Pilot Study of Opioid-receptor Antagonists to Reduce Pain and Inflammation among HIV-Infected Persons with Alcohol Problems – UH2 Component

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TABLE OF CONTENTS

1. INTRODUCTION

1.1 SUMMARY

Pain is a common co-morbidity for HIV-infected patients. Prevalence studies suggest that, on average, half of all HIV-infected persons suffer pain. Chronic pain can lead to heavy alcohol use among HIV-infected persons, which may in turn be a barrier to treatment/control of HIV and contribute to spread of HIV. Thus there is an urgent need to address pain among persons with HIV. Opioid receptor antagonists such as naltrexone and nalmefene, which are licensed for treatment of alcohol use disorders, show promise as being effective and safe treatments for chronic pain among persons with HIV. The specific aim of the research is to assess the feasibility, tolerability and safety of using opioid receptor antagonists (low-dose naltrexone and standard-dose nalmefene) to treat pain among HIV-infected persons with heavy alcohol use and chronic pain. If milestones are met, the next phase of the study - UH3, will aim to perform a 3-arm pilot randomized, double-blinded, placebo-controlled study of low-dose naltrexone and standard-dose nalmefene vs. placebo among HIV-infected persons with heavy alcohol use and chronic pain to provide estimates of their effects on: 1) pain (both self-reported and experimental/cold pressor test; 2) inflammation (i.e., levels of inflammatory cytokines IL-6 and TNF-α); and 3) measures of HIV control (CD4 count and viral load). We choose to conduct this research in St. Petersburg, Russia, given that: 1) nalmefene is licensed in Russia, but not currently in the US; 2) patients are seldom on chronic opioids (which are contraindicated to use with opioid receptor antagonists) due to the unavailability of opioid agonist therapy for addiction and restricted use of opioids for pain; and 3) a high prevalence of heavy drinking and HIV exists in Russia. Given the US epidemic of opioid use disorders, new pharmacotherapies without addictive potential are desperately needed for HIV-infected persons with chronic pain and alcohol problems.

2. OVERVIEW OF STUDY DESIGN

2.1 STUDY AIMS

Our Specific Aim will compare effects of low-dose naltrexone and standard-dose nalmefene among persons with HIV who have chronic pain:

UH2/Aim 1: To assess the feasibility, tolerability, and safety of using opioid receptor antagonists (naltrexone and nalmefene) to treat pain among HIV-infected persons with heavy alcohol use and chronic pain.

2.2 STUDY OUTCOMES

Primary Outcomes: The primary outcome for this study is tolerability of medication during treatment. Based on measurements used by other researchers, medication tolerability will be measured via a 0–100 visual analog scale with 0 anchored as “cannot tolerate at all” and 100 as “tolerate perfectly well.” Participants will be asked to estimated tolerability over the previous 2 weeks at each study visit: the primary outcome will be tolerability score at the week 8 visit.

Secondary Outcomes:

1) Alcohol reduction measured as a reduction in mean number of grams of pure ethanol consumed per day.

2) Treatment discontinuation: defined as patient self-report of stopping medication anytime during the treatment period. Participants will be instructed to notify the study staff in real-time if they discontinue medications, and they will be queried about discontinuation at the week 4 and 8 study visit assessments. Lost-to-follow-up will be assumed to be equivalent to treatment discontinuation.

3) Adherence: defined as self-report of the percentage of study medications taken in the past 2 weeks, using a visual analog scale (VAS) from 0 to 100, same as used to assess adherence to HIV medication. Participants will be asked to mark on the ruler what percentage of medication they have taken that week ("0% means no medication, 50% means half your medication, 100% means all your medication"). In addition, medication adherence will be assessed by Riboflavin (50 mg) that will be included in the capsules by the pharmaceutical laboratory. This allows for assessment of medication adherence in both medication arms. Visual inspection of the urine for the presence or absence of riboflavin using ultraviolet (UV) light at the long wave setting (33 mm) in a room with low ambient light will be conducted.

4) Reported side effects. We will use a Symptom Checklist based on side effects reported in prior studies of naltrexone, plus an open-ended question to assess for any side effects from study medications in the past 4 weeks at visits 4 and 8. Participants side effects will be rated by trained research assessors, using the Guidelines for Severity Grades (mild, moderate, severe, and life-threatening, death) (See Box 1).

5) Medication Satisfaction: This 14-item questionnaire assesses satisfaction with medication to treat chronic conditions and difficulty/inconvenience of use.

6) Severe hepatotoxicity: we will test aminotransferase levels (AST/ALT) at baseline and at 4 and 8 weeks to look for severe hepatotoxicity defined as AST/ALT >10X the level of normal. Hepatotoxicity rarely occurs in the setting of treatment with naltrexone among persons with HIV;[1] less is known of the safety of nalmefene among persons with HIV, however hepatoxicity is not listed as an adverse event in the product insert. This threshold was selected as it is 10X upper limit of normal (ULN) recognizing that the population with alcohol use and commonly hepatitis C may start off with AST and ALT above the ULN. Any elevation in AST/ALT beyond ULN will be evaluated by the investigators as a potential adverse event: if elevations are felt to be dangerous/life-threatening medications may be stopped at an even lower threshold. We consulted with experts in the field, with one (Yale Professor of Medicine, NIDA researcher who has done research involving Naltrexone) noting that "Grade 4 (10x) is the standard for STOPPING and monitoring for all of these trials UNLESS there is a clear indication that toxicity is a major concern (which it is not here based on a large amount of literature)."[2] (Springer et al., 2012)

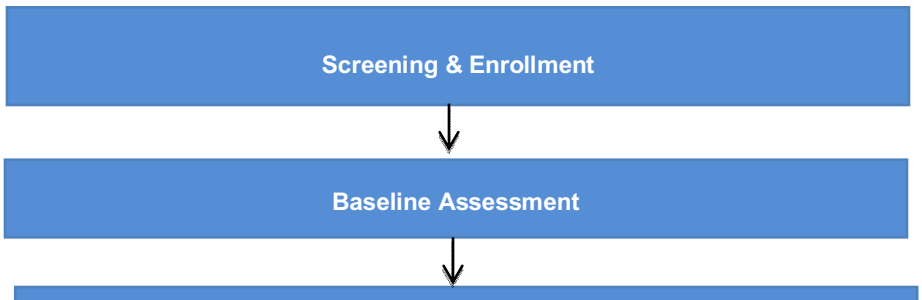
For feasibility, descriptive purposes, and to refine our measurements, we will also assess pain (self-reported and experimental) at baseline, week 4 and week 8.

2.3 STUDY DESIGN

This is a randomized, double-blinded, 2-arm study of 16 participants with HIV, chronic pain (defined as any bodily pain of moderate to severe intensity lasting for ≥3 months), and past-year heavy alcohol use, defined by NIAAA criteria. The 16 participants will be randomly assigned to either naltrexone or nalmefene with a 1:1 allocation ratio using permuted blocks to ensure equal numbers in each arm. Although we will not be formally testing differences between the naltrexone and nalmefene groups, participants will be randomized to the 2 arms in order to minimize selection bias and confounding in the allocation of interventions. Participants will be treated for 8 weeks, and outcomes (tolerability, alcohol use, side effects, medication adherence and discontinuation, and willingness/desire to continue to take medication at the end of study) will be evaluated at the end of treatment. In addition, we will review changes in pain during treatment with naltrexone and nalmefene to ensure that pain does not get worse and determine whether there is some improvement.

The study design and schedule for study visits and assessments is depicted in Figure 1. After consent and enrollment participants will be randomly assigned to either low-dose naltrexone or standard-dose nalmefene. The schedule of study in-person visits/assessments are as follows: screening visit, baseline, 2, 4, 6, and 8 weeks. At baseline, weeks 4 and 8, full study visits will occur, including assessments of tolerability of medication, medication discontinuation, treatment side effects, self-reported adherence and confirmation of adherence through riboflavin urine testing, self-reported pain, and experimental cold pain tolerance (cold-pressor test). Participants will also be instructed to keep a daily dairy to record pain severity, medication adherence, and alcohol use. Weeks 2 and 6 will be short visits at which time a brief assessment of tolerability, side effects, and adherence will occur. Throughout the course of the study, participants will be expected to come in for three in-person assessments and blood draw visits (screening/baseline, 4- and 8-weeks) and two shorter in-person visits.

