PRODUCT: LUCEMYRA (Lofexidine)
PROTOCOL NUMBER / AMENDMENT: USWM- LX1-3003-1 / 02

SPONSOR:

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

TITLE:

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1-7) Followed by Open-Label, Variable Dose Lofexidine Treatment (Days 8-14)

DOCUMENT DATE: 06MAY2013
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16.1 STUDY INFORMATION

16.1.1 PROTOCOL AND AMENDMENTS

CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1-7) Followed by Open-Label, Variable Dose Lofexidine Treatment (Days 8-14)

Protocol Number:	USWM-LX1-3003-1
Product:	Lofexidine
Investigational New Drug (IND) Number:	IND 47,857
Development Phase of Study:	Phase 3
Medical Monitor:	
Contract Research Organization (CRO):	
Sponsor:	US WorldMeds, LLC 4010 Dupont Circle, Ste L-07 Louisville, KY 40207
Protocol Date:	August 10, 2012
Amendment No. 01 Date:	March 8, 2013
Amendment No. 02 Date:	May 6, 2013

1 PROTOCOL AMENDMENT SUMMARY

Changes made in this amendment to the protocol for Study USWM-LX1-3003-1 (Amendment No. 02) are listed below along with the rationale to support these changes.

Location	Modification/Rationale
Synopsis; 11.2.2	Exclusion criterion #3: For clarity, the footnote regarding infectious disease panel was removed from footnotes and the sentence inserted into the text. Exclusion criterion #5 was modified to not only exclude subjects with self-reported AIDS but also subjects who are HIV positive and taking retroviral medications.
Synopsis; Table 1; 13.2.1; 13.2.2; 15.2; 15.3.1; 15.3.2; 15.3.3; 15.5.2	Text was clarified to indicate that vital signs will be recorded at rest (i.e., sitting or recumbent, if required, for treatment of an adverse event) and standing. Respiration and temperature were added as items to be measured along with blood pressure and pulse while at rest (i.e., respiration and temperature are not required measurements after standing) during Days 1-7. Also the requirement for the 3.5-hour post-dose measurement on Day 14 was removed, as was the requirement that pre-dose vital signs be measured before the "first daily dose." Now Day 14 measurements can be obtained before any dose that day.
Synopsis; Table 1; 15.3.2; 15.5.3	The requirement for the 3.5-hour post-dose ECGs on Day 14 was removed, as was the requirement that the pre-dose ECG be measured at the "first daily dose." Now the Day 14 ECG can be obtained before any dose that day.
Synopsis; Table 1; 15.3.2; 15.5.4.1; 15.5.4.4; 15.5.5	The requirement for clinical laboratory testing, pregnancy testing, and a complete physical exam on Day 14 was removed. Now these procedures are required at the time a subject exits the study (discontinues or end-of-study).
Synopsis; Table 1; 15.3.2; 15.3.3; 15.4.9	Text was clarified to indicate the follow up telephone contact is 30 days from last dose of study drug (clarified from "discharge" which can be interpreted as discharge from the inpatient clinic).
Synopsis; Table 1; 15.1; 15.2; 15.3.1; 15.3.2; 15.5.6; 17.2.11; 17.3.2; Appendices 9 & 10	Added Columbia Suicide Severity Rating Scale per FDA requirement because lofexidine is active in the central nervous system, is being developed for a psychiatric indication, and a prospective assessment for suicidal thoughts and behavior was not included in previous clinical trials.
Synopsis; 17.2.6	Clarified tertiary/exploratory endpoint regarding subject treatment status to be 30 days after last dose, not 30 days post-discharge.
Synopsis; Table 1; 15.3.1; 15.5.4.1; 15.5.5	Text was clarified to reflect that clinical laboratory testing and physical examinations will be done at the end of double-blind dosing and before initiating open-label dosing rather than at "discharge."

Location	Modification/Rationale
Synopsis; Table 1; 15.5.4.5	Additional PK blood sample collections were added on Days 3 and 6 to provide data at approximate steady state.
5	Abbreviations list was updated.
11.2.2; 15.5.4.2	The method for testing for syphilis was updated to the central laboratory's current method for syphilis testing.
12.3	Third paragraph was clarified to allow dispensing of 1 to 2 days of medication at each daily clinic visit during the open-label phase (Days 8-14) to accommodate flexible scheduling of clinic visits. Fourth paragraph was clarified that study medications could be dispensed by the site pharmacist "or designee" because not all study sites have an on-site pharmacist.
12.5	Several administrative clarifications were made to the study drug labels.
12.6	Text was clarified that investigational agents could be stored at the dispensing pharmacy "or site."
12.8	Text was revised to improve clarity.
13.2.2	Text was clarified to indicate that dose-hold criteria apply to pre-dose vital signs.
13.2.3	Sixth and seventh bullets were revised for consistency with subject discontinuation (Section 14.5.1).
13.4	Text was clarified to allow an "estimate" of the total number of tobacco products used daily during Days 1-14.
14.1	First paragraph was clarified to indicate that subjects would be inpatient at a hospital "or clinic" because not all study sites are located in a hospital. Second paragraph, second sentence was clarified that collection of demographic information is required before site personnel access the IWRS to obtain a unique subject number.
14.3.1	First sentence was clarified to indicate that subjects would be inpatient at a hospital "or clinic" because not all study sites are located in a hospital. Fourth sentence was clarified regarding when a subject was considered enrolled in the study.
14.3.2	Sentence was added to first paragraph regarding a subject's final eligibility requirements. Second paragraph was modified to reflect that the IWRS will assign a "kit number" number for drug dispensing according to the randomization scheme and that the subject's screening number will be used on all source documents and eCRFs.
14.4	Text was clarified to remove stipulation that subjects will receive their compensation for study participation at the end of the study, thus providing individual study sites flexibility per their standard or IRB-required payment schedule.

Location	Modification/Rationale
14.5.1	Item #4 was revised to specify only during Days 1-7 of the study, because subjects with a positive urine drug screen during Days 8-14 will be allowed to remain in the open-label phase of the study as long as their continued participation is deemed safe by investigator.
14.6	First paragraph was added to allow a single administration of a short-acting opioid to keep a subject reasonably comfortable in the event the subject is admitted to the inpatient study unit the day before Baseline (i.e., Day -1). Last paragraph was added to allow psychosocial therapy per standard of care at individual study sites.
15	Table 1 was modified to provide a separate column for Study Discontinuation/End of Study procedures and table footnotes updated accordingly.
15.3.3	Section was added to clarify what procedures/assessments will be done at discontinuation from the study (after last dose of study medication).
15.4.1	Text was clarified to indicate that for each daily SOWS-Gossop evaluation, subjects should consider their symptoms over the last 24-hour period or since the last time they took this test.
15.4.2	Third paragraph was clarified to provide ambient room temperature range (67-75°F) during assessment of OOWS-Handelsman.
15.5.3	Text was clarified to indicate duplicate 12-lead ECGs would be done at discontinuation from the study during Days 8-14.
15.5.4.1	Table 5 was updated for consistency with the laboratory tests conducted routinely by the central laboratory.
15.5.4.2	Abbreviations for hepatitis analytes were revised for consistency with the central laboratory's abbreviations for these tests.
16.7	Second paragraph, second sentence was revised to indicate that a clinically significant finding on C-SSRS will be reported as an adverse event.
18.1; 18.2; 18.3	Clarified which CRO is responsible for data collection, eCRFs, and data analysis
Appendix 1	SOWS-Gossop scale was replaced with an exact copy of the scale the subject will complete.
Appendix 2	OOWS-Handelsman text was corrected to reflect that subjects will be observed for 5 minutes (not 10 minutes).
Appendix 3	MCGI - Subject version was replaced with an exact copy of the scale the subject will complete.
Appendix 4	Visual Analog Scale for Efficacy was replaced with an exact copy of the scale the subject will complete.
Appendix 8	Outpatient Vital Signs Diary was replaced with an exact copy of the diary the subject will complete. Also, correction was made to indicate that vital signs will be recorded after 3 minutes (not 5 minutes) of rest (sitting or lying down) and 3 minutes standing.

Prior changes made in Amendment No. 01 are listed below.

Location	Modification/Rationale
Title Page, Synopsis	Protocol title was clarified to better reflect the 2-part design of the study.
Synopsis, 11.2.1, 11.2.2	Inclusion criterion #2, exclusion criterion #4, and exclusion criterion #9 were modified to use the Mini International Neuropsychiatric Interview (M.I.N.I.) rather than the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) to establish the appropriate dependence diagnosis on opioids, exclude other drug dependency, and determine the absence of major psychiatric disorders. The M.I.N.I. is a validated scale (Sheehan et al., 1998) and is used commonly in clinical practice and research studies.
Synopsis	Number of study sites was updated from 10 to approximately 12.
Synopsis; 6.6; 14.3.4; 17.2.5; 17.2.8.2	The definition of completion status was clarified to: whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) assessment on Day 7.
Synopsis; 9; 10.2	Text was added to allow additional study sites (up to 20) in the event that the enrollment rate is unsatisfactory.
Synopsis; 11.2.1	Inclusion criterion #8 was removed because completion of the Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) at baseline is covered in inclusion criterion #4.
Synopsis; 11.2.2; 13.2.3; 15.5.2; 15.5.3; 17.2.11	Text was modified to use QTc (Fridericia) instead of QTc (Bazett) for safety monitoring/subject termination purposes because QTcF is now more commonly used when correcting for low pulse rates.
Synopsis; 15.3.1; 15.3.2; 15.4.5; 17.2.6; 17.2.8.4; 17.3.1	Clinical Opiate Withdrawal Scale (COWS) was added as an efficacy measure for consistency with efficacy measures evaluated in other lofexidine clinical trials.
Synopsis, 17.2.6, 17.2.8.8	Text was added to allow for the potential analysis of single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop, as well as area under the curve (AUC) based on COWS scores from Days 1 through 7.
Synopsis; 17.2.6; 17.2.8.7	Status of detoxification on Day 7 or early termination was added as a tertiary/exploratory endpoint because these data are being collected.
Synopsis; 17.3.1	The tertiary endpoint (Days 8-14) was clarified for number of days required to complete detoxification “as assessed by the Site Investigator.”
5	Abbreviation list was updated.
6.1	Text was updated for consistency with other more current documents.
6.4	Text was updated to account for more current safety information.
10.1	Second paragraph was clarified regarding subject eligibility for treatment in the open-label part of the study.

Location	Modification/Rationale
12.4	First paragraph was clarified to indicate the biostatistician will be blinded to medication assignment groups and that the finger-prick pharmacokinetic samples from placebo subjects will not be analyzed. The third and fourth paragraphs were removed. A cross-reference to Section 14.3.5 was added, which details requirements should unblinding become necessary for the safety of the subject.
12.5	Text was clarified regarding labeling of investigational agents.
13.2.1	Second paragraph was clarified to require the Site Investigator's rationale for his/her decision to continue subject's treatment in either an inpatient or outpatient setting.
13.2.2	Dose-hold criteria was clarified for symptoms of hypotension and/or bradycardia and a statement was added regarding the need to record all instances of dose-holds in source documents.
14.3.2	Second paragraph was clarified to indicate randomization will be done using an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) managed by the CRO.
14.3.5	First and last paragraphs were clarified regarding breaking the study blind.
14.5.1	First paragraph was clarified regarding when subjects "may" or "must" be terminated from the study. Also, Item 8 was clarified regarding termination requirements for missed doses.
14.5.2	Item 2 was clarified regarding termination requirements for persistent symptomatic hypotension, either not responding to bed rest or fluids.
15	Table 1 was modified to: • Add SOWS-Gossop at baseline. • Add COWS at screening, baseline, and each day during treatment (Days 1-7 and Days 8-14). • Add OOWS-Handelsman at screening. • Replace the SCID with the M.I.N.I. • To allow subjects to record the 3.5-hour post-dose vital signs measurements using a portable digital blood pressure machine if they are being treated on an outpatient basis and cannot stay in the clinic for this required post-dose measurement (see footnote j).
15.1	Screening assessments were clarified to include alcohol history. Text was revised to use the M.I.N.I. rather than SCID.
15.2	SOWS-Gossop was added as a required baseline assessment so it can be used as a covariate in the analysis.
15.4.1	First paragraph was clarified to provide a window (± 10 minutes) for the 3.5-hour post first daily dose recording of the SOWS-Gossop. Also, text was clarified to indicate that for each daily evaluation, subjects should consider their symptoms over the last 24-hour period.
15.4.8; Appendix 6	Text was clarified regarding what should be recorded as withdrawal-related adverse events.

Location	Modification/Rationale
15.5.2	Second paragraph was clarified to provide a window (± 15 minutes) for the required 3.5-hour post-dose measurement of vital signs. Third paragraph, which pertains to the open-label part of the study (Days 8-14), was clarified to provide a window (± 30 minutes) for the required 3.5-hour post-dose measurement of vital signs. Also, a provision was added to allow subjects to record the 3.5-hour post-dose measurements using a portable digital blood pressure machine if they are being treated on an outpatient basis and cannot stay in the clinic for this required post-dose measurement.
15.5.3	Text was clarified to provide a window (± 15 minutes) for the required ECG recordings.
15.5.3	Text was clarified that an on-site qualified physician (rather than a cardiologist) will evaluate ECG tracings if there is significant abnormality.
16.2	Title of subsection and text was clarified to remove reference to FDA Form 3454 because the Sponsor (US WorldMeds) will provide a Financial Disclosure form (internal template) to each site for signature.
16.6.1	Text was revised to reflect the use of the National Institute on Drug Abuse (NIDA) Data and Safety Monitoring Board (DSMB) for this study.
16.8.1	Section was added to further clarify SAE requirements.
16.9	Section was added for Overdose.
17.2.8.1	Statistical methods were revised to use 4 disposition strata in assessing SOWS-Gossop AUC(1-7). Also, Item 2 (Modeling) was revised to include baseline SOWS-Gossop score as a covariate in the analysis.
18.1; 18.4; 18.5.2	Text was clarified to indicate that all data will be entered electronically (eCRFs) and no paper CRFs will be used.
18.2	Text was clarified regarding electronic data capture requirements.
22	References were added for COWS (Wesson and Ling, 2003) and for the M.I.N.I. (Sheehan et al., 1998; Medical Outcomes Systems, M.I.N.I. version 6.0).
Appendices 1-5	Scales used to assess efficacy were added as appendices.
Appendix 6	Item E was clarified to indicate where SAEs are to be reported.
Appendix 8	Outpatient Vital Signs Diary was added so subjects who cannot stay in the clinic for the 3.5-hour post-dose vital signs measurement can complete this measurement using a portable digital blood pressure machine and record the results in the diary.

Several administrative clarifications were made in Amendment No. 1, with updates throughout as appropriate:

- as the central IRB;
- as the Clinical Research Organization (CRO);

- as the pharmacy coordinating center/central pharmacy;
- as the central laboratory for analysis of blood and urine samples; and
- as the ECG core lab.

2 SIGNATURE PAGE

By signing below, US WorldMeds, LLC and the investigator indicate 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.

Protocol Approval:

Signature: **Date:** MAY 7, 2013

Name (print):
Medical Director
US WorldMeds, LLC

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ **Date:** _____

Name (print): _____

3 SYNOPSIS

Title	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1-7) Followed by Open-Label, Variable Dose Lofexidine Treatment (Days 8-14)
Objective	To investigate the efficacy, safety, and dose-response of lofexidine hydrochloride (2.4 mg or 3.2 mg per day) in reducing withdrawal signs and symptoms and facilitating completion of detoxification/extending treatment retention in subjects undergoing detoxification from short-acting opioids in a double-blind inpatient setting (Days 1-7) followed by an open-label inpatient/outpatient setting (Days 8-14).
Study Design	Two-part, multicenter study in the United States. The first part of the study will use an inpatient, randomized, double-blind, placebo-controlled design, which will be followed by a second part, an open-label, continuation treatment. The first part of the study will consist of 7 days of inpatient treatment with lofexidine 2.4 mg total daily dose (0.6 mg QID), lofexidine 3.2 mg total daily dose (0.8 mg QID), or matching placebo (Days 1-7). During the second part of the study (Days 8-14), all subjects, regardless of their treatment assignment (which will remain double-blinded), who successfully complete Days 1-7, will be eligible to receive open-label, variable dose lofexidine treatment as determined by the Site Investigator. Subjects can be treated as inpatients or outpatients during Days 8-14, depending on the wishes of the Site Investigator and the subject, for up to an additional 7 days. No subject will receive lofexidine for more than 14 days total from the onset of abstinence.
Sites	~12 (Target: ≥3-4 subjects/site/month. Recruitment time: 12-15 months) (In the event that the enrollment rate is unsatisfactory, additional centers will be added for a total site base of up to 20.)
Inclusion Criteria	1. Be male or female at least 18 years of age. 2. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.), on any opioid with a half-life similar to heroin or morphine, including Vicodin®, Lortab®, Lorcet®, Percocet®, Percodan®, Tylox®, or Hydrocodone (by any route of administration), or oxycodone (oxycodone and oxycodone time-released formulation when crushed and snorted, injected or swallowed after chewing). 3. Be seeking treatment for opioid dependence. 4. Have a score ≥2 on the Objective Opiate Withdrawal Scale (OOWS-Handelsman) at Baseline.

Inclusion Criteria *(continued)*	5. Have reported use of heroin, morphine, or any opioid with a half-life similar to heroin or morphine for at least 21 of the past 30 days. 6. Urine toxicology screen positive for opioids and negative for methadone or buprenorphine. 7. If female and of childbearing potential, subject must agree to use of one of the following methods of birth control: • oral contraceptives; • patch; • barrier (diaphragm, sponge or condom) plus spermicidal preparations; • intrauterine contraceptive system; • levonorgestrel implant; • medroxyprogesterone acetate contraceptive injection; • complete abstinence from sexual intercourse; • hormonal vaginal contraceptive ring; or • surgical sterilization or partner sterile (must have documented proof). 8. Be able to verbalize understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures and pass the study consent quiz with 100% accuracy (if necessary, quiz may be administered more than one time).
Exclusion Criteria	1. Be a female subject who is pregnant or lactating. 2. Have self-reported use of methadone or buprenorphine in the past 14 days. 3. Have serious medical illnesses including, but not limited to: • seizures, or those who have received anticonvulsant therapy during the past 5 years; • pancreatic disease such as insulin-dependent diabetes; • liver disease that requires medication or medical treatment, and/or aspartate aminotransferase or alanine aminotransferase levels greater than 5 times the upper limit of normal; o an infectious disease panel for hepatitis will be performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus; positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease; and • gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment. 4. Have a psychiatric disorder, based on the M.I.N.I., including but not limited to dementia or any disorder that, in the opinion of the study physician requires ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.

Exclusion Criteria *(continued)*	5. Have self-reported acquired immune deficiency syndrome (AIDS) or self-reported human immunodeficiency virus (HIV) positive status and taking retroviral medications currently or within the past 4 weeks. 6. Abnormal cardiovascular exam at screening and before randomization, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF interval greater than 450 msec for males and greater than 470 msec for females); • heart rate less than 55 bpm or symptomatic bradycardia; • systolic blood pressure less than 95 mmHg or symptomatic hypotension; • diastolic blood pressure less than 65 mmHg; • blood pressure greater than 155/95 mmHg; and • prior history of myocardial infarction. 7. Have clinically significant abnormal laboratory values. 8. Requiring any of the following medications currently or within the past 4 weeks: psychotropics (including sedatives/hypnotics, antidepressants, neuroleptics), prescription analgesics (excluding those listed in inclusion criterion #2 above), anticonvulsants, antihypertensives, antiarrhythmics, antiretroviral, and cholesterol lowering medications. Nicotine replacement therapy (patch, inhaler, gum, or nasal spray) is allowed for nicotine-dependent subjects. Note: Use of a short-acting benzodiazepine (e.g., oxazepam) for insomnia during Days 8-14 will not disqualify a subject. 9. Current dependence (based on the M.I.N.I.) on any psychoactive substance (other than that listed in inclusion criterion #2, caffeine, or nicotine) that requires detoxification. 10. Have donated blood within the last 8 weeks. 11. Have participated in an investigational drug study within the past 3 months. 12. Have such “poor” veins that even a single venipuncture cannot be obtained during screening. 13. Have active tuberculosis (positive tuberculin test and/or confirmatory diagnostic chest x-ray). 14. Have active syphilis.
N	A sufficient number of subjects will be screened to randomize 600 subjects in a 3:3:2 ratio (225 in each lofexidine group and 150 in the placebo group) at approximately 12 study sites in the US. The total number of subjects randomized at each site will depend on subject availability and will likely not be evenly distributed at all sites.

Primary Endpoint	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • Area under the curve (AUC) based on Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) scores from Days 1 through 7.
Secondary Endpoint	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • Completion status (whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7).
Tertiary/ Exploratory Endpoints	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • SOWS-Gossop, OOWS-Handelsman, Modified Clinical Global Impression (MCGI [Subject and Rater]), Visual Analog Scale for Efficacy (VAS-E), and Clinical Opiate Withdrawal Scale (COWS) scores on Days 1, 2, 3, 4, 5, 6, and 7; • Retention analysis (time to removal from study treatment) over the 7 inpatient days; • Status of detoxification on Day 7 or early termination as assessed by the Site Investigator; • Concomitant medication analysis; • Withdrawal-related adverse event analysis; • Evaluation of subject treatment status 30 days after last dose; and • In addition, single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed, as may AUC based on COWS scores from Days 1 through 7. Days 8-14: Open-Label, Continuation Treatment • Descriptive evaluation of SOWS-Gossop, OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS; • Duration of exposure; • Number/proportion of subjects successfully completing detoxification as assessed by the Site Investigator; • Distribution of number of days required to complete detoxification as assessed by the Site Investigator; • Average daily dose of lofexidine; and • Concomitant medications.
Duration	21 days (maximum duration per subject, including screening)
Visits	All subjects will undergo screening up to 7 days before study admission. Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • Inpatient confinement on Days 1 through 7 Days 8-14: Open-Label, Continuation Treatment • Inpatient or daily for up to 7 days if outpatient

Efficacy Assessments	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment The following efficacy assessments will be performed daily at estimated time of maximum plasma concentration (i.e., 3.5 hours after the first dose): • SOWS-Gossop; • OOWS-Handelsman; • MCGI (Subject and Rater); • VAS-E; • COWS; • Concomitant medication use; and • Completion of detoxification as assessed by the Site Investigator (at completion of Inpatient Treatment on Day 7 only or, if applicable, early termination during Days 1-7). Days 8-14: Open-Label, Continuation Treatment The following efficacy assessments will be performed daily before dosing: • SOWS-Gossop; • OOWS-Handelsman; • MCGI (Subject and Rater); • VAS-E; • COWS; • Concomitant medication use; and • Completion of detoxification as assessed by the Site Investigator.
Safety Assessments	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment The following safety assessments will be performed daily unless otherwise specified below: • Occurrence, seriousness, severity, and causality assessment of adverse events (AEs); • Vital signs (blood pressure and pulse at rest [sitting or recumbent, if required, for treatment of an AE] and standing; respiration, and temperature) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM; • 12-lead ECGs (in duplicate) will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, early termination during Days 1-7; • Clinical laboratory tests as clinically warranted and at the end of double-blind dosing and before initiating open-label dosing or early termination during Days 1-7; • Finger prick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG during Days 1-7, as well as on Days 3 and 6 at 9 PM and 10 PM (3 and 4 hours, respectively, after 6 PM dose);

Safety Assessments *(continued)*	• Physical examination at Baseline (update of Screening exam), a complete exam 3 to 4 hours after randomization on Day 1 and at the end of double-blind dosing and before initiating open-label dosing or early termination during Days 1-7; and • Columbia Suicide Severity Rating Scale (C-SSRS) at Baseline (before dosing on Day 1) and 3.5 hours after the first dose (8 AM) on Days 1-7, or, if applicable, early termination during Days 1-7. In addition, qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband. <u>Days 8-14: Open-Label, Continuation Treatment</u> The following safety assessments will be performed daily unless otherwise specified below: • Occurrence, seriousness, severity, and causality assessment of AEs; • Vital signs (blood pressure and pulse at rest (sitting or recumbent, if required, for treatment of an AE) and standing at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once before a dose on Day 14 or, if applicable, at discontinuation from the study; • 12-lead ECGs (in duplicate) will be done before the first daily dose and at 11:30 AM on Day 8; once pre-dose on Day 14 or, if applicable, at discontinuation from the study; • Clinical laboratory tests as clinically warranted and at discontinuation from the study; • Complete physical examination as clinically warranted and at discontinuation from the study; and • Pregnancy test at discontinuation from the study. • C-SSRS daily before dosing or, if applicable, at discontinuation from the study. Qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for illicit drug use. A follow-up telephone contact will be made 30 days after the subject's last dose of study drug for an adverse event evaluation and an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program).

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TABLES

APPENDICES

5 ABBREVIATIONS

Abs	Absolute
AE(s)	Adverse Event(s)
AIDS	Acquired Immune Deficiency Syndrome
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase
Anti-HCV	Hepatitis C Virus Antibody
aPTT	Activated Partial Thromboplastin Time
AUC	Area Under the Concentration-Time Curve
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic-Oxaloacetic Transaminase
BP	Blood Pressure
bpm	beats per minute
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act of 1988
CO_2	Carbon Dioxide
COWS	Clinical Opiate Withdrawal Scale
CRF(s)	Case Report Form(s)
CRO	Clinical Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
DAWN	Drug Abuse Warning Network
DBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EIA	Automated Enzyme Immunoassay
FDA	Food and Drug Administration
FWE	Familywise Error Rate
GCP	Good Clinical Practices
GGTP	Gamma-Glutamyl Transpeptidase
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase

IWRS	Interactive Web Response System
MCGI	Modified Clinical Global Impression
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MHOWS	Modified Himmelsbach Opiate Withdrawal Scale
M.I.N.I.	Mini International Neuropsychiatric Interview
mITT	Modified Intent-To-Treat
mmHg	Millimeters of Mercury
msec	Millisecond
NDA	New Drug Application
NIMH	National Institute of Mental Health
OOWS-Handelsman	Objective Opiate Withdrawal Scale of Handelsman
PK	Pharmacokinetic
PPD	Purified Protein Derivative (skin test for tuberculosis)
PRN	As Needed
PT	Prothrombin Time
QID	Four Times Daily
QT	QT interval of an electrocardiogram
QTc	Corrected QT interval
QTcB	Corrected QT interval – Bazett's method
QTcF	Corrected QT interval – Fridericia's method
QTcI	Individually corrected QT interval
RBC	Red Blood Cell
RDW	Red Blood Cell Distribution Width
RPR	Rapid Plasma Reagin
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
T4	Free Thyroxine
T_{max}	Time of Maximum Plasma Drug Concentration
TPPA	Treponema Pallidum Particle Agglutination Assay
TSH	Thyroid-Stimulating Hormone
UDS	Urine Drug Screening
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USWM	US WorldMeds, LLC
VAS-E	Visual Analog Scale for Efficacy
WBC	White Blood Cell

7 STUDY OBJECTIVES

The primary objective of this study is to investigate the efficacy, safety, and dose-response of lofexidine (2.4 mg or 3.2 mg per day) in reducing withdrawal signs and symptoms and facilitating completion of detoxification/extending treatment retention in subjects undergoing detoxification from short-acting opioids in a double-blind inpatient setting (Days 1-7) followed by an open-label inpatient/outpatient setting (Days 8-14).

It is hypothesized that a daily dose of either 2.4 mg or 3.2 mg lofexidine will achieve greater efficacy than placebo with respect to overall symptom relief over the first 7 days of opioid withdrawal (primary endpoint) and will increase the likelihood of subjects completing Days 1-7 of treatment (secondary endpoint). Further, safety measures in the 2.4 mg and 3.2 mg total daily dose groups will be compared descriptively to assess whether the lower dose results in fewer and less severe adverse events than does the higher dose.

8 STUDYSPONSOR

This study will be conducted under an Investigational New Drug (IND) application (#47,857) held by US WorldMeds, LLC.

9 STUDY SITES AND INVESTIGATORS

This study will be conducted at approximately 12 study sites in the US. In the event that the enrollment rate is unsatisfactory, additional centers will be added for a total site base of up to 20. It is the responsibility of the Site Investigators to make sure this protocol is conducted in full conformance with the ethical principles detailed in Section 16 of this protocol. All data will be collected at the study sites on source documents and entered at the site into electronic case report forms (eCRFs) as described in Section 18.1 of this protocol.

