PRODUCT: Lofexidine hydrochloride (HCl) tablets

PROTOCOL NUMBER / AMENDMENT: USWM-LX1-2010 / 1

SPONSOR:
USWM, LLC (dba US WorldMeds)
4441 Springdale Rd.
Louisville, KY 40241

TITLE:
A Randomized, Double-blind, Placebo-controlled Pilot Study to Evaluate the Safety and Effectiveness of LUCEMYRA in the Treatment of Opioid Withdrawal During an Opioid Taper in Subjects with Chronic Non-cancer Pain

DOCUMENT DATE: 16 July 2019
IND NUMBER: 047857
NCT NUMBER: NCT04070157

LUCEMYRA

PROTOCOL USWM-LX1-2010

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY TO EVALUATE THE SAFETY AND EFFECTIVENESS OF LUCEMYRA IN THE TREATMENT OF OPIOID WITHDRAWAL DURING AN OPIOID TAPER IN SUBJECTS WITH CHRONIC NON-CANCER PAIN

Protocol Number:	USWM-LX1-2010
Product:	LUCEMYRA™ (lofexidine hydrochloride)
Investigational New Drug #	47,857
Development Phase of Study:	2
Medical Monitor:	[redacted]
Sponsor:	US WorldMeds, LLC
Original Protocol Date:	15 May 2019
Protocol Amendment 1 Date:	16 July 2019

SIGNATURE PAGE

By signing below, US WorldMeds, LLC indicates approval of this protocol as well as assurance that this study will be conducted according to the procedures described in the protocol, Good Clinical Practices, and all applicable regulatory requirements.

[redacted]

7/16/2019
Date

Investigator's Agreement

I have received and read the package insert and Investigator's Brochure for LUCEMYRA. I have read Protocol USWM-LX1-2010 Amendment 1 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

1. STUDY CONTACTS

Table 1: Study Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted] US WorldMeds, LLC	4441 Springdale Road Louisville, KY 40241 502-815-8131
Responsible Physician	[redacted] Contract Medical Monitor	[redacted]
Drug Safety/Serious Adverse Event Reporting (24-hour emergency contact)	[redacted]	[redacted] will be notified of drug safety/serious events via email.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. PROTOCOL SUMMARY

3.1. Synopsis

Name of Sponsor/Company: US WorldMeds, LLC

Name of Investigational Product: Lofexidine hydrochloride (HCl) (LUCEMYRA™)

Name of Active Ingredient: Lofexidine

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Pilot Study to Evaluate the Safety and Effectiveness of LUCEMYRA in the Treatment of Opioid Withdrawal During an Opioid Taper in Subjects with Chronic Non-Cancer Pain

Study Center(s): 7

Studied Period (years):	**Phase of Development:** 2
Estimated date first subject enrolled: July 2019 Estimated date last subject completed: December 2019	

Objectives and Assessments:

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of LUCEMYRA versus placebo when used during an opioid taper in subjects with chronic non-cancer pain	AE reports, clinical laboratory assessments, monitoring of DILI, vital signs, C-SSRS
Secondary	
• Estimate the difference between treatment groups in measures related to opioid withdrawal and completion of opioid discontinuation when tapered	Taper completion status, reduction in opioid use, urine drug screen, COWS, MCGI-R, MCGI-S, SOWS-Gossop, SOWS-H
• Estimate the difference between treatment groups in measures of effectiveness in pain relief, quality of life, and treatment satisfaction	EQ-5D-5L, HADS, ISI, NRS, SF-36, Subject Satisfaction, and use of rescue medication for pain

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; DILI = drug-induced liver injury; EQ-5D-5L = EuroQol 5-Dimension 5-Level; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; MCGI-R = Modified Clinical Global Impression – Rater Version; MCGI-S = Modified Clinical Global Impression – Subject Version; NRS = Numeric Rating Scale; SF-36 = Short Form Health Survey– 36 items; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

Rationale: A significant portion of the public health issues related to long-term prescription opioid use are thought to arise from the difficulty of opioid discontinuation. Following the approval of LUCEMYRA for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults, its use in the setting of an opioid taper has become a topic of interest among clinicians managing physical opioid dependence in chronic pain patients.

Enhanced treatment options for emerging opioid withdrawal symptoms during opioid taper regimens may permit development of more efficient tapering protocols, which in turn would have significant

impact on reducing risk to patients on chronic opioids and may positively impact health economic outcomes.

There is a notable lack of well-controlled data on the opioid withdrawal syndrome during an opioid taper in chronic non-cancer pain patients. Gradually tapering a patient's opioid dose with small reductions in dose over a prolonged period of time is a practice inherently designed to mitigate the potential for opioid withdrawal. LUCEMYRA's effectiveness in treating opioid withdrawal symptoms has been established in the setting of abrupt opioid discontinuation; however, has not been thoroughly evaluated in the setting of an opioid taper. Opioid tapers are often conducted over several weeks, if not months, resulting in the potential for at least cumulative use of LUCEMYRA for beyond 14 days. A clinical trial is necessary to assess for a signal of serious hypotension, bradycardia, syncope, hepatotoxicity, or rebound hypertension, or identify potential unexpected serious risks of long-term use of LUCEMYRA in the setting of an opioid taper as the majority of the existing safety data for LUCEMYRA is on less than 14 days of use. This pilot study is intended to inform critical study design elements for a future pivotal study to assess the safety and efficacy of LUCEMYRA for use beyond 14 days in the setting of an opioid taper.

Methodology:

This is a pilot, multicenter, randomized, double-blind, placebo-controlled, outpatient clinical trial to assess the safety and tolerability, and to estimate the effectiveness of LUCEMYRA for mitigating the symptoms of opioid withdrawal in the setting of an opioid taper in subjects with chronic non-cancer pain.

After a Screening period of up to 28 days, subjects will begin a planned 14-day complete taper of their pre-study opioid and will be randomly assigned (1:1) to either LUCEMYRA or matching placebo. Study drug will be administered through the opioid taper and for 5 days after the opioid taper is completed. Study drug will then be tapered over a 4-day period for a total of approximately 21 days exposure to study drug (Figure 1).

Day 1 dosing with study drug will begin in the clinic as 1 tablet (LUCEMYRA 0.18 mg/tablet or matching placebo) 4 times per day (QID) for a total daily dose of LUCEMYRA 0.72 mg or matching placebo. Subjects will be instructed to take their study drug in the morning upon awakening and then every 5 to 6 hours thereafter. Doses should be taken 5 to 6 hours apart and no more than 4 times per day. At the Day 1 Visit (Visit 1), the Investigator should schedule a phone call with the subject, to occur prior to the second dose of study drug on Day 2, to review the subject's at-home vital signs measurement and how the subject is feeling. The subject will be instructed to contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) while continuing to dose at home on Day 1. If the subject contacts the site on Day 1 reporting these symptoms, the Investigator should consider reducing the planned first daily dose on Day 2.

On Day 2 the subject will be instructed to take 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo), unless Day 1 dosing was not well-tolerated. The subject should contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) after the first daily dose. The Investigator will contact the subject on Day 2, prior to the second dose of the day, to review the subject's at-home vital signs measurement and how the subject is feeling. The Investigator should discuss with the subject any changes to dosing of study drug. Dosing instructions may include an increase to 3 tablets per dose due to subject report of intolerable opioid withdrawal symptoms, or a reduction back to 1 tablet per dose, due to intolerability of study drug.

On Day 3 and beyond, dosing will be at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms.

The dose of study drug may be increased to manage opioid withdrawal symptoms. If an increased dose of study drug is not well tolerated, the dose can be decreased. A single dose of study drug should not exceed 4 tablets (LUCEMYRA 0.72 mg or matching placebo). The total daily dose of study drug should not exceed 4 tablets QID (LUCEMYRA 2.88 mg/day or matching placebo).

Subjects will be tapered from their baseline total daily dose of opioid (calculated as morphine equivalent dose [MED]) over a 14-day period. The opioid dose will be decreased as close as possible to achieve the following dose reduction targets: 50% from the baseline MED beginning with the last dose of the day on Day -1, an additional 25% of the baseline MED beginning on Day 6, and a final 25% of the baseline MED (to dose of zero) beginning on Day 13. Reminders for opioid dose reduction may be done via phone, text, or other electronic message.

Opioid dosing to achieve the required dose reductions in accordance with the protocol defined taper must be planned during Screening. Any changes in opioid prescription to facilitate the protocol taper should be discussed with the subject's primary pain physician, when applicable, and prescribed in advance of randomization. The Investigator should work with a preferred pharmacy informed about the subject's participation in a clinical trial in order to fulfill prescribing needs to facilitate the opioid taper. Opioid prescriptions should be written to accommodate the planned taper, as specified per protocol in Section 9.3. The subject's baseline opioid regimen and MED calculation as well as the opioid regimen planned to achieve each taper step should be submitted to and approved by the Medical Monitor prior to Day -1.

Non-opioid medications taken during the study should be in compliance with the allowed concomitant treatments in Section 9.4. Opioid dose reductions may not occur on a Friday or Saturday unless clinic can accommodate subjects on Saturday and Sunday. Qualified study personnel at the clinic should call the subject the day after the opioid dose is decreased (except on Day 1 since the subject will come to the clinic) to review the subject's at-home vital signs measurement and how the subject is feeling. Upon review by the Investigator or designee, changes to dosing of study drug should also be discussed with the subject if applicable.

Subjects who experience intolerable withdrawal symptoms, despite increasing their dose of study drug to the maximum tolerated dose (not to exceed 4 tablets QID), will be allowed to pause the opioid taper once. Pausing the opioid taper includes either a return to the last stable opioid dose for the remainder of the current opioid dose reduction period, or remaining on the current opioid dose instead of reducing at the next scheduled reduction, resulting in an overall extended opioid taper period and study duration. For example, if a subject experiences intolerable withdrawal at the second opioid dose reduction step [25% of baseline MED], they may either 1) return to the first reduction dose [50% of baseline MED]) or, 2) when the withdrawal persists until the next scheduled reduction step, they may remain for longer at the current opioid dose [25% of baseline MED]. In both cases, the taper must be resumed following the single pause in accordance with the protocol schedule. Subjects who cannot or are unwilling to continue the opioid taper after one pause will be discontinued from the study.

Decisions on whether to pause the opioid taper will be based on subject request and an evaluation (in clinic or over the phone) of the subject's status by the Investigator. Subjects may request to pause the opioid taper due to opioid withdrawal symptoms. If the subject's last COWS score is ≥5 OR if based on i) the Investigator's discussion with the subject, ii) review of ongoing subject-reported withdrawal related AEs, and iii) most recent scores for subject reported withdrawal scales, the subject's desire to pause the taper is related primarily to opioid withdrawal discomfort in the Investigator's opinion, then the taper may be paused. In the event that the Investigator assesses the subject's desire to pause the taper to be primarily related to pain, a taper pause will not be permitted; however, if the subject is willing to continue the per protocol taper, recommended modifications to their concurrent pain management plan should be discussed and recorded. Subjects unwilling to continue the per protocol taper and not experiencing opioid withdrawal to permit a single pause should be discontinued from the study.

Study drug dosing for an opioid taper pause will remain at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms. The dose of study drug can be increased or decreased as needed.

Dosing of study drug will continue for 5 days after the last opioid dose. Study drug will then be tapered over an additional 4 days (Section 9.2.3).

Subjects will be given a diary to take home and will use it to complete daily questionnaires regarding withdrawal and other symptoms, average and worst daily pain, record opioid and study drug administration and concomitant treatment use (including use of medication for pain or opioid withdrawal symptoms).

Subjects will take their blood pressure and heart rate at home using a vital sign monitor. At home readings will be collected during phone calls conducted by study staff after each opioid dose reduction and twice daily (morning and evening) during the 4-day study drug taper through the End of Study (EOS) Visit. Subjects will record readings in their diary.

Subjects will return to the clinic on Day 3, Day 8, and then on a weekly basis following randomization during study drug administration for assessments. With the exception of Day 1 (Visit 1), clinic visits can occur ± 1 day from the study-specified timepoint. Subjects will return to the clinic approximately 7 days after their last dose of study drug. At 30 days following the last dose of study drug, subjects will receive a telephone call for a safety follow-up and assessment of the subject's current opioid usage, after which their participation in the study will be complete.

Subjects who prematurely discontinue the study will be instructed to taper study drug as described in Section 9.2.3 and to complete the at-home assessments for the study drug taper period (Table 4 or Table 5). Once discontinued, subjects may not re-enter the study.

Number of Subjects:

60 subjects (30 LUCEMYRA, 30 placebo)

A sample size of 30 subjects per group provides adequate precision for the estimated treatment difference for the incidence of adverse withdrawal events during opioid taper. Precision of the estimated difference is quantified by the width of the 95% confidence interval for the treatment difference.

Diagnosis and Main Criteria for Eligibility:

Inclusion Criteria

1. Subject can provide written informed consent.
2. Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Chronic non-cancer pain diagnosis such as low back pain, chronic neck pain, osteoarthritis, and prolonged post-surgical pain with daily pain for a minimum of 6 months.
4. Men and women at least 18 years of age at the time of signing informed consent.
5. Self-reported use of prescribed oral opioid medication(s), taken as tablets, pills, or capsules, of at least 50 morphine mg equivalent (MME) but no higher than 240 mg MME daily or near daily (≥5 days per week) for at least 12 weeks and seeking to discontinue their opioid medication. MMEs must be calculated using conversion factors recommended by the Center for Disease Control and Prevention to confirm the MED for the day is between 50-240 MME, including both breakthrough and around-the-clock pain medications, at Screening. The

Medical Monitor must review and approval all baseline opioid use consumption and planned taper dosing regimens prior to Day -1.

6. Willing to be treated with non-opioid treatments for pain (in addition to opioid being tapered) for the duration of the study.
7. Subject agrees to follow the opioid taper plan, both in terms of the planned changes in the doses of opioid medications and the schedule for when opioid dose reductions will be made, as outlined by the Investigator and approved by the study Medical Monitor.
8. Subject agrees to partner with his or her pain physician on a subject-centered pain management program during the study.
9. If the subject is not normally a patient at the clinic, the subject's normal pain physician must sign an attestation that the physician agrees to resume the subject's pain management care following the study.
10. In generally good health, in the opinion of the Investigator, other than the underlying chronic pain syndrome at Screening based upon the results of a medical history, physical examination, 12-lead electrocardiogram, and laboratory profile.
11. Subject agrees to abstain from use of alcohol during the study.
12. Women of childbearing potential must have a negative pregnancy test at Screening.
13. Non-pregnant, non-lactating women who are postmenopausal, naturally or surgically sterile, or who agree to use acceptable contraceptive methods throughout the course of the study. Postmenopausal is defined as at least 12 months of amenorrhea, or at least 6 weeks following surgical menopause, defined as bilateral oophorectomy, tubal ligation, or hysterectomy. If of childbearing potential, subject must have been using birth control for at least 30 days and must agree to use one of the following methods of birth control:
    - Oral contraceptives
    - Patch
    - Barrier method (diaphragm, sponge, or condom) with spermicidal preparations
    - Intrauterine contraceptive system
    - Levonorgestrel implant
    - Medroxyprogesterone acetate contraceptive injection
    - Complete abstinence from sexual intercourse
    - Hormonal vaginal contraceptive ring; surgical sterilization, or partner sterile
14. If male, must agree to use one of the birth control methods listed in inclusion criterion 13 throughout the entire study period and for 90 days after the last dose of study drug. Must not donate sperm for 90 days after the last dose of study drug.
15. Able to speak, write, and understand English, understand the consent form, and be able to effectively communicate with the study staff.

Exclusion Criteria

1. Has a primary diagnosis of complex regional pain syndrome, central neuropathic pain, somatoform pain syndromes, acute nerve root compression, any acute or progressive infectious, inflammatory, or neurological process.
2. Liver disease that requires medication or medical treatment, and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 3 times the upper limit of normal (ULN).
3. Gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment.
4. Has a diagnosis of epilepsy or history of seizures.
5. Has clinically significant abnormal laboratory value(s).
6. Self-reported or evidence of opioid use disorder (OUD) or other substance use disorder within last 12 months prior to Screening using the Sponsor-provided Mini-International Neuropsychiatric Interview.
7. Urine toxicology screen positive for any illicit or non-prescribed opioid drugs prior to randomization.
8. Taking prescription methadone, buprenorphine, fentanyl rapid acting products, tapentadol, tramadol, butorphanol, meperidine, or levorphanol for any reason.
9. Known or suspected pregnancy, planned pregnancy, or lactation.
10. Any of the following cardiovascular abnormalities at Screening and before randomization:
    a. Resting heart rate ≥105 bpm or <55 bpm or symptomatic bradycardia;
    b. Resting systolic blood pressure ≥160 mmHg or <95 mmHg or symptomatic hypotension;
    c. Resting diastolic blood pressure ≥90 mmHg or <65 mmHg;
    d. Clinically significant abnormal electrocardiogram (eg, second- or third-degree heart block, uncontrolled arrhythmia; QT corrected by heart rate by Fridericia's method (QTcF) of ≥450 msec or a history of QT interval prolongation;
    e. New York Heart Association class III or IV; or
    f. History of myocardial infarction within 6 months of Screening.

