Discussion by the Advisory Committee

Chronic pain is generally defined as pain lasting longer than 3 months or beyond the expected time for normal tissue healing. In 2016, an estimated 20% of U.S. adults (approximately 50 million) experienced chronic pain. Patients with chronic pain may receive nonpharmacologic and pharmacologic treatments, which may include opioids.

Severe chronic pain is a challenging clinical entity first addressed by treatment of the pain generator, if identified and amenable to treatment. Following diagnosis and treatment of the underlying pathology, treatment is geared toward symptom relief and escalates proportionate to the severity of the pain. Treatment starts with nonpharmacologic treatment (physical therapy, acupuncture), over-the-counter and prescription analgesics including acetaminophen, nonsteroidal anti-inflammatory drugs, gamma-aminobutyric-acid-ergic agents, local anesthetics, capsaicin, antidepressant medications, and interventional therapy. Some classes of drugs including tricyclic antidepressants are used off-label for neuropathic pain conditions. Routes of administration include topical, oral, transdermal, intrathecal, and by injection into or near implicated structures. Due to the potential for addiction, opioids are generally avoided although opioids can be a component of multimodal treatment for treatment-resistant chronic pain.

Extended-release and long-acting (ER/LA) opioids constitute a class of analgesics that may be prescribed for treatment of chronic, painful conditions. The labeled indication for ER/LA opioid products is 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. The postmarketing requirement (PMR) that is the subject of this Advisory Committee (AC) meeting pertains to ER/LA opioids for historical reasons. While recent prescribing patterns suggest that immediate-release (IR) opioids may also fulfill this medical need, this document is limited to ER/LA opioids due to the wording of the current PMR.

ER/LA opioid products contain *Limitations of Use* in the *Indications and Usage* section of the label as follows: a) Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with ER opioid formulations, reserve [Tradename] for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or IR opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain and b) [Tradename] is not indicated as an as-needed (prn) analgesic.

Beyond the well-known risks associated with opioid analgesics (e.g., misuse, overdose), there are additional concerns related to long-term opioid use, such as the potential development of opioid-induced hyperalgesia (OIH). OIH (discussed further in Section 3.2.7) can be defined as a condition of increased nociception caused by opioids. The existence of OIH is supported in nonclinical models and some human models in experimental and acute pain settings. The mechanism of OIH has not been established, and a definitive link between the existing data related to OIH and implications for patients on long-term opioid therapy has not been made. Other risks of long-term opioid therapy such as overdose, misuse, abuse, and death have been described elsewhere (Ballantyne 2012; Nury et al. 2022).

Historically, Phase 3 studies[1] of opioid analgesics have studied the drug over a 12-week double-blind randomized treatment period, with long-term safety extensions (single-arm, unblinded) of 6 to 12 months. Accordingly, there are limited controlled study data evaluating the effectiveness of opioids beyond 12 weeks. Due to the paucity of pertinent high-quality data and safety concerns

[1] In this document, the terms “trial” and “study” are used interchangeably.

for opioid therapy over an extended period of time, there is a need for clinical trial data to better inform the benefit-risk balance of long-term opioid use. This is the impetus for the PMR under discussion today.

The FDA (also, *the Agency*) has the authority to require postmarketing studies of approved drugs should a new safety issue be identified. Thus, over the past decade, the FDA has endeavored to obtain data to inform the efficacy of long-term opioid therapy over periods of time >12 weeks. Our efforts have included an assessment of the literature and requiring and working with Industry (Opioid Postmarketing Requirements Consortium [OPC]) to design, execute, and report a study to inform this question. One such trial was initiated but terminated, primarily due to an inability to recruit patients.

It is important to define the research question to be addressed by a postmarketing study to address this public health question. Decades of clinical experience and multiple adequate and well-controlled studies have established that opioids are effective analgesics over a 12-week period of study. The risks of short-term use of opioid therapy are similarly well defined (nausea, vomiting, sedation, pruritus, misuse, abuse, addiction, overdose, etc.). Thus, the knowledge gaps are whether opioids remain effective analgesics over longer periods of time and whether other risks may be associated with long-term use, such as OIH. The primary objective of the current PMR is to assess the effectiveness of long-term opioid therapy.

This document addresses the goal of designing a clinical study that: 1. Can be successfully executed and 2. Is likely to yield data useful for regulatory decision making. In this document, we have approached this task on three levels: 1. High-level study design options (Section 1.2), 2. Challenges in clinical trials of patients with treatment-resistant, chronic pain (Section 2.3), and 3. Protocol-specific design issues with a proposed enriched enrollment randomized withdrawal (EERW) study design (Section 3.2). At the time that this document was drafted, there is agreement between the OPC and the FDA that, while there is no perfect study design to address the research question articulated above, the EERW design may offer the best compromise.

1.1 Objective of the AC Meeting

The Agency seeks the advice of the AC on evaluating study design options to inform this important public health question.

The FDA is convening this AC meeting to discuss PMR 3033-11, issued to application holders of new drug applications (NDAs) for ER/LA opioid analgesics. The objectives of the PMR were to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia.

The discussion at this AC meeting will focus on a proposed clinical trial designed to address these PMR objectives. The objective of this AC meeting is to stimulate scientific discussion as a basis for consideration in determining the most appropriate clinical trial design(s) to meet the stated objectives of the PMR.

1.2 Context for Issues to Be Discussed at the AC/Study Designs Considered

The Agency has taken numerous steps in an effort to determine the best approach to evaluate the long-term efficacy of opioids.

See Section 2.3 for a detailed discussion of considerations in the design and interpretation of clinical trials of patients with chronic pain.

The Agency and OPC agreed that common features of any proposed potential long-term efficacy opioid trial design should include the following:

- *Objective:* Safety (OIH) and efficacy of long-term opioid therapy.
- *Design:* Randomized, double-blind.
- *Duration*: 12 months (if possible).
- *Key outcome measures*: Pain intensity (PI), indices of function, adverse events (AEs), quantitative sensory testing (QST).

As noted in the Executive Summary/Draft Points for Discussion by the Advisory CommitteeExecutive Summary/Draft Points for Discussion by the Advisory Committee, the following protocol designs meet at least one of the above criteria and were considered as possible options. Also note that the studies described following pertain to a study in this patient population. Options considered included:

1. *Enriched enrollment randomized withdrawal (EERW) study:* The EERW design envisioned is a randomized, double-blind, placebo-controlled, parallel-group design. This design varies from the conventional clinical trial design in the timing of randomization and dichotomization to two treatment groups, opioid or placebo. In the EERW design, there is a long prerandomization period and a relatively short period where patients will be on double-blind drug.

   An EERW study in this patient population would enroll “opioid-ready” patients. These patients would reasonably meet current standards to consider long-term opioid therapy but would not have been on long-term opioid therapy. The prerandomization period, which would be prolonged in duration, would treat patients appropriate for ERLA medications, and over this run-in period patients with either insufficient pain control or who do not tolerate the opioid study medication will be excluded prior to entering the randomized treatment period.