10 INVESTIGATIONAL PLAN

10.1 Overall Design

This is a Phase 3, two-part, multicenter study to evaluate the dose-response, efficacy, and safety of lofexidine in alleviation of symptoms in subjects undergoing total and abrupt withdrawal from short-acting opioids. Any subject dependent on short-acting opioids (the primary projected indication for lofexidine) about to undergo opioid withdrawal will be eligible. Subjects will be evaluated for their compliance with protocol inclusion/exclusion criteria during a screening period, lasting up to 7 days.

The first part of the study will use an inpatient, randomized, double-blind, and placebo-controlled design (Days 1-7) followed by a second part, an open-label, continuation treatment (Days 8-14). A total of 600 subjects will be randomized to receive lofexidine 2.4 mg total daily dose (0.6 mg QID), lofexidine 3.2 mg total daily dose (0.8 mg QID), or matching placebo in a 3:3:2 ratio (225:225:150) for 7 days (i.e., during the most intense stage of

withdrawal). During the second part of the study (Days 8-14), all subjects, regardless of their treatment assignment (which will remain double-blinded), who successfully meet the definition for "completer" based on Days 1-7 (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7), will be eligible to receive open-label, variable dose lofexidine treatment (as determined by the Site Investigator, but not to exceed 3.2 mg/day) for up to an additional 7 days in either an inpatient or outpatient setting depending on the wishes of the investigator and the subject. No subject will receive lofexidine for more than 14 days total from the onset of abstinence. There will be no initial dose run-up and no mandated terminal dose taper. Efficacy and safety assessments will be made daily (see detailed Schedule of Assessments in Table 1 of Section 15). Qualitative urine drug screening will be done every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

10.2 Number of Subjects

A sufficient number of subjects will be screened to randomize 600 subjects (225 in each lofexidine group and 150 in the placebo group) at approximately 12 study sites in the US (should the enrollment rate be unsatisfactory, additional centers will be added for a total site base of up to 20). The total number of subjects randomized at each site will depend on subject availability and will likely not be evenly distributed across all sites.

10.3 Duration of Study

The maximum duration of participation for each subject in this study will be 21 days, including the Screening/Baseline period, which can last up to 7 days, followed by up to 14 days of treatment with study medication (lofexidine and/or placebo).

During Inpatient Treatment (Days 1-7), randomized subjects will receive lofexidine 2.4 mg total daily dose (0.6 QID), lofexidine 3.2 mg total daily dose (0.8 QID), or matching placebo treatment for up to 7 days. For Days 8-14, subjects will receive open-label, variable dose lofexidine for up to 7 additional days (open-label, continuation treatment). Full randomization into the study is anticipated to take 12 to 15 months to achieve (3-4 subjects per month per site), with the total clinical duration of the study anticipated to be 15 to 18 months.

11 SELECTION OF STUDY POPULATION

11.1 Population Base

Any opioid-dependent subject about to undergo withdrawal from short-acting opioids will be evaluated for study eligibility after providing written informed consent. Entry into this study is open to both men and women and to all racial and ethnic subgroups. An attempt will be made to include at least 25% female subjects and a mix of ethnicities reflecting the distribution in the local geographic regions of the study sites. Subjects will be recruited from a variety of sources, including subjects seeking treatment for opioid dependence via referrals from local treatment providers, word of mouth among subjects themselves also seeking treatment, and advertising in the local media. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB).

Potential subjects may be accepted for screening after the nature and purpose of the investigation have been explained to them and after they have voluntarily given written informed consent (see Section 16.4).

11.2 Study Entrance Requirements

11.2.1 Inclusion Criteria

To be eligible for participation, subjects must meet all of the following criteria:

1. Be male or female at least 18 years of age.
2. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.) [17, 18], on any opioid with a half-life similar to heroin or morphine, including Vicodin®, Lortab®, Lorcet®, Percocet®, Percodan®, Tylox®, or Hydrocodone (by any route of administration), or oxycodone (oxycodone and oxycodone time-released formulation when crushed and snorted, injected or swallowed after chewing).
3. Be seeking treatment for opioid dependence.
4. Have a score ≥2 on the Objective Opiate Withdrawal Scale (OOWS–Handelsman) at Baseline.
5. Have reported use of heroin, morphine, or any opioid with a half-life similar to heroin or morphine for at least 21 of the past 30 days.
6. Urine toxicology screen positive for opioids but negative for methadone and buprenorphine.
7. If female and of childbearing potential, subject must agree to use of one of the following methods of birth control:
   - oral contraceptives;
   - patch;
   - barrier (diaphragm, sponge or condom) plus spermicidal preparations;
   - intrauterine contraceptive system;
   - levonorgestrel implant;
   - medroxyprogesterone acetate contraceptive injection;
   - complete abstinence from sexual intercourse;
   - hormonal vaginal contraceptive ring; or
   - surgical sterilization or partner sterile (must have had documented proof).
8. Be able to verbalize understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures, and pass the study consent quiz with 100% accuracy (if necessary, quiz may be administered more than one time).

11.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be allowed to participate:

1. Be a female subject who is pregnant or lactating.

2. Have self-reported use of methadone or buprenorphine in the past 14 days.
3. Have serious medical illnesses including, but not limited to:
   - seizures, or those who have received anticonvulsant therapy during the past 5 years;
   - pancreatic disease such as insulin-dependent diabetes;
   - liver disease that requires medication or medical treatment, and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 5 times the upper limit of normal;
     - an infectious disease panel for hepatitis will be performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus; positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease;
   - gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment.
4. Have a psychiatric disorder, based on the M.I.N.I., including but not limited to dementia or any disorder that, in the opinion of the study physician requires ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.
5. Have self-reported acquired immune deficiency syndrome (AIDS) or self-reported human immunodeficiency virus (HIV) positive status and taking retroviral medications currently or within the past 4 weeks.
6. Abnormal cardiovascular exam at screening and before randomization, including any of the following:
   - clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF interval greater than 450 msec for males and greater than 470 msec for females);
   - heart rate less than 55 bpm or symptomatic bradycardia;
   - systolic blood pressure (SBP) less than 95 mmHg or symptomatic hypotension;
   - diastolic blood pressure (DBP) less than 65 mmHg;
   - blood pressure (BP) greater than 155/95 mmHg; and
   - prior history of myocardial infarction.
7. Have clinically significant abnormal laboratory values.
8. Requiring any of the following medications currently or within the past 4 weeks: psychotropics (including sedatives/hypnotics, antidepressants, neuroleptics), prescription analgesics (excluding those listed in inclusion criterion #2 above), anticonvulsants, antihypertensives, antiarrhythmics, antiretroviral, and cholesterol lowering medications. Nicotine replacement therapy (patch, inhaler, gum, or nasal spray) will be allowed for nicotine-dependent subjects.

   Note: Use of a short-acting benzodiazepine (e.g., oxazepam) for insomnia during Days 8-14 will not disqualify a subject.

9. Current dependence (based on the M.I.N.I.) on any psychoactive substance (other than that listed in inclusion criterion #2, caffeine or nicotine) that requires detoxification.
10. Have donated blood within the last 8 weeks.
11. Have participated in an investigational drug study within the past 3 months.
12. Have such "poor" veins that even a single venipuncture cannot be obtained during screening.
13. Have active tuberculosis (positive tuberculin test and/or confirmatory diagnostic chest x-ray).
14. Have active syphilis.

Notes on inclusion/exclusion criterion: Potential subjects who are positive for syphilis (as detailed in Section 15.5.4.2) will not be eligible for study participation and will be referred for appropriate follow-up and/or treatment, if required.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease.

Tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray will be performed on all subjects. A positive PPD result does not exclude a prospective subject from participation, but if diagnostic tests (e.g., chest x-ray) indicate that active disease is present, subjects will be excluded from participation.

If any tests are positive, the subject will be notified of the test results and referred for treatment.

11.3 Screening Failures

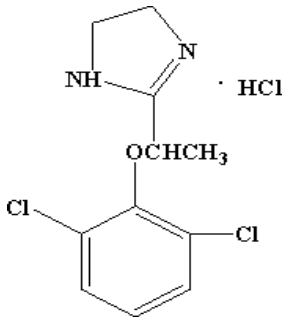
Screening failures are potential study subjects who provide informed consent and fail inclusion and/or exclusion criteria or for other reasons are not allowed to participate. A screening log for all subjects who are screened will be maintained. The screening log will uniquely identify each subject and report whether he or she passed or failed screening, and, if he or she did not pass, the reasons for the screening failure.

Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.

12 INVESTIGATIONAL AGENTS

12.1 Lofexidine Hydrochloride

Lofexidine hydrochloride is an α2-adrenergic agonist with mild to moderate antihypertensive actions. It has the empirical formula $C_{11}H_{13}Cl_3N_2O$ representing a molecular weight of 295.61. The structural formula is:



Lofexidine hydrochloride is a synthetic product and has the chemical designation of 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride. It is a white to off-white crystalline powder that is very soluble in water and ethanol. It is lightly soluble in 2-propanol and practically insoluble in ether. Lofexidine hydrochloride melts at approximately 126-128°C.

Lofexidine will be supplied by the Sponsor (USWM) in peach colored tablets containing 0.2 mg of active medication for oral administration.

Lofexidine should be stored at room temperature in a secure area.

12.2 Placebo

Placebo will be supplied by the Sponsor (USWM) as an exact match of lofexidine, less the active ingredient.

12.3 Dispensing Investigational Agents

All investigational agents will be distributed from (the pharmacy coordinating center) in "Subject Kits."

For the Inpatient Treatment part of the study (Days 1-7), a supply of unassigned subject kits will be maintained at each participating site. Each subject kit will contain 7 blister cards (packaged by with the appropriate dosing of lofexidine and/or matched placebo for each day of the inpatient phase of the study.

For Days 8-14 (open-label treatment), lofexidine tablets will be supplied in uniquely-identified 80-count bottles, which will be dispensed by the study pharmacist as determined clinically appropriate by the Site Investigator to the subject in individual prescription bottles. One to 2 days of medication may be dispensed at each daily clinic visit to accommodate flexible scheduling (e.g., day and a half worth of medication to supply subject from one morning to the next afternoon depending on availability for clinic visit). The site will

maintain a dispensing log for each bottle and document the number of tablets dispensed to each subject along with the number of tablets returned, if any, by the subject at each outpatient visit. Returned tablets will not be re-dispensed to future subjects.

All study medications will be dispensed by the site pharmacist or designee to the Site Investigators or their designee.

12.4 Blinding Plan

The subjects, Site Investigators, site personnel, Sponsor (USWM), and clinical personnel at the CRO (including the biostatistician will be blinded to medication assignment groups. The study pharmacist at the central pharmacy ( ) and bioanalytical personnel at the CRO will not be blinded to medication assignment. The bioanalytical personnel will not be blinded because they will need to identify finger-prick pharmacokinetic samples from placebo subjects; these samples will not be analyzed.

The investigational agents, lofexidine (2.4 mg or 3.2 mg) and placebo, will be packaged in blister cards of matched appearance and labeling for the Inpatient Treatment part of the study (Days 1-7). Days 8-14 will be open-label, although subjects' treatment assignment during Days 1-7 will remain blinded. Refer to Section 14.3.5 should breaking the blind become necessary for the safety of the subject.

12.5 Labeling

The investigational agents, lofexidine and placebo, will be packaged in blister cards for the Inpatient Treatment part of the study (Days 1-7) and further packaged in an outer carton (blister card kit). Lofexidine will be packaged in bottles for Days 8-14 (open-label treatment).

The blister card kit (outer carton) will be labeled with the following information:

- kit number
- space for site personnel to enter subject's number,
- space for site personnel to enter subject initials/name code,
- sponsor's name,
- protocol number,
- number of tablets (per card and total for kit),
- name/address of the pharmacy coordinating center
- 24-hour emergency telephone number, and
- the following statement – "Caution: New Drug – Limited by Federal Law to Investigational Use."

The individual blister card labels will include the following information:

- kit number,
- space for site personnel to enter subject's number,
- space for site personnel to enter subject initials/ name code,
- sponsor's name,
- protocol number,
- study day (e.g., Day 1, Day 2) and each row of tablets will be delineated with dosing times (i.e., 8AM, 1PM, 6PM, 11PM) to ensure that the appropriate tablets are given at each protocol-specified dosing time, and
- a description of the investigational product: "Lofexidine HCl 2.4 mg, Lofexidine HCl 3.2 mg, or Placebo," thus identifying the drug but preserving the blind.

The bottle product label will include the following information:

- sponsor's name,
- protocol number,
- a unique bottle number for purposes of investigational product accountability, and
- a description of the investigational product, i.e., "Lofexidine HCl 0.2 mg tablets" as the portion of the study that will use bottled study drug under open-label conditions.

In the open-label phase of the study (Days 8-14), sites may dispense 1 to 2 days of medication at each daily clinic visit to accommodate flexible scheduling for use in an outpatient setting (e.g., day and a half worth of medication to supply subject from one morning to the next afternoon depending on availability for clinic visit). In such cases, the redispensing container will include a subject label, supplied by the study site, and will include the following information:

- sponsor's name,
- protocol number,
- subject initials,
- subject number,
- study physician's name,
- site emergency contact telephone number,
- description of the medication (i.e., "Lofexidine HCl 0.2 mg tablets"),
- number of tablets dispensed, and
- directions for use.

12.6 Storage

Investigational agents will be stored at room temperature in a secure location at the dispensing pharmacy or site.

12.7 Record of Administration

Accurate recording of all investigational agents received, dispensed, administered, and returned will be maintained by study site personnel.

12.8 Used/Unused Supplies

Unused investigational agents will be retained at the participating sites to enable a full investigational drug inventory by the sites' respective monitor. If any investigational agent is lost or damaged, its disposition should be documented. The Sponsor will provide instructions to return the unused study drug to the pharmacy coordinating center periodically throughout the study (following monitor review) or at the end of the study for proper destruction in accordance with local and federal regulations.

12.9 Contraindications

To avoid drug-drug interactions, lofexidine should not be administered concurrently with:

- tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives;
- alcohol, sedatives, and anaesthetics – may interact with lofexidine and enhance its central sedative effects; and
- beta-receptor blockers – the combination of lofexidine and beta-receptor blockers should be used with caution to avoid the risk of excessive bradycardia.

13 TREATMENT PLAN

13.1 Investigational Agents

On Day 1 of the Inpatient Treatment part of the study, subjects will be randomized to one of two dose levels of lofexidine or placebo and receive the following daily treatment regimens through Day 7: lofexidine 2.4 mg/day (administered as 3 x 0.2 mg tablets and 1 placebo tablet QID), lofexidine 3.2 mg/day (administered as 4 x 0.2 mg tablets QID), or matching placebo (administered as 4 x placebo tablets QID). In order to maintain the treatment blind, all subjects will receive a total of 16 tablets per day whether active, placebo, or in combination to achieve the assigned dose. Tablets will be provided in subject-specific kits, containing 7 blister cards (one for each study day). Each blister card will contain 4 rows of 4 tablets each, appropriately marked to indicate which row of tablets should be administered at each of the specified dosing times (8 AM, 1 PM, 6 PM, and 11 PM). Dose kits for subjects randomized to lofexidine 3.2 mg/day will contain full blister cards of active tablets. Dose kits for subjects randomized to lofexidine 2.4 mg/day will contain blister cards in which each dose row contains 3 active tablets and 1 placebo tablet. Dose kits for subjects randomized to placebo will contain full blister cards of placebo tablets.

For the Open-Label, Continuation Treatment part of the study (Days 8-14), subjects will receive lofexidine at variable dose, as determined by the Site Investigator (see Section 13.2).

13.2 Dose Administration

13.2.1 Administration of Doses

During Inpatient Treatment (Days 1-7), subjects must take study medication orally, within a 30-minute window, 15 minutes before or after 8 AM, 1 PM, 6 PM, and 11 PM. The actual date and time of each dose will be recorded in the subject's source document and on the eCRF. Placebo will appear identical to lofexidine. Vital signs (blood pressure and pulse [sitting or recumbent and standing], respiration, and temperature) will be measured before each dose and 3.5 hours after each dose (with the exception of the dose taken at 11 PM, where the measurement at 3.5 hours post-dose will not be done). Details for obtaining vital sign are provided in Section 15.5.2.

During Open-Label, Continuation Treatment (Days 8-14), there will be no mandated lofexidine dose regimen and subjects may receive lofexidine treatment during this time in either an inpatient or outpatient setting depending on the wishes of the Site Investigator and the subject. The rationale for the decision to continue treatment or not and the Site Investigator's decision to continue treatment through either an inpatient or outpatient setting must be documented in the subject's source document. The dose regimen will be determined by the Site Investigators as clinically indicated for relief of subjects' symptoms, with supporting rationale for any dose changes recorded in the subject's source document. In no case is the dose of lofexidine to exceed 3.2 mg/day (or a single dose of 0.8 mg). Previous studies have shown that dose titration is not necessary to reach a maximum intended dose. Also, abrupt withdrawal of lofexidine has not been found to have any significant safety issues. Nevertheless, a dose taper may be appropriate given the dissipating severity of symptoms in the later days of withdrawal. Vital signs (blood pressure and pulse [sitting or recumbent and standing]) should be assessed for one dose every day at pre-dose and 3.5 hours post-dose on Days 8-13, with vital signs measured once pre-dose on Day 14.

As further guidance, the dosing regimen recommended for lofexidine (BritLofex™) in the UK is as follows:

> "The dosage of lofexidine should be titrated according to the patient's response. Initial dosage should be 0.8 mg per day in divided doses. The dosage may be increased by increments of 0.4 to 0.8 mg per day up to a maximum of 2.4 mg daily. Maximum single dose should not exceed 4 x 0.2 mg tablets (0.8 mg). Each patient should be assessed on an individual basis; those undergoing acute detoxification will usually require the highest recommend dose and dosage increments to provide optimum relief at the time of expected peak withdrawal symptoms."

The lower maximum dose allowed in the UK (2.4 mg/day) may be reflective of the less severe opioid dependence experienced by patients in the UK. US studies have shown that 3.2 mg/day can be safely administered (see Sections 6.3 and 6.4).

Note: In order to prevent dehydration from opioid withdrawal, increased fluid intake will be encouraged from the beginning of the study. Instances in which study medication is not administered within the 30-minute windows as noted above will be documented as protocol deviations.

13.2.2 Dose-Hold Criteria

Study medication will be held if pre-dose vital signs meet any of the following criteria:

Resting (sitting or recumbent, if required, for treatment of an adverse event)

- Systolic blood pressure <90 mmHg and >20% below screen value;
- Diastolic blood pressure <50 mmHg and >20% below screen value;
- Heart rate <50 bpm and >20% below screen value; and
- Symptoms of hypotension and/or bradycardia (e.g., lightheadedness, dizziness, syncope).

Orthostatic (after standing for 3 minutes)

- Systolic blood pressure diastolic blood pressure, or pulse >25% below recumbent values.

All instances of dose-holds must be clearly documented in the subject's source document.

13.2.3 Discontinuation Criteria

A subject will be discontinued from the study if any of the following criteria are met:

- Systolic blood pressure <70 mmHg and >20% below screen value;
- Diastolic blood pressure <40 mmHg and >20% below screen value;
- Heart rate <40 bpm and >20% below screen value;
- QTcF >500 msec[1] or >25% above screen value for both males and females;
- Syncope;
- Subject misses more than 2 doses in 24 hours during Days 1-7 prior to meeting "completer" criteria (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7);
- Subject misses more than a total of 6 doses during Days 1-7 prior to meeting "completer" criteria (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7); and
- Concomitant medication use (other than alumina, magnesia, and simethicone) for intolerable nausea and emesis.

[1] See Section 15.5.3 for procedures for assessment of prolonged QTcF interval.

Additional discontinuation criteria based on cardiovascular events are provided in Section 14.5.2.

13.3 Treatment Compliance

Each of the inpatient doses during Days 1-7 will be observed by the site staff. Following administration of the oral study medication, hand and mouth checks will be performed to ensure that the dose is swallowed. In an inpatient setting during Days 8-14, each dose will be observed by study staff and hand and mouth checks will be performed. In an outpatient setting during Days 8-14, self-dosing compliance will be evaluated by pill count and subject report at each clinic visit. Subjects will be instructed to call the physician's office before taking the next dose of study medication if they notice any marked dizziness, especially when standing from a sitting or lying position. The physician will determine if the next dose should be delayed, skipped, or the subject should be seen. Any change in physician-prescribed dosing will be noted in the study file and confirmed also by pill count and subject report at the next visit.

13.4 Nicotine Replacement Therapy

Subjects may be permitted to smoke during their participation in the Inpatient Treatment part of the study (Days 1-7) based on individual site policy. If they usually use tobacco products, the study physician will offer and encourage these subjects to use nicotine replacement therapy (patch, gum, inhaler, or nasal spray) while they are in the hospital to treat their nicotine withdrawal symptoms. If smoking is permitted by a participating site, smoking breaks outside of the inpatient unit must be constantly observed and supervised.

The estimated total number of tobacco products used by subjects per day (Days 1-14) will be recorded in the subject's source document and on the eCRF.

14 STUDY PROCEDURES

14.1 Subject Recruitment and Consent

Interested subjects, who respond to recruitment materials and are available to stay in the hospital or clinic for the 7-day Inpatient Treatment part of the study, will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. During the initial interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry.

If still interested after receiving an explanation of the study, subjects will be given an opportunity to review, inquire about, and sign the study informed consent form (see Section 16.4). The subject will then be given a copy of the signed consent form. After collecting demographic information (date of birth, gender, race, and ethnicity), site personnel will access the IWRS to obtain a unique subject number. Subjects will proceed to the screening phase of the study. Screening assessments must be completed within a 7-day time period, but can be completed as early as screening day 1, and randomization may be performed on the next calendar clinic visit day. Subjects must be randomized no later than the 7th day of screening (Day 1). At no time during the screening process should individuals

be given information regarding inclusion or exclusion criteria, with the exception that subjects will be informed that they must exhibit signs of opioid withdrawal immediately before randomization into the study. When individuals are evaluated, questions should be asked in a way that the criteria are not discernible.

Any subject who has difficulty understanding the information contained in the consent form will reread the misunderstood portion(s) of the consent and discuss with a research staff member until s/he shows complete understanding of the information in the consent form, and may thus give full consent. Subjects must complete a consent quiz with 100% accuracy before being randomized. Research staff will work closely with the subject in an effort to help them understand the requirements of their participation. Subjects with literacy problems will be assisted to the extent possible.

Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment at the subject's sole expense. Subjects who are excluded, or who decline participation, may not be rescreened at a later time and will be given referrals to other resources in the area. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

14.2 Screening

Screening assessments will be conducted as shown in Table 1 (Section 15). The screening period will last up to 7 days during which the subjects must satisfy the eligibility criteria and complete all required screening assessments.

14.3 Treatment Phase

14.3.1 Baseline

After a potential participant has completed all screening assessments and has met all eligibility criteria to participate in the study, the Site Investigator or study coordinator will arrange for an early morning hospital or clinic study admission (Day 1). The Baseline period is the morning of Day 1 after the subject has completed final eligibility testing (OOWS-Handelsman) and has been admitted to the inpatient study unit, but before randomization. Baseline assessments to be done are shown in Table 1 and explained in Section 15.2. Subjects admitted to the inpatient unit and successfully complete all Baseline measures will be randomized. The Site Investigator or study coordinator will have the investigational agent dispensed and ready to administer, before the Day 1 8 AM dosing window.

14.3.2 Subject Randomization

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be randomized into the study. The final eligibility criterion is a score of at least 2 on the OOWS-Handelsman at Baseline.

A stratified randomization procedure will be used to separately allocate male and female subjects in 1 of the 3 treatment groups: 2.4 mg lofexidine, 3.2 mg lofexidine, or placebo. Randomization will be implemented centrally, that is, take place across all investigational sites using an Interactive Web Response System (IWRS) managed by the CRO Once eligibility criteria are confirmed at the Baseline visit, site personnel will access the IWRS and complete randomization procedures. The system will assign a unique kit number for drug dispensation according to the randomization scheme. The subject number assigned at screening should be used throughout the study in all source documents and eCRFs.

The Site Investigator or study coordinator will arrange for hospital or clinic admission (in the event that the subject was not admitted the night before randomization) of the subject and for investigational agent to be dispensed to initiate treatment. Even if a subject does not actually receive any investigational agent after s/he has been randomized, s/he is considered to be in the intent-to-treat (ITT) population. should be notified of any irregularities that occur during randomization.

14.3.3 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

After randomization, subjects will receive their first dose of study medication (lofexidine or placebo) during the 8 AM dosing window on Day 1. Subjects will be dosed 4 times daily from Day 1 through Day 7 at 8 AM, 1 PM, 6 PM, and 11 PM. Vital signs will be recorded within 30 minutes before every dose and 3.5 hours after the 8 AM, 1 PM, and 6 PM dose. Other clinical assessments will be gathered between 11:00 AM and noon each day. These clinical assessments are described in detail in Sections 15.4 and 15.5.

14.3.4 Days 8-14 (Open-Label, Continuation Treatment)

Subjects who successfully meet the definition for "completer" based on Days 1-7 (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7) and if clinically indicated (as determined by the Site Investigator) may continue to receive lofexidine to control symptoms for up to an additional 7 days during Days 8-14. Subjects may be treated as inpatients or outpatients, depending on the wishes of the investigator and the subject, using open-label, variable dose lofexidine (as determined by the Site Investigator, but not to exceed 3.2 mg/day). The rationale for the decision to continue treatment or not and the Site Investigator's decision to continue treatment through either an inpatient or outpatient setting must be documented in the subject's source document and eCRF. Lofexidine treatment will terminate and the subject will be discontinued from the study when the Site Investigator judges that the acute phase of opioid withdrawal is essentially complete and the subject no longer needs treatment for abstinence. In any event, no subject will continue to receive lofexidine treatment for more than 14 days total from the onset of abstinence. If being treated as an outpatient, the subject must return to the clinic daily for assessment (see a complete list of assessments in Table 1 of Section 15).

14.3.5 Maintaining and Breaking the Blind

In circumstances where breaking of the blind is necessary for subject safety, Investigators or emergent care professionals requesting to break the blind must call the Sponsor's Medical Monitor (or designee) for consultation before unblinding unless immediate action is required. The decision to break the study blind should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management.

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

If, after discussion with the Medical Monitor, it is determined that the study treatment should be disclosed, medical personnel will be able to access this information via IWRS. 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 following information must be recorded in the subject's record: the reason for unblinding the code, the person who has unblinded the code, and the date and time of unblinding.

14.4 Subject Reimbursement

All compensation will be described in the informed consent form used by each site and approved by the site's IRB or central IRB ( ).

14.5 Study Discontinuation

14.5.1 Subject Discontinuation

A subject can withdraw his/her consent for participation in the study at any time without prejudice. The Site Investigator may discontinue a subject if s/he deems it clinically appropriate for any reason. Additionally, the Site Investigator must discontinue a subject for any of the following reasons:

1. Cardiovascular events (see Section 14.5.2).
2. Serious medical problem thought to be related or unrelated to the study medications.
3. Intercurrent illness or medical complications that, in the opinion of the site investigator, preclude safe administration of study medications.
4. Evidence of illicit drug use while participating in the study during Days 1-7.
5. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study.
6. Requiring therapy with an exclusionary drug.
7. Lack of compliance with protocol and/or unit procedures.
8. During Days 1-7, missing more than 2 doses of study medication in a single 24-hour period or missing more than 6 doses of study medication prior to meeting "completer" criteria (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7).

At any time after a subject meets "completer" criteria, they may be discontinued by the Investigator if s/he feels that the subject has achieved the treatment goal of acute detoxification/ transition. This judgment by the Site Investigator will be made and recorded daily in the subject's source document and on the eCRF on Days 7 (after end of double-blind dosing but before initiating open label dosing) through 14.

Subjects who are removed from study treatment because of adverse events (AEs) or serious adverse (SAEs) will be followed until they are medically stabilized to the satisfaction of the attending physician (see Sections 15.5.1, 16.7, and 16.8). Appropriate safety evaluations will continue to be collected until the subject is discharged from the treatment center or the maximum 14-day treatment period has expired. This stabilization can include medically supervised opioid withdrawal (involving behavioral therapy, rescue opioid medications, and/or non-opioid pharmacotherapy) or referral to an appropriate methadone or buprenorphine therapy program.

Any subject that discontinues from the study, regardless of the reason, will be requested to complete all Study Discontinuation/End of Study assessments and procedures (see Table 1).