    Medications taken for stable hypertension are permitted when dose/regimen has been consistent for a minimum of 3 month prior to screening.
11. Any severe or unstable psychiatric disorder including post-traumatic stress disorder, schizophrenia, bipolar disorder, major depression, substance abuse, or suicidality as determined by the Investigator.
12. Subject answers “yes” to “suicidal ideation” in prior 24 months to any items 1 through 5 on the C-SSRS, or subject answers “yes” to any lifetime “suicidal behavior” item on the C-SSRS.
13. Requires any of the following medications currently or within the past 30 days:
    a. Alpha-2 adrenergic agonists
    b. Antiarrhythmics
    c. Barbiturates

d. Paraldehyde
e. Stiripentol
f. Psychoactive herbal preparations (including St. John's Wort, Kratom, cannabis, and products containing cannabinoids)
g. Aspirin (baby aspirin permitted if taking prior to study for cardioprotective purposes)

14. Medications given for stable neuro-psychiatric diagnoses must be at a consistent dose/regimen for at least 30 days prior to randomization. Central nervous system (CNS) depressants in combination with lofexidine may increase the risk of hypotension and bradycardia. Acceptable regular, stable-dosing medications within this category include:

    a. Strong cytochrome P450-2D6 inhibitors, muscle relaxants, benzodiazepines, hypnotics, soporifics, tricyclic antidepressants, selective serotonin reuptake inhibitors, permitted anticonvulsants (including but not limited to gabapentin and pregabalin) must be taken at doses within the ranges recommended per product labeling.
    b. Subject must meet all other eligibility criteria while at the established stable dose/regimen and the medication must be continued at the same dose/regimen for the duration of the study drug administration period.
    c. If taken on an as needed basis, subjects should discontinue medications in these categories 2 weeks prior to randomization and avoid use for the duration of the study drug administration period.
    d. No more than 1 drug in each class should be part of the stable regimen (eg, subjects taking 2 permitted muscle relaxants, 2 anticonvulsants, 2 hypnotics, or 2 soporifics should be excluded until they are taking no more than 1 drug in each class).

15. Treatment with an investigational drug, device, or biological agent within 30 days before Screening or while participating in this study.

16. Any anticipated or scheduled surgery during the study period.

17. Major surgery within 30 days before Screening.

18. Metastatic cancer diagnosed within the previous year or diagnosis of any malignancy or neoplasm within 3 months prior to Screening, exclusive of basal cell carcinoma.

19. Has self-reported acquired immunodeficiency syndrome or self-reported human immunodeficiency virus positive status.

20. History of lack of tolerance or lack of response to LUCEMYRA which, in the Investigator's opinion, makes the subject a poor candidate for the study.

Study Drug Dosage and Mode of Administration:

LUCEMYRA 0.18-mg tablets or placebo taken orally. A single dose of study drug should not exceed 4 tablets (LUCEMYRA 0.72 mg or matching placebo). The total daily dose of study drug should not exceed 4 tablets QID (LUCEMYRA 2.88 mg/day or matching placebo).

Duration of Treatment and Study:

The study duration for each subject will be up to 85 days. The Screening period is up to 28 days, the study drug administration period (including a 4-day study drug taper) is 21 to 27 days (the latter for those requiring an extended opioid taper), and a 30-day safety follow-up period.

Criteria for Evaluation:

Safety:

The following safety endpoints will be assessed:

- Number and percent of subjects reporting treatment-emergent adverse events (TEAEs) by system organ class and preferred term.
- Number and percent of subjects reporting treatment-emergent serious adverse events (SAEs) by system organ class and preferred term.
- Number and percent of subjects reporting TEAEs resulting in study drug discontinuation by system organ class and preferred term.
- Change in vital signs from Baseline to each scheduled evaluation.
- Change in clinical laboratory values from Baseline to each scheduled evaluation.
- Percentage of subjects with treatment-emergent ALT, AST, or alkaline phosphatase >3 × ULN and total bilirubin >2.0 mg/dL at the same evaluation.
- Percentage of subjects identified as suicide risk with C-SSRS.

Effectiveness:

The following effectiveness endpoints will assess withdrawal symptoms and pain:

- Percentage of subjects who successfully complete each scheduled dose reduction and the opioid taper to complete opioid discontinuation, with or without a pause.
- Change in COWS from Baseline to peak value and to each scheduled evaluation.
- Change in SOWS-H from Baseline to peak value and to each scheduled evaluation.
- Change in SOWS-Gossop from Baseline to peak value and to each scheduled evaluation.
- MCGI-R by each scheduled evaluation.
- MCGI-S by each scheduled evaluation.
- Time to study drug discontinuation.
- Change in daily opioid dose, expressed as MED, and as a percentage of the baseline MED.
- Number of non-opioid concomitant medications for withdrawal symptoms used by study day.
- Change in average and worst daily pain from Baseline to peak value as measured by the NRS.
- Change in EQ-5D-5L from Baseline to each scheduled evaluation.
- Change in SF-36 from Baseline to each scheduled evaluation.
- Change in ISI from Baseline to each scheduled evaluation.
- Change in HADS from Baseline to each scheduled evaluation.

Statistical Methods:

The treatment group difference in proportions will be summarized descriptively with a 95% confidence interval. The 95% confidence interval will be calculated based on the normal approximation for the binomial distribution, using the Wald continuity correction. In addition, the treatment group difference will be tested with Cochran-Mantel-Haenszel (CMH) test stratified by total opioid dose (<90 MED, ≥90 MED.

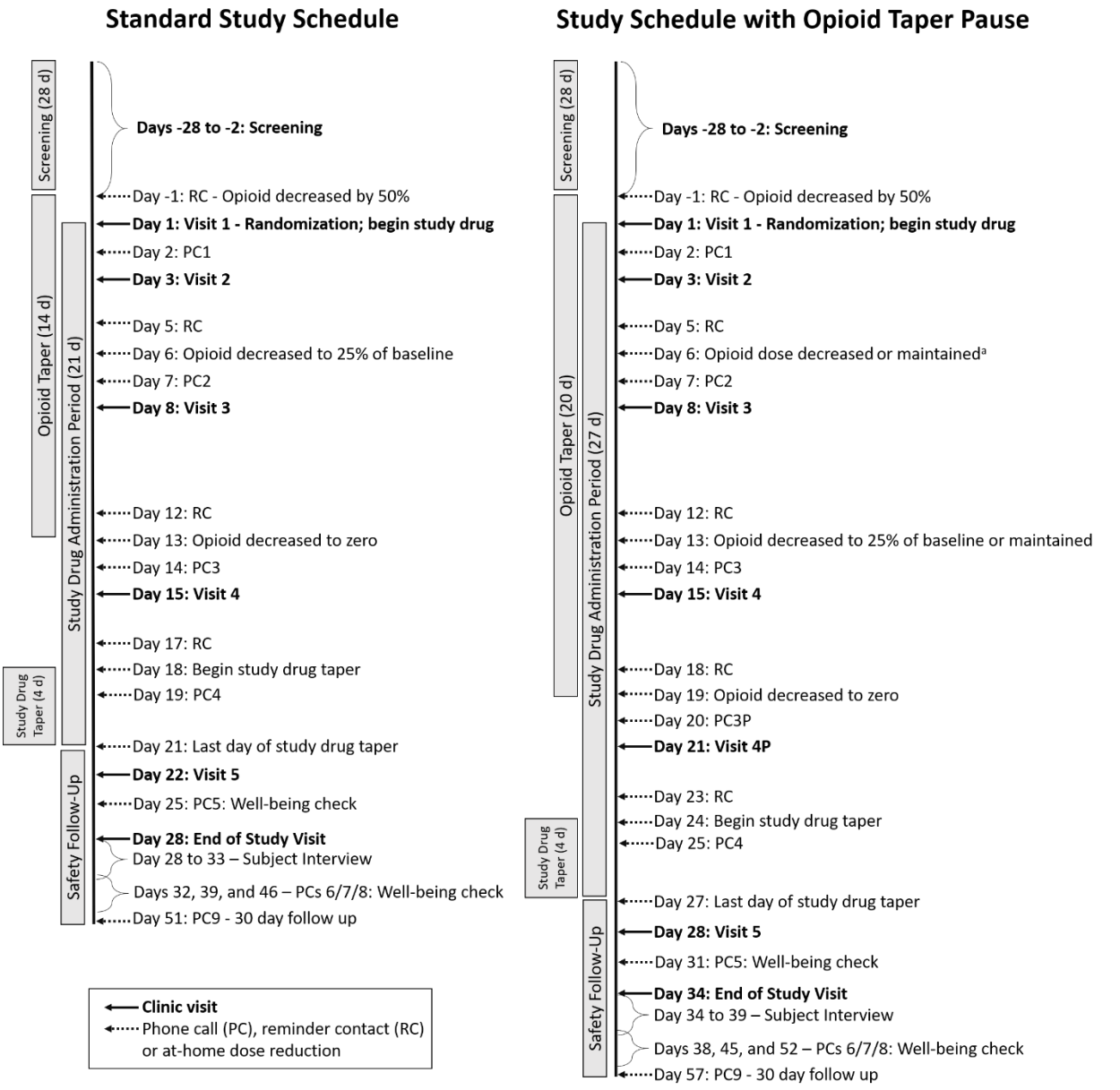
The treatment group difference for mean change will be summarized descriptively with 95% confidence intervals. The 95% confidence intervals for the treatment group differences will be calculated within the framework of analysis of covariance (ANCOVA). The ANCOVA will have treatment and total opioid dose (<90 MED, ≥90 MED) as fixed factors and baseline as covariate. In addition, the treatment group difference will be tested within the ANCOVA framework.

Safety data will be summarized with descriptive statistics. Adverse events (AEs) will be categorized by system organ class and preferred term with the Medical Dictionary for Regulatory Activities.

An interim analysis will be conducted after approximately 30 subjects have completed or discontinued the study. Based on the interim analysis, the study may be stopped for futility but will not be stopped for a positive demonstration of effectiveness. Therefore, no adjustment of Type I error is necessary.

3.2. Schema

Figure 1: Opioid Taper



[a] Subjects experiencing intolerable opioid withdrawal symptoms may pause the opioid taper, as described in Section 9.3. An opioid taper pause includes either a return to the last stable opioid dose for the remainder of the current opioid dose reduction period (eg, if a subject experiences intolerable withdrawal at the second reduction stage [25% of baseline MED], they can return to the first reduction dose [50% of baseline MED]), or remaining on the current opioid dose instead of reducing at the next scheduled reduction, resulting in an overall extended opioid taper period and study duration.

3.3. Schedule of Assessments

Table 2: Schedule of Assessments Performed at the Clinic and Phone Calls: Standard Study Schedule

	Screening[a]		Study Drug Administration[b]													Safety Follow-up				
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 17**	**Days 18-21**	**Day 22**	**Days 23-27**	**Day 28**	**Days 29-50**	**Follow -up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Informed consent and HIPAA authorization	X																			
Inclusion/exclusion	X																			
Demographics	X																			
Medical history	X		update																	
Record Pain Management Plan	X	Updates should be captured throughout the study																		
Characterize Baseline pain condition	X																			
Characterize opioid use and opioid withdrawal history[d]	X																			
MINI	X																			
Randomization			X																	
Complete PE	X																			
Brief PE			X		X				X				X			X		X		
Height	X																			
Weight	X																	X		
Urine pregnancy test[e]	X																	X		
Urine test for opioids	X		X		X				X				X			X		X		
Urine drug screen for illicit substances[f]	X		X		X				X				X			X		X		

	Screening[a]		Study Drug Administration[b]													Safety Follow-up				
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 17**	**Days 18-21**	**Day 22**	**Days 23-27**	**Day 28**	**Days 29-50**	**Follow -up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Urine test for alcohol[g]	X		X		X				X				X			X		X		
Clinical chemistry	X												X					X		
Hematology	X																			
Urinalysis	X																			
Vital signs[h]	X		X	X	X			X	X			X	X			X		X		
Electrocardiogram	X		X		X				X				X			X		X		
COWS			X		X				X				X			X		X		
SOWS-H and SOWS-Gossop			X		X				X				X			X		X		
MCGI-S					X				X				X			X		X		
MCGI-R					X				X				X			X		X		
NRS chronic pain scales	X		X		X				X				X			X		X		X
NRS all over body pain scales			X		X				X				X			X		X		
EQ-5D-5L	X																	X		
SF-36	X																	X		
ISI	X												X					X		
HADS	X																	X		
C-SSRS[i]	X		X		X				X				X			X		X		
Dispense diary	X																			

	Screening[a]		Study Drug Administration[b]													Safety Follow-up				
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 17**	**Days 18-21**	**Day 22**	**Days 23-27**	**Day 28**	**Days 29-50**	**Follow -up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Diary review and check compliance			X		X				X				X			X		X		
Phone call[j]				X				X				X			X[k]		X[l]		X[m]	X
Reminder contact[n]		X				X				X				X						
Opioid dose reduction[o]		X					X				X									
Return study drug					X				X				X			X				
Dispense/re-dispense study drug			X		X				X				X							
Study drug dosing[p]			Continuously as directed in protocol																	
Subject satisfaction																		X		
Subject interview[q]																		X		
Opioid compliance			X		X				X				X			X		X		
Subject training – Reporting of pain and opioid withdrawal symptoms	X	Training should be repeated or reinforced if necessary																		
Subject training – Vital signs[r]			X	Training should be repeated if subject has issues using the monitor or demonstrates lack of protocol compliance																
Subject training – At home diary completion[s]	X	Training should be repeated if subject demonstrates lack of protocol compliance																		
AEs			X	X	X			X	X			X	X		X	X	X	X	X	X

	Screening[a]		Study Drug Administration[b]													Safety Follow-up				
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 17**	**Days 18-21**	**Day 22**	**Days 23-27**	**Day 28**	**Days 29-50**	**Follow-up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Prior and concomitant treatments	X		X		X				X				X			X		X		X

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; EOS = end of study; EQ-5D-5L = EuroQol 5-Dimension 5-Level; HADS = Hospital Anxiety and Depression Scale; HIPAA = Heath Insurance Portability and Accountability Act; ISI = Insomnia Severity Index; MCGI-R = Modified Clinical Global Impression – Rater Version; MCGI-S = Modified Clinical Global Impression – Subject Version; MED = morphine equivalent dose; MINI = Mini-International Neuropsychiatric Interview; PC = phone call; PE = physical examination; RC = reminder contact; SF-36 = Short Form Health Survey– 36 items; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

[a] The Screening Visit may be conducted over the course of multiple visits, as needed.

[b] Subjects who experience intolerable withdrawal symptoms may temporarily suspend the opioid taper once (Section 9.3). See study drug taper schedule in Section 9.2.3.

[c] Phone call 30 days after the last dose of study drug. See Table 4 for other assessments to be captured during the phone call, in addition to follow-up on any outstanding AEs or concomitant treatment usage.

[d] The subject's baseline opioid use and changes to doses for planned taper reductions should be submitted to and approved by the Medical Monitor prior to Day -1.

[e] All female subjects, regardless of childbearing potential.

[f] Confirmatory quantitative testing for illicit substances identified in qualitative testing results may be performed.

[g] Subjects should refrain from alcohol consumption during the study. Repeated alcohol use (eg, 2 positive tests for alcohol after Screening) during the study requires subject discontinuation.

[h] On Day 1, orthostatic vital signs should be assessed pre-dose and 1-hour post-dose of study drug. A post-dose assessment is not required after Day 1 at clinic visits. During phone calls, at-home vital signs (systolic and diastolic blood pressure and pulse) should be recorded after the subject rest for at least 5 minutes.

[i] Baseline version at Screening and 'Since Last Visit' version at subsequent visits.

[j] Phone calls will include review of an at-home vital signs assessment by the subject, an assessment of how the subject is feeling, and review of any changes to study drug dosing.

[k] Phone call will take place on Day 19, to check on the subject's well-being and to assess how the subject is feeling.

[l] Phone call will take place on Day 25, to check on the subject's well-being and to assess how the subject is feeling.

[m] Phone calls will take place on Days 32, 39, and 46, to check on the subject's well-being and to assess how the subject is feeling.

[n] Reminders contacts may be done via phone, text, or other electronic message. Remind the subjects about opioid dose reductions or, at Day 17, study drug dose reductions.

[o] Opioid dose will be decreased 50% from baseline MED beginning with the last dose of the day on Day -1, an additional 25% of baseline MED beginning on Day 6, and a final 25% (to dose of zero) beginning on Day 13. Opioid dose reduction may not occur on a Friday or Saturday unless the clinic can accommodate

subjects on Saturday and Sunday. Subjects who experience intolerable withdrawal symptoms despite increasing their dose of study drug to the maximum tolerated dose will be allowed to pause the opioid taper once. See Table 3 for the opioid taper schedule for subjects who must pause the taper.

[p] Detailed study drug dosing information can be found in Section 9.2.3. Study drug taper begins on Day 18.

[q] Subject interview will be conducted via a centralized interviewer through a phone call. The interview should take place no more than 5 days after the EOS Visit.

[r] Training includes when to call the site due to symptoms of hypertension or hypotension, or if the subject records a vital signs measurement that meets the criteria to contact the site.

[s] Training includes recording all pharmacologic and non-pharmacologic concomitant treatments (including opioid medications), study drug dose administration, scale assessments for both pain (Average Daily and Worst Daily NRS) and opioid withdrawal scales (SOWS-Gossop, SOWS-Handelsman, and MCGI-Subject), and recording of at-home vital signs (during study drug taper and through EOS only).