   During this long prerandomization run-in period, patients would undergo opioid titration for 6 weeks and continue for 36 weeks on chronic titrated doses of ER opioids (including repeated efforts to withdraw opioids, consistent with appropriate opioid management), Patients completing the prerandomization period (i.e., who do not discontinue due to inadequate pain control or inability to tolerate opioid treatment) are to be randomized to remain on opioids or to be tapered from opioids over a period of 1 to 8 weeks.

   This EERW study design may have two potential primary endpoints. One potential endpoint is a time-to-treatment failure concept, which might include sustained increased PI or the need for repeated doses of opioid rescue medication. Patients would exit the study upon reaching this endpoint. The other potential endpoint could be the PI change from baseline to the end-of the double-blind treatment period (10 weeks postrandomization).

   Although there are limitations to this study design, the EERW study design may have advantages over other designs, acknowledging that each design considered, including EERW, has significant limitations. An advantage of the EERW design is avoiding a high extent of dropout over a long randomized treatment period undermining a robust assessment of effectiveness. For context, there are data for eight pertinent registrational studies of ER/LA opioids. The mean completer rate for patients randomized to placebo in a 12-week double-blind period was 62% (range 45% to 75%). For patients randomized to stay on opioids, the mean completer rate was 66% (range 52% to 77%). The key advantages and limitations of this design are discussed below and are a key discussion point for the Committee.

2. *Placebo-controlled study:* In the traditional randomized, double-blind, placebo-controlled study design, patients eligible for this study would have to be on a 20 to 40 morphine milligram equivalents (MME) dose regimen chronically but with inadequate pain control (pain score of 5 to 9 on a 0-to-10-point scale). The patients would go through a 1-week opioid taper followed by a 1-week opioid-free period and 6 weeks of open-label short-acting opioids (SAO)—to a maximum of 40 MME. Patients with unsatisfactory control would then be randomized to a 52-week course of either ER opioids or placebo, with up to 40 MME as rescue allowed. Patients would continue their baseline nonopioid analgesia regimen. Both the EERW and this design are both randomized, double-blind, placebo-controlled, parallel-group designs. However, this design would represent relatively "early randomization" as opposed to "late randomization" in the EERW paradigm. Patients already taking a stable regimen of nonopioid analgesics could continue taking them. Because of the long duration of potentially ineffective therapy, the primary limitation of this design is that it would likely lead to a high dropout rate in both arms (although expected to be higher in the placebo arm), which if this occurred, would result in uninterpretable trial results. Moreover, a high level of rescue use in the placebo group would limit comparisons of pain intensity (and patients not responding to rescue with adequate pain control would likely discontinue).
3. *Active-controlled study:* In the active-controlled model, opioid-ready patients are screened and randomized to either flexible-dose opioid therapy or nonopioid therapy for a period of 12 months. This also represents "early" randomization. The primary limitation of this design is that it targets patients failing nonopioid treatment and due to a risk of drop out with long-term treatment, it may recruit patients with less severe pain.

1.3 Brief Description of Issues for Discussion at the AC

Due to the unique clinical considerations regarding patients with chronic pain appropriate for long-term opioid therapy, the design of the clinical trials intended to evaluate the treatment effect of analgesics in this patient population poses certain challenges. There are different options with respect to clinical trial designs, each with their own advantages and disadvantages. The issues to be discussed by the AC include the potential trial designs that could be used to assess the treatment effect of an analgesic in a chronic pain patient population, and the points to consider when analyzing the results of the trial.

1.4 Draft Points for Discussion

Discussion of study designs:

1. Discuss the advantages and limitations of using the EERW design to assess long-term effectiveness; discuss the advantages and limitations of using a placebo-controlled design to assess long term effectiveness.
    a. Include in your discussion the likelihood of maintaining sufficient patients in the randomized treatment period in each of these study designs to assure an adequate assessment of effectiveness at the end of the double-blind treatment period.
2. Discuss other designs that should be considered in the assessment of long-term effectiveness of opioids.

Specific questions related to this protocol:

1. Is 38 to 52 weeks an adequate duration to assess the long-term effectiveness of opioids?

2. What degree of dropout is expected in a study in this patient population? Will enough patients be expected to complete this study in order for the results to be interpretable?
3. Is the time-to-treatment-failure endpoint appropriate? If yes, should use of rescue above a prespecified threshold be added as a treatment failure criterion? If no, why not? Given the pain scores could be variable, are there measures that could be employed to assure that the threshold for increase in pain is clinically meaningful and does not represent short-term variability?
4. Does the proposed tapering scheme adequately mitigate concerns about unblinding?
5. Is the proposed definition of OIH and surveillance for development of the condition appropriate? To better characterize OIH, should patients diagnosed with OIH undergo a diagnostic/therapeutic opioid taper?

2 Introduction and Background

The primary focus of this background document and the AC discussion is the clinical trial design to fulfill PMR 3033-11 (previously known as PMR 2065-5). PMR 3033-11 is 1 of a total of 11 PMRs for these products. The rationale and history of the initial establishment of these PMRs (and subsequent PMR release and reissuance) are described below.

2.1 PMR 3033-11 Regulatory History

On May 30, 2012, a discussion of the efficacy of analgesics in chronic noncancer pain took place at a public scientific workshop held by the National Institutes of Health (NIH 2012). During the discussion, presenters raised concerns about the safety of opioids at higher doses, including those pertaining to known serious risks of opioid use, such as misuse, abuse, hyperalgesia (Chapman et al. 2011), addiction, overdose, and death. Stakeholders also raised concerns about the appropriate scope of the indication for opioid analgesics and the possibility of limiting the dosage and duration of treatment with these drugs (FDA 2012).

Stakeholder and commenter concerns regarding the safety of high-dose opioid analgesics, and requests made for limits on dosage and duration of opioid analgesic treatment resulted in a review of stakeholder and commenter submissions, as well as additional issue-specific literature reviews, to more fully understand what is known about the serious risks associated with ER/LA opioid analgesics. Based on the FDA's review of relevant literature, FDA concluded that more data were needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics. Thus, FDA required ER/LA opioid analgesic NDA holders to conduct postmarketing studies and a clinical trial to assess these risks.

Section 505(o)(3) of the Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

On September 10, 2013, FDA issued requirements for safety labeling changes and five PMRs. The PMRs included four observational studies (PMRs 2065-1, 2065-2, 2065-3, 2065-4) to evaluate misuse, abuse, overdose, and death; and a clinical trial (PMR 2065-5) to evaluate the long-term efficacy of opioids and the risk of hyperalgesia. The initial PMR read, "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."

Based on feedback obtained from stakeholders on the design and conduct of the PMRs (FDA 2014), FDA determined that the 5 PMRs should be reissued as 10 PMRs to redefine the

requirements for the four pharmacoepidemiologic observational studies. Additional details regarding this PMR release and reissue action and the PMRs for the observational studies are available on the FDA website (FDA 2023). In the course of this reissuance, PMR 2065-5 for the clinical trial, was renumbered as PMR 3033-11. Irrespective of the administrative change to the PMR number, the PMR description remained unchanged: "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. Thus, the PMR objectives included both an assessment of OIH risk and an assessment of effectiveness greater than one year. The PMR description delineates the study purpose, which remained constant throughout the protocol iterations, and continues to be the intended focus of the scientific discussion at this AC meeting.

