PRODUCT: LUCEMYRA (Lofexidine)
PROTOCOL NUMBER / AMENDMENT: USWM- LX1-3003-2 / 02

SPONSOR:

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

TITLE:

A Phase 3, Open-Label, Safety Study of Lofexidine

DOCUMENT DATE: 21MAY2015
NDA NUMBER: 209229
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16.1 STUDY INFORMATION

16.1.1 PROTOCOL AND AMENDMENTS

CLINICAL STUDY PROTOCOL

A Phase 3, Open-Label, Safety Study of Lofexidine

Protocol Number:	USWM-LX1-3003-2
Product:	Lofexidine
Investigational New Drug (IND) Number:	IND 47,857
Development Phase of Study:	Phase 3
Medical Monitor:	
Sponsor:	US WorldMeds, LLC 4010 Dupont Circle, Suite L-07 Louisville, KY 40207
Protocol Date:	February 3, 2012
Amendment No. 01	January 22, 2015
Amendment No. 02	May 21, 2015

1 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:** 21 MAY 2015

Name (print):

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

Signature: _____ **Date:** _____

Name (print): _____

2 PROTOCOL AMENDMENT SUMMARY

This section provides a summary of major changes made in this current amendment (No. 02) to the protocol for Study USWM-LX1-3003-2 along with changes made in the prior amendment (No. 01). Section 23 provides a detailed accounting of all changes made in these amendments.

SUMMARY OF MAJOR CHANGES

Amendment No. 02 (May 21, 2015)

- The protocol was revised to update subject reimbursement to account for up to 3 in-office screening visits (see Section 14.4).
- The protocol was clarified to indicate that subjects receiving lofexidine treatment on an outpatient basis are required to take a dose of lofexidine in the clinic at each daily clinic visit, thus allowing assessments to be performed before and after dosing as detailed in Table 1.
- The protocol was clarified to indicate that should confirmatory vital sign measurements be required with waiting between measurements, the timing of the measurement will not be considered a protocol deviation (i.e., outside the protocol-specified window).
- The protocol was revised to add an electrocardiogram at 3.5 hours after dosing (or as close to this time as possible) for the end-of-study visit (see Section 15.5.3).
- The protocol was revised to clarify syphilis testing results and interpretation for determination of subject study eligibility (see Table 4 in Section 15.5.4.2).
- Three urinary drug screen panels were added, including oxycodone, phencyclidine and methylenedioxymethamphetamine (see Section 15.5.4.3).

Amendment No. 01 (January 22, 2015)

- The protocol was revised to allow enrollment of subjects with clinical treatment goals for full or partial withdrawal from any opioid (including methadone and buprenorphine), which would be expected to elicit opioid abstinence syndrome requiring treatment for at least 7 days. Treatment goals may include abrupt and total withdrawal, agonist-assisted total withdrawal, dose reduction of maintenance treatment (e.g., methadone, buprenorphine), and transition from an opioid or opioid agonist to naltrexone or buprenorphine maintenance. An attempt will be made to include a minimum of 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose

reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios). The change was introduced to enable the study of lofexidine's utility in any situation in which mitigation of opioid withdrawal symptoms would be beneficial to reaching the end treatment goal. Both buprenorphine and methadone clinical scenarios are being evaluated as clinically relevant scenarios where lofexidine's use is likely. Results of prior interaction studies do not suggest a significant safety concern with coadministration of lofexidine and both methadone and buprenorphine. Further evaluation of the safety and clinical utility of lofexidine coadministered with methadone or buprenorphine will help confirm that a contraindication for use of lofexidine with agonists is unnecessary.

- The protocol was revised 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. M.I.N.I. is being used for consistency with eligibility assessment in companion study, USWM-LX1-3003-1. Like SCID, the M.I.N.I. is a validated scale (Sheehan et al., 1998) and is commonly used in clinical practice and research studies.

- Number of subjects needed for enrollment was increased from 200 to 400 to 250 to 500 based on the projected number of subjects completing 7 days of lofexidine treatment in the companion study (USWM-LX1-3003-1) and FDA's safety database requirements. Enrollment in USWM-LX1-3003-2 will continue until a minimum of 300 subjects across the lofexidine studies have received active treatment at clinically relevant doses for at least 7 days.

- Number of study sites was increased from 10 to approximately 20 to account for the potentially higher enrollment requirements and target study completion timelines.

- The protocol was revised from flexible dosing to standardized dosing of 7 days of lofexidine treatment, starting at 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. The standard dosing approach is being adopted to limit variability across sites and treatment scenarios to ensure interpretability of safety data at clinically relevant doses and to evaluate the same doses as used in the controlled programs with demonstrated efficacy.

- The protocol was revised to require 3 days of mandatory in-clinic (inpatient housing/ clinic facilities) treatment with lofexidine (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive all 4 daily doses of lofexidine in the clinic or can be treated as outpatients for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Subjects can continue receiving lofexidine on a semi-standardized taper in an outpatient setting as long as acute withdrawal symptoms persist at the Principal Investigator's discretion; however, in no event is treatment to exceed an additional 7 days (maximum of

14 days treatment over entire study). The required initial 3 days of in-clinic treatment was introduced to enable more frequent safety monitoring during anticipated peak withdrawal and initiation of lofexidine therapy. Outpatient treatment for continuation of therapy begins at Day 4 to enable assessment, as clinically appropriate at the discretion of the Principal Investigator, in a more flexible, real-world setting as patients with a variety of treatment goals, as being studied in the current design, may not require a longer-term clinic stay and in many situations it may be impractical to require inpatient treatment for more than a few days (e.g., work schedules).

- The protocol was revised to require daily (rather than every other day) assessments, including during in-clinic treatment and at daily clinic visits during outpatient treatment. As the primary objective of the study is to assess safety of lofexidine at clinically relevant doses, daily evaluations regardless of inpatient or outpatient status are appropriate.

- The Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) was added because this scale has been evaluated in nearly all other lofexidine studies in opioid withdrawal, serving as the instrument to evaluate efficacy as the primary endpoint in the 2 pivotal programs conducted for the drug; and the SOWS-Gossop data will be used to evaluate lofexidine's effectiveness in a variety of open-label clinical scenarios studied under the current protocol.

- Requirements for vital signs were expanded during in-clinic treatment with lofexidine, similar to requirements in the companion study (USWM-LX1-3003-1). Also a subject diary (Appendix 3) was added if the required post-dose blood pressure/pulse measurement cannot be obtained in the clinic. These changes were introduced to ensure the most robust safety data collection possible during the in-clinic portion of the study and providing a mechanism for additional data collection in the outpatient setting, consistent with the primary objective of the study.

- A fingerprick blood sample concurrently with each scheduled ECG was added to enable QTc-concentration analyses.

- A fingerprick blood sample was added for analysis of plasma lofexidine concentration to monitor compliance during outpatient treatment.

- Columbia Suicide Severity Rating Scale (C-SSRS) was added as a safety assessment, consistent with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.

3 SYNOPSIS

Title	A Phase 3, Open-Label, Safety Study of Lofexidine
Objective	The primary objective of the study is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.
Study Design	Multicenter, open-label study in the United States in which subjects will receive lofexidine treatment for 7 days, starting at a dose of 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. Note that all subjects will start lofexidine administration (Day 1) on the first day of his/her planned opioid agonist dose reduction/discontinuation regardless of the clinical situation in which the subject is seeking treatment (see Inclusion Criterion No. 3). All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total. Subjects will receive a telephone follow-up call 30 days after their last dose. During in-clinic treatment, subjects must take lofexidine within a 1-hour window, 30 minutes before or after 8 AM and within a 30-minute window, 15 minutes before or after 1 PM, 6 PM, and 11 PM. In the event a subject is not dosed within this window as a result of completion of confirmatory vital sign assessments (Section 10.4), this will not constitute as a protocol deviation. Source documents must note, however, the reason for dose delay. For subjects receiving outpatient treatment (elective) on Days 4-7 and those continuing lofexidine treatment in a mandatory outpatient setting for up to an additional 7 days (Days 8-14), prescribed dosing will remain on the same QID schedule (8 AM, 1 PM, 6 PM, 11 PM).
Sites	Approximately 20 (Target: ≥3-4 subjects/site/month. Recruitment time: 4 to 10 months, depending on total enrollment requirements)
Inclusion Criteria	1. Be able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete study procedure . 2. Be male or female at least 18 years of age.

Inclusion Criteria *(continued)*	3. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.), on any opioid (including methadone and buprenorphine maintenance treatment). 4. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or buprenorphine maintenance. 5. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include methadone and buprenorphine) at Screening. 6. If female and of childbearing potential, subject must agree to use 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).
Exclusion Criteria	1. Be a female subject who is pregnant or lactating. 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate);

Exclusion Criteria *(continued)*	➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (subject is excluded if positive for active syphilis as per required laboratory tests; see also Section 15.5.4.2) and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation; see also Section 15.5.4.2). • Have active 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. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). 3. Current dependence (based on the M.I.N.I.) on any psychoactive substance (excluding caffeine, nicotine, and the subject's current opioid-dependence agent, which can include methadone or buprenorphine for example, in agonist-maintained subjects) that requires detoxification or dose reduction as part of the pre-defined individual subject withdrawal treatment goal. 4. Have participated in an investigational drug study within the past 30 days. 5. Have history of lofexidine exposure in a prior clinical trial or otherwise. 6. Abnormal cardiovascular exam at Screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; or • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.

Exclusion Criteria *(continued)*	7. To avoid drug-drug interactions, subjects requiring the following will be excluded: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.
N	Total enrollment will depend on subject drop-out rates. Approximately 250 to 500 subjects: enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. A target of at least 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment will be enrolled (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios).
Safety Endpoints	• Occurrence, seriousness, severity, and causality assessment of adverse events (AEs). • Occurrence of AEs of special interest (i.e., orthostatic hypotension, orthostatic bradycardia, syncope). • Occurrence of AEs not related to opioid withdrawal. • Descriptive evaluation of vital signs (actual and change from baseline) for each time point. • Descriptive evaluation of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation). • Shifts from baseline in physical examination findings. • Descriptive evaluation of clinical laboratory tests of hematology, chemistry, and urinalysis (actual and change from baseline). • Descriptive evaluation of ECG (actual and change from baseline).
Effectiveness Endpoints	• Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (e.g., planned detoxification/ transition) as assessed by the Principal Investigator. • Distribution of number of days required to complete withdrawal treatment goal by category. • Descriptive evaluation of SOWS-Gossop. • Descriptive evaluation of COWS numerical score and severity score (i.e., mild, moderate, moderately severe, severe). • Concomitant medication analysis. • Evaluation of subject treatment status 30 days after last dose.

Duration	23 days (maximum duration per subject, including screening)
Visits	All subjects will undergo screening up to 9 days before study admission. Days 1-3 • In-clinic setting: Subjects may be admitted to the clinic on Day -1. Days 4-7 • In-clinic setting OR daily visits for 4 days if outpatient Days 8-14 • Daily outpatient visits for up 7 days Day 30 • Telephone follow-up contact
Safety Assessments	The following safety assessments will be performed daily unless otherwise specified below: • Occurrence, seriousness, severity, and causality assessment of AEs; • Vital signs during in-clinic treatment (Days 1-3 mandatory; Days 4-7 if subject receives all lofexidine doses in the clinic), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (respiration and temperature before 8 AM dose only); • Vital signs during outpatient treatment (Days 4-7 optional; Days 8-14 if subject continues taking lofexidine), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) before an in-clinic dose of lofexidine and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 or, if applicable, at discontinuation from the study (note: if subjects 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, with values recorded in a subject diary); • 12-lead ECGs (in duplicate) recorded as follows: ➢ Day 1 before the first dose at 8 AM and at 3.5 hours after dosing; ➢ Before subject's last dose and 3.5 hours after dosing (or as close to this time as possible) or, if applicable, at discontinuation from the study; • Clinical laboratory tests as clinically warranted and at discontinuation from the study; • Complete physical examination 3 to 4 hours after first dose on Day 1, as clinically warranted, and at discontinuation from the study; • Pregnancy test at discontinuation from the study;

Safety Assessments *(continued)*	• C-SSRS 3.5 hours after the first dose (8 AM) during in-clinic treatment, once daily before an in-clinic dose of lofexidine during outpatient treatment, or, if applicable, at discontinuation from the study; • A qualitative urine drug screening (by on-site use of "dipsticks") for specific drug or metabolite classification will be done every day during in-clinic treatment to monitor for contraband and every day during outpatient treatment to monitor for illicit drug use; • A fingerprick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG; and • A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance. A follow-up telephone contact will be attempted 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).
Effectiveness Assessments	The following effectiveness assessments will be performed daily unless otherwise specified below: • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine during outpatient treatment; • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine during outpatient treatment; • Completion of withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator; • Concomitant medication use; and • Evaluation of subject treatment status 30 days after last dose.

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TABLES

APPENDICES

5 ABBREVIATIONS AND DEFINITION OF TERMS

Abs	Absolute
AE(s)	Adverse Event(s)
AIDS	Acquired Immune Deficiency Syndrome
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
Anti-HCV	Hepatitis C Virus Antibody
aPTT	Activated Partial Thromboplastin Time
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
CIA	Chemiluminescence Immnoaasay
CLIA	Clinical Laboratory Improvement Act of 1988
CO_2	Carbon Dioxide
COWS	Clinical Opiate Withdrawal Scale
CRF(s)	Case Report Form(s)
C-SSRS	Columbia Suicide Severity Rating Scale
DAWN	Drug Abuse Warning Network
DBP/dBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
EDC	Electronic Data Capture
EIA	Enzyme Immunoassay
eCRF(s)	Electronic Case Report Form(s)
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
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
LDH	Lactate Dehydrogenase

MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MFI	Multiplex Fluorescent Immunoassay
MHOWS	Modified Himmelsbach Opiate Withdrawal Scale
M.I.N.I.	Mini International Neuropsychiatric Interview
mmHg	Millimeters of Mercury
msec	Millisecond
NSAIDs	Nonsteroidal anti-inflammatory drugs
NDA	New Drug Application
NIMH	National Institute of Mental Health
OL	Open Label
PK	Pharmacokinetic
PP	Per Protocol
PPD	Purified Protein Derivative (skin test for tuberculosis)
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	Subject-specific QT
RBC	Red Blood Cell
RBM	Risk Based Monitoring
RDW	Red Blood Cell Distribution Width
RPR	Rapid Plasma Reagin
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SBP/sBP	Systolic Blood Pressure
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
TEAEs	Treatment-Emergent Adverse Events
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
WBC	White Blood Cell

7 STUDY OBJECTIVES

The primary objective is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.

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 20 study sites in the US. It is the responsibility of the Principal 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, multicenter, open-label study to evaluate the safety and effectiveness of lofexidine in alleviation of withdrawal signs and symptoms in subjects undergoing abstinence from any opioid, including methadone and buprenorphine maintenance treatment, which would likely require at least 7 days of lofexidine treatment for alleviation of withdrawal. Any subject seeking treatment for partial or total opioid withdrawal will be eligible. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur, such as (but not limited to) abrupt and total withdrawal (including from methadone and buprenorphine), agonist-assisted total withdrawal, dose reduction of maintenance treatment (e.g., methadone, buprenorphine), and transition from an opioid agonist to naltrexone or buprenorphine maintenance. Subjects will be evaluated for their compliance with protocol inclusion/exclusion criteria during a screening period, lasting up to 9 days. Approximately 250 to 500 subjects will receive lofexidine treatment for 7 days, starting at a dose of 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. Lofexidine administration should be initiated in concurrence with the change in opioid dose which is anticipated to elicit withdrawal symptoms (e.g., first day of dose reduction, or first day of abrupt cessation) or on the first day of emergence/anticipated emergence of such symptoms as determined at the Investigator's discretion. Details regarding the timing of lofexidine therapy initiation relative to change in opioid dose and onset/expected onset of symptoms should be captured in the source. All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine

treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total. All subjects receiving lofexidine treatment on an outpatient basis will be required to take a dose of lofexidine in the clinic at each daily clinic visit, with required clinical assessments performed before and after dosing as listed in Table 1 of Section 15. Also during outpatient treatment, subjects will be required to undergo qualitative urine drug screening at each clinic visit.

10.2 Number of Subjects

The total enrollment in this study will depend on subject drop-out rates in this protocol. Enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. It is estimated that approximately 250 to 500 subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation.

10.3 Duration of Study

This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be 23 days, including the Screening period, which can last up to 9 days, followed by up to 14 days of treatment with lofexidine.

The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. Enrollment is anticipated to take 4 to 10 months to achieve, with the total clinical duration of USWM-LX1-3003-2 anticipated to be 8 to 12 months.

10.4 Dose Hold and Discontinuation Criteria (2 of 3 Rule)

When a blood pressure, heart rate, or QTcF interval value meets criteria for withholding a dose (Section 13.2.2) or discontinuation from the study (Section 13.2.3), the value needs to be confirmed by the site personnel by repeating the vital sign measurement or ECG recording, approximately 10 to 15 minutes later. If the value is confirmed by the second measurement, the appropriate action will be taken (dose hold or study discontinuation) and the confirmatory value will be recorded in the subject's source document and appropriate eCRF. If the second value does not meet the specified criteria, a third measurement will be taken approximately 10 to 15 minutes later. If this value is confirmatory, the appropriate action will be taken (dose hold or study discontinuation) and the last confirmatory value will be recorded in the subject's source document and appropriate eCRF. If the third value does not confirm the initial finding, then no action should be taken and the third value should be entered in the subject's source and appropriate eCRF. Note that should a second or third measurement be required with waiting between measurements, the timing of the

measurement will not be considered a protocol deviation (i.e., outside the protocol-specified window).

Whenever blood pressure, heart rate, or QTcF interval values meet dose hold or study discontinuation criteria, these are to be recorded on the subject's eCRF as an adverse event (AE) or serious adverse event (SAE), as applicable. Examples are:

Item	Record Adverse Event of:
Resting Vital Signs	
SBP <90 mmHg and >20% below screen value	Hypotension
DBP <50 mmHg and >20% below screen value	Hypotension
Pulse <50 bpm and >20% below screen value	Bradycardia
Orthostatic Vital Signs	
SBP >25% below recumbent values	Postural hypotension
DBP <25% below recumbent values	Postural hypotension
Pulse >25% below recumbent values	Postural bradycardia

DBP = diastolic blood pressure, SBP = systolic blood pressure

11 SELECTION OF STUDY POPULATION

11.1 Population Base

Any opioid-dependent subject about to undergo complete or partial opioid withdrawal and could benefit for a minimum of a 7-day treatment with lofexidine will be eligible for the study. 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, a mix of ethnicities reflecting the distribution in the local geographic regions of the study sites, and a minimum of 50 subjects each on methadone or buprenorphine maintenance treatment. 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 able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.
2. Be male or female at least 18 years of age.

3. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.) [18, 19], on any opioid (including methadone and buprenorphine maintenance treatment).
4. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include:
   - abrupt and total withdrawal (including from methadone and buprenorphine);
   - agonist-assisted total withdrawal;
   - dose reduction of maintenance treatment (e.g., methadone, buprenorphine); and
   - transition from an opioid agonist to naltrexone or buprenorphine maintenance.
5. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include methadone and buprenorphine) at Screening.
6. 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).

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 a very serious medical illness not under control as detailed below.
   - Serious medical illness will be determined at Screening by:
     - medical history;
     - physical examination;
     - 12-lead electrocardiogram (duplicate);

- clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (subject is excluded if positive for active syphilis as per required laboratory tests; see also Section 15.5.4.2) and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and
- tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation; see also Section 15.5.4.2).

- Have active 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.
- Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment).

3. Current dependence (based on the M.I.N.I.) on any psychoactive substance (excluding caffeine, nicotine, and the subject's current opioid-dependence agent, which can include methadone and buprenorphine, for example, in agonist-maintained subjects) that requires detoxification or dose reduction as part of the pre-defined individual subject withdrawal treatment goal.
4. Have participated in an investigational drug study within the past 30 days.
5. Have history of lofexidine exposure in a prior clinical trial or otherwise.
6. Abnormal cardiovascular exam at screening, including any of the following:
   - clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females);
   - resting pulse less than 55 bpm or symptomatic bradycardia;
   - resting systolic blood pressure less than 95 mmHg or symptomatic hypotension;
   - resting diastolic blood pressure less than 65 mmHg;
   - resting blood pressure greater than 155/95 mmHg; or
   - prior history of myocardial infarction.

   Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.
7. To avoid drug-drug interactions, subjects requiring the following will be excluded:
   - tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and
   - beta-receptor blockers, to avoid the risk of excessive bradycardia.

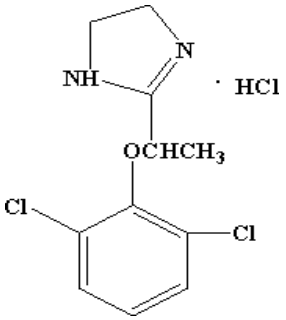
11.3 Screening Failures

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.

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.

12.2 Dispensing Investigational Agent

Lofexidine will be packaged and distributed through the pharmacy coordinating center (Sharp). Lofexidine tablets will be supplied in uniquely-identified 80-count bottles. During in-clinic treatment, lofexidine doses will be dispensed directly from the 80-count bottles, whereas for outpatient treatment doses will be dispensed by the study pharmacist as determined clinically appropriate by the Principal Investigator or designee 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 medication will be dispensed by the site pharmacist or designee.

12.3 Blinding Plan

This is an open-label study.

12.4 Labeling

The investigational agent, lofexidine, will be packaged in labeled bottles (80 count pills) and during the outpatient portion of the study dispensed to subjects in labeled prescription bottles (i.e., redispensing container). The product label will include the sponsor's name, protocol number, the number of tablets in the bottle, address, 24-hour emergency phone number, and the following statement – "Caution: New Drug – Limited by Federal Law to Investigational Use."

During outpatient treatment (Days 4-14), 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:

- Principal Investigator's name and number,
- Subject number,
- Date of dispensing,
- Directions for use,
- Drug name / dose or protocol number,
- Number of pills dispensed,
- Sponsor's name, and
- For Investigational Use Only.

12.5 Storage

The investigational agent, lofexidine, will be stored at 68-77°F in a secure location at the dispensing pharmacy or site. Temperature of the investigational agent will be maintained at 68-77°F during transport. Temperature of the investigational agent will be monitored during storage and transport. Temperature excursions will be reported to the Sponsor and the Sponsor will determine if the investigational agent is fit for use.

12.6 Record of Administration

Accurate recording of all investigational agent received, dispensed, administered, and returned will be maintained by study site personnel. During outpatient treatment (Days 4-14), subjects are to record doses taken in his/her subject diary.

12.7 Used/Unused Supplies

Unused investigational agent 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.

12.8 Contraindications

Clonidine is specifically prohibited in this study.

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

- tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; and
- beta-receptor blockers – the combination of lofexidine and beta-receptor blockers should be used with caution to avoid the risk of excessive bradycardia.

Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study.

Lofexidine should generally not be administered concurrently with alcohol, sedatives, and anesthetics as these may interact with lofexidine and enhance its central sedative effects.

13 TREATMENT PLAN

13.1 Investigational Agent

All subjects in this study will receive lofexidine, as described in Section 13.2.

13.2 Dose Administration

13.2.1 Administration of Doses

Lofexidine administration should be initiated in concurrence with the change in opioid dose which is anticipated to elicit withdrawal symptoms (e.g., first day of dose reduction, or first day of abrupt cessation) or on the first day of emergence/anticipated emergence of such symptoms as determined at the Investigator's discretion. Details regarding the timing of lofexidine therapy initiation relative to change in opioid dose and onset/expected onset of symptoms should be captured in the source. All subjects will take lofexidine orally for 7 days, starting on Day 1 at a dose of 3.2 mg per day (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. The subject's dose may be changed back to 3.2 mg/day, per Principal Investigator judgment, but in no case is the dose of lofexidine to exceed 3.2 mg/day (or a single dose of 0.8 mg). Supporting rationale for any dose changes must be recorded in the subject's source document.

All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Note that the decision to allow outpatient treatment should take into account the subject's sensitivity to the hypotensive effects of the study medication (as observed over Days 1-3) and the subject's potential for noncompliance. Furthermore, the rationale for the decision to continue treatment through either an in-clinic or outpatient setting must be documented in the subject's source document.

During in-clinic treatment, subjects must take lofexidine within a 1-hour window, 30 minutes before or after 8 AM and within a 30-minute window, 15 minutes before or after 1 PM, 6 PM, and 11 PM, with the actual date and time of each dose recorded in the subject's source document and in the eCRF. For subjects receiving outpatient treatment (elective) on Days 4-7 and those continuing optional lofexidine treatment in an outpatient setting for up to an additional 7 days (Days 8-14), prescribed dosing will remain on the same QID schedule (8 AM, 1 PM, 6 PM, 11 PM) with compliance assessed at the next day's clinic visit by pill count, subject report of dosing in diary (Appendix 3), and a fingerprick blood sample to assess plasma lofexidine concentrations. Note that if the subject is receiving outpatient treatment, he/she is required to take a dose of lofexidine in the clinic at each daily clinic visit.

Optional Outpatient Treatment (Days 8-14)

Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days, per the dose schedule listed below, including taking a dose of lofexidine in the clinic at each daily clinic visit. The rationale for the decision to continue lofexidine treatment must be documented in the subject's source document. Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total in this study.

Day	If Dose Regimen on Day 7 is 3.2 mg/day (0.8 mg QID)	If Dose Regimen on Day 7 is 2.4 mg/day (0.6 mg QID)
8	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
9	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
10	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
11	1.6 mg/day (0.4 mg QID)	0.8 mg/day (0.2 mg QID)
12	1.6 mg/day (0.4 mg QID)	0.8 mg/day (0.2 mg QID)
13	0.8 mg/day (0.2 mg QID)	0.8 mg/day (0.2 mg QID)
14	0.8 mg/day (0.2 mg QID)	0.8 mg/day (0.2 mg QID)

Note: In order to prevent dehydration from opioid withdrawal, increased fluid intake will be encouraged from the beginning of the study.

13.2.2 Dose Hold Criteria

Study medication will be held if pre-dose vital signs meet any of the criteria listed below (see Section 10.4 for details on repeat confirmatory requirements).

Resting (sitting [or recumbent if necessary because of an AE])

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

Orthostatic (after standing for 3 minutes)

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

During outpatient treatment, if the subject experiences symptoms of hypotension and/or bradycardia (see below), he/she should call the study site and the site should instruct the subject on whether the next dose should be delayed, skipped, or he/she should be seen in the clinic. The subject should record this information in the subject diary (Appendix 3).

- marked dizziness
- fainting (especially when standing from a sitting or lying position)
- light headedness
- Fatigue
- Weakness
- shortness of breath
- chest pains
- easily tiring during physical activity
- confusion or memory problems
- blurred vision
- nausea
- cold, clammy pale skin
- rapid shallow breathing
- depression
- thirst

All instances of dose-holds must be clearly documented in the subject's source document and dosing eCRF, and the event causing the dose hold should be recorded on the AE or SAE eCRF, as applicable.

13.2.3 Discontinuation Criteria

A subject will be discontinued from the study if any of the criteria listed below are met (see Section 10.4 for details on repeat confirmatory requirements). All instances should be recorded in the subject's source document and AE or SAE eCRF, as applicable.

- Resting systolic blood pressure <70 mmHg;
- Resting diastolic blood pressure <40 mmHg;
- Resting pulse <40 bpm;
- QTcF >500 msec[1] or >25% above screen value for both males and females; or
- Syncope.

Additional discontinuation criteria based on cardiovascular events are:

- New onset of clinically significant abnormal ECG per Investigator judgment (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval).
- Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids).
- Single occurrence of symptomatic bradycardia (as assessed by Principal Investigator/study physician/assigned staff, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.
- Persistent hypertension – resting blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued.
- Medical Intervention for Cardiovascular Event: Any medical intervention (nonmedication or medication inclusive) used for the treatment of any cardiovascular event, with the exception of a positional intervention in subjects displaying hypotension.
- Any other clinically significant cardiovascular signs or symptoms that would place the subject at risk.
- Subject misses more than a total of 6 doses during Days 1-7.