Figure 1: Study Design (UH2 Phase)



2.4 STUDY SITE

Recruitment, enrollment, and all study visits will take place at the Laboratory of Clinical Pharmacology of Addictions at the First St. Petersburg Pavlov State Medical University (PSMU) in St. Petersburg, Russia. PSMU is the major educational, scientific, and clinical medical institution for northwestern Russia. Blood specimens will be processed and analyzed at ImmunoBioService (IBS).

2.5 INCLUSION CRITERIA

To be eligible to participate in the trial, participants will need to meet the following inclusion criteria:

1. 18 years or older
2. HIV-positive
3. Chronic pain (present ≥3 mo) of moderate to severe intensity
4. Heavy drinking past year (Based on NIAAA criteria: > 14 standard drinks per week/ > 4 drinks in a day for men; > 7 drinks in the past week/ > 3 drinks in a day for women.[33])
5. If female, negative pregnancy test and willing to use adequate birth control
6. Provision of contact information for 2 contacts to assist with follow-up
7. Address within 100 kilometers of St. Petersburg
8. Possession of a telephone (home or cell)
9. Able and willing to comply with all study protocols and procedures

2.6 EXCLUSION CRITERIA AT STUDY ENTRY

1. Not fluent in Russian
2. Cognitive impairment resulting in inability to provide informed consent based on research assessor (RA) assessment
3. Known active TB or current febrile illness
4. Breastfeeding
5. Known uncontrolled psychiatric illness (such as active psychosis)
6. History of hypersensitivity to naltrexone, nalmefene, or naloxone
7. Current use (past week) of illicit or prescribed opiates as documented by either self-report or positive urine drug test
8. Unwilling to abstain from opiates during the treatment period
9. Current use of neuroleptics
10. History of seizure disorder
11. Known liver failure
12. ALT/AST levels >5x normal
13. History of Raynaud's disease
14. Planned surgeries in the next 3 months
15. Enrolled in another HIV and/or substance use medication intervention study
16. Taking naltrexone in the past 30 days
17. Taking nalmefene in the past 30 days

2.7 RECRUITMENT GOALS

We aim to randomize 16 participants into the trial and a total of up to 30 may be enrolled, but not randomized due to not meeting study entry criteria. Existing Russia ARCH (H-31200) participants will be offered to be screened for PETER PAIN. We will also screen St PETER (H-35288) participants at their final St PETER study visit for eligibility. Recruitment beyond PSMU will occur at local NGOs and Russia ARCH network hospitals including the major clinical HIV hospitals (Botkin Infectious Disease Hospital, Leningrad Regional AIDS Center, St. Petersburg City AIDS Center) and addiction hospitals (Leningrad Regional Center for Addictions, St. Petersburg City Addiction Hospital).

2.7.A. SAMPLE SIZE CALCULATION AND POWER

The goal of this study is to assess the feasibility, tolerability and safety of low-dose naltrexone and standard-dose nalmefene to inform a larger pilot RCT. The study will not be powered to detect statistically significant differences in outcomes and formal statistical testing will not be conducted. If we detect substantial intolerability to medication (mean tolerability rated < 80), and/or if other results qualitatively suggest intolerability (i.e. we have a larger than expected percentage who report discontinuation, non-adherence, side effects, and that they would not want to continue meds), we will not proceed to the next phase (UH3). To illustrate the limits of this phase of study, we provide the width of the CIs for the tolerability outcome within each treatment group. We expect < 15% loss to follow-up at 8 weeks and assume 7 evaluable subjects in each arm. Younger et al. observed a standard deviation of 15.1 for tolerability score. Assuming a similar standard deviation for each arm of this study, the length of a 95% confidence interval for mean tolerability would be approximately 22.4 (e.g., if mean tolerability were 80, the 95% CI would span from 68.8 to 91.2) for either arm.

3. INTERVENTION

3.1 INTERVENTION OVERVIEW

The study will randomize 16 HIV+ persons with past year heavy alcohol consumption (by NIAAA definition of at risk drinking) and chronic pain (defined as bodily pain of moderate to severe intensity lasting for ≥ 3 months). Existing Russia ARCH participants will be offered to be screened for this study. Recruitment beyond First St. Petersburg Pavlov State Medical University (PSMU) will occur at local NGOs, Russia ARCH network hospitals including the major clinical HIV and addiction hospitals. Some participants may be screened over the phone, but all interested potential study participants will ultimately be invited for an in-person screening of eligibility at PSMU. After eligible participants are consented and enrolled, the RA will complete screening for eligibility by conducting a rapid HIV test for non-ARCH participants, a urine drug test, and blood draw for AST/ALT testing and testing all women for pregnancy (urine). Once AST/ALT results are received, participants will be notified by phone and if eligible, will be invited to return to Pavlov for their baseline visit.

At the baseline visit, participants will be administered the naloxone challenge and observed for signs of opioid withdrawal for 20 minutes. Naloxone blocks the effects of opioids. It works only if it is injected and lasts about 30 minutes. It is used in hospitals and by emergency services to reverse the effects of a heroin or other opioid overdose. It will cause withdrawal if injected into someone who is currently physically dependent on opioids and will be administered to make sure that the participant is not physically dependent on heroin or other opioids before s/he is given oral naltrexone. The naloxone challenge will only be administered if the information the participant provides to the staff indicates that s/he is not physically dependent on heroin or other opioids and if his/her urine drug test is negative. The challenge will be done by administering 0.8-mg naloxone slowly intramuscularly. The participant will be observed by a research assessor for signs of withdrawal for 5-20 minutes. If the participant experiences withdrawal after the naloxone test, his/her symptoms may be treated with 150mcg clonidine or 2mg of benzodiazepine orally and will go away in 45-60 minutes. As withdrawal symptoms precipitated by naloxone typically resolve within 20 minutes without treatment, use of these medications will be decided on a case-by-case basis by the treating Russian physician-investigator.

In the consent form, participants will be alerted that they may experience the following side effects if they need to be treated with clonidine or benzodiazepine:

The most frequent side effects (which appear to be dose-related) of clonidine are dry mouth, drowsiness, dizziness, constipation and sedation. The most frequent side effects of phenazepam are drowsiness, sedation, muscle weakness, and ataxia. These side effects generally decrease on continued administration and are a consequence of CNS depression.

The participant will not be started on the study medication until s/he passes a naloxone challenge, which means that s/he has no signs or symptoms of opioid withdrawal after naloxone is administered.

If the participant fails the naloxone challenge, s/he will be invited to come back within a week to repeat the challenge. Participants who pass the naloxone challenge will then complete the study assessment, cold-pressor testing and be randomly assigned to either low-dose naltrexone or standard-dose nalmefene. Study medication will be provided by trained physicians, who will instruct participants in proper medication administration and adherence.

Study participants, investigators, staff, and physicians administering the medications will be unaware of specific group assignment.

Participants will be treated for 8 weeks, and outcomes (alcohol reduction, tolerability, side effects, medication adherence and discontinuation, and willingness/desire to continue to take medication at the end of the study) will be evaluated at the end of treatment.

Throughout the course of the study, participants will be expected to come in for five in-person assessments. The schedule of study in-person visits/assessments are as follows: baseline, 2, 4, 6, and 8 weeks. At weeks 4 and 8, full study visits will occur, including assessments of tolerability of medication, reduction in alcohol use, medication discontinuation, treatment side effects, self-reported pain, and experimental cold pain tolerance (cold-pressor test). Participants will also be instructed to keep a daily diary to record pain severity, alcohol use, and medication adherence. Weeks 2 and 6 will be short visits, at which a brief assessment of tolerability, side effects, and adherence will occur.