2.2 Protocol Iterations and Discussions

As described throughout this document, the design of a study to address the research question has proven to be challenging. Following issuance of the PMR in 2013, FDA and OPC have worked cooperatively to design and execute a study to fulfill the PMR. Over these years, the objectives of the study have evolved to include long-term efficacy (Table 1).

Table 1. Simplified Chronology

Date (Approximate or Range)	Event
September 2013	Original PMR issued.
2013-2014	Discussions between FDA and OPC on trial design
~2016	OPC initiated a 26-week study in patients with high (≥120 MME/day) opioid requirements.
~2018	Ongoing study terminated (29 patients enrolled) due to a. Changes in opioid prescribing practices, b. Centers not interested in conducting the trial, and c. Potential patients expressed fears of i. Loss of access to opioids after end of trial, ii. Requirement to discontinue opioids, and iii. Opioid withdrawal.
February 2018	OPC submitted a protocol for a 12-month randomized, double-blind, nominally placebo-controlled study of ER/LA opioids vs. placebo + prn SAO. The Agency expressed concerns about this trial design related to potential differences between patients who complete in the placebo and active arms. The Agency asked OPC to consider using an open-label, observational study.
May 2019	OPC submitted a protocol for a randomized, open-label, parallel-group design. Treatment groups were to be open-label SAO or ER/LA opioids. The Agency expressed concern that the permitted dose of SAO opioid (60 MME) might preclude a separation between arms.
January 2020	OPC submitted a protocol for a 12-month, randomized, double-blind trial of ER/LA opioids vs. placebo + up to 40 MME of prn SAO in patients failing up to 40 mg of SAO at screening. The Agency expressed concerns about this design because of the likelihood that the actual treatment groups would be ER/LA opioid vs. ~40 MME of SAO and might not adequately address the research question.
January 2020–July 2021	Internal vetting at FDA resulted in FDA conveying to OPC that an EERW study design might be the best compromise between feasibility and scientific rigor for a 12-month study in this patient population.
July 2021–present	FDA and OPC have continued to refine an EERW protocol, now for discussion at this Advisory Committee.

Source: FDA.
Abbreviations: EERW, enriched enrollment randomized withdrawal; ER/LA, extended-release/long-acting; FDA/Agency, Food and Drug Administration; MME, morphine milligram equivalents; OPC, Opioid Postmarketing Requirements Consortium; prn, as-needed; SAO, short-acting opioid

2.3 Considerations in the Design and Interpretation of Clinical Studies of Patients with Chronic Pain Appropriate for Long-term Opioids

There are unique considerations for design and interpretation of chronic pain trials in this patient population (Moore et al. 2013; Katz 2021; Kennedy et al. 2022). Key challenges in designing clinical trials to evaluate the long-term efficacy of opioids include the following: definition of an appropriate patient population, determination of the appropriate study drug and choice of comparator(s), appropriate endpoint, logistical challenges such as management of dropouts, concomitant medications, patient comorbidities, duration of therapy, and limitations in interpretation of the results.

Many factors influence the type of clinical trial design that would be used for any given clinical situation, and a comprehensive discussion is beyond the scope of this briefing document. Although the list below is not exhaustive, some key considerations of chronic pain trials in opioids, and in the design of the present trial, are as follows:

1. Trial design considerations:
    a. *Patient population (Inclusion criterion):* A basic issue for this clinical trial is the selection of the pain type(s) (and corresponding inclusion criteria) to be studied. Integral in that selection is the assessment of whether the results obtained in the studied patient population (including specific types of chronic pain conditions) can be extrapolated to other patient populations (with distinct pain conditions). The present study proposes to include a number of different pain conditions that may present with severe and chronic pain that may require opioid treatment. The study will exclude pain conditions that are typically successfully treated with nonopioid medications and/or do not usually respond well to opioid treatment.
    b. *Choice of active study drug*: The intent of the present study is to evaluate both safety (in particular, characterization of OIH) and long-term effectiveness. Although optimally, several different opioids (e.g., both IR and ER/LA, and potentially even agents within each class) might be included, using multiple different opioid medications in one study poses clinical operations issues given the challenges around study drug supply, study drug titration (up- and then down-titration) and blinding. Selecting one type of opioid (e.g., an ERLA or an IR opioid) requires extrapolation of the results to the broader range of opioid agents. However, there is little evidence that durability of effect is contingent on the type of opioid agent. Thus, extrapolating findings from a study of a single ERLA agent to opioid agents in general is possible. Based upon these considerations, the present study will evaluate the effectiveness of a single ERLA opioid agent (morphine sulfate ER). Comments on whether this assumption is reasonable by the Advisory committee would be useful.
    c. *Choice of comparator arms:* The potential comparator treatments could include placebo or nonopioid analgesic with each posing advantages and disadvantages. For example, incorporating an active comparator that requires titration may create challenging logistical problems (e.g., how to provide blinded drug when the dose is adjusted based on tolerability) or interpretation problems (e.g., determining whether the titration algorithm for the drug that required titration was optimized). Although providing useful information on relative effectiveness, if the issue to be addressed is whether long-term effectiveness is seen with an opioid agent, comparison to placebo would seem appropriate. Further, an active-controlled study would likely require a much larger sample size to be adequately powered.

d. *Efficacy endpoints:* How best to measure the treatment effect of an analgesic requires assessment of the most appropriate tool(s), and the frequency and duration of assessment. Because pain is a subjective, patient-reported outcome, the tool should be one that has been established as being fit-for-purpose for the patient population being studied. The use of a primary endpoint in conjunction with key secondary endpoints, or a combined endpoint, will potentially yield different information on the treatment effect of the analgesic.

   In chronic pain trials, the primary endpoint is typically based on a well-defined and reliable patient-reported outcome measure of the subject's PI (PI score). Generally, a numerical rating scale is used (e.g., 11-point numerical rating scale). PI scores measured prior to randomization (here, at the end of the run-in treatment period) serve as the baseline for efficacy assessment. The randomized withdrawal phase is for a fixed duration with the primary efficacy endpoint being the change from baseline (prerandomization) in PI.

   An alternative endpoint that has been used is time-to-treatment failure—defined as the requirement for repeated doses of rescue analgesic or sustained increase in PI or study withdrawal due to inadequate pain control. This composite endpoint incorporates dropouts as one of the criteria thereby reducing the risk that patient withdrawal may compromise the assessment of effectiveness (since withdrawal is a component of the endpoint). The study will collect both of these endpoints (i.e., time-to-treatment failure and PI); however, the choice of which of these endpoints should be primary will be an important design issue. The currently proposed protocol uses the time-to-treatment failure as the primary endpoint to avoid the impact of discontinuations due to inadequate pain control.