13.3 Treatment Compliance

All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days of lofexidine treatment (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). No subject will receive lofexidine for more than 14 days total. In an in-clinic setting, each dose will be observed by study staff and hand and mouth checks will be performed. In an

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

outpatient setting, self-dosing compliance will be evaluated at the next day's clinic visit by pill count, subject report of dosing in diary (Appendix 3), and a fingerprick blood sample to assess plasma lofexidine concentrations. Subjects will be instructed to call the Principal Investigator's office before taking the next dose of study medication if they notice any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2), especially when standing from a sitting or lying position. The study physician or assigned staff will determine if the next dose should be delayed, skipped, or the subject should be seen. Any change in prescribed dosing will be recorded 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 in-clinic participation in study based on individual site policy. If they usually use tobacco products, they will be offered and encouraged to use nicotine replacement therapy (patch, gum, inhaler, or nasal spray) while they are in the in-clinic facility to treat their nicotine withdrawal symptoms. If smoking is permitted by a participating site, smoking breaks outside of the in-clinic facility must be constantly observed and supervised.

The estimated total number of tobacco products used by subjects per day during in-clinic treatment 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 for the mandatory 3-day in-clinic treatment part of the study and available for participation in either an in-clinic or outpatient setting for 4 additional days (total commitment of 7 days), 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, a qualified investigative site staff member will review the study informed consent form with subjects, and subjects will be given an opportunity to review on their own, inquire about, and sign the 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 subject number and proceed to the screening phase of the study. Screening assessments must be completed within a 9-day time period, but can be completed as early as the first screening day. At no time during the screening process should individuals be given information regarding inclusion or exclusion criteria. 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. 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 be rescreened at a later time, although at least 30 days must occur between screenings. 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 9 days during which the subjects must satisfy the eligibility criteria and complete all required screening assessments.

14.3 Treatment Phase

14.3.1 Days 1-3 (Mandatory In-clinic)

After a potential participant has completed all screening assessments and has met all eligibility criteria to participate in the study, the Principal Investigator or study coordinator will arrange for admission to the hospital or clinic in the evening (Day -1) or early morning (Day 1) before study drug administration on Day 1. After all Baseline requirements have been completed (Section 15.2), subjects will receive their first dose of lofexidine during the 8 AM dosing window on Day 1. Subjects will be dosed 4 times daily from Day 1 through Day 3 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 (±15 minutes) after the 8 AM, 1 PM, and 6 PM dose. 12-lead ECGs will also be collected before the first dose on Day 1 (8 AM) and 3.5 hours (±15 minutes) after dosing. Note that should a second or third measurement be required with waiting between measurements, the timing of the measurement will not be considered a protocol deviation (i.e., outside the protocol-specified window). Other clinical assessments will be gathered between 11:00 AM and noon each day (see a complete list of assessments in Table 1). These clinical assessments are described in detail in Sections 15.3.5 and 15.5.

14.3.2 Days 4-7 (In-clinic/Outpatient)

Per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine treatment in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). All subjects receiving lofexidine treatment on an outpatient basis will be required to take a dose of lofexidine in the clinic at each daily clinic visit, with required clinical assessments performed before and after dosing as detailed in Table 1. Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).

14.3.3 Days 8-14 (Outpatient Only)

Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days. Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total in this study. Subjects will be required to return to the clinic daily before a scheduled dose for clinical assessments (see a complete list of assessments in Table 1).

14.4 Subject Reimbursement

All compensation will be described in the informed consent form used by each site and approved by the site's 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 Principal Investigator may discontinue a subject if s/he deems it clinically appropriate or for any reason. Additionally, the Principal Investigator must discontinue a subject for any of the following reasons:

1. Cardiovascular events (see Section 14.5.2).
2. Abnormal vital signs or ECG meeting criteria in Section 13.2.3.
3. Serious medical problem thought to be related or unrelated to the study medications.
4. Intercurrent illness or medical complications that, in the opinion of the Principal Investigator, preclude safe administration of study medications.
5. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study (Days 1-3).
6. Requiring therapy with an exclusionary drug.
7. Lack of compliance with protocol and/or unit procedures.

Subjects who are removed from study treatment because of AEs or SAEs will be followed until they are medically stabilized to the satisfaction of the study physician or assigned staff (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 on the end of study form provided in the subject's eCRF. Once discontinued, subjects may not re-enter the study. Discontinued subjects will not 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 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 study physician.

1. New onset of clinically significant abnormal ECG per Investigator judgment (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 Principal Investigator/study physician/assigned staff, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.

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

4. Persistent hypertension – resting blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued.
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;
- data recording is inaccurate or incomplete; and
- the safety database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.

14.6 Concomitant Therapy

If the individual withdrawal treatment goal requires a specific concomitant medication (e.g., agonist-assisted total withdrawal, transition to buprenorphine or naltrexone, dose reduction of maintenance therapy), that concomitant medication is allowed. At no time are clonidine, tricyclic antidepressants, and beta-receptor blockers allowed (see Section 12.8).

Other concomitant medications or therapies are permitted throughout the study in either an in-clinic or outpatient setting, as clinically warranted. The following medications were found to be useful in earlier lofexidine efficacy/safety studies and, for consistency, the Principal Investigator/study physician/assigned staff may consider their use in this study as appropriate.

1. Guaifenesin (for cough).
2. Alumina, Magnesia, and Simethicone (for emesis and nausea).
3. Dioctyl sodium sulfosuccinate and psyllium hydrocolloid suspension (for constipation).
4. Bismuth sulfate (Pepto-Bismol®) and loperamide (Imodium®) (for diarrhea).
5. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (for headache, muscle aches, or other discomfort.

6. Zolpidem, trazadone, and other benzodiazepines (for insomnia, depression, anxiety).

The Principal Investigator/study physician/assigned staff should contact the Sponsor's Medical Monitor regarding any questions on concomitant medications.

The site should document in source any symptom that requires administration of any concomitant medication as an AE (see Section 15.5.1).

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

15 CLINICAL EVALUATIONS

A detailed Schedule of Study Assessments is provided in Table 1.

Table 1. Schedule of Study Assessments

Activity	Screening Days -8 to -1	Baseline (a) Day 1	In-clinic Treatment Days 1-3	In-clinic/Outpatient Treatment Days 4-7	Outpatient Treatment Days 8-14	Study Discontinuation/ End of Study*
Informed Consent Signed	X					
Subject Number Assigned	X					
Inclusion/Exclusion Criteria	X	X (b)				
Prior Medication History	Past 30 days	X (b)				
Demographics	X					
Medical and Smoking History	X					
Mini-International Neuropsychiatric Interview	X					
Infectious Disease Assessments (c)	X					
Chest X-Ray (c)	X					
Pregnancy Test (d)	X	X				X
Height	X					
Weight	X					X
Complete Physical Exam	X	X (b)	X (e)	As needed	As needed	X
Admission to In-clinic Facility		X (f)				
Study Medication Administration			X (QID)	X (QID) (g)	Optional	
Medication Compliance			X	X	X	X
Study Medication Taper					X	
Discharge from In-clinic Facility				Variable, but by Day 7		
Clinic Visit				Daily if outpatient	Daily	
Issue Subject Diary				Daily if outpatient	Daily	
12-Lead Electrocardiogram (duplicate)	X (h)	X (i)	X (i)			X (j)
Urine Drug Screen (k)	X	X	X	X	X	X
Vital Signs (Sitting/Recumbent & Standing BP and pulse; respiration; and temperature)	X	X	X (l)	X (l) (m)	X (m)	X
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X	As needed	As needed	As needed	As needed	X
Adverse Events Assessment			X	X	X	X
C-SSRS Baseline Version		X				
C-SSRS Since Last Visit Version			X (n)	X (n)	X (n)	X
Short Opiate Withdrawal Scale of Gossop (o)		X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS) (o)		X	X	X	X	X
Fingerprick Blood Sample			X (p)	X (q)	X (p) (q)	X (p)
Concomitant Medications Assessment			X	X	X	X

Table 1. Schedule of Study Assessments

Activity	Screening Days -8 to -1	Baseline (a) Day 1	In-clinic Treatment Days 1-3	In-clinic/Outpatient Treatment Days 4-7	Outpatient Treatment Days 8-14	Study Discontinuation/ End of Study*
Define Subject-Specific Withdrawal Treatment Goal	X					
Assessment of Completion of Pre-defined Withdrawal Treatment Goal (r)			X	X	X	X
Telephone Follow Up Contact						X (s)

Abbreviations: BP = blood pressure, C-SSRS = Columbia Suicide Severity Scale, PK = pharmacokinetic, PPD = purified protein derivative, QID = 4 times daily

* The study discontinuation/end of study assessments/procedures should always be done when subject exits from the study.

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

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

(c) A chest x-ray is required only if a PPD 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) A complete physical exam will be done on Day 1 (3-4 hours after first dose) and as clinically warranted.

(f) Subjects may be admitted to the hospital or clinic in the evening (Day -1) before study drug administration on Day 1.

(g) Per Investigator judgment, subjects can be discharged from the study after receipt of at least one dose of study drug on Day 7 and after completion of all end-of-study procedures.

(h) Baseline 12-lead electrocardiograms (ECGs) will be done on one day during the screening period at 8 AM (or as close to 8 AM as possible) and at 11:30 AM. Note that a time delay for the 8 AM ECG will not be considered a protocol deviation, but that the second ECG should be taken 3.5 hours after the first ECG.

(i) 12-lead ECGs (duplicate) before dosing on Day 1 at 8 AM and 3.5 hours (± 15 minutes) after dosing.

(j) 12-lead ECGs (duplicate) before subject's last dose and 3.5 hours after dosing (or as close to this time as possible) or, if applicable, at discontinuation from the study.

(k) Urine drug screen will be done every day in an in-clinic setting to monitor for contraband and every day in an outpatient setting to monitor illicit drug use.

(l) During in-clinic treatment, resting (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) 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; respiration and temperature before 8 AM dose only.

(m) During outpatient treatment, resting (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) blood pressure and pulse will be measured before an in-clinic dose of lofexidine each day and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 and at the End of Treatment/Study Discontinuation visit. Oral temperature and respiration are not required measurements during outpatient treatment.

(n) C-SSRS will be completed 3.5 hours after the first dose (8 AM) during in-clinic treatment or once daily before an in-clinic dose of lofexidine during outpatient treatment.

(o) During in-clinic treatment, effectiveness scales will be completed once daily: the Short Opiate Withdrawal Scale of Gossop 3.5 hours (±10 minutes) after the first dose of study medication followed by COWS, and the assessment of completion of pre-defined withdrawal treatment goal. Effectiveness scales will be completed daily before an in-clinic dose of lofexidine during outpatient treatment.

(p) A fingerprick blood sample for PK analysis will be collected concurrently with each scheduled ECG.

(q) A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.

(r) This form is to be completed by the Principal Investigator after completion of the SOWS-Gossop and COWS.

(s) A follow-up telephone contact will be attempted 30 days after the subject's last dose and will include 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).

15.1 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 9-day time period. The screening visit will have a visit window of ±2 days. Subjects will not be out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a screening within the ±2-day window (e.g., holidays, vacations, personal emergencies). Determination of the maximum visit window deviation is, however, at the discretion of the medical monitor. 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 determining eligibility and written informed consent is obtained: height; weight; vital signs (sitting/standing blood pressure and pulse; respiration; and temperature); 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 ECGs (in duplicate) will be done on one day during the screening period at 8 AM (or as close to 8 AM as possible) and at 11:30 AM. Note that a time delay for the 8 AM ECG will not be considered a protocol deviation, but that the second ECG should be taken 3.5 hours after the first ECG.
- Medical and smoking/alcohol history.
- Complete physical examination.
- Mini International Neuropsychiatric Interview (M.I.N.I.) [18, 19]. 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) and (2) determine the absence of major psychiatric disorders (exclusion criterion #3).
- Prior medications will be recorded to capture all medications taken in the past 30 days.
- All opioids of abuse the subject has used will be recorded.

In addition, each subject will have a short-term (within the 14-day study period) withdrawal treatment goal defined according the criteria below (see Appendix 4 for further details on this assessment).

- Abrupt and total withdrawal (e.g., quitting heroin abruptly and totally), including whether naltrexone maintenance will be initiated as part of the short-term treatment goal.

- Agonist-assisted total withdrawal (e.g., quitting heroin with methadone or other agonist, including buprenorphine, given as needed to alleviate symptoms), including whether naltrexone maintenance will be initiated as part of the short-term treatment goal.
- Step-down/dose reduction resulting in partial withdrawal (e.g., lowering methadone or buprenorphine maintenance dose or chronic pain medication dose).
- Transition (e.g., transitioning from heroin or methadone to buprenorphine maintenance).

15.2 Baseline Assessments

The Baseline period is the morning of admission to the study, before 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 (±30 minutes).

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

- 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 to capture any new medications since screening.
- Update complete physical exam form to capture any new physical findings since screening.
- Columbia Suicide Severity Rating Scale (C-SSRS) (Baseline version; Appendix 5).
- 12-lead ECGs (in duplicate) before the first dose on Day 1 at 8 AM.

15.3 Assessments During Treatment

15.3.1 Days 1-3 (Mandatory In-clinic)

The assessments or procedures listed below will be performed daily (unless otherwise specified) on Days 1-3 (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM.

- Effectiveness assessments at estimated time of maximum plasma concentration (T_{max}, i.e., 3.5 hours after the first daily dose) including:
  - SOWS-Gossop; and
  - COWS.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Vital signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (7 times per day); respiration and temperature before 8 AM dose only.
- Continuous monitoring for AEs.
- 12-lead ECGs (in duplicate) before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing.
- A fingerprick blood sample for PK analysis will be collected concurrently with each scheduled ECG.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination 3 to 4 hours after dosing on Day 1 and as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) on Days 1-3.
- A qualitative urine drug screening (by on-site use of "dipsticks") will be done every day to monitor for contraband.

15.3.2 Days 4-7 (In-clinic/Outpatient)

The assessments or procedures listed below will be performed daily (unless otherwise specified) on Days 4-7 (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM. Note that if subject is receiving outpatient treatment, he/she is required to take a dose of lofexidine in the clinic at each daily clinic visit.
- SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine during outpatient treatment.
- COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine during outpatient treatment.

- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses if being treated as an outpatient.
- Vital signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) during in-clinic treatment before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (7 times per day); respiration and temperature before 8 AM dose only.
- Vital Signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) during outpatient treatment before an in-clinic dose of lofexidine each day and 3.5 hours after dosing. Note that if the subject cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 4-7, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. Subjects will also be provided a diary (Appendix 3) to record the measurements along with any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) the subject may have experienced.
- A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.
- AE assessment.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) during in-clinic treatment; once daily before an in-clinic dose of lofexidine during outpatient treatment.
- Qualitative urine drug screening (by on-site use of "dipsticks") will be done every day in an in-clinic setting to monitor for contraband and every day in an outpatient setting to monitor for illicit drug use.
- Daily clinic visits and completion of subject diary for outpatients.

Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).

15.3.3 Days 8-14 (Outpatient Only)

Study medication is optional on Days 8-14 for subjects continuing to have withdrawal symptoms per the Principal Investigator's judgment. The assessments and procedures listed

below will be performed daily (unless otherwise specified) (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Daily clinic visits and completion of subject diary.
- SOWS-Gossop before an in-clinic dose of lofexidine.
- COWS before an in-clinic dose of lofexidine.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses.
- Vital Signs, including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) before an in-clinic dose of lofexidine and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14. Note that if subjects 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. Subjects will also be provided a diary (Appendix 3) to record the measurements along with any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) the subject may have experienced.
- AE assessment.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) before an in-clinic dose of lofexidine.
- A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.
- Qualitative urine drug screening (by on-site use of "dipsticks") will be done every day in an outpatient setting to monitor for illicit drug use.

15.3.4 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.

- SOWS-Gossop.
- COWS.

- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses if not already performed.
- Vitals signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able); respiration; and temperature.
- AE assessment.
- 12-lead ECGs (in duplicate) before the subject's last dose and 3.5 hours after dosing (or as close to this time as possible).
- Clinical laboratory tests.
- Complete physical examination (including body weight).
- Pregnancy test.
- Urine drug screen.
- C-SSRS (Since Last Visit version; Appendix 6).

15.3.5 30-Day Telephone Follow-up Contact

A follow-up telephone contact will be attempted 30 days after the subject's last dose and will include 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). Repeated attempts will be made to reach the subject (defined as a minimum of 3 telephone calls, followed by sending a letter). If repeated attempts are unsuccessful, this will be recorded in the subject's source document and eCRF.

15.4 Effectiveness Assessment Methods

15.4.1 Assessment of Completion of Pre-Defined Withdrawal Treatment Goal

The Principal Investigator will indicate if the subject has completed his/her pre-defined withdrawal treatment goal (Appendix 4) on Days 1-7 by responding to the following question: "Has the subject's withdrawal treatment goal been reached?" Note that, per protocol, subjects are required to continue on their dose of lofexidine through Day 7 even though the subject may have completed his/her withdrawal treatment goal before Day 7. This same assessment will be made at each visit during the 7 days of optional outpatient treatment (Days 8-14). This assessment should be completed after the SOWS-Gossop and COWS assessments.

15.4.2 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)

The SOWS-Gossop [16] will be completed by the subject at baseline, once daily at 3.5 hours (± 10 minutes) after the first dose of study medication during in-clinic treatment and once

daily before an in-clinic dose of lofexidine during outpatient treatment. 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 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.

15.4.3 Clinical Opiate Withdrawal Scale (COWS)

The COWS [17] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal, and will be completed after the SOWS-Gossop and before the assessment of completion of pre-defined withdrawal treatment goal. It will be completed at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during in-clinic treatment, and once daily before an in-clinic dose of lofexidine during outpatient treatment. The COWS is a clinician-administered instrument that rates 11 common opioid withdrawal signs and symptoms (Appendix 2). 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).

15.5 Safety Assessment Methods

15.5.1 Adverse Events

The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.

Adverse events will be assessed and recorded around the same time each day by study staff during in-clinic lofexidine treatment. If an AE requires medical attention, it should be reported to a study physician immediately. A study physician or assigned staff 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 or assigned staff must review with the subject and assess any AEs unresolved from the previous day. For each daily AE assessment, details will be recorded in the subject's source document and AE eCRF, according to the procedures described in Section 16.7, the type of AE and whether it is serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.5.1.1). 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 until the event is resolved to the satisfaction of the Principal Investigator and Sponsor's Medical Monitor. If the AE is unrelated, the subject will be followed 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 outpatient treatment, subjects will be queried about AEs at each daily clinic visit. All subjects will be instructed to contact the study physician or assigned staff if he or she experiences any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until further instructed.

All reported AEs will be recorded as described above.

15.5.1.1 Withdrawal-Related Adverse Events

The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal. Individual items reported on the efficacy scales (i.e., SOWS-Gossop, COWS) do not automatically qualify as a withdrawal-related AE unless the subject specifically reports them in response to the 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 each specific symptom can be recorded on the AE eCRF. In general, an AE/SAE should not be marked as withdrawal related AND related to study medication.

15.5.2 Vital Signs

Vital signs (sitting/standing systolic and diastolic blood pressure, pulse) will be measured at screening for all subjects.

During in-clinic treatment (Days 1-3 mandatory; Days 4-7 if subject receives all lofexidine doses in the clinic), resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) systolic and diastolic blood pressure and pulse will be measured within 30 minutes before every dose and 3.5 hours (±15 minutes) after administration of study medication at 8 AM, 1 PM, and 6 PM; oral temperature and respiration before 8 AM dose only.

During outpatient treatment (Days 4-14) resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) systolic and diastolic blood pressure and pulse will be measured before an in-clinic dose of lofexidine and 3.5 hours (±30 minutes) after dosing on Days 4-13 and once before any dose on Day 14. If the subject cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 4-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point and the values will be recorded in a subject diary (Appendix 3).

For the orthostatic vital sign (i.e., blood pressure and pulse) readings, subjects will remain at rest for 3 minutes before a vital sign reading, and then stand for 3 minutes before a second vital sign reading is taken. If a subject demonstrates potentially clinically significant vital signs (whether pre- or post-dose), as per the pre-defined criteria detailed in Sections 13.2.2 and 13.2.3, the event should be recorded on the subject's 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 study physician.

Additionally, when the subject is experiencing blood pressure- or pulse-related symptoms (e.g., lightheaded, dizziness, palpitations), these should be recorded on the subject's 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 pre-defined criteria detailed in Sections 13.2.2 and 13.2.3.

15.5.3 12-Lead Electrocardiograms

Using the 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 at 8 AM (or as close to 8 AM as possible) and at 11:30 AM. Note that a time delay for the 8 AM ECG will not be considered a protocol deviation, but that the second ECG should be taken 3.5 hours after the first ECG. Duplicate 12-lead ECGs will also be conducted before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing; before the subject's last dose and 3.5 hours after dosing (or as close to this time as possible); or, if applicable, at discontinuation from the study. 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 a 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);
- QTc (Fridericia) — QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject discontinuation 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 Principal Investigator and if 2 of the 3 QTcF intervals exceed the gender-specific cut-off, then the subject should be judged a screen failure.

  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 Principal 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 discontinued 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 3) will be performed for all subjects at screening, as needed at the study physician's discretion throughout the study, 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 3. Hematology, Chemistry, and Urinalysis Tests

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

Any subject with active liver disease, active tuberculosis, or active syphilis (see Table 4 for interpretation of the syphilis testing sequence) will not be eligible for study participation and

the subject will be referred, at subject's sole expense, for appropriate follow-up and/or treatment.

Table 4. Syphilis Testing Sequence

Subject History	Test and Result			Interpretation	Eligibility
	EIA/CIA/MFI	RPR	TPPA		
Unknown history of syphilis	Non-reactive	N/A	N/A	No serologic evidence	Meets eligibility
	Reactive	Reactive	N/A	Untreated or recently treated syphilis	Excluded
	Reactive	Non-reactive	Non-reactive	Probably false-positive screening test	Meets eligibility
	Reactive	Non-reactive	Reactive	Possible syphilis (e.g., early or latent) or previously treated	May be eligible; consult Medical Monitor
Known history of syphilis	Reactive	Non-reactive	Reactive	Past, successfully treated syphilis	Probably eligible; consult Medical Monitor

Abbreviations: CIA = chemiluminescence assay; EIA = enzyme immunoassay; MFI = multiplex fluorescent immunoassay; N/A = not applicable; RPR = rapid plasma reagin; TPPA = treponema pallidum particle agglutination assay

15.5.4.3 Urine Toxicology Screening

A qualitative urine drug screen (UDS) will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and every day during in-clinic lofexidine treatment and outpatient lofexidine treatment for the following drugs: amphetamines/methamphetamines, methylenedioxymethamphetamine, cocaine, barbiturates, opiates, benzodiazepines, cannabinoids, oxycodone, phencyclidine, 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 "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening for all subjects, at Baseline (Day 1 before dosing), 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 fingerprick blood sample will be collected concurrently with each scheduled ECG during the study.

A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.

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 will be performed at screening for all subjects.

An update of the Physical Exam is required at Baseline (before dosing on Day 1) and then a complete physical examination should be performed 3 to 4 hours after the first dose on Day 1, as clinically warranted throughout the study, 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) during in-clinic lofexidine treatment, once daily before an in-clinic dose of lofexidine during outpatient treatment or, if applicable, at discontinuation from the study. The Baseline version of the C-SSRS (Appendix 5) 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 6) 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 documented on the Prior Medication eCRF. The reported medications will be reviewed and approved by the Principal Investigator/study physician/assigned staff for entry into the study.

All opioids of abuse the subject has used will also be recorded at the screening visit.

15.6.2 Concomitant Medication Administration

Concomitant medication administration will be recorded daily. All concomitant medications will be recorded in source and in the subject's Concomitant Medication eCRF along with dose, dates of administration, and reason for use.

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 Investigational Site File binder will be provided to all investigational sites with additional instruction as well as a place to store regulatory and study documents. The monitoring of the sites participating in the trial (either remote or on site) will be executed according to GCP guidelines and with a focused data review approach (Risk Based Monitoring [RBM]).

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 Principal Investigator, site coordinator, and Sponsor's Clinical Project Manager.

16.2 FDA Forms 1572 and Financial Disclosure

The Principal 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 Principal Investigator and sub-investigators will also sign Financial Disclosure forms before initiating this study.

16.3 Institutional Review Board Approval

Before initiating the study, the Principal Investigator will obtain written IRB approval to conduct the study. Study medication will not 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 Principal 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 approved by the Sponsor before submission to the site's IRB. 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 Principal 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. 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 original 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 original 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 Medical Monitor

The Sponsor's (USWM) Medical Monitors, and/or will be responsible for attempting to establish concurrence with the Principal 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 an SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 7). 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 Principal Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications) and can be reached at
and/or

16.6.2 Clinical Monitors

All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, eCRFs and corresponding source documents as noted in the monitoring plan for each subject. Using an RBM approach, monitoring may also occur remotely. Monitoring both on site and via an RBM approach 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 defined data outlined in the monitoring plan 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.

In lieu of an investigator meeting, USWM will host a web-based initiation meeting with study sites providing at a minimum protocol training, GCP training, CRF completion training, and a review of monitoring expectations. For sites that did not participate in study USWM-LX1-3003-1, monitors will additionally conduct a site initiation visit before the start of the study. 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.

Periodic monitoring visits by USWM will be scheduled at appropriate intervals. 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 Principal Investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix 7. The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.

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 Principal 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 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. Opioid withdrawal symptoms experienced by subjects during screening will be recorded on the Medical History eCRF and such symptoms will be recorded as AEs during the study even if they do not change or worsen. Stable chronic conditions, such as arthritis, which are present before entry into the clinical trial and do not worsen are not considered AEs.

For each daily AE assessment, details will be recorded in the subject's source document and AE eCRF regarding 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal. In general, an AE should not be marked as withdrawal related AND related to study medication. Also, if the

sign or symptom is evaluated as part of the COWS assessment, it should generally be considered as withdrawal related and so marked if it is also reported as an AE.

A study physician or assigned staff must review the AE eCRF for any events 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 Principal Investigator or physician designee 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 serious adverse event (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; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject, in the view of the Investigator, was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- 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 7. 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).

16.9 Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Principal Investigator or his/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 taking study medication. All subjects who become pregnant must be withdrawn from the study and stop taking study medication. The site must make appropriate effort (i.e., monthly calls) to follow the subject until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor. If the subject cannot be reached after 3 telephone attempts, a certified letter should be sent. Documentation of follow-up will be recorded in the source documents.

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 the study population overall as well as by gender.

Detailed methodology for the summary and statistical analyses of the data collected is this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared and finalized before completion of the study.

17.2 Assessment of Effectiveness

Effectiveness measures will be summarized for the following subject cohorts:

- All exposed subjects;
- Subjects undergoing abrupt and total withdrawal;
- Subjects undergoing buprenorphine-assisted withdrawal;
- Subjects transitioning to naltrexone maintenance;
- Subjects transitioning to buprenorphine maintenance;
- Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and
- Any other identifiable cohorts not otherwise noted.

Descriptive statistics will be provided for:

- Demographics and baseline characteristics;
- SOWS-Gossop;
- COWS numerical score;
- COWS severity category (i.e., mild, moderate, moderately severe, severe);
- Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator;
- Distribution of number of days required to complete withdrawal treatment goal by category;
- Concomitant medications; and
- Evaluation of subject treatment status 30 days after last dose.

17.3 Assessment of Safety

Safety summaries will be provided for subjects who received lofexidine; any safety information on subjects who provide informed consent but do not receive lofexidine will be included in listings.