Table 3: Schedule of Assessments Performed at the Clinic and Phone Calls: Study Schedule with Opioid Taper Pause

	Screening[a]		Study Drug Administration[b]																		Safety Follow-up			
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**		**PC 3P**	**Visit 4P**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 18**	**Day 19**	**Day 20**	**Day 21**	**Day 23**	**Days 24-27**	**Day 28**	**Days 29-33**	**Day 34**	**Days 35-56**	**Follow-up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Informed consent and HIPAA authorization	X																							
Inclusion/exclusion	X																							
Demographics	X																							
Medical history	X		update																					
Record Pain Management Plan	X	Updates should be captured throughout the study																						
Characterize Baseline pain condition	X																							
Characterize opioid use and opioid withdrawal history[d]	X																							
MINI	X																							
Randomization			X																					
Complete PE	X																							
Brief PE			X		X				X				X				X			X		X		
Height	X																							
Weight	X																					X		

	Screening[a]		Study Drug Administration[b]																			Safety Follow-up			
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**		**PC 3P**	**Visit 4P**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 18**	**Day 19**	**Day 20**	**Day 21**	**Day 23**	**Days 24-27**	**Day 28**	**Days 29-33**	**Day 34**	**Days 35-56**	**Follow-up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Urine pregnancy test[e]	X																					X		
Urine test for opioids	X		X		X				X				X				X			X		X		
Urine drug screen for illicit substances[f]	X		X		X				X				X				X			X		X		
Urine test for alcohol[g]	X		X		X				X				X				X			X		X		
Clinical chemistry	X												X									X		
Hematology	X																							
Urinalysis	X																							
Vital signs[h]	X		X	X	X			X	X			X	X			X	X			X		X		
Electrocardiogram	X		X		X				X				X				X			X		X		
COWS			X		X				X				X				X			X		X		
SOWS-H and SOWS-Gossop			X		X				X				X				X			X		X		
MCGI-S					X				X				X				X			X		X		
MCGI-R					X				X				X				X			X		X		
NRS chronic pain scales	X		X		X				X				X				X			X		X		X
NRS all over body pain scales			X		X				X				X				X			X		X		
EQ-5D-5L	X																					X		

	Screening[a]		Study Drug Administration[b]																		Safety Follow-up			
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**		**PC 3P**	**Visit 4P**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 18**	**Day 19**	**Day 20**	**Day 21**	**Day 23**	**Days 24-27**	**Day 28**	**Days 29-33**	**Day 34**	**Days 35-56**	**Follow-up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
SF-36	X																					X		
ISI	X												X									X		
HADS	X																					X		
C-SSRS[i]	X		X		X				X				X				X			X		X		
Dispense diary	X																							
Diary review and check compliance			X		X				X				X				X			X		X		
Phone call[j]				X				X				X				X			X[k]		X[l]		X[m]	X
Reminder contact[n]		X				X				X				X				X						
Opioid dose reduction[o]		X					X				X				X									
Return study drug					X				X				X				X			X				
Dispense/re-dispense study drug			X		X				X				X				X							
Study drug dosing[p]			Continuously as directed in protocol																					
Subject satisfaction																						X		
Subject interview[q]																						X		
Opioid compliance			X		X				X				X				X			X		X		

	Screening[a]		Study Drug Administration[b]																		Safety Follow-up			
Method	**Screening**	**RC**	**Visit 1**	**PC 1**	**Visit 2**	**RC**		**PC 2**	**Visit 3**	**RC**		**PC 3**	**Visit 4**	**RC**		**PC 3P**	**Visit 4P**	**RC**	**PC 4**	**Visit 5**	**PC 5**	**EOS**	**PCs 6,7,8**	**30-day PC 9**
Timing	**Days -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 12**	**Day 13**	**Day 14**	**Day 15**	**Day 18**	**Day 19**	**Day 20**	**Day 21**	**Day 23**	**Days 24-27**	**Day 28**	**Days 29-33**	**Day 34**	**Days 35-56**	**Follow-up[c]**
Visit window					**±1 day**				**±1 day**				**±1 day**				**±1 day**			**±1 day**		**±1 day**		
Subject training – Reporting of pain and opioid withdrawal symptoms	X	Training should be repeated or reinforced if necessary																						
Subject training – Vital signs[r]	X		X	Training should be repeated if subject has issues using the monitor or demonstrates lack of protocol compliance																				
Subject training – At home diary completion[s]	X	Training should be repeated if subject demonstrates lack of protocol compliance																						
AEs	X		X	X	X			X	X			X	X			X	X		X	X	X	X	X	X
Prior and concomitant treatments	X		X		X				X				X				X			X		X		X

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; EOS = end of study; EQ-5D-5L = EuroQol 5-Dimension 5-Level; HADS = Hospital Anxiety and Depression Scale; HIPAA = Heath Insurance Portability and Accountability Act; ISI = Insomnia Severity Index; MCGI-R = Modified Clinical Global Impression – Rater Version; MCGI-S = Modified Clinical Global Impression – Subject Version; MED = morphine equivalent dose; MINI = Mini-International Neuropsychiatric Interview; PC = phone call; PE = physical examination; RC = reminder contact; SF-36 = Short Form Health Survey– 36 items; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

[a] The Screening Visit may be conducted over the course of multiple visits, as needed.

[b] Subjects who experience intolerable withdrawal symptoms may temporarily suspend the opioid taper once (Section 9.3). See study drug taper schedule in Section 9.2.3.

[c] Phone call 30 days after the last dose of study drug. See Table 5 for other assessments to be captured during the phone call, in addition to follow-up on any outstanding AEs or concomitant treatment usage.

[d] The subject's baseline opioid use and changes to doses for planned taper reductions should be submitted to and approved by the Medical Monitor prior to Day -1.

[e] All female subjects, regardless of childbearing potential.

[f] Confirmatory quantitative testing for illicit substances identified in qualitative testing results may be performed.

[g] Subjects should refrain from alcohol consumption during the study. Repeated alcohol use (eg, 2 positive tests for alcohol after Screening) during the study requires subject discontinuation.
[h] On Day 1, orthostatic vital signs should be assessed pre-dose and 1-hour post-dose of study drug. A post-dose assessment is not required after Day 1 at clinic visits. During phone calls, at-home vital signs (systolic and diastolic blood pressure and pulse) should be recorded after the subject rest for at least 5 minutes.
[i] Baseline version at Screening and 'Since Last Visit' version at subsequent visits.
[j] Phone calls will include review of an at-home vital signs assessment by the subject, an assessment of how the subject is feeling, and review of any changes to study drug dosing.
[k] Phone call will take place on Day 25, to check on the subject's well-being and to assess how the subject is feeling.
[l] Phone call will take place on Day 31, to check on the subject's well-being and to assess how the subject is feeling.
[m] Phone calls will take place on Days 38, 45, and 52, to check on the subject's well-being and to assess how the subject is feeling.
[n] Reminders contacts may be done via phone, text, or other electronic message. Remind the subjects about opioid dose reductions or, at Day 24, study drug dose reductions.
[o] Opioid dose will be decreased 50% from baseline MED beginning with the last dose of the day on Day -1. The opioid dose will be decreased or maintained beginning on Day 6. The opioid dose will be decreased an additional 25% of baseline MED or maintained beginning on Day 13. A final 25% (to dose of zero) reduction will be made beginning on Day 19. Subjects who experience intolerable withdrawal symptoms despite increasing their dose of study drug to the maximum tolerated dose will be allowed to pause the opioid taper once. Pausing the opioid taper includes either a return to the last stable opioid dose for the remainder of the current opioid dose reduction period (eg, if a subject experiences intolerable withdrawal at the second reduction stage [25% of baseline MED], they can return to the first reduction dose [50% of baseline MED]), or remaining on the current opioid dose instead of reducing at the next scheduled reduction, resulting in an overall extended opioid taper period and study duration. In this scenario, a subject will taper to a dose of zero beginning on Day 19. Opioid dose reduction may not occur on a Friday or Saturday unless the clinic can accommodate subjects on Saturday and Sunday.
[p] Detailed study drug dosing information can be found in Section 9.2.3. Study drug taper begins on Day 24.
[q] Subject interview will be conducted via a centralized interviewer through a phone call. The interview should take place no more than 5 days after the EOS Visit.
[r] Training includes when to call the site due to symptoms of hypertension or hypotension, or if the subject records a vital signs measurement that meets the criteria to contact the site.
[s] Training includes recording all pharmacologic and non-pharmacologic concomitant treatments (including opioid medications), study drug dose administration, scale assessments for both pain (Average Daily and Worst Daily NRS) and opioid withdrawal scales (SOWS-Gossop, SOWS-Handelsman, and MCGI-Subject), and recording of at-home vital signs (during study drug taper and through EOS only).

Table 4: Schedule of Assessments Performed at Home: Standard Study Schedule

Timing	Screening		Study Drug Administration[a]																				Safety Follow-up	
	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Days 22-27	Follow-up[b]
Site contact[c]		X		X			X		X					X		X			X		X			X	X
SOWS-H and SOWS-Gossop[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MCGI-S[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NRS chronic pain scales[d,e]	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
NRS all over body pain scales[d]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L																									X
Record study drug and concomitant treatment use[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs – Phone report[f]				X					X							X									
Vital signs – Subject diary[g]																				X	X	X	X	X	
AEs				X					X							X									X

AE = adverse event; EOS = end of study; EQ-5D-5L = EuroQol 5-Dimension 5-Level; MCGI-S = Modified Clinical Global Impression – Subject Version; NRS = Numeric Rating Scale; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

[a] Subjects who experience intolerable withdrawal symptoms may temporarily suspend the opioid taper once (Section 9.3). See study drug taper schedule (Section 9.2.3). See Table 5 for the schedule of assessments to be performed at home for subjects who must pause the taper.

[b] Phone call 30 days after the last dose of study drug. Subjects will be asked to report their current opioid dose/regimen and complete several scales (EQ-5D-5L and NRS pain scales) over the phone.

[c] Reminder contacts will take place on Days -1, 5, 12, and 17. Phone calls from the clinic staff will take place on Days 2, 7, 14, 25, 32, 39, 46, and 30 days following the last dose of study drug (follow-up phone call). A subject phone interview, conducted by a centralized interviewer, will take place between Days 28 and 33.

[d] Completed at home before bedtime.

[e] Subjects will continue to complete the NRS chronic pain scales every day between the EOS Visit and the phone call 30 days following the last dose of study drug (follow-up phone call).

[f] During the phone call to the subject, the site should ask the subject to collect and report their vital signs. The subject will not record this reading in their diary.

[g] Readings will be taken once in the morning and once in the evening and reported in the subject's diary.

Table 5: Schedule of Assessments Performed at Home: Study Schedule with Opioid Taper Pause

	Screening		Study Drug Administration[a]																										Safety Follow-up	
Timing	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Days 28-33	Follow-up[b]
Site contact[c]		X		X			X		X					X		X				X		X			X		X			X	X
SOWS-H and SOWS-Gossop[d]			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	
MCGI-S[d]			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	
NRS chronic pain scales[d,e]	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
NRS all over body pain scales[d]			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	
EQ-5D-5L																															X
Record study drug and concomitant treatment use[d]		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	
Vital signs – Phone report[f]				X					X							X						X								
Vital signs – Subject diary[g]																										X	X	X	X	X	
AEs				X					X							X						X								X

AE = adverse event; EOS = end of study; EQ-5D-5L = EuroQol 5-Dimension 5-Level; MCGI-S = Modified Clinical Global Impression – Subject Version; NRS = Numeric Rating Scale; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

[a] Subjects who experience intolerable withdrawal symptoms may temporarily suspend the opioid taper once (Section 9.3). See study drug taper schedule (Section 9.2.3).

[b] Phone call 30 days after the last dose of study drug. Subjects will be asked to report their current opioid dose/regimen and complete several scales (EQ-5D-5L and NRS pain scales) over the phone.

[c] Reminder contacts will take place on Days -1, 5, 12, 18, and 23. Phone calls from the clinic staff will take place on Days 2, 7, 14, 20, 25, 31, 38, 45, 52, and 30 days following the last dose of study drug (follow-up phone call). A subject phone interview, conducted by a centralized interviewer, will take place between Days 34 and 39.

[d] Completed at home before bedtime.

[e] Subjects will continue to complete the NRS chronic pain scales every day between the EOS Visit and the phone call 30 days following the last dose of study drug (follow-up phone call).

[f] During the phone call to the subject, the site should ask the subject to collect and report their vital signs. The subject will not record this reading in their diary.

[g] Readings will be taken once in the morning and once in the evening and reported in the subject's diary.

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

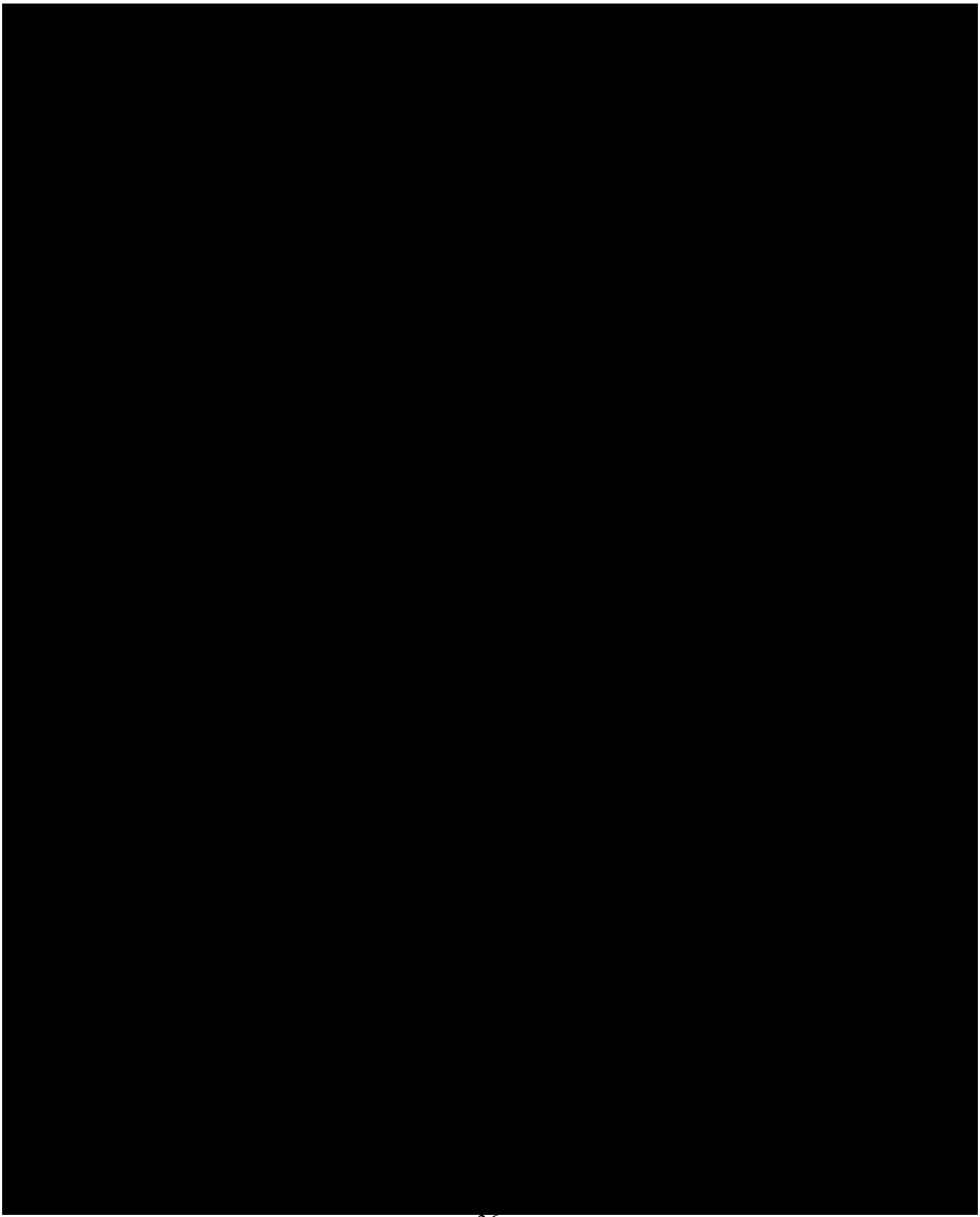
Table 6: List of Abbreviations

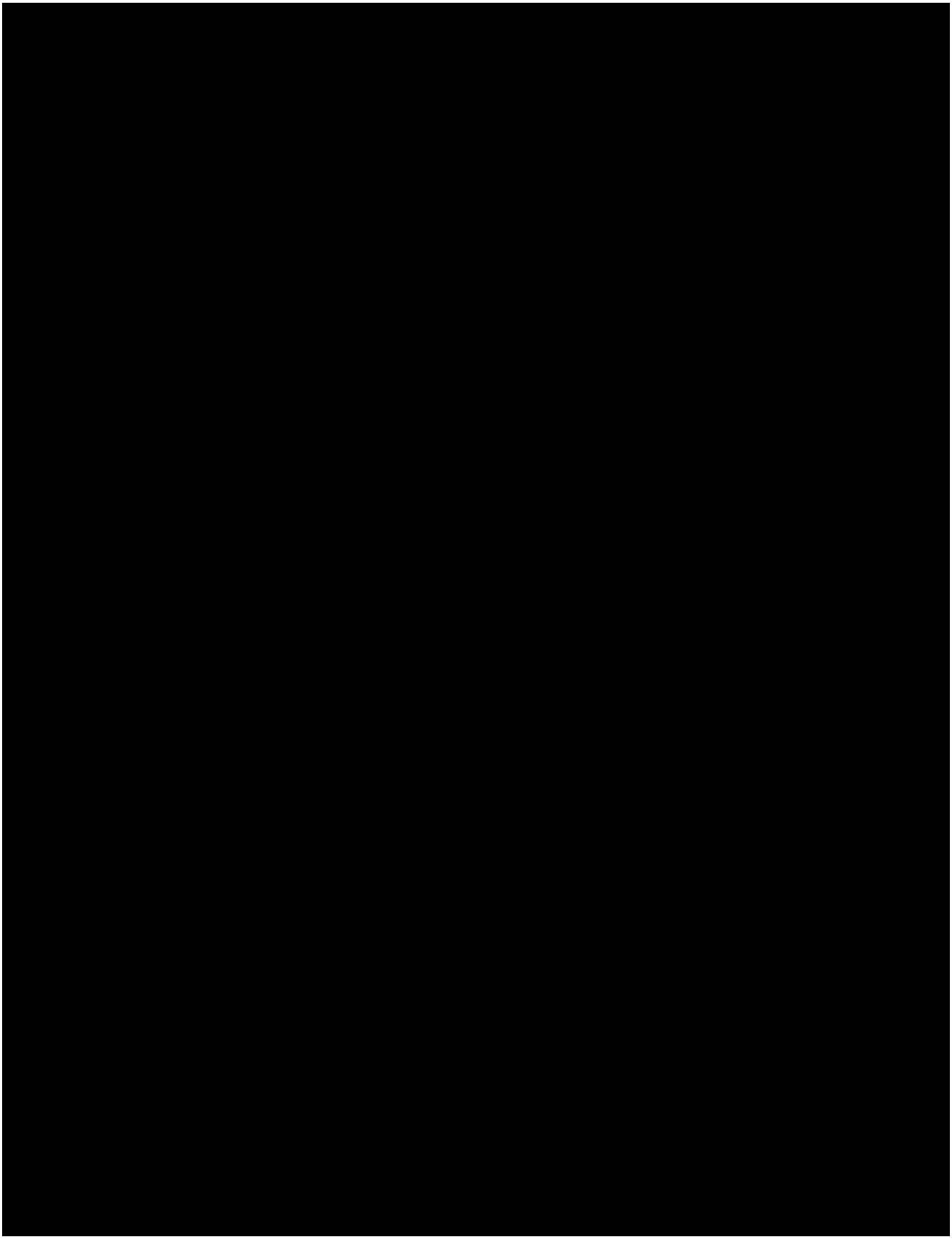
Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AMDG	Agency Medical Director's Group
ANOVA	Analysis of variance
AST	aspartate aminotransferase
CDC	Centers for Disease Control
CFR	Code of Federal Regulation
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
C-SSRS	Columbia-Suicide Severity Rating Scale
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EERW	Enriched enrollment randomized withdrawal
EOS	End of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISI	Insomnia Severity Index
ITT	Intent-to-treat
MCGI-R	Modified Clinical Global Impression – Rater Version
MCGI-S	Modified Clinical Global Impression – Subject Version
MED	Morphine equivalent dose
MME	Morphine mg equivalents