   Secondary endpoints and outcome measures further characterize the efficacy of an analgesic and support the primary efficacy endpoint. Some secondary endpoint considerations unique to chronic opioid clinical trials include the development of opioid tolerance, opioid-induced hyperalgesia, and other secondary effects of long-term opioid use. The protocol proposed now includes several pertinent secondary endpoints.

e. Background therapy and rescue medication

   i. *Background therapy*: Patients with chronic pain may be on background nonpharmacologic (e.g., physical therapy, acupuncture, psychological support, ice, and heat) and/or pharmacologic treatments. The protocol will prespecify the allowed background therapy. The management of these background therapies will be addressed in the protocol, as they could confound the results. Protocols should generally prespecify the allowed background therapy. The protocol will recommend maintaining the background therapy generally stable, especially during the randomized treatment period. If background therapies are to be adjusted, appropriate titration and tapering schedules should be incorporated in the protocol.

   ii. *Rescue medication*: Rescue medication is a critical design feature of chronic pain trials given the importance of ensuring adequate pain control in study participants, but it can confound the evaluation of the study drug effect. The protocol will contain provisions for the use of rescue medications in order to promote enrollment and patient retention, but the type of rescue medications permitted has the potential to affect the interpretability of the results. In the

present study, short acting morphine and acetaminophen are permitted during the open-label maintenance and double-blind phases.

f. *Duration of study:* Various factors will influence what would be considered the most appropriate duration of the clinical trial, with the intent to demonstrate durability of effect. Prior registrational randomized trials of opioids have been limited to 12 weeks in duration largely due to concerns about the feasibility of longer duration placebo-controlled study periods. To evaluate long-term effectiveness, a treatment period of 52 weeks would be appropriate, as it is reasonable to conclude that efficacy over that time period, if demonstrated, could be extrapolated to longer periods of use. The duration of the trial, however, will affect the recruitment and retention of participants. Since the protocol involves tapering of the dosing regimen, the possibility of unblinding needs to be considered and appropriate measures implemented to minimize the risk of it occurring. In the present study, tapering during the randomized withdrawal period is intended to be performed gradually.

g. *Surveillance for development of OIH*: As noted elsewhere in this review, there is no consensus on criteria for the diagnosis of OIH. However, the preponderance of clinicians and experts agree that there is a constellation of clinical findings related to escalating pain on stable dose or escalating opioid doses and some objective perturbations in pain thresholds. Pain thresholds are objectively measured using Quantitative Sensory Testing (QST). In this study, pain intensity, use of rescue and concomitant therapies, and QST will be monitored in a subset (~50%) of patients enrolled

2. *Data interpretation*: Inherent in the study designs are means of managing heterogenicity across patients, including in baseline medications, baseline PI ratings, baseline medical diagnoses, and comorbidities. These can limit the generalizability of the findings across patient populations and across opioids.

3. *Statistical considerations*: A full discussion of the statistical considerations for chronic pain trials is beyond the scope of this background document. However, certain issues related to the statistical analyses of the data for the proposed protocol for PMR 3033-11 are described in Section 3.2.6.

3 Summary of Study Design for Study 3033-11

The study protocol described below is the outcome of discussion between OPC and the Agency but is considered to be draft. The purpose of convening this AC is to solicit expert opinion on the proposed protocol.

3.1 Study Objectives

Study Protocol 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" Version Draft 0.8, dated March 1, 2022 (Section 5.2)

Primary Objective

To evaluate the persistence of the analgesic efficacy of an 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

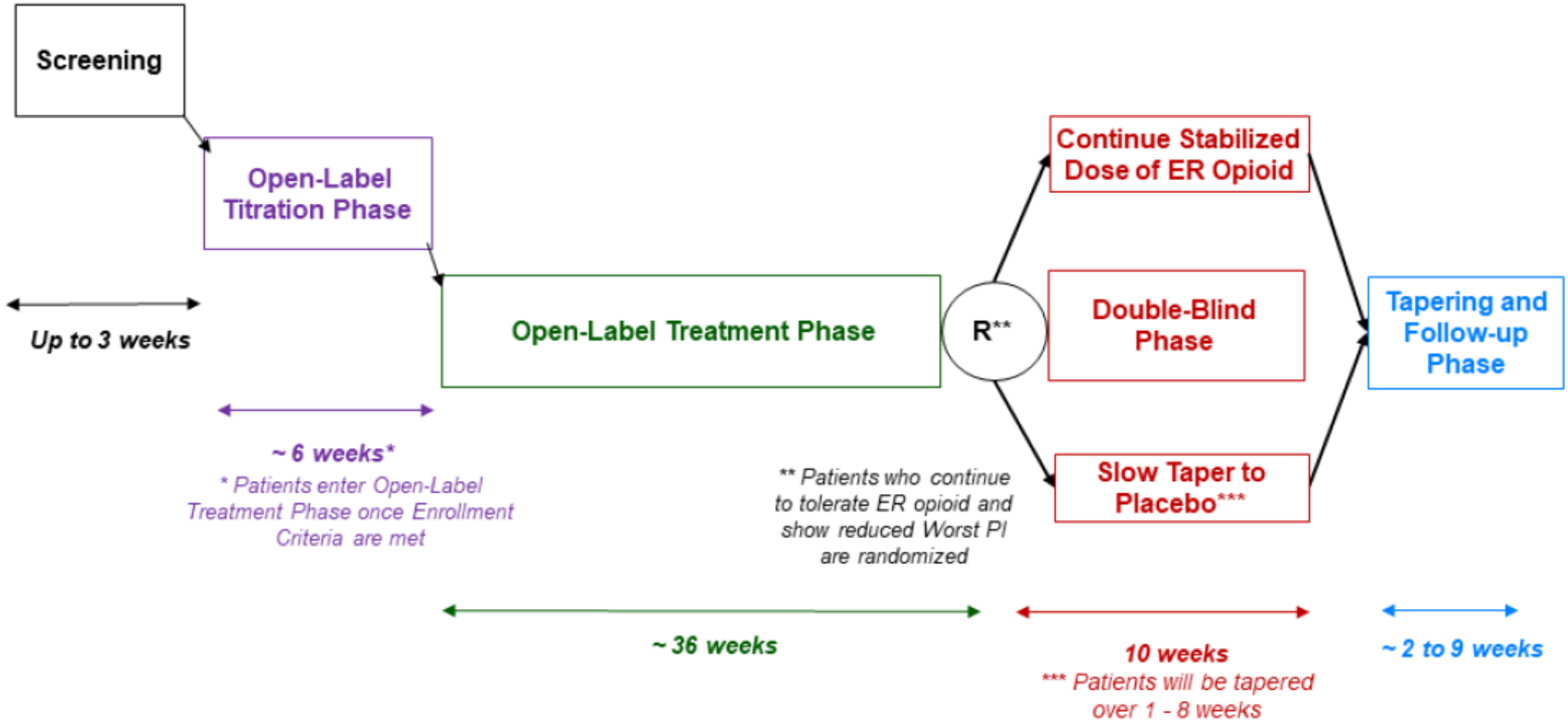
- To explore the incidences of OIH and opioid tolerance.
- To evaluate changes in pain sensitivity over time.
- To identify potential predictors of the opioid analgesic response and nonresponse.
- To evaluate changes in physical function and in levels of anxiety and depression.
- To evaluate the safety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

3.2 Study Design

Study Design

The planned trial is a Phase 4, 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. An overview of the trial design is provided in Figure 1.

Figure 1. Study Design Schematic



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.
Source: Protocol (Section 5.2).