The reason for discontinuation will be recorded in the subject's source document and on the end of study form provided in the subject's eCRF. Once discontinued, subjects may not re-enter the study. No randomized subject will be replaced.

Study subjects discontinued from the protocol secondary to a medical or psychiatric concern deemed to be unrelated to lofexidine therapy will be referred, at the subject's sole expense, for appropriate treatment, and may include psychological and lifestyle counseling, support groups, pharmacological, and medical treatment. Subjects will be asked to sign a general consent for the release of information to the referred healthcare provider. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

14.5.2 Cardiovascular Events Requiring Subject Discontinuation From Study

Subjects should be discontinued from the study for any of the reasons listed below, and the event should be recorded in the subject's document and in the eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) and the subject followed until medically stabilized to the satisfaction of the attending physician.

1. New onset of clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval[2]).
2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids).
3. 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.
4. Persistent hypertension – blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If all 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be terminated.
5. 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.
6. Any other clinically significant cardiovascular signs or symptoms that would place the subject at risk.

14.5.3 Trial Discontinuation

The Sponsor (USWM) has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- the incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects;
- subject enrollment is unsatisfactory; and
- data recording is inaccurate or incomplete.

[2] See Section 15.5.3 for procedures for assessment of prolonged QTcF interval.

14.6 Concomitant Therapy

If the subject is admitted to the inpatient study unit the day before Baseline (i.e., Day -1), a single dose of a short-acting opioid (e.g., morphine) may be administered if needed to keep the subject reasonably comfortable; however, the administration may not occur after 8 PM on Day -1.

The concomitant medications or therapies listed below are permitted during Days 1-7 and Days 8-14 of the study.

1. Multivitamins (≤1 tablet orally, administered daily at 9 AM).
2. Guaifenesin (for cough) (≤2 teaspoons orally every 2 hours, as needed [PRN]).
3. Alumina, Magnesia, and Simethicone (for emesis and nausea) (≤30 mL orally every 4 hours, PRN).
4. Dioctyl sodium sulfosuccinate (for constipation) (≤100 mg orally every 8 hours, PRN).
5. Psyllium hydrocolloid suspension (for constipation) (≤1 tablespoon orally every 12 hours, PRN).
6. Bismuth sulfate (Pepto-Bismol®) (for diarrhea) (≤6 doses of 30 mL orally every 24 hours, PRN).
7. Acetaminophen (for headache, muscle aches, or other discomfort) (≤4 doses of ≤650 mg orally every 24 hours).
8. Zolpidem (for insomnia) (≤10 mg orally, PRN, may repeat 1 time if administered before 5:00 AM (i.e., 3 hours before the first morning dose of lofexidine or placebo). Zolpidem must not be administered before 11:00 PM (which is the time of the last daily dose of lofexidine or placebo).

   8a. Note: A short-acting benzodiazepine (e.g., oxazepam) may be used ad libitum for insomnia during the second part of the study (i.e., Days 8-14).
9. Nicotine replacement therapy (patch, inhaler, gum, nasal spray).

All other medications must be approved by the Sponsor's Medical Monitor before administration. If a subject requires any other medication for intolerable nausea and emesis (including a prescription opioid or non-opioid or an over-the-counter opioid or non-opioid) other than alumina, magnesia and simethicone, the subject will be discontinued from the study and given appropriate treatment according to the standard of care (see Section 14.5.1).

All medications taken will be recorded in the subject's source document and eCRF along with dose, dates of administration, and reason for use.

Psychosocial therapy (e.g., art, music, group sessions) will be allowed per standard of care at individual study sites. Acupuncture, however, will not be allowed. All therapies will be recorded in the subject's source document and eCRF.

15 CLINICAL EVALUATIONS

A detailed Schedule of Assessments to be done in the study is provided in Table 1.

Table 1. Schedule of Study Assessments

Activity	Screening Days -6 to -1	Baseline Day 1	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)		Study Discontinuation/ End of Study*
			Inpatient Treatment Days 1-7	In/Outpatient Treatment Days 8-14	
Informed Consent Signed	X				
Screening Number Assigned	X				
Inclusion/Exclusion Criteria	X	X (b)			
Prior Medication History	X	X (b)			
Demographics	X				
Medical and Smoking History	X				
Mini-International Neuropsychiatric Interview	X				
Infectious Disease Assessments (c)	X				
Pregnancy Test (d)	X	X			X
Height	X				
Weight	X				X
Admission to Inpatient Unit		X			
Randomization		X			
Study Medication Administration			X (QID)	X (variable)	
Medication Compliance			X	X	X
Discharge from Inpatient Unit			Day 7		
Efficacy Assessments					
Short Opiate Withdrawal Scale of Gossop (e)		X	X	X	X
Objective Opiate Withdrawal Scale of Handelsman (e)	X	X (f)	X	X	X
Modified Clinical Global Impression (e)			X	X	X
Visual Analog Scale for Efficacy (e)			X	X	X
Clinical Opiate Withdrawal Scale (e)	X	X	X	X	X
Concomitant Medications Assessment			X	X	X
Assessment of Detoxification Completion			X (g)	X	X
Safety Assessments					
Adverse Events Assessment			X	X	X
Vital Signs (Sitting/Recumbent & Standing BP and pulse; respiration, and temperature)	X	X	X (i)	X (j)	X
12-Lead Electrocardiogram (duplicate)	X (k)		X (l)	Day 8 and 14 (m)	X
Pharmacokinetic Sampling			X (n)		
Pharmacokinetic Sampling			Day 3 and 6 (r)		
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X		X (o)	X (o)	X
Physical Exam (p)	X	X	X	X	X

Table 1. Schedule of Study Assessments

Activity	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)				
	Screening Days -6 to -1	Baseline Day 1	Inpatient Treatment Days 1-7	In/Outpatient Treatment Days 8-14	Study Discontinuation/ End of Study*
C-SSRS Baseline Version		X			
C-SSRS Since Last Visit Version			X (s)	X(t)	X
Urine Drug Screen (q)	X	X	X	X	X
Telephone Follow Up (h)					X

Abbreviations: BP = blood pressure; C-SSRS = Columbia Suicide Severity Scale; QID = 4 times daily

* The study discontinuation/end of study assessments/procedures should always be done upon exit from the study.

(a) The Baseline period is the morning of admission, before randomization.

(b) This form is to be updated at Baseline.

(c) A chest x-ray is required only if a PPD (purified protein derivative) skin test for tuberculosis is not done, the current PPD is positive, or if a past PPD was positive.

(d) The urine sample collected on the first day of screening will be divided into two aliquots. One sample will be sent to the central lab ( ) for urinalysis and the other sample will be used for urine drug screening and immediate "dipstick" analysis of pregnancy (females only).

(e) During Inpatient Treatment (Days 1-7), efficacy scales will be completed daily: the Short Opiate Withdrawal Scale of Gossop 3.5 hours (±10 minutes) after the first dose of study medication followed by the other efficacy scales shortly thereafter. Efficacy scales will be completed daily before dosing during Days 8-14.

(f) The Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) will be completed at Baseline to determine final eligibility as subjects must have a score ≥2 in order to participate in the study (inclusion criterion #4).

(g) To be done at the end of double-blind dosing and before initiating open-label dosing.

(h) The follow-up telephone contact will be 30 days after the subject's last dose and will include an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program) and an adverse event evaluation.

(i) Vital signs (resting [sitting/recumbent] and standing blood pressure and pulse; respiration, and temperature) will be measured before every dose and 3.5 hours after study medication administration at 8 AM, 1 PM, and 6 PM (7 times per day).

(j) Vital signs (resting [sitting/recumbent] and standing blood pressure, and pulse) will be measured at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14. Oral temperature and respiration are not required measurements Days 8-14. Note that if subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 8-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary to record the measurements.

(k) Baseline 12-lead electrocardiograms (ECGs) will be done on one day during the screening period, time-matched to the post randomization ECG schedule (i.e., pre-1 PM [before 1 PM dose], 4 PM [3 hours post-dose], and 5 PM [4 hours post-dose]).

(l) 12-lead ECGs will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; and before the first daily dose only on Days 2 and 4..

(m) 12-lead ECGs will be done before the first daily dose and 3.5 hours after first daily dose on Day 8; on Day 14, the ECGs will be done before a dose on that day.

(n) A finger prick blood sample will be collected concurrently with each scheduled ECG during Days 1-7.

(o) Clinical lab testing will be done as clinically warranted throughout the study and at the end of double-blind dosing and before initiating open-label dosing.

(p) A complete physical examination will be performed during screening and the physical exam form will be updated at Baseline. A complete physical examination will be performed on Day 1 (3-4 hours after randomization) and at the end of double-blind dosing and before initiating open-label dosing. During Days 8-14, a complete physical exam will be performed as clinically warranted and at discontinuation from the study.

(q) Urine drug screen will be done at least every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

(r) A finger prick blood sample will be collected at 9 PM and 10 PM (3 and 4 hours, respectively, after the 6 PM dose).

Table 1. Schedule of Study Assessments

Activity	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)				
	Screening	Baseline	Inpatient Treatment	In/Outpatient Treatment	Study Discontinuation/ End of Study*
	Days -6 to -1	Day 1	Days 1-7	Days 8-14	

(s) C-SSRS will completed at 3.5 hours after the first dose (8 AM) on Days 1-7.
(t) C-SSRS will be completed once daily on Days 8-14.

15.1 Screening Assessments

Subjects seeking treatment for opioid dependence at one of the study sites will be screened for study enrollment. Screening assessments must be completed within a 7-day time period. Subjects cannot be admitted later than the morning of the 7th day of the screening period. Written informed consent must be obtained from all study subjects before initiation of any study procedures.

The following screening assessments must be completed during screening after written informed consent is obtained: height; weight; vital signs; blood collection for standard clinical safety laboratory assessments (including hematology and biochemistry); urine sample for confirmatory drug testing, urinalysis, and pregnancy assessment (if female); and infectious disease assessment (see Section 15.5.4.2) and a chest x-ray if a past PPD skin test for tuberculosis was positive.

The urine sample collected will be divided into two aliquots. One sample will go to the central lab (for urinalysis; the other sample will be used for "dipstick" analysis of pregnancy and qualitative drug screening.

The assessments listed below must also be performed during screening.

- 12-lead ECG (in duplicate) will be done on one day during the screening period, time-matched to the post randomization ECG schedule, i.e., pre-1 PM (before 1 PM dose), 4 PM (3 hours post-dose), and 5 PM (4 hours post-dose).
- Medical and smoking/alcohol history.
- Complete physical examination.
- Mini International Neuropsychiatric Interview (M.I.N.I.) [17, 18]. The M.I.N.I will be performed once at screening only to (1) establish that each potential subject is opioid-dependent (inclusion criterion #2), (2) exclude other drug dependency (exclusion criterion #4), and (3) determine the absence of major psychiatric disorders (exclusion criterion #9).
- Prior medications will be recorded to capture all medications taken in the past 30 days.
- OOWS-Handelsman.
- Clinical Opiate Withdrawal Scale (COWS).

15.2 Baseline Assessments

The Baseline period is the morning of admission to the study, before randomization and dosing. Prospective subjects who meet all eligibility criteria must be randomized to the study in time to give the first dose of study medication at 8 AM.

The assessments listed below will be performed during the Baseline period.

- OOWS-Handelsman (score must be ≥2 for randomization).
- SOWS-Gossop.
- COWS.
- Vital signs (resting [sitting or recumbent, if applicable]) and standing blood pressure and pulse; respiration, temperature) measurements.
- Repeat pregnancy assessment (by "dipstick"), if female.
- Repeat urine drug screen (by "dipstick").
- Update Inclusion/Exclusion Criteria form to reflect Baseline assessments.
- Update prior medication form and physical examination form to capture any new medications and/or medical problems since screening.
- Columbia Suicide Severity Rating Scale (C-SSRS) (Baseline version; Appendix 9).

15.3 Assessments During Treatment

15.3.1 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

The assessments listed below will be performed daily (unless otherwise specified) on Days 1-7 (see Section 15.3.3 for assessments/procedures required for early termination from the study).

- Efficacy assessments at estimated time of maximum plasma concentration (T_{max}, i.e., 3.5 hours after the first daily dose) including:
  - SOWS-Gossop;
  - OOWS-Handelsman;
  - Modified Clinical Global Impressions Scale (MCGI) (Subject and Rater);
  - Visual Analog Scale for Efficacy (VAS-E); and
  - COWS.
- C-SSRS at 3.5 hours after the first dose (8 AM) on Days 1-7 (Since Last Visit version; Appendix 10).
- Concomitant medication assessment.
- Completion of detoxification as assessed by the Site Investigator (after completion of the SOWS-Gossop and other efficacy scales) at the end of double-blind dosing and before initiating open-label dosing
- Resting (sitting or recumbent, if applicable, for treatment of an adverse event) and standing blood pressure and pulse; respiration, and temperature before every dose and 3.5 hours after the 8 AM, 1 PM, and 6 PM dose (7 times per day).
- Continuous monitoring for AEs.

- 12-lead ECGs (in duplicate) will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; and before the first daily dose only on Days 2 and 4.
- Complete physical examination 3 to 4 hours after randomization on Day 1 and at the end of double-blind dosing and before initiating open-label dosing.
- Finger prick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG during Days 1-7, and on Days 3 and 6 at 3 and 4 hours post the 6 PM dose (9 PM and 10 PM).
- Clinical laboratory tests as clinically warranted and at the end of double-blind dosing and before initiating open-label dosing.

In addition, qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband.

15.3.2 Days 8-14 (Open-Label, Continuation Treatment)

The assessments listed below will be performed daily (unless otherwise specified) on Days 8-14 (see Section 15.3.3 for assessments/procedures required for discontinuation from the study).

- Efficacy assessments before dosing including:
  - SOWS-Gossop;
  - OOWS-Handelsman;
  - MCGI (Subject and Rater);
  - VAS-E; and
  - COWS.
- C-SSRS before dosing (Since Last Visit version; Appendix 10).
- Concomitant medication assessment.
- Completion of detoxification as assessed by the Site Investigator.
- Pill count to measure compliance with previous day's doses.
- Resting (sitting or recumbent, if required, for treatment of an AE) and standing blood pressure and pulse at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once pre-dose Day 14. Note that if subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 8-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary (Appendix 8) to record the measurements.
- AE assessment.

- 12-lead ECGs (in duplicate) will be done before the first daily dose and 3.5 hours after the first daily dose on Day 8. On Day 14, 12-lead ECGs (in duplicate) will be done once before a dose on that day.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination as clinically warranted.

Qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

15.3.3 Study Discontinuation/End of Study

Any subject that discontinues from the study, regardless of the reason (see all scenarios listed in Section 14.5.1), will be requested to complete all Study Discontinuation/End of Study assessments and procedures as listed below after the last dose of study medication:

- Concomitant medication assessment.
- Completion of detoxification as assessed by the Site Investigator.
- Pill count to measure compliance with previous day's doses if not already performed.
- Blood pressure and pulse at rest (sitting or recumbent, if required, for treatment of an AE) and standing; respiration, and temperature.
- AE assessment.
- 12-lead ECGs (in duplicate).
- Clinical laboratory tests.
- Complete physical examination (including body weight).
- Pregnancy test.
- Urine drug screen.
- C-SSRS (Since Last Visit version; Appendix 10).
- SOWS-Gossop.
- OOWS-Handelsman.
- MCGI (Subject and Rater).
- VAS-E.
- COWS.

A 30-day post discharge follow-up telephone contact will be made 30 days after the subject's last dose for an adverse event evaluation and an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program).

15.4 Efficacy Assessment Methods

15.4.1 Short Opiate Withdrawal Scale (SOWS-Gossop)

The SOWS-Gossop [16] will be completed by the subject at baseline (before randomization), once daily at 3.5 hours (± 10 minutes) after the first dose of study medication on Days 1-7, and once daily before dosing on Days 8-14. Note that at the time of each daily evaluation, subjects should consider their symptoms over the last 24-hour period or since the last time the subject took this test. Also, this scale should be completed before completion of the OOWS-Handelsman, MCGI, VAS-E, and COWS.

The SOWS-Gossop scale assesses subjective symptoms of opioid withdrawal (Appendix 1). 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) (see Table 2 below). The overall score will be the simple sum of the 10-item scores. Lower observed values in SOWS-Gossop scores indicate a more positive clinical outcome.

Table 2. SOWS-Gossop Scoring Method

Condition	Score			
	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/Problems Sleeping	0	1	2	3

Note: Possible score range = 0 to 30.

15.4.2 Objective Opiate Withdrawal Scale (OOWS-Handelsman)

The OOWS-Handelsman [19] will be performed by a trained observer during screening, twice on Day 1 (during Baseline to confirm final eligibility for randomization [score of ≥2 is required per inclusion criterion #4] and 3.5 hours after the first dose of study medication, after completion of the SOWS-Gossop), once daily at 3.5 hours after the first dose of study medication on Days 2-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop).

The subject will be observed for 5 minutes, and the presence or absence of 13 physical signs of opioid withdrawal will be recorded (Appendix 2). The presence of a sign will be assigned 1 point, yielding a possible total score ranging from 0 to 13 (see Table 3 below). Lower observed values in OOWS-Handelsman scores indicate a more positive clinical outcome.

Ambient room temperature (should be 67-75°F) will be recorded on the eCRF for all OOWS-Handelsman observations.

Table 3. OOWS-Handelsman Scoring Method

Symptom (a)	Score (b)	
	0	1
Yawning(Frequency = # of yawns per observation period)	None	≥1
Rhinorrhea(Frequency = # of sniffs per observation period)	0-2	≥3
Piloerection (Gooseflesh - observe subject's arm)	None	Present
Perspiration	None	Present
Lacrimation	None	Present
Mydriasis	None	Present
Tremors (hands)	None	Present
Hot and Cold Flashes (shivering or huddling for warmth)	None	Present
Restlessness (frequent shifts in position)	None	Present
Vomiting (c)	None	Any
Muscle Twitches	None	Any
Abdominal Cramps (holding stomach)	None	Present
Anxiety (d)	None	Mild, Moderate or Severe

(a) Observed over a 5-minute period.
(b) For total score: Minimum = 0; Maximum = 13.
(c) Present during 5-minute observation period.
(d) Mild = observable manifestations, such as foot shaking, fidgeting, finger tapping.
Moderate to severe = agitation, unable to sit, trembling, panicky, complains of difficulty in breathing, choking sensations, palpitations.

15.4.3 Modified Clinical Global Impressions Scale (MCGI)

The Clinical Global Impressions rating scale (1985) was developed by the National Institute of Mental Health (NIMH), and originally contained 3 questions. For this study, Questions #1 and #3 have been modified from the original scale, and Question #2 was not included (Appendix 3).

In the original scale, Question #1 (severity of illness) evaluates the subject using a severity scale from 0 (not assessed), 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The language of this question has been modified in this study for the subject assessment to make the scale more appropriate to opioid withdrawal. The original Question #2 referred to "global improvement" and is omitted from this study, since all subjects will be treated, and there is no untreated screen withdrawal. Question #3 (efficacy index) records responses on a factorial grid – side effects on one side and therapeutic effects on the other side. Since there is no untreated screen withdrawal data, the therapeutic effect cannot be assessed; therefore, only the side effect responses will be examined.

The MCGI scale is used to estimate the overall clinical benefit of lofexidine treatment. The MCGI will be completed once daily at 3.5 hours after the first dose of study medication on Days 1-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). The modified subject and observer scales used in this study are presented below in Table 4. Lower observed values in MCGI scores indicate a more positive clinical outcome.

Table 4. MCGI Scoring Method

MCGI	Score						
	1	2	3	4	5	6	7
Subject Scale							
Severity of Opiate Withdrawal Symptoms (a)	None	Between none and mild	Mild	Moderate	Marked	Severe	Most severe I ever had
Side Effects (b)	None	Slight, does not significantly interfere with daily activities	Moderate, significantly interferes with daily activities	Severe, greater than symptom relief			
Observer Scale							
Severity of Illness (a)	Not at all ill	Borderline ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Among the most extremely ill subjects
Side Effects (b)	None	Does not significantly interfere with subject's functioning	Significantly interferes with subject's functioning	Out-weighs therapeutic effect			

(a) Maximum score of 7.
(b) Maximum score of 4.

15.4.4 Visual Analog Scale for Efficacy (VAS-E)

The effectiveness of lofexidine in alleviation of withdrawal sickness will be assessed by subjects using the VAS-E, which will be completed once daily on Days 1-7, 3.5 hours after the first dose of study medication (after completion of the SOWS-Gossop) and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). Subjects will make a mark on a 100-mm VAS scale to reflect the effectiveness of lofexidine in relieving withdrawal sickness from Not Effective at all (0 mm) to Completely Effective (100 mm). Greater observed values in VAS-E scores indicate a more positive clinical outcome (Appendix 4).

15.4.5 Clinical Opiate Withdrawal Scale (COWS)

The COWS [20] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal, and will be completed during screening, at baseline (before randomization), once daily at 3.5 hours after the first dose of study medication on Days 1-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). The COWS is a clinician-administered instrument that rates 11 common opioid withdrawal signs and symptoms (Appendix 5). These include: resting pulse rate; sweating; restlessness; pupil size; bone or joint aches; runny nose or tearing; gastrointestinal (GI) upset; tremor; yawning; anxiety or irritability; and gooseflesh skin. The score for each item reflects the severity of the sign or symptom, and the total scores are grouped as mild (5-12 points), moderate (13-24 points), moderately severe (25-36 points), and severe (>36 points).

15.4.6 Assessment of Completion of Detoxification

At the completion of Inpatient Treatment on Day 7 or, if applicable at early termination from Days 1-7, the Site Investigator will indicate if the subject has completed detoxification and can be discharged without further lofexidine treatment. The same assessment will be made at each visit during Days 8-14.

15.4.7 Concomitant Medication Use

Multivitamins, nicotine replacement therapy, and several other concomitant medications for minor complaints (e.g., diarrhea, constipation, mild nausea, headache, muscle aches, cough, insomnia) will be allowed during the study. All concomitant medications administered will be recorded daily.

15.4.8 Withdrawal-Related Adverse Events

The Site Investigator will indicate, using his/her best judgment, whether any adverse event that occurs during the study is secondary to opioid withdrawal. Individual items reported on the efficacy scales (i.e., SOWS-Gossop, OOWS-Handelsman) do not automatically qualify as a withdrawal-related AE unless the subject specifically reports them in response to a non-leading question (i.e., "How have you been feeling since I saw you last?"). In the event a subject reports "withdrawal" or a similar event encompassing a collection of potential withdrawal symptoms, the subject should be asked to elaborate so that specific symptoms can be recorded on the AE eCRF. In this case, the AEs recorded should include both the original reported condition (e.g., "withdrawal syndrome") as well as the individual symptoms that the subject lists after further inquiry (e.g., anxiety, upset stomach).

15.4.9 Subject Treatment Status 30 Days After Last Dose

A follow-up telephone contact will be made 30 days after the subject's last dose by the Site Investigator, including an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program) and an adverse event evaluation.

15.5 Safety Assessment Methods

15.5.1 Adverse Events

Adverse events will be assessed and recorded around the same time each day by study staff during Days 1-7. If an AE requires medical attention, it should be reported to a study physician immediately. A study physician must meet with the subject to assess all medical and psychiatric AEs reported by the subject, as well as those recorded by other study staff. Adverse events will be assessed by asking the subject, "How have you been feeling since I saw you last?" After current AEs are assessed, the study physician must review with the subject and assess any AEs unresolved from the previous day. After each daily AE assessment, the physician will record in the subject's source document and AE eCRF, according to the procedures described in Section 16.7, the type of AE and whether serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the physician's best judgment of the severity and relatedness of

each AE. The physician will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.4.8). In general, an AE should not be marked as withdrawal related AND related to study medication.

Any study subject with a related AE will be followed by the attending physician until the event is resolved to the satisfaction of the Site Investigator and Sponsor's Medical Monitor. If the AE is unrelated, the subject will not be discharged until medically stable, and then will be referred, at the subject's sole expense, for ongoing care and/or treatment, which may include psychological and lifestyle counseling, support groups, or pharmacological and medical treatment.

During Days 8-14, in either an inpatient or outpatient setting, subjects will be queried about adverse events daily. All subjects will be instructed to contact the treating physician if he or she feels dizzy (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until instructed by the physician. All reported AEs will be recorded as described above.

15.5.2 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse, respiration, temperature) are to be measured at screening for all subjects.

During Days 1-7, resting (sitting or recumbent, if required, for treatment of an adverse event) and standing systolic and diastolic blood pressure and pulse; respiration, and temperature will be measured at Baseline and on Days 1-7, within 30 minutes before receipt of study medication at 8 AM, 1 PM, 6 PM, and 11 PM and 3.5 hours (±15 minutes) after receipt of study medication at 8 AM, 1 PM, and 6 PM.

During open-label treatment, in an inpatient or outpatient setting, vital signs including resting (sitting or recumbent, if required, for treatment of an adverse event) and standing systolic and diastolic blood pressure and pulse will be measured at least once daily before dosing and 3.5 hours (±30 minutes) after dosing on Days 8-13 and once before a dose on Day 14. If subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 8-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary (Appendix 8) to record the measurements.

For the orthostatic blood pressure readings, subjects will remain at rest for 3 minutes before a blood pressure reading, and then stand for 3 minutes before a second blood pressure reading is taken. If a subject demonstrates potentially clinically significant vital signs, as per any one of the criteria (i.e., systolic values, diastolic values, or pulse values meet the specified criteria) in the guidelines shown below, the event should be recorded in the subject's source document and eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) and the subject should be followed until medically stabilized to the satisfaction of the attending physician. Additional dose-hold and discontinuation criteria are provided in Sections 13.2.2 and 13.2.3, respectively.

Vital Sign Parameter	Observed Value		Change Relative to Screen
Systolic Blood Pressure	≥180 mmHg ≤90 mmHg	A N D	Increase of ≥20 mmHg Decrease of ≥20 mmHg
Diastolic Blood Pressure	≥105 mmHg ≤50 mmHg		Increase of ≥15 mmHg Decrease of ≥15 mmHg
Pulse	≥120 bpm ≤50 bpm		Increase of ≥15 bpm Decrease of ≥15 bpm

Operational Note: When a vital sign or QTcF reading meets any of the defined cut-off criteria for discontinuation, the values will be confirmed by repeating the measurement twice, approximately 10 to 15 minutes apart. If 2 of the 3 total readings confirm that the subject meets discontinuation criteria, the subject will be terminated from the study. If 2 of the 3 total readings are within acceptable limits (and they do not meet the other discontinuation criteria detailed in Section 14.5.2), the subject may continue in the study.

Additionally, when the subject is experiencing blood pressure- or pulse-related symptoms (e.g., lightheaded, dizziness, palpitations), these should be recorded in the subject's source document and eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) even if the vital signs values do not meet the predefined criteria shown above.

15.5.3 12-Lead Electrocardiograms

Using ECG core lab-provided and validated instruments, baseline paper tracing 12-lead ECG (in duplicate) will be conducted on one day during the screening period, time-matched (± 15 minutes) to the post randomization ECG schedule, i.e., pre-1 PM (before 1 PM dose), 4 PM (3 hours post-dose), and 5 PM (4 hours post-dose). During Days 1-7, 12-lead ECGs (in duplicate) will be conducted before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, early termination during Days 1-7. During open-label treatment, 12-lead ECGs (in duplicate) will be conducted as follows: before the first daily dose and 3.5 hours after the first daily dose on Day 8; once before a dose on Day 14; and, if applicable, at discontinuation from the study during Days 8-14. ECG intervals and abnormalities will be read centrally by a computer and confirmed by an individual accredited to read ECGs at the ECG core lab . A qualified physician on site will evaluate tracings if there is significant abnormality. The following intervals will be computed:

- Ventricular Rate — Number of R waves appearing within a 6-second period, multiplied by 10;
- PR Interval — Measured from the onset of the P wave to the onset of the QRS complex;
- QRS Complex — Measured from the beginning of the down stroke of the Q wave to the completion of the upstroke of the S wave;

- QT Interval — Measured from the beginning of the down stroke of the Q wave to the completion of the T wave;
- QTc (Bazett) — QT interval corrected for heart rate using Bazett's formula (QT/square root of RR) (for analysis purposes);
- QTc (Fridericia) — QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject termination purposes).

  At screening (baseline assessment), a QTcF interval greater than 450 msec for males and greater than 470 msec for females will exclude the subject from study participation (see exclusion criterion #6 in Section 11.2.2). In such cases, 2 additional ECGs should be taken at 10- to 15-minute intervals. The QTcF interval on all 3 ECGs should be confirmed by the Site Investigator and if 2 of the 3 QTcF intervals exceed the gender-specific cut-off, then the subject should be judged a screen failure and not randomized to treatment.