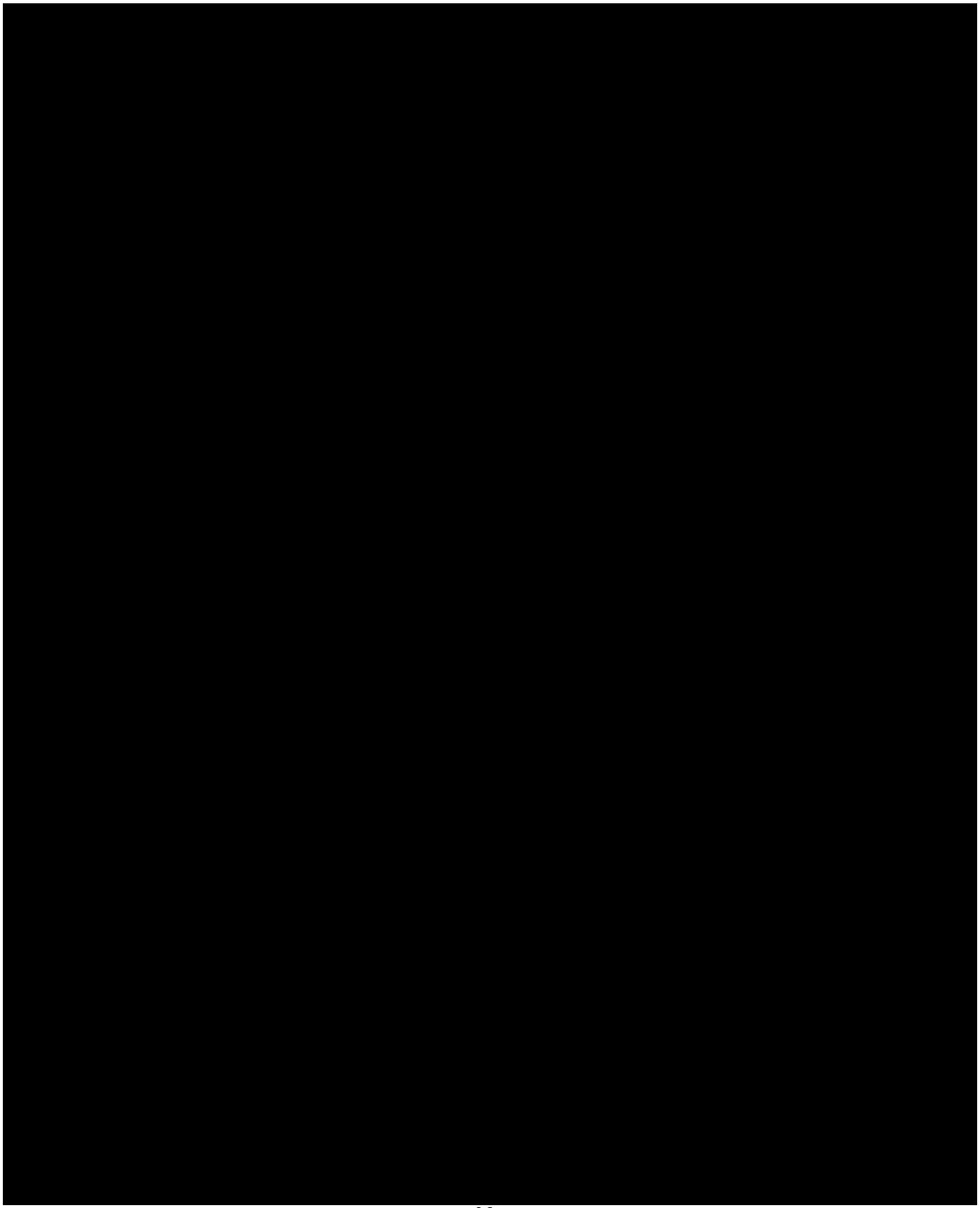
Abbreviation	Definition
NRS	Numeric Rating Scale
OIC	Opioid-induced constipation
OUD	Opioid use disorder
QID	4 times per day
QTcF	QT corrected by heart rate by Fridericia's method
SAE	Serious adverse event
SF-36	Short Form Health Survey– 36 items
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
SOWS-H	Subjective Opiate Withdrawal Scale of Handelsman
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States

Abbreviations that appear only in tables or figures are defined with the relevant tables and figures.

5. INTRODUCTION







[redacted]

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective is to evaluate the safety and tolerability of LUCEMYRA versus placebo when used during an opioid taper in subjects with chronic non-cancer pain.

6.2. Secondary Objectives

The secondary objectives of this study are to estimate the difference between treatment groups in:

- Measures related to opioid withdrawal and completion of opioid discontinuation when tapered
- Measures of effectiveness in pain relief, quality of life, and treatment satisfaction

[redacted]

6.4. Assessment Tools Used to Achieve Objectives

The assessment tools used to achieve the study objectives are presented in Table 7. Effectiveness and safety endpoints, based on these assessment tools, are defined in Section 7.2.

Table 7: Assessment Tools Used to Achieve Objectives

Objective	Assessment Tools
Primary Objective	
Evaluate the safety and tolerability of LUCEMYRA versus placebo when used during an opioid taper in subjects with chronic non-cancer pain	AE reports, clinical laboratory assessments, monitoring of DILI, vital signs, and C-SSRS
Secondary Objectives	
Estimate the difference between treatment groups in measures related to opioid withdrawal and completion of opioid discontinuation when tapered	Taper completion status, reduction in opioid use, urine drug screen, COWS, MCGI-R, MCGI-S, SOWS-Gossop, SOWS-H
Estimate the difference between treatment groups in measures of effectiveness in pain relief, quality of life, and treatment satisfaction	EQ-5D-5L, HADS, ISI, NRS, SF-36, subject satisfaction, and use of rescue medication for pain
[redacted]	

AE = adverse event; COWS = Clinical Opiate Withdrawal Scale; C-SSRS = Columbia-Suicide Severity Rating Scale; DILI = drug-induced liver injury; EQ-5D-5L = EuroQol 5-Dimension 5-Level; HADS = Hospital Anxiety and Depression Scale; ISI = Insomnia Severity Index; MCGI-R = Modified Clinical Global Impression – Rater Version; MCGI-S = Modified Clinical Global Impression – Subject Version; NRS = Numeric Rating Scale; SF-36 = Short Form Health Survey – 36 Items; SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop; SOWS-H = Subjective Opiate Withdrawal Scale of Handelsman

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a pilot, multicenter, randomized, double-blind, placebo-controlled, outpatient clinical trial to assess the safety and tolerability, and to estimate the effectiveness of LUCEMYRA for mitigating the symptoms of opioid withdrawal in the setting of an opioid taper in subjects with chronic non-cancer pain.

After a Screening period of up to 28 days, subjects will begin a planned 14-day complete taper of their pre-study opioid and will be randomly assigned (1:1) to either LUCEMYRA or matching placebo. Study drug will be administered through the opioid taper and for 5 days after the opioid taper is completed. Study drug will then be tapered over a 4-day period for a total of approximately 21 days exposure to study drug (Figure 1).

Day 1 dosing with study drug will begin in the clinic as 1 tablet (LUCEMYRA 0.18 mg/tablet or matching placebo) 4 times per day (QID) for a total daily dose of LUCEMYRA 0.72 mg or matching placebo. Subjects will be instructed to take their study drug in the morning upon awakening and then every 5 to 6 hours thereafter. Doses should be taken 5 to 6 hours apart and no more than 4 times per day. At the Day 1 Visit (Visit 1), the Investigator should schedule a phone call with the subject, to occur prior to the second dose of study drug on Day 2, to review the subjects at-home vital signs measurement and how the subject is feeling. The subject will be instructed to contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) while continuing to dose at home on Day 1. If the subject contacts the site on Day 1 reporting these symptoms, the Investigator should consider reducing the planned first daily dose on Day 2.

On Day 2 the subject will be instructed to take 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo), unless Day 1 dosing was not well-tolerated. The subject should contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) after the first daily dose. The Investigator will contact the subject on Day 2, prior to the second dose of the day, to review the subject's at-home vital signs measurement and how the subject is feeling. The Investigator should discuss with the subject any changes to dosing of study drug. Dosing instructions may include an increase to 3-tablets per dose due to subject report of intolerable opioid withdrawal symptoms, or a reduction back to 1 tablet per dose, due to intolerability of study drug.

On Day 3 and beyond, dosing will be at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms.

The dose of study drug may be increased to manage opioid withdrawal symptoms. If an increased dose of study drug is not well-tolerated, the dose can be decreased. A single dose of study drug should not exceed 4 tablets (LUCEMYRA 0.72 mg or matching placebo). The total daily dose of study drug should not exceed 4 tablets QID (LUCEMYRA 2.88 mg/day or matching placebo).

Subjects will be tapered from their baseline total daily dose of opioid (calculated as MED) over a 14-day period. The opioid dose will be decreased as close as possible to achieve the following

dose reduction targets: 50% from the baseline MED beginning with the last dose of the day on Day -1, an additional 25% of the baseline MED beginning on Day 6, and a final 25% of the baseline MED (to dose of zero) beginning on Day 13 (Figure 1). Reminders for opioid dose reduction may be done via phone, text, or other electronic message.

The Investigator will instruct the subject on how to reduce their opioid dosing regimen for each dose reduction. Opioid dosing to achieve the required dose reductions in accordance with the protocol defined taper must be planned during Screening. Any changes in opioid prescription to facilitate the protocol taper should be discussed with the subject's primary pain physician, when applicable, and prescribed in advance of randomization. The Investigator should work with a preferred pharmacy informed about the subject's participation in a clinical trial in order to fulfill prescribing needs to facilitate the opioid taper. Opioid prescriptions should be written to accommodate the planned taper, as specified per protocol in Section 9.3. The subject's baseline opioid regimen and MED calculation as well as the opioid regimen planned to achieve each taper step should be submitted to and approved by the Medical Monitor prior to Day -1.

Non-opioid medications taken during the study should be in compliance with the allowed concomitant treatments in Section 9.4. Opioid dose reductions may not occur on a Friday or Saturday unless clinic can accommodate subjects on Saturday and Sunday. Qualified study personnel at the clinic should call the subject the day after the opioid dose is decreased (except on Day 1 since the subject will come to the clinic) to review the subject's at-home vital signs measurement and how the subject is feeling. Upon review by the Investigator or designee, changes to dosing of study drug should also be discussed with the subject if applicable.

Subjects who experience intolerable withdrawal symptoms despite increasing their dose of study drug to the maximum tolerated dose (not to exceed 4 tablets QID) will be allowed to pause the opioid taper once. Pausing the opioid taper includes either a return to the last stable opioid dose for the remainder of the current opioid dose reduction period, or remaining on the current opioid dose instead of reducing at the next scheduled reduction, resulting in an overall extended opioid taper period and study duration. For example, if a subject experiences intolerable withdrawal at the second opioid dose reduction step [25% of baseline MED], they may either 1) return to the first reduction dose [50% of baseline MED]) or, 2) when the withdrawal persists until the next scheduled reduction step, they may remain for longer at the current opioid dose [25% of baseline MED]. In both cases, the taper must be resumed following the single pause in accordance with the protocol schedule. Subjects who cannot or are unwilling to continue the opioid taper after one pause will be discontinued from the study.

Decisions on whether to pause the opioid taper will be based on subject request and an evaluation (in clinic or over the phone) of the subject's status by the Investigator. Subjects may request to pause the opioid taper due to opioid withdrawal symptoms. If the subject's last COWS score is ≥5 OR if based on i) the Investigator's discussion with the subject, ii) review of ongoing subject-reported withdrawal related AEs, and iii) most recent scores for subject reported withdrawal scales, the subject's desire to pause the taper is related primarily to opioid withdrawal discomfort in the Investigator's opinion, then the taper may be paused. In the event that the Investigator assesses the subject's desire to pause the taper to be primarily related to pain, a taper pause will not be permitted; however, if the subject is willing to continue the per protocol taper, recommended modifications to their concurrent pain management plan should be

discussed and recorded. Subjects unwilling to continue the per protocol taper and not experiencing opioid withdrawal to permit a single pause should be discontinued from the study.

Study drug dosing for an opioid taper pause will remain at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms. The dose of study drug can be increased or decreased as needed.

Dosing of study drug will continue for 5 days after the last opioid dose. Study drug will then be tapered over an additional 4 days (Section 9.2.3).

Subjects will be given a diary to take home and will use it to complete daily questionnaires regarding withdrawal and other symptoms, average and worst daily pain, record opioid and study drug administration and concomitant treatment use (including use of medication for pain or opioid withdrawal symptoms).

Subjects will take their blood pressure and heart rate at home using a vital sign monitor. At home readings will be collected during phone calls conducted by study staff after each opioid dose reduction and twice daily (morning and evening) during the 4-day study drug taper through the EOS Visit. Subjects will record readings in their diary.

Subjects who experience pain will be allowed to take treatments described in Section 9.4.2. Use of treatments for pain and concomitant medications to treat withdrawal symptoms will be recorded daily by subjects using their diary.

Subjects will return to the clinic on Day 3, Day 8, and then on a weekly basis following randomization during the study drug administration for assessments. With the exception of Day 1 (Visit 1), clinic visits can occur ±1 day from the study-specified timepoint. Subjects will return to the clinic approximately 7 days after their last dose of study drug. At 30 days following the last dose of study drug, subjects will receive a telephone call for a safety follow-up and assessment of the subject's current opioid usage, after which their participation in the study will be complete.

Subjects who prematurely discontinue the study will be instructed to taper study drug as described in Section 9.2.3 and to complete the at-home assessments for the study drug taper period (Table 4 or Table 5). Once discontinued, subjects may not re-enter the study.

7.2. Study Endpoints

7.2.1. Safety Endpoints

The following safety endpoints will be assessed:

- Number and percent of subjects reporting treatment-emergent adverse events (TEAEs) by system organ class and preferred term.
- Number and percent of subjects reporting treatment-emergent serious adverse events (SAEs) by system organ class and preferred term.
- Number and percent of subjects reporting TEAEs resulting in study drug discontinuation by system organ class and preferred term.
- Change in vital signs from Baseline to each scheduled evaluation.

- Change in clinical laboratory values from Baseline to each scheduled evaluation.
- Percentage of subjects with treatment-emergent alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase >3 × the upper limit of normal (ULN) and total bilirubin >2.0 mg/dL at the same evaluation.
- Percentage of subjects identified as suicide risk with Columbia-Suicide Severity Rating Scale (C-SSRS).

7.2.2. Effectiveness Endpoints

The following effectiveness endpoints will assess withdrawal symptoms and pain:

- Percentage of subjects who successfully complete each scheduled dose reduction and the opioid taper to complete opioid discontinuation, with or without a pause.
- Change in COWS from Baseline to peak value and to each scheduled evaluation.
- Change in SOWS-H from Baseline to peak value and to each scheduled evaluation.
- Change in SOWS-Gossop from Baseline to peak value and to each scheduled evaluation.
- Modified Clinical Global Impression – Rater Version (MCGI-R) by each scheduled evaluation.
- Modified Clinical Global Impression – Subject Version (MCGI-S) by each scheduled evaluation.
- Time to study drug discontinuation.
- Change in daily opioid dose, expressed as MED, and as a percentage of the baseline MED.
- Number of non-opioid concomitant medications for withdrawal symptoms used by study day.
- Change in average and worst daily pain from Baseline to peak value as measured by the Numeric Rating Scale (NRS).
- Change in EuroQol 5-Dimension 5-Level (EQ-5D-5L) scale from Baseline to each scheduled evaluation.
- Change in Short Form Health Survey – 36 Items (SF-36) scale from Baseline to each scheduled evaluation.
- Change in Insomnia Severity Index (ISI) from Baseline to each scheduled evaluation.
- Change in Hospital Anxiety and Depression Scale (HADS) from Baseline to each scheduled evaluation.