The trial is planned to include five phases: a) Screening Phase, b) Open-Label Titration Phase, c) Open-Label Treatment Phase, d) Double-Blind Randomized Withdrawal Phase, and e) Post-Double-blind Period 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 (the 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 Randomized Withdrawal Phase, and approximately 2 to 9 weeks for the Tapering (post the Randomized Withdrawal Phase) and Follow-up Phase.

3.2.1 Study Population

The planned sample size is 200 patients randomized into each treatment group in the Double-Blind Phase (400 patients in total).

Key Entry Criteria

Generally healthy adult (≥18 years of age) males, or nonpregnant, nonlactating females, with a clinical diagnosis of daily CNCP (chronic pain that is not directly cancer related, including chronic low back pain, osteoarthritis of the hip/knee, diabetic peripheral neuropathy, painful peripheral neuropathy, or post-cancer-treatment–related pain in patients without active cancer), who have been taking SAO therapy at least twice per day (≥30 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.

Key Inclusion Criteria

1. Is male or a nonpregnant (confirmed by pregnancy test), nonlactating female, aged ≥18 years.
2. Has had a clinical diagnosis of CNCP for a minimum of 12 months that:
    a. Occurs daily, AND
    b. Includes chronic low-back pain, osteoarthritis of the hip or knee, diabetic peripheral neuropathy, painful peripheral neuropathy, or post-cancer-treatment–related pain (i.e., post-thoracotomy pain, radiation plexopathy, postchemotherapy pain).
    c. Note: Patients with overlapping CNCP conditions are permitted to enroll in the trial, provided that the patient reports that pain associated with the nonindex 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:
    a. Taken at least twice 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
    b. Total daily dose is ≥30 MME (refer to Appendix 16.2 of the protocol opioid conversion chart). 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 Pain Profile Questionnaire.
6. Has not responded or has contraindications to at least two nonpharmacologic classes and at least two nonpharmacologic therapies for the index pain condition(s), according to the investigator's judgement, following review of the Patient Trauma Response Questionnaire responses, as well as external documentation, if available. Note: Guidance regarding appropriate trials of prior therapies is provided in Appendix 16.3 of the protocol.
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 electrocardiogram, and laboratory profile.
9. Female patients of nonchildbearing potential must be surgically sterile or postmenopausal (postmenopausal is defined as at least 1 year without menses and confirmed by a serum level of follicle-stimulating hormone ≥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.

   Female patients of childbearing potential must be using a medically accepted method of contraception (minimum required use 30 days prior to the first dose of ER study drug, if not otherwise specified) and agree to continued use of this method for the duration of the study and for 30 days after the last dose of ER study drug. 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 [≥ 90 days prior]), partner vasectomy (≥6 months prior), or double-barrier method of contraception (e.g., male condom in addition to a diaphragm, contraceptive sponge, or spermicide).

Key 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.
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 known allergies or hypersensitivity to naloxone, morphine, or other opioids.
4. Has any sensory loss in the arms that, in the opinion of the clinician, is likely to interfere with QST (OIH Population only).

5. 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.
6. Has a diagnosis, per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition of any substance-use disorder (except for nicotine or caffeine) or has a positive urine drug test for illicit drugs (including cannabis), nonprescribed controlled substances (opioid or nonopioid), or alcohol at Screening (refer to Appendix 16.4 of the protocol for analytes and instructions on management of positive results).
7. 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.
8. 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).
9. 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 one type of benzodiazepine drug within 1 month prior to Screening.

3.2.2 Study Treatments

- *Screening Phase:* Patients are to 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 PI score over the prior 7 days of ≥5 and ≤9 on a 0-to-10 numerical rating scale and must express dissatisfaction with SAO therapy (pain control on SAO), 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.
- *Open-Label Titration Phase:* 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.
  - *Dosing*: Open-label, oral titrated doses of morphine sulfate ER, administered twice daily (BID) to a maximum dose of 240 mg per day for ~6 weeks. The total daily dose of morphine sulfate ER is to 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.
  - No rescue medications allowed.
- *Open-Label Treatment Phase:* Patients who meet the 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 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 between visits.
- *Dosing*: 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.
- Rescue medications: Oral SAO up to 2×15 mg IR morphine tablets per day and acetaminophen up to 3000 mg per day will be permitted as-needed. Additional rescue medications such as nonsteroidal anti-inflammatory drugs will not be permitted during the trial.
  - 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.

- *Randomization:* Patients who meet the 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.
- *Double-Blind Treatment Phase:* Patients in the placebo group will be tapered gradually in a double-blinded manner over 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 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.
  - *Dosing*: 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.
  - *Rescue medications*: Oral SAO up to 2×15 mg IR morphine tablets per day and acetaminophen up to 3000 mg per day will be permitted as-needed. Additional rescue medications such as nonsteroidal anti-inflammatory drugs will not be permitted during the trial.
- *Tapering Phase:* At the end of the Double-Blind Phase (Week 52) or early discontinuation, patients will enter the Tapering and Follow-up Phase. ER trial study drug will be tapered down over the course of 1 to 8 weeks, depending on the ER study drug dose. Guidelines for Opioid Tapering after Treatment Completion are provided in the protocol (Protocol Appendix 16.1).
- *Follow-Up Phase:* Patients will be asked to attend a final safety follow-up visit within 5 days of the last dose of ER study drug, 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.

3.2.3 Assessment of OIH

- The OIH population is planned to include all patients who enter the Open-Label Titration Phase and have at least one post-treatment QST evaluation.
- 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).
- Up to 30 research sites are planned to perform QST and contribute to the OIH population, which is planned to comprise at least 200 patients who enter the Open-Label Titration Phase and have at least one post-treatment QST evaluation.

3.2.4 Study Endpoints

Primary Efficacy Endpoint

The data to be captured for the current, protocol-specified, primary efficacy endpoint are the daily worst pain intensity scores (collected via daily diary), concomitant medication and treatment data, and disposition data. These will be used to determine whether patients entering the double-blind period have met endpoint criteria. The criteria to meet the primary endpoint of Time to loss of efficacy are:

- At least 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 therapy for the index chronic pain condition, OR
- Study drug is discontinued due to lack of efficacy.
- The current version of the protocol does not include a criterion related to increased use of rescue.

Secondary Efficacy Endpoints

The protocol requires the collection of a variety of data for secondary efficacy and safety endpoints including the Clinical and Subjective Opioid Withdrawal Scales (COWS/SOWS), a “Pain Profile Questionnaire” (PPQ), Patient-Reported Outcomes Measurement Information System (PROMISpPF-SF-8b), Quantitative Sensory Testing (QST), Columbia Suicide Severity Rating Scale (C-SSRS), Hamilton Anxiety and Depression Scale (HADS), Insomnia Severity Index (ISI), data on endocrine and sexual function, Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), Brief Pain Inventory Short Form (BPI-SF), and the EuroQoL,

five-dimension, five-level (EQ-5D-5L). A patient global assessment of change and an unblinding questionnaire will be administered at end-of-study.