Safety measures will be summarized for the following subject cohorts:

- All exposed subjects;
- Subjects undergoing abrupt and total withdrawal;
- Subjects undergoing buprenorphine-assisted withdrawal;
- Subjects transitioning to naltrexone maintenance;
- Subjects transitioning to buprenorphine maintenance;
- Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and
- Any other identifiable cohorts not otherwise noted.

Descriptive statistics will be provided for:

- AEs;
- AEs of special interest, including orthostatic hypotension, orthostatic bradycardia, and syncope;
- Vital signs;
- ECGs;
- Clinical laboratory tests; and
- C-SSRS.

18 DATA MANAGEMENT AND CASE REPORT FORMS (CRFS)

Data management activities, construction and accuracy of the study database, and statistical analytical support will be coordinated through USWM.

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). CRFs are to be completed on an ongoing basis during the study within 2 to 3 business days of a visit. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the Investigational Site File binder.

The Principal Investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The Principal 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's representatives, the central IRB or 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 Sponsor or designee. 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. Feedback regarding CRF issues will be provided to all sites.

The Principal Investigators agree to routine data audits by the staff of USWM or their designee. USWM monitors will periodically visit each site to assure that data entered in the EDC system are in agreement with source documents at the sites per the monitoring plan.

18.3 Data Analysis

When the study is completed, all data have been entered into the clinical database, and the final database has been checked by Quality Assurance and then locked, statistical analysis of the data will be performed by USWM'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, USWM or designee will also prepare summary reports of the data so that progress of the study can be monitored.

18.4 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms, workbooks, source documents (paper or electronic), 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 an eCRF should maintain patient 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 Principal Investigator and IRB.

By participating in this protocol, the Principal Investigator affirms to USWM that information furnished to the Principal 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, CRFs (electronic or paper), reports, and other records will be coded using subject number and initials. Only research staff and USWM staff or their designee 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 8).

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 DISSEMINATION AND PUBLICATION OF STUDY RESULTS

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

20 PROTOCOL ADHERENCE AND AMENDMENTS

The Principal 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 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 Sponsor or designee 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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23 PROTOCOL AMENDMENT DETAILS

Table 5 lists changes made in Amendment No. 01 to the protocol for Study USWM-LX1-3003-2.

Table 6 lists changes made in Amendment No. 02 to the protocol for Study USWM-LX1-3003-2.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Pages 1-53 --	Pages 1-113 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)	Global change to add SOWS-Gossop as an assessment, consistent with other lofexidine clinical trials.
Pages 1-53 --	Pages 1-113 Columbia Suicide Severity Rating Scale (C-SSRS)	Global change to add C-SSRS as a safety assessment, consistent with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.
Pages 1-53 Site Investigator	Pages 1-113 Principal ~~Site~~ Investigator	Global change for protocol clarity.
Pages 1-53 Attending physician	Pages 1-113 Study~~attending~~ physician/ staff	Global change to improve clarity of the protocol.
Pages 1-53 Case Report Form (CRF)	Pages 1-113 ~~Case Report Form (CRF)~~	Global change to remove reference to CRF as electronic CRFs will be used in the study.
Pages 1-53 CRO	Pages 1-113 ~~CRO~~	Global change to remove reference to CRO.
Pages 1-53 Number of subjects 200-400	Pages 1-113 Number of subjects 250-500~~200-400~~	Global change based on the projected number of subjects completing 7 days of lofexidine treatment in the companion study (USWM-LX1-3003-1) and earlier lofexidine clinical programs expected to be appropriate for the FDA's safety database requirements.
Pages 1-53 10 study sites	Pages 1-113 Approximately 20~~10~~ study sites	Global change to allow additional sites to account for the potentially higher enrollment requirements and target study completion timelines
Pages 1-53 Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)	Pages 1-113 Mini International Neuropsychiatric Interview (M.I.N.I.)~~Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)~~	Global change for consistency with eligibility assessment in the companion study, USWM-LX1-3003-1.
Pages 1-53 Assessments at clinic visits every other day	Pages 1-113 Daily assessments including while inpatient and at daily clinic visits during outpatient treatment~~Clinic visits every other day~~	Global change to more fully monitor the safety of lofexidine.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Pages 1-53 --	Pages 1-113 Subject Diary	Global change to allow collection of vital signs data in an outpatient setting.
Pages 1-53	Pages 1-113	Minor editorial changes made for consistency and to improve clarity of the protocol.
Title Page, Page 1 --	Title Page, Page 1 Amendment No. 01 Date: January 22, 2015	Administrative change.
Title Page, Page 1 Contract Research Organization TBD	Title Page, Page 1 ~~Contract Research Organization TBD~~	Administrative change.
Header, Pages 2-53 Protocol No. USWM-LX1-3003-2 February 3, 2012	Header, Pages 2-113 Protocol No. . USWM-LX1-3003-2, Amendment No. 01, January 22, 2015	Administrative change.
--	Section 2, Pages 3-5 This section provides a summary of major changes made to the protocol for Study USWM-LX1-3003-2 in this current amendment (Amendment No. 01). Section 23 provides a detailed accounting of all changes made in this amendment. [See protocol for summary/rationale of major changes.]	Administrative change.
Section 2, Page 3, Objective The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.	Section 3, Page 6, Objective To primary objective of this study is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness is also of interest.~~The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.~~	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 3, Study Design --	Section 3, Page 6, Study Design [Section extensively revised. See protocol for revisions.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 2, Page 3, Inclusion Criteria 1. 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).	Section 3, Page 6, Inclusion Criteria 1~~7~~. Be able to verbalize understanding of the consent form, able to provide written informed consent, and 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).~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 2, Page 3, Inclusion Criteria 3. Be seeking treatment for partial or total withdrawal from current opioid. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include abrupt and total withdrawal, agonist-assisted withdrawal (with the exception of methadone), transition to naltrexone or from buprenorphine, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).	Section 3, Page 7, Inclusion Criteria 4~~3~~. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal ~~(with the exception of methadone),~~; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or ~~from~~ buprenorphine maintenance.~~, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).~~	Revised to allow subjects with clinical treatment goals for full or partial withdrawal from methadone or buprenorphine.
Section 2, Page 3, Inclusion Criteria 4. Urine toxicology screen positive for opioids (including buprenorphine).	Section 3, Page 7, Inclusion Criteria 5~~4~~. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include~~ing~~ methadone and buprenorphine) at Screening.	Revised for consistency with changes made in Inclusion Criterion #3.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 4, Inclusion Criteria 6. Have completed the Clinical Opiate Withdrawal Scale (COWS) during the Screening period.	Section 3, Page 7, Inclusion Criteria ~~6. Have completed the Clinical Opiate Withdrawal Scale (COWS) during the Screening period.~~	Administrative change.
Section 2, Page 4, Exclusion Criteria 2. Be currently taking methadone, by self report or positive urine drug screen.	Section 3, Page 7, Exclusion Criteria ~~2. Be currently taking methadone, by self report or positive urine drug screen.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 2, Page 4, Exclusion Criteria 3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.	Section 3, Page 7, Exclusion Criteria ~~3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 2, Page 4, Exclusion Criteria 4. Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.	Section 3, Pages 7-8, Exclusion Criteria 2~~4~~. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation). • Have active self-reported acquired immune deficiency syndrome (AIDS) or self-reported human immunodeficiency virus (HIV) positive status and taking	Revised for clarity and consistency with companion study, USWM-LX1-3003-1.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	retroviral medications currently or within the past 4 weeks. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). ~~Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.~~	
Section 2, Page 4, Exclusion Criteria 6. Have participated in an investigational drug study within the past 3 months.	Section 3, Page 8, Exclusion Criteria 4. Have participated in an investigational drug study within the past 30 days~~3 months~~.	Revised for consistency with other protocols.
--	Section 3, Page 8, Exclusion Criteria 5. Have history of lofexidine exposure in a prior clinical trial or otherwise.	Administrative change.
Section 2, Page 5, Exclusion Criteria 7. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTF 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.	Section 3, Page 8, Exclusion Criteria 6. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse~~heart rate~~ less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; and • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.	Administrative clarification/update.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 3, Page 9, Exclusion Criteria 7. To avoid drug-drug interactions, subjects requiring the following will be excluded: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.	Added to improve clarity of the protocol.
Section 2, Page 5 N Total enrollment will depend on subject drop-out rates. Approximately 200 to 400 subjects will need to be enrolled and enrollment will remain open until a minimum total of 300 subjects (among this protocol and companion Protocol USWM LX1 3003 1) have been treated with lofexidine for a minimum of 7 days.	Section 3, Page 9 N Total enrollment will depend on subject drop-out rates. Approximately 250~~200~~ to 500~~400~~ subjects: ~~will need to be enrolled and~~ enrollment will continue~~remain open~~ until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) ~~(among this protocol and companion Protocol USWM LX1 3003 1)~~ have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. A target of at least 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment will be enrolled (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios).	Administrative update.
--	Section 3, Page 9, Safety Endpoints • Occurrence, seriousness, severity, and causality assessment of adverse events. • Occurrence of adverse events of special interest (i.e., orthostatic hypotension, orthostatic bradycardia, syncope). • Occurrence of adverse events not related to opioid withdrawal. • Descriptive evaluation of vital signs (actual and change from baseline) for each time point.	Added to align with study objectives.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	• Descriptive evaluation of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation). • Shifts from baseline in physical examination findings will be summarized. • Descriptive evaluation of clinical laboratory tests of hematology, chemistry, and urinalysis (actual and change from baseline). • Descriptive evaluation of ECG (actual and change from baseline).	
Section 2, Page 5, Endpoints • Number/proportion of subjects successfully completing planned detoxification/transition as assessed by the Site Investigator. • Descriptive evaluation of COWS numerical score, COWS severity score (i.e., mild, moderate, moderately severe, severe), duration of exposure; distribution of number of days required to complete detoxification, average daily dose of lofexidine, concomitant medications, and linkage to long term care (through subject treatment status report at the 30-day post discharge follow-up telephone contact).	Section 3, Page 9, Effectiveness Endpoints • Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (i.e., planned detoxification/transition) as assessed by the Principal ~~Site~~ Investigator. • Distribution of number of days required to complete withdrawal treatment goal by category. • Descriptive evaluation of SOWS-Gossop. • Descriptive evaluation of COWS numerical score and ~~COWS~~ severity score (i.e., mild, moderate, moderately severe, severe) • Concomitant medication analysis. • ~~duration of exposure; distribution of number of days required to complete treatment goal by categorydetoxification, average daily dose of lofexidine, concomitant medications, and linkage to long term care (through~~Evaluation of subject treatment status ~~report at the~~ 30 days after last dose.~~post discharge follow-up telephone contact).~~	Revised to align with study objectives and improve clarity of the protocol.
Section 2, Page 5, Duration 21 days (maximum duration per subject, including screening)	Section 3, Page 10, Duration 23~~21~~ days (maximum duration per subject, including screening)	Administrative change.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 5, Visits All subjects will undergo screening up to 7 days before study admission and will have clinic visits at least every other day for up to 14 days.	Section 3, Page 10, Visits All subjects will undergo screening up to 9~~7~~ days before study admission ~~and will have clinic visits at least every other day for up to 14 days~~. Days 1-3 • In-clinic setting: Subjects may be admitted to clinic on Day -1 Days 4-7 • In-clinic setting OR daily visits for 4 days if outpatient Days 8-14 • Daily outpatient visits for up 7 days Day30 • Telephone follow-up contact	Revised to require mandatory inpatient treatment for 3 days to allow more frequent safety monitoring during anticipated peak withdrawal and initiation of lofexidine therapy. Also, option for inpatient/ outpatient treatment on Days 4-7 enables assessment, as clinically appropriate at the discretion of the Investigator, in a more flexible, real-world setting.
Section 2, Page 5, Effectiveness Assessments	Section 3, Pages 10-11, Safety Assessments [Section extensively revised. See protocol for revisions.]	Revised for consistency with study design changes.
Section 2, Page 6, Safety Assessments	Section 3, Page 11, Effectiveness Assessments [Section extensively revised. See protocol for revisions.]	Revised to align with study objectives and improve clarity of the protocol.
Section 3, Pages 7-10 Table of Contents, Appendices --	Section 4, Pages 12-15 TOC updated to add the following appendices: Appendix 1 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) Appendix 2 Clinical Opiate Withdrawal Scale (COWS) Appendix 3 Subject Diary Appendix 4 Short-term Withdrawal Treatment Goal Appendix 5 Columbia Suicide Severity Rating Scale (C-SSRS) Baseline Version Appendix 6 Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version	Administrative change.
Section 4, Pages 11-12 --	Section 5, Pages 16-17 [Abbreviation list updated.]	Administrative change.
Section 5.1, Pages 12-13 --	Section 6.1, Page 18 [Section extensively revised. See protocol for revisions.]	Administrative update.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 5.3, Page 13, First Paragraph USWM has conducted 3 clinical trials (open-label tolerability and dose-response study and 2 randomized, double-blind, placebo-controlled efficacy/safety studies) in support of the use of lofexidine in acute withdrawal from short-acting opioids.	Section 6.3, Page 19, First Paragraph USWM has completed~~conducted~~ 3 clinical trials (open-label tolerability and dose-response study and 2 randomized, double-blind, placebo-controlled efficacy/safety studies) in support of the use of lofexidine in acute withdrawal from short-acting opioids. In addition, USWM is currently conducting a randomized, double-blind, placebo-controlled efficacy/safety study (USWM-LX1-3003-1) of 2 doses of lofexidine (2.4 and 3.2 mg/day).	Administrative update.
Section 5.4, Page 14, First Paragraph, 1st & 2nd Sentences A total of 2,032 subjects from clinical investigations of lofexidine (both USWM and externally sponsored) have been exposed to doses ranging from 0.1 mg to 4.0 mg total daily doses in a variety of dosing schedules from single doses to four times daily (QID) treatment over durations ranging from 1 day to 52 months (in the case of one antihypertension study). In addition, an estimated 214,000 documented BritLofex™ prescriptions have been sold in the UK where the standard dosing regimen prescribed is 2.4 mg total daily dose (0.8 mg three times daily or 0.6 mg QID) introduced on a dose escalation and maintained typically for 7 to 10 days.	Section 6.4, Page 20, First Paragraph, 1st & 2nd Sentences A total of 2,044~~2,032~~ subjects from clinical investigations of lofexidine (both USWM and externally sponsored) have been exposed to doses ranging from 0.1 mg to 4.0 mg total daily doses in a variety of dosing schedules from single doses to four times daily (QID) treatment over durations ranging from 1 day to 52 months (in the case of one antihypertension study).In addition, over 266,000 ~~an estimated 214,000 documented~~ BritLofex™ prescriptions have been sold in the UK (since product launch in 1992) where the standard dosing regimen prescribed is 2.4 mg total daily dose (0.8 mg three times daily or 0.6 mg QID) introduced on a dose escalation and maintained typically for 7 to 10 days.	Administrative update.
Section 5.5, Page 15 --	Section 6.5, Page 21 [Section extensively revised. See protocol for revisions.]	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).
Section 5.6, Page 16 --	Section 6.6, Page 21 [Section extensively revised. See protocol for revisions.]	Revised to add rationale for including SOWS-Gossop as an outcome measure.
Section 6, Page 16 The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.	Section 7, Page 22 The primary objective is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.~~The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient~~	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	~~detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.~~	
Section 9.1, Pages 16-17 --	Section 10.1, Pages 22-23 [Section extensively revised. See protocol for revisions.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 9.2, Page 17 The total enrollment in this study will depend on subject drop-out rates in this protocol and in companion study, Protocol USWM-LX1-3003-1. It is estimated that approximately 200 to 400 subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation. Enrollment will remain open until a minimum of 300 subjects (among this protocol and companion Protocol USWM-LX1-3003-1) complete a minimum of 7 days of treatment with lofexidine.	Section 10.2, Page 23 The total enrollment in this study will depend on subject drop-out rates in this protocol. Enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. ~~and in companion study, Protocol USWM-LX1-3003-1.~~ It is estimated that approximately 250~~200~~ to 500~~400~~ subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation. ~~Enrollment will remain open until a minimum of 300 subjects (among this protocol and companion Protocol USWM-LX1-3003-1) complete a minimum of 7 days of treatment with lofexidine.~~	Administrative update.
Section 9.3, Page 17 This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be **21 days, including the Screening period, which can last up to 7 days, followed by up to 14 days of flexible dose treatment with lofexidine.** The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects, among this protocol and companion Protocol USWM-LX1-3003-1, completing at least 7 days of treatment with lofexidine. Enrollment is anticipated to take 5 to 10 months to achieve, with the total clinical duration of	Section 10.3, Page 23 This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be 23~~21~~ **days, including the Screening period, which can last up to 9~~7~~ days, followed by up to 14 days of ~~flexible dose~~ treatment with lofexidine.** The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. ~~among this protocol~~	Revised for consistency with study design changes and to improve clarity of the protocol.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
USWM-LX1-3003-2 anticipated to be 8 to 12 months.	~~and companion Protocol USWM-LX1-3003-1, completing at least 7 days of treatment with lofexidine.~~ Enrollment is anticipated to take 4~~5~~ to 10 months to achieve, with the total clinical duration of USWM-LX1-3003-2 anticipated to be 8 to 12 months.	
--	Section 10.4, Pages 23-24 [Section added. See protocol.]	Added to improve clarity of the protocol.
Section 10.1, Page 17, First Paragraph, First 3 Sentences Any opioid-dependent subject about to undergo complete or partial withdrawal from short-acting opioids or on buprenorphine maintenance treatment will be eligible for the study. 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.	Section 11.1, Page 24, First Paragraph, First 3 Sentences Any opioid-dependent subject about to undergo complete or partial opioid withdrawal and could benefit for a minimum of a 7-day treatment with lofexidine ~~from short-acting opioids or on buprenorphine maintenance treatment~~ will be eligible for the study. 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, and a minimum of 50 subjects each on methadone or buprenorphine maintenance treatment.	Revised for consistency with study design changes.
Section 10.2.1, Page 19 7. 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).	Section 11.2.1, Page 24 1~~7~~. Be able to verbalize understanding of the consent form, able to provide written informed consent, and 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).~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.2.1, Page 18 3. Be seeking treatment for partial or total withdrawal from current opioid. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include abrupt and total withdrawal, agonist-assisted withdrawal (with the exception of methadone), transition to naltrexone or from buprenorphine, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).	Section 11.2.1, Page 25 4~~3~~. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal ~~(with the exception of methadone),~~; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or ~~from~~ buprenorphine maintenance.~~, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).~~	Revised to allow subjects with clinical treatment goals for full or partial withdrawal from methadone or buprenorphine.
Section 10.2.1, Page 18 4. Urine toxicology screen positive for opioids (including buprenorphine).	Section 11.2.1, Page 25 5~~4~~. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include~~ing~~ methadone and buprenorphine) at Screening.	Revised for consistency with changes made in Inclusion Criterion #3.
Section 10.2.1, Page 18 6. Have completed the COWS during the Screening period.	Section 11.2.1, Page 25 ~~6. Have completed the COWS during the Screening period.~~	Administrative change.
Section 10.2.2, Page 19 2. Be currently taking methadone, by self report or positive urine drug screen.	Section 11.2.2, Page 25 ~~2. Be currently taking methadone, by self report or positive urine drug screen.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 10.2.2, Page 19 3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.	Section 11.2.2, Page 25 ~~3. Seeking methadone-assisted withdrawal. The use of lofexidine co-administered with methadone is contraindicated.~~	Revised for consistency with changes made in Inclusion Criterion #3.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 10.2.2, Page 19 4. Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.	Section 11.2.2, Pages 25-26 24. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation). • Have active 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. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). ~~Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.~~	Revised for clarity and consistency with companion study, USWM-LX1-3003-1.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.2.2, Page 19 6. Have participated in an investigational drug study within the past 3 months.	Section 11.2.2, Page 26 4~~6~~. Have participated in an investigational drug study within the past 30days~~3 months~~.	Revised for consistency with other protocols.
--	Section 11.2.2, Page 26 5. Have history of lofexidine exposure in a prior clinical trial or otherwise.	Administrative change.
Section 10.2.2, Page 19 7. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTF 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.	Section 11.2.2, Page 26 6. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse~~heart rate~~ less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; or~~and~~ • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.	Administrative clarification.
--	Section 11.2.2, Page 26 7. To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.	Added to improve clarity of the protocol.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.3, Page 20, First Full Paragraph Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.	Section 11.3, Page 26, Second Paragraph ~~Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.~~	Administrative change.
Section 11.2, Page 20, First Paragraph Lofexidine will be packaged and distributed through the pharmacy coordinating center (TBD). 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. 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.	Section 12.2, Page 27, First Paragraph Lofexidine will be packaged and distributed through the pharmacy coordinating center (Sharp~~TBD~~). Lofexidine tablets will be supplied in uniquely-identified 80-count bottles. During in-clinic treatment, lofexidine doses will be dispensed directly from the 80-count bottles, whereas for outpatient treatment, doses ~~which~~ will be dispensed by the study pharmacist as determined clinically appropriate by the ~~Site~~ Principal Investigator or designee 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.	Administrative change/update.
Section 11.4, Page 21	Section 12.4, Page 28 [Section extensively revised. See protocol for revisions.]	Administrative change.
Section 11.5, Page 21 The investigational agent, lofexidine, will be stored at room temperature in a secure location at the dispensing pharmacy.	Section 12.5, Page 28 ~~The investigational agent, lofexidine, will be stored at room temperature in a secure location at the dispensing pharmacy.~~The investigational agent, lofexidine, will be stored at 68-77°F in a secure location at the dispensing pharmacy or site. Temperature of the investigational agent will be maintained at 68-77°F during transport. Temperature of the investigational agent will be monitored during storage and transport. Temperature excursions will be reported to the Sponsor and the Sponsor will determine if the investigational agent is fit for use.	Administrative clarification.