[redacted]

7.3. Number of Subjects

A total of 60 subjects will be randomized in a 1:1 ratio to LUCEMYRA (30 subjects) and placebo (30 subjects).

7.4. Duration of Subject Participation

The study duration for each subject will be up to 85 days. The Screening period is up to 28 days, the study drug administration period (including a 4-day study drug taper) is 21 to 27 days (the latter for those requiring an extended opioid taper), and a 30-day safety follow-up period.

7.5. Treatment Assignment

See Section 9.1.1.

7.6. Adjustment Criteria for Opioid Taper

See Section 9.3.

7.7. Sponsor Criteria for Study Termination

The Sponsor has the right to terminate the study or suspend enrollment at an individual site at any time. The Investigator will be notified by telephone and in writing if the Sponsor decides to suspend or terminate the study for any reason. The written notice will provide the Investigator with the reason that the site and/or study was suspended or terminated along with instructions on how the site should proceed.

Reasons for terminating the study may include, but are not limited to, the following:

- Discovery (from this or other studies) of an unexpected, serious, or unacceptable health hazard to subjects
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Evidence from the data that there are sufficient technical problems with the study to believe with a high degree of certainty that subjects are being exposed without a realistic expectation of evaluable data
- Subject enrollment is unsatisfactory
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data that threaten the scientific integrity of the study

Reasons for suspending enrollment at a site may include, but are not limited to, the following:

- Failure of the Investigator to comply with pertinent regulatory regulations
- Submission of knowingly false information from the research facility to the Sponsor
- Subject enrollment is unsatisfactory
- Insufficient adherence to protocol requirements or an unacceptably high rate of missing, erroneous, or improperly collected data that threaten the scientific integrity of the study

8. SELECTION AND DISCONTINUATION OF SUBJECTS

Before performing any study-specific procedure, the appropriate written informed consent and Health Insurance Portability and Accountability Act authorization must be obtained. A screening window of up to 28 days is provided to ensure the Investigator has adequate time to evaluate the subject's medical history, Screening laboratory tests, and other eligibility criteria. The Screening Visit may be conducted over the course of multiple visits, as needed. Investigators will be expected to maintain a Screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of Screening).

8.1. Subject Inclusion Criteria

1. Subject can provide written informed consent.
2. Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
3. Chronic non-cancer pain diagnosis such as low back pain, chronic neck pain, osteoarthritis, and prolonged post-surgical pain with daily pain for a minimum of 6 months.
4. Men and women at least 18 years of age at the time of signing informed consent.
5. Self-reported use of prescribed oral opioid medication(s), taken as tablets, pills, or capsules, of at least 50 morphine mg equivalent (MME) but no higher than 240 mg MME daily or near daily (≥5 days per week) for at least 12 weeks and seeking to discontinue their opioid medication. MMEs must be calculated using conversion factors recommended by the Center for Disease Control and Prevention to confirm the MED for the day is between 50-240 MME, including both breakthrough and around-the-clock pain medications, at Screening. The Medical Monitor must review and approve all baseline opioid use consumption and planned taper dosing regimens prior to Day -1.
6. Willing to be treated with non-opioid treatments for pain (in addition to opioid being tapered) for the duration of the study.
7. Subject agrees to follow the opioid taper plan, both in terms of the planned changes in the doses of opioid medications and the schedule for when opioid dose reductions will be made, as outlined by the Investigator and approved by the study Medical Monitor.
8. Subject agrees to partner with his or her pain physician on a subject-centered pain management program during the study.
9. If the subject is not normally a patient at the clinic, the subject's normal pain physician must sign an attestation that the physician agrees to resume the subject's pain management care following the study.
10. In generally good health, in the opinion of the Investigator, other than the underlying chronic pain syndrome at Screening based upon the results of a medical history, physical examination, 12-lead electrocardiogram, and laboratory profile.
11. Subject agrees to abstain from use of alcohol during the study.
12. Women of childbearing potential must have a negative pregnancy test at Screening.

13. Non-pregnant, non-lactating women who are postmenopausal, naturally or surgically sterile, or who agree to use acceptable contraceptive methods throughout the course of the study. Postmenopausal is defined as at least 12 months of amenorrhea, or at least 6 weeks following surgical menopause, defined as bilateral oophorectomy, tubal ligation, or hysterectomy. If of childbearing potential, subject must have been using birth control for at least 30 days and must agree to use one of the following methods of birth control:
    - Oral contraceptives
    - Patch
    - Barrier method (diaphragm, sponge, or condom) with spermicidal preparations
    - Intrauterine contraceptive system
    - Levonorgestrel implant
    - Medroxyprogesterone acetate contraceptive injection
    - Complete abstinence from sexual intercourse
    - Hormonal vaginal contraceptive ring; surgical sterilization, or partner sterile
14. If male, must agree to use one of the birth control methods listed in inclusion criterion 13 throughout the entire study period and for 90 days after the last dose of study drug. Must not donate sperm for 90 days after the last dose of study drug.
15. Able to speak, write, and understand English, understand the consent form, and be able to effectively communicate with the study staff.

8.2. Subject Exclusion Criteria

1. Has a primary diagnosis of complex regional pain syndrome, central neuropathic pain, somatoform pain syndromes, acute nerve root compression, any acute or progressive infectious, inflammatory, or neurological process.
2. Liver disease that requires medication or medical treatment, and/or AST or ALT levels greater than 3 times the ULN.
3. Gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment.
4. Has a diagnosis of epilepsy or history of seizures.
5. Has clinically significant abnormal laboratory value(s).
6. Self-reported or evidence of OUD or other substance use disorder within last 12 months prior to Screening using the Sponsor-provided Mini-International Neuropsychiatric Interview.
7. Urine toxicology screen positive for any illicit or non-prescribed opioid drugs prior to randomization.
8. Taking prescription methadone, buprenorphine, fentanyl rapid acting products, tapentadol, tramadol, butorphanol, meperidine, or levorphanol for any reason.

9. Known or suspected pregnancy, planned pregnancy, or lactation.
10. Any of the following cardiovascular abnormalities at Screening and before randomization:
    a. Resting heart rate ≥105 bpm or <55 bpm or symptomatic bradycardia;
    b. Resting systolic blood pressure ≥160 mmHg or <95 mmHg or symptomatic hypotension;
    c. Resting diastolic blood pressure ≥90 mmHg or <65 mmHg;
    d. Clinically significant abnormal electrocardiogram (eg, second- or third-degree heart block, uncontrolled arrhythmia; QT corrected by heart rate by Fridericia's method (QTcF) of ≥450 msec or a history of QT interval prolongation;
    e. New York Heart Association class III or IV; or
    f. History of myocardial infarction within 6 months of Screening.

    Medications taken for stable hypertension are permitted when dose/regimen has been consistent for a minimum of 3 months prior to screening.
11. Any severe or unstable psychiatric disorder including post-traumatic stress disorder, schizophrenia, bipolar disorder, major depression, substance abuse, or suicidality as determined by the Investigator.
12. Subject answers “yes” to “suicidal ideation” in prior 24 months to any items 1 through 5 on the C-SSRS, or subject answers “yes” to any lifetime “suicidal behavior” item on the C-SSRS.
13. Requires any of the following medications currently or within the past 30 days:
    a. Alpha-2 adrenergic agonists
    b. Antiarrhythmics
    c. Barbiturates
    d. Paraldehyde
    e. Stiripentol
    f. Psychoactive herbal preparations (including St. John’s Wort, Kratom, cannabis, and products containing cannabinoids)
    g. Aspirin (baby aspirin permitted if taking prior to study for prophylactic purposes)
14. Medications given for stable neuro-psychiatric diagnoses must be at a consistent dose/regimen for at least 30 days prior to randomization. CNS depressants in combination with lofexidine may increase the risk of hypotension and bradycardia. Acceptable regular, stable-dosing medications within this category include:
    a. Strong cytochrome P450-2D6 inhibitors, muscle relaxants, benzodiazepines, hypnotics, soporifics, tricyclic antidepressants, selective serotonin reuptake inhibitors, permitted anticonvulsants (including but not limited to gabapentin and pregabalin) must be taken at doses within the ranges recommended per product labeling.
    b. Subject must meet all other eligibility criteria while at the established stable dose/regimen and the medication must be continued at the same dose/regimen for the duration of the study drug administration period.

c. If taken on an as needed basis, subjects should discontinue medications in these categories 2 weeks prior to randomization and avoid use for the duration of the study drug administration period.
d. No more than 1 drug in each class should be part of the stable regimen (eg, subjects taking 2 permitted muscle relaxants, 2 anticonvulsants, 2 hypnotics, or 2 soporifics should be excluded until they are taking no more than 1 drug in each class).

15. Treatment with an investigational drug, device, or biological agent within 30 days before Screening or while participating in this study.
16. Any anticipated or scheduled surgery during the study period.
17. Major surgery within 30 days before Screening.
18. Metastatic cancer diagnosed within the previous year or diagnosis of any malignancy or neoplasm within 3 months prior to Screening, exclusive of basal cell carcinoma.
19. Has self-reported acquired immunodeficiency syndrome or self-reported human immunodeficiency virus positive status.
20. History of lack of tolerance or lack of response to LUCEMYRA which in the Investigator's opinion, makes the subject a poor candidate for the study.

8.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the study but are not subsequently enrolled. An enrolled subject is defined as one for which appropriate written informed consent has been obtained, who meets all eligibility criteria and is randomized to receive study drug. Subjects who fail to meet entry criteria may be eligible to rescreen at a later time.

8.4. Lifestyle Considerations

Subjects must refrain from consuming alcohol for the duration of the study.

CNS depressants in combination with lofexidine may increase the risk of hypotension and bradycardia. Subjects should be advised to be cautious prior to driving or operating heavy machinery if on concomitant CNS depressants during the study until they know how they react to study drug.

8.5. Subject Discontinuation Criteria

The Investigator or Sponsor may discontinue individual subjects from the study at any time if it is deemed clinically appropriate or for any reason, including the following:

- Cardiovascular events
  - QTcF >500 msec or >25% above screening value for both males and females.
  - New onset of clinically significant abnormal electrocardiogram (eg, second- or third-degree heart block or uncontrolled arrhythmia, prolonged QTcF interval).
  - Persistent signs or symptoms of hypotension, bradycardia, or hypoperfusion.

  - Single occurrence of symptomatic bradycardia (as assessed by the Investigator, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.
  - Medical intervention for cardiovascular event: Any medical intervention (nonmedication or medication inclusive) used for the treatment of any cardiovascular event, with the exception of a positional intervention in subjects displaying hypotension.
  - Any other clinically significant cardiovascular signs or symptoms that would place the subject at risk.
- Evidence of repeated alcohol use (eg, 2 positive alcohol tests after Screening) during the study. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study.
- More than 2 repeat occurrences of opioid rescue medication usage reported by the subject after Screening.
- An intolerable AE or SAE; the relationship to study drug must be recorded in source.
- Requirement for a treatment that is prohibited (Section 9.4) by the protocol.
- Noncompliance with the protocol, including but not limited to showing evidence of illicit drug use while participating in the study or refusal or inability to continue opioid taper schedule per protocol.
- Lost to follow up: If a subject is lost to follow-up, repeated attempts (defined as a minimum of 3 telephone calls, followed by sending a letter) will be made to reach the subject. If repeated attempts are unsuccessful, lost to follow up will be recorded in the subject's source document and electronic case report form (eCRF) as the reason for early discontinuation.
- Withdrawal of consent: Subjects are free to withdraw from the study at any time, regardless of their reasons, and without prejudice to further treatment. In such cases, the subject will be asked about the reason(s) for the decision to withdraw consent and the reason(s) clearly documented in the subject's source document and eCRF. Subjects withdrawing consent will be asked to complete early discontinuation procedures but have the option to refuse.

8.6. Early Discontinuation Visit

If a subject is discontinued from the study before completion, regardless of whether they have received study drug, the reason for discontinuation must be documented in the subject’s source document and eCRF. Whenever a subject is discontinued, the procedures/assessments listed for the EOS Visit in the Schedule of Assessments (Table 2 or Table 3) should be performed. If a subject discontinues on a scheduled visit, assessments completed at that visit should be entered into the eCRF for that scheduled visit. Assessments required for the EOS Visit that are not required at the scheduled visit (eg, a complete physical examination, clinical laboratory tests) should be completed and entered into the eCRF for the EOS Visit.

Subjects who prematurely discontinue the study will be instructed to taper study drug as described in Section 9.2.3 and to complete the at-home assessments for the study drug taper period (Table 4 or Table 5). Once discontinued, subjects may not re-enter the study.

8.6.1. Early Discontinuation Follow-up

If a subject discontinues from the study, the subject will be contacted 30 days after the last day of study drug administration, unless the subject withdraws consent and refuses post-study contact. This telephone contact will be recorded in the source document. If a subject discontinues participation due to an AE/SAE that is at least possibly related to study drug, the subject will be followed until the event has resolved, stabilized or otherwise explained.

9. TREATMENT OF SUBJECTS

9.1. Randomization and Blinding

9.1.1. Randomization

Eligible subjects will be randomized in a 1:1 ratio to LUCEMYRA or placebo. The randomization will be stratified by total opioid dose, in MED, captured at Screening (<90 MED, ≥90 MED). The subject's baseline opioid use and changes to doses for planned taper reductions should be submitted to and approved by the Medical Monitor prior to Day -1.

Subject randomization will be performed using a computer-generated randomization schedule, providing site staff with a randomization code linked to the study drug kit number to be used.

Hard copies of the study drug randomization schedule will be stored securely. Only medically necessary unblinding(s) will be allowed.

9.1.2. Maintaining and Breaking the Blind

All subjects, study personnel (including the Investigator, study coordinator(s), pharmacist/designee), and the Sponsor will be blinded to the identity of the study drug (active or placebo) administered to subjects.

An interim analysis will be conducted after approximately 30 subjects have completed or discontinued the study. For the interim analysis, the blind will be broken for the statistical programmers and Sponsor-designated reviewers. Unblinded results and individual subject treatment assignments will not be provided to subjects, Investigators, or other study personnel.

If an Investigator believes it is necessary to break the blind for reasons of subject safety, the Investigator must call the Sponsor's Medical Monitor (or designee) for consultation before unblinding. The decision to break the study blind should be made in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management. If, after discussion with the Medical Monitor, it is determined that the study drug should be disclosed, medical personnel will be able to access this information via the randomization system. Circumstances surrounding unblinding of subjects must be documented in writing. Subject completion and withdrawal causality should be assessed by the Investigator before unblinding of treatment assignment but must not delay treatment in an emergency situation. The date and reason for the unblinding must be recorded in the subject's source record.

Contact information for the Sponsor's Medical Monitor is as follows:

9.2. Treatments Administered

9.2.1. Multimodal Pain Management Plan

Prior to randomization, the Investigator and subject should discuss and agree upon a multimodal pain management plan to be instituted during and after the opioid taper to help the subject

manage pain. A plan must be agreed upon and recorded prior to randomization; however, it can be updated throughout the study, as needed. Updates made to the plan should be recorded. Planned pharmacologic and non-pharmacologic treatments should be in compliance with Section 9.4.

9.2.2. Study Drug Preparation

No special preparation is required before dosing of study drug.

9.2.3. Study Drug Administration

Day 1 dosing with study drug will begin in the clinic as 1 tablet (LUCEMYRA 0.18 mg/tablet or matching placebo) QID for a total daily dose of LUCEMYRA 0.72 mg or matching placebo. Subjects will be instructed to take their study drug in the morning upon awakening and then every 5 to 6 hours thereafter. Doses should be taken 5 to 6 hours apart and no more than 4 times per day. At the Day 1 Visit (Visit 1), the Investigator should schedule a phone call with the subject, to occur prior to the second dose of study drug on Day 2, to review the subjects at-home vital signs measurement and how the subject is feeling. The subject will be instructed to contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) while continuing to dose at home on Day 1. If the subject contacts the site on Day 1 reporting these symptoms, the Investigator should consider reducing the planned first daily dose on Day 2.

On Day 2 the subject will be instructed to take 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo), unless Day 1 dosing was not well-tolerated. The subject should contact the site if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) after the first daily dose. The Investigator will contact the subject on Day 2, prior to the second dose of the day, to review the subject's at-home vital signs measurement and how the subject is feeling. The Investigator should discuss with the subject any changes to dosing of study drug. Dosing instructions may include an increase to 3-tablets per dose due to subject report of intolerable opioid withdrawal symptoms, or a reduction back to 1 tablet per dose, due to intolerability of study drug.

On Day 3 and beyond, dosing will be at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms.

The dose of study drug may be increased to manage opioid withdrawal symptoms. If an increased dose of study drug is not well-tolerated, the dose can be decreased. A single dose of study drug should not exceed 4 tablets (LUCEMYRA 0.72 mg or matching placebo). The total daily dose of study drug should not exceed 4 tablets QID (LUCEMYRA 2.88 mg/day or matching placebo).