Visits will be preceded by phone/text reminders to the participant or alternate contacts.

The text message will read: "This is a reminder that your visit to Pavlov Medical University is scheduled for_____at_____. Please reply to confirm or call 973-53-96 to reschedule."

3.2 RANDOMIZATION

After consent and enrollment, participants will be randomly assigned to either low-dose naltrexone or standard-dose nalmefene with a 1:1 allocation ratio using permuted blocks to ensure equal numbers in each arm. Participants and research staff will be blinded to randomization arm.

Study medications will be obtained in St. Petersburg and delivered to the study pharmacist at PSMU prior to initiation of recruitment processes. The study pharmacist will deliver a supply of packaged boxes of study medication labeled with the group assignment to the study team.

Following completion of the baseline assessment, the RA will be directed to the electronic randomization screen in REDCap, which, once submitted, automatically assigns the participant to a randomization group. The RA then retrieves the bottle of study medication from the identified group, labels the bottle with the participant study ID, and enters the group number into REDCap, thus linking the two numbers.

3.3 INTERVENTION

As of September 18th, 2018, enrollment into arm A of the study was discontinued due to concerns about tolerability of the medication. Enrollment into arm B of the study will continue until we reach the target sample size for this arm (N=8).

Eligible participants will be randomly assigned into one of two study arms: 1) 4.5 mg naltrexone or2) 18mg nalmefene. Study medication will be provided by trained physicians, who will instruct participants in proper medication administration and adherence.

Drug capsules containing naltrexone hydrochloride (4.5mg) and nalmefene hydrochloride dihydrate (18mg) will be prepared by NonStopPharma, a compounding pharmacy in St. Petersburg, Russia. Doses will look identical; participants and providers will be blinded to assigned medication. Both medication capsules will include Riboflavin. Participants will be instructed to take one capsule orally once per day for 8 weeks. Participants will be given 28 days' worth of medications, with instructions to bring pill bottles/leftover medications to the following visit. Although medication visits will occur every two weeks, providing participants with 28 days of medications will ensure that they will not run out even if they miss the 2 and 6 week visits.

The Food and Drug Administration (FDA) has indicated that an Investigational New Drug (IND) is not needed for studies conducted outside the United States.

3.3.A. NALTREXONE

Participants randomized to this group will receive low-dose naltrexone for 8 weeks.

Participants will be instructed to take the medication once daily for 8 weeks. Naltrexone dosing will start on the day of the baseline visit, after successful passing of the naloxone challenge. If the participant does not pass the naloxone challenge, they will be brought back within a week to try again.

The most common side effects (reported in more than 1 in 10 people) of naltrexone are difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

Uncommon side effects (reported in less than 1 and 10 people, but more than 1 in 100 people) of naltrexone are loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

Rare side effects (reported in less than 1 in 100 people) of naltrexone include nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath, nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG

changes, palpitations, tachycardia, excessive gas, hemorrhoids, diarrhea, ulcer, painful shoulders, legs or knees; tremors, twitching, increased frequency of, or discomfort during, urination; increased or decreased sexual interest, oily skin, pruritus, acne, athlete's foot, cold sores, alopecia, depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams, eyes–blurred, burning, light sensitive, swollen, aching, strained; ears–"clogged," aching, tinnitus, Increased appetite, weight loss, weight gain, yawning, somnolence, fever, and dry mouth,

Please note that these side effects were reported among people taking 50mg of naltrexone. This study will use low dose naltrexone (4.5mg) and side effects are expected to be milder. In order to help prevent these adverse effects, participants will be instructed not to take more medication than what is provided by the study. Study clinicians will also be monitoring for signs of naltrexone overdose. These adverse effects are not expected to be likely.

3.3.B. NALMEFENE

Participants randomized to this group will receive nalmefene for 8 weeks.

Participants will be instructed to take the medication once daily for 8 weeks. Nalmefene dosing will start on the day of the baseline visit after successful passing of the naloxone challenge. If the participant does not pass the naloxone challenge, they will be brought back within a week to try again.

Very common side effects (reported in more than 1 in 10 people) of nalmefene are feeling sick, dizziness, insomnia, and headache.

Common side effects (reported in less than 1 in 10 people, but more than 1 in 100) of nalmefene include loss of appetite, difficulty sleeping, confusion, feeling restless, reduced sex drive, drowsiness, body twitches, feeling less alert, peculiar sensations in the skin like pins and needles, reduced sense of touch, racing heart, a sensation of rapid, forceful, or irregular beating of the heart, vomiting, dry mouth, excessive sweating, muscle spasms, feeling of exhaustion, weakness, discomfort or uneasiness, feeling strange, and weight loss.

Rare side effects of nalmefene (frequency of side effects cannot be estimated from available data) include seeing, hearing or sensing things that are not there and feeling detached from oneself.

3.4 MEDICATION CONSIDERATIONS

3.4.A SYMPTOM MONITORING

The study staff (research clinicians [addiction physicians with extensive experience performing pharmacotherapy trials]) will provide participants with the correct medication packages and advice on how to take the capsules. The staff will be trained to assess for adverse medication effects and will follow established protocols for identifying and monitoring any ongoing adverse events, including referral to treatment as appropriate. Study participants will be actively monitored for adverse events. Symptoms will be assessed every two weeks (and monitored more frequently, if necessary) by trained clinical staff,

while the participants are administered study medications. Processes have been set up to address any adverse event brought to the attention of study staff during the trial.

3.4.B. ADHERENCE

As one of the study outcomes, medication adherence will be assessed at each study visit using the direct (Riboflavin) and indirect (capsule counts and self-report) measures.

Direct Adherence Measures

Riboflavin (50 mg), a vitamin yielding a change in urine color, will be added to both study medications. Participants will be informed that the color change is harmless. At this dose, Riboflavin is expected to remain in the system at detectable levels for up to 24 hours. At each study visit post-baseline (while taking study medication), participants will be asked to provide a urine sample which will be visually inspected for the presence or absence of Riboflavin in a room with low ambient light, using ultraviolet (UV) light at the long wave setting (33 mm).

Indirect Adherence Measures

Capsule Counts

Participants will be instructed to bring any unused medication to each study visit post-baseline. The RA will count and record the number of remaining capsules. We will extrapolate the amount of medication taken and determine the measure of adherence.

Self-Report

Medication adherence will also be measured through self-report using the modified Adult AIDS Clinical Trial Group (AACTG) ART adherence questions.

Adherence Aids

During each study visit medication instructions will be reviewed and strategies for adherence discussed with each participant. Adherence plans will be individually tailored to each participant, depending on his or her reason for non-adherence.

Participants will also be encouraged to set a reminder in their phone to take the study medication each day.

3.4.C. MEDICATION DISBURSEMENT

Medication inserts will be provided to participants at baseline.

Medication distribution will be as follows:

Naltrexone:

- 28 capsules/bottle

- Participants will receive 1 bottle of 28 capsules at baseline and week 2.

Nalmefene:

- 28 capsules/bottle
- Participants will receive 1 bottle of 28 capsules at baseline and week 2.

Medication bottles will also be labeled. The medication labels will contain the following information:

FOR CLINICAL TRIAL USE ONLY

NALTREXONE/NALMEFENE

STORAGE: Don't store medication above 25°C.

KEEP OUT OF REACH OF CHILDREN AND PETS.

Return all unused medication to the study site.

DATE OF MANUFACTURE:

SHELF LIFE:

3.4.D. LOST OR STOLEN STUDY MEDICATION

If participants report lost or stolen medication, they will be provided with extra study medication. If participants report losing medication more than once, the study team will be alerted and the case discussed to determine a plan of action.