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Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 12.6, Page 28, Second Sentence During outpatient treatment (Days 4-14), subjects are to record doses taken in his/her subject diary.	Added to improve clarity of the protocol.
Section 11.8, Pages 21-22 To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; • alcohol, sedatives, and anesthetics – 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. Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study.	Section 12.8, Page 29 Clonidine is specifically prohibited in this study. To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; and ~~• alcohol, sedatives, and anesthetics – 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. Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study. Lofexidine should generally not be administered concurrently with alcohol, sedatives, and anesthetics as these may interact with lofexidine and enhance its central sedative effects.	Revised to improve clarity of the protocol.
Section 12.2.1, Page 22	Section 13.2.1, Pages 29-30 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require in-clinic treatment for 3 days, either in-clinic or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 12.2.2, Page 23	Section 13.2.2, Pages 30-31 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol.
Section 12.2.3, Page23	Section 13.2.3, Pages 31-32 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol.
Section 12.3, Page 23	Section 13.3, Pages 32-33 [Section extensively revised. See protocol for changes.]	Revised for consistency with study design changes.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 13.4, Page 33 Section 13.4 Nicotine Replacement Therapy [Section added. See protocol.]	Added per study design change requiring in-clinic treatment for at least 3 days.
Section 13.1, Page 24, First Paragraph, First Sentence Interested subjects, who respond to recruitment materials, will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language.	Section 14.1, Page 33, First Paragraph, First Sentence Interested subjects, who respond to recruitment materials and are available to stay for the mandatory 3-day in-clinic treatment part of the study and available for participation in either an in-clinic or outpatient setting for 4 additional days (total commitment of 7 days), will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language.	Revised based on study design change requiring in-clinic treatment for at least 3 days.
Section 13.1, Page 24, Second Paragraph, First Sentence 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 15.4).	Section 14.1, Page 33, Second Paragraph, First Sentence If still interested after receiving an explanation of the study, a qualified investigative site staff member will review the study informed consent form with subjects, and subjects will be given an opportunity to review on their own, inquire about, and sign the ~~study~~ informed consent form (see Section 16.4).	Administrative clarification.
Section 13.1, Page 24, Second Paragraph, 4th & 5th Sentences Screening assessments must be completed within a 7-day time period, but can be completed as early as 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.	Section 14.1, Page 33, Second Paragraph, 4th & 5th Sentences Screening assessments must be completed within a 97-day time period, but can be completed as early as the first 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~~.	Administrative clarification.
Section 13.1, Page 24, Third Paragraph, Second Sentence Subjects must complete a consent quiz with 100% accuracy.	Section 14.1, Page 33, Third Paragraph, Second Sentence ~~Subjects must complete a consent quiz with 100% accuracy.~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 13.1, Page 24, Last Paragraph, Second Sentence 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.	Section 14.1, Pages 33-34, Last Paragraph, Second Sentence Subjects who are excluded, or who decline participation, may ~~not~~ be rescreened at a later time, although at least 30 days must occur between screenings~~and will be given referrals to other resources in the area~~.	Administrative change.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 13.3, Pages 24-25	Section 14.3, Page 34 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require in-clinic treatment for 3 days, either in-clinic or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 13.4, Page 25	Section 14.4, Page 35 [Section extensively revised. See protocol for changes.]	Administrative update.
Section 13.5.1, Page 25, Numbered Items --	Section 14.5.1, Page 35, Numbered Items 2. Abnormal vital signs or ECG meeting criteria in Section 13.2.3.	Administrative clarification.
Section 13.5.1, Page 25, Numbered Items 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.	Section 14.5.1, Page 35, Numbered Items ~~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 (Days 1-3).	Administrative clarification.
Section 13.5.2, Page 26, Numbered Items 1. New onset of clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTc interval[5]). 2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest). 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.	Section 14.5.2, Page 36, Numbered Items 1. New onset of clinically significant abnormal ECG per Investigator judgment (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval[5]). 2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids). 4. Persistent hypertension – resting 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~~ 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued. ~~terminated~~	Administrative clarification.
Section 13.5.3, Page 27 --	Section 14.5.3, Page 37, Last Bullet • the safety database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.	Administrative update.
Section 13.6, Page 27	Section 14.6, Page 37 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol and to relax requirements for concomitant therapy.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14, Page28, Table 1	Section 15, Pages 39-40, Table 1 [Table 1 extensively revised. See protocol for changes.]	Revised for consistency with study design changes.
Section 14.1, Page 29	Section 15.1, Pages 41-42 [Section extensively revised. See protocol for changes.]	Administrative update and revised for consistency with study design changes.
--	Section 15.2, Page 42 Section 15.2 Baseline Assessments [Section added. See protocol for changes.]	Added based on study design changes.
Section 14.2, Pages 29-30	Section 15.3, Pages 42-46 Section extensively revised, including the following subheadings: 15.3.1 Days 1-3 (Mandatory In-clinic) 15.3.2 Days 4-7 (In-clinic/Outpatient) 15.3.3 Days 8-14 (Outpatient Only) 15.3.4 Study Discontinuation/End of Study 15.3.5 30-Day Telephone Follow-up Contact [See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 14.3.1, Page 30 At each visit, the Site Investigator will indicate if the subject has completed the planned withdrawal or transition and can be discharged without further lofexidine treatment.	Section 15.4.1, Page 46 **15.4.1 Assessment of Completion of Pre-Defined Withdrawal Treatment Goal~~Planned Detoxification/Transition~~** ~~At each visit,~~ The ~~Site~~ Principal Investigator will indicate if the subject has completed~~the planned withdrawal or transition and can be discharged without further lofexidine treatment.~~his/her pre-defined withdrawal treatment goal (Appendix 4) on Days 1-7 by responding the following question: "Has the subject's withdrawal treatment goal been reached?" Note that, per protocol, subjects are required to continue on their dose of lofexidine through Day 7 even though the subject may have competed his/her withdrawal treatment goal before Day 7. This same assessment will be made at each visit during the 7 days of optional outpatient treatment (Days 8-14). This assessment should be completed after the SOWS-Gossop and COWS assessments.	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
--	Section 15.4.2, Pages 46-47 **15.4.2 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop** [Section added. See protocol.]	Added as an assessment, consistent with other lofexidine clinical trials.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14.3.2, Page 30, First Sentence The COWS will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal (at least every other day before dosing).	Section 15.4.3, Page 47, First and Second Sentences The COWS [17] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal~~(at least every other day before dosing)~~, and will be completed after the SOWS-Gossop and before the assessment of completion of pre-defined withdrawal treatment goal. It will be completed during screening, at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during inpatient treatment, and once daily before dosing during outpatient treatment.	Administrative clarification.
Section 14.4.1, Page 31, First Paragraph --	Section 15.5.1, Page 47, First Paragraph The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.	Administrative clarification.
Section 14.4.1, Page 31, First Paragraph, First Sentence Subjects will be queried about adverse events at least every other day by study staff. If an AE requires medical attention, it should be reported to a study physician immediately.	Section 15.5.1, Page 47, Second Paragraph, First Sentence Adverse events will be assessed and recorded around the same time each day by study staff during in-clinic lofexidine treatment.~~Subjects will be queried about adverse events at least every other day by study staff~~.	Added based on study design change requiring in-clinic treatment.
Section 14.4.1, Page 31, First Paragraph, 5th and 6th Sentences After each AE assessment, the physician will record on the AE eCRF, according to the procedures described in Section 15.7, 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.	Section 15.5.1, Pages 47-48, Second Paragraph, 6th, 7th & 8th Sentences For~~After~~ each daily AE assessment, ~~the physician~~ details will be recorded in the subject's source document and ~~on the~~ 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.5.1.1).	Administrative clarification.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.1, Page 31, Third Paragraph 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.	Section 15.5.1, Page 48, Fourth and Fifth Paragraphs During outpatient treatment, subjects will be queried about AEs at each daily clinic visit. All subjects will be instructed to contact the study~~treating~~ physician or assigned staff if he or she experiences any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) ~~feels dizzy~~ (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until further instructed~~ by the physician~~. All reported AEs will be recorded as described above.	Revised for consistency with study design changes.
--	Section 15.5.1.1, Page 48 **15.5.1.1 Withdrawal-Related Adverse Events** [Section added. See protocol.]	Revised for consistency with companion study USWM-LX1-3003-1.
Section 14.4.2, Pages 31-32	Section 15.5.2, Pages 48-49 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment. Also, potentially clinically significant vital signs were clarified to improve clarity of the protocol.
Section 14.4.3, Pages 32-33, First Paragraph 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first daily dose and 3.5 hours after the first daily dose on Days 1 and 14 or, if applicable, early discharge/termination from the study. 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 (TBD). A cardiologist on site will evaluate tracings if there is significant abnormality. The following intervals will be computed:	Section 15.5.3, Page 49, First Paragraph Using the 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first ~~daily~~ dose on Day 1 at 8 AM and 3.5 hours (± 15 minutes) after dosing; before subject's last dose and after dosing;~~the first daily dose on Days 1 and 14~~ or, if applicable, ~~early discharge/termination~~at discontinuation from the study. 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~~cardiologist~~ on site will evaluate tracings if there is a significant abnormality. The following intervals will be computed:	Administrative update and revised to improved clarity of the protocol.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.3, Pages 32-33, Bulleted List --	Section 15.5.3, Page 50, Bulleted List • QTc (Fridericia) QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject discontinuation purposes).	Added for consistency with companion study USWM-LX1-3003-1.
Section 14.4.3, Page 33, Last Paragraph Any time that 2 of the 3 QTc measurements exceed 500 msec, contact the Sponsor's Medical Safety Monitor, discuss the subject and the AE/SAE determination.	Section 15.5.3, Page 50, Last Paragraph 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.	Administrative update to add as back up Medical Monitor.
Section 14.4.4.1, Page 33, First Paragraph Standard clinical laboratory safety evaluations (see Table 2) will be performed for all subjects at screening, as needed at the physician's discretion throughout the study, and on Day 14 or, if applicable, early discharge/termination from the study. For this multicenter study, a central laboratory will be identified by the Sponsor which 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).	Section 15.5.4.1, Page 50, First Paragraph Standard clinical laboratory safety evaluations (see Table 3) will be performed for all subjects at screening, as needed at the study physician's discretion throughout the study, and ~~on Day 14 or, if applicable, early discharge/termination~~ at discontinuation from the study. For this multicenter study, a central laboratory will be ~~identified by the Sponsor which~~ 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).	Administrative clarification/update.
Section 14.4.4.1, Page 34, Table 2	Section 15.5.4.1, Page 51, Table 3 [Table 3 updated. See protocol.]	Table 3 was updated for consistency with the laboratory tests routinely conducted by the central laboratory.
Section 14.4.4.2, Page 34, First Paragraph, Seventh Sentence A rapid plasma reagin (RPR) test for syphilis will be performed. If positive, a confirmatory test (FTA-ABS or MHA-TP) will be performed.	Section 15.5.4.2, Page 51, First Paragraph, Seventh Sentence ~~A rapid plasma reagin (RPR) test for s~~Syphilis antibody testing will be performed using an automated enzyme immunoassay (EIA). If the EIA is positive, a confirmatory rapid plasma reagin (RPR) test ~~(FTA-ABS or MHA-TP)~~ will be performed. If the RPR test is non-reactive, a confirmatory TPPA (treponema pallidum particle agglutination assay) will be performed.	Revised for consistency with tests used by the central laboratory.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.4.2, Page 34, Second Paragraph 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.	Section 15.5.4.2, Page 52, Second Paragraph If ~~either~~ the PPD with chest x-ray, chest x-ray, or ~~the confirmatory test for~~ 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.	Revised for consistency with tests used by the central laboratory.
Section 14.4.4.3, Page 35 Qualitative urine drug screening will be performed at screening for all subjects and at least every other day during lofexidine treatment. Urine will be sent to a central laboratory for qualitative analysis for drugs of abuse. The methodology will detect specific drugs or metabolites in the urine.	Section 15.5.4.3, Page 52 A q~~Q~~ualitative urine drug screen (UDS)~~ing~~ will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and ~~at least~~ every ~~other~~ day during in-clinic lofexidine treatment and outpatient treatment 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.~~Urine will be sent to a central laboratory for qualitative analysis for drugs of abuse. The methodology will detect specific drugs or metabolites in the urine.~~	Revised to more fully monitor the safety of lofexidine.
Section 14.4.4.4, Page 35 A "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening for all subjects and on Day 14 or early completion/early termination for all female subjects regardless of their childbearing capacity. Sites may use any FDA-approved urine pregnancy test.	Section 15.5.4.4, Page 52 A "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening~~for all subjects~~, at Baseline (Day 1 before dosing), and ~~on Day 14 or early completion/early termination~~ 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.~~Sites may use any FDA-approved urine pregnancy test.~~	Revised for consistency with companion study USWM-LX1-3003-1.
--	Section 15.5.4.5, Page 52 **15.5.4.5 Pharmacokinetic Sampling** A fingerprick blood sample will be collected concurrently with each scheduled ECG during the study. A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.	Added to enable QTc-concentration analyses as well as to monitor compliance during outpatient treatment.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.5, Page 35 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, as clinically warranted during lofexidine treatment, and on Day 14 or, if applicable, early discharge/termination from the study. Height should be recorded at screening only.	Section 15.5.5, Page 52 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 will~~should~~ be performed at screening for all subjects.~~, as clinically warranted during lofexidine treatment, and on Day 14 or, if applicable, early discharge/termination from the study.~~ An update of the Physical Exam is required at Baseline (before dosing on Day 1) and then a complete physical examination should be performed 3 to 4 hours after the first dose on Day 1, as clinically warranted throughout the study, and at discontinuation from the study. Height should be recorded at screening only.	Revised for consistency with study design changes.
--	Section 15.5.6, Pages 52-53 **15.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)** [Section added. See protocol.]	Added for consistency with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.
Section 14.5.1, Page 35, Second Paragraph --	Section 15.6.1, Page 53, Second Paragraph All opioids of abuse the subject has used will also be recorded at the screening visit.	Administrative clarification.
Section 14.5.2, Page 35 Concomitant medication administration will be recorded at least every other day during the study. All concomitant medications should be recorded on the Concomitant Medication eCRF. The Site Investigator should treat the subject according to his/her usual standard of care for opioid withdrawal, with the exception that methadone is contraindicated for use in subjects taking lofexidine.	Section 15.6.2, Page 53 Concomitant medication administration will be recorded daily~~at least every other day during the study~~. All concomitant medications will~~should~~ be recorded in source and in the subject's Concomitant Medication eCRF along with dose, dates of administration, and reason for use.~~The Site Investigator should treat the subject according to his/her usual standard of care for opioid withdrawal, with the exception that methadone is contraindicated for use in subjects taking lofexidine.~~	Revised for consistency with changes made in other parts of the protocol.
Section 15.1, Pages 35-36, Second and Third Sentences 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	Section 16.1 Page 53, Second and Third Sentences An Investigator Site Binder~~Operations Manual~~ will be provided to all investigational sites with additional instruction as well as a place to store regulatory and study documents~~as a study quality assurance~~	Administrative update.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
guidelines.	~~tool~~. The monitoring of the sites participating in the trial (either remote or on site) will be executed according to GCP guidelines and with a focused data review approach (Risk Based Monitoring [RBM]).	
Section 15.4, Page 37, Second Paragraph, Fourth Sentence Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%.	Section 16.4, Page 54, Second Paragraph, Fourth Sentence ~~Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%.~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 15.6.1, Page 37 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 1). 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).	Section 16.6.1, Page 55 The Sponsor's (USWM) Medical Monitors, will be responsible for attempting to establish concurrence with the ~~Site~~ Principal 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 an~~the~~ SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 6~~1~~). 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~~ Principal Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications) and can be reached at and/or	Administrative update to add as back up Medical Monitor.
Section 15.6.2, Page 37, First Paragraph All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, all CRFs (paper and electronic) 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.	Section 16.6.2, Page 55, First Paragraph All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, ~~all~~ eCRFs ~~(paper and electronic)~~ and corresponding source documents as noted in the monitoring plan for each subject. Using an RBM approach, monitoring may also occur remotely. ~~These monitoring visits~~Monitoring both on site and via an RBM approach will provide an opportunity for evaluation of the progress of the study and to inform the Sponsor of potential problems.	Administrative update.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 15.6.2, Page 38, Third Paragraph Monitors will conduct a site initiation visit before the start of the study. 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.	Section 16.6.2, Page 55, Third Paragraph In lieu of an investigator meeting, USWM will host a web-based initiation meeting with study sites providing at a minimum protocol training, GCP training, CRF completion training, and a review of monitoring expectations. For sites that did not participate in study USWM-LX1-3003-1, m~~M~~onitors will additionally conduct a site initiation visit before the start of the study. 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.	Administrative change.
Section 15.6.2, Page 38, Fourth Paragraph, First Sentence Routine monitoring visits by USWM 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.	Section 16.6.2, Page 55, Fourth Paragraph, First Sentence Periodic~~Routine~~ monitoring visits by USWM 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.~~	Administrative clarification.
Section 15.7, Page 38, First Paragraph, Last Sentence The occurrence of AEs will be assessed starting at the treatment phase of the protocol.	Section 16.7, Page 56, First Paragraph, 2nd, 3rd, & 4th Sentences The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.	Administrative clarification.
Section 15.7, Page 38, Second Paragraph 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 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	Section 16.7, Page 56, Second Paragraph 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 Principal Investigator on physical examination, ~~or~~ laboratory evaluation, or C-SSRS (for example, score of 3 or more on the scale) will be considered an AE and will be recorded on the AE eCRF. A new illness, symptom, sign or clinically significant	Administrative clarification/update.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
as arthritis, which are present before clinical trial entry and do not worsen are not considered AEs.	clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Opioid withdrawal symptoms experienced by subjects during screening will be recorded on the Medical History eCRF and such symptoms will be recorded as AEs during the study even if they do not change or worsen. Stable chronic conditions, such as arthritis, which are present before entry into the clinical trial and do not worsen are not considered AEs.	
Section 15.7, Page 38, Third Paragraph, 1st & 2nd Sentences After each AE assessment, the physician will record 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.	Section 16.7, Page 56, Third Paragraph, 1st & 2nd Sentences For~~After~~ each daily AE assessment, ~~the physician~~ details will be recorded in the subject's source document and ~~on the~~AE eCRF regarding 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE.	Administrative clarification.
Section 15.9, Page 40 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.	Section 16.9, Page 57 Although pregnancy is not considered an AE, it is the responsibility of the Principal~~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 taking~~completing the~~ study medication. All subjects who become pregnant must be withdrawn from the study and stop taking study medication. ~~and must be followed to the completion/ termination of the pregnancy~~. The site must make appropriate effort (i.e., monthly calls) to follow the subject until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor. If the subject cannot be reached after 3 telephone attempts, a certified letter should be sent. Documentation of follow-up will be recorded in the source documents.	Administrative update.
Section 16.2, Page 40, Fourth Bullet • Subjects completing final buprenorphine withdrawal;	Section 17.2, Page 58, Fourth Bullet ~~• Subjects completing final buprenorphine withdrawal;~~	Revised to improve clarity of the protocol.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 16.2, Page 41, Bulleted Items Descriptive statistics will be provided for: • Demographics and baseline characteristics; • COWS numerical score; • COWS severity category (i.e., mild, moderate, moderately severe, severe); • Duration of exposure to lofexidine; • Number of subjects successfully completing planned detoxification/transition as assessed by the Site Investigator; • Distribution of number of days required to complete detoxification; • Average daily dose of lofexidine; • Concomitant medications; • Linkage to long-term care (through subject treatment status report at the 30-day post discharge follow-up telephone contact); and • Compliance in taking lofexidine (based on pill counts).	Section 17.2, Pages 58-59, Bulleted Items Descriptive statistics will be provided for: • Demographics and baseline characteristics; • SOWS-Gossop; • COWS numerical score; • COWS severity category (i.e., mild, moderate, moderately severe, severe); ~~• Duration of exposure to lofexidine;~~ • Number/proportion of subjects successfully completing the pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the ~~Site~~ Principal Investigator; • Distribution of number of days required to complete withdrawal treatment goal by category~~detoxification~~; ~~• Average daily dose of lofexidine;~~ • Concomitant medications; and • ~~Linkage to long-term care (through~~Evaluation of subject treatment status~~report at the~~ 30 -days after last dose.~~post discharge follow-up telephone contact).; and~~ ~~• Compliance in taking lofexidine (based on pill counts).~~	Revised for consistency with study design changes.
Section 16.3, Page 41, Bulleted Items 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: • AEs; • Vital signs; • ECGs; and • Clinical laboratory tests.	Section 17.3, Page 59, Bulleted Items Safety measures will be summarized for the following subject cohorts: • All exposed subjects; • Subjects undergoing abrupt and total withdrawal; • Subjects undergoing buprenorphine-assisted withdrawal; • Subjects transitioning to naltrexone maintenance; • Subjects transitioning to buprenorphine maintenance; • Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and • Any other identifiable cohorts not otherwise noted. ~~• All treated subjects;~~ ~~• Treated subjects without urinary evidence of illicit drug use; and~~	Revised for consistency with study design changes.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	~~• 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: • AEs; • AEs of special interest, including orthostatic hypotension, orthostatic bradycardia, and syncope; • Vital signs; • ECGs; ~~and~~ • Clinical laboratory tests; and • C-SSRS.	
Section 17, Page 42 Data management activities and statistical analytical support will be coordinated through the CRO (TBD). The CRO will be responsible for the construction and accuracy of the study database.	Section 18, Page 59 Data management activities, construction and accuracy of the study database, and statistical analytical support will be coordinated through USWM.~~the CRO (TBD). The CRO will be responsible for the construction and accuracy of the study database.~~	Administrative change.
Section 17.1, Page 42, First Paragraph Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs), except for the COWS assessment, which is a validated paper instrument and thus will be collected on paper, scanned, and appended to the subject's eCRF for entry into the database. The eCRFs and paper CRFs 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.	Section 18.1, Pages 59-60, First Paragraph Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs).~~, except for the COWS assessment, which is a validated paper instrument and thus will be collected on paper, scanned, and appended to the subject's eCRF for entry into the database.The eCRFs and paper CRFs will be supplied by the CRO.~~ CRFs are to be completed on an ongoing basis during the study within 2 to 3 business days of a visit. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the Investigational Site File binder~~study operations manual~~.	Administrative change.
Section 17.1, Page 42, Third Paragraph Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor representatives, and the site's IRB.	Section 18.1, Page 60, Third Paragraph Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor's representatives, the central IRB , or~~and~~ the site's IRB.	Administrative update.

Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 17.2, Page 42	Section 18.2, Page 60 **18.2 Electronic Data Capture~~Data Processing, Editing, and Control~~** [Section extensively revised. See protocol for changes.]	Administrative change.
Section 17.5.2, Page 44, First Paragraph, First and Second Sentences To maintain subject confidentiality, all laboratory specimens, CRFs (electronic or paper), reports, and other records will be coded using alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet.	Section 18.5.2, Page 61, First Paragraph, First and Second Sentences To maintain subject confidentiality, all laboratory specimens, CRFs (electronic or paper), reports, and other records will be coded using subject number and initials.~~alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet.~~	Administrative change.
Section 18, Pages 44-45 **18. 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	Section 19, Page 61 **19. DISSEMINATION AND PUBLICATION~~S~~ OF ~~THE~~ STUDY RESULTS** The Sponsor recognizes the importance of communicating medical study data and therefore encourages ~~their~~publication of such data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study is described in the Clinical Trial Agreement between the Sponsor and the institution of the Investigator. ~~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~~	Administrative clarification.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
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).	~~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).~~	
Section 21, Page 46 --	Section 22, Pages 62-63 [Reference list updated. See protocol.]	Administrative change.

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Table 5. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
--	Section 23, Pages 64-96 Section 23 Protocol Amendment Details [Section added. See protocol.]	Section added to detail the changes made in Amendment No. 1.
--	Appendix 1, Page 97 Appendix 1 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop [Appendix added. See protocol.]	Appendix added for protocol completeness.
--	Appendix 2, Page 98 Appendix 2 Clinical Opiate Withdrawal Scale (COWS) [Appendix added. See protocol.]	Appendix added for protocol completeness.
--	Appendix 3, Page 99 Appendix 3 Subject Diary [Appendix added. See protocol.]	Appendix added for protocol completeness.
--	Appendix 4, Page100 Appendix 4 Short-term Withdrawal Treatment Goal [Appendix added. See protocol.]	Appendix added for protocol completeness.
--	Appendix 5, Pages 101-103 Appendix 5 Columbia Suicide Severity Rating Scale (C-SSRS) Baseline Version [Appendix added. See protocol.]	Appendix added for protocol completeness.
--	Appendix 6, Pages 104-106 Appendix 6 Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version [Appendix added. See protocol.]	Appendix added for protocol completeness.

Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Pages 1-113	Pages 1-120	Minor editorial changes made for consistency and to improve clarity of the protocol.
Title Page, Page 1 --	Title Page, Page 1 **Amendment No. 02 Date:** May 21, 2015	Administrative change.
Header, Pages 2-113 Protocol No. USWM-LX1-3003-2, Amendment No. 01 January 22, 2015	Header, Pages 2-120 Protocol No. USWM-LX1-3003-2, Amendment No. 02~~01~~ May 21, 2015~~January 22, 2015~~	Administrative change.
Section 2, Pages 3-5 --	Section 2, Page 3 [Section updated. See protocol for revisions.]	Revised to include a summary of the changes made in Amendment No. 02.
Section 3, Pages 6-7, Exclusion Criteria 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and	Section 3, Pages 7-8, Exclusion Criteria 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (subject is excluded if positive for active syphilis as per required laboratory tests; see also Section 15.5.4.2), ~~hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease),~~ and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and	Revised to improve clarity of the protocol.
Section 3, Page 10, Safety Assessments, Third Bullet • Vital signs during outpatient treatment (Days 4-7 optional; Days 8-14 if subject continues taking lofexidine), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 or, if applicable, at discontinuation from the study (note: if subjects cannot stay in	Section 3, Page 10, Safety Assessments, Third Bullet • Vital signs during outpatient treatment (Days 4-7 optional; Days 8-14 if subject continues taking lofexidine), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) ~~at least once daily~~ before an in-clinic dose of lofexidine~~dosing~~ and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 or, if applicable, at discontinuation from the study	Revised to improve clarity of the protocol.

Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
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, with values recorded in a subject diary);	(note: if subjects 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, with values recorded in a subject diary);	
Section 3, Page 10, Safety Assessments, Fourth Bullet • 12-lead ECGs (in duplicate) recorded as follows: ➢ Day 1 before the first dose at 8 AM and at 3.5 hours after dosing; ➢ Before subject's last dose and after dosing or, if applicable, at discontinuation from the study;	Section 3, Page 10, Safety Assessments, Fourth Bullet • 12-lead ECGs (in duplicate) recorded as follows: ➢ Day 1 before the first dose at 8 AM and at 3.5 hours after dosing; ➢ Before subject's last dose and 3.5 hours after dosing (or as close to this time as possible) or, if applicable, at discontinuation from the study;	Revised to include a post-dose ECG assessment.
Section 3, Page 11, Safety Assessments, First Bullet • C-SSRS 3.5 hours after the first dose (8 AM) during in-clinic treatment, once daily before dosing during outpatient treatment, or, if applicable, at discontinuation from the study;	Section 3, Page 11, Safety Assessments, First Bullet • C-SSRS 3.5 hours after the first dose (8 AM) during in-clinic treatment, once daily before an in-clinic dose of lofexidine~~dosing~~ during outpatient treatment, or, if applicable, at discontinuation from the study;	Revised to improve clarity of the protocol.
Section 3, Page 11, Effectiveness Assessments, First Bullet • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment;	Section 3, Page 11, Effectiveness Assessments, First Bullet • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine~~dosing~~ during outpatient treatment;	Revised to improve clarity of the protocol.
Section 3, Page 11, Effectiveness Assessments, Second Bullet • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment;	Section 3, Page 11, Effectiveness Assessments, First Bullet • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose of lofexidine~~dosing~~ during outpatient treatment;	Revised to improve clarity of the protocol.
Section 5, Pages 16-17 --	Section 5, Pages 16-17 [Abbreviation list updated.]	Administrative change.
Section 10.1, Page 23, Last Sentence All subjects receiving lofexidine treatment on an outpatient basis will be required to return to the clinic daily to undergo specific assessments (including qualitative urine drug screening) as listed in Table 1 of Section 15.	Section 10.1, Page 23, Last 2 Sentences All subjects receiving lofexidine treatment on an outpatient basis will be required to take a dose of lofexidine in the clinic at each daily clinic visit, with required clinical ~~return to the clinic daily to undergo specific~~ assessments performed before and after dosing ~~(including qualitative urine drug screening)~~ as listed in Table 1 of	Revised to improve clarity of the protocol.

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Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
	Section 15. Also during outpatient treatment, subjects will be required to undergo qualitative urine drug screening at each clinic visit.	
Section 10.4, Page 23 --	Section 10.4, Pages 23-24 , First Paragraph, Last Sentence Note that should a second or third measurement be required with waiting between measurements, the timing of the measurement will not be considered a protocol deviation (i.e., outside the protocol-specified window).	Revised to improve clarity of the protocol.
Section 11.2.2, Pages 25-26 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and	Section 11.2.2, Pages 25-26 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (subject is excluded if positive for active syphilis as per required laboratory tests; see also Section 15.5.4.2), ~~hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease),~~ and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and	Revised to improve clarity of the protocol.
Section 13.2.1, Page 30, Second Paragraph --	Section 13.2.1, Page 30, Second Paragraph, Last Sentence Note that if the subject is receiving outpatient treatment, he/she is required to take a dose of lofexidine in the clinic at each daily clinic visit.	Revised to improve clarity of the protocol.
Section 13.2.1, Page 30, Third Paragraph, First Sentence Optional Outpatient Treatment (Days 8-14) Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days, per the dose schedule listed below.	Section 13.2.1, Page 30, Third Paragraph, First Sentence Optional Outpatient Treatment (Days 8-14) Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days, per the dose schedule listed below, including taking a dose of lofexidine in the clinic at each daily clinic visit.	Revised to improve clarity of the protocol.

Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14.3.1, Page 34, First Paragraph --	Section 14.3.1, Page 34, First Paragraph, Sixth Sentence Note that should a second or third measurement be required with waiting between measurements, the timing of the measurement will not be considered a protocol deviation (i.e., outside the protocol-specified window).	Revised to improve clarity of the protocol.
Section 14.3.2, Page 34 Per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine treatment in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Required clinical assessments are detailed in Table 1. All subjects receiving lofexidine treatment on an outpatient basis will be required to return to the clinic daily before a scheduled dose for these clinical assessments. Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).	Section 14.3.2, Page 34 Per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine treatment in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). ~~Required clinical assessments are detailed in Table 1.~~ All subjects receiving lofexidine treatment on an outpatient basis will be required to take a dose of lofexidine in the clinic at each daily clinic visit, with required clinical assessments performed before and after dosing as detailed in Table 1.~~return to the clinic daily before a scheduled dose for these clinical assessments.~~ Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).	Revised to improve clarity of the protocol.
Section 14.4, Page 35, First Paragraph	Section 14.4, Page 35, First Paragraph	Revised to account for up to 3 in-office screening visits.
Section 14.4, Page 35, Fourth Paragraph, First Sentence	Section 14.4, Page 35, Fourth Paragraph, First Sentence	Revised to reflect the increased amount for up to 3 in-office screening visits.
Section 15, Pages 39-40, Table 1	Section 15, Pages 39-40, Table 1 [Footnotes revised. See protocol for revisions.]	Revised for consistency with changes made in other parts of the protocol.
Section 15.1, Page 41, Fourth Paragraph, First Bullet • 12-lead ECGs (in duplicate) will be done on one day during the screening period at 8 AM and 11:30 AM.	Section 15.1, Page 41, Fourth Paragraph, First Bullet • 12-lead ECGs (in duplicate) will be done on one day during the screening period at 8 AM (or as close to 8 AM as possible) and at 11:30 AM. Note that a time delay for the 8 AM ECG will not be considered a protocol deviation, but that the second ECG should be taken 3.5 hours after the first ECG.	Revised to improve clarity of the protocol.

Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 15.3.2, Page 43, First, Second, and Third Bullets • Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM. • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment. • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment.	Section 15.3.2, Page 43, First, Second, and Third Bullets • Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM. Note that if subject is receiving outpatient treatment, he/she is required to take a dose of lofexidine in the clinic at each daily clinic visit. • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment. • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment.	Revised to improve clarity of the protocol.
Section 15.3.2, Page 44, Fourth Bullet, First Sentence • Vital Signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing during outpatient treatment.	Section 15.3.2, Page 44, Fifth Bullet, First Sentence • Vital Signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) during outpatient treatment~~at least once daily~~ before an in-clinic dose of lofexidine each day~~dosing~~ and 3.5 hours after dosing ~~during outpatient treatment~~.	Revised to improve clarity of the protocol.
Section 15.3.2, Page 44, Ninth Bullet • C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) during in-clinic treatment; once daily before dosing during outpatient treatment.	Section 15.3.2, Page 44, Tenth Bullet • C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) during in-clinic treatment; once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment.	Revised to improve clarity of the protocol.
Section 15.3.3, Page 44, Second Bullet • SOWS-Gossop before dosing.	Section 15.3.3, Page 45, Second Bullet • SOWS-Gossop before an in-clinic dose~~ing~~ of lofexidine.	Revised to improve clarity of the protocol.
Section 15.3.3, Page 45, First Bullet • COWS before dosing.	Section 15.3.3, Page 45, Third Bullet • COWS before an in-clinic dose~~ing~~ of lofexidine.	Revised to improve clarity of the protocol.
Section 15.3.3, Page 45, Fifth Bullet, First Sentence • Vital Signs, including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14.	Section 15.3.3, Page 45, Seventh Bullet, First Sentence • Vital Signs, including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) ~~at least once daily~~ before an in-clinic dose of lofexidine ~~dosing~~ and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14.	Revised to improve clarity of the protocol.

Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 15.3.3, Page 45, Ninth Bullet • C-SSRS (Since Last Visit Version; Appendix 6) before dosing.	Section 15.3.3, Page 45, Eleventh Bullet • C-SSRS (Since Last Visit Version; Appendix 6) before an in-clinic dose~~ing~~ of lofexidine.	Revised to improve clarity of the protocol.
Section 15.3.4, Page 46, Third Bullet • 12-lead ECGs (in duplicate) before the subject's last dose and after dosing.	Section 15.3.4, Page 46, Sixth Bullet • 12-lead ECGs (in duplicate) before the subject's last dose and 3.5 hours after dosing (or as close to this time as possible).	Revised to include a post-dose ECG assessment.
Section 15.4.2, Page 46, First Paragraph, First Sentence The SOWS-Gossop [16] will be completed by the subject at baseline, once daily at 3.5 hours (± 10 minutes) after the first dose of study medication during in-clinic treatment and once daily before dosing during outpatient treatment.	Section 15.4.2, Pages 46-47, First Paragraph, First Sentence The SOWS-Gossop [16] will be completed by the subject at baseline, once daily at 3.5 hours (± 10 minutes) after the first dose of study medication during in-clinic treatment and once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment.	Revised to improve clarity of the protocol.
Section 15.4.3, Page 47, Second Sentence It will be completed during screening, at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during in-clinic treatment, and once daily before dosing during outpatient treatment.	Section 15.4.3, Page 47, Second Sentence It will be completed ~~during screening,~~ at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during in-clinic treatment, and once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment.	Correction and clarification.
Section 15.5.2, Pages 48-49, Third Paragraph, First Sentence During outpatient treatment (Days 4-14) resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) 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 4-13 and once before any dose on Day 14.	Section 15.5.2, Page 49, Second Paragraph, First Sentence During outpatient treatment (Days 4-14) resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) systolic and diastolic blood pressure and pulse will be measured ~~at least once daily~~ before an in-clinic dose of lofexidine ~~dosing~~ and 3.5 hours (±30 minutes) after dosing on Days 4-13 and once before any dose on Day 14.	Revised to improve clarity of the protocol.
Section 15.5.3, Page 49, First Paragraph Using the 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing; before the subject's last dose and after dosing; or, if applicable, at discontinuation from the study. 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 a	Section 15.5.3, Page 49, First Paragraph Using the 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 at 8 AM (or as close to 8 AM as possible) and at 11:30 AM. Note that a time delay for the 8 AM ECG will not be considered a protocol deviation, but that the second ECG should be taken 3.5 hours after the first ECG. Duplicate 12-lead ECGs will also be conducted before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing; before the subject's last dose and 3.5 hours after dosing (or as close to this time as possible); or, if applicable, at discontinuation from the	Revised to improve clarity of the protocol.

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Table 6. Changes for USWM-LX1-3003-2 Protocol Amendment No. 01 (January 22, 2015) → USWM-LX1-3003-2, Amendment No. 02 (May 21, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
significant abnormality. The following intervals will be computed:	study. 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 a significant abnormality. The following intervals will be computed:	
Section 15.5.4.2, Page 52, First Paragraph 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.	Section 15.5.4.2, Pages 51-52, Second Paragraph Any subject with active liver disease, active tuberculosis, or active syphilis (see Table 4 for interpretation of the syphilis testing sequence) will not be eligible for study participation and the subject~~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.	Revised to improve clarity of the protocol.
Section 15.5.4.2, Page 52 --	Section 15.5.4.2, Page 52 [Table 4 added. See protocol.]	Table 4 added to clarify syphilis testing results and interpretation for determination of subject study eligibility.
Section 15.5.4.3, Page 52 A qualitative urine drug screen (UDS) will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and every day during in-clinic lofexidine treatment and outpatient lofexidine treatment 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.	Section 15.5.4.3, Page 52 A qualitative urine drug screen (UDS) will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and every day during in-clinic lofexidine treatment and outpatient lofexidine treatment for the following drugs: amphetamines/ methamphetamines, methylenedioxymethamphetamine, cocaine, barbiturates, opiates, benzodiazepines, cannabinoids, oxycodone, phencyclidine, methadone, and buprenorphine. The central lab will provide standard sets of UDS "dipsticks" for use across all sites.	Revised per updated testing procedures at the central lab.
Section 15.5.6, Page 52, First Sentence 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) during in-clinic lofexidine treatment, once daily before dosing during outpatient treatment or, if applicable, at discontinuation from the study.	Section 15.5.6, Page 53, First Sentence 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) during in-clinic lofexidine treatment, once daily before an in-clinic dose~~ing~~ of lofexidine during outpatient treatment or, if applicable, at discontinuation from the study.	Revised to improve clarity of the protocol.
Section 23, Pages 64-96 --	Section 23, Pages 97-103 [Table 6 added. See protocol.]	Table 6 added to detail the changes made in Amendment No. 02.

CLINICAL STUDY PROTOCOL

A Phase 3, Open-Label, Safety Study of Lofexidine

Protocol Number:	USWM-LX1-3003-2
Product:	Lofexidine
Investigational New Drug (IND) Number:	IND 47,857
Development Phase of Study:	Phase 3
Medical Monitor:	
Sponsor:	US WorldMeds, LLC 4010 Dupont Circle, Suite L-07 Louisville, KY 40207
Protocol Date:	February 3, 2012
Amendment No. 01	January 22, 2015

1 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:** 22 JAN 2015

Name (print):

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

Signature: _____ **Date:** _____

Name (print): _____

2 PROTOCOL AMENDMENT SUMMARY

This section provides a summary of major changes made in this current amendment (No. 01) to the protocol for Study USWM-LX1-3003-2. Section 23 provides a detailed accounting of all changes made in this amendment.

AMENDMENT No. 01: RATIONALE AND SUMMARY OF MAJOR CHANGES

- The protocol was revised to allow enrollment of subjects with clinical treatment goals for full or partial withdrawal from any opioid (including methadone and buprenorphine), which would be expected to elicit opioid abstinence syndrome requiring treatment for at least 7 days. Treatment goals may include abrupt and total withdrawal, agonist-assisted total withdrawal, dose reduction of maintenance treatment (e.g., methadone, buprenorphine), and transition from an opioid or opioid agonist to naltrexone or buprenorphine maintenance. An attempt will be made to include a minimum of 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios). The change was introduced to enable the study of lofexidine's utility in any situation in which mitigation of opioid withdrawal symptoms would be beneficial to reaching the end treatment goal. Both buprenorphine and methadone clinical scenarios are being evaluated as clinically relevant scenarios where lofexidine's use is likely. Results of prior interaction studies do not suggest a significant safety concern with coadministration of lofexidine and both methadone and buprenorphine. Further evaluation of the safety and clinical utility of lofexidine coadministered with methadone or buprenorphine will help confirm that a contraindication for use of lofexidine with agonists is unnecessary.

- The protocol was revised 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. M.I.N.I. is being used for consistency with eligibility assessment in companion study, USWM-LX1-3003-1. Like SCID, the M.I.N.I. is a validated scale (Sheehan et al., 1998) and is commonly used in clinical practice and research studies.

- Number of subjects needed for enrollment was increased from 200 to 400 to 250 to 500 based on the projected number of subjects completing 7 days of lofexidine treatment in the companion study (USWM-LX1-3003-1) and FDA's safety database requirements. Enrollment in USWM-LX1-3003-2 will continue until a minimum of 300 subjects across the lofexidine studies have received active treatment at clinically relevant doses for at least 7 days.

- Number of study sites was increased from 10 to approximately 20 to account for the potentially higher enrollment requirements and target study completion timelines.

- The protocol was revised from flexible dosing to standardized dosing of 7 days of lofexidine treatment, starting at 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. The standard dosing approach is being adopted to limit variability across sites and treatment scenarios to ensure interpretability of safety data at clinically relevant doses and to evaluate the same doses as used in the controlled programs with demonstrated efficacy.

- The protocol was revised to require 3 days of mandatory in-clinic (inpatient housing/clinic facilities) treatment with lofexidine (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive all 4 daily doses of lofexidine in the clinic or can be treated as outpatients for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Subjects can continue receiving lofexidine on a semi-standardized taper in an outpatient setting as long as acute withdrawal symptoms persist at the Principal Investigator's discretion; however, in no event is treatment to exceed an additional 7 days (maximum of 14 days treatment over entire study). The required initial 3 days of in-clinic treatment was introduced to enable more frequent safety monitoring during anticipated peak withdrawal and initiation of lofexidine therapy. Outpatient treatment for continuation of therapy begins at Day 4 to enable assessment, as clinically appropriate at the discretion of the Principal Investigator, in a more flexible, real-world setting as patients with a variety of treatment goals, as being studied in the current design, may not require a longer-term clinic stay and in many situations it may be impractical to require inpatient treatment for more than a few days (e.g., work schedules).

- The protocol was revised to require daily (rather than every other day) assessments, including during in-clinic treatment and at daily clinic visits during outpatient treatment. As the primary objective of the study is to assess safety of lofexidine at clinically relevant doses, daily evaluations regardless of inpatient or outpatient status are appropriate.

- The Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) was added because this scale has been evaluated in nearly all other lofexidine studies in opioid withdrawal, serving as the instrument to evaluate efficacy as the primary endpoint in the 2 pivotal programs conducted for the drug; and the SOWS-Gossop data will be used to evaluate lofexidine's effectiveness in a variety of open-label clinical scenarios studied under the current protocol.

- Requirements for vital signs were expanded during in-clinic treatment with lofexidine, similar to requirements in the companion study (USWM-LX1-3003-1). Also a subject diary (Appendix 3) was added if the required post-dose blood pressure/pulse measurement cannot be obtained in the clinic. These changes were introduced to ensure the most robust safety data collection possible during the in-clinic portion of the study and providing a mechanism for additional data collection in the outpatient setting, consistent with the primary objective of the study.

- A fingerprick blood sample concurrently with each scheduled ECG was added to enable QTc-concentration analyses.

- A fingerprick blood sample was added for analysis of plasma lofexidine concentration to monitor compliance during outpatient treatment.

- Columbia Suicide Severity Rating Scale (C-SSRS) was added as a safety assessment, consistent with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.

3 SYNOPSIS

Title	A Phase 3, Open-Label, Safety Study of Lofexidine
Objective	The primary objective of the study is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.
Study Design	Multicenter, open-label study in the United States in which subjects will receive lofexidine treatment for 7 days, starting at a dose of 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. Note that all subjects will start lofexidine administration (Day 1) on the first day of his/her planned opioid agonist dose reduction/discontinuation regardless of the clinical situation in which the subject is seeking treatment (see Inclusion Criterion No. 3). All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total. Subjects will receive a telephone follow-up call 30 days after their last dose. During in-clinic treatment, subjects must take lofexidine within a 1-hour window, 30 minutes before or after 8 AM and within a 30-minute window, 15 minutes before or after 1 PM, 6 PM, and 11 PM. In the event a subject is not dosed within this window as a result of completion of confirmatory vital sign assessments (Section 10.4), this will not constitute as a protocol deviation. Source documents must note, however, the reason for dose delay. For subjects receiving outpatient treatment (elective) on Days 4-7 and those continuing lofexidine treatment in a mandatory outpatient setting for up to an additional 7 days (Days 8-14), prescribed dosing will remain on the same QID schedule (8 AM, 1 PM, 6 PM, 11 PM).
Sites	Approximately 20 (Target: ≥3-4 subjects/site/month. Recruitment time: 4 to 10 months, depending on total enrollment requirements)
Inclusion Criteria	1. Be able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete study procedure . 2. Be male or female at least 18 years of age.

Inclusion Criteria *(continued)*	3. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.), on any opioid (including methadone and buprenorphine maintenance treatment). 4. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or buprenorphine maintenance. 5. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include methadone and buprenorphine) at Screening. 6. If female and of childbearing potential, subject must agree to use 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).
Exclusion Criteria	1. Be a female subject who is pregnant or lactating. 2. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate);

Exclusion Criteria *(continued)*	➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation). • Have active 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. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). 3. Current dependence (based on the M.I.N.I.) on any psychoactive substance (excluding caffeine, nicotine, and the subject's current opioid-dependence agent, which can include methadone or buprenorphine for example, in agonist-maintained subjects) that requires detoxification or dose reduction as part of the pre-defined individual subject withdrawal treatment goal. 4. Have participated in an investigational drug study within the past 30 days. 5. Have history of lofexidine exposure in a prior clinical trial or otherwise. 6. Abnormal cardiovascular exam at Screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; or • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.

Exclusion Criteria *(continued)*	7. To avoid drug-drug interactions, subjects requiring the following will be excluded: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.
N	Total enrollment will depend on subject drop-out rates. Approximately 250 to 500 subjects: enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. A target of at least 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment will be enrolled (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios).
Safety Endpoints	• Occurrence, seriousness, severity, and causality assessment of adverse events (AEs). • Occurrence of AEs of special interest (i.e., orthostatic hypotension, orthostatic bradycardia, syncope). • Occurrence of AEs not related to opioid withdrawal. • Descriptive evaluation of vital signs (actual and change from baseline) for each time point. • Descriptive evaluation of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation). • Shifts from baseline in physical examination findings. • Descriptive evaluation of clinical laboratory tests of hematology, chemistry, and urinalysis (actual and change from baseline). • Descriptive evaluation of ECG (actual and change from baseline).
Effectiveness Endpoints	• Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (e.g., planned detoxification/ transition) as assessed by the Principal Investigator. • Distribution of number of days required to complete withdrawal treatment goal by category. • Descriptive evaluation of SOWS-Gossop. • Descriptive evaluation of COWS numerical score and severity score (i.e., mild, moderate, moderately severe, severe). • Concomitant medication analysis. • Evaluation of subject treatment status 30 days after last dose.

Duration	23 days (maximum duration per subject, including screening)
Visits	All subjects will undergo screening up to 9 days before study admission. Days 1-3 • In-clinic setting: Subjects may be admitted to the clinic on Day -1. Days 4-7 • In-clinic setting OR daily visits for 4 days if outpatient Days 8-14 • Daily outpatient visits for up 7 days Day 30 • Telephone follow-up contact
Safety Assessments	The following safety assessments will be performed daily unless otherwise specified below: • Occurrence, seriousness, severity, and causality assessment of AEs; • Vital signs during in-clinic treatment (Days 1-3 mandatory; Days 4-7 if subject receives all lofexidine doses in the clinic), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (respiration and temperature before 8 AM dose only); • Vital signs during outpatient treatment (Days 4-7 optional; Days 8-14 if subject continues taking lofexidine), including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 or, if applicable, at discontinuation from the study (note: if subjects 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, with values recorded in a subject diary); • 12-lead ECGs (in duplicate) recorded as follows: ➢ Day 1 before the first dose at 8 AM and at 3.5 hours after dosing; ➢ Before subject's last dose and after dosing or, if applicable, at discontinuation from the study; • Clinical laboratory tests as clinically warranted and at discontinuation from the study; • Complete physical examination 3 to 4 hours after first dose on Day 1, as clinically warranted, and at discontinuation from the study; • Pregnancy test at discontinuation from the study;

Safety Assessments *(continued)*	• C-SSRS 3.5 hours after the first dose (8 AM) during in-clinic treatment, once daily before dosing during outpatient treatment, or, if applicable, at discontinuation from the study; • A qualitative urine drug screening (by on-site use of "dipsticks") for specific drug or metabolite classification will be done every day during in-clinic treatment to monitor for contraband and every day during outpatient treatment to monitor for illicit drug use; • A fingerprick blood sample for pharmacokinetic (PK) analysis will be collected concurrently with each scheduled ECG; and • A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance. A follow-up telephone contact will be attempted 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).
Effectiveness Assessments	The following effectiveness assessments will be performed daily unless otherwise specified below: • SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment; • COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment; • Completion of withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator; • Concomitant medication use; and • Evaluation of subject treatment status 30 days after last dose.

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TABLES

APPENDICES

5 ABBREVIATIONS AND DEFINITION OF TERMS

Abs	Absolute
AE(s)	Adverse Event(s)
AIDS	Acquired Immune Deficiency Syndrome
ALT/SGPT	Alanine Aminotransferase/Serum Glutamic-Pyruvic Transaminase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
Anti-HCV	Hepatitis C Virus Antibody
aPTT	Activated Partial Thromboplastin Time
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)
C-SSRS	Columbia Suicide Severity Rating Scale
DAWN	Drug Abuse Warning Network
DBP/dBP	Diastolic Blood Pressure
DHHS	Department of Health and Human Services
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
EDC	Electronic Data Capture
EIA	Enzyme Immunoassay
eCRF(s)	Electronic Case Report Form(s)
ED	Emergency Department
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
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
LDH	Lactate Dehydrogenase
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
mmHg	Millimeters of Mercury
msec	Millisecond
NSAIDs	Nonsteroidal anti-inflammatory drugs
NDA	New Drug Application
NIMH	National Institute of Mental Health
OL	Open Label
PK	Pharmacokinetic
PP	Per Protocol
PPD	Purified Protein Derivative (skin test for tuberculosis)
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	Subject-specific QT
RBC	Red Blood Cell
RBM	Risk Based Monitoring
RDW	Red Blood Cell Distribution Width
RPR	Rapid Plasma Reagin
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SBP/sBP	Systolic Blood Pressure
SOWS-Gossop	Short Opiate Withdrawal Scale of Gossop
TEAEs	Treatment-Emergent Adverse Events
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
WBC	White Blood Cell

7 STUDY OBJECTIVES

The primary objective is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.

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 20 study sites in the US. It is the responsibility of the Principal 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, multicenter, open-label study to evaluate the safety and effectiveness of lofexidine in alleviation of withdrawal signs and symptoms in subjects undergoing abstinence from any opioid, including methadone and buprenorphine maintenance treatment, which would likely require at least 7 days of lofexidine treatment for alleviation of withdrawal. Any subject seeking treatment for partial or total opioid withdrawal will be eligible. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur, such as (but not limited to) abrupt and total withdrawal (including from methadone and buprenorphine), agonist-assisted total withdrawal, dose reduction of maintenance treatment (e.g., methadone, buprenorphine), and transition from an opioid agonist to naltrexone or buprenorphine maintenance. Subjects will be evaluated for their compliance with protocol inclusion/exclusion criteria during a screening period, lasting up to 9 days. Approximately 250 to 500 subjects will receive lofexidine treatment for 7 days, starting at a dose of 3.2 mg daily (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. Lofexidine administration should be initiated in concurrence with the change in opioid dose which is anticipated to elicit withdrawal symptoms (e.g., first day of dose reduction, or first day of abrupt cessation) or on the first day of emergence/anticipated emergence of such symptoms as determined at the Investigator's discretion. Details regarding the timing of lofexidine therapy initiation relative to change in opioid dose and onset/expected onset of symptoms should be captured in the source. All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine

treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total. All subjects receiving lofexidine treatment on an outpatient basis will be required to return to the clinic daily to undergo specific assessments (including qualitative urine drug screening) as listed in Table 1 of Section 15.

10.2 Number of Subjects

The total enrollment in this study will depend on subject drop-out rates in this protocol. Enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. It is estimated that approximately 250 to 500 subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation.

10.3 Duration of Study

This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be 23 days, including the Screening period, which can last up to 9 days, followed by up to 14 days of treatment with lofexidine.

The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. Enrollment is anticipated to take 4 to 10 months to achieve, with the total clinical duration of USWM-LX1-3003-2 anticipated to be 8 to 12 months.

10.4 Dose Hold and Discontinuation Criteria (2 of 3 Rule)

When a blood pressure, heart rate, or QTcF interval value meets criteria for withholding a dose (Section 13.2.2) or discontinuation from the study (Section 13.2.3), the value needs to be confirmed by the site personnel by repeating the vital sign measurement or ECG recording, approximately 10 to 15 minutes later. If the value is confirmed by the second measurement, the appropriate action will be taken (dose hold or study discontinuation) and the confirmatory value will be recorded in the subject's source document and appropriate eCRF. If the second value does not meet the specified criteria, a third measurement will be taken approximately 10 to 15 minutes later. If this value is confirmatory, the appropriate action will be taken (dose hold or study discontinuation) and the last confirmatory value will be recorded in the subject's source document and appropriate eCRF. If the third value does not confirm the initial finding, then no action should be taken and the third value should be entered in the subject's source and appropriate eCRF.

Whenever blood pressure, heart rate, or QTcF interval values meet dose hold or study discontinuation criteria, these are to be recorded on the subject's eCRF as an adverse event (AE) or serious adverse event (SAE), as applicable. Examples are:

Item	Record Adverse Event of:
Resting Vital Signs	
SBP <90 mmHg and >20% below screen value	Hypotension
DBP <50 mmHg and >20% below screen value	Hypotension
Pulse <50 bpm and >20% below screen value	Bradycardia
Orthostatic Vital Signs	
SBP >25% below recumbent values	Postural hypotension
DBP <25% below recumbent values	Postural hypotension
Pulse >25% below recumbent values	Postural bradycardia

DBP = diastolic blood pressure, SBP = systolic blood pressure

11 SELECTION OF STUDY POPULATION

11.1 Population Base

Any opioid-dependent subject about to undergo complete or partial opioid withdrawal and could benefit for a minimum of a 7-day treatment with lofexidine will be eligible for the study. 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, a mix of ethnicities reflecting the distribution in the local geographic regions of the study sites, and a minimum of 50 subjects each on methadone or buprenorphine maintenance treatment. 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 able to verbalize understanding of the consent form, able to provide written informed consent, and verbalize willingness to complete study procedures.
2. Be male or female at least 18 years of age.

3. Have current dependence, according to the Mini International Neuropsychiatric Interview (M.I.N.I.) [18, 19], on any opioid (including methadone and buprenorphine maintenance treatment).
4. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include:
   - abrupt and total withdrawal (including from methadone and buprenorphine);
   - agonist-assisted total withdrawal;
   - dose reduction of maintenance treatment (e.g., methadone, buprenorphine); and
   - transition from an opioid agonist to naltrexone or buprenorphine maintenance.
5. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include methadone and buprenorphine) at Screening.
6. 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).

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 a very serious medical illness not under control as detailed below.
   - Serious medical illness will be determined at Screening by:
     - medical history;
     - physical examination;
     - 12-lead electrocardiogram (duplicate);

- clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and
- tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation).

- Have active 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.
- Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment).

3. Current dependence (based on the M.I.N.I.) on any psychoactive substance (excluding caffeine, nicotine, and the subject's current opioid-dependence agent, which can include methadone and buprenorphine, for example, in agonist-maintained subjects) that requires detoxification or dose reduction as part of the pre-defined individual subject withdrawal treatment goal.
4. Have participated in an investigational drug study within the past 30 days.
5. Have history of lofexidine exposure in a prior clinical trial or otherwise.
6. Abnormal cardiovascular exam at screening, including any of the following:
   - clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females);
   - resting pulse less than 55 bpm or symptomatic bradycardia;
   - resting systolic blood pressure less than 95 mmHg or symptomatic hypotension;
   - resting diastolic blood pressure less than 65 mmHg;
   - resting blood pressure greater than 155/95 mmHg; or
   - prior history of myocardial infarction.

   Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.
7. To avoid drug-drug interactions, subjects requiring the following will be excluded:
   - tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and
   - beta-receptor blockers, to avoid the risk of excessive bradycardia.

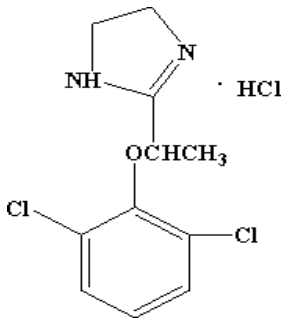
11.3 Screening Failures

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.

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.

12.2 Dispensing Investigational Agent

Lofexidine will be packaged and distributed through the pharmacy coordinating center (Sharp). Lofexidine tablets will be supplied in uniquely-identified 80-count bottles. During in-clinic treatment, lofexidine doses will be dispensed directly from the 80-count bottles, whereas for outpatient treatment doses will be dispensed by the study pharmacist as determined clinically appropriate by the Principal Investigator or designee 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 medication will be dispensed by the site pharmacist or designee.

12.3 Blinding Plan

This is an open-label study.

12.4 Labeling

The investigational agent, lofexidine, will be packaged in labeled bottles (80 count pills) and during the outpatient portion of the study dispensed to subjects in labeled prescription bottles (i.e., redispensing container). The product label will include the sponsor's name, protocol number, the number of tablets in the bottle, address, 24-hour emergency phone number, and the following statement – "Caution: New Drug – Limited by Federal Law to Investigational Use."

During outpatient treatment (Days 4-14), 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:

- Principal Investigator's name and number,
- Subject number,
- Date of dispensing,
- Directions for use,
- Drug name / dose or protocol number,
- Number of pills dispensed,
- Sponsor's name, and
- For Investigational Use Only.

12.5 Storage

The investigational agent, lofexidine, will be stored at 68-77°F in a secure location at the dispensing pharmacy or site. Temperature of the investigational agent will be maintained at 68-77°F during transport. Temperature of the investigational agent will be monitored during storage and transport. Temperature excursions will be reported to the Sponsor and the Sponsor will determine if the investigational agent is fit for use.

12.6 Record of Administration

Accurate recording of all investigational agent received, dispensed, administered, and returned will be maintained by study site personnel. During outpatient treatment (Days 4-14), subjects are to record doses taken in his/her subject diary.

12.7 Used/Unused Supplies

Unused investigational agent 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.

12.8 Contraindications

Clonidine is specifically prohibited in this study.

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

- tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; and
- beta-receptor blockers – the combination of lofexidine and beta-receptor blockers should be used with caution to avoid the risk of excessive bradycardia.

Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study.

Lofexidine should generally not be administered concurrently with alcohol, sedatives, and anesthetics as these may interact with lofexidine and enhance its central sedative effects.

13 TREATMENT PLAN

13.1 Investigational Agent

All subjects in this study will receive lofexidine, as described in Section 13.2.

13.2 Dose Administration

13.2.1 Administration of Doses

Lofexidine administration should be initiated in concurrence with the change in opioid dose which is anticipated to elicit withdrawal symptoms (e.g., first day of dose reduction, or first day of abrupt cessation) or on the first day of emergence/anticipated emergence of such symptoms as determined at the Investigator's discretion. Details regarding the timing of lofexidine therapy initiation relative to change in opioid dose and onset/expected onset of symptoms should be captured in the source. All subjects will take lofexidine orally for 7 days, starting on Day 1 at a dose of 3.2 mg per day (0.8 mg QID), with lowering of the dose allowed to 2.4 mg daily (0.6 mg QID) if required for tolerability based on the subject's individual treatment goal and response per clinical judgment of the Principal Investigator. The subject's dose may be changed back to 3.2 mg/day, per Principal Investigator judgment, but in no case is the dose of lofexidine to exceed 3.2 mg/day (or a single dose of 0.8 mg). Supporting rationale for any dose changes must be recorded in the subject's source document.

All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Note that the decision to allow outpatient treatment should take into account the subject's sensitivity to the hypotensive effects of the study medication (as observed over Days 1-3) and the subject's potential for noncompliance. Furthermore, the rationale for the decision to continue treatment through either an in-clinic or outpatient setting must be documented in the subject's source document.

During in-clinic treatment, subjects must take lofexidine within a 1-hour window, 30 minutes before or after 8 AM and within a 30-minute window, 15 minutes before or after 1 PM, 6 PM, and 11 PM, with the actual date and time of each dose recorded in the subject's source document and in the eCRF. For subjects receiving outpatient treatment (elective) on Days 4-7 and those continuing optional lofexidine treatment in an outpatient setting for up to an additional 7 days (Days 8-14), prescribed dosing will remain on the same QID schedule (8 AM, 1 PM, 6 PM, 11 PM) with compliance assessed at the next day's clinic visit by pill count, subject report of dosing in diary (Appendix 3), and a fingerprick blood sample to assess plasma lofexidine concentrations.