Dosing of study drug will continue for 5 days after the last opioid dose. Study drug will then be tapered over an additional 4 days. The following schedule will be followed over the study drug taper period:

- If taking 4 tablets QID (LUCEMYRA 2.88 mg/day or matching placebo) on fifth day after the last opioid dose
  - 3 tablets QID (LUCEMYRA 2.16 mg/day or matching placebo) for 1 day

  - 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo) for 2 days
  - 1 tablet QID (LUCEMYRA 0.72 mg/day or matching placebo) for 1 day
  - Study drug discontinued
- If taking 3 tablets QID (LUCEMYRA 2.16 mg/day or matching placebo) on fifth day after the last opioid dose
  - 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo) for 2 days
  - 1 tablet QID (LUCEMYRA 0.72 mg/day or matching placebo) for 2 days
  - Study drug discontinued
- If taking 2 tablets QID (LUCEMYRA 1.44 mg/day or matching placebo) on fifth day after the last opioid dose
  - 1 tablet QID (LUCEMYRA 0.72 mg/day or matching placebo) for 2 days
  - 1 tablet twice daily (LUCEMYRA 0.36 mg/day or matching placebo) for 2 days
  - Study drug discontinued
- If taking 1 tablet QID (LUCEMYRA 0.72 mg/day or matching placebo) on the fifth day after the last opioid dose
  - 1 tablet twice daily (LUCEMYRA 0.36 mg/day or matching placebo) for 4 days
  - Study drug discontinued

9.3. Adjustment Criteria for Opioid Taper

Subjects will be tapered from their baseline total daily dose of opioid (calculated as MED) over a 14-day period. The opioid dose will be decreased as close as possible to achieve the following dose reduction targets: 50% from the baseline MED beginning with the last dose of the day on Day -1, an additional 25% of the baseline MED beginning with the first dose of the day on Day 6, and a final 25% of the baseline MED (to dose of zero) beginning with the first dose of the day on Day 13 (Figure 1). Reminders for opioid dose reduction may be done via phone, text, or other electronic message.

Opioid dosing to achieve the required dose reductions in accordance with the protocol defined taper must be planned during Screening. Any changes in opioid prescription to facilitate the protocol taper should be discussed with the subject's primary pain physician, when applicable, and prescribed in advance of randomization. The Investigator should work with a preferred pharmacy informed about the subject's participation in a clinical trial in order to fulfill prescribing needs to facilitate the opioid taper. Opioid prescriptions should be written to accommodate the planned taper, based on the following considerations:

- Subjects should be maintained on the same opioid molecule throughout the taper and not converted to new molecules.
- Priority should be given to eliminating opioid medications for breakthrough pain as part of the first opioid dose reduction (50% of baseline MED) if possible. If not possible, dosing of opioid medications being taken for breakthrough pain should be

changed to be part of a fixed dose regimen appropriate to achieve the target MED reduction.

- Opioid dose reductions should be as close as possible to the nominal reductions specified per protocol (ie, 50% or 25% reduction). Round up on the dose of the available opioid formulation if unable to adjust exactly to meet nominal MED reduction criteria.

The subject's baseline opioid regimen and MED calculation as well as the opioid regimen planned to achieve each taper step should be submitted to and approved by the Medical Monitor prior to Day -1. The Investigator will discuss and confirm the subject's agreement to comply with the opioid dosing regimen for each opioid taper step based on the Medical Monitor-approved plan.

Non-opioid medications taken during the study should be in compliance with the allowed concomitant treatments in Section 9.4. Opioid dose reductions may not occur on a Friday or Saturday unless clinic can accommodate subjects on Saturday and Sunday. Qualified study personnel at the clinic should call the subject the day after the opioid dose is decreased (except on Day 1 since the subject will come to the clinic) to review the subject's at-home vital signs measurement and how the subject is feeling. Upon review by the Investigator or designee, changes to dosing of study drug should also be discussed with the subject, if applicable.

Subjects who experience intolerable withdrawal symptoms despite increasing their dose of study drug to the maximum tolerated dose (not to exceed 4 tablets QID) will be allowed to pause the opioid taper once. Pausing the opioid taper includes either a return to the last stable opioid dose for the remainder of the current opioid dose reduction period, or remaining on the current opioid dose instead of reducing at the next scheduled reduction, resulting in an overall extended opioid taper period and study duration. For example, if a subject experiences intolerable withdrawal at the second opioid dose reduction step [25% of baseline MED], they may either 1) return to the first reduction dose [50% of baseline MED]) or, 2) when the withdrawal persists until the next scheduled reduction step, they may remain for longer at the current opioid dose [25% of baseline MED]. In both cases, the taper must be resumed following the single pause in accordance with the protocol schedule. Subjects who cannot or are unwilling to continue the opioid taper after one pause will be discontinued from the study.

Decisions on whether to pause the opioid taper will be based on subject request and an evaluation (in clinic or over the phone) of the subject's status by the Investigator. Subjects may request to pause the opioid taper due to opioid withdrawal symptoms. If the subject's last COWS score is ≥5 OR if based on i) the Investigator's discussion with the subject, ii) review of ongoing subject-reported withdrawal related AEs, and iii) most recent scores for subject reported withdrawal scales, the subject's desire to pause the taper is related primarily to opioid withdrawal discomfort in the Investigator's opinion, then the taper may be paused. In the event that the Investigator assesses the subject's desire to pause the taper to be primarily related to pain, a taper pause will not be permitted; however, if the subject is willing to continue the per protocol taper, recommended modifications to their concurrent pain management plan should be discussed and recorded. Subjects unwilling to continue the per protocol taper and not experiencing opioid withdrawal to permit a single pause should be discontinued from the study.

Study drug dosing for an opioid taper pause will remain at the discretion of the Investigator, as guided by subject tolerability of study drug and opioid withdrawal symptoms. The dose of study drug can be increased or decreased as needed.

9.4. Prior and Concomitant Treatments

Prior treatments are defined as treatments taken within 30 days before randomization, regardless if usage continues after randomization. Concomitant treatments are defined as treatments taken after randomization.

Prior treatments will be documented on the eCRF. The reported treatments will be reviewed and approved by the Investigator/study physician/assigned staff for entry into the study.

All concomitant treatments will be recorded in subject diaries and on the eCRF along with dose, dates of administration, and reason for use.

9.4.1. Prohibited Treatments

The following treatments are not allowed within 30 days prior to Screening or throughout the study:

- Alpha-2 adrenergic agonists
- Antiarrhythmics
- Barbiturates
- Paraldehyde
- Stiripentol
- Psychoactive herbal preparations (including St. John's Wort, Kratom, cannabis, and products containing cannabinoids)
- Aspirin (baby aspirin permitted if taking prior to study for prophylactic purposes)

9.4.2. Permitted Treatments

Medications taken for stable hypertension are permitted when dose/regimen has been consistent for a minimum of 3 months prior to screening.

Strong cytochrome P450-2D6 inhibitors, muscle relaxants, benzodiazepines, hypnotics, soporifics, tricyclic antidepressants, selective serotonin reuptake inhibitors, permitted anticonvulsants (including but not limited to gabapentin and pregabalin) and medications given for stable neuro-psychiatric diagnoses at a consistent dose/regimen for at least 30 days prior to randomization are permitted in accordance with exclusion criterion 14. These medications must be continued at the same dose/regimen for the duration of the study drug administration period. In the event the subject reports new regular or chronic use of any of the above-mentioned medication (whether over-the-counter or prescription), eligibility to continue in the study must be evaluated in consultation with the Medical Monitor.

CNS depressants in combination with lofexidine may increase the risk of hypotension and bradycardia. Subjects should be advised to be cautious prior to driving or operating heavy

machinery if on concomitant benzodiazepines during the study until they know how they react to study drug.

Other concomitant treatments are permitted throughout the study, as clinically warranted, for the treatment of symptoms related to opioid withdrawal. The following treatments may be used in this study as appropriate:

- Guaifenesin (for cough).
- Alumina, magnesia, and simethicone (for emesis and nausea)
- Dioctyl sodium sulfosuccinate and psyllium hydrocolloid suspension (for constipation)
- Bismuth sulfate (Pepto-Bismol®) (for diarrhea)
- Diphenhydramine, melatonin and zolpidem (for insomnia)

Subjects taking a prescribed medication for opioid-induced constipation (OIC) prior to Screening may continue to use the medication on an as needed basis. Subjects should be advised to consider avoiding use of OIC medications during the opioid taper to not exacerbate withdrawal-induced diarrhea.

Use of concomitant treatments to treat withdrawal symptoms will be recorded daily by subjects using the diary.

Subjects experiencing pain requiring medication will be allowed to use the following treatments:

- Acetaminophen (up to 4 g per day, dispensed as 500-mg tablets). Subjects receiving acetaminophen-containing opioid products should not receive acetaminophen as part of their pain management plan.
- Nonsteroidal anti-inflammatory drugs provided dosing is within product label recommendations
- Non-opioid topical treatments (compounded or non-compounded)
- Non-prescription medications that are often taken to treat pain, depression and anxiety (excluding St. John's Wort, Kratom, cannabis and products containing cannabinoids)
- Non-pharmacologic modalities/interventions (eg, physical therapy, psychotherapy, hypnosis, acupuncture, massage, chiropracty, ice packs, moist or dry heat, etc)

Use of opioid medication as a rescue for breakthrough pain should be strongly discouraged. Subjects experiencing intolerable pain during the study should be instructed to call the site to discuss further modifications to their non-opioid pain management plan. Subject reported use of any opioid rescue medication should be recorded and discussed by the Investigator and Medical Monitor to assess eligibility to continue in the study and will include a review of safety concerns, impact on effectiveness measures, and consistency with required MED-percent reduction targets. More than 2 repeat occurrences of opioid rescue medication usage reported by the subject will require study discontinuation.

Use of any medication or non-pharmacologic intervention or treatment for pain will be recorded daily by subjects using the diary.

9.5. Treatment Compliance

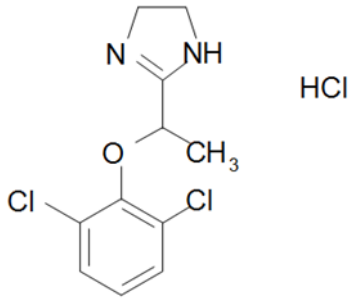
Self-dosing compliance will be evaluated at each clinic visit by pill count and subject's diary report of dosing. Subjects will be instructed to call the Investigator's office before taking the next dose of study drug if they notice any symptoms of hypotension, bradycardia, and/or orthostasis, especially when standing from a sitting or lying position. The study physician or assigned staff will determine if the next dose should be delayed, skipped, or the subject should be seen. Any change in prescribed dosing will be recorded in source documents and confirmed also by pill count and subject report at the next visit.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Lofexidine Hydrochloride

Lofexidine hydrochloride (HCl) tablets contain lofexidine, which is a selective adrenergic α2 receptor agonist, as the HCl salt. Lofexidine HCl is chemically designated as 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride with a molecular formula of $C_{11}H_{12}Cl_2N_2O$•HCl. Its molecular weight is 295.6 and its structural formula is:



The description of the study drug is presented in Table 8.

Table 8: Investigational Product

	Investigational Product
Product Name:	Lofexidine HCl (LUCEMYRA™)
Dosage Form:	Tablet
Unit Dose:	Each LUCEMYRA tablet is 0.18 mg. See Section 9.2.3 for dose adjustments and taper regimens.
Route of Administration:	Oral
Physical Description:	Lofexidine HCl is a synthetic product and has the chemical designation of 2 [1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1H- imidazole monohydrochloride. Lofexidine HCl will be supplied in peach-colored tablets containing 0.18 mg of active medication for oral administration.
Manufacturer:	[redacted]

HCl = hydrochloride; [redacted] QID = 4 times daily

10.1.2. Placebo

Placebo tablets will be identical in appearance to LUCEMYRA tablets.

10.2. Study Drug Packaging and Labeling

The study drug will be packaged in bottles of 112 tablets. The package product label will include the following information:

- Sponsor's name
- Protocol number
- A unique package number for purposes of study drug accountability
- A description of the study drug (ie, "Lofexidine or Placebo")
- Statement that the study drug is for investigational use only

10.3. Study Drug Storage

Lofexidine HCl and placebo should be stored in the original package at controlled room temperature 20 to 25°C (68 to 77°F), with excursions permitted between 15 to 30°C (59 to 86°F).

10.4. Study Drug Preparation

See Section 9.2.2.

10.5. Administration

See Section 9.2.3.

10.6. Study Drug Accountability

All study drug required for completion of this study will be provided by the Sponsor. Accurate recording of all study drug received, dispensed, administered, and returned will be maintained by study site personnel. All study drug is to be used only as described by this study protocol by appropriately licensed Investigators named in Form FDA 1572.

Study staff should retain the original individual containers, including those empty, partially empty, or full. Study drug must be inventoried. If any study drug is lost or damaged, its disposition should be documented. Unused study drug will be retained at the participating sites to enable a full study drug inventory by the sites' respective monitors [redacted]

10.7. Study Drug Handling and Disposal

At the end of the study, all unused study drug must be inventoried. If any study drug is lost or damaged, its disposition should be documented. Unused study drug will be retained at the participating sites pending instructions for disposition by the Sponsor at the end of the study.

11. ASSESSMENTS OF EFFECTIVENESS

11.1. Numeric Rating Scale (NRS) of Pain Intensity

The NRS of pain intensity is a unidimensional, segmented numeric version of the visual analog scale. A subject selects a whole number (0 to 10) that best indicates the intensity of his/her pain. The format consists of a horizontal line which is anchored by terms defining pain levels where 0 represents no pain and 10 represents worst pain imaginable.

At bedtime, subjects will answer the following questions regarding daily pain intensity:

> How would you rate the average pain due to your current chronic pain condition over the last 24 hours?
>
> How would you rate the worst pain due to your current chronic pain condition over the last 24 hours?
>
> Sometimes when people come off opioids, they feel aches and pains all over their body. How would you rate the average pain, all over your body over the last 24 hours?
>
> Sometimes when people come off opioids, they feel aches and pains all over their body. How would you rate the worst pain, all over your body over the last 24 hours?

NRS chronic pain scales will be completed daily at home before bedtime beginning at Screening through the 30-day follow-up phone call and at clinic visits (and Early Termination, if applicable). NRS all over body pain scales will be completed at home before bedtime beginning on Day 1 through the EOS Visit and at clinic visits (and Early Termination, if applicable). NRS scales completed at the Day 1 Visit (Visit 1) should be completed prior to the first dose of study drug.

A copy of the NRS is provided in Section 16.1.

11.2. Clinical Opiate Withdrawal Scale (COWS)

The COWS will be used to assess effectiveness of LUCEMYRA in alleviation of opioid withdrawal [Wesson 2003]. The COWS is a clinician-administered instrument that rates 11 common opioid withdrawal signs and symptoms. These include: resting pulse rate; sweating; restlessness; pupil size; bone or joint aches; runny nose or tearing; gastrointestinal upset; tremor; yawning; anxiety or irritability; and gooseflesh skin. Lower total scores indicate a more positive clinical outcome.

The COWS completed at the Day 1 Visit (Visit 1) should be completed prior to the first dose of study drug.

A copy of the COWS assessment tool is provided in Section 16.4.

11.3. Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)

The SOWS-Gossop scale assesses subjective symptoms of opioid withdrawal [Vernon 2016, Gossop 1990]. It is a subject-rated scale consisting of 10 items that are scored on a 4-point scale of 0 = none, 1 = mild, 2 = moderate, and 3 = severe (minimum score of 0, maximum score of 30) (Table 9). The overall score is the simple sum of the 10 item scores. Lower observed values in

SOWS-Gossop scores indicate a more positive clinical outcome. The SOWS-Gossop will be completed daily beginning at Day 1 at home at bedtime and at clinic visits (and Early Termination, if applicable). The SOWS-Gossop completed at the Day 1 Visit (Visit 1) should be completed prior to the first dose of study drug.

Table 9: SOWS-Gossop Scoring Method

	Score			
Condition	**None**	**Mild**	**Moderate**	**Severe**
Feeling sick	0	1	2	3
Stomach cramps	0	1	2	3
Muscle spasms/twitching	0	1	2	3
Feeling of coldness	0	1	2	3
Heart pounding	0	1	2	3
Muscular tension	0	1	2	3
Aches and pains	0	1	2	3
Yawning	0	1	2	3
Runny eyes	0	1	2	3
Insomnia/problem sleeping	0	1	2	3

SOWS-Gossop = Short Opiate Withdrawal Scale of Gossop
Note: possible score range is 0 to 30.

A copy of the SOWS-Gossop is provided in Section 16.5.

11.4. Subjective Opiate Withdrawal Scale of Handelsman (SOWS-H)

The SOWS-H scale assesses subjective symptoms of opioid withdrawal [Handelsman 1987]. It is a subject-rated scale consisting of 19 items that are scored on a 5-point scale of 0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, and 4 = extremely. The overall score is the simple sum of the 19 item scores. Lower observed values in SOWS-H scores indicate a more positive clinical outcome. The SOWS-H will be completed daily beginning at Day 1 at home at bedtime and at clinic visits (and Early Termination, if applicable). The SOWS-H completed at the Day 1 Visit (Visit 1) should be completed prior to the first dose of study drug.

Item 16 of the SOWS-H was rephrased to be more appropriate for this population [FDA 2014].

A copy of the SOWS-H is provided in Section 16.6.

11.5. Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-reported screening tool for anxiety and depression in nonpsychiatric clinical populations. The scale consists of 14 items (7 each for anxiety and depression), each rated on a 4-point scale. Responses are based on the relative frequency of symptoms over the preceding week. Possible scores range from 0 to 21 for each subscale. An analysis of scores on the 2 subscales supported the differentiation of each mood state into 4 ranges: non-cases (scores 0 to

7), mild cases (scores 8 to 10), moderate cases (scores 11 to 15), and severe cases (scores 16 or higher) [Zigmond 1983].

A copy of the HADS is provided in Section 16.7.

11.6. Insomnia Severity Index (ISI)

The ISI is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The recall period is the last 2 weeks and the dimensions evaluated are: severity of sleep onset, sleep maintenance and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item, yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0–7); sub-threshold insomnia (8-14); moderate insomnia (15–21); and severe insomnia (22–28) [Bastien 2001].

A copy of the ISI is provided in Section 16.8.