  During the treatment phase of the study, when any QTcF interval exceeds 495 msec, 2 additional ECGs should be taken at 10- to 15-minute intervals. The QTcF interval on all 3 ECGs should be confirmed by the Site Investigator. If it is determined that 2 of the 3 QTcF intervals exceed 500 msec or >25% above screen value, then the subject will be terminated from the study.

  Any time that 2 of the 3 QTcF measurements exceed 500 msec, contact the Sponsor's Medical Safety Monitor, to discuss the subject and the AE/SAE determination.

15.5.4 Clinical Laboratory Evaluations

15.5.4.1 Standard Laboratory Tests

Standard clinical laboratory safety evaluations (see Table 5) will be performed for all subjects at screening, as needed at the physician's discretion throughout the study, at the end of double-blind dosing and before initiating open-label dosing, and at discontinuation from the study. For this multicenter study, a central laboratory ( ) will be used that is directly accredited by the College of American Pathologists (CAP) and licensed by the Clinical Laboratory Improvement Act of 1988 (CLIA); both certification and accreditation must be renewed every 2 years. The laboratory will need to provide a copy of current certification and provide the normal values for all analytes to determine the upper limit of normal (ULN).

Table 5. Hematology, Chemistry, and Urinalysis Tests

Hematology (a)	Chemistry (b)	Urinalysis
Hemoglobin	Cholesterol	Color
Hematocrit	Triglycerides	Clarity
Platelet count	Sodium	pH
Red blood cell (RBC) count	Potassium	Specific gravity
MCV	Chloride	Protein
MCH	Carbon dioxide (CO_2)	Glucose
MCHC	Glucose	Ketones
RDW	Creatinine	Bilirubin
White blood cell (WBC) count	Albumin	Nitrite
WBC differential (% and Abs)	Total protein	Blood
neutrophils	Calcium	Urobilinogen
lymphocytes	Phosphorus	Leukocyte esterase
monocytes	Aspartate aminotransferase (AST)	WBC
eosinophils	Alanine aminotransferase (ALT)	RBC
basophils	Gamma-glutamyl transpeptidase (GGTP)	Epithelial cells
Prothrombin time (PT)	Total bilirubin	Bacteria
aPTT	Lactate dehydrogenase (LDH)	Mucus
	Alkaline phosphatase	Casts
	Blood urea nitrogen (BUN)	Crystals
	Thyroid-stimulating hormone (TSH)	
	Free thyroxine (T4)	

Abbreviations: Abs = absolute; aPTT = activated partial thromboplastin time; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; RDW = red blood cell distribution width

(a) Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™).

(b) Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures.

15.5.4.2 Infectious Disease Panel and Syphilis Tests

The infectious disease panel and syphilis tests will be assayed at screening only. Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), and Hepatitis C virus antibody (anti-HCV). A PPD skin test for tuberculosis and/or a chest x-ray will be performed on all subjects. If the PPD is positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. Syphilis antibody testing will be performed using an automated enzyme immunoassay (EIA). If the EIA is positive, a confirmatory rapid plasma reagin (RPR) test will be performed. If the RPR test is non-reactive, a confirmatory TPPA (treponema pallidum particle agglutination assay) test will be performed.

If the PPD with chest x-ray, chest x-ray, or RPR/confirmatory TPPA test is positive, subjects will not be eligible for study participation and will be referred, at subject's sole expense, for appropriate follow-up and/or treatment.

15.5.4.3 Urine Toxicology Screening

Qualitative urine drug screening (UDS) will be performed at screening for all subjects, at Baseline, and at least every other day for the following drugs: amphetamines/ methamphetamines, cocaine, barbiturates, opiates, benzodiazepines, cannabinoids, methadone, and buprenorphine. The central lab will provide standard sets of UDS "dipsticks" for use across all sites.

15.5.4.4 Pregnancy Test

A "dipstick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening, at Baseline, and at discontinuation from the study for all female subjects regardless of their childbearing capacity. The central lab will provide study sites with a supply of pregnancy dipsticks.

15.5.4.5 Pharmacokinetic Sampling

A finger prick blood sample will be collected concurrently with each scheduled ECG during Days 1-7 only. In addition, finger prick blood samples will be collected on Days 3 and 6 at 9 PM and 10 PM (3 and 4 hours, respectively, after the 6 PM dose).

15.5.5 Physical Examination

A complete physical examination of 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 should be performed at screening for all subjects.

An update of the Physical Exam is required at Baseline (before randomization on Day 1) and then a complete physical examination should be performed 3 to 4 hours after randomization on Day 1 and at the end of double-blind dosing and before initiating open-label dosing. For Days 8-14, a complete physical examination should be performed as clinically warranted and at discontinuation from the study.

Height should be recorded at screening only.

15.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS measures both suicidal ideation and suicidal behavior and will be completed at Baseline (before dosing on Day 1), 3.5 hours after the first dose (8 AM) on Days 1-7, and once daily pre-dose on Days 8-14 or, if applicable, at discontinuation from the study. The Baseline version of the C-SSRS (Appendix 9) will be used to assess lifetime suicidality on Day 1 (before dosing). At all other protocol-specified time points, the C-SSRS – Since Last Visit version (Appendix 10) will be used to assess the subject's suicidality since the last assessment.

15.6 Other Assessments

15.6.1 Prior Medications

All medications taken by the subject for the 30 days before screening and during the screening period will be recorded in the subject's source document and on the Prior Medication eCRF. Prior medication usage should be updated at Baseline. The reported medications will be reviewed and approved by the Site Investigator/study physician for entry into the study.

15.6.2 Concomitant Medication Administration

Concomitant medication administration will be recorded daily. All concomitant medications should be recorded in the subject's source document and on the Concomitant Medication eCRF. All medications taken by the subject during study participation that are not on the list of permitted concomitant medications (see Section 14.6) must be pre-approved by the Site Investigator/study physician with concurrence of the Sponsor's Medical Monitor and recorded on the concomitant medication administration form.

16 REGULATORY AND REPORTING REQUIREMENTS

16.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool. The monitoring of the sites participating in the trial will be executed according to GCP guidelines. Monitors will examine subjects' study files including source documents in both the clinic files and subjects' official medical records, and will also review regulatory/essential documents such as correspondence with the IRB and the Sponsor (USWM). Areas of particular concern will be subject informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, safety reports/regulatory forms, subject records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following each visit and forwarded to the Sponsor's Clinical Project Manager. Monitors will also prepare follow-up letters detailing their findings and any items requiring further resolution or attention by the site. Follow-up letters will be provided to the Site Investigator, site coordinator, and Sponsor's Clinical Project Manager.

16.2 FDA Form 1572 and Financial Disclosure

The Site Investigator will sign a Statement of Investigator (FDA Form 1572) before initiating this study. The names of any sub-investigators must appear on this form.

The Site Investigator and any sub-investigators will also sign a Financial Disclosure form before initiating this study.

16.3 Institutional Review Board Approval

Before initiating the study, Site Investigator will obtain written IRB approval to conduct the study. No study medication will be shipped until IRB approval is obtained. Should changes to the study protocol become necessary, protocol amendments (provided by the Sponsor) will be submitted in writing to the central IRB and the Site Investigator's IRB for IRB approval before implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The IRB must be a properly constituted board or committee operating in accordance with GCP Title 21 Part 56 of the US CFR relating to IRBs and the ICH Guideline for GCP (E6).

16.4 Informed Consent/HIPAA Authorization

Properly executed written informed consent, in compliance with 21 CFR 50 and ICH guidelines, shall be obtained from each subject before entering the subject into the trial. Attention is directed to the basic elements that are required in the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]). Additional elements of informed consent, if appropriate, must be included in the informed consent document (21 CFR 50.25[b]). A standard Informed Consent document will be approved by a central IRB Any study site that requires a site-specific Informed Consent document must have the document IRB-approved and the final IRB-approved document must be provided to the Sponsor for regulatory purposes.

All potential subjects for the study will be given a current copy of the Informed Consent Form to read. The Site Investigator, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all of the subject's questions regarding the study. If the subject desires to participate in the study, s/he will be asked to sign the Informed Consent. Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%. No subject will undergo any study procedures before signing the Informed Consent form, which should be signed before screening. A signed copy will be given to the subject and a signed copy shall be maintained in the subject's clinical file as well as the Regulatory Binder at each study site. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

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

16.5 Drug Accountability

All study drug required for completion of this study will be provided by the Sponsor (USWM). Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be returned to the Sponsor.

16.6 Outside Monitoring

16.6.1 Data and Safety Monitoring Board (DSMB)

Adverse event data reported during the study will be reviewed by a Data and Safety Monitoring Board (DSMB) comprised of outside experts in substance abuse treatment, clinical trials, and biostatistics. The DSMB will meet by conference call or WebEx every 3 months during the life of the study to review adverse event and serious adverse data tables and data listings. Any serious adverse event requiring expedited reporting to the FDA will be reviewed immediately by the DSMB. The board will be blinded to subjects' actual treatment assignments, but may break the blind if safety concerns arise from the blinded data. Although the DSMB may also have access to efficacy data, it will not be commissioned to recommend trial termination due to superior treatment efficacy versus placebo, and the trial will not be stopped prematurely for that reason.

16.6.2 Medical Monitor

The Sponsor's (USWM) Medical Monitor will be responsible for attempting to establish concurrence with the Site Investigator on the severity and seriousness of any AEs and SAEs, the relatedness to the study treatments, the expectedness of the event, and for determining if the SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 6). The Sponsor's Medical Monitor will also be responsible for tracking and assessing trends in the SAEs reported. Further, the Medical Monitor is available to consult with the Site Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications).

16.6.3 Clinical Monitors

All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, all eCRFs and corresponding source documents for each subject. These monitoring visits will provide an opportunity for evaluation of the progress of the study and to inform the Sponsor of potential problems.

The study will be monitored according to an approved monitoring plan. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for; verify that subjects' consent for study participation has been properly obtained and documented; confirm that research subjects entered into the study meet inclusion and exclusion criteria; and assure that all essential documentation required by GCP guidelines are appropriately filed.

Monitors will conduct a site initiation visit before the start of the study for any investigational site not represented at the investigator meeting. At this visit, the monitor will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by USWM or designee will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify

that study procedures are being conducted according to the protocol guidelines and review AEs and SAEs. At the end of the study, they will advise on storage of study records and return of unused study agents. All sites should anticipate visits by the Sponsor, its representatives, and the FDA.

16.7 Adverse Event Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the Site Investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix 6. The occurrence of AEs will be assessed starting at the treatment phase of the protocol.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent or clinically significant. For this study, events reported by the subject, as well as clinically significant abnormal findings in the opinion of the Investigator on physical examination, laboratory evaluation, or C-SSRS (for example, score of 3 or more on the scale) will be considered an AE and will be recorded in the subject's source document and on the AE eCRF. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present before clinical trial entry and do not worsen are not considered AEs.

After each AE assessment, the physician will record in the subject's source document and on the AE eCRF the type of AE and whether serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the physician's best judgment of the severity and relatedness of each AE. The physician will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.4.8). In general, an AE should not be marked as withdrawal related AND related to study medication.

Each day, a study physician must review any AEs that are reported as beginning or as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by a study physician until satisfactory resolution.

16.8 Serious Adverse Events (SAEs)

Each adverse event or reaction will be classified by the Site Investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed.

The Code of Federal Regulations (CFR) Title 21 part 312.32 and ICH Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the US FDA, defines a SAE or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death during the period of protocol-defined surveillance;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity; or
- results in a congenital anomaly/birth defect.

Important medical events that may not result in death, be life–threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, the event may jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the product package insert or Investigator's Brochure.

All subjects with SAEs must be followed up for outcome. If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization.

Reporting requirements for SAEs are described in detail in Appendix 6. There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to the FDA. Any SAEs, including death due to any cause, which occurs to any subject entered into treatment in this study or within 30 days following cessation of the last dose of treatment with the study medication, whether or not considered related to the investigational product, must be reported within 24 hours, from the time any study staff member is made aware of such, to the Sponsor (USWM).

16.8.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study treatment(s).
- All deaths, regardless of cause or relationship, must be reported for subjects on study and for deaths occurring within 30 days of last study treatment or within 30 days of last study evaluation, whichever is longer.

- "Occurring at any dose" does not imply that the subject is receiving study treatment at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE; however, administration of study drug may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as severe should not be confused with a SAE. Severity is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe (see Appendix 6 for assessment of the intensity of an AE). An event is defined as "serious" when it meets one of the predefined outcomes described above.

16.9 Overdose

Any accidental or intentional overdose (any increase in frequency or dosage of study treatment [lofexidine] that exceeds total dosing of 3.2 mg per day), misuse or abuse of study treatment, whether suspected or confirmed, and whether or not associated with an adverse experience, must be reported within 24 hours to USWM or designee. This will include providing details of signs or symptoms, clinical management, and outcome if available.

Any clinical sequelae in association with the overdose should be reported as an AE as outlined in Section 16.7 or SAE as outlined in Section 16.8. An overdose will be considered a SAE only if any of the seriousness criteria are met in Section 16.8.

16.10 Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Site Investigator or his or her designee 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 of completing the study medication. All subjects who become pregnant must be withdrawn from study medication and must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor.

17 STATISTICAL APPROACH

17.1 General Considerations

Continuous or ordered categorical variables not subject to censoring will be summarized with the mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. Continuous or ordered categorical variables subject to censoring (e.g., time to removal from study treatment) will be summarized by the 25th percentile, median, 75th percentile derived from Kaplan-Meier estimates of probabilities. Unordered categorical variables will be summarized with counts and percentages. Descriptive statistics will be provided for each treatment group separately as well as all subjects combined. Additionally, descriptive statistics will be provided by gender.

Detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared as a standalone document and finalized before database lock and unblinding of treatment assignments.

17.2 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

It is hypothesized that a daily dose of either 2.4 mg or 3.2 mg lofexidine will achieve greater efficacy than placebo with respect to overall symptom relief over the first 7 days of opioid withdrawal (primary endpoint) and will increase the likelihood of subjects completing Days 1-7 of treatment (secondary endpoint). Further, safety measures in the 2.4 mg and 3.2 mg total daily dose groups will be compared descriptively to assess whether the lower dose results in fewer and less severe adverse events than does the higher dose.

17.2.1 Analysis Populations

Three principal analysis populations are defined as follows:

- Intent-to-treat (ITT), consisting of all randomized subjects. Subjects will be assigned for analysis according to the group to which they are randomized.
- Modified intent-to-treat (mITT), consisting of all subjects in the ITT group who received at least one dose of study medication.
- Safety consisting of all subjects who received at least one dose of study medication.

The principal analysis population for the analyses of demographics and baseline characteristics and efficacy will be the mITT population. Sensitivity analyses of the completion status endpoint will be carried out on the ITT population. Safety summaries will be provided for the Safety population. Data recorded on subjects who are in the ITT but not in the mITT or Safety populations will be included in data listings.

17.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

17.2.3 Subject Disposition

Subject disposition will be summarized descriptively.

17.2.4 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- AUC based on SOWS-Gossop scores from Days 1 through 7.

17.2.5 Secondary Efficacy Endpoint

The secondary efficacy endpoint is:

- Completion status (i.e., whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7).

17.2.6 Tertiary/Exploratory Endpoints

The tertiary/exploratory endpoints are:

- SOWS-Gossop, OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS scores on Days 1, 2, 3, 4, 5, 6, and 7;
- Retention analysis (time to removal from study treatment) over the 7 inpatient days;
- Concomitant medication analysis;
- Withdrawal-related AE analysis;
- Evaluation of subject treatment status 30 days after last dose;
- Status of detoxification on Day 7 or early termination as assessed by the Site Investigator; and
- In addition, single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed, as may AUC based on COWS scores from Days 1 through 7.

17.2.7 Control of the False Positive Rate and Statistical Testing Strategy

All statistical tests for efficacy will be one-sided. For the primary and secondary endpoints, the treatment comparisons subject to control of the false positive rate will be 3.2 mg lofexidine vs. placebo and 2.4 mg lofexidine vs. placebo. (Comparisons of 3.2 mg vs. 2.4 mg will be descriptive.) The familywise error rate (FWE) for the collection of primary and secondary endpoint comparisons will be controlled at the 0.025 level, one-sided, by a sequential testing strategy in which hypotheses are tested in the following order, each at the 0.025 level, one-sided.

1. Primary: AUC(1-7), 3.2 mg lofexidine versus placebo;
2. Primary: AUC(1-7), 2.4 mg lofexidine versus placebo;
3. Secondary: Completion rate, 3.2 mg lofexidine versus placebo; and

4. Secondary: Completion rate, 2.4 mg lofexidine versus placebo.

Adjusted p-values for these 4 treatment comparisons, based on this sequence of statistical tests, are defined in the table below.

Test Order	Endpoint Comparison	P-value	
		Unadjusted (a)	Adjusted
1	AUC(1-7), 3.2 mg vs placebo	p_1	p_1
2	AUC(1-7), 2.4 mg vs placebo	p_2	$\max(p_1, p_2)$
3	Completion rate, 3.2 mg vs placebo	p_3	$\max(p_1, p_2, p_3)$
4	Completion rate, 2.4 mg vs placebo	p_4	$\max(p_1, p_2, p_3, p_4)$

(a) P-values p_1 and p_2 are one-sided, derived from the statistical test described in Section 17.2.8.1; p-values p_3 and p_4 are one-sided, derived from the statistical test described in Section 17.2.8.2.

Any adjusted p-value less than 0.025 in magnitude will be declared statistically significant.

The tertiary/exploratory endpoints will be tested without multiplicity adjustment.

17.2.8 Statistical Methods for Efficacy

17.2.8.1 SOWS-Gossop AUC(1-7)

A pattern-mixture approach [21], with subjects stratified by disposition within Days 1-7, will be used in assessing SOWS-Gossop AUC(1-7). The 4 disposition strata are subjects: who complete Days 1-7 of the study (see Section 17.2.5); who discontinue due to lack of efficacy (including adverse events related to opioid withdrawal); who discontinue due to adverse events related to intolerability or toxicity to study drug; and who discontinue for other reasons. The inference is comprised of several steps:

1. Transformation. Because of the inherent skewness in the SOWS-Gossop scores the raw data will first be transformed to the logarithm of the score plus 1.0.
2. Modeling. A linear mixed effects repeated-measures model will be constructed for the SOWS-Gossop score. The fixed effects will be disposition stratum, treatment and time, and their interactions, as well as a main effect of gender (randomization stratification factor) and baseline SOWS-Gossop score as a one degree of freedom covariate. For each combination of treatment and stratum, the time course will be modeled as a linear change point model, allowing for one slope between Days 1 and 2 and a possibly different slope from Days 2 through 7. The model will parameterized to ensure that the predictions from the two line segments agree at Day 2. Subjects will be treated as a random effect, and the slope and intercept parameters will be treated as random coefficients. Modeling the time course, rather than using each time point as a discrete level of a model factor, allows estimation of group means through Day 7 even in the non-completer strata. The choice of Day 2 as the change point is based on prior lofexidine studies, in which SOWS-Gossop mean scores in the placebo group increased from Day 1 to Day 2 and then decreased through Day 7. The modeling allows a different time course for each of the lofexidine dose groups.

3. Point estimates of AUC(1-7). For each combination of disposition stratum, treatment and study day, the estimated least squares means SOWS-Gossop (on the log scale) for males and females will be combined using a weighted average, the weights being the relative proportions of males and females in the mITT population. The results will then be transformed back to the original SOWS-Gossop scale of measurement, from which point estimates of AUC(1-7) for each combination of stratum and treatment will be computed using the trapezoidal rule. It should be noted that these calculations will not be derived from AUC(1-7) computed within individual subjects, many of whom will have incomplete data for the later study days in Days 1-7. In particular, there will be no imputation of data for individual subjects.
4. Estimates of treatment effect. For each active treatment, the treatment effect (lofexidine 3.2 mg versus placebo or lofexidine 2.4 mg versus placebo) will be estimated with respect to AUC(1-7) within each disposition stratum. Then a weighted average of treatment effects will be computed, where the weights are the relative proportions of subjects in the 4 strata.
5. Interval estimates of AUC(1-7) and hypothesis testing. The covariance matrix of the mixed model's estimated fixed effects will be used with standard linear model methods to derive the covariance matrix of the weighted average of male and female log-transformed SOWS-Gossop scores. The multivariate delta method will be used to derive the covariance matrix of the back-transformed SOWS-Gossop time course. Standard linear model methods will then be used to derive the covariance matrix of the weighted average of AUC(1-7) treatment effects, from which confidence intervals and p-values will be derived.

17.2.8.2 Completion Status

The proportion of subjects in each treatment arm who receive at least one dose of study medication on Day 7 and complete the 3.5-hour post-dose SOWS-Gossop assessment on Day 7 will be analyzed using Cochran-Mantel-Haenszel tests, with gender as the stratifying factor. One test will compare the 3.2 mg lofexidine group to placebo; a second will compare the 2.4 mg lofexidine group to placebo.

17.2.8.3 SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7

The pattern-mixture approach, with the same stratification and treatment of gender used for the AUC(1-7) analysis, will be used to assess treatment effect with respect to SOWS-Gossop on Days 1, 2, 3, 4, 5 and 6 (but not 7). A single linear mixed effects repeated-measures model will be constructed for the transformed SOWS-Gossop score. Subject will be a random effect. The fixed effects will be disposition stratum, treatment and time, with each study day as a discrete level of the time factor, and their interactions. Estimated means for each combination of stratum, treatment and day will be back-transformed to the original SOWS-Gossop scale of measurement. Like the AUC(1-7) calculation, the weighted average of treatment effects will be calculated along with confidence intervals and p-values. This approach will provide no information on the non-completer strata on Day 7. Therefore, the modeled time course from the AUC(1-7) analysis will be used to estimate SOWS-Gossop on Day 7 for all combinations of disposition stratum and treatment, and Day 7 comparisons will be based on these estimates.

17.2.8.4 OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS

The same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7 will be used for OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS scores on Days 1, 2, 3, 4, 5, 6, and 7. Types of data transformation, if any, to be used before mixed effects modeling, will be specified in the SAP.

17.2.8.5 Retention Analysis (Time to Removal from Study Treatment)

Time to removal from study treatment is defined as the last study day on which the subject received treatment. The time for subjects who complete some but not all treatment on Day 7 will be Day 7, uncensored. Subjects who complete all treatments on Day 7 will be censored at Day 7. This endpoint will be summarized descriptively for each combination of treatment group and gender with Kaplan-Meier curves and tabulations of the number and percentage of subjects newly removed from receiving study treatment on each of inpatient Days 1 to 7. Each lofexidine dose group will be compared inferentially to placebo with a Cox proportional hazards regression model of time to removal from study, stratified by gender, with treatment as the independent variable. The estimated hazards ratio will be reported as a descriptive measure. The p-value on the log hazards ratio will be converted to a one-tailed p-value by considering whether the hazard ratio indicates a delay in time to removal in the lofexidine group versus the placebo group.

17.2.8.6 Concomitant Medication Analysis

For each of Days 1 to 7, each subject's number of concomitant medication doses taken will be treated as a continuous variable. Descriptive statistics will be provided on the as-observed data on each study day. In addition, least squares means and p-values comparing each treatment to placebo will be obtained with the same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7. Types of data transformation, if any, to be used before mixed effects modeling, will be specified in the SAP.

17.2.8.7 Status of Detoxification on Day 7 or Early Termination as Assessed by the Site Investigator

Descriptive statistics (numbers and percentages) on the status of detoxification (successful/unsuccessful) as assessed by the Site Investigator at Day 7 or early termination will be presented by treatment group overall and by gender within treatment group.

17.2.8.8 Single Items from the OOWS-Handelsman and COWS, and COWS AUC(1-7)

Single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed; the scores will be treated as continuous variables and analyzed using the same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7. COWS AUC(1-7) may also be analyzed; a modeling approach analogous to the modeling of SOWS-Gossop AUC(1-7) will be used. While the functional form of the time course for SOWS-Gossop is based on historical data, the functional form of the time course for COWS will be based on the data from this study.

17.2.9 Power Calculations

Treatment effect and subject variability with respect to SOWS-Gossop scores were estimated from the prior Phase 3 study (USWM-LX1-3002), using the random coefficients model planned for the present study and estimating the treatment effect of 3.2 mg lofexidine versus placebo with respect to AUC(1-7). It was assumed that the treatment effect of the 2.4 mg lofexidine dose will be three-fourths the treatment effect of the 3.2 mg dose. The table below shows the power to find a significant treatment effect for the comparisons of the two lofexidine treatments versus placebo, assuming a sample size allocation ratio of 3:3:2 (3.2 mg lofexidine : 2.4 mg lofexidine : placebo) and accounting for the sequential testing approach described in Section 17.2.7. The power to find a statistically significant effect of the 3.2 mg lofexidine dose with respect to AUC(1-7) is in excess of 90% with the planned total sample size of 600.

	Power (%) with Respect to AUC(1-7)	
Total Sample Size	**3.2 mg Lofexidine versus Placebo**	**2.4 mg Lofexidine versus Placebo**
600	94.6	72.6
550	92.6	67.6
500	90.1	62.2
450	86.8	55.7

17.2.10 Subgroup Analyses

The models used for the primary analysis will be modified for each of several subgroups to include the subgroup and its interaction with treatment as a fixed effect. Subgroups include age, gender, and race. The SAP will list all subgroups to be analyzed, their classifications (e.g., age dichotomization, race groupings), and modeling details.

17.2.11 Safety Measures

The safety measures during Days 1-7 of the study are AEs, vital signs, ECGs (primarily evaluated for changes in QTcF versus time-matched controls for both doses of lofexidine and placebo), clinical laboratory measures, physical exams, and suicidal ideation and behavior. Adverse event summaries will include tabulations overall and by seriousness, severity, and causality assessment. The data from these measures recorded during Days 1-7 will be summarized descriptively by treatment group. In addition, each lofexidine group will be compared inferentially to the placebo group using chi-square tests for categorical variables and t-tests within an analysis of variance for continuous variables; the resulting p-values will not be adjusted for multiple testing.

17.3 Days 8-14 (Open-Label, Continuation Treatment)

Safety and effectiveness endpoints for Days 8-14 will be summarized by randomized treatment group.

17.3.1 Assessment of Effectiveness

Summary statistics will be provided by treatment day (overall and by gender) for:

- SOWS-Gossop;
- OOWS-Handelsman;
- MCGI (Subject and Rater);
- VAS-E; and
- COWS.

In addition, the following will be summarized overall and by gender over Days 8-14:

- Duration of exposure;
- Number and proportion of subjects successfully completing detoxification as assessed by the Site Investigator;
- Distribution of number of days required to complete detoxification as assessed by the Site Investigator;
- Average daily dose of lofexidine; and
- Concomitant medications.

17.3.2 Assessment of Safety

Safety measures will be summarized for the following subject cohorts:

- All treated subjects;
- Treated subjects without urinary evidence of illicit drug use; and
- Treated subjects with urinary evidence of illicit drug use (may be further subdivided by type of illicit drug used).

Descriptive statistics will be provided for:

- All AEs;
- New onset AEs (including those observed during Days 1-7 whose severity during Days 8-14 is greater than observed during Days 1-7);
- Vital signs;
- ECGs;
- Clinical laboratory tests;
- Physical examinations; and
- C-SSRS.

18 DATA MANAGEMENT AND CASE REPORT FORMS (CRFs)

Data management activities and statistical analytical support will be coordinated through the CRO ( ). The CRO will be responsible for the construction and accuracy of the study database.

18.1 Data Collection

Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs). The eCRFs will be supplied by the CRO ( ). CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual.

The Site Investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The Site Investigator is also responsible for maintaining any source documentation related to the study, including any films, lab reports, or ECG tracings.

Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor representatives, the central IRB and the site's IRB.

18.2 Electronic Data Capture

Data entered by site personnel into the electronic data capture (EDC) system will be reviewed by the CRO ( ). If incomplete or inaccurate data are found, a query in the EDC system will be generated for response by the clinical site. Sites will promptly resolve data inconsistencies and errors. An audit trail of any corrections or changes to the data in the EDC system will be maintained. USWM will receive reports at least monthly regarding the quality and quantity of data submitted to the CRO.

Site Investigators agree to routine data audits by the staff of USWM. USWM monitors will routinely visit each site to assure that data entered in the EDC system are in agreement with source documents at the sites. The monitors will also verify that investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented in the subject's progress notes, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol.