3.4.E. DISCONTINUATION OF STUDY MEDICATION

If as a result of study testing at week 4, a participant is found to have AST/ALT >10x normal, medications will be discontinued and the participants will be appropriately monitored for resolution of the abnormalities. If a participant has AST/ALT >5x normal as a result of study testing at week 4, participant will be rechecked at their 6-week visit to ensure levels do not increase to the threshold of discontinuation. Any participant with symptoms of acute hepatic failure (jaundice, dark urine) will have AST/ALT checked.

Those who discontinue medication will be followed and analyzed by intention to treat.

Participants found to be pregnant during the study will have their study medication discontinued, but will still be followed-up for the duration of the study. Participants who report pregnancy outside of study visits will be instructed to immediately discontinue their study medication and requested to come in for a confirmatory urine pregnancy test.

3.5 SCHEDULE OF DATA COLLECTION

		Screen	Baseline Visit	2 week visit	4 week visit	6 week visit	8 week visit
Screening	Screening Questions	X					
	Verification of HIV, non-pregnancy, urine tox, and ALT/AST	X					
Enrollment	Sign Informed Consent	X					
	Complete contact information/verify numbers	X					
	Randomization		X				
Laboratory	Clinical Values		X		X		X
	Pregnancy Test	X	X	X	X	X	
	Urine Drug Test	X	X				
	AST, ALT	X			X	X (if indicated)	X
	Cold Pressor Test		X		X		X
	Naloxone Challenge		X				
Assessment	Full Study Assessment		X		X		X
	Short Assessment			X		X	
Intervention	Symptom Management/Adverse Events		X	X	X	X	X
	Provide Medication Instructions		X				
	Give Study Medication		X	X			
	Discuss Adherence		X	X	X	X	
	Assess Adherence			X	X	X	X
Other	Provide Resource Card		X				
	Compensate for Participation	X	X	X	X	X	X
	Report Adverse Events		X	X	X	X	X
	Complete Tracking Forms	X	X	X	X	X	X

3.5.A. VISIT WINDOWS

Baseline Visit

- Window open: 1 day post screening
- Target date: 3 days post screening
- Window close: 28 days post screening
- Window length: 27 days

2 Week Visit

- Window open: 7 days post baseline
- Target date: 14 days post baseline
- Window close: 20 days post baseline

- Window length: 13 days

4 Week Visit
- Window open: 21 days post baseline
- Target date: 28 days post baseline
- Window close: 34 days post baseline
- Window length: 13 days

6 Week Visit
- Window open: 35 days post baseline
- Target date: 42 days post baseline
- Window close: 48 days post baseline
- Window length: 13 days

8 Week Visit
- Window open: 49 days post baseline
- Target date: 56 days post baseline
- Window close: 62 days post baseline
- Window length: 13 days

3.6 DATA SOURCES

3.6.A QUESTIONNAIRES

Questionnaires will be administered at baseline, 2-, 4-, 6-, and 8-week study visits. At weeks 4 and 8, assessments of tolerability of medication, medication discontinuation, treatment side effects, self-reported adherence, and self-reported pain will occur. At weeks 2 and 6, brief assessment of tolerability, side effects, and adherence will occur.

3.6.B. URINE

A pregnancy test will be administered by trained clinical research staff at screening to determine eligibility and at each study visit (except for 8-weeks).

Pregnant women will be excluded from the study due to some reports suggesting possible adverse events with study medications. Participants found to be pregnant will discontinue their study medication but will still be followed-up for the duration of the study.

Urine will also be checked at screening and baseline, as part of the naloxone challenge, to ensure that participants have not recently used opiates (as opioid receptor antagonists would be contraindicated as they could precipitate withdrawal). The urine drug test will test for a range of opioids, specifically opiates (products of the poppy plant – morphine, heroin) and synthetic opioids (specifically methadone).

If new opioids appear on the scene in Russia, such as fentanyl, then we will begin testing for this, but currently that is not thought to be an issue.

A urine sample will be collected from all participants at each study visit post-baseline while on study medication to be inspected for the presence or absence of Riboflavin, as a measure of medication adherence, as described in section 3.4b Adherence.

3.6.C. BLOOD

Blood will be collected at screening, 4- and 8-week study visits to assess AST/ALT levels. Blood may also be collected at the 6-week study visit for liver function testing, if indicated at the participant's 4-week study visit (see Section 3.4E).

3.6.D. COLD-PRESSOR TESTING

The cold-pressor test (CPT) is an experimental model that assesses cold pain threshold and tolerance. It is a research paradigm that has been used by researchers for decades, and has been utilized to measure enhanced sensitivity to cold pain (hyperalgesia). The investigators will use an automatic cooling water bath that keeps a constant temperature of 0–2 degrees Celsius. Participants are instructed to place their dominant arm in the cold water bath so that ice water covers the hand and approximately 10 cm of the forearm, to verbally indicate when they first perceive pain and, to rate their pain on a scale of 0-100 at its very worse, and when they can no longer tolerate the ice bath, to remove their arm from the water. The time from submersion to those events will be measured using a stopwatch. Cold pain threshold is measured as number of seconds to the initial perception of pain, and cold pain tolerance is measured as seconds until withdrawal of hand. Trials will be discontinued at 3 minutes since after this time pain severity diminishes as numbness sets in. This data will be collected at baseline, week 4 and week 8. Participants will be requested to refrain from over the counter analgesic use (non-steroidal anti-inflammatory pain medications or acetaminophen) for 24 hours prior to the study visit.

3.6.E. DAILY PAIN DIARY

Participants will be asked to keep a daily written record ("daily diary") of pain severity, medication adherence, and alcohol use. Although the daily diary responses may more accurately measure changes in pain compared to monthly assessments (which are subject to recall bias), it is uncertain whether this sample of participants will be able to comply with the request to record daily measurements. This study will test the feasibility of capturing data in this fashion.

4. STUDY PROCEDURES

4.1 RECRUITMENT

Existing Russia ARCH, who have agreed to be contacted for future studies, will be screened for the study. St PETER participants will also be screened for the study at their final St PETER study visit. Recruitment beyond the Russia ARCH cohort will occur at local NGOs and Russia ARCH network hospitals including the major clinical HIV hospitals (Botkin Infectious Disease Hospital, Leningrad Regional AIDS Center, St. Petersburg City AIDS Center) and addiction hospitals (Leningrad Regional Center for Addictions, St. Petersburg City Addiction Hospital) through notification of patients and providers at these sites. At each

of the recruitment sites flyers with information about the trial will be distributed to clinicians and peers working with HIV-positive patients. Flyers will provide a phone number (at Pavlov) for interested individuals to call to find out more about the study and undergo initial screening over the phone. On occasion, Pavlov research assessors may travel to screen participants at the affiliated clinical locations.

4.2 SCREENING

Screening may take place over the phone or in-person. Verbal consent for screening will be obtained from all potential participants. Potential participants will be asked by a research assessor, either on the phone or in-person, their age, HIV infection status, past year alcohol consumption, chronic pain, and pregnancy status, confirm residence within 100km of St. Petersburg, and possession of a phone, and two contacts to assist with follow-up, and ability and willingness to comply with all study protocols and procedures. If the participant is not fluent in Russian, has a cognitive impairment resulting in inability to provide informed consent, reports breastfeeding, has known uncontrolled psychiatric illness (such as active psychosis), has known active tuberculosis or current febrile illness, has a history of hypersensitivity to naltrexone, nalmefene, or naloxone, has known liver failure, has a history of Reynaud's disease, has ALT/AST levels >5x ULN, is currently using (past week) illicit or prescribed opiates, is unwilling to abstain from opiates in during the treatment period, is currently using psychotropic or neuroleptic medications or has a history of seizure disorder, has any planned surgeries in the next three months, if the participant is enrolled in another HIV and/or substance use intervention study, or has taken naltrexone or nalmefene in the past 30 days then s/he will be deemed ineligible. We will also collect information on participants' average pain in the past week, pain interference with their enjoyment of life in the past week, and pain interference with their general activity in the past week. These data will be used to describe the sample, including those individuals who screen ineligible, but will not be used for assessing eligibility. After informed consent is signed, a confirmatory pregnancy test will be done for all female participants and urine drug test for all. Rapid HIV testing will be conducted, via an Alere Determine™ HIV-1/2 visual read, qualitative immunoassay for the detection of HIV-1 and HIV-2 antibodies, for all non-Russia ARCH/St PETER participants. Participants have the option of bringing in a recent (must be dated within 4 weeks of the screening visit) liver function test result to the screening visit to assess for eligibility, all other participants will have their blood drawn and sent for AST/ALT testing. Data collected on participants who screen out will be kept in order to have an accurate record of the rate of enrollment among those screened for participation and to be able to identify reasons why potential participants are ineligible. The data will not contain identifying information.