11.7. Modified Clinical Global Impression – Subject Version (MCGI-S)

The MCGI-S includes 2 items:

- A 7-point scale that allows subjects to rate the severity of opiate withdrawal symptoms.
- A 4-point scale that allows subjects to rate the degree of side effects from their study drug.

The MCGI-S will be completed once daily beginning at Day 1 at home at bedtime and at clinic visits (and Early Termination, if applicable).

A copy of the MCGI-S is provided in Section 16.9.

11.8. Modified Clinical Global Impression – Rater Version (MCGI-R)

The MCGI-R includes 2 items:

- A 7-point scale that allows clinicians to rate the severity of a subject's opiate withdrawal symptoms.
- A 4-point scale that allows clinicians to rate the degree of a subject's side effects from study drug.

A copy of the MCGI-R is provided in Section 16.10.

11.9. EuroQol 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L is a health state utility instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-5L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which are rated on 5 levels of severity. Responses to the 5 items encode a discrete health state which is mapped to a preference (utility) specific for different societies. Subjects also rate their perception of their overall health on a separate visual analogue scale.

A copy of the EQ-5D-5L is provided in Section 16.11.

11.10. Short Form Health Survey – 36 Items (SF-36)

The SF-36 assesses 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health.

A copy of the SF-36 is provided in Section 16.12.

11.11. Subject Satisfaction Questionnaire

Subject satisfaction will be scored from 0 (very satisfied) to 4 (very dissatisfied) based on the following question: Overall, how would you rate your satisfaction with the treatment you received in this study to help you discontinue using your opioid?

0 = very satisfied

1 = satisfied

2 = neither satisfied nor dissatisfied

3 = dissatisfied

4 = very dissatisfied

A copy of the Subject Satisfaction questionnaire is provided in Section 16.13.

11.12. Subject Interview

The primary purpose of the qualitative interview is to provide additional data to augment the data collected from quantitative instruments to assess withdrawal, pain intensity, quality of life, treatment satisfaction, and others. The results of this interview will provide information that may be useful for planning future studies to evaluate the safety and efficacy of LUCEMYRA in the setting of an opioid taper in subjects with chronic non-cancer pain. The interview will be conducted via a centralized interviewer through a phone call. The interview should take place no more than 5 days after the EOS Visit.

The qualitative interview will be designed to collect information about: (1) subjects' experiences with opioid withdrawal syndrome while gradually tapering their opioids and the relevance, utility, and interpretability of the opioid withdrawal scales used in the study to assess their opioid withdrawal symptoms; (2) factors that may facilitate or interfere with subject recruitment and retention in a large clinical trial for the discontinuation of opioid therapy; (3) subjects' experiences in the clinical trial, including questions about how they would improve the experience and whether they would participate in future trials; and (4) subjects' experiences and preferences regarding the treatments administered in the clinical trial. Questions will be organized from more general (open-ended) to more specific.

Audio from each interview will be recorded.

12. ASSESSMENTS OF SAFETY

Safety assessments will be performed at the time points outlined in Table 2, Table 3 and Table 4.

12.1. Safety Parameters

12.1.1. Demographic/Medical History

The medical history will include demographic information, current co-morbidities, relevant past illnesses, and surgical procedures performed within the prior 6 months. Assessments will also include characterization of the subject's baseline pain state, condition, opioid use, and opioid withdrawal history.

12.1.2. Vital Signs

Orthostatic vital signs will be measured in-clinic. Orthostatic vital signs will be measured first after the subject has been sitting for at least 5 minutes (systolic/diastolic blood pressure, pulse, and temperature) and then after the subject has been standing for at least 3 minutes (systolic/diastolic blood pressure and pulse). On Day 1, orthostatic vital signs should be assessed pre-dose and 1-hour post-dose of study drug. A post-dose assessment is not required after Day 1. When repeat vital signs are performed, temperature does not need to be collected (only systolic/diastolic blood pressure and pulse).

Resting vital signs (systolic/diastolic blood pressure and pulse) only will be measured at home using a vital sign monitor during phone calls after dose reductions, and every day during the 4-day study drug taper through the EOS Visit. Resting vital signs will be measured after the subject has been sitting quietly for at least 5 minutes and, during the study drug taper and after, will be taken twice daily, once in the morning and once in the evening.

Subjects should contact the Investigator if they experience signs or symptoms of hypotension, bradycardia, or orthostasis (eg, lightheadedness, slow heart rate, dizziness, feeling faint at rest or when standing up) or hypertension (eg, pounding headache, dizziness, palpitations). Subjects should contact the Investigator if they record an at-home vital signs measurement reaching or exceeding a systolic blood pressure of ≥180 mmHg, diastolic blood pressure ≥105 mmHg, or heart rate of ≥120 bpm. Symptomatic episodes of hypotension should be captured as an AE. Confirmed instances of meeting criteria for hypertension should be captured as AEs regardless of symptomology.

During phone calls, the Investigator should ask the subject for a vital sign measurement and review subject-measured at-home vital signs.

Blood pressure and pulse measurements taken in-clinic or at-home should be repeated after a 15-30 minute rest if they meet the following criteria:

- Hypertension: systolic blood pressure of ≥180 mmHg, diastolic blood pressure ≥105 mmHg, or heart rate of ≥120 bpm
- Hypotension: systolic blood pressure of ≤90 or a diastolic blood pressure of ≤60, and a heart rate <50 bpm

If the subject has a confirmed systolic blood pressure of ≥180 mmHg, diastolic blood pressure ≥105 mmHg, or heart rate of ≥120 bpm, and is symptomatic, the subject should be seen (preferably by the Investigator).

If the subject has a confirmed systolic blood pressure of ≤90 or a diastolic blood pressure of ≤60, and a heart rate <50 bpm, and is symptomatic, the Investigator should advise the subject to either decrease or hold the next dose of study drug.

12.1.3. Weight and Height

For measuring weight, a scale with appropriate range and resolution will be used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Height will be measured without shoes.

12.1.4. Physical Examination

Physical examinations will be performed by the Investigator or qualified designee. A complete physical examination will include the oral cavity, head, eyes, ears, nose and throat, cardiovascular system, lungs, abdomen (liver/spleen), extremities, skin, neuropsychiatric mental status and sensory/motor status, musculoskeletal system, and general appearance. A brief physical examination will consist of cardiac and pulmonary auscultation.

The individual performing the physical examination will characterize findings as either normal or abnormal. Clinically significant abnormal physical examination findings found during Screening should be reported on the medical history eCRF. Clinically significant abnormal physical examination findings found after the subject has received study drug will be reported as AEs on the eCRF.

12.1.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS measures both suicidal ideation and suicidal behavior. When administered, all responses recorded on the scale must be provided by the subject either verbally or by gesture. The Baseline version of the C-SSRS (Section 16.2) will be used during Screening to assess lifetime suicidality. At all other protocol-specified time points, the C-SSRS – Since Last Visit version (Section 16.3) will be used to assess the subject's suicidality since the last assessment. Any changes from baseline assessment should be reported as an AE on the eCRF.

If any item(s) on the C-SSRS are answered with "yes", a physician Investigator must review the subject's responses in order to determine the subject's study eligibility, or continued participation, and potential need for referral to a mental health professional. A significant risk of suicide is defined as a "yes" in answer to: a) questions 4 or 5 on the suicidal ideation section, or b) any questions on any item in the suicidal behavior section. This must be reported as an SAE and followed up accordingly. Additionally, if a subject responds "yes" to any of the suicidal ideation questions 1 to 3, the Investigator should apply clinical judgment to determine the need for reporting as an AE or SAE and the need for any referral.

12.1.6. Electrocardiogram

Standard 12-lead electrocardiograms will be performed. Electrocardiograms should be performed before blood draws and after the subject has rested quietly for at least 10 minutes in a supine position. The Investigator (or Investigator's designee who is a physician) will interpret the electrocardiogram and will record his/her global interpretation of the electrocardiogram (ie, normal or abnormal) on the tracing. Each electrocardiogram tracing must also include the signature of the Investigator and the date that the electrocardiogram was interpreted. If the global interpretation is abnormal, the Investigator will indicate on the tracing whether the abnormality is clinically significant or not clinically significant. Clinically significant electrocardiograms should be repeated up to 2 times after another rest of at least 10 minutes. A copy of each electrocardiogram and the physician's assessment will be filed with the source documents.

During the study, when any QTcF interval is ≥495 msec, 2 additional electrocardiograms should be taken at 10- to 15-minute intervals (electrocardiograms should be done after the subject has been resting for at least 10 min). The QTcF interval on all electrocardiograms should be confirmed by the Investigator. If it is determined that 2 of the 3 QTcF intervals exceed 500 msec or >25% above screening value, then the subject will be discontinued from the study.

12.1.7. Laboratory Assessments

See Table 10 for the list of clinical laboratory tests to be performed. Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. All study-required laboratory assessments will be performed by a central laboratory.

The Investigator must review the laboratory report and document this review. The laboratory reports must be filed with the source documents. Clinically relevant changes during the study that result in changes in study drug, study participation, or concomitant treatment use will be recorded as AEs on the eCRF. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

All testing for opioids in the urine is qualitative, including confirmatory testing. Qualitative results will be reported for opioids by class with dipstick tests and by opioid analyte for urine specimens sent to the Sponsor's central laboratory. No quantitative testing for opioids will be performed or reported throughout the study.

All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual.

Table 10: Clinical Laboratory Tests

Hematology[a]	**Chemistry**[b]	**Urinalysis**
Hemoglobin	Cholesterol	Color
Hematocrit	Triglycerides	Clarity
Red blood cells	Sodium	pH
Mean corpuscular volume	Potassium	Specific gravity
Mean corpuscular hemoglobin	Chloride	Protein
Mean corpuscular hemoglobin concentration	Carbon dioxide	Glucose
Red blood cell distribution width	Glucose	Ketones
White blood cell count	Creatinine	Bilirubin
Neutrophils	Albumin	Nitrite
Lymphocytes	Total protein	Blood
Monocytes	Calcium	Urobilinogen
Eosinophils	Phosphorus	White blood cell count
Basophils	Aspartate aminotransferase	Red blood cell count
Platelet count	Alanine aminotransferase	Epithelial cells
Prothrombin time	Gamma-glutamyl transpeptidase	Bacteria
Activated partial thromboplastin time	Total bilirubin	Casts
	Lactate dehydrogenase	Crystals
	Alkaline phosphatase	Leukocyte esterase
	Blood urea nitrogen	
	Thyroid-stimulating hormone	
	Free thyroxine	

[a] Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (eg, Vacutainer™).
[b] Blood will be collected in serum separation evacuated venous blood collection tubes (eg, Vacutainer™) and serum separated according to standard procedures.

Urine testing will be done for ethyl glucuronide, a metabolite of ethanol that is stable in urine and detectable up to 3 days after ingestion of alcohol. The first positive test for alcohol during the study should prompt subject counseling about the important in abstaining from alcohol use during the study. More than 2 positive tests for alcohol after Screening will require discontinuation from the study.

Qualitative urine drug screening for illicit use will be performed at Screening for all subjects and at every clinic visit for the following drugs: amphetamines/methamphetamines, cocaine, barbiturates, opiates, benzodiazepines, cannabinoids, methadone, and buprenorphine. The central lab will provide standard sets of urine drug screen “dipsticks” for use across all sites. Quantitative confirmatory testing for illicit substances may be performed when results contradict subject self-report. Confirmed evidence of use of illicit substances will require discontinuation from the study.

A urine pregnancy test designed to measure human chorionic gonadotropin will be performed for all female subjects, regardless of childbearing potential.

12.1.7.1. Evaluation of Treatment-emergent Elevated Liver Function Tests

The following assessments should be performed in the event one of the following laboratory results occurs after study drug administration:

- ALT >3 × ULN OR
- AST >3 × ULN OR
- Total bilirubin >2 × ULN

1. Review of medical history and concomitant treatment or drug use.

In this study of opioid withdrawal symptoms during opioid dose tapering, the occurrence of significant hepatic injury is most likely to arise from etiologies that are extraneous to the treatment protocol. Study subjects, though voluntarily seeking reduction or cessation of chronic opioid treatment, are known to have both physiological as well as psychologic responses to large reductions in opioid dose. These responses may include maladaptive behaviors that can result in hepatotoxic outcomes; thus, initial medical history and laboratory investigation should focus on whether any of the following has occurred:

- Hepatoxic doses of acetaminophen with or without co-consumption of alcohol

  Note: If the medical history confirms high dose acetaminophen use, ***immediately*** refer the subject to a hospital emergency room where a serum tox screen should be performed that includes acetaminophen levels. Acetaminophen toxicity can be subtle yet does respond to acute intervention.

- Hepatic injury due to acute binge alcohol consumption
- Acute hepatitis due to viral transmission from the unsterile injection of illegally obtained narcotics
- Hepatoxicity arising from the compensatory use of legal or illegal herbal supplements taken to address opioid withdrawal syndrome

2. Assess for symptoms and perform repeat laboratory tests within 48-72 hours.

Determine if subject is symptomatic (ie, assess for nausea, vomiting, anorexia, abdominal pain, or fatigue) and perform repeat testing (including ALT, AST, international normalized ratio, total and direct bilirubin, viral hepatitis panel, a urine drug screen, and if necessary, urine test for ethyl glucuronide) within 48-72 hours. A urine test for ethyl glucuronide is needed as part of repeat laboratory testing if alcohol use is suspected (ie, necessary if Visit 4 urine test results for ethyl glucuronide showed presence of the metabolite in the urine).

If symptoms persist OR repeat testing shows either of the following, initiate close observation follow-up plan:

- ALT and/or AST >3 × ULN for subjects with normal baseline measures OR
- ALT and/or AST of a 2-fold increase above baseline values for subjects with elevated values before study drug exposure.

3. Develop and implement a close observation follow-up plan (if applicable).

A close observation follow-up plan should be determined as appropriate for the subject by the Investigator in consultation with the Medical Monitor. Close observation procedures include, but are not limited to, the following:

- Repeating liver enzyme and serum bilirubin tests 2-3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- In the absence of an etiology, consider evaluating for autoimmune or alcoholic hepatitis, nonalcoholic steatohepatitis, hypoxic/ischemic hepatopathy, and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All subjects meeting criteria for elevated liver function tests following study drug administration should be followed until all abnormalities return to normal or to the baseline state.

4. Discontinuation from study drug with safety follow-up through EOS period or until AE has resolved.

Subjects should be discontinued from the study drug if:

- ALT or AST >5 × ULN in 2 consecutive tests.
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

12.2. Adverse and Serious Adverse Events

AEs will be assessed by asking the subject, “How have you been feeling since I saw you last?” The study physician will review current AEs with the subject and assess any AEs unresolved from the previous visit. The type of AE, whether serious or non-serious, severity, and the relationship to study drug will be recorded by the physician in the subject’s source document and eCRF after each AE assessment. The physician’s clinical judgment will be used to assess the severity and relatedness of each AE.

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject participating in a clinical study. An AE includes any noxious, pathologic, or unintended change in anatomic, physiologic, or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes. An unexpected AE is an AE not identified in nature, severity, or frequency in the current package insert for LUCEMYRA [USWM 2018].

Anticipated fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening need not be considered AEs. Study events occurring after signing

informed consent, but prior to study drug administration, are to be documented in the subject's medical history source and eCRF.

For any pain-related AE, the subject will be questioned regarding changes since pre-study pain.

12.2.1.2. Serious Adverse Event

An SAE is defined as an AE meeting any of the criteria, in the view of either the Investigator or Sponsor, in Table 11.

Table 11: Definition of Serious Adverse Event

Serious Adverse Event Criterion	Guidance
Results in death	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the investigational product. The death of a subject enrolled in a study is per se not an event, but an outcome.
Is life-threatening	The term life-threatening refers to an adverse event in which the subject was at immediate risk of death at the time of the event. It does not refer to an event, which may have caused death if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. Overnight stay for observation, stay at emergency room, or treatment on an outpatient basis do not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (ie, if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute a serious adverse event. Hospital admissions and/or surgical operations planned before study inclusion are not considered adverse events, if the illness or disease existed before the subject was enrolled in the study, provided that the condition did not deteriorate during the study.
Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. In doubt, the decision should be left to medical judgment by the Investigator.
Is a congenital anomaly/birth defect	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the investigational product.
Is an important medical event	Important medical events are events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Examples of important medical events include adverse events that suggest a significant hazard, contraindication or precaution, occurrence of malignancy or development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether events qualify as medically important.

12.2.2. Relationship of Adverse Event to Study Drug

For each AE, the Investigator must assess the attribution of the study drug to the AE and determine whether the AE is or is not related to the study or test drug as defined below. When in doubt, the AE should be considered at least "possibly related" until further evidence becomes available to refute this assessment.

Definitely Not Related

Subject did not receive the test drug, the temporal sequence of the AE onset relative to administration of the test drug is not reasonable, or there is another obvious cause of the AE.

Possibly Related

There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, but the AE could have been due to another equally likely cause.

Probably Related

There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, and the AE is more likely explained by the test drug than by any other cause.

Definitely Related

There is evidence of exposure to the test drug, the temporal sequence of the AE onset relative to administration of the test drug is reasonable, and the AE is more likely explained by the test drug than by any other cause, and the AE shows a pattern consistent with previous knowledge of the test drug or test drug class.

12.2.3. Recording Adverse Events

All AEs and details for the events will be recorded in the subject's source document and eCRF. An AE should be documented in terms of a medical diagnosis and reported in standard medical terminology when possible. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed or reported. It is important for the Investigator to only record 1 AE per line on the eCRF. Combination events (eg, nausea/vomiting), should be entered as 2 events.