- 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 the Patient-Reported Outcomes Measurement Information System Item Bank v. 2.0–Physical Function–Short Form 8b.
- Change in Brief Pain Inventory–Short Form scores.
- Patient Global Impression of Change scores.
- Change in health-related quality of life, as measured using the EuroQOl, five-dimension, five-level descriptive system.

Other Secondary Efficacy Endpoints (OIH Substudy patients)

The surveillance for OIH was described in Section 3.2.4. The definition of a case of OIH is summarized below.

- 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 milligrams of IR morphine (SAO) and acetaminophen rescue medications used for each treatment group during the Double-Blind Phase.
- Proportion of patients who initiated new analgesic therapy (pharmacologic and nonpharmacologic) for index chronic pain condition(s) by trial phase.
- Fibromyalgianess, as measured by the Fibromyalgianess Scale (only as a predictor).

- Predictors of opioid analgesic response and nonresponse, 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 (in OIH substudy patients).
- Patient responses on the unblinding questionnaire.

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 findings, and use of concomitant medications.
- Proportion of patients who discontinue due to AEs or who experience serious AEs.
- Proportion of patients with abuse-related AEs of special interest.
- Proportion of patients who meet criteria for prescription opioid abuse, misuse, or both, according to the Prescription Opioid Misuse and Abuse Questionnaire.
- Proportion of patients with positive urine drug test results for illicit drugs or nonprescribed controlled substances.
- COWS and Subjective Opiate Withdrawal Scale scores over time.
- Proportion of patients who meet criteria for opioid withdrawal (COWS score ≥5).

Endocrine and Sexual Function Safety Endpoints

- Change in endocrine function tests (i.e., free and total testosterone, luteinizing hormone, follicle-stimulating hormone, estradiol [women only], insulin growth factor-1, cortisol, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, and thyroid-stimulating hormone) 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) from Screening to the final assessment.

Psychological Assessments, Sleep, and Other Safety Endpoints

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

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).

3.2.5 Study Duration

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 the Open-Label Titration/Treatment Phases; 10 weeks in the Double-Blind Phase; and 1 to 8 weeks of taper in the Tapering and Follow-up Phase) and 43 to 50 weeks for patients randomized to placebo (including 42 weeks in the Open-Label Titration/Treatment Phases and 1 to 8 weeks of tapering in the Double-Blind Phase).

3.2.6 Statistical Considerations

Sample size planning of 200 patients per group to achieve 90% power is based on a post hoc analysis and assumed a 15% rate of discontinuation for lack of therapeutic effect in the placebo group and a 5% rate in the active group with a hazard ratio of 0.346, and a minor adjustment to additional assumptions of 17% discontinuation due to other reasons for the active group and a 13% dropout for the placebo group. Sample size re-estimation based on time to loss of efficacy at 50% information time is also planned using conditional power approach. An unblinded independent interim analysis data monitoring committee will perform the unblinded interim analysis and only a recommended increase in sample size will be conveyed to the blinded trial staff. The conditional power is calculated at the interim analysis when 50% patients exited the Double-Blind Phase of the trial (either completed or discontinued). 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. The recommendation on sample-size change will use the smallest increase in blocks of 10 patients that will raise the conditional power to 90% if the interim assessment reveals that the conditional power is at least 30% and less than 90%. However, if the conditional power at the interim analysis is below 30% or at least 90%, the originally planned sample size will be retained without an increase. The Cui, Hung, Wang method (Cui et al. 1999) will be used to analyze the primary and key secondary efficacy endpoints in view of sample size re-estimation.

The analysis population for efficacy reporting is the full analysis set that include all patients randomized into the double-blind phase. The primary efficacy endpoint, time-to-treatment failure, will be analyzed using Kaplan-Meier methodology with stratification for the titrated dose levels. A stratified log-rank test against the hypothesis that there is no difference in the time to loss of efficacy in the trial arms will be used to compare between treatment 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 short-acting opioid and acetaminophen 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.

3.2.7 Evaluation of Opioid-Induced Hyperalgesia

OIH is a condition where a patient's increase in pain can be attributed to the treatment with an opioid (which would have typically been prescribed to relieve pain). While OIH may be observed when opioid dosage increases lead to increased pain, it may also be diagnosed when a

decrease in opioid use causes a decrease in pain. OIH is difficult to diagnose and consensus on definitive diagnosis criteria for OIH has not been reached within medical literature. OIH is often considered a diagnosis of exclusion, often made retrospectively; thus the proposed protocol for 3033-11 may produce a crude rate of incidence of OIH.

3.2.8 Summary of the Advantages and Disadvantages of the Potential Study Design for the Proposed Protocol for 3033-11

Several designs were considered in addressing this PMR including a parallel group, placebo-controlled randomized, long-term treatment study design, an EERW design, and an active controlled treatment design. It is understood that each of these designs have important advantages and limitations, discussed below.

As discussed in the March 2019 Guidance entitled, “Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products,” the randomized withdrawal design was initially proposed as a way to establish long-term effectiveness of drugs in settings in which long-term use of a placebo would not be acceptable on the basis of either ethical or practical grounds. The EERW design has been used in registrational trials for extended-release opioids, psychiatric treatments, and hypertensive treatments. While problematic in many respects, the Agency believes that the EERW design has the key advantage of feasibility in a trial of long duration where maintaining patients in the study is a key requirement.

With respect to the EERW design currently under consideration, this approach randomizes only a subset of patients who enter the study—those who have adequate pain control and who tolerate the medication through the long-term prerandomization run-in period. Hence, the study only evaluates effectiveness among those with an apparent sustained analgesic response and who tolerate the drug and does not evaluate effectiveness in the broad range of patients who might be prescribed an opioid agent. However, if the question to be addressed by the study is whether there are patients for whom the drug does provide long-term effectiveness, this design can address that issue. Further, it has been argued that this design has the advantage of evaluating effectiveness among patients similar to those in a clinical setting who stay on the drug long-term—that is, patients who are apparent responders/tolerators of the drug. This also provides another advantage of this design. Patients likely to withdraw from the study during the randomized treatment period in a “early randomization,” parallel arm, placebo-controlled design (i.e., due to inadequate pain control or intolerance) do so in an EERW designed trial prior to randomization. Based upon this, the randomized study population would not be expected to suffer from extensive dropouts that might undermine the robustness of the between-group comparison (especially since in a time to treatment failure endpoint, dropouts are informative, as a component of the endpoint). The disadvantage of the EERW design is that it does not provide robust information on either the proportion of patients prescribed the drug who respond and tolerate the drug, or on the effectiveness of the drug in the broad population of patients prescribed the drug.

A second issue with the EERW design is that unblinding can occur during the randomized withdrawal period. This may be a greater risk among patients who have remained on the drug for a longer duration of time, as in the current trial, and become familiar with the drug’s effects, and therefore are more sensitive to the effects of down-titration or discontinuation of treatment. It is argued that even if the pain control offered by the opioid is lost or attenuated over the longer treatment period, the diminution of other CNS drug effects or changes in bowel habits could alert the patient to their assigned treatment group. If patients are cognizant of whether they are on the active study drug or placebo, this is likely to alter their subjective assessment of pain intensity, confounding trial results. This issue is shared, albeit likely to a lesser extent, in a

placebo-controlled study design, as patients randomized to placebo are also likely to recognize that they are not receiving active opioid study drug (especially patients who have been on opioids prior to entry into the study), which similarly may impact both their willingness to remain in the study and their reporting of pain intensity. For the EERW study, this issue may be addressed by a very gradual titration, and a point of discussion will be whether the sponsor's proposed down-titration period is sufficient to minimize "unblinding" based upon withdrawal of the drug. The protocol includes COWS and SOWS during the double-blind period to assess for evidence of opioid withdrawal during opioid taper. The other prospective assessment of unblinding is an unblinding questionnaire to be administered at end-of-study.