If a participant is screened over the phone, the participant will be re-screened in-person.

Participants' screening IDs will be linked to their subject ID in an Excel spreadsheet. A separate Excel spreadsheet will link participants' ID numbers to their contact information.

4.3 INFORMED CONSENT

Research assessors will conduct the consent process as well as obtain written consent. After eligibility and interest in enrollment is determined, an RA will administer and document the informed consent of the participant in a private location. The study will be explained to eligible participants who will be offered participation in the study. Research assessors will answer any questions the participants may

have including risks, benefits and alternatives (including non-participation) to participation, and will provide written materials describing the study. If participants are unsure whether they would like to participate, they will be allowed any amount of time they need to consider participation in the study. If the participant is not able to make a decision on the day of the initial visit, s/he will be invited to contact the study team once they have made their decision, at which point s/he will be re-screened, if more than 3 days have passed since his/her initial screening. The written informed consent (in Russian), including the risks, benefits and alternatives, will be signed by the participant and the research assessor. As part of the informed consent process we will make it explicit to participants that their involvement in the study does not constitute medical treatment and that they will not receive any HIV medical care as part of the study. We will provide a handout with information on addiction and HIV treatment services to participants at the baseline visit. A copy of the informed consent will be provided to the participant and a copy will be maintained by the research team. The time the administration of the informed consent began, and the time the informed consent form was dated and signed by the participant will be captured in REDCap. Potential participants will be informed that refusal to participate will not affect their medical care at PSMU in any way and they will be informed of their right to drop out of the study at any time.

4.4 VISIT FLOW

Pre-screen (optional):

- Screening questions administered over the phone

Screening visit:

- Screening Questions
- Informed Consent and Enrollment
- Conduct HIV, urine drug test, draw blood for AST/ALT testing (if recent test result not provided), and pregnancy testing
- Compensate participant, collect locator/contact information and check contact phone numbers
- Schedule return visit, if eligible
- Provide resource document, appointment reminder card

Baseline visit:

- Review and update locator/contact information, verifying new numbers, as necessary
- Conduct urine drug testing and pregnancy testing
- Administer naloxone challenge
- Administer assessment questionnaire
- Assess baseline symptoms
- Randomize participant
- Conduct cold-pressor test
- Introduce study medication and instructions and develop an adherence plan
- Provide study medication
- Compensate participant; provide appointment reminder card, participation card, daily diary, and schedule next visit

2- and 6-week medication visit:

- Review and update locator/contact information, verifying new numbers, as necessary
- Collect a urine sample to check for pregnancy and adherence
- Administer a brief assessment of tolerability and side effects
- Assess medication adherence
- Provide study medication (2-week visit)
- Compensate participant and schedule next visit

4- and 8-week full study visit:

- Review and update locator/contact information, verifying new numbers, as necessary
- Collect a urine sample to check for pregnancy (4-week only) and adherence
- Assess medication adherence
- Administer assessment questionnaire
- Conduct cold-pressor test
- Compensate participant and schedule next visit (4-week only)

4.5 QUALITY ASSURANCE

Informed consent quality assurance

The RA will review Informed Consent Forms (ICFs) for completeness with the participant present. Items to check will include, but are not limited to: responses/initials collected for all questions, correct version of ICF used, signed and dated by both subject and RA. Both the RA and project manager will review ICFs weekly for completeness.

Assessment quality assurance

During the assessment, if the participant provides conflicting answers or answers that did not make logical sense (either within the same section or between sections), the RA will gently try to help the participant arrive at more logical answers. However, the RA will not force the participant to change his or her answers. Certain quality assurance checks are built into the assessment. The system will flag any inappropriate responses and prevent the RA from continuing until the issue is resolved. The RA will never guess to correct a mistake. The only instance when a change can be made to the completed assessment is in the event that the RA is 100% certain that an error was made in data entry.

4.6 COMPENSATION

Participants will receive the equivalent of US $8 in goods or cash for the screening visit, as this will require the collection of blood for laboratory testing. Participants will receive $16 in goods or cash for their participation in baseline and 4-week visits, and $24 for participation in the 8-week visit, which will require the collection of blood for laboratory testing and cold pressor testing. Participants will also be compensated for completing short medication visits at weeks 2 and 6 for a total of $13 per visit.

4.7 RETENTION

Baseline visit: Retention begins at baseline by ensuring that the participant enjoys the experience of participating in the study, by explaining the informed consent and what would happen in the study, and by collecting excellent contact information, including both the address where the participant is registered and the address where the participant is currently staying. Participants will be asked to provide contact information for 4-5 alternative contacts who may know their whereabouts. Alternative contacts can include friends, family members, and social workers. Participants will be asked if any of their friends are participating in the study and to include them as alternative contacts, if possible. Contact numbers must be verified by calling the numbers with the participant present, using the following script:

> I am calling from Pavlov University. Your friend/relative [NAME] is here with me and just enrolled in a study. They listed you as an alternative contact. We will only call you if we are having trouble reaching [NAME] to see if you can help us connect with them. Today I am just calling to confirm that this number is active.

If the alternate contact cannot be reached at the baseline visit, the RA will try to reach the contact again at the next in-person study visit. If the RA is unable to reach the contact at the following study visit, the participant will be asked to provide a different alternative contact. Participants will also be asked for their email address and membership to any social networking platforms.

All visits: Participants will be offered tea, coffee, water, and snacks at each study visit to make their experience in the research study more enjoyable.

RA will offer to help participants add the next scheduled study visit to the calendar in their phone and set a reminder in their phone.

Follow-up visits: Contact information for participant and alternatives will be reviewed and updated at every visit.

Other strategies: Participants will be contacted by telephone with appointment reminders and email, if one is provided. The study team will also utilize social networking to connect with participants. If participants are unable to be reached via phone, in addition to attempting to reach them via text messaging and email, participants will be sent private messages on Vkontakte (Russian social network) utilizing an existing standard script to remind them of their upcoming study visit. No sensitive information will be revealed or ascertained using this method. Study participants will be asked to contact the study team if their phone number changes between study visits; participants will be compensated 300 rubles in goods or currency for this information. All no-shows will be followed up to reschedule appointments.

Transportation will be arranged (i.e., a social taxi or Uber) for participants who are unable to come to First St. Petersburg Pavlov State Medical University due to a lack of available transportation.