The Investigator must determine the intensity of the AE as defined by:

- Mild: no medical interventions required, short lasting discomfort, and does not interfere with subject's daily activities
- Moderate: activity may be limited, and subject may require minimal medical therapy, intervention, or assistance
- Severe: definitely limits subject's daily activity that may require hospitalization and or intervention/therapy assess whether or not the study drug caused the AE

The Investigator will record whether the AE or AEs led to discontinuation of the subject from the study, record the outcome of the AE (unresolved, resolved, resolved with sequelae, death, or unknown), and determine if the AE is serious.

For this study, AEs and SAEs will be collected beginning with the start of dosing on Day 1 and will end 30 days after the last dose of study drug.

12.2.4. Follow-up of Adverse Events

The clinical course of each AE should be followed until resolution, stabilization, or until it has been determined that the study drug or participation is not the cause. The Investigator must provide the Sponsor with all relevant follow-up information necessary to facilitate a thorough understanding of the event and judgment regarding the relationship to the study drug or placebo. If a subject discontinues participation due to an AE/SAE that is at least possibly related to study

drug, the subject will be followed until the event has resolved, stabilized, or otherwise explained. This telephone contact will be documented in source.

12.2.5. Expedited Reporting of Events

12.2.5.1. Events Requiring Expedited Reporting to [redacted]

The following events should be forwarded to the Sponsor's pharmacovigilance group, [redacted], via the study event form within 24 hours of becoming aware of any of the following events:

- All SAEs, regardless of causality
- Overdose (with or without an AE)
- Inadvertent or accidental exposure
- Pregnancy

12.2.5.2. Timeframe for Collecting and Reporting Serious Adverse Events and Other Immediately Reportable Events

SAEs and other events requiring expedited reporting occurring after administration of study drug and through 30 days after the last dose of study drug (or for discontinued subjects, within 30 days after his/her last dose of study drug) must be reported to [redacted] ***within 24 hours*** of the time any study staff member is made aware of the event. Event information should be emailed to [redacted] and to relevant study team members. Additional eCRF and/or paper documentation may need to be supplied to [redacted].

12.2.5.3. Regulatory Notification

US WorldMeds is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events that occur outside of this study or at other sites in this study. Each site is responsible for notifying his or her IRB or IEC of these additional SAEs.

12.2.6. Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Investigator to report any pregnancy in a subject (spontaneously reported to them or discovered during a protocol-defined pregnancy test) that occurs during the study or within 30 days after the last dose of study drug to [redacted]. All subjects who become pregnant must be discontinued and must be followed until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) and status of mother and child must also be reported to [redacted].

13. STATISTICS

13.1. General Statistical Considerations

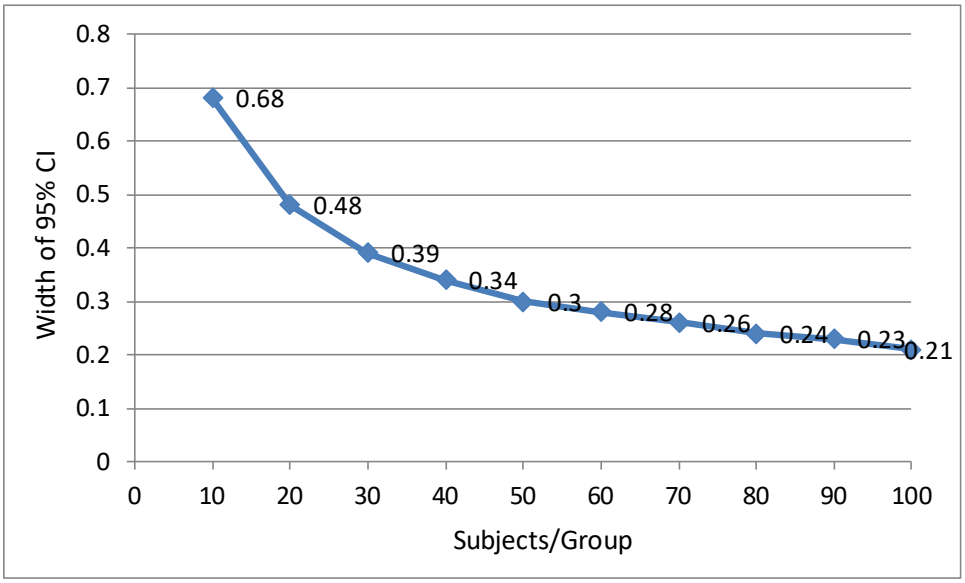
This section is an overview of the planned statistical analyses. Additional analyses and details will be provided in the statistical analysis plan, which will be finalized before database lock.

Continuous or ordered categorical variables will be summarized with the mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized with counts and percentages.

13.2. Sample Size Determination

A sample size of 30 subjects per group provides adequate precision for the estimated treatment difference for the incidence of adverse withdrawal events during an opioid taper. Precision of the estimated difference is quantified by the width of the 95% confidence interval for the treatment difference. When the difference in proportions is 0.2, the 95% confidence interval is 0.2 ± 0.24 when n=20/group and is 0.20 ± 0.17 when n=40/group (Figure 2).

Figure 2: Width of 95% Confidence Interval as a Function of Sample Size



13.3. Analysis Populations

Analysis populations are defined in Table 12.

Table 12: Analysis Populations

Analysis Population	Description
Safety	All subjects who take at least 1 dose of study drug. Subjects will be analyzed according to the treatment they actually received.
Intent-to-Treat	All subjects in the Safety Population who have at least 1 effectiveness assessment after Baseline. Subjects will be analyzed according to the treatment they are actually randomized to.

13.4. Statistical Analyses

13.4.1. Effectiveness Analyses

13.4.1.1. Successful Completion of Opioid Taper

The treatment group difference in the proportion of subjects who successfully complete the opioid taper will be summarized descriptively with a 95% confidence interval. The 95% confidence interval will be calculated based on the normal approximation for the binomial distribution, using the Wald continuity correction [(1/n1 + 1/n2)/2]. In addition, the treatment group difference will be tested with Cochran-Mantel-Haenszel (CMH) test stratified by total opioid dose (<90 MED, ≥90 MED) in ITT population.

The percentage of subjects who meet each of the components of successful completion of opioid taper will be summarized.

13.4.1.2. COWS, SOWS-Gossop, and SOWS-H

The treatment group difference for change in COWS, SOWS-Gossop, and SOWS-H total scores from Baseline to peak value and to each scheduled evaluation will be summarized descriptively with 95% confidence intervals. The treatment group differences will be calculated within the framework of analysis of covariance (ANCOVA) with treatment and total opioid dose (<90 MED, ≥90 MED) as fixed factors and baseline score as a covariate.

13.4.1.3. MCGI-R and MCGI-S

MCGI-R and MCGI-S will be summarized descriptively and analyzed by a CMH test stratified by total opioid dose (<90 MED, ≥90 MED) in ITT population.

The frequency distribution across response scores will also be summarized.

13.4.1.4. Time to Study Drug Discontinuation

Time to study drug discontinuation will be summarized descriptively with a Kaplan-Meier curve stratified by total opioid dose (<90 MED, ≥90 MED) in ITT population. In addition, the treatment group difference will be assessed with the log-rank test.

13.4.1.5. Numerical Rating Scale

Treatment group differences for each NRS score will be assessed as follows:

- Average of daily values from Day 1 through EOS Visit
- Change from Baseline (average of Days -3 to -1) to the average of the last 3 days before the EOS Visit
- Graphical display of daily means

Treatment differences for average of daily values and for change from baseline will be assessed with an ANCOVA with treatment and total opioid dose (<90 MED, ≥90 MED) as fixed factors and Baseline value (average of Days -3 to -1) as covariate. In addition, 95% confidence intervals for the treatment group differences will be calculated within the framework of the ANCOVA.

13.4.1.6. ISI, HADS, EQ-5D-5L, and SF-36

The treatment group difference for change in ISI, HADS, EQ-5D-5L, and SF-36 total scores and published subscale scores from Baseline to peak value and to each scheduled evaluation will be summarized descriptively with 95% confidence intervals. The 95% confidence intervals for the treatment group differences will be calculated within the framework of ANCOVA. The ANCOVA will have treatment and total opioid dose (<90 MED, ≥90 MED) as fixed factors and Baseline value as covariate. In addition, the treatment group difference will be tested within the ANCOVA framework.

Scoring the SF-36 is a 2-step process.

Step 1: Precoded numeric values are recoded per the scoring key given in Table 13. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved.

Step 2: Items in the same scale are averaged together to create the 8 scale scores. Table 14 lists the items averaged together to create each scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table 13: Recoding Items for the Short Form Health Survey

Item Number	Original Response Category	Recoded Value
1, 2, 20, 22, 34, 36	1	100
	2	75
	3	50
	4	25
	5	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1	0
	2	50
	3	100
13, 14, 15, 16, 17, 18, 19	1	0
	2	100
21, 23, 26, 27, 30	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
32, 33, 35	1	0
	2	25
	3	50
	4	75
	5	100

Table 14: Definition of Average Scale Scores for Short Form Health Survey

Scale	Items Averaged for Scale Score
Physical functioning	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	13 14 15 16
Role limitations due to emotional problems	17 18 19
Energy/fatigue	23 27 29 31
Emotional well-being	24 25 26 28 30
Social functioning	20 32
Pain	21 22
General health	1 33 34 35 36

13.4.1.7. Daily Dose of Opioids and Number of Non-Opioid Concomitant Medications for Withdrawal Symptoms

The following endpoints will be summarized descriptively for each study day:

- Change from Baseline to final, daily opioid dose, expressed as MED and as a percentage of this baseline MED
- Number of non-opioid concomitant medications for withdrawal symptoms used by study day

13.4.2. Safety Analysis

All safety analyses will be performed on the Safety Population using the treatment actually received. All safety summaries will be descriptive; no statistical testing will be performed.

13.4.2.1.1. Adverse Events

A TEAE is defined as an AE with an onset that occurs after receiving study drug, or a continuing AE diagnosed prior to the date of first dose of study drug, which increases in severity after the start of dosing. AEs will be categorized by system organ class and preferred term with the Medical Dictionary for Regulatory Activities.

Summary tables for TEAEs will include number and percent of subjects experiencing TEAEs by system organ class and preferred term. If a subject has more than 1 TEAE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than 1 TEAE within a system organ class category, the subject will be counted only once in that system organ class category.

The following TEAE summaries will be provided:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- Drug-related TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and severity

Serious TEAEs and TEAEs leading to study drug discontinuation will be identified.

13.4.2.1.2. Clinical Laboratory Tests

Change from Baseline will be summarized descriptively for each analyte.

The percentage of subjects with treatment-emergent ALT, AST, or alkaline phosphatase >3 × ULN and total bilirubin >2.0 mg/dL at the same evaluation will be summarized by treatment group.

Clinical laboratory results considered clinically important by the Investigator will be identified. Individual results for clinical laboratory tests (serum chemistry, hematology, and urinalysis) outside the normal range will be flagged in the data listings. Criteria to identify potentially clinically significant values will be defined in the Statistical Analysis plan.

13.4.2.1.3. Electrocardiogram

The interpretation of electrocardiogram and interval duration measurements by the designated electrocardiogram laboratory cardiologists will be reviewed by the Investigator. Clinically significant deteriorations from Baseline will be reported and summarized as TEAEs.

13.4.2.1.4. Vital Signs

Change from Baseline to each scheduled measurement will be summarized descriptively. Criteria to identify potentially clinically significant values will be defined in the Statistical Analysis plan.

13.5. Interim Analysis

A Data Monitoring Committee (DMC) will be established to review safety and efficacy data in an unblinded manner. The DMC will consist of, at a minimum, 3 subject matter experts including a pain physician, psychiatrist/psychologist, and a statistician. A formal charter will be developed and signed prior to the unblinded interim analysis. The charter will address the review of safety data including AEs (eg, incidence of drop-outs due to AEs or intolerable opioid withdrawal, suicidality, cardiovascular events, urine drug screen results, alcohol test results, other laboratory results, etc) and stopping rules that will render the study unfeasible to continue (eg, a lack of measurable opioid withdrawal symptoms).

The interim analysis will be conducted after approximately 30 subjects have completed or discontinued the study. There will be no formal statistical analysis for futility; however, the study may be stopped for futility, but it will not be stopped for a positive demonstration of effectiveness, providing the DMC determines the risk-benefit ratio is acceptable. Therefore, no adjustment of Type I error is necessary.

14. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines
- US Code of Federal Regulations (CFRs) dealing with Protection of Human Subjects (21 CFR Part 50), Financial Disclosure (21 CFR Part 54), IRBs (21 CFR Part 56) and Investigational New Drugs (21 CFR Part 312)
- the Nuremberg Code
- the Declaration of Helsinki, revised version of Seoul, October 2008 (in compliance with FDA guidance)
- Applicable laws and regulations

The purpose of these regulations, legal obligations, and guidelines is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research. Copies of these materials can be downloaded from the FDA website at www.fda.gov.

The protocol, protocol amendments, informed consent form (ICF), package insert for LUCEMYRA [USWM 2018], and any other relevant documents must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

14.2. Informed Consent

Properly executed informed consent, in compliance with 21 CFR 50, ICH guidelines, and regional/local regulations, shall be obtained from each subject before entering the subject into the study. Attention is directed to the basic elements that are required in the informed consent under US CFR for Protection of Human Subjects (21 CFR 50.25) and/or ICH E6 4.8.10. Where applicable, the consent form or appended document must also include required elements to maintain compliance with 45 CFR Part 164 (Heath Insurance Portability and Accountability Act) and/or 21 CFR Part 50.27/ICH E6 4.8.8.

Informed consent is a process of interaction between the Investigator and a potential subject in which the Investigator (or appropriate designee) explains the aims, methods, anticipated benefits (or lack thereof), and potential risks of participating in a study, and informs the potential subject of their rights. The subject will be given ample time and opportunity to inquire about details of the study so the subject can voluntarily make an informed decision about whether or not to participate in the study. All potential subjects will be given a current IRB- and Sponsor-approved copy of the ICF to read to ensure they are given accurate information, and to assist in verifying that consent was obtained. Information provided verbally, as supplemental explanation and/or answers to questions, must be accurate and consistent with the ICF, and must not be coercive or misleading. No subject will undergo any study procedures before the subject signs and dates the ICF, which should be signed before Screening. A completed, signed copy will be given to the subject and a signed original shall be maintained in the subject's clinical file. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Potential subjects are to be consented using an ICF that is written in a language they understand. If the person obtaining consent is not fluent in the language in which the consent is written (ie, is not able to explain the consent/answer questions to the subject), the subject's consent must be witnessed by someone who is fluent in the language in which the consent is written, and must have the ability to translate any questions/explanations during the consent process.

Each subject must also sign a Health Insurance Portability and Accountability Act authorization form before his/her participation in the study. A signed copy must be provided to the subject and a signed original shall be maintained in the subject's clinical file.

14.3. Source Documents and Retention

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Information recorded on source documents are to be attributable, legible, contemporaneous, original and accurate and allow reconstruction of the trial from start to finish. It is the responsibility of the Investigator to ensure that source documents capture all required information needed for the verification of data required by the protocol and that data captured on the eCRF match information recorded in source. The Investigator may need to request previous medical records from the subject's primary care or other relevant physician. There may be instances where eCRF data are considered source data. These include the following assessments:

- Subject completed questionnaires (electronic patient reported outcome)
- Opioid Use Characterization
- Characterization of Opioid Withdrawal History
- Characterization of Pain Condition

Source documents and site study records including signed informed consent forms are to be maintained on site during the duration of the study and retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

14.4. Subject Confidentiality

Subject confidentiality and privacy will be strictly held in trust by the participating Investigators, their staff, and the Sponsor(s) and authorized representatives of the Sponsor. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies or the pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

Subjects will be assigned a unique identifier by the site. Any subject record or dataset that is transferred to the Sponsor or authorized representative of the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Subject confidentiality will be maintained in any publications or presentations that result from this study

14.5. Study Monitoring and Data Quality

The Sponsor or a clinical research organization will monitor the study. Study monitors perform source data verification to confirm that:

- data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents
- the safety and rights of subjects are being protected
- the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements

The Study Monitor serves as the investigative site's primary contact. The Investigator should contact the Study Monitor if additional supplies are required, if there are changes to study personnel, or if the Investigator has questions regarding any aspects of the study.

Study data monitoring may be conducted remotely by use of software that allows sites to scan, redact, and certify subject source records. The study monitoring plan will identify instances where an onsite visit is required, including monitoring report requirements. The purpose of monitoring is to verify that the clinical trial is being conducted and data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Findings of remote monitoring, or centralized review, may result in onsite visits, additional site training, corrective action plans, or site closure. The Data Coordinating Center will implement quality control procedures beginning with the data entry system (eCRF) and generate data quality control checks that will be run on the database. Any missing data or data anomalies will

be communicated to the site for clarification and resolution. In addition to data quality checks, centralized monitoring checks will be employed with the purpose of reviewing study performance metrics in addition to identifying trends of key data points within and across research centers. Findings of the centralized monitoring review may result in fewer or more onsite visits, additional site training, corrective action plans or site closure. The purpose of centralized monitoring is to ensure quality data throughout the study.

14.6. Audits and Inspections

The Investigator is required to make all study records promptly available for inspection, review, or audit at the study site upon request by the monitor, Sponsor, its representatives, or any appropriate regulatory agencies.

The Sponsor may also request the Investigator to scan and email source documents with subject identifying information redacted to de-identify subject protected information. Additionally, as part of the informed consent process the Investigator should inform subjects about the potential of an audit by authorized representatives of the Sponsor and/or regulatory authorities and that confidentiality of the subject's data will be maintained in accordance with local laws.

14.7. Publication Policy

The Sponsor recognizes the importance of communicating medical study data and therefore encourages publication of such data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study is described in the Clinical Trial Agreement between the Sponsor and the institution of the Investigator.

15. LIST OF REFERENCES

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