A third issue is the endpoint to be employed. FDA has typically required the use of an assessment of pain intensity at the trial primary timepoint (typically at 12 weeks for prior EERW trials). FDA considered whether a pain intensity endpoint (i.e., using a NRS 0-10) after discontinuation of study drug at Week 12 post-randomization would be appropriate. This would have the advantage of providing information on the extent of effectiveness, among patients who had an apparent response to drug and were tolerating the drug. However, if there are a significant number of dropouts over the randomized treatment period (i.e., the "withdrawal" period), the between-group comparison may be compromised. The time to event endpoint has previously been proposed and can provide evidence that the drug is providing pain relief but does not quantitate the extent of effectiveness in a scale meaningful to clinicians. Nonetheless, a secondary objective can assess the between-group difference in pain intensity, so this information would still be available. FDA is interested in the AC panel's input on the endpoint construction.

With respect to the parallel-group, placebo-controlled randomized controlled study, this approach poses the challenges of recruiting patients into a long duration placebo-controlled study—in patients who have severe pain intensity having failed other treatments. The prior study included a long-term placebo-controlled period and failed due to recruitment issues. Whether the prolonged placebo treatment period contributed to the recruitment challenges is not clear, but may have been a concern to potential participants. In addition, this design has the challenge of dropouts of patients not tolerating or without an adequate response to an opioid treatment (or for other reasons). Our prior experience suggests a substantial dropout rate even over the 12 weeks of prior randomized trials (in the 40-50% range), and therefore raises the real concern that a dropout rate in a 52-week duration trial would be higher, undermining the robustness of the between-group comparison at the trial primary timepoint. It is likely that only patients with milder pain would consider participating, and this will also skew the results and limit the ability to detect effectiveness. Finally, patients in both groups—but, in particular, in the placebo group—would likely require extensive rescue treatment, with those with satisfactory response to rescue remaining in the trial but confounding the between-group comparison with PI as the primary endpoint.

Other advantages of the proposed Protocol for 3033-11 include the following:

1. Trial design:
    a. The study design is not confounded by patients withdrawing during the long-term open-label treatment period for intolerance, inadequate pain control, or if they no longer require opioid treatment. Therefore, withdrawals do not compromise a robust assessment of effectiveness.
    b. Patients are more likely to remain in the trial based on their individual decisions regarding the adequacy of pain control and tolerance of treatment.

c. The design randomizes patients who remain *after* the open-label treatment period which allows for the study to evaluate the effectiveness in patients continuing in the study to randomization.

d. OIH and the EERW design:

i. The current PMR requires 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 1 year.

ii. The EERW study design, although effectively open-label, single-arm for ~42 weeks, may inform the incidence of OIH provided that the protocol includes appropriate OIH surveillance and a prospective definition of OIH.

iii. Additional information about the phenomenon of OIH may be obtained in this study design if patients who discontinue for increased pain and meet the definition of OIH have their opioids tapered and the hyperalgesia/allodynia assessed and documented in a clinical trial setting.

2. *Data interpretation*: Results from the study should support the conclusion that in the population of patients continuing opioid treatment for chronic pain for 36 weeks, the opioid agent has provided sustained effectiveness. This represents a robust assessment of effectiveness in those who appeared to have a persistent response. Supportive information should come from the PI change from prerandomization.

The disadvantages of the Proposed Trial Protocol for 3033-11 include the following:

1. Trial design:

a. Enrolled patients are to be generally healthy adult males or females with a clinical diagnosis of daily CNCP (chronic pain that is not directly cancer related, including chronic low back pain, osteoarthritis of the hip/knee, diabetic peripheral neuropathy, painful peripheral neuropathy, or post-cancer-treatment–related pain in patients without active cancer), who have been taking SAO therapy at least twice per day (≥30 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. This patient population may be a subset not representative of other chronic pain populations.

b. While there are some features incorporated into this protocol to minimize withdrawal and dropout, risk of unblinding is a concern, and if substantial, could confound the results.

c. A 1-year study presents the challenge of retention of subjects.

d. Regarding OIH, there is no effective comparator arm to provide contextual data.

2. Data interpretation:

a. While the broad inclusion criteria should address some of the recruitment challenges, this will lead to a very heterogenous patient population, which ultimately will affect data interpretation and the generalizability of the findings.

b. It is unclear if the results of this trial are generalizable to other opioid products.

3.2.9 Conclusion

We recognize the advantages and disadvantages of the considered trial designs in this challenging patient population. There are also challenges in selecting appropriate patients, controls, and endpoints, as well as to retain enough patients to generate interpretable data. The EERW design, while not ideal, appears to offer the best compromise to answer this public health question. The Agency welcomes the Committee's discussion on this matter.

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5 Appendix

5.1 New Drug Applications for Extended-Release/Long-Acting Opioid Analgesic Products Under PMR 3033-11

Table 2. New Drug Applications for Extended-Release/Long-Acting Opioid Analgesic Products Under PMR 3033-11

Approval Date	Product	New Drug Application
May 29, 1987	MS Contin (morphine sulfate ER tablets)	019516
July 3, 1996	Kadian (morphine sulfate ER capsules)	020616
June 22, 2006	Opana ER (oxymorphone HCl ER tablets)	021610
June 30, 2010	Butrans (buprenorphine transdermal film)	021306
April 5, 2010	OxyContin (oxycodone HCl controlled-release tablets)	022272
August 25, 2011	Nucynta ER (tapentadol HCl ER tablets)	200533
November 20, 2014	Hysingla ER (hydrocodone bitartrate ER tablets)	206627
October 23, 2015	Belbuca (buprenorphine buccal film)	207932
April 26, 2016	Xtampza ER (oxycodone ER capsules)	208090

Source: FDA.
Note that this table does not include generic ER/LA opioid analgesic products because Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes. However, this authority does not apply to abbreviated new drug applications.
Abbreviations: ER, extended release; FDA, Food and Drug Administration; LA, long-acting; PMR, postmarketing requirement

5.2 Clinical Study Protocol and Appendices for PMR 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 (Version: Original Protocol: 0.8, March 1, 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.

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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.