Optional Outpatient Treatment (Days 8-14)

Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days, per the dose schedule listed below. The rationale for the decision to continue lofexidine treatment must be documented in the subject's source document. Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total in this study.

Day	If Dose Regimen on Day 7 is 3.2 mg/day (0.8 mg QID)	If Dose Regimen on Day 7 is 2.4 mg/day (0.6 mg QID)
8	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
9	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
10	2.4 mg/day (0.6 mg QID)	1.6 mg/day (0.4 mg QID)
11	1.6 mg/day (0.4 mg QID)	0.8 mg/day (0.2 mg QID)
12	1.6 mg/day (0.4 mg QID)	0.8 mg/day (0.2 mg QID)
13	0.8 mg/day (0.2 mg QID)	0.8 mg/day (0.2 mg QID)
14	0.8 mg/day (0.2 mg QID)	0.8 mg/day (0.2 mg QID)

Note: In order to prevent dehydration from opioid withdrawal, increased fluid intake will be encouraged from the beginning of the study.

13.2.2 Dose Hold Criteria

Study medication will be held if pre-dose vital signs meet any of the criteria listed below (see Section 10.4 for details on repeat confirmatory requirements).

Resting (sitting [or recumbent if necessary because of an AE])

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

Orthostatic (after standing for 3 minutes)

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

During outpatient treatment, if the subject experiences symptoms of hypotension and/or bradycardia (see below), he/she should call the study site and the site should instruct the subject on whether the next dose should be delayed, skipped, or he/she should be seen in the clinic. The subject should record this information in the subject diary (Appendix 3).

- marked dizziness
- fainting (especially when standing from a sitting or lying position)
- light headedness
- Fatigue
- Weakness
- shortness of breath
- chest pains
- easily tiring during physical activity
- confusion or memory problems
- blurred vision
- nausea
- cold, clammy pale skin
- rapid shallow breathing
- depression
- thirst

All instances of dose-holds must be clearly documented in the subject's source document and dosing eCRF, and the event causing the dose hold should be recorded on the AE or SAE eCRF, as applicable.

13.2.3 Discontinuation Criteria

A subject will be discontinued from the study if any of the criteria listed below are met (see Section 10.4 for details on repeat confirmatory requirements). All instances should be recorded in the subject's source document and AE or SAE eCRF, as applicable.

- Resting systolic blood pressure <70 mmHg;
- Resting diastolic blood pressure <40 mmHg;
- Resting pulse <40 bpm;

- QTcF >500 msec[1] or >25% above screen value for both males and females; or
- Syncope.

Additional discontinuation criteria based on cardiovascular events are:

- New onset of clinically significant abnormal ECG per Investigator judgment (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval).
- Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids).
- Single occurrence of symptomatic bradycardia (as assessed by Principal Investigator/study physician/assigned staff, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.
- Persistent hypertension – resting blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued.
- Medical Intervention for Cardiovascular Event: Any medical intervention (nonmedication or medication inclusive) used for the treatment of any cardiovascular event, with the exception of a positional intervention in subjects displaying hypotension.
- Any other clinically significant cardiovascular signs or symptoms that would place the subject at risk.
- Subject misses more than a total of 6 doses during Days 1-7.

13.3 Treatment Compliance

All subjects will receive all 4 doses of lofexidine in a clinic setting for the first 3 days of lofexidine treatment (Days 1-3) and then, per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine doses in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Per Principal Investigator judgment, subjects can continue lofexidine treatment beyond Day 7 on an outpatient basis only for up to an additional 7 days (Days 8-14). No subject will receive lofexidine for more than 14 days total. In an in-clinic setting, each dose will be observed by study staff and hand and mouth checks will be performed. In an outpatient setting, self-dosing compliance will be evaluated at the next day's clinic visit by pill count, subject report of dosing in diary (Appendix 3), and a fingerprick blood sample to assess plasma lofexidine concentrations. Subjects will be instructed to call the Principal Investigator's office before taking the next dose of study medication if they notice any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2), especially when

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

standing from a sitting or lying position. The study physician or assigned staff will determine if the next dose should be delayed, skipped, or the subject should be seen. Any change in prescribed dosing will be recorded 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 in-clinic participation in study based on individual site policy. If they usually use tobacco products, they will be offered and encouraged to use nicotine replacement therapy (patch, gum, inhaler, or nasal spray) while they are in the in-clinic facility to treat their nicotine withdrawal symptoms. If smoking is permitted by a participating site, smoking breaks outside of the in-clinic facility must be constantly observed and supervised.

The estimated total number of tobacco products used by subjects per day during in-clinic treatment 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 for the mandatory 3-day in-clinic treatment part of the study and available for participation in either an in-clinic or outpatient setting for 4 additional days (total commitment of 7 days), 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, a qualified investigative site staff member will review the study informed consent form with subjects, and subjects will be given an opportunity to review on their own, inquire about, and sign the 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 subject number and proceed to the screening phase of the study. Screening assessments must be completed within a 9-day time period, but can be completed as early as the first screening day. At no time during the screening process should individuals be given information regarding inclusion or exclusion criteria. 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. 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 be rescreened at a later time, although at least 30 days must occur between screenings. 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 9 days during which the subjects must satisfy the eligibility criteria and complete all required screening assessments.

14.3 Treatment Phase

14.3.1 Days 1-3 (Mandatory In-clinic)

After a potential participant has completed all screening assessments and has met all eligibility criteria to participate in the study, the Principal Investigator or study coordinator will arrange for admission to the hospital or clinic in the evening (Day -1) or early morning (Day 1) before study drug administration on Day 1. After all Baseline requirements have been completed (Section 15.2), subjects will receive their first dose of lofexidine during the 8 AM dosing window on Day 1. Subjects will be dosed 4 times daily from Day 1 through Day 3 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 (±15 minutes) after the 8 AM, 1 PM, and 6 PM dose. 12-lead ECGs will also be collected before the first dose on Day 1 (8 AM) and 3.5 hours (±15 minutes) after dosing. Other clinical assessments will be gathered between 11:00 AM and noon each day (see a complete list of assessments in Table 1). These clinical assessments are described in detail in Sections 15.3.5 and 15.5.

14.3.2 Days 4-7 (In-clinic/Outpatient)

Per clinical judgment of the Principal Investigator, subjects can continue to receive lofexidine treatment in a clinic setting or can be treated outside of the clinic (outpatient) for the remaining 4 days of mandatory lofexidine treatment (Days 4-7). Required clinical assessments are detailed in Table 1. All subjects receiving lofexidine treatment on an outpatient basis will be required to return to the clinic daily before a scheduled dose for these clinical assessments. Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).

14.3.3 Days 8-14 (Outpatient Only)

Per Principal Investigator judgment, subjects can continue lofexidine treatment on an outpatient basis for up to an additional 7 days. Note that lofexidine dosing may be stopped at any time during Days 8-14. No subject will receive lofexidine for more than 14 days total in this study. Subjects will be required to return to the clinic daily before a scheduled dose for clinical assessments (see a complete list of assessments in Table 1).

14.4 Subject Reimbursement

All compensation will be described in the informed consent form used by each site and approved by the site's 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 Principal Investigator may discontinue a subject if s/he deems it clinically appropriate or for any reason. Additionally, the Principal Investigator must discontinue a subject for any of the following reasons:

1. Cardiovascular events (see Section 14.5.2).
2. Abnormal vital signs or ECG meeting criteria in Section 13.2.3.
3. Serious medical problem thought to be related or unrelated to the study medications.
4. Intercurrent illness or medical complications that, in the opinion of the Principal Investigator, preclude safe administration of study medications.
5. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study (Days 1-3).
6. Requiring therapy with an exclusionary drug.
7. Lack of compliance with protocol and/or unit procedures.

Subjects who are removed from study treatment because of AEs or SAEs will be followed until they are medically stabilized to the satisfaction of the study physician or assigned staff (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 on the end of study form provided in the subject's eCRF. Once discontinued, subjects may not re-enter the study. Discontinued subjects will not 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 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 study physician.

1. New onset of clinically significant abnormal ECG per Investigator judgment (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 Principal Investigator/study physician/assigned staff, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness.
4. Persistent hypertension – resting blood pressure ≥185/110 mmHg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued.
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.

[2] 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;
- data recording is inaccurate or incomplete; and
- the safety database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.

14.6 Concomitant Therapy

If the individual withdrawal treatment goal requires a specific concomitant medication (e.g., agonist-assisted total withdrawal, transition to buprenorphine or naltrexone, dose reduction of maintenance therapy), that concomitant medication is allowed. At no time are clonidine, tricyclic antidepressants, and beta-receptor blockers allowed (see Section 12.8).

Other concomitant medications or therapies are permitted throughout the study in either an in-clinic or outpatient setting, as clinically warranted. The following medications were found to be useful in earlier lofexidine efficacy/safety studies and, for consistency, the Principal Investigator/study physician/assigned staff may consider their use in this study as appropriate.

1. Guaifenesin (for cough).
2. Alumina, Magnesia, and Simethicone (for emesis and nausea).
3. Dioctyl sodium sulfosuccinate and psyllium hydrocolloid suspension (for constipation).
4. Bismuth sulfate (Pepto-Bismol®) and loperamide (Imodium®) (for diarrhea).
5. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (for headache, muscle aches, or other discomfort.
6. Zolpidem, trazadone, and other benzodiazepines (for insomnia, depression, anxiety).

The Principal Investigator/study physician/assigned staff should contact the Sponsor's Medical Monitor regarding any questions on concomitant medications.

The site should document in source any symptom that requires administration of any concomitant medication as an AE (see Section 15.5.1).

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

15 CLINICAL EVALUATIONS

A detailed Schedule of Study Assessments is provided in Table 1.

Table 1. Schedule of Study Assessments

Activity	Screening Days -8 to -1	Baseline (a) Day 1	In-clinic Treatment Days 1-3	In-clinic/Outpatient Treatment Days 4-7	Outpatient Treatment Days 8-14	Study Discontinuation/ End of Study*
Informed Consent Signed	X					
Subject Number Assigned	X					
Inclusion/Exclusion Criteria	X	X (b)				
Prior Medication History	Past 30 days	X (b)				
Demographics	X					
Medical and Smoking History	X					
Mini-International Neuropsychiatric Interview	X					
Infectious Disease Assessments (c)	X					
Chest X-Ray (c)	X					
Pregnancy Test (d)	X	X				X
Height	X					
Weight	X					X
Complete Physical Exam	X	X (b)	X (e)	As needed	As needed	X
Admission to In-clinic Facility		X (f)				
Study Medication Administration			X (QID)	X (QID) (t)	Optional	
Medication Compliance			X	X	X	X
Study Medication Taper					X	
Discharge from In-clinic Facility				Variable, but by Day 7		
Clinic Visit				Daily if outpatient	Daily	
Issue Subject Diary				Daily if outpatient	Daily	
12-Lead Electrocardiogram (duplicate)	X (g)	X (h)	X (h)			X (i)
Urine Drug Screen (j)	X	X	X	X	X	X
Vital Signs (Sitting/Recumbent & Standing BP and pulse; respiration; and temperature)	X	X	X (k)	X (k) (l)	X (l)	X
Clinical Laboratory Tests (hematology, chemistry, urinalysis)	X	As needed	As needed	As needed	As needed	X
Adverse Events Assessment			X	X	X	X
C-SSRS Baseline Version		X				
C-SSRS Since Last Visit Version			X (n)	X (n)	X (n)	X
Short Opiate Withdrawal Scale of Gossop (o)		X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS) (o)		X	X	X	X	X
Fingerprick Blood Sample			X (p)	X (q)	X (p) (q)	X (p)
Concomitant Medications Assessment			X	X	X	X

Table 1. Schedule of Study Assessments

Activity	Screening Days -8 to -1	Baseline (a) Day 1	In-clinic Treatment Days 1-3	In-clinic/Outpatient Treatment Days 4-7	Outpatient Treatment Days 8-14	Study Discontinuation/ End of Study*
Define Subject-Specific Withdrawal Treatment Goal	X					
Assessment of Completion of Pre-defined Withdrawal Treatment Goal (r)			X	X	X	X
Telephone Follow Up Contact						X (s)

Abbreviations: BP = blood pressure, C-SSRS = Columbia Suicide Severity Scale, PK = pharmacokinetic, PPD = purified protein derivative, QID = 4 times daily

* The study discontinuation/end of study assessments/procedures should always be done when subject exits from the study.

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

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

(c) A chest x-ray is required only if a PPD 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) A complete physical exam will be done on Day 1 (3-4 hours after first dose) and as clinically warranted.

(f) Subjects may be admitted to the hospital or clinic in the evening (Day -1) before study drug administration on Day 1.

(g) Baseline 12-lead electrocardiograms (ECGs) will be done on one day during the screening period at 8 AM and 11:30 AM.

(h) 12-lead ECGs (duplicate) before dosing on Day 1 at 8 AM and 3.5 hours (± 15 minutes) after dosing.

(i) 12-lead ECGs (duplicate) before subject's last dose and after dosing or, if applicable, at discontinuation from the study.

(j) Urine drug screen will be done every day in an in-clinic setting to monitor for contraband and every day in an outpatient setting to monitor illicit drug use.

(k) During in-clinic treatment, resting (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) 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; respiration and temperature before 8 AM dose only.

(l) During outpatient treatment, resting (sitting [or recumbent if necessary because of an adverse event]) and standing (if able) blood pressure and pulse will be measured at least once daily before dosing and 3.5 hours after dosing on Days 4-13 and once before any dose on Day 14 and at the End of Treatment/Study Discontinuation visit. Oral temperature and respiration are not required measurements during outpatient treatment.

(m) C-SSRS will be completed at 3.5 hours after the first dose (8 AM) on Days 1-3.

(n) C-SSRS will be completed 3.5 hours after the first dose (8 AM) during in-clinic treatment or once daily before dosing during outpatient treatment.

(o) During in-clinic treatment, effectiveness scales will be completed once daily: the Short Opiate Withdrawal Scale of Gossop 3.5 hours (±10 minutes) after the first dose of study medication followed by COWS, and the assessment of completion of pre-defined withdrawal treatment goal. Effectiveness scales will be completed daily before dosing during outpatient treatment.

(p) A fingerprick blood sample for PK analysis will be collected concurrently with each scheduled ECG.

(q) A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.

(r) This form is to be completed by the Principal Investigator after completion of the SOWS-Gossop and COWS.

(s) A follow-up telephone contact will be attempted 30 days after the subject's last dose and will include 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).

(t) Per Investigator judgment, subjects can be discharged from the study after receipt of at least one dose of study drug on Day 7 and after completion of all end-of-study procedures.

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 9-day time period. The screening visit will have a visit window of ±2 days. Subjects will not be out of compliance if visit windows extend because of extraordinary events that make it impossible for subjects to complete a screening within the ±2-day window (e.g., holidays, vacations, personal emergencies). Determination of the maximum visit window deviation is, however, at the discretion of the medical monitor. 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 determining eligibility and written informed consent is obtained: height; weight; vital signs (sitting/standing blood pressure and pulse; respiration; and temperature); 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 ECGs (in duplicate) will be done on one day during the screening period at 8 AM and 11:30 AM.
- Medical and smoking/alcohol history.
- Complete physical examination.
- Mini International Neuropsychiatric Interview (M.I.N.I.) [18, 19]. 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) and (2) determine the absence of major psychiatric disorders (exclusion criterion #3).
- Prior medications will be recorded to capture all medications taken in the past 30 days.
- All opioids of abuse the subject has used will be recorded.

In addition, each subject will have a short-term (within the 14-day study period) withdrawal treatment goal defined according the criteria below (see Appendix 4 for further details on this assessment).

- Abrupt and total withdrawal (e.g., quitting heroin abruptly and totally), including whether naltrexone maintenance will be initiated as part of the short-term treatment goal.

- Agonist-assisted total withdrawal (e.g., quitting heroin with methadone or other agonist, including buprenorphine, given as needed to alleviate symptoms), including whether naltrexone maintenance will be initiated as part of the short-term treatment goal.
- Step-down/dose reduction resulting in partial withdrawal (e.g., lowering methadone or buprenorphine maintenance dose or chronic pain medication dose).
- Transition (e.g., transitioning from heroin or methadone to buprenorphine maintenance).

15.2 Baseline Assessments

The Baseline period is the morning of admission to the study, before 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 (±30 minutes).

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

- 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 to capture any new medications since screening.
- Update complete physical exam form to capture any new physical findings since screening.
- Columbia Suicide Severity Rating Scale (C-SSRS) (Baseline version; Appendix 5).
- 12-lead ECGs (in duplicate) before the first dose on Day 1 at 8 AM.

15.3 Assessments During Treatment

15.3.1 Days 1-3 (Mandatory In-clinic)

The assessments or procedures listed below will be performed daily (unless otherwise specified) on Days 1-3 (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM.

- Effectiveness assessments at estimated time of maximum plasma concentration (T_{max}, i.e., 3.5 hours after the first daily dose) including:
  - SOWS-Gossop; and
  - COWS.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Vital signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (7 times per day); respiration and temperature before 8 AM dose only.
- Continuous monitoring for AEs.
- 12-lead ECGs (in duplicate) before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing.
- A fingerprick blood sample for PK analysis will be collected concurrently with each scheduled ECG.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination 3 to 4 hours after dosing on Day 1 and as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) on Days 1-3.
- A qualitative urine drug screening (by on-site use of "dipsticks") will be done every day to monitor for contraband.

15.3.2 Days 4-7 (In-clinic/Outpatient)

The assessments or procedures listed below will be performed daily (unless otherwise specified) on Days 4-7 (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Study medication administration QID at 8 AM, 1 PM, 6 PM, and 11 PM.
- SOWS-Gossop 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment.
- COWS 3.5 hours after the first daily dose during in-clinic treatment; once daily before dosing during outpatient treatment.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).

- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses if being treated as an outpatient.
- Vital signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) during in-clinic treatment before every dose and 3.5 hours after administration of study medication at 8 AM, 1 PM, and 6 PM (7 times per day); respiration and temperature before 8 AM dose only.
- Vital Signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing during outpatient treatment. Note that if the subject cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 4-7, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point. Subjects will also be provided a diary (Appendix 3) to record the measurements along with any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) the subject may have experienced.
- A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.
- AE assessment.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) at 3.5 hours after the first dose (8 AM) during in-clinic treatment; once daily before dosing during outpatient treatment.
- Qualitative urine drug screening (by on-site use of "dipsticks") will be done every day in an in-clinic setting to monitor for contraband and every day in an outpatient setting to monitor for illicit drug use.
- Daily clinic visits and completion of subject diary for outpatients.

Subjects not requiring extended lofexidine treatment can be discharged from the study on Day 7 after receipt of at least one dose of study drug and after all end-of-study procedures have been completed (see Section 15.3.4).

15.3.3 Days 8-14 (Outpatient Only)

Study medication is optional on Days 8-14 for subjects continuing to have withdrawal symptoms per the Principal Investigator's judgment. The assessments and procedures listed below will be performed daily (unless otherwise specified) (see Section 15.3.4 for assessments/procedures required for discontinuation from the study).

- Daily clinic visits and completion of subject diary.
- SOWS-Gossop before dosing.

- COWS before dosing.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses.
- Vital Signs, including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able) at least once daily before dosing and 3.5 hours after dosing on Days 8-13 and once before any dose on Day 14. Note that if subjects 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. Subjects will also be provided a diary (Appendix 3) to record the measurements along with any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) the subject may have experienced.
- AE assessment.
- Clinical laboratory tests as clinically warranted.
- Complete physical examination as clinically warranted.
- C-SSRS (Since Last Visit Version; Appendix 6) before dosing.
- A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.
- Qualitative urine drug screening (by on-site use of "dipsticks") will be done every day in an outpatient setting to monitor for illicit drug use.

15.3.4 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.

- SOWS-Gossop.
- COWS.
- Completion of pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator (after completion of the SOWS-Gossop and COWS).
- Concomitant medication assessment.
- Pill count and review of subject diary (Appendix 3) to measure compliance with previous day's doses if not already performed.

- Vitals signs including blood pressure and pulse at rest (sitting [or recumbent if necessary because of an AE]) and standing (if able); respiration; and temperature.
- AE assessment.
- 12-lead ECGs (in duplicate) before the subject's last dose and after dosing.
- Clinical laboratory tests.
- Complete physical examination (including body weight).
- Pregnancy test.
- Urine drug screen.
- C-SSRS (Since Last Visit version; Appendix 6).

15.3.5 30-Day Telephone Follow-up Contact

A follow-up telephone contact will be attempted 30 days after the subject's last dose and will include 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). Repeated attempts will be made to reach the subject (defined as a minimum of 3 telephone calls, followed by sending a letter). If repeated attempts are unsuccessful, this will be recorded in the subject's source document and eCRF.

15.4 Effectiveness Assessment Methods

15.4.1 Assessment of Completion of Pre-Defined Withdrawal Treatment Goal

The Principal Investigator will indicate if the subject has completed his/her pre-defined withdrawal treatment goal (Appendix 4) on Days 1-7 by responding to the following question: "Has the subject's withdrawal treatment goal been reached?" Note that, per protocol, subjects are required to continue on their dose of lofexidine through Day 7 even though the subject may have completed his/her withdrawal treatment goal before Day 7. This same assessment will be made at each visit during the 7 days of optional outpatient treatment (Days 8-14). This assessment should be completed after the SOWS-Gossop and COWS assessments.

15.4.2 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)

The SOWS-Gossop [16] will be completed by the subject at baseline, once daily at 3.5 hours (± 10 minutes) after the first dose of study medication during in-clinic treatment and once daily before dosing during outpatient treatment. 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 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.

15.4.3 Clinical Opiate Withdrawal Scale (COWS)

The COWS [17] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal, and will be completed after the SOWS-Gossop and before the assessment of completion of pre-defined withdrawal treatment goal. It will be completed during screening, at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during in-clinic treatment, and once daily before dosing during outpatient treatment. The COWS is a clinician-administered instrument that rates 11 common opioid withdrawal signs and symptoms (Appendix 2). 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).

15.5 Safety Assessment Methods

15.5.1 Adverse Events

The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.

Adverse events will be assessed and recorded around the same time each day by study staff during in-clinic lofexidine treatment. If an AE requires medical attention, it should be reported to a study physician immediately. A study physician or assigned staff 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 or assigned staff must review with the subject and assess any AEs unresolved from the previous day. For each daily AE assessment, details will be recorded in the subject's

source document and AE eCRF, according to the procedures described in Section 16.7, the type of AE and whether it is serious (SAE) or non-serious, severity of each AE, and the relationship to the study agent. These categories are asking for the Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.5.1.1). 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 until the event is resolved to the satisfaction of the Principal Investigator and Sponsor's Medical Monitor. If the AE is unrelated, the subject will be followed 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 outpatient treatment, subjects will be queried about AEs at each daily clinic visit. All subjects will be instructed to contact the study physician or assigned staff if he or she experiences any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until further instructed.

All reported AEs will be recorded as described above.

15.5.1.1 Withdrawal-Related Adverse Events

The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal. Individual items reported on the efficacy scales (i.e., SOWS-Gossop, COWS) do not automatically qualify as a withdrawal-related AE unless the subject specifically reports them in response to the 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 each specific symptom can be recorded on the AE eCRF. In general, an AE/SAE should not be marked as withdrawal related AND related to study medication.

15.5.2 Vital Signs

Vital signs (sitting/standing systolic and diastolic blood pressure, pulse) will be measured at screening for all subjects.

During in-clinic treatment (Days 1-3 mandatory; Days 4-7 if subject receives all lofexidine doses in the clinic), resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) systolic and diastolic blood pressure and pulse will be measured within 30 minutes before every dose and 3.5 hours (±15 minutes) after administration of study medication at 8 AM, 1 PM, and 6 PM; oral temperature and respiration before 8 AM dose only.

During outpatient treatment (Days 4-14) resting (sitting [or recumbent if necessary because of an AE]) and standing (if able) 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 4-13 and once before any dose on Day 14. If the subject cannot stay in the clinic for measurement of the 3.5-hour post-dose vital signs required on Days 4-13, they will be given a portable digital blood pressure machine for measurement of their vital signs at this required time point and the values will be recorded in a subject diary (Appendix 3).

For the orthostatic vital sign (i.e., blood pressure and pulse) readings, subjects will remain at rest for 3 minutes before a vital sign reading, and then stand for 3 minutes before a second vital sign reading is taken. If a subject demonstrates potentially clinically significant vital signs (whether pre- or post-dose), as per the pre-defined criteria detailed in Sections 13.2.2 and 13.2.3, the event should be recorded on the subject's 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 study physician.

Additionally, when the subject is experiencing blood pressure- or pulse-related symptoms (e.g., lightheaded, dizziness, palpitations), these should be recorded on the subject's 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 pre-defined criteria detailed in Sections 13.2.2 and 13.2.3.

15.5.3 12-Lead Electrocardiograms

Using the 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first dose on Day 1 at 8 AM and 3.5 hours (±15 minutes) after dosing; before the subject's last dose and after dosing; or, if applicable, at discontinuation from the study. 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 a 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);

- QTc (Fridericia) — QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject discontinuation 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 Principal Investigator and if 2 of the 3 QTcF intervals exceed the gender-specific cut-off, then the subject should be judged a screen failure.

  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 Principal 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 discontinued 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 3) will be performed for all subjects at screening, as needed at the study physician's discretion throughout the study, 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 3. Hematology, Chemistry, and Urinalysis Tests

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

A qualitative urine drug screen (UDS) will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and every day during in-clinic lofexidine treatment and outpatient lofexidine treatment 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 "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening for all subjects, at Baseline (Day 1 before dosing), 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 fingerprick blood sample will be collected concurrently with each scheduled ECG during the study.

A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.

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 will be performed at screening for all subjects.

An update of the Physical Exam is required at Baseline (before dosing on Day 1) and then a complete physical examination should be performed 3 to 4 hours after the first dose on Day 1, as clinically warranted throughout the study, 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) during in-clinic lofexidine treatment, once daily before dosing during outpatient treatment or, if applicable, at discontinuation from the study. The Baseline version of the C-SSRS (Appendix 5) 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 6) 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 documented on the Prior Medication eCRF. The reported medications will be reviewed and approved by the Principal Investigator/study physician/assigned staff for entry into the study.

All opioids of abuse the subject has used will also be recorded at the screening visit.

15.6.2 Concomitant Medication Administration

Concomitant medication administration will be recorded daily. All concomitant medications will be recorded in source and in the subject's Concomitant Medication eCRF along with dose, dates of administration, and reason for use.

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 Investigational Site File binder will be provided to all investigational sites with additional instruction as well as a place to store regulatory and study documents. The monitoring of the sites participating in the trial (either remote or on site) will be executed according to GCP guidelines and with a focused data review approach (Risk Based Monitoring [RBM]). 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 Principal Investigator, site coordinator, and Sponsor's Clinical Project Manager.

16.2 FDA Forms 1572 and Financial Disclosure

The Principal 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 Principal Investigator and sub-investigators will also sign Financial Disclosure forms before initiating this study.

16.3 Institutional Review Board Approval

Before initiating the study, the Principal Investigator will obtain written IRB approval to conduct the study. Study medication will not 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 Principal 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 approved by the Sponsor before submission to the site's IRB. 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 Principal 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. 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 original 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 original 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 Medical Monitor

The Sponsor's (USWM) Medical Monitors,
will be responsible for attempting to establish concurrence with the Principal 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 an SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 7). 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 Principal Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications) and can be reached at
and/or

16.6.2 Clinical Monitors

All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, eCRFs and corresponding source documents as noted in the monitoring plan for each subject. Using an RBM approach, monitoring may also occur remotely. Monitoring both on site and via an RBM approach 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 defined data outlined in the monitoring plan 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.

In lieu of an investigator meeting, USWM will host a web-based initiation meeting with study sites providing at a minimum protocol training, GCP training, CRF completion training, and a review of monitoring expectations. For sites that did not participate in study USWM-LX1-3003-1, monitors will additionally conduct a site initiation visit before the start of the study. 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.