5. ASSESSMENTS

5.1 BASELINE ASSESSMENT

Participants will be assessed as part of this study using validated interview instruments covering the following topics:

- Demographics (marital status, education, employment, individual Income/security, date of birth, spouse HIV status, living situation)
- Alcohol use by the Timeline Followback (TLFB) calendar method with a 30-day assessment
    - Participants will also be provided with a calendar to record daily alcohol use. They will be asked to complete this calendar at home and bring it back to all subsequent study visits. The calendar will be used as an aid by the RA when completing the TLFB with the participant.
- Depressive symptoms through the Center for Epidemiologic Studies Depression Scale (CES-D)
- Anxiety by the Generalized Anxiety Disorder 7-item Scale (GAD-7)
- ART use and adherence, using modified Adult AIDS Clinical Trial Group (AACTG) ART adherence questions
- Co-morbidities by an adapted Veterans Aging Cohort Study patient questionnaire
- HIV symptoms through a validated HIV Symptom Index from the NIAID Adult AIDS Clinical Trials Group
- Prescription and non-prescription medication use
- Brief Pain Inventory using a modified Short Form of the Russian Brief Pain Inventory
- Adjunct treatments of pain
- Drug use by an adapted version of the Risk Behavior Survey
- General health, quality of life, and cognitive function by the Veterans RAND 12-Item Health Survey (VR-12) and the Medical Outcomes Study HIV Health Survey (MOS-HIV)

5.2 FOLLOW-UP ASSESSMENTS

Content of assessments administered at the 4- and 8-week visits will be subsets of the baseline assessment. Please see table of study questionnaires at the end of this section. Sections not administered at baseline, but administered at follow-up visits include:

- Medication adherence using modified Adult AIDS Clinical Trial Group (AACTG) ART adherence questions
- Medication satisfaction via the Treatment Satisfaction Questionnaire for Medication (TSQM)
- Medication tolerability using modified Adult AIDS Clinical Trial Group (AACTG) ART adherence questions
- Willingness to Continue Medication

5.2.A. MEDICATION VISITS ASSESSMENTS

Medication adherence and symptoms will be assessed at weeks 2 and 6.

	Study Time Point	

Administered Assessment	Baseline	2-week	4-week	6-week	8-week
Demographics	X				
30-day Alcohol Timeline Followback (TLFB)	X		X		X
Depressive Symptoms (CES-D)	X		X		X
Anxiety (GAD-7)	X		X		X
ART Use & Adherence	X		X		X
Co-Morbidities	X		X		X
HIV Symptom Index	X				
Medications	X		X		X
Brief Pain Inventory	X	X	X	X	X
Adjunct Treatments of Pain	X				
Drug Use (modified RBS)	X		X		X
VR-12 Health Survey & MOS HIV	X		X		X
Baseline Symptom Monitoring	X				
Follow-Up Symptom Checklist		X	X	X	X
Medication Adherence		X	X	X	X
Medication Satisfaction (TSQM)			X		X
Medication Tolerability		X	X	X	X
Willingness to Continue Medication					X

6. PARTICIPANT SAFETY

Participant safety will be monitored every two weeks and more frequently, if necessary.

6.1. SPECIFICATION OF SAFETY PARAMETERS

An **Adverse Event (AE)** is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

An AE can therefore be any new sign, reaction, symptom, event, disease or a worsening in frequency or severity of a preexisting condition that occurs during the course of the study.

Stable chronic conditions that were present prior to study entry and do not worsen are not considered AEs.

SERIOUS Adverse Event (SAE) – for an event to be defined as serious, it will be Grade 1-6 below. Grade 0 would be "not serious".

Grade (1) results in death;

Grade (2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);

Grade (3) results in inpatient hospitalization or prolongation of existing hospitalization;

Grade (4) results in a persistent or significant disability/incapacity;

Grade (5) results in a congenital anomaly/birth defect; or

Grade (6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated Problem (UP) – for an event to be an Unanticipated Problem it must
- be unexpected AND
- be related or possibly related to participation in the research AND
- suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. OR meet the definition of SERIOUS

Suspected Adverse Drug Reaction – Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suspect a causal relationship. It is considered unexpected if it is not consistent with the risk information described in the general investigational plan. A suspected adverse drug reaction will be defined as a recorded adverse event that is unexpected and deemed to be possibly, probably, or definitely related to the study drug.

6.2 THE METHODS AND TIME FOR ASSESSING, RECORDING, AND ANALYZING SAFETY PARAMETERS

- Participant symptoms will be assessed at baseline to document any chronic conditions or symptoms that existed prior to introduction of study medication. These will be documented on the Baseline AE log. This list will be reviewed and compared to reported events throughout the study. *If the participant reports the same ongoing symptom (same severity) during subsequent visits, the symptom should not be recorded as an Adverse Event (AE). If the event is new (not previously reported) or worsened, as determined by RA, then the AE should be reported.*

- During each scheduled visit, the RA will ask the participant how he or she feels and review the list of symptoms of concern (starting with the symptoms recorded at the previous visit). Any event that meets the above criteria for an AE/SAE/UP must be recorded. In the case of unresolved AEs, clinical staff will update the AE log with any follow-up information that is gathered during their investigation.

- The site will receive the results of all blood work that is performed on study participants from the designated lab. If the lab results meet the criteria described in the protocol as an AE and are considered clinically significant by the site clinician then an AE will be recorded. **See "Study Outcomes" and "Discontinuation of Medications" for severe hepatoxicity thresholds.**

- Participants will be alerted of abnormal lab results and will receive a recommendation to see their local provider. All abnormal lab results obtained at the baseline visit will be listed on the Baseline AE log.

- All AEs will be assessed to determine if they meet criteria for a Serious Adverse Event (SAE). If the AE is serious, then the SAE form must be completed and appropriate reporting measures followed (see below). Investigators are encouraged to consult with the US team, if they are uncertain how to classify an event.

- The list of subject's current medications will be reviewed and updated at every study visit, starting at baseline.

The study will take place in a medical setting where standard procedures are in place to assist patients who experience acute events. If consequences arise due to research procedures (e.g. distress, anxiety, suicidal thoughts,) the physician investigators will be available to assess participants and make appropriate interventions or referrals based on the clinical circumstances. Any participant who voices current suicidality or is experiencing a psychiatric emergency during the assessments will be reported to an on-site physician, immediately. That physician will determine the appropriate course of action, which will depend on location of the event and the clinical situation. Patients will be escorted to receive care by appropriate staff if deemed necessary.

- If an event is discovered outside of the scheduled study visits, it must still be recorded accordingly.
- Action Taken will be determined by the RAs for all AEs that are Mild and Moderate (unless specified below) and by Site PI or other designee for SAEs and AEs that are severe, life-threatening or fatal.

6.3. PROCEDURES FOR ELICITING REPORTS OF AND FOR RECORDING AND REPORTING ADVERSE EVENT AND INTERCURRENT ILLNESSES

For any reported side effect: While with the participant, study personnel will listen, identify, and document the symptoms. The following symptoms will be assessed at baseline and during medication check-ins and study visits while participant is taking the study medication. All events will be documented on the Symptom Checklist and on AE forms.

Symptom
Agitation and/or Irritability
Depressed mood
Anxiety (includes nervousness and panic attacks)
Dry mouth or throat
Insomnia and/or other sleep problems
Abnormal dreams and/or nightmares
Headaches
Dizziness
Nausea and/or upset stomach

Fatigue
Shortness of breath
Increased hair growth
Increased sweating
Weight gain
Decreased appetite

6.3.A. OTHER EVENTS

- Other events may or may not be associated with study drug use, but will be recorded, AE form completed and the Site PI or other designee will be notified immediately to address the report.
- Site PI or other designee will evaluate the reported symptoms using clinical judgment to determine if they are related to the study and if study medication should be adjusted or ceased.
- If Site PI or other designee determine that study medications should be ceased, study personnel will attempt to contact the participant as soon as possible.
- If applicable, staff can advise participants to contact their physician immediately or call emergency services.
- Participants will receive a card to provide to medical staff in the case of a hospitalization or emergency stating that they are involved in a research study and are randomized to one of two study medications.

6.3.B. ADVERSE EVENT REPORTING

The following information should be present to complete AE and SAE forms during the initial report (on the day of finding out about the event):

- Description of the event
- Date of onset and resolution (if known)

- Severity – based on established criteria: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf * See Box 1

Box 1. Guidelines for Severity Grades

*Research assessor will refer to the guide for unique clinical descriptions of severity for each AE, which will follow the general guideline below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Assessment of expectedness (is the event anticipated in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB protocol and informed consent document; and (b) the characteristics of the subject population being studied

- Assessment of relatedness to study drug

- Any actions taken

  Following the initial report, additional information may need to be gathered to complete the AE and SAE forms and to evaluate the event for relatedness. This process may include obtaining hospital discharge reports, physician records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event.