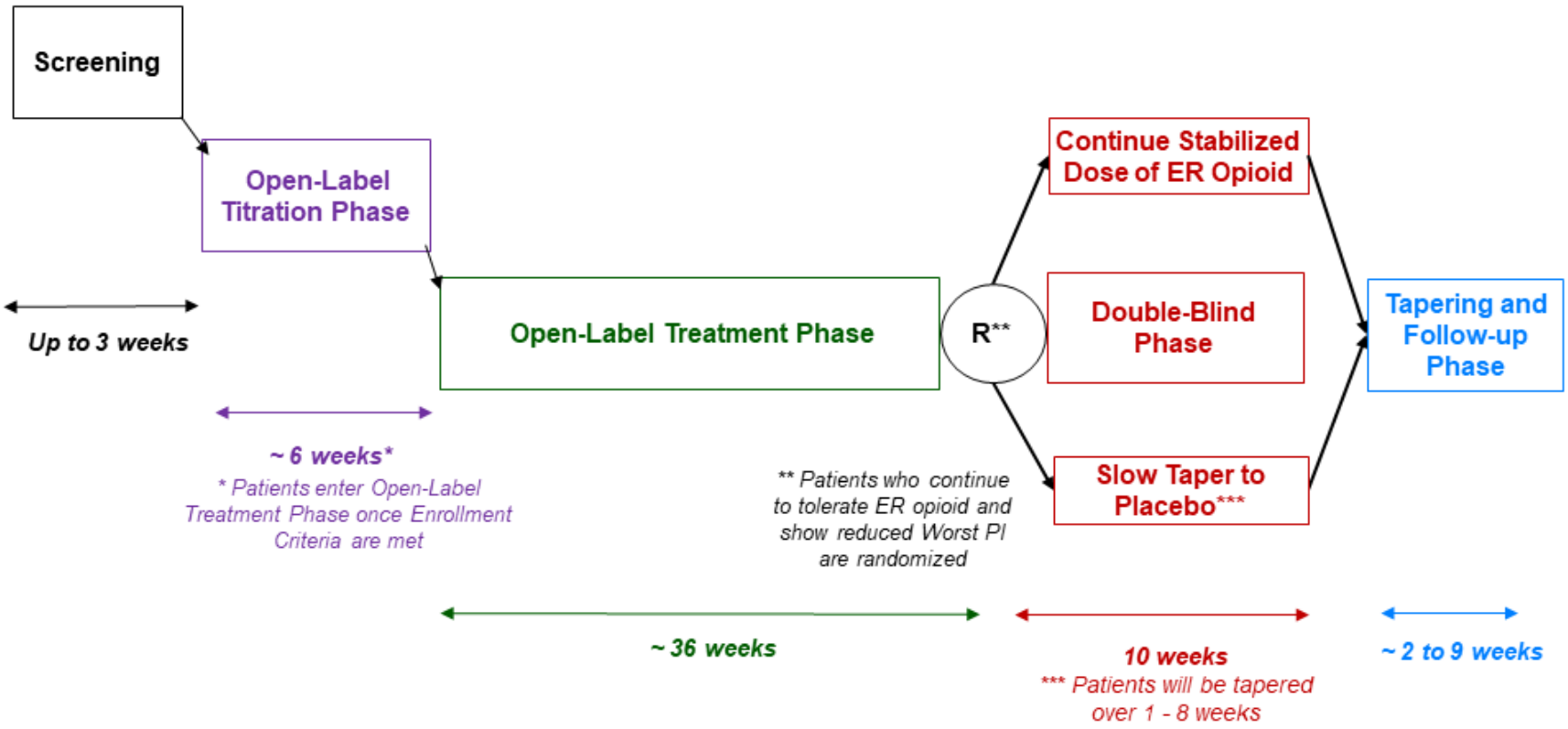
Reasonable efforts will be made to ensure continuity of care for patients. At Screening, patients will be asked to provide the investigator with contact information for their primary care or other qualified healthcare provider (HCP) involved in their pain management. The consenting process will ensure 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.

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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.

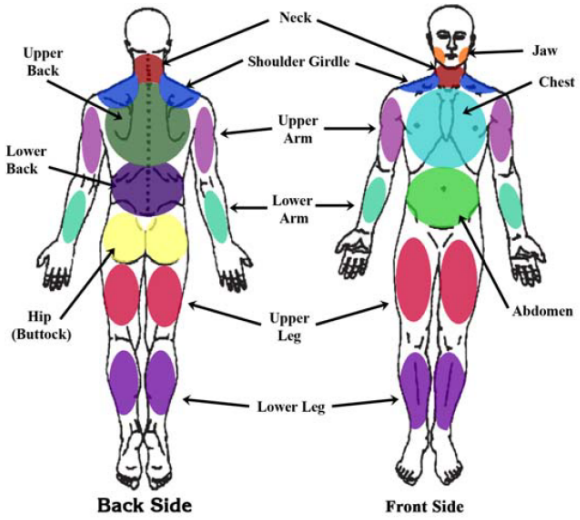
To answer the following questions, patients should take into consideration

- 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?**

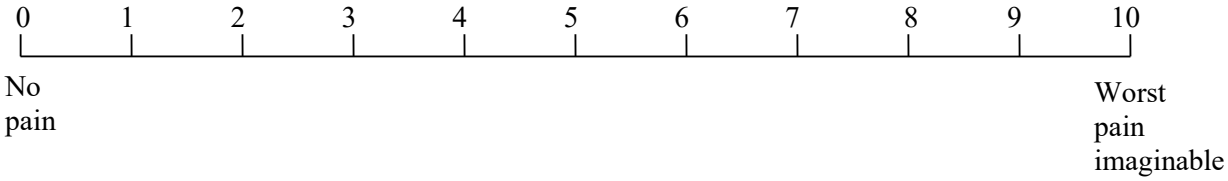
Scoring Criteria:

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)

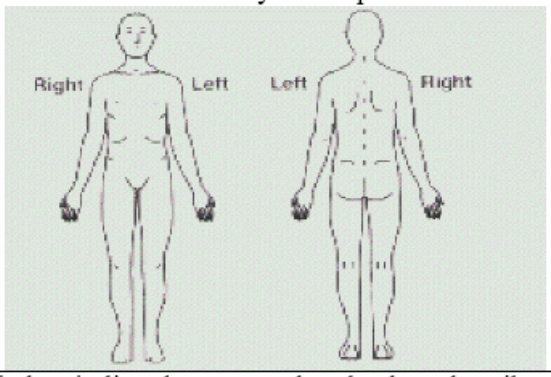
The BPI-SF is shown in its entirety. However, for this study, questions 2 and 7 are not relevant and that information will not be entered into the eCRF.

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

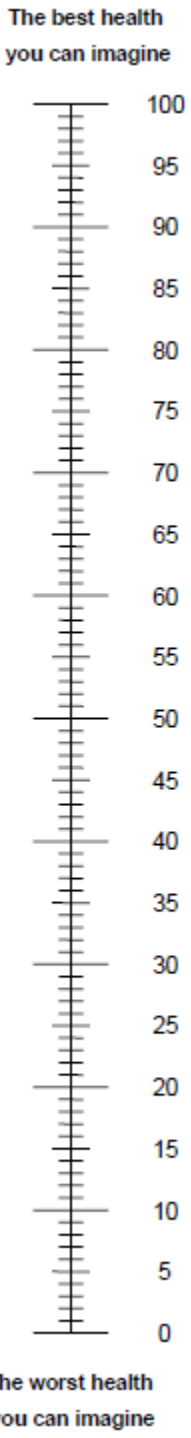
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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	____
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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* _____

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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	____

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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.