18.3 Data Analysis

When the study is completed, all data have been entered into the clinical database, and the final database has been locked, statistical analysis of the data will be performed by the CRO's ( ) statisticians or an independent statistician in accordance with the Analytical Plan of this protocol (see Section 17) and detailed in the SAP. Periodically, during the investigation, the CRO will also prepare summary reports of the data, with no identification or grouping by randomized treatment, so that progress of the study can be monitored. Various reports will be prepared for USWM and others, as appropriate.

18.4 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document. Any duplicate of a source document to be retained as a part of a eCRF should maintain subject confidentiality per HIPAA.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of 2 years after the approval of a new drug application (NDA) and finalization of all marketing strategies, or if the NDA is not approved, for 2 years after discontinuation of the IND, whichever is the later. In all instances sites must get permission from USWM before disposition of any study documentation and materials.

18.5 Confidentiality

18.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the Site Investigator and IRB.

By participating in this protocol the Site Investigator affirms to USWM that information furnished to the Site Investigator by USWM will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee (or similar or expert committee), affiliated institution, and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

18.5.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports, and other records will be coded using alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet. Only research staff and USWM officials will have access to the records. Subject information will not be released without written permission,

except as necessary for monitoring by the FDA or USWM. USWM will file for a Certificate of Confidentiality that will cover all sites participating in the study (see Appendix 7).

By participating in this protocol the investigator agrees that within local regulatory restrictions and ethical considerations, USWM or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

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

19 PUBLICATIONS OF THE STUDY RESULTS

It is understood by the Site Investigator that the information generated in this study will be used by the Sponsor (USWM) in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Site Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Because this is a multicenter study, the combined results of the study will be published before the Investigator submits site-specific results for publication. Any results of medical investigations with the Sponsor's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Site Investigator and Sponsor representative(s) 60 days before submission for publication or presentation. Due regard shall be given to the Sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

The Sponsor shall be furnished with a copy of any proposed publication. In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating investigators and the prior review of the Sponsor. In case of disagreement amongst the investigators participating in a multicenter investigation, the Sponsor will be the final arbiter. Sponsor comments shall be given without undue delay, and not later than within 60 days. If they are not accepted, the senior author of the manuscript and the Sponsor's representatives shall promptly meet to discuss further and endeavor to agree on the final wording and/or disposition of the publication. The above procedure also applies to studies that are not completed, including those that are prematurely discontinued.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

20 PROTOCOL ADHERENCE AND AMENDMENTS

The Site Investigator and each sub-investigator must adhere to the protocol as detailed in this document. Only the Sponsor (USWM) may modify the protocol. All amendments that have an impact on subject risk or the study objectives, or require revision of the informed consent document, must receive approval from the DSMB and central IRB/individual site's IRB before their implementation.

21 QUALITY CONTROL AND QUALITY ASSURANCE

Following written standard operating procedures, study monitors will verify that the clinical trial is conducted and data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Reports on monitoring activities will be submitted to the Sponsor.

The Sponsor (USWM) will secure agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

The CRO (will be the Data Coordinating Center and will implement quality control procedures in accordance with GCPs and their internal Standard Operating Procedures, beginning with the data entry system 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.

22 REFERENCES

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March 12, 2013

USWM-LX1-3003-1 Administrative Change #1

To Whom It May Concern:

US WorldMeds, LLC would like to notify you of a change being made in the protocol-specified clinical trial material labeling requirements for protocol USWM-LX1-3003-1 Protocol Amendment 1 dated 08-MAR-2013.

The name of the study (ie, full protocol title), will not be included in final clinical trial material labeling. The Sponsor's name and the protocol number will be provided, in addition to the information as outlined in Section 12.5.

US WorldMeds, LLC will notify all Site Investigators this change in protocol-specified labeling requirements, and the change will be incorporated into any future Protocol Amendments.

Thank you, and please do not hesitate to contact me with any questions.

Best regards,

Clinical Operations Lead
US WorldMeds, LLC

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CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1-7) Followed by Open-Label, Variable Dose Lofexidine Treatment (Days 8-14)

Protocol Number:	USWM-LX1-3003-1
Product:	Lofexidine
Investigational New Drug (IND) Number:	IND 47,857
Development Phase of Study:	Phase 3
Medical Monitor:	
Contract Research Organization (CRO):	
Sponsor:	US WorldMeds, LLC 4010 Dupont Circle, Ste L-07 Louisville, KY 40207
Protocol Date:	August 10, 2012
Amendment No. 01 Date:	March 8, 2013

1 PROTOCOL AMENDMENT SUMMARY

Changes made in this amendment to the protocol for Study USWM-LX1-3003-1 (Amendment No. 1) and the rationale supporting these changes are listed below.

Location	Modification/Rationale
Title Page, Synopsis	Protocol title was clarified to better reflect the 2-part design of the study.
Synopsis, 11.2.1, 11.2.2	Inclusion criterion #2, exclusion criterion #4, and exclusion criterion #9 were modified to use the Mini International Neuropsychiatric Interview (M.I.N.I.) rather than the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) to establish the appropriate dependence diagnosis on opioids, exclude other drug dependency, and determine the absence of major psychiatric disorders. The M.I.N.I. is a validated scale (Sheehan et al., 1998) and is used commonly in clinical practice and research studies.
Synopsis	Number of study sites was updated from 10 to approximately 12.
Synopsis; 6.6; 14.3.4; 17.2.5; 17.2.8.2	The definition of completion status was clarified to: whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) assessment on Day 7.
Synopsis; 9; 10.2	Text was added to allow additional study sites (up to 20) in the event that the enrollment rate is unsatisfactory.
Synopsis; 11.2.1	Inclusion criterion #8 was removed because completion of the Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) at baseline is covered in inclusion criterion #4.
Synopsis; 11.2.2; 13.2.3; 15.5.2; 15.5.3; 17.2.11	Text was modified to use QTc (Fridericia) instead of QTc (Bazett) for safety monitoring/subject termination purposes because QTcF is now more commonly used when correcting for low pulse rates.
Synopsis; 15.3.1; 15.3.2; 15.4.5; 17.2.6; 17.2.8.4; 17.3.1	Clinical Opiate Withdrawal Scale (COWS) was added as an efficacy measure for consistency with efficacy measures evaluated in other lofexidine clinical trials.
Synopsis, 17.2.6, 17.2.8.8	Text was added to allow for the potential analysis of single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop, as well as area under the curve (AUC) based on COWS scores from Days 1 through 7.
Synopsis; 17.2.6; 17.2.8.7	Status of detoxification on Day 7 or early termination was added as a tertiary/exploratory endpoint because these data are being collected.
Synopsis; 17.3.1	The tertiary endpoint (Days 8-14) was clarified for number of days required to complete detoxification “as assessed by the Site Investigator.”
5	Abbreviation list was updated.
6.1	Text was updated for consistency with other more current documents.

Location	Modification/Rationale
6.4	Text was updated to account for more current safety information.
10.1	Second paragraph was clarified regarding subject eligibility for treatment in the open-label part of the study.
12.4	First paragraph was clarified to indicate the biostatistician will be blinded to medication assignment groups and that the finger-prick pharmacokinetic samples from placebo subjects will not be analyzed. The third and fourth paragraphs were removed. A cross-reference to Section 14.3.5 was added, which details requirements should unblinding become necessary for the safety of the subject.
12.5	Text was clarified regarding labeling of investigational agents.
13.2.1	Second paragraph was clarified to require the Site Investigator's rationale for his/her decision to continue subject's treatment in either an inpatient or outpatient setting.
13.2.2	Dose-hold criteria was clarified for symptoms of hypotension and/or bradycardia and a statement was added regarding the need to record all instances of dose-holds in source documents.
14.3.2	Second paragraph was clarified to indicate randomization will be done using an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) managed by the CRO.
14.3.5	First and last paragraphs were clarified regarding breaking the study blind.
14.5.1	First paragraph was clarified regarding when subjects "may" or "must" be terminated from the study. Also, Item 8 was clarified regarding termination requirements for missed doses.
14.5.2	Item 2 was clarified regarding termination requirements for persistent symptomatic hypotension, either not responding to bed rest or fluids.
15	Table 1 was modified to: • Add SOWS-Gossop at baseline. • Add COWS at screening, baseline, and each day during treatment (Days 1-7 and Days 8-14). • Add OOWS-Handelsman at screening. • Replace the SCID with the M.I.N.I. • To allow subjects to record the 3.5-hour post-dose vital signs measurements using a portable digital blood pressure machine if they are being treated on an outpatient basis and cannot stay in the clinic for this required post-dose measurement (see footnote j).
15.1	Screening assessments were clarified to include alcohol history. Text was revised to use the M.I.N.I. rather than SCID.
15.2	SOWS-Gossop was added as a required baseline assessment so it can be used as a covariate in the analysis.

Location	Modification/Rationale
15.4.1	First paragraph was clarified to provide a window (± 10 minutes) for the 3.5-hour post first daily dose recording of the SOWS-Gossop. Also, text was clarified to indicate that for each daily evaluation, subject's should consider their symptoms over the last 24-hour period.
15.4.8; Appendix 6	Text was clarified regarding what should be recorded as withdrawal-related adverse events.
15.5.2	Second paragraph was clarified to provide a window (± 15 minutes) for the required 3.5-hour post-dose measurement of vital signs. Third paragraph, which pertains to the open-label part of the study (Days 8-14), was clarified to provide a window (± 30 minutes) for the required 3.5-hour post-dose measurement of vital signs. Also, a provision was added to allow subjects to record the 3.5-hour post-dose measurements using a portable digital blood pressure machine if they are being treated on an outpatient basis and cannot stay in the clinic for this required post-dose measurement.
15.5.3	Text was clarified to provide a window (± 15 minutes) for the required ECG recordings.
15.5.3	Text was clarified that an on-site qualified physician (rather than a cardiologist) will evaluate ECG tracings if there is significant abnormality.
16.2	Title of subsection and text was clarified to remove reference to FDA Form 3454 because the Sponsor (US WorldMeds) will provide a Financial Disclosure form (internal template) to each site for signature.
16.6.1	Text was revised to reflect the use of the National Institute on Drug Abuse (NIDA) Data and Safety Monitoring Board (DSMB) for this study.
16.8.1	Section was added to further clarify SAE requirements.
16.9	Section was added for Overdose.
17.2.8.1	Statistical methods were revised to use 4 disposition strata in assessing SOWS-Gossop AUC(1-7). Also, Item 2 (Modeling) was revised to include baseline SOWS-Gossop score as a covariate in the analysis.
18.1; 18.4; 18.5.2	Text was clarified to indicate that all data will be entered electronically (eCRFs) and no paper CRFs will be used.
18.2	Text was clarified regarding electronic data capture requirements.
22	References were added for COWS (Wesson and Ling, 2003) and for the M.I.N.I. (Sheehan et al., 1998; Medical Outcomes Systems, M.I.N.I. version 6.0).
Appendices 1-5	Scales used to assess efficacy were added as appendices.
Appendix 6	Item E was clarified to indicate where SAEs are to be reported.
Appendix 8	Outpatient Vital Signs Diary was added so subjects who cannot stay in the clinic for the 3.5-hour post-dose vital signs measurement can complete this measurement using a portable digital blood pressure machine and record the results in the diary.

Several administrative clarifications were also made to the protocol, with updates throughout as appropriate:

- as the central IRB;
- as the Clinical Research Organization (CRO);
- as the pharmacy coordinating center/central pharmacy;
- as the central laboratory for analysis of blood and urine samples; and
- as the ECG core lab.

2 SIGNATURE PAGE

By signing below, US WorldMeds, LLC and the investigator indicate 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.

Protocol Approval:

Signature: **Date:** MARCH 8, 2013

Name (print)

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ **Date:** _____

Name (print): _____

3 SYNOPSIS

Title	A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Dose-Response Study of Lofexidine in the Treatment of Opioid Withdrawal (Days 1-7) Followed by Open-Label, Variable Dose Lofexidine Treatment (Days 8-14)
Objective	To investigate the efficacy, safety, and dose-response of lofexidine hydrochloride (2.4 mg or 3.2 mg per day) in reducing withdrawal signs and symptoms and facilitating completion of detoxification/extending treatment retention in subjects undergoing detoxification from short-acting opioids in a double-blind inpatient setting (Days 1-7) followed by an open-label inpatient/outpatient setting (Days 8-14).
Study Design	Two-part, multicenter study in the United States. The first part of the study will use an inpatient, randomized, double-blind, placebo-controlled design, which will be followed by a second part, an open-label, continuation treatment. The first part of the study will consist of 7 days of inpatient treatment with lofexidine 2.4 mg total daily dose (0.6 mg QID), lofexidine 3.2 mg total daily dose (0.8 mg QID), or matching placebo (Days 1-7). During the second part of the study (Days 8-14), all subjects, regardless of their treatment assignment (which will remain double-blinded), who successfully complete Days 1-7, will be eligible to receive open-label, variable dose lofexidine treatment as determined by the Site Investigator. Subjects can be treated as inpatients or outpatients during Days 8-14, depending on the wishes of the Site Investigator and the subject, for up to an additional 7 days. No subject will receive lofexidine for more than 14 days total from the onset of abstinence.
Sites	~12 (Target: ≥3-4 subjects/site/month. Recruitment time: 12-15 months) (In the event that the enrollment rate is unsatisfactory, additional centers will be added for a total site base of up to 20.)
Inclusion Criteria	1. Be male or female at least 18 years of age. 2. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.), on any opioid with a half-life similar to heroin or morphine, including Vicodin®, Lortab®, Lorcet®, Percocet®, Percodan®, Tylox®, or Hydrocodone (by any route of administration), or oxycodone (oxycodone and oxycodone time-released formulation when crushed and snorted, injected or swallowed after chewing). 3. Be seeking treatment for opioid dependence. 4. Have a score ≥2 on the Objective Opiate Withdrawal Scale (OOWS-Handelsman) at Baseline.

Inclusion Criteria *(continued)*	5. Have reported use of heroin, morphine, or any opioid with a half-life similar to heroin or morphine for at least 21 of the past 30 days. 6. Urine toxicology screen positive for opioids and negative for methadone or buprenorphine. 7. If female and of childbearing potential, subject must agree to use of one of the following methods of birth control: • oral contraceptives; • patch; • barrier (diaphragm, sponge or condom) plus spermicidal preparations; • intrauterine contraceptive system; • levonorgestrel implant; • medroxyprogesterone acetate contraceptive injection; • complete abstinence from sexual intercourse; • hormonal vaginal contraceptive ring; or • surgical sterilization or partner sterile (must have documented proof). 8. Be able to verbalize understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures and pass the study consent quiz with 100% accuracy (if necessary, quiz may be administered more than one time).
Exclusion Criteria	1. Be a female subject who is pregnant or lactating. 2. Have self-reported use of methadone or buprenorphine in the past 14 days. 3. Have serious medical illnesses including, but not limited to: • seizures, or those who have received anticonvulsant therapy during the past 5 years; • pancreatic disease such as insulin-dependent diabetes; • liver disease that requires medication or medical treatment, and/or aspartate aminotransferase or alanine aminotransferase levels greater than 5 times the upper limit of normal;[1] and • gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment. 4. Have a psychiatric disorder, based on the M.I.N.I., including but not limited to dementia or any disorder that, in the opinion of the study physician requires ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.

[1] The infectious disease panel for hepatitis will be performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease.

Exclusion Criteria *(continued)*	5. Have self-reported acquired immune deficiency syndrome (AIDS). 6. Abnormal cardiovascular exam at screening and before randomization, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF interval greater than 450 msec for males and greater than 470 msec for females); • heart rate less than 55 bpm or symptomatic bradycardia; • systolic blood pressure less than 95 mmHg or symptomatic hypotension; • diastolic blood pressure less than 65 mmHg; • blood pressure greater than 155/95 mmHg; and • prior history of myocardial infarction. 7. Have clinically significant abnormal laboratory values. 8. Requiring any of the following medications currently or within the past 4 weeks: psychotropics (including sedatives/hypnotics, antidepressants, neuroleptics), prescription analgesics (excluding those listed in inclusion criterion #2 above), anticonvulsants, antihypertensives, antiarrhythmics, antiretroviral, and cholesterol lowering medications. Nicotine replacement therapy (patch, inhaler, gum, or nasal spray) is allowed for nicotine-dependent subjects. Note: Use of a short-acting benzodiazepine (e.g., oxazepam) for insomnia during Days 8-14 will not disqualify a subject. 9. Current dependence (based on the M.I.N.I.) on any psychoactive substance (other than that listed in inclusion criterion #2, caffeine, or nicotine) that requires detoxification. 10. Have donated blood within the last 8 weeks. 11. Have participated in an investigational drug study within the past 3 months. 12. Have such "poor" veins that even a single venipuncture cannot be obtained during screening. 13. Have active tuberculosis (positive tuberculin test and/or confirmatory diagnostic chest x-ray). 14. Have active syphilis.
N	A sufficient number of subjects will be screened to randomize 600 subjects in a 3:3:2 ratio (225 in each lofexidine group and 150 in the placebo group) at approximately 12 study sites in the US. The total number of subjects randomized at each site will depend on subject availability and will likely not be evenly distributed at all sites.
Primary Endpoint	<u>Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment</u> • Area under the curve (AUC) based on Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) scores from Days 1 through 7.

Secondary Endpoint	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • Completion status (whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7).
Tertiary/ Exploratory Endpoints	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • SOWS-Gossop, OOWS-Handelsman, Modified Clinical Global Impression (MCGI [Subject and Rater]), Visual Analog Scale for Efficacy (VAS-E), and Clinical Opiate Withdrawal Scale (COWS) scores on Days 1, 2, 3, 4, 5, 6, and 7; • Retention analysis (time to removal from study treatment) over the 7 inpatient days; • Status of detoxification on Day 7 or early termination as assessed by the Site Investigator; • Concomitant medication analysis; • Withdrawal-related adverse event analysis; • Evaluation of subject treatment status 30 days post discharge; and • In addition, single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed, as may AUC based on COWS scores from Days 1 through 7. Days 8-14: Open-Label, Continuation Treatment • Descriptive evaluation of SOWS-Gossop, OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS; • Duration of exposure; • Number/proportion of subjects successfully completing detoxification as assessed by the Site Investigator; • Distribution of number of days required to complete detoxification as assessed by the Site Investigator; • Average daily dose of lofexidine; and • Concomitant medications.
Duration	21 days (maximum duration per subject, including screening)
Visits	All subjects will undergo screening up to 7 days before study admission. Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment • Inpatient confinement on Days 1 through 7 Days 8-14: Open-Label, Continuation Treatment • Inpatient or daily for up to 7 days if outpatient

Efficacy Assessments	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment The following efficacy assessments will be performed daily at estimated time of maximum plasma concentration (i.e., 3.5 hours after the first dose): • SOWS-Gossop; • OOWS-Handelsman; • MCGI (Subject and Rater); • VAS-E; • COWS; • Concomitant medication use; and • Completion of detoxification as assessed by the Site Investigator (at completion of Inpatient Treatment on Day 7 only or, if applicable, early termination during Days 1-7). Days 8-14: Open-Label, Continuation Treatment The following efficacy assessments will be performed daily before dosing: • SOWS-Gossop; • OOWS-Handelsman; • MCGI (Subject and Rater); • VAS-E; • COWS; • Concomitant medication use; and • Completion of detoxification as assessed by the Site Investigator.
Safety Assessments	Days 1-7: Randomized, Double-Blind, Placebo-Controlled Treatment The following safety assessments will be performed daily: • Occurrence, seriousness, severity, and causality assessment of adverse events (AEs); • Vital signs (sitting/standing blood pressure and pulse) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (7 times/day); • 12-lead ECGs (in duplicate) will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, early termination during Days 1-7. • Clinical laboratory tests as clinically warranted and at discharge or early termination during Days 1-7; • Finger prick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG during Days 1-7; and • Physical examination at Baseline (update of Screening exam), a complete exam 3 to 4 hours after randomization on Day 1 and at discharge or early termination during Days 1-7.

Safety Assessments *(continued)*	In addition, qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband. Days 8-14: Open-Label, Continuation Treatment The following safety assessments will be performed daily: • Occurrence, seriousness, severity, and causality assessment of AEs; • Vital signs (sitting blood pressure and pulse) at least once daily before dosing and 3.5 hours after dosing; • 12-lead ECGs (in duplicate) will be done before the first daily dose and at 11:30 AM on Days 8 and 14 or, if applicable, early discharge/termination from the study. • Clinical laboratory tests as clinically warranted and on Day 14 or, if applicable, early discharge/termination from the study; • Complete physical examination as clinically warranted and on Day 14 or, if applicable, early discharge/termination from the study; and • Pregnancy test on Day 14 or, if applicable, early discharge/termination from the study. Qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for illicit drug use. A 30-day post discharge follow-up telephone contact will be made for an adverse event evaluation and an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program).

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TABLES

APPENDICES

5 ABBREVIATIONS AND DEFINITION OF TERMS

AE(s)	Adverse Event(s)
AIDS	Acquired Immune Deficiency Syndrome
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase
Anti-HBc	Hepatitis B Core Antibody
Anti-HBs	Hepatitis B Surface Antibody
AUC	Area Under the Concentration-Time Curve
AST/SGOT	Aspartate Aminotransferase/Serum Glutamic-Oxaloacetic Transaminase
BP	Blood Pressure
bpm	beats per minute
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act of 1988
CO_2	Carbon Dioxide
COWS	Clinical Opiate Withdrawal Scale
CRF(s)	Case Report Form(s)
CRO	Clinical Research Organization
DAWN	Drug Abuse Warning Network
DBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
eCRF(s)	Electronic Case Report Form(s)
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWE	Familywise Error Rate
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
Hbs Ag	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat
LDH	Lactate Dehydrogenase
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MCGI	Modified Clinical Global Impression
MHOWS	Modified Himmelsbach Opiate Withdrawal Scale
M.I.N.I.	Mini International Neuropsychiatric Interview

mITT	Modified Intent-To-Treat
mmHg	Millimeters of Mercury
msec	Millisecond
NDA	New Drug Application
NIMH	National Institute of Mental Health
OOWS-Handelsman	Objective Opiate Withdrawal Scale of Handelsman
PK	Pharmacokinetic
PPD	Purified Protein Derivative (skin test for tuberculosis)
PRN	As Needed
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QID	Four Times Daily
QT	QT interval of an electrocardiogram
QTc	Corrected QT interval
QTcB	Corrected QT interval – Bazett's method
QTcF	Corrected QT interval – Fridericia's method
QTcI	Individually corrected QT interval
RBC	Red Blood Cell
RPR	Rapid Plasma Reagin
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
T4	Free Thyroxine
T_{max}	Time of Maximum Plasma Drug Concentration
TSH	Thyroid-Stimulating Hormone
UDS	Urine Drug Screening
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
USWM	US WorldMeds, LLC
VAS-E	Visual Analog Scale for Efficacy
WBC	White Blood Cell

7 STUDY OBJECTIVES

The primary objective of this study is to investigate the efficacy, safety, and dose-response of lofexidine (2.4 mg or 3.2 mg per day) in reducing withdrawal signs and symptoms and facilitating completion of detoxification/extending treatment retention in subjects undergoing detoxification from short-acting opioids in a double-blind inpatient setting (Days 1-7) followed by an open-label inpatient/outpatient setting (Days 8-14).

It is hypothesized that a daily dose of either 2.4 mg or 3.2 mg lofexidine will achieve greater efficacy than placebo with respect to overall symptom relief over the first 7 days of opioid withdrawal (primary endpoint) and will increase the likelihood of subjects completing Days 1-7 of treatment (secondary endpoint). Further, safety measures in the 2.4 mg and 3.2 mg total daily dose groups will be compared descriptively to assess whether the lower dose results in fewer and less severe adverse events than does the higher dose.

8 STUDY SPONSOR

This study will be conducted under an Investigational New Drug (IND) application (#47,857) held by US WorldMeds, LLC.

9 STUDY SITES AND INVESTIGATORS

This study will be conducted at approximately 12 study sites in the US. In the event that the enrollment rate is unsatisfactory, additional centers will be added for a total site base of up to 20. It is the responsibility of the Site Investigators to make sure this protocol is conducted in full conformance with the ethical principles detailed in Section 16 of this protocol. All data will be collected at the study sites on source documents and entered at the site into electronic case report forms (eCRFs) as described in Section 18.1 of this protocol.

10 INVESTIGATIONAL PLAN

10.1 Overall Design

This is a Phase 3, two-part, multicenter study to evaluate the dose-response, efficacy, and safety of lofexidine in alleviation of symptoms in subjects undergoing total and abrupt withdrawal from short-acting opioids. Any subject dependent on short-acting opioids (the primary projected indication for lofexidine) about to undergo opioid withdrawal will be eligible. Subjects will be evaluated for their compliance with protocol inclusion/exclusion criteria during a screening period, lasting up to 7 days.

The first part of the study will use an inpatient, randomized, double-blind, and placebo-controlled design (Days 1-7) followed by a second part, an open-label, continuation treatment (Days 8-14). A total of 600 subjects will be randomized to receive lofexidine 2.4 mg total daily dose (0.6 mg QID), lofexidine 3.2 mg total daily dose (0.8 mg QID), or matching placebo in a 3:3:2 ratio (225:225:150) for 7 days (i.e., during the most intense stage of withdrawal). During the second part of the study (Days 8-14), all subjects, regardless of their treatment assignment (which will remain double-blinded), who successfully meet the definition for "completer" based on Days 1-7 (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7), will be eligible to receive open-label, variable dose lofexidine treatment (as determined by the Site Investigator, but not to exceed 3.2 mg/day) for up to an additional 7 days in either an inpatient or outpatient setting depending on the wishes of the investigator and the subject. No subject will receive lofexidine for more than 14 days total from the onset of abstinence. There will be no initial dose run-up and no mandated terminal dose taper. Efficacy and safety assessments will be made daily (see detailed Schedule of Assessments in

Table 1 of Section 15). Qualitative urine drug screening will be done every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

10.2 Number of Subjects

A sufficient number of subjects will be screened to randomize 600 subjects (225 in each lofexidine group and 150 in the placebo group) at approximately 12 study sites in the US (should the enrollment rate be unsatisfactory, additional centers will be added for a total site base of up to 20). The total number of subjects randomized at each site will depend on subject availability and will likely not be evenly distributed across all sites.

10.3 Duration of Study

The maximum duration of participation for each subject in this study will be 21 days, including the Screening/Baseline period, which can last up to 7 days, followed by up to 14 days of treatment with study medication (lofexidine and/or placebo).

During Inpatient Treatment (Days 1-7), randomized subjects will receive lofexidine 2.4 mg total daily dose (0.6 QID), lofexidine 3.2 mg total daily dose (0.8 QID), or matching placebo treatment for up to 7 days. For Days 8-14, subjects will receive open-label, variable dose lofexidine for up to 7 additional days (open-label, continuation treatment). Full randomization into the study is anticipated to take 12 to 15 months to achieve (3-4 subjects per month per site), with the total clinical duration of the study anticipated to be 15 to 18 months.

11 SELECTION OF STUDY POPULATION

11.1 Population Base

Any opioid-dependent subject about to undergo withdrawal from short-acting opioids will be evaluated for study eligibility after providing written informed consent. Entry into this study is open to both men and women and to all racial and ethnic subgroups. An attempt will be made to include at least 25% female subjects and a mix of ethnicities reflecting the distribution in the local geographic regions of the study sites. Subjects will be recruited from a variety of sources, including subjects seeking treatment for opioid dependence via referrals from local treatment providers, word of mouth among subjects themselves also seeking treatment, and advertising in the local media. Recruitment advertisements will be approved by each site's Institutional Review Board (IRB).

Potential subjects may be accepted for screening after the nature and purpose of the investigation have been explained to them and after they have voluntarily given written informed consent (see Section 16.4).