- All adverse events (including serious adverse events) will be followed until the event is resolved, stabilized, or until the end of individual's participation in the study. Study investigators and clinicians will determine a follow-up plan (i.e., frequency and type of follow-up) on a case-by-case basis based on their clinical judgment.

If the SAE is not resolved or stabilized at this time or new information becomes available after the SAE form is completed, the SAE form should be updated as soon as possible. Any changes or updates to the SAE form will need to be re-reviewed and re-authorized by the study clinician.

In some cases, the study clinician may be unsure upon first learning of an SAE whether it is study related and/or expected, because study staff are awaiting more complete medical records. In such cases, the study clinician should make his/her best estimate of relatedness and expectedness, understanding that these determinations can be updated later. When updating determinations at a later date, the rationale for the change should be included in the SAE narrative.

SAEs and unanticipated events which are considered "at least possibly related" during the treatment and follow-up phases will be reported to the local IRB and to NIAAA within 48 hours of knowledge of the SAE and all other SAEs and unanticipated events will be reported within the time period mandated by the local IRB as indicated below.

The site must actively seek information about the SAE until the SAE is resolved, stabilized or until the participant is lost to follow-up and terminated from the study.

To summarize: upon determining an Adverse Event is Serious, the following procedures should be followed:

- The study staff, while meeting/talking with the participant or person providing details on the event, will gather as much information about the event from the participant as possible and complete the appropriate forms.
- The completed AE and SAE forms will be reviewed by key personnel on the Pavlov team. Any relevant clinical documents (labs, physician notes) available at that time will be provided to key personnel on the Pavlov team within 24 hours of finding out about the event.
- After initial notification, the SAE must be updated with any additional information.

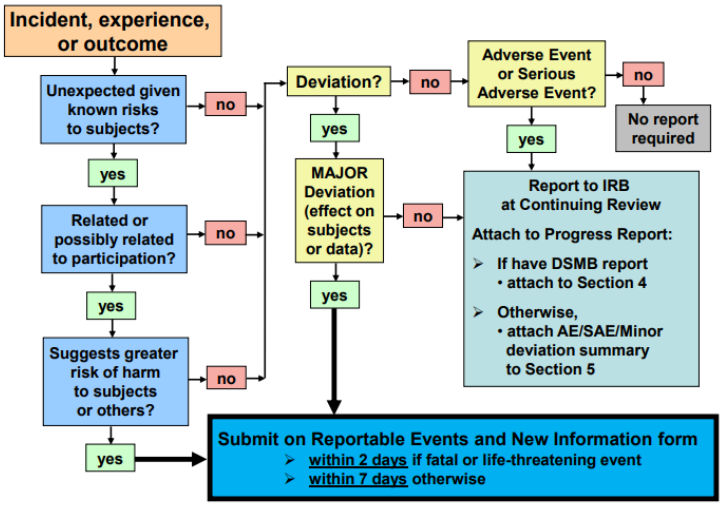
All unanticipated problems must be reported to the US team immediately.

AEs and SAEs will be reported to the URBAN ARCH Data Safety Monitoring Board every six months and as needed.

BUMC Reporting Guidelines:

BMC-BU Medical Campus IRB Version 1.7 1/11/17

Algorithm for Reporting Unanticipated Problems, Adverse Events, and Deviations



Reporting to the Boston Medical Center and Boston University Medical Campus IRB

Information	Description	Form to use	When to Report
1. Unanticipated Problem associated with a fatal or life-threatening event	A fatal or life-threatening event that qualifies as an Unanticipated Problem (event was unexpected *AND* related/possibly related *AND* suggests greater risk, see definitions above)	**Reportable Events and New Information** *AND*	Within **2 days** of the PI learning of a **fatal** or **life-threatening** event
		Change Request & Amendments addressing needed changes	As soon as practical
2. Unanticipated Problem NOT associated with a fatal or life-threatening event	An event that qualifies as an Unanticipated Problem (event was unexpected AND related/possibly related AND suggests greater risk, see definitions above) – whether or not it is also an Adverse Event or Serious Adverse Event	**Reportable Events and New Information** *AND*	Within **7 days** of the PI learning of event
		Change Request & Amendments addressing needed changes	As soon as practical
3. Safety Monitors' Reports **with**	DSMB reports, Data Monitoring Committee reports, Adverse Event Monitoring Committee reports, audit	**Reportable Events and New Information**	Within **7 days** of the PI receiving the recommendations

recommended changes	reports, etc. **with** recommendations for changes to the study	*AND* **Change Request & Amendments** addressing needed changes	 As soon as practical
4. Major Deviations	A violation of IRB requirements or an unapproved change in the research study design or procedures that may affect the participant's rights, safety or well-being, that may affect the reliability of the study data, or was the result of willful misconduct.	**Reportable Events and New Information**	Within **7 days** of the PI learning of the deviation
5. Adverse Events that are NOT Unanticipated Problems	All Adverse Events and Serious Adverse Events (see definitions above) that do *NOT* qualify as an Unanticipated Problem (event was expected *OR* unrelated *OR* suggests no new risk).	**Continuing Review Submission**: • Section 4 if a Data Safety Monitoring Board (DSMB) report • Section 5 if no DSMB (AE/SAE summary report - must include PI's conclusion that the pattern of events does not suggest a greater risk of harm)	At the time of Continuing Review
6. Safety Monitors' Reports **without** recommended changes	DSMB reports, Data Monitoring Committee reports, Adverse Event Monitoring Committee reports, audit reports etc. **without** recommended changes to the study	Attached to **Continuing Review Submission** Section 4 (The most recent report must be attached)	At the time of Continuing Review

Pavlov Reporting Guidelines:

What Event is Reported	When is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within 7 calendar days of initial receipt of information

Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within 15 calendar days of initial receipt of information
AEs and UPs	On a quarterly basis

6.4. THE TYPE AND DURATION OF THE FOLLOW-UP OF SUBJECTS AFTER ADVERSE EVENTS

All non-mild adverse events (including serious adverse events) should be followed until the event is resolved, stabilized, or until the end of individual's participation in the study. The Site PI or designee will determine a follow-up plan on a case-by-case basis based on their clinical judgment.

6.5. UNBLINDING PROTOCOL

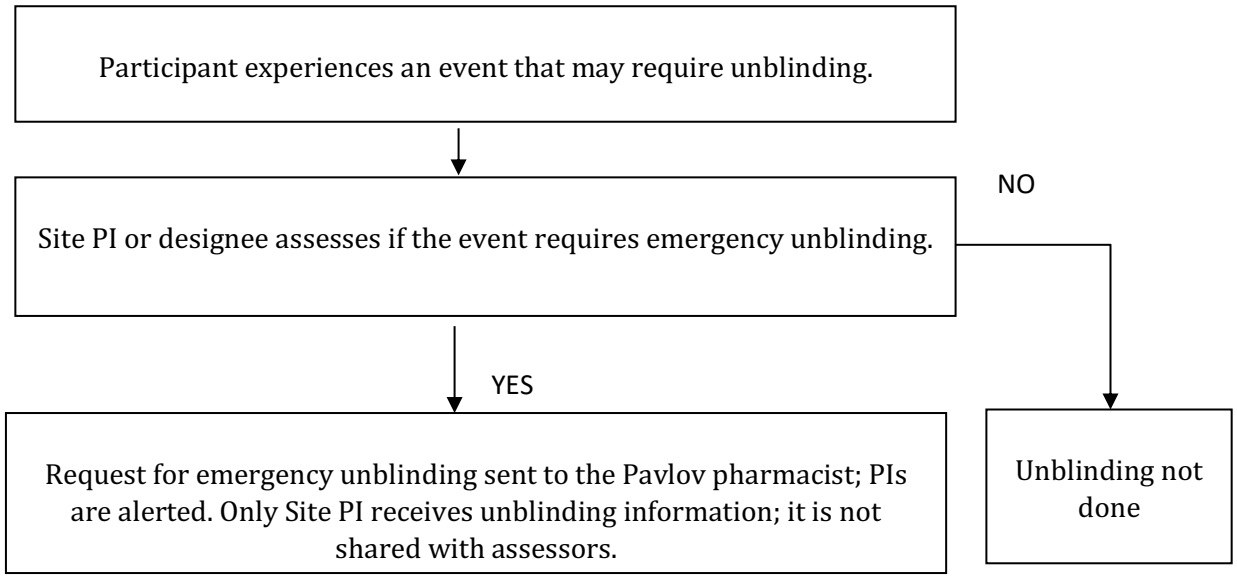
Participants may be unblinded if there is an urgent medical need, as determined by the clinician evaluating the participant. If a participant is unblinded, study medication may be discontinued.