Periodic monitoring visits by USWM will be scheduled at appropriate intervals. 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 Principal Investigator or sub-investigators according to the specific instructions detailed in this section of the protocol and Appendix 7. The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.

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 Principal 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 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. Opioid withdrawal symptoms experienced by subjects during screening will be recorded on the Medical History eCRF and such symptoms will be recorded as AEs during the study even if they do not change or worsen. Stable chronic conditions, such as arthritis, which are present before entry into the clinical trial and do not worsen are not considered AEs.

For each daily AE assessment, details will be recorded in the subject's source document and AE eCRF regarding 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal. In general, an AE should not be marked as withdrawal related AND related to study medication. Also, if the sign or symptom is evaluated as part of the COWS assessment, it should generally be considered as withdrawal related and so marked if it is also reported as an AE.

A study physician or assigned staff must review the AE eCRF for any events 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 Principal Investigator or physician designee 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 serious adverse event

(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; *(NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject, in the view of the Investigator, was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)*
- 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 7. 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).

16.9 Pregnancy

Although pregnancy is not considered an AE, it is the responsibility of the Principal Investigator or his/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 taking study medication. All subjects who become pregnant must be withdrawn from the study and stop taking study medication. The site must make appropriate effort (i.e., monthly calls) to follow the subject until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor. If the subject cannot be reached after 3 telephone attempts, a

certified letter should be sent. Documentation of follow-up will be recorded in the source documents.

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 the study population overall as well as by gender.

Detailed methodology for the summary and statistical analyses of the data collected is this study will be documented in a Statistical Analysis Plan (SAP), which will be prepared and finalized before completion of the study.

17.2 Assessment of Effectiveness

Effectiveness measures will be summarized for the following subject cohorts:

- All exposed subjects;
- Subjects undergoing abrupt and total withdrawal;
- Subjects undergoing buprenorphine-assisted withdrawal;
- Subjects transitioning to naltrexone maintenance;
- Subjects transitioning to buprenorphine maintenance;
- Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and
- Any other identifiable cohorts not otherwise noted.

Descriptive statistics will be provided for:

- Demographics and baseline characteristics;
- SOWS-Gossop;
- COWS numerical score;
- COWS severity category (i.e., mild, moderate, moderately severe, severe);
- Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the Principal Investigator;
- Distribution of number of days required to complete withdrawal treatment goal by category;

- Concomitant medications; and
- Evaluation of subject treatment status 30 days after last dose.

17.3 Assessment of Safety

Safety summaries will be provided for subjects who received lofexidine; any safety information on subjects who provide informed consent but do not receive lofexidine will be included in listings.

Safety measures will be summarized for the following subject cohorts:

- All exposed subjects;
- Subjects undergoing abrupt and total withdrawal;
- Subjects undergoing buprenorphine-assisted withdrawal;
- Subjects transitioning to naltrexone maintenance;
- Subjects transitioning to buprenorphine maintenance;
- Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and
- Any other identifiable cohorts not otherwise noted.

Descriptive statistics will be provided for:

- AEs;
- AEs of special interest, including orthostatic hypotension, orthostatic bradycardia, and syncope;
- Vital signs;
- ECGs;
- Clinical laboratory tests; and
- C-SSRS.

18 DATA MANAGEMENT AND CASE REPORT FORMS (CRFS)

Data management activities, construction and accuracy of the study database, and statistical analytical support will be coordinated through USWM.

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). CRFs are to be completed on an ongoing basis during the study within 2 to 3 business days of a visit. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the Investigational Site File binder.

The Principal Investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The Principal 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's representatives, the central IRB or 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 Sponsor or designee. 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. Feedback regarding CRF issues will be provided to all sites.

The Principal Investigators agree to routine data audits by the staff of USWM or their designee. USWM monitors will periodically visit each site to assure that data entered in the EDC system are in agreement with source documents at the sites per the monitoring plan.

18.3 Data Analysis

When the study is completed, all data have been entered into the clinical database, and the final database has been checked by Quality Assurance and then locked, statistical analysis of the data will be performed by USWM'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, USWM or designee will also prepare summary reports of the data so that progress of the study can be monitored.

18.4 Study Documentation and Records Retention

Study documentation includes all eCRFs, data correction forms, workbooks, source documents (paper or electronic), 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 an eCRF should maintain patient 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 Principal Investigator and IRB.

By participating in this protocol, the Principal Investigator affirms to USWM that information furnished to the Principal 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, CRFs (electronic or paper), reports, and other records will be coded using subject number and initials. Only research staff and USWM staff or their designee 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 8).

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 DISSEMINATION AND PUBLICATION OF STUDY RESULTS

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

20 PROTOCOL ADHERENCE AND AMENDMENTS

The Principal 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 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 Sponsor or designee 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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23 PROTOCOL AMENDMENT DETAILS

Table 4 lists changes made in Amendment No. 01 to the protocol for Study USWM-LX1-3003-2.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Pages 1-53 --	Pages 1-113 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop)	Global change to add SOWS-Gossop as an assessment, consistent with other lofexidine clinical trials.
Pages 1-53 --	Pages 1-113 Columbia Suicide Severity Rating Scale (C-SSRS)	Global change to add C-SSRS as a safety assessment, consistent with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.
Pages 1-53 Site Investigator	Pages 1-113 Principal ~~Site~~ Investigator	Global change for protocol clarity.
Pages 1-53 Attending physician	Pages 1-113 Study~~attending~~ physician/ staff	Global change to improve clarity of the protocol.
Pages 1-53 Case Report Form (CRF)	Pages 1-113 ~~Case Report Form (CRF)~~	Global change to remove reference to CRF as electronic CRFs will be used in the study.
Pages 1-53 CRO	Pages 1-113 ~~CRO~~	Global change to remove reference to CRO.
Pages 1-53 Number of subjects 200-400	Pages 1-113 Number of subjects 250-500~~200-400~~	Global change based on the projected number of subjects completing 7 days of lofexidine treatment in the companion study (USWM-LX1-3003-1) and earlier lofexidine clinical programs expected to be appropriate for the FDA's safety database requirements.
Pages 1-53 10 study sites	Pages 1-113 Approximately 20~~10~~ study sites	Global change to allow additional sites to account for the potentially higher enrollment requirements and target study completion timelines
Pages 1-53 Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)	Pages 1-113 Mini International Neuropsychiatric Interview (M.I.N.I.)~~Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID)~~	Global change for consistency with eligibility assessment in the companion study, USWM-LX1-3003-1.
Pages 1-53 Assessments at clinic visits every other day	Pages 1-113 Daily assessments including while inpatient and at daily clinic visits during outpatient treatment~~Clinic visits every other day~~	Global change to more fully monitor the safety of lofexidine.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Pages 1-53 --	Pages 1-113 Subject Diary	Global change to allow collection of vital signs data in an outpatient setting.
Pages 1-53	Pages 1-113	Minor editorial changes made for consistency and to improve clarity of the protocol.
Title Page, Page 1 --	Title Page, Page 1 Amendment No. 01 Date: January 22, 2015	Administrative change.
Title Page, Page 1 Contract Research Organization TBD	Title Page, Page 1 ~~Contract Research Organization TBD~~	Administrative change.
Header, Pages 2-53 Protocol No. USWM-LX1-3003-2 February 3, 2012	Header, Pages 2-113 Protocol No. . USWM-LX1-3003-2, Amendment No. 01, January 22, 2015	Administrative change.
--	Section 2, Pages 3-5 This section provides a summary of major changes made to the protocol for Study USWM-LX1-3003-2 in this current amendment (Amendment No. 01). Section 23 provides a detailed accounting of all changes made in this amendment. [See protocol for summary/rationale of major changes.]	Administrative change.
Section 2, Page 3, Objective The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.	Section 3, Page 6, Objective To primary objective of this study is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness is also of interest.~~The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.~~	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 3, Study Design --	Section 3, Page 6, Study Design [Section extensively revised. See protocol for revisions.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 2, Page 3, Inclusion Criteria 1. 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).	Section 3, Page 6, Inclusion Criteria 1~~7~~. Be able to verbalize understanding of the consent form, able to provide written informed consent, and 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).~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 2, Page 3, Inclusion Criteria 3. Be seeking treatment for partial or total withdrawal from current opioid. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include abrupt and total withdrawal, agonist-assisted withdrawal (with the exception of methadone), transition to naltrexone or from buprenorphine, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).	Section 3, Page 7, Inclusion Criteria 4~~3~~. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal ~~(with the exception of methadone),~~; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or ~~from~~ buprenorphine maintenance.~~, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).~~	Revised to allow subjects with clinical treatment goals for full or partial withdrawal from methadone or buprenorphine.
Section 2, Page 3, Inclusion Criteria 4. Urine toxicology screen positive for opioids (including buprenorphine).	Section 3, Page 7, Inclusion Criteria 5~~4~~. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can includ~~ing~~ methadone and buprenorphine) at Screening.	Revised for consistency with changes made in Inclusion Criterion #3.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 4, Inclusion Criteria 6. Have completed the Clinical Opiate Withdrawal Scale (COWS) during the Screening period.	Section 3, Page 7, Inclusion Criteria ~~6. Have completed the Clinical Opiate Withdrawal Scale (COWS) during the Screening period.~~	Administrative change.
Section 2, Page 4, Exclusion Criteria 2. Be currently taking methadone, by self report or positive urine drug screen.	Section 3, Page 7, Exclusion Criteria ~~2. Be currently taking methadone, by self report or positive urine drug screen.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 2, Page 4, Exclusion Criteria 3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.	Section 3, Page 7, Exclusion Criteria ~~3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 2, Page 4, Exclusion Criteria 4. Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.	Section 3, Pages 7-8, Exclusion Criteria 24. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation). • Have active self-reported acquired immune deficiency syndrome (AIDS) or self-reported human immunodeficiency virus (HIV) positive status and taking	Revised for clarity and consistency with companion study, USWM-LX1-3003-1.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
	retroviral medications currently or within the past 4 weeks. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). ~~Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.~~	
Section 2, Page 4, Exclusion Criteria 6. Have participated in an investigational drug study within the past 3 months.	Section 3, Page 8, Exclusion Criteria 4. Have participated in an investigational drug study within the past 30 days~~3 months~~.	Revised for consistency with other protocols.
--	Section 3, Page 8, Exclusion Criteria 5. Have history of lofexidine exposure in a prior clinical trial or otherwise.	Administrative change.
Section 2, Page 5, Exclusion Criteria 7. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTF 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.	Section 3, Page 8, Exclusion Criteria 6. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse~~heart rate~~ less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; and • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.	Administrative clarification/update.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 3, Page 9, Exclusion Criteria 7. To avoid drug-drug interactions, subjects requiring the following will be excluded: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.	Added to improve clarity of the protocol.
Section 2, Page 5 N Total enrollment will depend on subject drop-out rates. Approximately 200 to 400 subjects will need to be enrolled and enrollment will remain open until a minimum total of 300 subjects (among this protocol and companion Protocol USWM LX1 3003 1) have been treated with lofexidine for a minimum of 7 days.	Section 3, Page 9 N Total enrollment will depend on subject drop-out rates. Approximately 250~~200~~ to 500~~400~~ subjects: ~~will need to be enrolled and~~ enrollment will continue~~remain open~~ until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) ~~(among this protocol and companion Protocol USWM LX1 3003 1)~~ have been treated with clinically relevant doses of lofexidine for a minimum of 7 days. A target of at least 50 subjects each treated for clinical scenarios involving methadone or buprenorphine treatment will be enrolled (i.e., a total of 50 subjects receiving full or partial dose reduction from methadone, methadone-assisted withdrawal, and other methadone treatment scenarios and a total of 50 subjects receiving full or partial dose reduction from buprenorphine, transition to buprenorphine maintenance, and other buprenorphine treatment scenarios).	Administrative update.
--	Section 3, Page 9, Safety Endpoints • Occurrence, seriousness, severity, and causality assessment of adverse events. • Occurrence of adverse events of special interest (i.e., orthostatic hypotension, orthostatic bradycardia, syncope). • Occurrence of adverse events not related to opioid withdrawal. • Descriptive evaluation of vital signs (actual and change from baseline) for each time point.	Added to align with study objectives.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	• Descriptive evaluation of the three C-SSRS subscales (suicidal ideation, suicidal behavior, and intensity of suicidal ideation). • Shifts from baseline in physical examination findings will be summarized. • Descriptive evaluation of clinical laboratory tests of hematology, chemistry, and urinalysis (actual and change from baseline). • Descriptive evaluation of ECG (actual and change from baseline).	
Section 2, Page 5, Endpoints • Number/proportion of subjects successfully completing planned detoxification/transition as assessed by the Site Investigator. • Descriptive evaluation of COWS numerical score, COWS severity score (i.e., mild, moderate, moderately severe, severe), duration of exposure; distribution of number of days required to complete detoxification, average daily dose of lofexidine, concomitant medications, and linkage to long term care (through subject treatment status report at the 30 day post dischargefollow-up telephone contact).	Section 3, Page 9, Effectiveness Endpoints • Number/proportion of subjects successfully completing their pre-defined withdrawal treatment goal (i.e., planned detoxification/transition) as assessed by the Principal ~~Site~~ Investigator. • Distribution of number of days required to complete withdrawal treatment goal by category. • Descriptive evaluation of SOWS-Gossop. • Descriptive evaluation of COWS numerical score and ~~COWS~~ severity score (i.e., mild, moderate, moderately severe, severe) • Concomitant medication analysis. • ~~duration of exposure; distribution of number of days required to complete treatment goal by categorydetoxification, average daily dose of lofexidine, concomitant medications, and linkage to long term care (through~~Evaluation of subject treatment status ~~report at the~~ 30 days after last dose.~~post discharge follow-up telephone contact).~~	Revised to align with study objectives and improve clarity of the protocol.
Section 2, Page 5, Duration 21 days (maximum duration per subject, including screening)	Section 3, Page 10, Duration 23~~21~~ days (maximum duration per subject, including screening)	Administrative change.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 2, Page 5, Visits All subjects will undergo screening up to 7 days before study admission and will have clinic visits at least every other day for up to 14 days.	Section 3, Page 10, Visits All subjects will undergo screening up to 9~~7~~ days before study admission ~~and will have clinic visits at least every other day for up to 14 days~~. Days 1-3 • In-clinic setting: Subjects may be admitted to clinic on Day -1 Days 4-7 • In-clinic setting OR daily visits for 4 days if outpatient Days 8-14 • Daily outpatient visits for up 7 days Day30 • Telephone follow-up contact	Revised to require mandatory inpatient treatment for 3 days to allow more frequent safety monitoring during anticipated peak withdrawal and initiation of lofexidine therapy. Also, option for inpatient/ outpatient treatment on Days 4-7 enables assessment, as clinically appropriate at the discretion of the Investigator, in a more flexible, real-world setting.
Section 2, Page 5, Effectiveness Assessments	Section 3, Pages 10-11, Safety Assessments [Section extensively revised. See protocol for revisions.]	Revised for consistency with study design changes.
Section 2, Page 6, Safety Assessments	Section 3, Page 11, Effectiveness Assessments [Section extensively revised. See protocol for revisions.]	Revised to align with study objectives and improve clarity of the protocol.
Section 3, Pages 7-10 Table of Contents, Appendices --	Section 4, Pages 12-15 TOC updated to add the following appendices: Appendix 1 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop) Appendix 2 Clinical Opiate Withdrawal Scale (COWS) Appendix 3 Subject Diary Appendix 4 Short-term Withdrawal Treatment Goal Appendix 5 Columbia Suicide Severity Rating Scale (C-SSRS) Baseline Version Appendix 6 Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version	Administrative change.
Section 4, Pages 11-12 --	Section 5, Pages 16-17 [Abbreviation list updated.]	Administrative change.
Section 5.1, Pages 12-13 --	Section 6.1, Page 18 [Section extensively revised. See protocol for revisions.]	Administrative update.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 5.3, Page 13, First Paragraph USWM has conducted 3 clinical trials (open-label tolerability and dose-response study and 2 randomized, double-blind, placebo-controlled efficacy/safety studies) in support of the use of lofexidine in acute withdrawal from short-acting opioids.	Section 6.3, Page 19, First Paragraph USWM has completed~~conducted~~ 3 clinical trials (open-label tolerability and dose-response study and 2 randomized, double-blind, placebo-controlled efficacy/safety studies) in support of the use of lofexidine in acute withdrawal from short-acting opioids. In addition, USWM is currently conducting a randomized, double-blind, placebo-controlled efficacy/safety study (USWM-LX1-3003-1) of 2 doses of lofexidine (2.4 and 3.2 mg/day).	Administrative update.
Section 5.4, Page 14, First Paragraph, 1st & 2nd Sentences A total of 2,032 subjects from clinical investigations of lofexidine (both USWM and externally sponsored) have been exposed to doses ranging from 0.1 mg to 4.0 mg total daily doses in a variety of dosing schedules from single doses to four times daily (QID) treatment over durations ranging from 1 day to 52 months (in the case of one antihypertension study). In addition, an estimated 214,000 documented BritLofex™ prescriptions have been sold in the UK where the standard dosing regimen prescribed is 2.4 mg total daily dose (0.8 mg three times daily or 0.6 mg QID) introduced on a dose escalation and maintained typically for 7 to 10 days.	Section 6.4, Page 20, First Paragraph, 1st & 2nd Sentences A total of 2,044~~2,032~~ subjects from clinical investigations of lofexidine (both USWM and externally sponsored) have been exposed to doses ranging from 0.1 mg to 4.0 mg total daily doses in a variety of dosing schedules from single doses to four times daily (QID) treatment over durations ranging from 1 day to 52 months (in the case of one antihypertension study).In addition, over 266,000 ~~an estimated 214,000 documented~~ BritLofex™ prescriptions have been sold in the UK (since product launch in 1992) where the standard dosing regimen prescribed is 2.4 mg total daily dose (0.8 mg three times daily or 0.6 mg QID) introduced on a dose escalation and maintained typically for 7 to 10 days.	Administrative update.
Section 5.5, Page 15 --	Section 6.5, Page 21 [Section extensively revised. See protocol for revisions.]	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).
Section 5.6, Page 16 --	Section 6.6, Page 21 [Section extensively revised. See protocol for revisions.]	Revised to add rationale for including SOWS-Gossop as an outcome measure.
Section 6, Page 16 The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.	Section 7, Page 22 The primary objective is to continue to investigate the safety of lofexidine when administered for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day) to alleviate symptoms of acute withdrawal from opioids in a variety of clinical scenarios in both in-clinic and outpatient settings. The effectiveness of lofexidine is also of interest.~~The primary objective is to investigate whether variable dose lofexidine treatment can be safely and effectively used along with usual standard of care in inpatient/outpatient~~	Revised based on study design change from variable dosing to standardized dosing (3.2 or 2.4 mg/day for at least 7 days).

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	~~detoxification from short-acting opioids in a variety of clinical situations in which the subject is experiencing opioid withdrawal, excluding only co-administration of methadone.~~	
Section 9.1, Pages 16-17 --	Section 10.1, Pages 22-23 [Section extensively revised. See protocol for revisions.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 9.2, Page 17 The total enrollment in this study will depend on subject drop-out rates in this protocol and in companion study, Protocol USWM-LX1-3003-1. It is estimated that approximately 200 to 400 subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation. Enrollment will remain open until a minimum of 300 subjects (among this protocol and companion Protocol USWM-LX1-3003-1) complete a minimum of 7 days of treatment with lofexidine.	Section 10.2, Page 23 The total enrollment in this study will depend on subject drop-out rates in this protocol. Enrollment will continue until a minimum total of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.~~ and in companion study, Protocol USWM-LX1-3003-1.~~ It is estimated that approximately 250~~200~~ to 500~~400~~ subjects will be enrolled in this open-label study in order to accrue a sufficiently large safety database for evaluation.~~Enrollment will remain open until a minimum of 300 subjects (among this protocol and companion Protocol USWM-LX1-3003-1) complete a minimum of 7 days of treatment with lofexidine.~~	Administrative update.
Section 9.3, Page 17 This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be **21 days, including the Screening period, which can last up to 7 days, followed by up to 14 days of flexible dose treatment with lofexidine.** The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects, among this protocol and companion Protocol USWM-LX1-3003-1, completing at least 7 days of treatment with lofexidine. Enrollment is anticipated to take 5 to 10 months to achieve, with the total clinical duration of	Section 10.3, Page 23 This study will be initiated after completion of the companion study, USWM-LX1-3003-1. The maximum duration of participation for each subject in USWM-LX1-3003-2 will be 23~~21~~ **days, including the Screening period, which can last up to 9~~7~~ days, followed by up to 14 days of ~~flexible dose~~ treatment with lofexidine.** The study will be terminated when the database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.~~among this protocol~~	Revised for consistency with study design changes and to improve clarity of the protocol.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
USWM-LX1-3003-2 anticipated to be 8 to 12 months.	~~and companion Protocol USWM-LX1-3003-1, completing at least 7 days of treatment with lofexidine.~~ Enrollment is anticipated to take 4~~5~~ to 10 months to achieve, with the total clinical duration of USWM-LX1-3003-2 anticipated to be 8 to 12 months.	
--	Section 10.4, Pages 23-24 [Section added. See protocol.]	Added to improve clarity of the protocol.
Section 10.1, Page 17, First Paragraph, First 3 Sentences Any opioid-dependent subject about to undergo complete or partial withdrawal from short-acting opioids or on buprenorphine maintenance treatment will be eligible for the study. 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.	Section 11.1, Page 24, First Paragraph, First 3 Sentences Any opioid-dependent subject about to undergo complete or partial opioid withdrawal and could benefit for a minimum of a 7-day treatment with lofexidine ~~from short-acting opioids or on buprenorphine maintenance treatment~~ will be eligible for the study. 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, and a minimum of 50 subjects each on methadone or buprenorphine maintenance treatment.	Revised for consistency with study design changes.
Section 10.2.1, Page 19 7. 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).	Section 11.2.1, Page 24 1~~7~~. Be able to verbalize understanding of the consent form, able to provide written informed consent, and 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).~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.2.1, Page 18 3. Be seeking treatment for partial or total withdrawal from current opioid. This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include abrupt and total withdrawal, agonist-assisted withdrawal (with the exception of methadone), transition to naltrexone or from buprenorphine, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).	Section 11.2.1, Page 25 4~~3~~. Be seeking treatment for partial or total withdrawal from current opioid and expected, as determined by the Principal Investigator, to benefit from lofexidine treatment for at least 7 days at clinically relevant doses (3.2 or 2.4 mg/day). This can include a variety of clinical situations where opioid withdrawal illness is likely to occur. Examples include: • abrupt and total withdrawal (including from methadone and buprenorphine); • agonist-assisted total withdrawal ~~(with the exception of methadone),~~; • dose reduction of maintenance treatment (e.g., of methadone or buprenorphine); and • transition from an opioid agonist to naltrexone or ~~from~~ buprenorphine maintenance.~~, or decrease in dose (e.g., of chronic opioid medication for pain or of buprenorphine for opioid maintenance treatment).~~	Revised to allow subjects with clinical treatment goals for full or partial withdrawal from methadone or buprenorphine.
Section 10.2.1, Page 18 4. Urine toxicology screen positive for opioids (including buprenorphine).	Section 11.2.1, Page 25 5~~4~~. Urine toxicology screen positive for opioid(s) relevant to the subject's withdrawal treatment goal (can include~~ing~~ methadone and buprenorphine) at Screening.	Revised for consistency with changes made in Inclusion Criterion #3.
Section 10.2.1, Page 18 6. Have completed the COWS during the Screening period.	Section 11.2.1, Page 25 ~~6. Have completed the COWS during the Screening period.~~	Administrative change.
Section 10.2.2, Page 19 2. Be currently taking methadone, by self report or positive urine drug screen.	Section 11.2.2, Page 25 ~~2. Be currently taking methadone, by self report or positive urine drug screen.~~	Revised for consistency with changes made in Inclusion Criterion #3.
Section 10.2.2, Page 19 3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.	Section 11.2.2, Page 25 ~~3. Seeking methadone-assisted withdrawal. The use of lofexidine co administered with methadone is contraindicated.~~	Revised for consistency with changes made in Inclusion Criterion #3.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 10.2.2, Page 19 4. Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.	Section 11.2.2, Pages 25-26 24. Have a very serious medical illness not under control as detailed below. • Serious medical illness will be determined at Screening by: ➢ medical history; ➢ physical examination; ➢ 12-lead electrocardiogram (duplicate); ➢ clinical laboratory tests, including standard lab tests, an infectious disease panel for syphilis (excluded if positive), hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease), and hepatitis (positive results do not exclude a prospective subject from participation unless there is an indication of active liver disease); and ➢ tuberculin test (purified protein derivative [PPD]) and/or a chest x-ray (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, the subject will be excluded from participation). • Have active 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. • Have an unstable psychiatric condition (e.g., suicide risk, per Investigator judgment). ~~Have a very serious medical illness not under control[2]; have active self-reported acquired immune deficiency syndrome (AIDS); or have an unstable psychiatric condition (e.g., suicide risk). It is the intent of the study to approach as closely as feasible real-life conditions of treatment of opioid withdrawal.~~	Revised for clarity and consistency with companion study, USWM-LX1-3003-1.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.2.2, Page 19 6. Have participated in an investigational drug study within the past 3 months.	Section 11.2.2, Page 26 4~~6~~. Have participated in an investigational drug study within the past 30days~~3 months~~.	Revised for consistency with other protocols.
--	Section 11.2.2, Page 26 5. Have history of lofexidine exposure in a prior clinical trial or otherwise.	Administrative change.
Section 10.2.2, Page 19 7. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTF 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.	Section 11.2.2, Page 26 6. Abnormal cardiovascular exam at screening, including any of the following: • clinically significant abnormal electrocardiogram (ECG) (e.g., second or third degree heart block, uncontrolled arrhythmia, or QTcF intervals greater than 450 msec for males and greater than 470 msec for females); • resting pulse~~heart rate~~ less than 55 bpm or symptomatic bradycardia; • resting systolic blood pressure less than 95 mmHg or symptomatic hypotension; • resting diastolic blood pressure less than 65 mmHg; • resting blood pressure greater than 155/95 mmHg; or~~and~~ • prior history of myocardial infarction. Note: if a QTcF interval, blood pressure, or pulse value meets the above criteria, the value should be confirmed by repeating the measurement (twice, if necessary). If 2 of 3 values meet the above criteria, the subject will be excluded from participation.	Administrative clarification.
--	Section 11.2.2, Page 26 7. To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants, which may reduce the efficacy of imidazoline derivatives; and • beta-receptor blockers, to avoid the risk of excessive bradycardia.	Added to improve clarity of the protocol.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 10.3, Page 20, First Full Paragraph Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.	Section 11.3, Page 26, Second Paragraph ~~Subjects who fail screening for any reason cannot be rescreened for study participation at a later time.~~	Administrative change.
Section 11.2, Page 20, First Paragraph Lofexidine will be packaged and distributed through the pharmacy coordinating center (TBD). 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. 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.	Section 12.2, Page 27, First Paragraph Lofexidine will be packaged and distributed through the pharmacy coordinating center (Sharp~~TBD~~). Lofexidine tablets will be supplied in uniquely-identified 80-count bottles. During in-clinic treatment, lofexidine doses will be dispensed directly from the 80-count bottles, whereas for outpatient treatment, doses ~~which~~ will be dispensed by the study pharmacist as determined clinically appropriate by the ~~Site~~ Principal Investigator or designee 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.	Administrative change/update.
Section 11.4, Page 21	Section 12.4, Page 28 [Section extensively revised. See protocol for revisions.]	Administrative change.
Section 11.5, Page 21 The investigational agent, lofexidine, will be stored at room temperature in a secure location at the dispensing pharmacy.	Section 12.5, Page 28 ~~The investigational agent, lofexidine, will be stored at room temperature in a secure location at the dispensing pharmacy.~~The investigational agent, lofexidine, will be stored at 68-77°F in a secure location at the dispensing pharmacy or site. Temperature of the investigational agent will be maintained at 68-77°F during transport. Temperature of the investigational agent will be monitored during storage and transport. Temperature excursions will be reported to the Sponsor and the Sponsor will determine if the investigational agent is fit for use.	Administrative clarification.