11.2 Study Entrance Requirements

11.2.1 Inclusion Criteria

To be eligible for participation, subjects must meet all of the following criteria:

1. Be male or female at least 18 years of age.

2. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.) [17, 18], on any opioid with a half-life similar to heroin or morphine, including Vicodin®, Lortab®, Lorcet®, Percocet®, Percodan®, Tylox®, or Hydrocodone (by any route of administration), or oxycodone (oxycodone and oxycodone time-released formulation when crushed and snorted, injected or swallowed after chewing).
3. Be seeking treatment for opioid dependence.
4. Have a score ≥2 on the Objective Opiate Withdrawal Scale (OOWS–Handelsman) at Baseline.
5. Have reported use of heroin, morphine, or any opioid with a half-life similar to heroin or morphine for at least 21 of the past 30 days.
6. Urine toxicology screen positive for opioids but negative for methadone and buprenorphine.
7. If female and of childbearing potential, subject must agree to use of one of the following methods of birth control:
   - oral contraceptives;
   - patch;
   - barrier (diaphragm, sponge or condom) plus spermicidal preparations;
   - intrauterine contraceptive system;
   - levonorgestrel implant;
   - medroxyprogesterone acetate contraceptive injection;
   - complete abstinence from sexual intercourse;
   - hormonal vaginal contraceptive ring; or
   - surgical sterilization or partner sterile (must have had documented proof).
8. Be able to verbalize understanding of the consent form, able to provide written informed consent, verbalize willingness to complete study procedures, and pass the study consent quiz with 100% accuracy (if necessary, quiz may be administered more than one time).

11.2.2 Exclusion Criteria

Subjects who meet any of the following criteria will not be allowed to participate:

1. Be a female subject who is pregnant or lactating.
2. Have self-reported use of methadone or buprenorphine in the past 14 days.
3. Have serious medical illnesses including, but not limited to:
   - seizures, or those who have received anticonvulsant therapy during the past 5 years;
   - pancreatic disease such as insulin-dependent diabetes;

- liver disease that requires medication or medical treatment, and/or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels greater than 5 times the upper limit of normal;[2] and
- gastrointestinal or renal disease, which would significantly impair absorption, metabolism or excretion of study drug, or would require medication or medical treatment.

4. Have a psychiatric disorder, based on the M.I.N.I., including but not limited to dementia or any disorder that, in the opinion of the study physician requires ongoing treatment that would make study participation unsafe or which would make treatment compliance difficult.
5. Have self-reported acquired immune deficiency syndrome (AIDS).
6. Abnormal cardiovascular exam at screening and before randomization, including any of the following:
   - clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF interval greater than 450 msec for males and greater than 470 msec for females);
   - heart rate less than 55 bpm or symptomatic bradycardia;
   - systolic blood pressure (SBP) less than 95 mmHg or symptomatic hypotension;
   - diastolic blood pressure (DBP) less than 65 mmHg;
   - blood pressure (BP) greater than 155/95 mmHg; and
   - prior history of myocardial infarction.
7. Have clinically significant abnormal laboratory values.
8. Requiring any of the following medications currently or within the past 4 weeks: psychotropics (including sedatives/hypnotics, antidepressants, neuroleptics), prescription analgesics (excluding those listed in inclusion criterion #2 above), anticonvulsants, antihypertensives, antiarrhythmics, antiretroviral, and cholesterol lowering medications. Nicotine replacement therapy (patch, inhaler, gum, or nasal spray) will be allowed for nicotine-dependent subjects.

   Note: Use of a short-acting benzodiazepine (e.g., oxazepam) for insomnia during Days 8-14 will not disqualify a subject.
9. Current dependence (based on the M.I.N.I.) on any psychoactive substance (other than that listed in inclusion criterion #2, caffeine or nicotine) that requires detoxification.
10. Have donated blood within the last 8 weeks.
11. Have participated in an investigational drug study within the past 3 months.
12. Have such "poor" veins that even a single venipuncture cannot be obtained during screening.

[2] The infectious disease panel for hepatitis will be performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease.

13. Have active tuberculosis (positive tuberculin test and/or confirmatory diagnostic chest x-ray).
14. Have active syphilis.

Notes on inclusion/exclusion criterion: Potential subjects who are positive for syphilis by a treponemal-specific test (FTA-ABS or MHA-TP) will not be eligible for study participation and will be referred for appropriate follow-up and/or treatment, if required.

The infectious disease panel for hepatitis is performed as an aid to determine if the prospective subject has been exposed to a hepatitis virus. Positive hepatitis results do not exclude a prospective subject from participation unless there is an indication of active liver disease.

Tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray will be performed on all subjects. A positive PPD result does not exclude a prospective subject from participation, but if diagnostic tests (e.g., chest x-ray) indicate that active disease is present, subjects will be excluded from participation.

If any tests are positive, the subject will be notified of the test results and referred for treatment.

11.3 Screening Failures

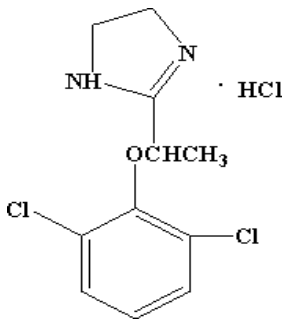
Screening failures are potential study subjects who provide informed consent and fail inclusion and/or exclusion criteria or for other reasons are not allowed to participate. A screening log for all subjects who are screened will be maintained. The screening log will uniquely identify each subject and report whether he or she passed or failed screening, and, if he or she did not pass, the reasons for the screening failure.

Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.

12 INVESTIGATIONAL AGENTS

12.1 Lofexidine Hydrochloride

Lofexidine hydrochloride is an α2-adrenergic agonist with mild to moderate antihypertensive actions. It has the empirical formula $C_{11}H_{13}Cl_3N_2O$ representing a molecular weight of 295.61. The structural formula is:



Lofexidine hydrochloride is a synthetic product and has the chemical designation of 2-[1-(2,6-dichlorophenoxy)ethyl]-4,5 dihydro-1*H*- imidazole monohydrochloride. It is a white to off-white crystalline powder that is very soluble in water and ethanol. It is lightly soluble in 2-propanol and practically insoluble in ether. Lofexidine hydrochloride melts at approximately 126-128°C.

Lofexidine will be supplied by the Sponsor (USWM) in peach colored tablets containing 0.2 mg of active medication for oral administration.

Lofexidine should be stored at room temperature in a secure area.

12.2 Placebo

Placebo will be supplied by the Sponsor (USWM) as an exact match of lofexidine, less the active ingredient.

12.3 Dispensing Investigational Agents

All investigational agents will be distributed from (the pharmacy coordinating center) in "Subject Kits."

For the Inpatient Treatment part of the study (Days 1-7), a supply of unassigned subject kits will be maintained at each participating site. Each subject kit will contain 7 blister cards (packaged by with the appropriate dosing of lofexidine and/or matched placebo for each day of the inpatient phase of the study.

For Days 8-14 (open-label treatment), lofexidine tablets will be supplied in uniquely-identified 80-count bottles, which will be dispensed by the study pharmacist as determined clinically appropriate by the Site Investigator to the subject in individual prescription bottles containing their doses for only the following 1 or 2 days, as appropriate. The site will maintain a dispensing log for each bottle and document the number of tablets dispensed to each subject along with the number of tablets returned, if any, by the subject at each outpatient visit. Returned tablets will not be re-dispensed to future subjects.

All study medications will be dispensed by the site pharmacists to the Site Investigators or their designee.

12.4 Blinding Plan

The subjects, Site Investigators, site personnel, Sponsor (USWM), and clinical personnel at the CRO including the biostatistician will be blinded to medication assignment groups. The study pharmacist at the central pharmacy and bioanalytical personnel at the CRO will not be blinded to medication assignment. The bioanalytical personnel will not be blinded because they will need to identify finger-prick pharmacokinetic samples from placebo subjects; these samples will not be analyzed.

The investigational agents, lofexidine (2.4 mg or 3.2 mg) and placebo, will be packaged in blister cards of matched appearance and labeling for the Inpatient Treatment part of the study (Days 1-7). Days 8-14 will be open-label, although subjects' treatment assignment during Days 1-7 will remain blinded. Refer to Section 14.3.5 should breaking the blind become necessary for the safety of the subject.

12.5 Labeling

The investigational agents, lofexidine and placebo, will be packaged in blister cards for the Inpatient Treatment part of the study (Days 1-7) and further packaged in an outer carton (blister card kit). Lofexidine will be packaged in bottles for Days 8-14 (open-label treatment).

The blister card kit (outer carton) will be labeled with the following information:

- subject randomization number,
- space for site personnel to enter subject initials/name code,
- name of study,
- protocol number,
- number of tablets (per card and total for kit),
- name/address of the pharmacy coordinating center
- 24-hour emergency telephone number, and
- the following statement – "Caution: New Drug – Limited by Federal Law to Investigational Use."

The individual blister card labels will include the following information:

- subject randomization number,
- space for site personnel to enter subject initials/ name code,
- name of study,
- protocol number,
- study day (e.g., Day 1, Day 2) and each row of tablets will be delineated with dosing times (i.e., 8AM, 1PM, 6PM, 11PM) to ensure that the appropriate tablets are given at each protocol-specified dosing time, and
- a description of the investigational product: "Lofexidine HCl 2.4 mg, Lofexidine HCl 3.2 mg, or Placebo," thus identifying the drug but preserving the blind.

The bottle product label will include the following information:

- name of study,
- protocol number,

- a unique bottle number for purposes of investigational product accountability, and
- a description of the investigational product, i.e., "Lofexidine HCl 0.2 mg tablets" as the portion of the study that will use bottled study drug under open-label conditions.

In the open-label phase of the study (Days 8-14), sites may dispense 1 to 2 days of investigational product to the subject for use in an outpatient setting. In such cases, the redispensing container will include a subject label, supplied by the study site, and will include the following information:

- name of study,
- protocol number,
- subject initials,
- subject randomization number,
- study physician's name,
- site emergency contact telephone number,
- description of the medication (i.e., "Lofexidine HCl 0.2 mg tablets"),
- number of tablets dispensed,
- directions for use, and
- the name/address of the pharmacy coordinating center

12.6 Storage

Investigational agents will be stored at room temperature in a secure location at the dispensing pharmacy.

12.7 Record of Administration

Accurate recording of all investigational agents received, dispensed, administered, and returned will be maintained by study site personnel.

12.8 Used/Unused Supplies

At the end of the study, all unused investigational agents must be inventoried. If any investigational agent is lost or damaged, its disposition should be documented. Unused investigational agents will be retained at the participating sites to enable a full investigational drug inventory by the sites' respective monitors. Sponsor will provide instructions to return the unused study drug to the pharmacy coordinating center periodically throughout the study (following monitor review) or at the end of the study for proper destruction in accordance with local and federal regulations.

12.9 Contraindications

To avoid drug-drug interactions, lofexidine should not be administered concurrently with:

- tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives;
- alcohol, sedatives, and anaesthetics – may interact with lofexidine and enhance its central sedative effects; and
- beta-receptor blockers – the combination of lofexidine and beta-receptor blockers should be used with caution to avoid the risk of excessive bradycardia.

13 TREATMENT PLAN

13.1 Investigational Agents

On Day 1 of the Inpatient Treatment part of the study, subjects will be randomized to one of two dose levels of lofexidine or placebo and receive the following daily treatment regimens through Day 7: lofexidine 2.4 mg/day (administered as 3 x 0.2 mg tablets and 1 placebo tablet QID), lofexidine 3.2 mg/day (administered as 4 x 0.2 mg tablets QID), or matching placebo (administered as 4 x placebo tablets QID). In order to maintain the treatment blind, all subjects will receive a total of 16 tablets per day whether active, placebo, or in combination to achieve the assigned dose. Tablets will be provided in subject-specific kits, containing 7 blister cards (one for each study day). Each blister card will contain 4 rows of 4 tablets each, appropriately marked to indicate which row of tablets should be administered at each of the specified dosing times (8 AM, 1 PM, 6 PM, and 11 PM). Dose kits for subjects randomized to lofexidine 3.2 mg/day will contain full blister cards of active tablets. Dose kits for subjects randomized to lofexidine 2.4 mg/day will contain blister cards in which each dose row contains 3 active tablets and 1 placebo tablet. Dose kits for subjects randomized to placebo will contain full blister cards of placebo tablets.

For the Open-Label, Continuation Treatment part of the study (Days 8-14), subjects will receive lofexidine at variable dose, as determined by the Site Investigator (see Section 13.2).

13.2 Dose Administration

13.2.1 Administration of Doses

During Inpatient Treatment (Days 1-7), subjects must take study medication orally, within a 30-minute window, 15 minutes before or after 8 AM, 1 PM, 6 PM, and 11 PM. The actual date and time of each dose will be recorded in the subject's source document and on the eCRF. Placebo will appear identical to lofexidine. Blood pressure and pulse (both sitting and standing) will be measured before each dose and 3.5 hours after each dose (with the exception of the dose taken at 11 PM, where the measurement at 3.5 hours post-dose will not be done). Details for obtaining vital sign are provided in Section 15.5.2.

During Open-Label, Continuation Treatment (Days 8-14), there will be no mandated lofexidine dose regimen and subjects may receive lofexidine treatment during this time in either an inpatient or outpatient setting depending on the wishes of the Site Investigator and the subject. The rationale for the decision to continue treatment or not and the Site

Investigator's decision to continue treatment through either an inpatient or outpatient setting must be documented in the subject's source document. The dose regimen will be determined by the Site Investigators as clinically indicated for relief of subjects' symptoms, with supporting rationale for any dose changes recorded in the subject's source document. In no case is the dose of lofexidine to exceed 3.2 mg/day (or a single dose of 0.8 mg). Previous studies have shown that dose titration is not necessary to reach a maximum intended dose. Also, abrupt withdrawal of lofexidine has not been found to have any significant safety issues. Nevertheless, a dose taper may be appropriate given the dissipating severity of symptoms in the later days of withdrawal. During Days 8-14, blood pressure and pulse (both sitting and standing) should be assessed for one dose every day at pre-dose and 3.5 hours post-dose.

As further guidance, the dosing regimen recommended for lofexidine (BritLofex™) in the UK is as follows:

> "The dosage of lofexidine should be titrated according to the patient's response. Initial dosage should be 0.8 mg per day in divided doses. The dosage may be increased by increments of 0.4 to 0.8 mg per day up to a maximum of 2.4 mg daily. Maximum single dose should not exceed 4 x 0.2 mg tablets (0.8 mg). Each patient should be assessed on an individual basis; those undergoing acute detoxification will usually require the highest recommend dose and dosage increments to provide optimum relief at the time of expected peak withdrawal symptoms."

The lower maximum dose allowed in the UK (2.4 mg/day) may be reflective of the less severe opioid dependence experienced by patients in the UK. US studies have shown that 3.2 mg/day can be safely administered (see Sections 6.3 and 6.4).

Note: In order to prevent dehydration from opioid withdrawal, increased fluid intake will be encouraged from the beginning of the study. Instances in which study medication is not administered within the 30-minute windows as noted above will be documented as protocol deviations.

13.2.2 Dose-Hold Criteria

Study medication will be held if vital signs meet any of the following criteria:

Recumbent

- Systolic blood pressure <90 mmHg and >20% below screen value;
- Diastolic blood pressure <50 mmHg and >20% below screen value;
- Heart rate <50 bpm and >20% below screen value; and
- Symptoms of hypotension and/or bradycardia (e.g., lightheadedness, dizziness, syncope).

Orthostatic (after standing for 3 minutes)

- Systolic blood pressure diastolic blood pressure, or pulse >25% below recumbent values.

All instances of dose-holds must be clearly documented in the subject's source document.

13.2.3 Discontinuation Criteria

A subject will be discontinued from the study if any of the following criteria are met:

- Systolic blood pressure <70 mmHg and >20% below screen value;
- Diastolic blood pressure <40 mmHg and >20% below screen value;
- Heart rate <40 bpm and >20% below screen value;
- QTcF >500 msec[3] or >25% above screen value for both males and females;
- Syncope;
- Subject misses 2 doses in 24 hours;
- Subject misses a total of 6 doses during Days 1-7 of the study; and
- Concomitant medication use (other than alumina, magnesia, and simethicone) for intolerable nausea and emesis.

Additional discontinuation criteria based on cardiovascular events are provided in Section 14.5.2.

13.3 Treatment Compliance

Each of the inpatient doses during Days 1-7 will be observed by the site staff. Following administration of the oral study medication, hand and mouth checks will be performed to ensure that the dose is swallowed. In an inpatient setting during Days 8-14, each dose will be observed by study staff and hand and mouth checks will be performed. In an outpatient setting during Days 8-14, self-dosing compliance will be evaluated by pill count and subject report at each clinic visit. Subjects will be instructed to call the physician's office before taking the next dose of study medication if they notice any marked dizziness, especially when standing from a sitting or lying position. The physician will determine if the next dose should be delayed, skipped, or the subject should be seen. Any change in physician-prescribed dosing will be noted in the study file and confirmed also by pill count and subject report at the next visit.

13.4 Nicotine Replacement Therapy

Subjects may be permitted to smoke during their participation in the Inpatient Treatment part of the study (Days 1-7) based on individual site policy. If they usually use tobacco products, the study physician will offer and encourage these subjects to use nicotine replacement

[3] See Section 15.5.3 for procedures for assessment of prolonged QTcF interval.

therapy (patch, gum, inhaler, or nasal spray) while they are in the hospital to treat their nicotine withdrawal symptoms. If smoking is permitted by a participating site, smoking breaks outside of the inpatient locked unit must be constantly observed and supervised. The number of tobacco products used by subjects per day will be recorded in the subject's source document and on the eCRF.

No control or record for use of tobacco products will be required during Days 8-14 of the study.

14 STUDY PROCEDURES

14.1 Subject Recruitment and Consent

Interested subjects, who respond to recruitment materials and are available to stay in the hospital for the 7-day Inpatient Treatment part of the study, will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. During the initial interview, the interviewer should not ask questions in a manner that reveals the eligibility criteria for study entry.

If still interested after receiving an explanation of the study, subjects will be given an opportunity to review, inquire about, and sign the study informed consent form (see Section 16.4). The subject will then be given a copy of the signed consent form. After that, subjects will be given a screening number and proceed to the screening phase of the study. Screening assessments must be completed within a 7-day time period, but can be completed as early as screening day 1, and randomization may be performed on the next calendar clinic visit day. Subjects must be randomized no later than the 7th day of screening (Day 1). At no time during the screening process should individuals be given information regarding inclusion or exclusion criteria, with the exception that subjects will be informed that they must exhibit signs of opioid withdrawal immediately before admission into the study. When individuals are evaluated, questions should be asked in a way that the criteria are not discernible.

Any subject who has difficulty understanding the information contained in the consent form will reread the misunderstood portion(s) of the consent and discuss with a research staff member until s/he shows complete understanding of the information in the consent form, and may thus give full consent. Subjects must complete a consent quiz with 100% accuracy before being randomized. Research staff will work closely with the subject in an effort to help them understand the requirements of their participation. Subjects with literacy problems will be assisted to the extent possible.

Any subject who is unable to demonstrate understanding of the information contained in the informed consent will be excluded from study participation and assisted in finding other sources of treatment at the subject's sole expense. Subjects who are excluded, or who decline participation, may not be rescreened at a later time and will be given referrals to other resources in the area. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

14.2 Screening

Screening assessments will be conducted as shown in Table 1 (Section 15). The screening period will last up to 7 days during which the subjects must satisfy the eligibility criteria and complete all required screening assessments.

14.3 Treatment Phase

14.3.1 Baseline

After a potential participant has completed all screening assessments and has met all eligibility criteria to participate in the study, the Site Investigator or study coordinator will arrange for an early morning hospital study admission (Day 1). The Baseline period is the morning of Day 1 after the subject has completed final eligibility testing (OOWS-Handelsman) and has been admitted to the inpatient study unit, but before randomization. Baseline assessments to be done are shown in Table 1 and explained in Section 15.2. Subjects will be admitted to the study, will complete all Baseline measures, and will be randomized. The Site Investigator or study coordinator will have the investigational agent dispensed and ready to administer, before the Day 1 8 AM dosing window.

14.3.2 Subject Randomization

A prospective subject who meets all of the study inclusion criteria and does not meet any of the exclusion criteria may be randomized into the study.

A stratified randomization procedure will be used to separately allocate male and female subjects in 1 of the 3 treatment groups: 2.4 mg lofexidine, 3.2 mg lofexidine, or placebo. Randomization will be implemented centrally, that is, take place across all investigational sites using an Interactive Voice Response System (IVRS) or an Interactive Web Response System (IWRS) managed by the CRO At randomization, the system will assign a unique subject identification number to each subject. The subject's identification number will be used on all of that subject's case report forms.

The Site Investigator or study coordinator will arrange for hospital admission (in the event that the subject was not admitted the night before randomization) of the subject and for investigational agent to be dispensed to initiate treatment. Even if a subject does not actually receive any investigational agent after s/he has been randomized, s/he is considered to be in the intent-to-treat (ITT) population. should be notified of any irregularities that occur during randomization.

14.3.3 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

After randomization, subjects will receive their first dose of study medication (lofexidine or placebo) during the 8 AM dosing window on Day 1. Subjects will be dosed 4 times daily from Day 1 through Day 7 at 8 AM, 1 PM, 6 PM, and 11 PM. Vital signs will be recorded within 30 minutes before every dose and 3.5 hours after the 8 AM, 1 PM, and 6 PM dose. Other clinical assessments will be gathered between 11:00 AM and noon each day. These clinical assessments are described in detail in Sections 15.4 and 15.5.

14.3.4 Days 8-14 (Open-Label, Continuation Treatment)

Subjects who successfully meet the definition for "completer" based on Days 1-7 (i.e., receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7) and if clinically indicated (as determined by the Site Investigator) may continue to receive lofexidine to control symptoms for up to an additional 7 days during Days 8-14. Subjects may be treated as inpatients or outpatients, depending on the wishes of the investigator and the subject, using open-label, variable dose lofexidine (as determined by the Site Investigator, but not to exceed 3.2 mg/day). The rationale for the decision to continue treatment or not and the Site Investigator's decision to continue treatment through either an inpatient or outpatient setting must be documented in the subject's source document. Lofexidine treatment will terminate and the subject will be discharged from the study when the Site Investigator judges that the acute phase of opioid withdrawal is essentially complete and the subject no longer needs treatment for abstinence. In any event, no subject will continue to receive lofexidine treatment for more than 14 days total from the onset of abstinence. If being treated as an outpatient, the subject must return to the clinic daily for assessment (see a complete list of assessments in Table 1 of Section 15).

14.3.5 Maintaining and Breaking the Blind

In circumstances where breaking of the blind is necessary for subject safety, Investigators or emergent care professionals requesting to break the blind must call the Sponsor's Medical Monitor (or designee) for consultation before unblinding unless immediate action is required. The decision to break the study blind should be resorted to only in cases of life-threatening emergency when knowledge of the treatment arm investigational agent will influence clinical management.

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

If, after discussion with the Medical Monitor, it is determined that the study treatment should be disclosed, medical personnel will be able to access this information via IVRS/IWRS. 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 following information must be recorded in the subject's record: the reason for unblinding the code, the person who has unblinded the code, and the date and time of unblinding.

14.4 Subject Reimbursement

14.5 Study Termination

14.5.1 Subject Termination

A subject can withdraw his/her consent for participation in the study at any time without prejudice. The Site Investigator may terminate a subject if s/he deems it clinically appropriate for any reason. Additionally, the Site Investigator must terminate a subject for any of the following reasons:

1. Cardiovascular events (see Section 14.5.2).
2. Serious medical problem thought to be related or unrelated to the study medications.
3. Intercurrent illness or medical complications that, in the opinion of the site investigator, preclude safe administration of study medications.
4. Evidence of illicit drug use while participating in the study.
5. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study.
6. Requiring therapy with an exclusionary drug.
7. Lack of compliance with protocol and/or unit procedures.
8. During Days 1-7, missing more than 2 doses of study medication in a single 24-hour period or missing more than 6 doses of study medication over the course of the inpatient treatment phase.

Subjects who are removed from study treatment because of adverse events (AEs) or serious adverse (SAEs) will be followed until they are medically stabilized to the satisfaction of the attending physician (see Sections 15.5.1, 16.7, and 16.8). Appropriate safety evaluations will continue to be collected until the subject is discharged from the treatment center or the

maximum 14-day treatment period has expired. This stabilization can include medically supervised opioid withdrawal (involving behavioral therapy, rescue opioid medications, and/or non-opioid pharmacotherapy) or referral to an appropriate methadone or buprenorphine therapy program.

Any subject that discontinues prematurely, regardless of the reason, will be requested to complete all assessments and procedures scheduled for Day 14 (see Table 1).

The reason for premature removal will be recorded in the subject's source document and on the termination form provided in the subject's eCRF. Once withdrawn, subjects may not re-enter the study. Similarly, the Site Investigator's assessment of completion of detoxification/transition will also be recorded in the subject's source document and on the eCRF. Withdrawn or early-completer subjects will not be replaced.

Study subjects withdrawn from the protocol secondary to a medical or psychiatric concern deemed to be unrelated to lofexidine therapy will be referred, at the subject's sole expense, for appropriate treatment, and may include psychological and lifestyle counseling, support groups, pharmacological, and medical treatment. Subjects will be asked to sign a general consent for the release of information to the referred healthcare provider. Study staff may request transportation for emergency treatment of a subject if medically appropriate (e.g., for acutely psychotic or suicidal subjects).

14.5.2 Cardiovascular Events Requiring Subject Termination From Study

Subjects should be discontinued from the study for any of the reasons listed below, and the event should be recorded in the subject's document and on the eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) and the subject followed until medically stabilized to the satisfaction of the attending physician.

1. New onset of clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval[4]).
2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids).
3. 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.
4. Persistent hypertension – blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If all 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be terminated.
5. 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.

[4] See Section 15.5.3 for procedures for assessment of prolonged QTcF interval.

6. Any other clinically significant cardiovascular signs or symptoms that would place the subject at risk.

14.5.3 Trial Discontinuation

The Sponsor (USWM) has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- the incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects;
- subject enrollment is unsatisfactory; and
- data recording is inaccurate or incomplete.

14.6 Concomitant Therapy

The concomitant medications listed below are permitted during Days 1-7 and Days 8-14 of the study.

1. Multivitamins (≤1 tablet orally, administered daily at 9 AM).
2. Guaifenesin (for cough) (≤2 teaspoons orally every 2 hours, as needed [PRN]).
3. Alumina, Magnesia, and Simethicone (for emesis and nausea) (≤30 mL orally every 4 hours, PRN).
4. Dioctyl sodium sulfosuccinate (for constipation) (≤100 mg orally every 8 hours, PRN).
5. Psyllium hydrocolloid suspension (for constipation) (≤1 tablespoon orally every 12 hours, PRN).
6. Bismuth sulfate (Pepto-Bismol®) (for diarrhea) (≤6 doses of 30 mL orally every 24 hours, PRN).
7. Acetaminophen (for headache, muscle aches, or other discomfort) (≤4 doses of ≤650 mg orally every 24 hours).
8. Zolpidem (for insomnia) (≤10 mg orally, PRN, may repeat 1 time if administered before 5:00 AM (i.e., 3 hours before the first morning dose of lofexidine or placebo). Zolpidem must not be administered before 11:00 PM (which is the time of the last daily dose of lofexidine or placebo).

   8a. Note: A short-acting benzodiazepine (e.g., oxazepam) may be used ad libitum for insomnia during the second part of the study (i.e., Days 8-14).

9. Nicotine replacement therapy (patch, inhaler, gum, nasal spray).

All other medications must be approved by the Sponsor's Medical Monitor before administration. If a subject requires any other medication for intolerable nausea and emesis (including a prescription opioid or non-opioid or an over-the-counter opioid or non-opioid) other than alumina, magnesia and simethicone, the subject will be withdrawn from the study and given appropriate treatment according to the standard of care (see Section 14.5.1).

All medications taken will be recorded in the subject's source document and eCRF along with dose, dates of administration, and reason for use.

15 CLINICAL EVALUATIONS

A detailed Schedule of Assessments to be done in the study is provided in Table 1.