<u>The following are examples of events that may result in emergency unblinding:</u>

-An SAE occurs that is thought to be most likely or definitely related to the study drug.

-An AE or SAE occurs and the clinician treating the patient concludes that knowledge of the treatment arm is necessary to determine the therapy provided to the patient.

-The study drug is accidentally ingested by a child.



6.6. DATA SAFETY AND MONITORING BOARD

The DSMB is responsible for ensuring subject safety (by reviewing blinded and unblinded safety data on a regular basis and assessing the safety of study procedures) and for monitoring the overall conduct of the study. No interim efficacy analyses will be conducted.

The DSMB is an independent group advisory to the PIs and the NIAAA, and is required to provide recommendations about starting, continuing, temporarily suspending the trial until certain conditions are met, and stopping the studies. In addition, the DSMB is asked to make recommendations, as appropriate, about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Protocol violations and adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Participant safety
- Notification of and referral for abnormal findings

The Board will be composed of three full members (inclusive of the DSMB Chair) and 1 adjunct member.

This DSMB will meet every six months. In cases where Institutional Review Boards or the NIH require more frequent monitoring, procedures will be put into place to conform to those requirements. An agenda will be provided detailing the studies to be discussed. It is estimated that the meeting will be scheduled for 1.5 hours. Each protocol and data review meeting will consist of two sessions: Open Session and Closed Session. Communication in the interim will be as needed. Unscheduled meetings can be requested by any party with the responsibility of overseeing the study. Requests can be made to the DSMB Chair, PIs, or NIAAA officials. The Chair, in collaboration with the Admin Core or NIAAA, will schedule any unplanned meetings.

The DSMB will provide recommendations about temporarily suspending or stopping the study. No interim efficacy or futility analyses are planned because of the risk level of the study and because patient outcomes are very unlikely to be worse in the intervention group in the study. The study team, including the project manager, statistician, co-investigators and research associates, led by the PIs, will evaluate the progress of the study, including periodic assessments of data quality, participant recruitment, accrual and retention, and factors external to the study when interpreting the data, such as scientific developments or the new availability of proven clinical services that could have an impact on the safety of the participants, the performance of the study or the ethics of the study.

7. DATA MANAGEMENT

7.1 DATA COLLECTION

All study data will be captured electronically on netbooks via a secure, web-based data capture system with the exception of: TLFB data and daily pain diaries, which will be collected on paper calendars.

7.2 QUALITY CONTROL PROCESS

Quality control measures will include: detailed and unambiguous specifications for completion of data forms, including rules for coding skipped questions and missing data, training of study staff responsible for data collection and built-in validation rules, error checks, question skips for electronic data capture, and computer algorithms to check for out-of-range codes and internal inconsistencies. All data, regardless of capture method, will be reviewed for logic, skip patterns, response ranges, out-of-range codes, and internal inconsistencies. The RAs will be queried monthly regarding any noted inconsistencies.

7.3 DATA SECURITY AND CONFIDENTIALITY

Screening forms and most other research paperwork will not include the participant's name; instead, a unique ID will be assigned to each person screened, and another number assigned to those who enroll.

Any documents with identifiable participant data will only be accessible to the Russian Co-Investigators, the project manager, and the RAs who recruit and follow participants, and perform QC.

Tracking information will be kept similarly using a Microsoft Excel spreadsheet. The Russian RAs will upload the Excel file to box.com for quality control purposes. Computer data will be password protected, and accessible only to research associates needing the information for follow-up purposes.

Electronic research data will be entered directly into REDCap, which is maintained on secure BU servers. All central systems are secured physically behind two card-access doors with access to the primary door restricted to key personnel. Data will be kept indefinitely. The mastercode will be kept separate from any study data.

7.4 WEB SYSTEMS

The study will use REDCap and Excel. REDCap is a secure web application for building and managing online surveys and databases and will be used for screening and assessments purposes. Excel will be used for participant tracking and scheduling purposes. The study will also use box.com, a HIPAA-compliant, cloud-based content management platform, for quality control purposes. Study forms will be completed according to the schedule below.

FORM	STUDY VISIT							
	Phone Screen	Screen & Baseline Visit		2 week visit	4 week visit	6 week visit	8 week visit	As Needed
		Screen	Baseline					
REDCap								

Pre-Screener	X							
Screener		X						
Consent and enrollment form		X						
Full assessment			X		X		X	
Short assessment (adherence)				X		X		
Baseline Event Form			X					
Medication visit checklist			X		X		X	
Symptom Monitoring Form				X	X	X	X	
Naloxone Challenge Form			X					
Excel								
Contact info		X	X	X	X	X	X	X
Contact log								X
Baseline tracking form			X					
Follow-up tracking form				X	X	X	X	
Participant tracking overview			X	X	X	X	X	
Paper								
Medication collection			X	X	X	X	X	
Study conclusion form								X
AE/SAE form								X

8. STATISTICAL ANALYSIS

This study will use an intent-to-treat analysis that includes all participants according to their randomized assignment. Descriptive statistics will be calculated for variables at baseline and each follow-up time to assess whether there appear to be any differences across treatment arms.

The main focus of this aim is the evaluation of tolerability within each group (naltrexone and nalmefene).

8.1 PRIMARY ANALYSES

Descriptive statistics and graphic displays of all outcome measures will be generated.

The main focus of this aim is the evaluation of tolerability within each treatment group (naltrexone and nalmefene), thus the analysis set will be all participants who receive at least one dose of their assigned intervention. We will report descriptives such as mean tolerability score at 8 weeks within each treatment group along with 95% confidence intervals (CIs). No formal testing will be conducted in this aim. If the data are skewed, transformations will be performed (e.g., log transformation) or the median will be reported if no appropriate transformation is identified. We anticipate that mean tolerability

scores at 8 weeks will not be lower than 80 (this is based on prior study of low-dose naltrexone which reported tolerability scores of 89 in both intervention and placebo). We will also evaluate: 1) mean number of grams of pure ethanol consumed per day, 2) the percentage in each group that discontinue medication during the 8 week treatment period, 3) the mean % adherence to medications in each group, 4) the percentage of participants who report severe or life threatening side effects, or experience hepatotoxicity during treatment and 5 the percentage who say that they would continue the medication if given the option. Corresponding 95% confidence intervals will be reported for each of the above variables. For binary variables, 95% exact binomial confidence intervals (CIs) will be reported.

9. STAFF TRAINING

All study staff will be trained on the study protocol, including administration of study medication, symptom monitoring, cold-pressor testing, and participant assessment prior to initiation of recruitment and enrollment. Training will take place in-person in St. Petersburg and via webinars.

10. STUDY CONTACTS

This study was led by 2 US PIs: Dr. Samet and Dr. Tsui.

REFERENCES

1. Tetrault JM, Tate JP, McGinnis KA, et al. Hepatic safety and antiretroviral effectiveness in HIV-infected patients receiving naltrexone. *Alcohol Clin Exp Res*. 2012;36(2):318-324.

2. Springer SA, Altice FL, Herme M, Di Paola A. Design and methods of a double blind randomized placebo-controlled trial of extended-release naltrexone for alcohol dependent and hazardous drinking prisoners with HIV who are transitioning to the community. *Contemp Clin Trials*. 2014;37(2):209-218.