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Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 12.6, Page 28, Second Sentence During outpatient treatment (Days 4-14), subjects are to record doses taken in his/her subject diary.	Added to improve clarity of the protocol.
Section 11.8, Pages 21-22 To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; • alcohol, sedatives, and anesthetics – 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. Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study.	Section 12.8, Page 29 Clonidine is specifically prohibited in this study. To avoid drug-drug interactions, lofexidine should not be administered concurrently with: • tricyclic antidepressants – may reduce the efficacy of imidazoline derivatives; and • ~~alcohol, sedatives, and anesthetics – 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. Lofexidine may enhance the effects of antihypertensive drug therapy and appropriate caution is warranted in subjects on such therapy. The Principal Investigator may need to lower the subject's antihypertensive dose during the study. Lofexidine should generally not be administered concurrently with alcohol, sedatives, and anesthetics as these may interact with lofexidine and enhance its central sedative effects.	Revised to improve clarity of the protocol.
Section 12.2.1, Page 22	Section 13.2.1, Pages 29-30 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require in-clinic treatment for 3 days, either in-clinic or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 12.2.2, Page 23	Section 13.2.2, Pages 30-31 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol.
Section 12.2.3, Page23	Section 13.2.3, Pages 31-32 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol.
Section 12.3, Page 23	Section 13.3, Pages 32-33 [Section extensively revised. See protocol for changes.]	Revised for consistency with study design changes.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
--	Section 13.4, Page 33 Section 13.4 Nicotine Replacement Therapy [Section added. See protocol.]	Added per study design change requiring in-clinic treatment for at least 3 days.
Section 13.1, Page 24, First Paragraph, First Sentence Interested subjects, who respond to recruitment materials, will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language.	Section 14.1, Page 33, First Paragraph, First Sentence Interested subjects, who respond to recruitment materials and are available to stay for the mandatory 3-day in-clinic treatment part of the study and available for participation in either an in-clinic or outpatient setting for 4 additional days (total commitment of 7 days), will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language.	Revised based on study design change requiring in-clinic treatment for at least 3 days.
Section 13.1, Page 24, Second Paragraph, First Sentence 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 15.4).	Section 14.1, Page 33, Second Paragraph, First Sentence If still interested after receiving an explanation of the study, a qualified investigative site staff member will review the study informed consent form with subjects, and subjects will be given an opportunity to review on their own, inquire about, and sign the ~~study~~ informed consent form (see Section 16.4).	Administrative clarification.
Section 13.1, Page 24, Second Paragraph, 4th & 5th Sentences Screening assessments must be completed within a 7-day time period, but can be completed as early as 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.	Section 14.1, Page 33, Second Paragraph, 4th & 5th Sentences Screening assessments must be completed within a 97-day time period, but can be completed as early as the first 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~~.	Administrative clarification.
Section 13.1, Page 24, Third Paragraph, Second Sentence Subjects must complete a consent quiz with 100% accuracy.	Section 14.1, Page 33, Third Paragraph, Second Sentence ~~Subjects must complete a consent quiz with 100% accuracy.~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 13.1, Page 24, Last Paragraph, Second Sentence 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.	Section 14.1, Pages 33-34, Last Paragraph, Second Sentence Subjects who are excluded, or who decline participation, may ~~not~~ be rescreened at a later time, although at least 30 days must occur between screenings~~and will be given referrals to other resources in the area~~.	Administrative change.

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Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 13.3, Pages 24-25	Section 14.3, Page 34 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require in-clinic treatment for 3 days, either in-clinic or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 13.4, Page 25	Section 14.4, Page 35 [Section extensively revised. See protocol for changes.]	Administrative update.
Section 13.5.1, Page 25, Numbered Items --	Section 14.5.1, Page 35, Numbered Items 2. Abnormal vital signs or ECG meeting criteria in Section 13.2.3.	Administrative clarification.
Section 13.5.1, Page 25, Numbered Items 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.	Section 14.5.1, Page 35, Numbered Items ~~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 (Days 1-3).	Administrative clarification.
Section 13.5.2, Page 26, Numbered Items 1. New onset of clinically significant abnormal ECG (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTc interval[5]). 2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest). 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.	Section 14.5.2, Page 36, Numbered Items 1. New onset of clinically significant abnormal ECG per Investigator judgment (e.g., second or third degree heart block or uncontrolled arrhythmia, prolonged QTcF interval[5]). 2. Persistent symptomatic hypotension (e.g., hypotension not responding to bed rest or fluids). 4. Persistent hypertension – resting 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~~ 2 of 3 readings are ≥185/110 mmHg (either systolic ≥185 mmHg or diastolic ≥110 mmHg) the subject must be discontinued. ~~terminated~~	Administrative clarification.
Section 13.5.3, Page 27 --	Section 14.5.3, Page 37, Last Bullet • the safety database is judged to be sufficient, i.e., a minimum of 300 subjects (across this protocol and earlier lofexidine clinical studies expected to meet FDA safety database requirements) have been treated with clinically relevant doses of lofexidine for a minimum of 7 days.	Administrative update.
Section 13.6, Page 27	Section 14.6, Page 37 [Section extensively revised. See protocol for changes.]	Revised to improve clarity of the protocol and to relax requirements for concomitant therapy.

Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14, Page28, Table 1	Section 15, Pages 39-40, Table 1 [Table 1 extensively revised. See protocol for changes.]	Revised for consistency with study design changes.
Section 14.1, Page 29	Section 15.1, Pages 41-42 [Section extensively revised. See protocol for changes.]	Administrative update and revised for consistency with study design changes.
--	Section 15.2, Page 42 Section 15.2 Baseline Assessments [Section added. See protocol for changes.]	Added based on study design changes.
Section 14.2, Pages 29-30	Section 15.3, Pages 42-46 Section extensively revised, including the following subheadings: 15.3.1 Days 1-3 (Mandatory In-clinic) 15.3.2 Days 4-7 (In-clinic/Outpatient) 15.3.3 Days 8-14 (Outpatient Only) 15.3.4 Study Discontinuation/End of Study 15.3.5 30-Day Telephone Follow-up Contact [See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
Section 14.3.1, Page 30 At each visit, the Site Investigator will indicate if the subject has completed the planned withdrawal or transition and can be discharged without further lofexidine treatment.	Section 15.4.1, Page 46 **15.4.1 Assessment of Completion of Pre-Defined Withdrawal Treatment Goal~~Planned Detoxification/Transition~~** ~~At each visit,~~ The ~~Site~~ Principal Investigator will indicate if the subject has completed~~the planned withdrawal or transition and can be discharged without further lofexidine treatment.~~his/her pre-defined withdrawal treatment goal (Appendix 4) on Days 1-7 by responding the following question: "Has the subject's withdrawal treatment goal been reached?" Note that, per protocol, subjects are required to continue on their dose of lofexidine through Day 7 even though the subject may have competed his/her withdrawal treatment goal before Day 7. This same assessment will be made at each visit during the 7 days of optional outpatient treatment (Days 8-14). This assessment should be completed after the SOWS-Gossop and COWS assessments.	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment.
--	Section 15.4.2, Pages 46-47 **15.4.2 Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop** [Section added. See protocol.]	Added as an assessment, consistent with other lofexidine clinical trials.

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Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14.3.2, Page 30, First Sentence The COWS will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal (at least every other day before dosing).	Section 15.4.3, Page 47, First and Second Sentences The COWS [17] will be used to assess the effectiveness of lofexidine in alleviation of opioid withdrawal~~(at least every other day before dosing)~~, and will be completed after the SOWS-Gossop and before the assessment of completion of pre-defined withdrawal treatment goal. It will be completed during screening, at baseline (before dosing on Day 1), once daily at 3.5 hours after the first dose of study medication during inpatient treatment, and once daily before dosing during outpatient treatment.	Administrative clarification.
Section 14.4.1, Page 31, First Paragraph --	Section 15.5.1, Page 47, First Paragraph The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.	Administrative clarification.
Section 14.4.1, Page 31, First Paragraph, First Sentence Subjects will be queried about adverse events at least every other day by study staff. If an AE requires medical attention, it should be reported to a study physician immediately.	Section 15.5.1, Page 47, Second Paragraph, First Sentence Adverse events will be assessed and recorded around the same time each day by study staff during in-clinic lofexidine treatment.~~Subjects will be queried about adverse events at least every other day by study staff~~.	Added based on study design change requiring in-clinic treatment.
Section 14.4.1, Page 31, First Paragraph, 5th and 6th Sentences After each AE assessment, the physician will record on the AE eCRF, according to the procedures described in Section 15.7, 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.	Section 15.5.1, Pages 47-48, Second Paragraph, 6th, 7th & 8th Sentences For~~After~~ each daily AE assessment, ~~the physician~~ details will be recorded in the subject's source document and ~~on the~~ 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE. The Principal Investigator or physician designee will also record, based on his/her best judgment, whether the AE is secondary to opioid withdrawal (see Section 15.5.1.1).	Administrative clarification.

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Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 14.4.1, Page 31, Third Paragraph 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.	Section 15.5.1, Page 48, Fourth and Fifth Paragraphs During outpatient treatment, subjects will be queried about AEs at each daily clinic visit. All subjects will be instructed to contact the study~~treating~~ physician or assigned staff if he or she experiences any symptoms of hypotension and/or bradycardia (see list in Section 13.2.2) ~~feels dizzy~~ (especially on standing from a sitting or lying position) and delay additional lofexidine dosing until further instructed~~ by the physician~~. All reported AEs will be recorded as described above.	Revised for consistency with study design changes.
--	Section 15.5.1.1, Page 48 **15.5.1.1 Withdrawal-Related Adverse Events** [Section added. See protocol.]	Revised for consistency with companion study USWM-LX1-3003-1.
Section 14.4.2, Pages 31-32	Section 15.5.2, Pages 48-49 [Section extensively revised. See protocol for changes.]	Revised based on study design change to not allow flexible dosing, require inpatient treatment for 3 days, either inpatient or outpatient treatment for 4 days, and allow optional 7 days of outpatient treatment. Also, potentially clinically significant vital signs were clarified to improve clarity of the protocol.
Section 14.4.3, Pages 32-33, First Paragraph 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first daily dose and 3.5 hours after the first daily dose on Days 1 and 14 or, if applicable, early discharge/termination from the study. 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 (TBD). A cardiologist on site will evaluate tracings if there is significant abnormality. The following intervals will be computed:	Section 15.5.3, Page 49, First Paragraph Using the 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 at 8 AM and 11:30 AM. Duplicate 12-lead ECGs will also be conducted before the first ~~daily~~ dose on Day 1 at 8 AM and 3.5 hours (± 15 minutes) after dosing; before subject's last dose and after dosing;~~the first daily dose on Days 1 and 14~~ or, if applicable, ~~early discharge/termination~~at discontinuation from the study. 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~~cardiologist~~ on site will evaluate tracings if there is a significant abnormality. The following intervals will be computed:	Administrative update and revised to improved clarity of the protocol.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.3, Pages 32-33, Bulleted List --	Section 15.5.3, Page 50, Bulleted List • QTc (Fridericia) QT interval corrected for heart rate using Fridericia's formula (QT/cube root of RR) (for safety monitoring/subject discontinuation purposes).	Added for consistency with companion study USWM-LX1-3003-1.
Section 14.4.3, Page 33, Last Paragraph Any time that 2 of the 3 QTc measurements exceed 500 msec, contact the Sponsor's Medical Safety Monitor, to discuss the subject and the AE/SAE determination.	Section 15.5.3, Page 50, Last Paragraph 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.	Administrative update to add as back up Medical Monitor.
Section 14.4.4.1, Page 33, First Paragraph Standard clinical laboratory safety evaluations (see Table 2) will be performed for all subjects at screening, as needed at the physician's discretion throughout the study, and on Day 14 or, if applicable, early discharge/termination from the study. For this multicenter study, a central laboratory will be identified by the Sponsor which 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).	Section 15.5.4.1, Page 50, First Paragraph Standard clinical laboratory safety evaluations (see Table 3) will be performed for all subjects at screening, as needed at the study physician's discretion throughout the study, and ~~on Day 14 or, if applicable, early discharge/termination~~ at discontinuation from the study. For this multicenter study, a central laboratory will be ~~identified by the Sponsor which~~ 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).	Administrative clarification/update.
Section 14.4.4.1, Page 34, Table 2	Section 15.5.4.1, Page 51, Table 3 [Table 3 updated. See protocol.]	Table 3 was updated for consistency with the laboratory tests routinely conducted by the central laboratory.
Section 14.4.4.2, Page 34, First Paragraph, Seventh Sentence A rapid plasma reagin (RPR) test for syphilis will be performed. If positive, a confirmatory test (FTA-ABS or MHA-TP) will be performed.	Section 15.5.4.2, Page 51, First Paragraph, Seventh Sentence ~~A rapid plasma reagin (RPR) test for s~~Syphilis antibody testing will be performed using an automated enzyme immunoassay (EIA). If the EIA is positive, a confirmatory rapid plasma reagin (RPR) test ~~(FTA-ABS or MHA-TP)~~ will be performed. If the RPR test is non-reactive, a confirmatory TPPA (treponema pallidum particle agglutination assay) will be performed.	Revised for consistency with tests used by the central laboratory.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.4.2, Page 34, Second Paragraph 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.	Section 15.5.4.2, Page 52, Second Paragraph If ~~either~~ the PPD with chest x-ray, chest x-ray, or ~~the confirmatory test for~~ 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.	Revised for consistency with tests used by the central laboratory.
Section 14.4.4.3, Page 35 Qualitative urine drug screening will be performed at screening for all subjects and at least every other day during lofexidine treatment. Urine will be sent to a central laboratory for qualitative analysis for drugs of abuse. The methodology will detect specific drugs or metabolites in the urine.	Section 15.5.4.3, Page 52 A q~~Q~~ualitative urine drug screen (UDS)~~ing~~ will be performed at screening and Baseline (Day 1 before dosing) for all subjects, and ~~at least~~ every ~~other~~ day during in-clinic lofexidine treatment and outpatient treatment 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.~~Urine will be sent to a central laboratory for qualitative analysis for drugs of abuse. The methodology will detect specific drugs or metabolites in the urine.~~	Revised to more fully monitor the safety of lofexidine.
Section 14.4.4.4, Page 35 A "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening for all subjects and on Day 14 or early completion/early termination for all female subjects regardless of their childbearing capacity. Sites may use any FDA-approved urine pregnancy test.	Section 15.5.4.4, Page 52 A "dip-stick" pregnancy test designed to measure human chorionic gonadotropin will be performed on the first day of screening~~for all subjects~~, at Baseline (Day 1 before dosing), and ~~on Day 14 or early completion/early termination~~ 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.~~Sites may use any FDA-approved urine pregnancy test.~~	Revised for consistency with companion study USWM-LX1-3003-1.
--	Section 15.5.4.5, Page 52 **15.5.4.5 Pharmacokinetic Sampling** A fingerprick blood sample will be collected concurrently with each scheduled ECG during the study. A fingerprick blood sample will be collected during outpatient treatment when the subject reports to the clinic each day (before next scheduled dose) for analysis of plasma lofexidine concentration to monitor compliance.	Added to enable QTc-concentration analyses as well as to monitor compliance during outpatient treatment.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 14.4.5, Page 35 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, as clinically warranted during lofexidine treatment, and on Day 14 or, if applicable, early discharge/termination from the study. Height should be recorded at screening only.	Section 15.5.5, Page 52 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 will~~should~~ be performed at screening for all subjects.~~, as clinically warranted during lofexidine treatment, and on Day 14 or, if applicable, early discharge/termination from the study.~~ An update of the Physical Exam is required at Baseline (before dosing on Day 1) and then a complete physical examination should be performed 3 to 4 hours after the first dose on Day 1, as clinically warranted throughout the study, and at discontinuation from the study. Height should be recorded at screening only.	Revised for consistency with study design changes.
--	Section 15.5.6, Pages 52-53 **15.5.6 Columbia Suicide Severity Rating Scale (C-SSRS)** [Section added. See protocol.]	Added for consistency with the current guidance to assess suicidality in all clinical studies involving central nervous system acting drugs.
Section 14.5.1, Page 35, Second Paragraph --	Section 15.6.1, Page 53, Second Paragraph All opioids of abuse the subject has used will also be recorded at the screening visit.	Administrative clarification.
Section 14.5.2, Page 35 Concomitant medication administration will be recorded at least every other day during the study. All concomitant medications should be recorded on the Concomitant Medication eCRF. The Site Investigator should treat the subject according to his/her usual standard of care for opioid withdrawal, with the exception that methadone is contraindicated for use in subjects taking lofexidine.	Section 15.6.2, Page 53 Concomitant medication administration will be recorded daily~~at least every other day during the study~~. All concomitant medications will~~should~~ be recorded in source and in the subject's Concomitant Medication eCRF along with dose, dates of administration, and reason for use.~~The Site Investigator should treat the subject according to his/her usual standard of care for opioid withdrawal, with the exception that methadone is contraindicated for use in subjects taking lofexidine.~~	Revised for consistency with changes made in other parts of the protocol.
Section 15.1, Pages 35-36, Second and Third Sentences 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	Section 16.1 Page 53, Second and Third Sentences An Investigator Site Binder~~Operations Manual~~ will be provided to all investigational sites with additional instruction as well as a place to store regulatory and study documents~~as a study quality assurance~~	Administrative update.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
guidelines.	~~tool~~. The monitoring of the sites participating in the trial (either remote or on site) will be executed according to GCP guidelines and with a focused data review approach (Risk Based Monitoring [RBM]).	
Section 15.4, Page 37, Second Paragraph, Fourth Sentence Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%.	Section 16.4, Page 54, Second Paragraph, Fourth Sentence ~~Evidence of subject's understanding will be demonstrated by written examination that the subject must pass at 100%.~~	Revised to remove consent quiz, as deemed not essential for an open-label safety study.
Section 15.6.1, Page 37 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 1). 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).	Section 16.6.1, Page 55 The Sponsor's (USWM) Medical Monitors, will be responsible for attempting to establish concurrence with the ~~Site~~ Principal 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 an~~the~~ SAE should be reported to the FDA in a 7- or 15-day expedited report or an annual report (Appendix 6~~1~~). 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~~ Principal Investigators and coordinators on any medical issues related to the study (e.g., admission criteria, concomitant medications) and can be reached at and/or	Administrative update to add as back up Medical Monitor.
Section 15.6.2, Page 37, First Paragraph All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, all CRFs (paper and electronic) 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.	Section 16.6.2, Page 55, First Paragraph All Investigators will allow the Sponsor or its representatives to periodically audit, at mutually convenient times during and after the study, ~~all~~ eCRFs ~~(paper and electronic)~~ and corresponding source documents as noted in the monitoring plan for each subject. Using an RBM approach, monitoring may also occur remotely. ~~These monitoring visits~~Monitoring both on site and via an RBM approach will provide an opportunity for evaluation of the progress of the study and to inform the Sponsor of potential problems.	Administrative update.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
Section 15.6.2, Page 38, Third Paragraph Monitors will conduct a site initiation visit before the start of the study. 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.	Section 16.6.2, Page 55, Third Paragraph In lieu of an investigator meeting, USWM will host a web-based initiation meeting with study sites providing at a minimum protocol training, GCP training, CRF completion training, and a review of monitoring expectations. For sites that did not participate in study USWM-LX1-3003-1, m~~M~~onitors will additionally conduct a site initiation visit before the start of the study. 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.	Administrative change.
Section 15.6.2, Page 38, Fourth Paragraph, First Sentence Routine monitoring visits by USWM 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.	Section 16.6.2, Page 55, Fourth Paragraph, First Sentence Periodic~~Routine~~ monitoring visits by USWM 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.~~	Administrative clarification.
Section 15.7, Page 38, First Paragraph, Last Sentence The occurrence of AEs will be assessed starting at the treatment phase of the protocol.	Section 16.7, Page 56, First Paragraph, 2nd, 3rd, & 4th Sentences The occurrence of AEs will be assessed starting at the treatment phase of the protocol (i.e., with the first dose of study drug). Any AE that occurs during screening will be recorded in the subject's Medical History eCRF. The occurrence of Serious Adverse Events (SAEs) will be assessed after signing of the informed consent form.	Administrative clarification.
Section 15.7, Page 38, Second Paragraph 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 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	Section 16.7, Page 56, Second Paragraph 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 Principal Investigator on physical examination, ~~or~~ laboratory evaluation, or C-SSRS (for example, score of 3 or more on the scale) will be considered an AE and will be recorded on the AE eCRF. A new illness, symptom, sign or clinically significant	Administrative clarification/update.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
as arthritis, which are present before clinical trial entry and do not worsen are not considered AEs.	clinical laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. Opioid withdrawal symptoms experienced by subjects during screening will be recorded on the Medical History eCRF and such symptoms will be recorded as AEs during the study even if they do not change or worsen. Stable chronic conditions, such as arthritis, which are present before entry into the clinical trial and do not worsen are not considered AEs.	
Section 15.7, Page 38, Third Paragraph, 1st & 2nd Sentences After each AE assessment, the physician will record 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.	Section 16.7, Page 56, Third Paragraph, 1st & 2nd Sentences For~~After~~ each daily AE assessment, ~~the physician~~ details will be recorded in the subject's source document and ~~on the~~AE eCRF regarding 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 Principal Investigator or physician designee's best judgment of the severity and relatedness of each AE.	Administrative clarification.
Section 15.9, Page 40 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.	Section 16.9, Page 57 Although pregnancy is not considered an AE, it is the responsibility of the Principal~~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 taking~~completing the~~ study medication. All subjects who become pregnant must be withdrawn from the study and stop taking study medication. ~~and must be followed to the completion/ termination of the pregnancy~~. The site must make appropriate effort (i.e., monthly calls) to follow the subject until completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor. If the subject cannot be reached after 3 telephone attempts, a certified letter should be sent. Documentation of follow-up will be recorded in the source documents.	Administrative update.
Section 16.2, Page 40, Fourth Bullet • Subjects completing final buprenorphine withdrawal;	Section 17.2, Page 58, Fourth Bullet ~~• Subjects completing final buprenorphine withdrawal;~~	Revised to improve clarity of the protocol.

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Location (Section and Page Number) and Previous Wording	**Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red**	**Rationale**
Section 16.2, Page 41, Bulleted Items Descriptive statistics will be provided for: • Demographics and baseline characteristics; • COWS numerical score; • COWS severity category (i.e., mild, moderate, moderately severe, severe); • Duration of exposure to lofexidine; • Number of subjects successfully completing planned detoxification/transition as assessed by the Site Investigator; • Distribution of number of days required to complete detoxification; • Average daily dose of lofexidine; • Concomitant medications; • Linkage to long-term care (through subject treatment status report at the 30-day post discharge follow-up telephone contact); and • Compliance in taking lofexidine (based on pill counts).	Section 17.2, Pages 58-59, Bulleted Items Descriptive statistics will be provided for: • Demographics and baseline characteristics; • SOWS-Gossop; • COWS numerical score; • COWS severity category (i.e., mild, moderate, moderately severe, severe); ~~• Duration of exposure to lofexidine;~~ • Number/proportion of subjects successfully completing the pre-defined withdrawal treatment goal (e.g., planned detoxification/transition) as assessed by the ~~Site~~ Principal Investigator; • Distribution of number of days required to complete withdrawal treatment goal by category~~detoxification~~; ~~• Average daily dose of lofexidine;~~ • Concomitant medications; and • ~~Linkage to long-term care (through~~Evaluation of subject treatment status~~report at the~~ 30 -days after last dose.~~post discharge follow-up telephone contact).; and~~ ~~• Compliance in taking lofexidine (based on pill counts).~~	Revised for consistency with study design changes.
Section 16.3, Page 41, Bulleted Items 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: • AEs; • Vital signs; • ECGs; and • Clinical laboratory tests.	Section 17.3, Page 59, Bulleted Items Safety measures will be summarized for the following subject cohorts: • All exposed subjects; • Subjects undergoing abrupt and total withdrawal; • Subjects undergoing buprenorphine-assisted withdrawal; • Subjects transitioning to naltrexone maintenance; • Subjects transitioning to buprenorphine maintenance; • Subjects undergoing partial withdrawal to lower dose (e.g., chronic opioid medication for pain); and • Any other identifiable cohorts not otherwise noted. ~~• All treated subjects;~~ ~~• Treated subjects without urinary evidence of illicit drug use; and~~	Revised for consistency with study design changes.

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Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
	~~• 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: • AEs; • AEs of special interest, including orthostatic hypotension, orthostatic bradycardia, and syncope; • Vital signs; • ECGs; ~~and~~ • Clinical laboratory tests; and • C-SSRS.	
Section 17, Page 42 Data management activities and statistical analytical support will be coordinated through the CRO (TBD). The CRO will be responsible for the construction and accuracy of the study database.	Section 18, Page 59 Data management activities, construction and accuracy of the study database, and statistical analytical support will be coordinated through USWM.~~the CRO (TBD). The CRO will be responsible for the construction and accuracy of the study database.~~	Administrative change.
Section 17.1, Page 42, First Paragraph Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs), except for the COWS assessment, which is a validated paper instrument and thus will be collected on paper, scanned, and appended to the subject's eCRF for entry into the database. The eCRFs and paper CRFs 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.	Section 18.1, Pages 59-60, First Paragraph Data will be collected at the study sites on source documents, which will be entered at the site into electronic CRFs (eCRFs).~~, except for the COWS assessment, which is a validated paper instrument and thus will be collected on paper, scanned, and appended to the subject's eCRF for entry into the database.The eCRFs and paper CRFs will be supplied by the CRO.~~ CRFs are to be completed on an ongoing basis during the study within 2 to 3 business days of a visit. The medical chart and the source documents are the source of verification of data. CRFs should be completed according to the instructions in the Investigational Site File binder~~study operations manual~~.	Administrative change.
Section 17.1, Page 42, Third Paragraph Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor representatives, and the site's IRB.	Section 18.1, Page 60, Third Paragraph Data generated by this study must be available for inspection by representatives of the US FDA, the Sponsor (USWM), the Sponsor's representatives, the central IRB or~~and~~ the site's IRB.	Administrative update.

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Section 17.2, Page 42	Section 18.2, Page 60 **18.2 Electronic Data Capture~~Data Processing, Editing, and Control~~** [Section extensively revised. See protocol for changes.]	Administrative change.
Section 17.5.2, Page 44, First Paragraph, First and Second Sentences To maintain subject confidentiality, all laboratory specimens, CRFs (electronic or paper), reports, and other records will be coded using alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet.	Section 18.5.2, Page 61, First Paragraph, First and Second Sentences To maintain subject confidentiality, all laboratory specimens, CRFs (electronic or paper), reports, and other records will be coded using subject number and initials.~~alpha-numeric identifiers only. Only research and clinical records will be stored in a locked cabinet.~~	Administrative change.
Section 18, Pages 44-45 **18. 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	Section 19, Page 61 **19. DISSEMINATION AND PUBLICATION~~S~~ OF ~~THE~~ STUDY RESULTS** The Sponsor recognizes the importance of communicating medical study data and therefore encourages ~~their~~publication of such data in reputable scientific journals and at seminars or conferences. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study is described in the Clinical Trial Agreement between the Sponsor and the institution of the Investigator. ~~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~~	Administrative clarification.

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Table 4. Changes for USWM-LX1-3003-2 Protocol (February 3, 2012) → USWM-LX1-3003-2, Amendment No. 01 (January 22, 2015)

Location (Section and Page Number) and Previous Wording	Location (Section and Page Number) Revised Text in Blue and Deleted Text in Red	Rationale
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).	~~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).~~	
Section 21, Page 46 --	Section 22, Pages 62-63 [Reference list updated. See protocol.]	Administrative change.

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