Table 1. Schedule of Study Assessments

	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)			
	Screening	Baseline (a)	Inpatient Treatment	In/Outpatient Treatment
Activity **Day:**	**-6 to -1**	**1**	**1-7**	**8 to 14/ET***
Informed Consent Signed	X			
Screening Number Assigned	X			
Inclusion/Exclusion Criteria	X	X (b)		
Prior Medication History	X	X (b)		
Demographics	X			
Medical and Smoking History	X			
Mini-International Neuropsychiatric Interview	X			
Infectious Disease Assessments (c)	X			
Pregnancy Test (d)	X	X		Day 14/ET
Height	X			
Weight	X			Day 14/ET
Admission to Inpatient Unit		X		
Randomization		X		
Study Medication Administration			X (QID)	X (variable)
Medication Compliance			X	X
Discharge from Inpatient Unit			Day 7	
Efficacy Assessments				
Short Opiate Withdrawal Scale of Gossop (e)		X	X	X
Objective Opiate Withdrawal Scale of Handelsman (e)	X	X (f)	X	X
Modified Clinical Global Impression (e)			X	X
Visual Analog Scale for Efficacy (e)			X	X
Clinical Opiate Withdrawal Scale (e)	X	X	X	X
Concomitant Medications Assessment			X	X
Assessment of Detoxification Completion			X (g)	X
30-Day Post Discharge Phone Follow Up (h)				X
Safety Assessments				
Adverse Events Assessment			X	X
Vital Signs (Sitting & Standing)	X	X	X (i)	X (j)
12-Lead Electrocardiogram (duplicate)	X (k)		X (l)	X (m)
Pharmacokinetic Sampling			X (n)	
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X		X (o)	X (o)
Physical Exam (p)	X	X	X	X

Table 1. Schedule of Study Assessments

	Randomized, Double-Blind, Placebo-Controlled (Days 1-7) followed by Open-Label, Continuation Treatment (Days 8-14)			
	Screening	Baseline (a)	Inpatient Treatment	In/Outpatient Treatment
Activity Day:	**-6 to -1**	**1**	**1-7**	**8 to 14/ET***
Urine Drug Screen (q)	X	X	X	X
30-Day Post Discharge Phone Follow Up (h)				X

Abbreviations: ET = Early Termination, QID = 4 times daily

* Day 14 or and End of Study/Early Termination (ET) assessment, as applicable.

(a) The Baseline period is the morning of admission, before randomization.

(b) This form is to be updated at Baseline.

(c) A chest x-ray is required only if a PPD (purified protein derivative) skin test for tuberculosis is not done, the current PPD is positive, or if a past PPD was positive.

(d) The urine sample collected on the first day of screening will be divided into two aliquots. One sample will be sent to the central lab for urinalysis and the other sample will be used for urine drug screening and immediate "dipstick" analysis of pregnancy (females only).

(e) During Inpatient Treatment (Days 1-7), efficacy scales will be completed daily: the Short Opiate Withdrawal Scale of Gossop 3.5 hours (±10 minutes) after the first dose of study medication followed by the other efficacy scales shortly thereafter. Efficacy scales will be completed daily before dosing during Days 8-14.

(f) The Objective Opiate Withdrawal Scale of Handelsman (OOWS-Handelsman) will be completed at Baseline to determine final eligibility as subjects must have a score ≥2 in order to participate in the study (inclusion criterion #4).

(g) To be done at discharge from the Inpatient Treatment part of the study or early withdrawal (Days 1-7), and each day during Days 8-14 or, if applicable, early termination/discharge from Days 8-14.

(h) The 30-day post discharge follow-up telephone contact will include an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program) and an adverse event evaluation.

(i) Vital signs (sitting/standing blood pressure and pulse) will be measured before every dose and 3.5 hours after study medication administration at 8 AM, 1 PM, and 6 PM (7 times per day).

(j) Vital signs (sitting/standing blood pressure and pulse) will be measured at least once daily before dosing and 3.5 hours after dosing. Note that if subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary to record the measurements.

(k) Baseline 12-lead electrocardiograms (ECGs) will be done on one day during the screening period, time-matched to the post randomization ECG schedule (i.e., pre-1 PM [before 1 PM dose], 4 PM [3 hours post-dose], and 5 PM [4 hours post-dose]).

(l) 12-lead ECGs will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, at early termination from Days 1-7.

(m) 12-lead ECGs will be done before the first daily dose and 3.5 hours after first daily dose on Days 8 and 14 or, if applicable, at early termination/discharge during Days 8-14.

(n) A finger prick blood sample will be collected concurrently with each scheduled ECG during Days 1-7 only.

(o) Clinical lab testing will be done as clinically warranted, at discharge from the Inpatient Treatment part of the study or early termination (Days 1-7), and on Day 14 or, if applicable, early termination/discharge from Days 8-14.

(p) A complete physical examination will be performed during screening and the physical exam form will be updated at Baseline. A complete physical examination will be performed on Day 1 (3-4 hours after randomization) and at discharge or early termination from the Inpatient Treatment phase (Days 1-7). During Days 8-14, a complete physical exam will be performed as clinically warranted and on Day 14 or, if applicable, early discharge/termination from the study.

(q) Urine drug screen will be done at least every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

15.1 Screening Assessments

Subjects seeking treatment for opioid dependence at one of the study sites will be screened for study enrollment. Screening assessments must be completed within a 7-day time period. Subjects cannot be admitted later than the morning of the 7th day of the screening period. Written informed consent must be obtained from all study subjects before initiation of any study procedures.

The following screening assessments must be completed during screening after written informed consent is obtained: height; weight; vital signs; blood collection for standard clinical safety laboratory assessments (including hematology and biochemistry); urine sample for confirmatory drug testing, urinalysis, and pregnancy assessment (if female); and infectious disease assessment (see Section 15.5.4.2) and a chest x-ray if a past PPD skin test for tuberculosis was positive.

The urine sample collected will be divided into two aliquots. One sample will go to the central lab for urinalysis; the other sample will be used for "dipstick" analysis of pregnancy and qualitative drug screening.

The assessments listed below must also be performed during screening.

- 12-lead ECG (in duplicate) will be done on one day during the screening period, time-matched to the post randomization ECG schedule, i.e., pre-1 PM (before 1 PM dose), 4 PM (3 hours post-dose), and 5 PM (4 hours post-dose).
- Medical and smoking/alcohol history.
- Complete physical examination.
- Mini International Neuropsychiatric Interview (M.I.N.I.) [17, 18]. The M.I.N.I will be performed once at screening only to (1) establish that each potential subject is opioid-dependent (inclusion criterion #2), (2) exclude other drug dependency (exclusion criterion #4), and (3) determine the absence of major psychiatric disorders (exclusion criterion #9).
- Prior medications will be recorded to capture all medications taken in the past 30 days.
- OOWS-Handelsman.
- Clinical Opiate Withdrawal Scale (COWS).

15.2 Baseline Assessments

The Baseline period is the morning of admission to the study, before randomization and dosing. Prospective subjects who meet all eligibility criteria must be admitted to the study in time to give the first dose of study medication at 8 AM.

The assessments listed below will be performed during the Baseline period.

- OOWS-Handelsman (score must be ≥2 for randomization).

- SOWS-Gossop.
- COWS.
- Vital signs (sitting/standing blood pressure and pulse) measurements.
- Repeat pregnancy assessment (by "dipstick"), if female.
- Repeat urine drug screen (by "dipstick").
- Update Inclusion/Exclusion Criteria form to reflect Baseline assessments.
- Update prior medication form and physical examination form to capture any new medications and/or medical problems since screening.

15.3 Assessments During Treatment

15.3.1 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

The assessments listed below will be performed daily (unless otherwise specified) on Days 1-7.

- Efficacy assessments at estimated time of maximum plasma concentration (T_{max}, i.e., 3.5 hours after the first daily dose) including:
  - SOWS-Gossop;
  - OOWS-Handelsman;
  - Modified Clinical Global Impressions Scale (MCGI) (Subject and Rater);
  - Visual Analog Scale for Efficacy (VAS-E); and
  - COWS.
- Concomitant medication assessment.
- Completion of detoxification as assessed by the Site Investigator (after completion of the SOWS-Gossop and other efficacy scales) at completion of Inpatient Treatment on Day 7 only or, if applicable, early termination during Days 1-7).
- Vital signs (sitting/standing blood pressure and pulse) before every dose and 3.5 hours after the 8 AM, 1 PM, and 6 PM dose (7 times per day).
- Continuous monitoring for AEs.
- 12-lead ECGs (in duplicate) will be done before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, early termination during Days 1-7.
- Complete physical examination 3 to 4 hours after randomization on Day 1 and at discharge or, if applicable, early termination during Days 1-7.
- Finger prick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG during Days 1-7.

- Clinical laboratory tests as clinically warranted and at discharge or, if applicable, early termination during Days 1-7.
- Pregnancy test at early termination during Days 1-7.

In addition, qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband.

15.3.2 Days 8-14 (Open-Label, Continuation Treatment) The assessments listed below will be performed daily on Days 8-14.

- Efficacy assessments before dosing including:
  - SOWS-Gossop;
  - OOWS-Handelsman;
  - MCGI (Subject and Rater);
  - VAS-E; and
  - COWS.
- Concomitant medication assessment.
- Completion of detoxification as assessed by the Site Investigator daily on Days 8-14 and/or on early discharge/termination.
- Pill count to measure compliance with previous day's doses.
- Vital signs (sitting/standing blood pressure and pulse) at least once daily before dosing and 3.5 hours after dosing. Note that if subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary (Appendix 8) to record the measurements.
- AE assessment.
- 12-lead ECGs (in duplicate) will be done before the first daily dose and 3.5 hours after the first daily dose on Days 8 and 14 or, if applicable, early discharge/termination during Days 8-14.
- Clinical laboratory tests as clinically warranted and on Day 14 or, if applicable, early discharge/termination during Days 8-14.
- Complete physical examination as clinically warranted and on Day 14 or, if applicable, early discharge/termination during Days 8-14.
- Pregnancy test on Day 14 or, if applicable, early discharge/termination during Days 8-14.

Qualitative urine drug screening (by on-site use of "dipsticks") will be done at least every other day to monitor for contraband (inpatient setting) or illicit (outpatient setting) drug use.

A 30-day post discharge follow-up telephone contact will be made for an adverse event evaluation and an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program).

15.4 Efficacy Assessment Methods

15.4.1 Short Opiate Withdrawal Scale (SOWS-Gossop)

The SOWS-Gossop [16] will be completed by the subject at baseline (before randomization), once daily at 3.5 hours (± 10 minutes) after the first dose of study medication on Days 1-7, and once daily before dosing on Days 8-14. Note that at the time of each daily evaluation, subjects should consider their symptoms over the last 24-hour period. Also, this scale should be completed before completion of the OOWS-Handelsman, MCGI, VAS-E, and COWS.

The SOWS-Gossop scale assesses subjective symptoms of opioid withdrawal (Appendix 1). 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) (see Table 2 below). The overall score will be the simple sum of the 10-item scores. Lower observed values in SOWS-Gossop scores indicate a more positive clinical outcome.

Table 2. SOWS-Gossop Scoring Method

Condition	Score			
	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/Problems Sleeping	0	1	2	3

Note: Possible score range = 0 to 30.

15.4.2 Objective Opiate Withdrawal Scale (OOWS-Handelsman)

The OOWS-Handelsman [19] will be performed by a trained observer during screening, twice on Day 1 (during Baseline to confirm final eligibility for randomization [score of ≥2 is required per inclusion criterion #4] and 3.5 hours after the first dose of study medication, after completion of the SOWS-Gossop), once daily at 3.5 hours after the first dose of study medication on Days 2-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop).

The subject will be observed for 5 minutes, and the presence or absence of 13 physical signs of opioid withdrawal will be recorded (Appendix 2). The presence of a sign will be assigned 1 point, yielding a possible total score ranging from 0 to 13 (see Table 3 below). Lower observed values in OOWS-Handelsman scores indicate a more positive clinical outcome.

Ambient room temperature will be recorded on the eCRF for all OOWS-Handelsman observations.

Table 3. OOWS-Handelsman Scoring Method

Symptom (a)	Score (b)	
	0	1
Yawning(Frequency = # of yawns per observation period)	None	≥1
Rhinorrhea(Frequency = # of sniffs per observation period)	0-2	≥3
Piloerection (Gooseflesh - observe subject's arm)	None	Present
Perspiration	None	Present
Lacrimation	None	Present
Mydriasis	None	Present
Tremors (hands)	None	Present
Hot and Cold Flashes (shivering or huddling for warmth)	None	Present
Restlessness (frequent shifts in position)	None	Present
Vomiting (c)	None	Any
Muscle Twitches	None	Any
Abdominal Cramps (holding stomach)	None	Present
Anxiety (d)	None	Mild, Moderate or Severe

(a) Observed over a 5-minute period.
(b) For total score: Minimum = 0; Maximum = 13.
(c) Present during 5-minute observation period.
(d) Mild = observable manifestations, such as foot shaking, fidgeting, finger tapping.
Moderate to severe = agitation, unable to sit, trembling, panicky, complains of difficulty in breathing, choking sensations, palpitations.

15.4.3 Modified Clinical Global Impressions Scale (MCGI)

The Clinical Global Impressions rating scale (1985) was developed by the National Institute of Mental Health (NIMH), and originally contained 3 questions. For this study, Questions #1 and #3 have been modified from the original scale, and Question #2 was not included (Appendix 3).

In the original scale, Question #1 (severity of illness) evaluates the subject using a severity scale from 0 (not assessed), 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The language of this question has been modified in this study for the subject assessment to make the scale more appropriate to opioid withdrawal. The original Question #2 referred to "global improvement" and is omitted from this study, since all subjects will be treated, and there is no untreated screen withdrawal. Question #3 (efficacy index) records responses on a factorial grid – side effects on one side and therapeutic effects on the other side. Since there is no untreated screen withdrawal data, the therapeutic effect cannot be assessed; therefore, only the side effect responses will be examined.

The MCGI scale is used to estimate the overall clinical benefit of lofexidine treatment. The MCGI will be completed once daily at 3.5 hours after the first dose of study medication on Days 1-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). The modified subject and observer scales used in this study are presented below in Table 4. Lower observed values in MCGI scores indicate a more positive clinical outcome.

Table 4. MCGI Scoring Method

MCGI	Score						
	1	2	3	4	5	6	7
Subject Scale							
Severity of Opiate Withdrawal Symptoms (a)	None	Between none and mild	Mild	Moderate	Marked	Severe	Most severe I ever had
Side Effects (b)	None	Slight, does not significantly interfere with daily activities	Moderate, significantly interferes with daily activities	Severe, greater than symptom relief			
Observer Scale							
Severity of Illness (a)	Not at all ill	Borderline ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Among the most extremely ill subjects
Side Effects (b)	None	Does not significantly interfere with subject's functioning	Significantly interferes with subject's functioning	Out-weighs therapeutic effect			

(a) Maximum score of 7.
(b) Maximum score of 4.

15.4.4 Visual Analog Scale for Efficacy (VAS-E)

The effectiveness of lofexidine in alleviation of withdrawal sickness will be assessed by subjects using the VAS-E, which will be completed once daily on Days 1-7, 3.5 hours after the first dose of study medication (after completion of the SOWS-Gossop) and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). Subjects will make a mark on a 100-mm VAS scale to reflect the effectiveness of lofexidine in relieving withdrawal sickness from Not Effective at all (0 mm) to Completely Effective (100 mm). Greater observed values in VAS-E scores indicate a more positive clinical outcome (Appendix 4).

15.4.5 Clinical Opiate Withdrawal Scale (COWS)

The COWS [20] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal, and will be completed during screening, at baseline (before randomization), once daily at 3.5 hours after the first dose of study medication on Days 1-7 (after completion of the SOWS-Gossop), and once daily before dosing on Days 8-14 (after completion of the SOWS-Gossop). The COWS is a clinician-administered instrument that rates 11 common opioid withdrawal signs and symptoms (Appendix 5). These include: resting pulse rate; sweating; restlessness; pupil size; bone or joint aches; runny nose or tearing; gastrointestinal (GI) upset; tremor; yawning; anxiety or irritability; and gooseflesh skin. The score for each item reflects the severity of the sign or symptom, and the total scores are grouped as mild (5-12 points), moderate (13-24 points), moderately severe (25-36 points), and severe (>36 points).

15.4.6 Assessment of Completion of Detoxification

At the completion of Inpatient Treatment on Day 7 or, if applicable at early termination from Days 1-7, the Site Investigator will indicate if the subject has completed detoxification and can be discharged without further lofexidine treatment. The same assessment will be made at each visit during Days 8-14.

15.4.7 Concomitant Medication Use

Multivitamins, nicotine replacement therapy, and several other concomitant medications for minor complaints (e.g., diarrhea, constipation, mild nausea, headache, muscle aches, cough, insomnia) will be allowed during the study. All concomitant medications administered will be recorded daily.

15.4.8 Withdrawal-Related Adverse Events

The Site Investigator will indicate, using his/her best judgment, whether any adverse event that occurs during the study is secondary to opioid withdrawal. Individual items reported on the efficacy scales (i.e., SOWS-Gossop, OOWS-Handelsman) do not automatically qualify as a withdrawal-related AE unless the subject specifically reports them in response to a non-leading question (i.e., "How have you been feeling since I saw you last?"). In the event a subject reports "withdrawal" or a similar event encompassing a collection of potential withdrawal symptoms, the subject should be asked to elaborate so that specific symptoms can be recorded on the AE eCRF. In this case, the AEs recorded should include both the original reported condition (e.g., "withdrawal syndrome") as well as the individual symptoms that the subject lists after further inquiry (e.g., anxiety, upset stomach).

15.4.9 Subject Treatment Status 30 Days Post Discharge

A follow-up telephone contact will be made by the Site Investigator, including an evaluation of the subject's current treatment status (e.g., relapse, current psychosocial treatment, successful entry into a methadone, buprenorphine, or naltrexone program) and an adverse event evaluation.

15.5 Safety Assessment Methods

15.5.1 Adverse Events

Adverse events will be assessed and recorded around the same time each day by study staff during Days 1-7. If an AE requires medical attention, it should be reported to a study physician immediately. A study physician must meet with the subject to assess all medical and psychiatric AEs reported by the subject, as well as those recorded by other study staff. Adverse events will be assessed by asking the subject, "How have you been feeling since I saw you last?" After current AEs are assessed, the study physician must review with the subject and assess any AEs unresolved from the previous day. After each daily AE assessment, the physician will record in the subject's source document and AE eCRF, according to the procedures described in Section 16.7, the type of AE and whether serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the physician's best judgment of the severity and relatedness of

each AE. The physician will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.4.8). In general, an AE should not be marked as withdrawal related AND related to study medication.

Any study subject with a related AE will be followed by the attending physician until the event is resolved to the satisfaction of the Site Investigator and Sponsor's Medical Monitor. If the AE is unrelated, the subject will not be discharged until medically stable, and then will be referred, at the subject's sole expense, for ongoing care and/or treatment, which may include psychological and lifestyle counseling, support groups, or pharmacological and medical treatment.

During Days 8-14, in either an inpatient or outpatient setting, subjects will be queried about adverse events daily. All subjects will be instructed to contact the treating physician if he or she feels dizzy (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until instructed by the physician. All reported AEs will be recorded as described above.

15.5.2 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse) are to be measured at screening for all subjects.

During Days 1-7, vital signs (sitting/standing systolic and diastolic blood pressure, pulse) will be measured at Baseline and on Days 1-7, within 30 minutes before receipt of study medication at 8 AM, 1 PM, 6 PM, and 11 PM and 3.5 hours (±15 minutes) after receipt of study medication at 8 AM, 1 PM, and 6 PM.

During open-label treatment, in an inpatient or outpatient setting (Days 8-14), vital signs will be measured at least once daily before dosing and 3.5 hours (±30 minutes) after dosing. If subjects are being treated on an outpatient basis and cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. They will also be provided a diary (Appendix 8) to record the measurements.

For the orthostatic blood pressure readings, subjects will remain sitting for 3 minutes before a blood pressure reading, and then stand for 3 minutes before a second blood pressure reading is taken. If a subject demonstrates potentially clinically significant vital signs, as per any one of the criteria (i.e., systolic values, diastolic values, or pulse values meet the specified criteria) in the guidelines shown below, the event should be recorded in the subject's source document and eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) and the subject should be followed until medically stabilized to the satisfaction of the attending physician. Additional dose-hold and discontinuation criteria are provided in Sections 13.2.2 and 13.2.3, respectively.

Vital Sign Parameter	Observed Value		Change Relative to Screen
Systolic Blood Pressure	≥180 mmHg ≤90 mmHg	A N D	Increase of ≥20 mmHg Decrease of ≥20 mmHg
Diastolic Blood Pressure	≥105 mmHg ≤50 mmHg		Increase of ≥15 mmHg Decrease of ≥15 mmHg
Pulse	≥120 bpm ≤50 bpm		Increase of ≥15 bpm Decrease of ≥15 bpm

Operational Note: When a vital sign or QTcF reading meets any of the defined cut-off criteria for discontinuation, the values will be confirmed by repeating the measurement twice, approximately 10 to 15 minutes apart. If 2 of the 3 total readings confirm that the subject meets discontinuation criteria, the subject will be terminated from the study. If 2 of the 3 total readings are within acceptable limits (and they do not meet the other discontinuation criteria detailed in Section 14.5.2), the subject may continue in the study.

Additionally, when the subject is experiencing blood pressure- or pulse-related symptoms (e.g., lightheaded, dizziness, palpitations), these should be recorded in the subject's source document and eCRF as an AE or SAE (see Sections 15.5.1, 16.7, and 16.8) even if the vital signs values do not meet the predefined criteria shown above.

15.5.3 12-Lead Electrocardiograms

Using ECG core lab-provided and validated instruments, baseline paper tracing 12-lead ECG (in duplicate) will be conducted on one day during the screening period, time-matched (± 15 minutes) to the post randomization ECG schedule, i.e., pre-1 PM (before 1 PM dose), 4 PM (3 hours post-dose), and 5 PM (4 hours post-dose). During Days 1-7, 12-lead ECGs (in duplicate) will be conducted before the first daily dose, pre-1 PM dose, at 4 PM, and at 5 PM on Days 1 and 7; before the first daily dose only on Days 2 and 4; and, if applicable, early termination during Days 1-7. During Days 8-14, 12-lead ECGs (in duplicate) will be conducted before the first daily dose and 3.5 hours after the first daily dose on Days 8 and 14 or, if applicable, early termination/discharge during Days 8-14. ECG intervals and abnormalities will be read centrally by a computer and confirmed by an individual accredited to read ECGs at the ECG core lab A qualified physician on site will evaluate tracings if there is significant abnormality. The following intervals will be computed:

- Ventricular Rate — Number of R waves appearing within a 6-second period, multiplied by 10;
- PR Interval — Measured from the onset of the P wave to the onset of the QRS complex;
- QRS Complex — Measured from the beginning of the down stroke of the Q wave to the completion of the upstroke of the S wave;

- QT Interval — Measured from the beginning of the down stroke of the Q wave to the completion of the T wave;
- QTc (Bazett) — QT interval corrected for heart rate using Bazett's formula (QT/square root of RR) (for analysis purposes).
- QTc (Fridericia) — QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject termination purposes).

  At screening (baseline assessment), a QTcF interval greater than 450 msec for males and greater than 470 msec for females will exclude the subject from study participation (see exclusion criterion #6 in Section 11.2.2). In such cases, 2 additional ECGs should be taken at 10- to 15-minute intervals. The QTcF interval on all 3 ECGs should be confirmed by the Site Investigator and if 2 of the 3 QTcF intervals exceed the gender-specific cut-off, then the subject should be judged a screen failure and not randomized to treatment.

  During the treatment phase of the study, when any QTcF interval exceeds 495 msec, 2 additional ECGs should be taken at 10- to 15-minute intervals. The QTcF interval on all 3 ECGs should be confirmed by the Site Investigator. If it is determined that 2 of the 3 QTcF intervals exceed 500 msec or >25% above screen value, then the subject will be terminated from the study.

  Any time that 2 of the 3 QTcF measurements exceed 500 msec, contact the Sponsor's Medical Safety Monitor, to discuss the subject and the AE/SAE determination.

15.5.4 Clinical Laboratory Evaluations

15.5.4.1 Standard Laboratory Tests

Standard clinical laboratory safety evaluations (see Table 5) will be performed for all subjects at screening, as needed at the physician's discretion throughout the study, at discharge from the Inpatient Treatment part of the study or early termination (Days 1-7), and on Day 14 or, if applicable, early discharge/termination during Days 8-14. For this multicenter study, a central laboratory will be used that is directly accredited by the College of American Pathologists (CAP) and licensed by the Clinical Laboratory Improvement Act of 1988 (CLIA); both certification and accreditation must be renewed every 2 years. The laboratory will need to provide a copy of current certification and provide the normal values for all analytes to determine the upper limit of normal (ULN).

Table 5. Hematology, Chemistry, and Urinalysis Tests

Hematology (a)	Chemistry (b)	Urinalysis
Hemoglobin	Cholesterol	Specific gravity
Hematocrit	Triglycerides	pH
Red blood cell (RBC) count	Sodium	Bilirubin
White blood cell (WBC) count	Potassium	Urobilinogen
WBC differential (%)	Chloride	Glucose
neutrophils	Carbon dioxide (CO_2)	Protein
lymphocytes	Glucose	Ketones
monocytes	Creatinine	WBC
eosinophils	Albumin	RBC
basophils	Total protein	Epithelial cells
Prothrombin time (PT)	Calcium	
Partial thromboplastin time (PTT)	Phosphorus	
	Aspartate aminotransferase (AST)	
	Alanine aminotransferase (ALT)	
	Gamma-glutamyl transpeptidase (GGT)	
	Total bilirubin	
	Lactate dehydrogenase (LDH)	
	Alkaline phosphatase	
	Blood urea nitrogen (BUN)	
	Thyroid-stimulating hormone (TSH)	
	Free thyroxine (T4)	

(a) Blood will be collected in anticoagulant containing evacuated venous blood collection tubes (e.g., Vacutainer™).

(b) Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures.

15.5.4.2 Infectious Disease Panel and Syphilis Tests

The infectious disease panel and syphilis tests will be assayed at screening only. Blood will be collected in serum separation evacuated venous blood collection tubes (e.g., Vacutainer™) and serum separated according to standard procedures. Qualitative analysis reporting positive/negative results will be performed for the following analytes: Hepatitis B surface antigen (Hbs Ag), Hepatitis B surface antibody (anti-HBs), Hepatitis B core antibody (anti-HBc), and Hepatitis C virus antibody (HCV Ab). A PPD skin test for tuberculosis and/or a chest x-ray will be performed on all subjects. If the PPD is positive, a chest x-ray is required to assess active tuberculosis. If the subject reports that s/he has been previously positive for the PPD test, the PPD test will not be performed and only a chest x-ray will be required. A rapid plasma reagin (RPR) test for syphilis will be performed. If positive, a confirmatory test (FTA-ABS or MHA-TP) will be performed.

If either PPD with chest x-ray, chest x-ray, or the confirmatory test for RPR is positive, subjects will not be eligible for study participation and will be referred, at subject's sole expense, for appropriate follow-up and/or treatment.

15.5.4.3 Urine Toxicology Screening

Qualitative urine drug screening (UDS) will be performed at screening for all subjects, at Baseline, and at least every other day for the following drugs: amphetamines/methamphetamines, cocaine, barbiturates, opiates, benzodiazepines, cannabinoids, methadone, and buprenorphine. The central lab will provide standard sets of UDS "dipsticks" for use across all sites.

15.5.4.4 Pregnancy Test

A "dipstick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening, at Baseline, and on Day 14 or early completion/early termination for all female subjects regardless of their childbearing capacity. The central lab will provide study sites with a supply of pregnancy dipsticks.

15.5.4.5 Pharmacokinetic Sampling

A finger prick blood sample will be collected concurrently with each scheduled ECG during Days 1-7 only.

15.5.5 Physical Examination

A complete physical examination of 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 should be performed at screening for all subjects.

An update of the Physical Exam is required at Baseline (before randomization on Day 1) and then a complete physical examination should be performed 3 to 4 hours after randomization on Day 1 and at discharge or early termination from Days 1-7. For Days 8-14, a complete physical examination should be performed as clinically warranted and on Day 14 or, if applicable, early discharge/termination from the study.

Height should be recorded at screening only.

15.6 Other Assessments

15.6.1 Prior Medications

All medications taken by the subject for the 30 days before screening and during the screening period will be recorded in the subject's source document and on the Prior Medication eCRF. Prior medication usage should be updated at Baseline. The reported medications will be reviewed and approved by the Site Investigator/study physician for entry into the study.

15.6.2 Concomitant Medication Administration

Concomitant medication administration will be recorded daily. All concomitant medications should be recorded in the subject's source document and on the Concomitant Medication eCRF. All medications taken by the subject during study participation that are not on the list

of permitted concomitant medications (see Section 14.6) must be pre-approved by the Site Investigator/study physician with concurrence of the Sponsor's Medical Monitor and recorded on the concomitant medication administration form.

16 REGULATORY AND REPORTING REQUIREMENTS

16.1 Good Clinical Practices

This study will be conducted in accordance with the most current version of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP). An Operations Manual will be provided to all investigational sites as a study quality assurance tool. The monitoring of the sites participating in the trial will be executed according to GCP guidelines. Monitors will examine subjects' study files including source documents in both the clinic files and subjects' official medical records, and will also review regulatory/essential documents such as correspondence with the IRB and the Sponsor (USWM). Areas of particular concern will be subject informed consent issues, protocol adherence, safety monitoring, IRB reviews and approvals, safety reports/regulatory forms, subject records, study drug accountability, and principal investigator supervision and involvement in the trial. Reports will be prepared following each visit and forwarded to the Sponsor's Clinical Project Manager. Monitors will also prepare follow-up letters detailing their findings and any items requiring further resolution or attention by the site. Follow-up letters will be provided to the Site Investigator, site coordinator, and Sponsor's Clinical Project Manager.

16.2 FDA Form 1572 and Financial Disclosure

The Site Investigator will sign a Statement of Investigator (FDA Form 1572) before initiating this study. The names of any sub-investigators must appear on this form.

The Site Investigator and any sub-investigators will also sign a Financial Disclosure form before initiating this study.

16.3 Institutional Review Board Approval

Before initiating the study, Site Investigator will obtain written IRB approval to conduct the study. No study medication will be shipped until IRB approval is obtained. Should changes to the study protocol become necessary, protocol amendments (provided by the Sponsor) will be submitted in writing to the central IRB and the Site Investigator's IRB for IRB approval before implementation. In addition, IRBs will approve all advertising materials used for subject recruitment and any educational materials given to the subject. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB.

The IRB must be a properly constituted board or committee operating in accordance with GCP Title 21 Part 56 of the US CFR relating to IRBs and the ICH Guideline for GCP (E6).

16.4 Informed Consent/HIPAA Authorization

Properly executed written informed consent, in compliance with 21 CFR 50 and ICH guidelines, shall be obtained from each subject before entering the subject into the trial. Attention is directed to the basic elements that are required in the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]). Additional elements of informed consent, if appropriate, must be included in the informed consent document (21 CFR 50.25[b]). A standard Informed Consent document will be approved by a central IRB Any study site that requires a site-specific Informed Consent document must have the document IRB-approved and the final IRB-approved document must be provided to the Sponsor for regulatory purposes.

All potential subjects for the study will be given a current copy of the Informed Consent Form to read. The Site Investigator, sub-investigators, or study physician at each site will explain all aspects of the study in lay language and answer all of the subject's questions regarding the study. If the subject desires to participate in the study, s/he will be asked to sign the Informed Consent. Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%. No subject will undergo any study procedures before signing the Informed Consent form, which should be signed before screening. A signed copy will be given to the subject and a signed copy shall be maintained in the subject's clinical file as well as the Regulatory Binder at each study site. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

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

16.5 Drug Accountability

All study drug required for completion of this study will be provided by the Sponsor (USWM). Upon receipt, the investigator/pharmacist is responsible for taking inventory of the investigational agents. A record of this inventory must be kept and usage must be documented. Any unused or expired investigational agent shall be returned to the Sponsor.

16.6 Outside Monitoring

16.6.1 Data and Safety Monitoring Board (DSMB)

Adverse event data reported during the study will be reviewed by a Data and Safety Monitoring Board (DSMB) comprised of outside experts in substance abuse treatment, clinical trials, and biostatistics. The DSMB will meet by conference call or WebEx every 3 months during the life of the study to review adverse event and serious adverse data tables and data listings. Any serious adverse event requiring expedited reporting to the FDA will be reviewed immediately by the DSMB. The board will be blinded to subjects' actual treatment assignments, but may break the blind if safety concerns arise from the blinded data. Although the DSMB may also have access to efficacy data, it will not be commissioned to recommend trial termination due to superior treatment efficacy versus placebo, and the trial will not be stopped prematurely for that reason.

16.6.2 Medical Monitor

The Sponsor's (USWM) Medical Monitor will be responsible for attempting to establish concurrence with the Site Investigator on the severity and seriousness of any AEs and SAEs, the relatedness to the study treatments, the expectedness of the event, and for determining if the SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 6). The Sponsor's Medical Monitor will also be responsible for tracking and assessing trends in the SAEs reported. Further, the Medical Monitor is available to consult with the Site Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications).

16.6.3 Clinical Monitors

All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, all eCRFs and corresponding source documents for each subject. These monitoring visits will provide an opportunity for evaluation of the progress of the study and to inform the Sponsor of potential problems.

The study will be monitored according to an approved monitoring plan. The monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational agents are properly stored and accounted for; verify that subjects' consent for study participation has been properly obtained and documented; confirm that research subjects entered into the study meet inclusion and exclusion criteria; and assure that all essential documentation required by GCP guidelines are appropriately filed.

Monitors will conduct a site initiation visit before the start of the study for any investigational site not represented at the investigator meeting. At this visit, the monitor will assure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and assure that acceptable facilities are available to conduct the study.

Routine monitoring visits by USWM or designee will be scheduled at appropriate intervals but more frequently at the beginning of the study. At these visits, the monitors will verify that study procedures are being conducted according to the protocol guidelines and review AEs and SAEs. At the end of the study, they will advise on storage of study records and return of unused study agents. All sites should anticipate visits by the Sponsor, its representatives, and the FDA.

16.7 Adverse Event Reporting

In accordance with FDA reporting requirements, all AEs occurring during the course of the clinical trial will be collected, documented, and reported by the Site Investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix 6. The occurrence of AEs will be assessed starting at the treatment phase of the protocol.

An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial, whether or not the event is considered related to the investigational agent

or clinically significant. For this study, events reported by the subject, as well as clinically significant abnormal findings on physical examination or laboratory evaluation will be recorded in the subject's source document and on the AE eCRF. A new illness, symptom, sign or clinically significant clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Stable chronic conditions, such as arthritis, which are present before clinical trial entry and do not worsen are not considered AEs.

After each AE assessment, the physician will record in the subject's source document and on the AE eCRF the type of AE and whether serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the physician's best judgment of the severity and relatedness of each AE. The physician will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.4.8). In general, an AE should not be marked as withdrawal related AND related to study medication.

Each day, a study physician must review any AEs that are reported as beginning or as continuing. All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed by a study physician until satisfactory resolution.

16.8 Serious Adverse Events (SAEs)

Each adverse event or reaction will be classified by the Site Investigator as serious or non-serious. Based on the seriousness of the adverse event or reaction, appropriate reporting procedures will be followed.

The Code of Federal Regulations (CFR) Title 21 part 312.32 and ICH Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2A March 1995, as implemented by the US FDA, defines a SAE or serious adverse drug experience as any untoward medical occurrence at any dose that:

- results in death during the period of protocol-defined surveillance;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity; or
- results in a congenital anomaly/birth defect.

Important medical events that may not result in death, be life–threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, the event may jeopardize the subject and might require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An unexpected event is one that is not described with respect to nature, severity, or frequency in the product package insert or Investigator's Brochure.

All subjects with SAEs must be followed up for outcome. If a study subject withdraws from the study or if an investigator decides to discontinue the subject from the study because of a SAE, the subject must have appropriate follow-up medical monitoring including, if necessary, hospitalization.

Reporting requirements for SAEs are described in detail in Appendix 6. There can be serious consequences including ultimately, criminal and/or civil penalties for sponsors who fail to comply with FDA regulations governing the reporting of SAEs to the FDA. Any SAEs, including death due to any cause, which occurs to any subject entered into treatment in this study or within 30 days following cessation of the last dose of treatment with the study medication, whether or not considered related to the investigational product, must be reported within 24 hours, from the time any study staff member is made aware of such, to the Sponsor (USWM).

16.8.1 Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study treatment(s).
- All deaths, regardless of cause or relationship, must be reported for subjects on study and for deaths occurring within 30 days of last study treatment or within 30 days of last study evaluation, whichever is longer.
- "Occurring at any dose" does not imply that the subject is receiving study treatment at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE; however, administration of study drug may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE.
- "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as severe should not be confused with a SAE. Severity is a category used for rating the intensity of an event, and both AEs and SAEs can be assessed as severe (see Appendix 6 for assessment of the intensity of an AE). An event is defined as "serious" when it meets one of the predefined outcomes described above.

16.9 Overdose

Any accidental or intentional overdose (any increase in frequency or dosage of study treatment [lofexidine] that exceeds total dosing of 3.2 mg per day), misuse or abuse of study treatment, whether suspected or confirmed, and whether or not associated with an adverse experience, must be reported within 24 hours to USWM or designee. This will include providing details of signs or symptoms, clinical management, and outcome if available.

Any clinical sequelae in association with the overdose should be reported as an AE as outlined in Section 16.7 or SAE as outlined in Section 16.8. An overdose will be considered a SAE only if any of the seriousness criteria are met in Section 16.8.

16.10 Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Site Investigator or his or her designee 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 of completing the study medication. All subjects who become pregnant must be withdrawn from study medication and must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor.

17 STATISTICAL APPROACH

17.1 General Considerations

Continuous or ordered categorical variables not subject to censoring will be summarized with the mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. Continuous or ordered categorical variables subject to censoring (e.g., time to removal from study treatment) will be summarized by the 25th percentile, median, 75th percentile derived from Kaplan-Meier estimates of probabilities. Unordered categorical variables will be summarized with counts and percentages. Descriptive statistics will be provided for each treatment group separately as well as all subjects combined. Additionally, descriptive statistics will be provided by gender.

Detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared as a standalone document and finalized before database lock and unblinding of treatment assignments.

17.2 Days 1-7 (Randomized, Double-Blind, Placebo-Controlled Treatment)

It is hypothesized that a daily dose of either 2.4 mg or 3.2 mg lofexidine will achieve greater efficacy than placebo with respect to overall symptom relief over the first 7 days of opioid withdrawal (primary endpoint) and will increase the likelihood of subjects completing Days 1-7 of treatment (secondary endpoint). Further, safety measures in the 2.4 mg and 3.2 mg total daily dose groups will be compared descriptively to assess whether the lower dose results in fewer and less severe adverse events than does the higher dose.

17.2.1 Analysis Populations

Three principal analysis populations are defined as follows:

- Intent-to-treat (ITT), consisting of all randomized subjects. Subjects will be assigned for analysis according to the group to which they are randomized.
- Modified intent-to-treat (mITT), consisting of all subjects in the ITT group who received at least one dose of study medication.
- Safety consisting of all subjects who received at least one dose of study medication.

The principal analysis population for the analyses of demographics and baseline characteristics and efficacy will be the mITT population. Sensitivity analyses of the completion status endpoint will be carried out on the ITT population. Safety summaries will be provided for the Safety population. Data recorded on subjects who are in the ITT but not in the mITT or Safety populations will be included in data listings.

17.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively.

17.2.3 Subject Disposition

Subject disposition will be summarized descriptively.

17.2.4 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- AUC based on SOWS-Gossop scores from Days 1 through 7.

17.2.5 Secondary Efficacy Endpoint

The secondary efficacy endpoint is:

- Completion status (i.e., whether a subject receives at least one dose of study medication on Day 7 and completes the 3.5-hour post-dose SOWS-Gossop assessment on Day 7).

17.2.6 Tertiary/Exploratory Endpoints

The tertiary/exploratory endpoints are:

- SOWS-Gossop, OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS scores on Days 1, 2, 3, 4, 5, 6, and 7;
- Retention analysis (time to removal from study treatment) over the 7 inpatient days;
- Concomitant medication analysis;
- Withdrawal-related AE analysis;
- Evaluation of subject treatment status 30 days post discharge;

- Status of detoxification on Day 7 or early termination as assessed by the Site Investigator; and
- In addition, single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed, as may AUC based on COWS scores from Days 1 through 7.

17.2.7 Control of the False Positive Rate and Statistical Testing Strategy

All statistical tests for efficacy will be one-sided. For the primary and secondary endpoints, the treatment comparisons subject to control of the false positive rate will be 3.2 mg lofexidine vs. placebo and 2.4 mg lofexidine vs. placebo. (Comparisons of 3.2 mg vs. 2.4 mg will be descriptive.) The familywise error rate (FWE) for the collection of primary and secondary endpoint comparisons will be controlled at the 0.025 level, one-sided, by a sequential testing strategy in which hypotheses are tested in the following order, each at the 0.025 level, one-sided.

1. Primary: AUC(1-7), 3.2 mg lofexidine versus placebo;
2. Primary: AUC(1-7), 2.4 mg lofexidine versus placebo;
3. Secondary: Completion rate, 3.2 mg lofexidine versus placebo; and
4. Secondary: Completion rate, 2.4 mg lofexidine versus placebo.

Adjusted p-values for these 4 treatment comparisons, based on this sequence of statistical tests, are defined in the table below.

Test Order	Endpoint Comparison	P-value	
		Unadjusted (a)	Adjusted
1	AUC(1-7), 3.2 mg vs placebo	p_1	p_1
2	AUC(1-7), 2.4 mg vs placebo	p_2	$\max(p_1, p_2)$
3	Completion rate, 3.2 mg vs placebo	p_3	$\max(p_1, p_2, p_3)$
4	Completion rate, 2.4 mg vs placebo	p_4	$\max(p_1, p_2, p_3, p_4)$

(a) P-values p_1 and p_2 are one-sided, derived from the statistical test described in Section 17.2.8.1; p-values p_3 and p_4 are one-sided, derived from the statistical test described in Section 17.2.8.2.

Any adjusted p-value less than 0.025 in magnitude will be declared statistically significant.

The tertiary/exploratory endpoints will be tested without multiplicity adjustment.

17.2.8 Statistical Methods for Efficacy

17.2.8.1 SOWS-Gossop AUC(1-7)

A pattern-mixture approach [21], with subjects stratified by disposition within Days 1-7, will be used in assessing SOWS-Gossop AUC(1-7). The 4 disposition strata are subjects: who complete Days 1-7 of the study (see Section 17.2.5); who discontinue due to lack of efficacy (including adverse events related to opioid withdrawal); who discontinue due to adverse

events related to intolerability or toxicity to study drug; and who discontinue for other reasons. The inference is comprised of several steps:

1. Transformation. Because of the inherent skewness in the SOWS-Gossop scores the raw data will first be transformed to the logarithm of the score plus 1.0.
2. Modeling. A linear mixed effects repeated-measures model will be constructed for the SOWS-Gossop score. The fixed effects will be disposition stratum, treatment and time, and their interactions, as well as a main effect of gender (randomization stratification factor) and baseline SOWS-Gossop score as a one degree of freedom covariate. For each combination of treatment and stratum, the time course will be modeled as a linear change point model, allowing for one slope between Days 1 and 2 and a possibly different slope from Days 2 through 7. The model will parameterized to ensure that the predictions from the two line segments agree at Day 2. Subjects will be treated as a random effect, and the slope and intercept parameters will be treated as random coefficients. Modeling the time course, rather than using each time point as a discrete level of a model factor, allows estimation of group means through Day 7 even in the non-completer strata. The choice of Day 2 as the change point is based on prior lofexidine studies, in which SOWS-Gossop mean scores in the placebo group increased from Day 1 to Day 2 and then decreased through Day 7. The modeling allows a different time course for each of the lofexidine dose groups.
3. Point estimates of AUC(1-7). For each combination of disposition stratum, treatment and study day, the estimated least squares means SOWS-Gossop (on the log scale) for males and females will be combined using a weighted average, the weights being the relative proportions of males and females in the mITT population. The results will then be transformed back to the original SOWS-Gossop scale of measurement, from which point estimates of AUC(1-7) for each combination of stratum and treatment will be computed using the trapezoidal rule. It should be noted that these calculations will not be derived from AUC(1-7) computed within individual subjects, many of whom will have incomplete data for the later study days in Days 1-7. In particular, there will be no imputation of data for individual subjects.
4. Estimates of treatment effect. For each active treatment, the treatment effect (lofexidine 3.2 mg versus placebo or lofexidine 2.4 mg versus placebo) will be estimated with respect to AUC(1-7) within each disposition stratum. Then a weighted average of treatment effects will be computed, where the weights are the relative proportions of subjects in the 4 strata.
5. Interval estimates of AUC(1-7) and hypothesis testing. The covariance matrix of the mixed model's estimated fixed effects will be used with standard linear model methods to derive the covariance matrix of the weighted average of male and female log-transformed SOWS-Gossop scores. The multivariate delta method will be used to derive the covariance matrix of the back-transformed SOWS-Gossop time course. Standard linear model methods will then be used to derive the covariance matrix of the weighted average of AUC(1-7) treatment effects, from which confidence intervals and p-values will be derived.

17.2.8.2 Completion Status

The proportion of subjects in each treatment arm who receive at least one dose of study medication on Day 7 and complete the 3.5-hour post-dose SOWS-Gossop assessment on Day 7 will be analyzed using Cochran-Mantel-Haenszel tests, with gender as the stratifying factor. One test will compare the 3.2 mg lofexidine group to placebo; a second will compare the 2.4 mg lofexidine group to placebo.

17.2.8.3 SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7

The pattern-mixture approach, with the same stratification and treatment of gender used for the AUC(1-7) analysis, will be used to assess treatment effect with respect to SOWS-Gossop on Days 1, 2, 3, 4, 5 and 6 (but not 7). A single linear mixed effects repeated-measures model will be constructed for the transformed SOWS-Gossop score. Subject will be a random effect. The fixed effects will be disposition stratum, treatment and time, with each study day as a discrete level of the time factor, and their interactions. Estimated means for each combination of stratum, treatment and day will be back-transformed to the original SOWS-Gossop scale of measurement. Like the AUC(1-7) calculation, the weighted average of treatment effects will be calculated along with confidence intervals and p-values. This approach will provide no information on the non-completer strata on Day 7. Therefore, the modeled time course from the AUC(1-7) analysis will be used to estimate SOWS-Gossop on Day 7 for all combinations of disposition stratum and treatment, and Day 7 comparisons will be based on these estimates.

17.2.8.4 OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS

The same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7 will be used for OOWS-Handelsman, MCGI (Subject and Rater), VAS-E, and COWS scores on Days 1, 2, 3, 4, 5, 6, and 7. Types of data transformation, if any, to be used before mixed effects modeling, will be specified in the SAP.

17.2.8.5 Retention Analysis (Time to Removal from Study Treatment)

Time to removal from study treatment is defined as the last study day on which the subject received treatment. The time for subjects who complete some but not all treatment on Day 7 will be Day 7, uncensored. Subjects who complete all treatments on Day 7 will be censored at Day 7. This endpoint will be summarized descriptively for each combination of treatment group and gender with Kaplan-Meier curves and tabulations of the number and percentage of subjects newly removed from receiving study treatment on each of inpatient Days 1 to 7. Each lofexidine dose group will be compared inferentially to placebo with a Cox proportional hazards regression model of time to removal from study, stratified by gender, with treatment as the independent variable. The estimated hazards ratio will be reported as a descriptive measure. The p-value on the log hazards ratio will be converted to a one-tailed p-value by considering whether the hazard ratio indicates a delay in time to removal in the lofexidine group versus the placebo group.

17.2.8.6 Concomitant Medication Analysis

For each of Days 1 to 7, each subject's number of concomitant medication doses taken will be treated as a continuous variable. Descriptive statistics will be provided on the as-observed data on each study day. In addition, least squares means and p-values comparing each treatment to placebo will be obtained with the same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7. Types of data transformation, if any, to be used before mixed effects modeling, will be specified in the SAP.

17.2.8.7 Status of Detoxification on Day 7 or Early Termination as Assessed by the Site Investigator

Descriptive statistics (numbers and percentages) on the status of detoxification (successful/unsuccessful) as assessed by the Site Investigator at Day 7 or early termination will be presented by treatment group overall and by gender within treatment group.

17.2.8.8 Single Items from the OOWS-Handelsman and COWS, and COWS AUC(1-7)

Single items (e.g., sweating, anxiety) from the OOWS-Handelsman and COWS that are not included in the SOWS-Gossop may be analyzed; the scores will be treated as continuous variables and analyzed using the same methods used for SOWS-Gossop on Days 1, 2, 3, 4, 5, 6, and 7. COWS AUC(1-7) may also be analyzed; a modeling approach analogous to the modeling of SOWS-Gossop AUC(1-7) will be used. While the functional form of the time course for SOWS-Gossop is based on historical data, the functional form of the time course for COWS will be based on the data from this study.

17.2.9 Power Calculations

Treatment effect and subject variability with respect to SOWS-Gossop scores were estimated from the prior Phase 3 study (USWM-LX1-3002), using the random coefficients model planned for the present study and estimating the treatment effect of 3.2 mg lofexidine versus placebo with respect to AUC(1-7). It was assumed that the treatment effect of the 2.4 mg lofexidine dose will be three-fourths the treatment effect of the 3.2 mg dose. The table below shows the power to find a significant treatment effect for the comparisons of the two lofexidine treatments versus placebo, assuming a sample size allocation ratio of 3:3:2 (3.2 mg lofexidine : 2.4 mg lofexidine : placebo) and accounting for the sequential testing approach described in Section 17.2.7. The power to find a statistically significant effect of the 3.2 mg lofexidine dose with respect to AUC(1-7) is in excess of 90% with the planned total sample size of 600.

Total Sample Size	Power (%) with Respect to AUC(1-7)	
	3.2 mg Lofexidine versus Placebo	2.4 mg Lofexidine versus Placebo
600	94.6	72.6
550	92.6	67.6
500	90.1	62.2
450	86.8	55.7

17.2.10 Subgroup Analyses

The models used for the primary analysis will be modified for each of several subgroups to include the subgroup and its interaction with treatment as a fixed effect. Subgroups include age, gender, and race. The SAP will list all subgroups to be analyzed, their classifications (e.g., age dichotomization, race groupings), and modeling details.

17.2.11 Safety Measures

The safety measures during Days 1-7 of the study are AEs, vital signs, ECGs (primarily evaluated for changes in QTcF versus time-matched controls for both doses of lofexidine and placebo), clinical laboratory measures, and physical exams. Adverse event summaries will include tabulations overall and by seriousness, severity, and causality assessment. The data from these measures recorded during Days 1-7 will be summarized descriptively by treatment group. In addition, each lofexidine group will be compared inferentially to the placebo group using chi-square tests for categorical variables and t-tests within an analysis of variance for continuous variables; the resulting p-values will not be adjusted for multiple testing.

17.3 Days 8-14 (Open-Label, Continuation Treatment)

Safety and effectiveness endpoints for Days 8-14 will be summarized by randomized treatment group.

17.3.1 Assessment of Effectiveness

Summary statistics will be provided by treatment day (overall and by gender) for:

- SOWS-Gossop;
- OOWS-Handelsman;
- MCGI (Subject and Rater);
- VAS-E; and
- COWS.

In addition, the following will be summarized overall and by gender over Days 8-14:

- Duration of exposure;
- Number and proportion of subjects successfully completing detoxification as assessed by the Site Investigator;
- Distribution of number of days required to complete detoxification as assessed by the Site Investigator;
- Average daily dose of lofexidine; and
- Concomitant medications.

17.3.2 Assessment of Safety

Safety measures will be summarized for the following subject cohorts:

- All treated subjects;
- Treated subjects without urinary evidence of illicit drug use; and
- Treated subjects with urinary evidence of illicit drug use (may be further subdivided by type of illicit drug used).

Descriptive statistics will be provided for:

- All AEs;
- New onset AEs (including those observed during Days 1-7 whose severity during Days 8-14 is greater than observed during Days 1-7);
- Vital signs;
- ECGs;
- Clinical laboratory tests; and
- Physical examinations.

18 DATA MANAGEMENT AND CASE REPORT FORMS (CRFs)

Data management activities and statistical analytical support will be coordinated through the CRO The CRO will be responsible for the construction and accuracy of the study database.

18.1 Data Collection

Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs). The eCRFs will be supplied by the CRO. CRFs are to be completed on an ongoing basis during the study. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the study operations manual.

The Site Investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The Site Investigator is also responsible for maintaining any source documentation related to the study, including any films, lab reports, or ECG tracings.

Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor representatives, the central IRB , and the site's IRB.

18.2 Electronic Data Capture

Data entered by site personnel into the electronic data capture (EDC) system will be reviewed by the CRO. If incomplete or inaccurate data are found, a query in the EDC system will be generated for response by the clinical site. Sites will promptly resolve data inconsistencies and errors. An audit trail of any corrections or changes to the data in the EDC system will be maintained. USWM will receive reports at least monthly regarding the quality and quantity of data submitted to the CRO.

Site Investigators agree to routine data audits by the staff of USWM. USWM monitors will routinely visit each site to assure that data entered in the EDC system are in agreement with source documents at the sites. The monitors will also verify that investigational agents have been properly stored and accounted for, subject informed consent for study participation has been obtained and documented in the subject's progress notes, all essential documents required by GCP regulations are on file, and sites are conducting the study according to the research protocol.

18.3 Data Analysis

When the study is completed, all data have been entered into the clinical database, and the final database has been locked, statistical analysis of the data will be performed by the CRO's statisticians or an independent statistician in accordance with the Analytical Plan of this protocol (see Section 17) and detailed in the SAP. Periodically, during the investigation, the CRO will also prepare summary reports of the data, with no identification or grouping by randomized treatment, so that progress of the study can be monitored. Various reports will be prepared for USWM and others, as appropriate.

18.4 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence and regulatory documents (e.g., signed protocol and amendments, IRB correspondence and approved consent form and signed informed consent forms, Statement of Investigator form, and clinical supplies receipt and distribution records).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts or pharmacy records, and any other

similar reports or records of any procedure performed in accordance with the protocol. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document. Any duplicate of a source document to be retained as a part of a eCRF should maintain subject confidentiality per HIPAA.

Government agency regulations and directives require that the investigator must retain all study documentation pertaining to the conduct of a clinical trial. These documents must be kept for a minimum of 2 years after the approval of a new drug application (NDA) and finalization of all marketing strategies, or if the NDA is not approved, for 2 years after discontinuation of the IND, whichever is the later. In all instances sites must get permission from USWM before disposition of any study documentation and materials.

18.5 Confidentiality

18.5.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that proprietary information furnished to clinical investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the Site Investigator and IRB.

By participating in this protocol the Site Investigator affirms to USWM that information furnished to the Site Investigator by USWM will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee (or similar or expert committee), affiliated institution, and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees.

18.5.2 Confidentiality of Subject Records

To maintain subject confidentiality, all laboratory specimens, eCRFs, reports, and other records will be coded using alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet. Only research staff and USWM officials will have access to the records. Subject information will not be released without written permission, except as necessary for monitoring by the FDA or USWM. USWM will file for a Certificate of Confidentiality that will cover all sites participating in the study (see Appendix 7).

By participating in this protocol the investigator agrees that within local regulatory restrictions and ethical considerations, USWM or any regulatory agency may consult and/or copy study documents in order to verify eCRF data.

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

19 PUBLICATIONS OF THE STUDY RESULTS

It is understood by the Site Investigator that the information generated in this study will be used by the Sponsor (USWM) in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use

of information derived from the study, it is understood that the Site Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. Because this is a multicenter study, the combined results of the study will be published before the Investigator submits site-specific results for publication. Any results of medical investigations with the Sponsor's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Site Investigator and Sponsor representative(s) 60 days before submission for publication or presentation. Due regard shall be given to the Sponsor's legitimate interests, e.g., manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information.

The Sponsor shall be furnished with a copy of any proposed publication. In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating investigators and the prior review of the Sponsor. In case of disagreement amongst the investigators participating in a multicenter investigation, the Sponsor will be the final arbiter. Sponsor comments shall be given without undue delay, and not later than within 60 days. If they are not accepted, the senior author of the manuscript and the Sponsor's representatives shall promptly meet to discuss further and endeavor to agree on the final wording and/or disposition of the publication. The above procedure also applies to studies that are not completed, including those that are prematurely discontinued.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by investigators in its scientific information and/or promotional material without full acknowledgment of the source (i.e., author and reference).

20 PROTOCOL ADHERENCE AND AMENDMENTS

The Site Investigator and each sub-investigator must adhere to the protocol as detailed in this document. Only the Sponsor (USWM) may modify the protocol. All amendments that have an impact on subject risk or the study objectives, or require revision of the informed consent document, must receive approval from the DSMB and central IRB/individual site's IRB before their implementation.

21 QUALITY CONTROL AND QUALITY ASSURANCE

Following written standard operating procedures, study monitors will verify that the clinical trial is conducted and data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Reports on monitoring activities will be submitted to the Sponsor.

The Sponsor (USWM) will secure agreement from all involved parties to ensure direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

The CRO will be the Data Coordinating Center and will implement quality control procedures in accordance with GCPs and their internal Standard Operating Procedures, beginning with the data entry system 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.

22 REFERENCES

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