PRODUCT: LUCEMYRA (Lofexidine)
STATISTICAL ANALYSIS PLAN PROTOCOL NUMBER: USWM-LX1-3003-2 / 02

SPONSOR:

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TITLE:

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

DOCUMENT DATE: 06APR2016
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16.1.9 DOCUMENTATION OF STATISTICAL METHODS

Table 1: Statistical Analysis Plans

Statistical Analysis Plans Included in Appendix 16.1.9
16.1.9.1 Statistical Analysis Plan: Clinical Study Report- Version 1.0- 06 April 2016

STATISTICAL ANALYSIS PLAN

USWM-LX1-3003-2

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

Protocol Ref: USWM-LX1-3003-2

Final Version: 1.0

Date effective: 06-APR-2016

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1. INTRODUCTION

This document details the statistical analysis of the data that will be performed by for the US WorldMeds, LLC study USWM-LX1-3003-2.

The proposed analysis is based on the contents of the Final Version of the protocol (dated 03-Feb-2012) and amendments 1 and 2 (dated 22-Jan-2015 and 21-May-2015 respectively).

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.

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).

2. SAMPLE SIZE

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.

3. RANDOMIZATION

No randomization was performed.

4. INTERIM ANALYSIS

No interim analysis is planned.

5. STATISTICAL METHODS

5.1 Continuous

Continuous variables and ordered categorical variables not subject to censoring will be summarized with the number of non-missing observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum.

For summary statistics, means, medians and percentiles will be displayed to one more decimal place than the raw data, dispersion statistics (e.g. standard deviation) will have two more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

5.2 Categorical

Unordered categorical and ordered categorical (depending on the number of categories) variables will be presented in contingency tables with cell frequencies and percentages for the number of non-missing observations and frequencies for the number of missing observations apart from disposition of subjects, concomitant medications, measurement of treatment compliance and adverse events where percentages will be presented for the population.

6. ANALYSIS PLAN

6.1 General

The treatment will be labelled as Lofexidine for presentation of efficacy and safety data. Subject data in Appendix 16.2 listings will be ordered by treatment, site, subject, and study day when applicable.

All tabulations, data listings and figures will be produced using SAS Version 9.3[1] or higher.

All summaries and analyses documented below will be presented in the final integrated statistical/clinical report and tables that will be based on the E3 guidelines published by ICH.

However, it is noted here that no analysis plan prepared in advance of the data can be absolutely definitive and so the final report may contain additional tables or statistical tests if warranted by the data obtained. The justification for any such additional analyses will be fully documented in the final report.

6.2 Derived Data

- Definition of baseline

With the exception of vital signs measurements, baseline is defined as the last non-missing value prior to the receiving the first dose of study medication. For vital signs measurements, the last screening measurement will be used as baseline.

All tabulations involving change from baseline data will only include subjects with cohort data i.e. with data at baseline and at follow-up. Change from baseline will be calculated as follow-up values minus baseline value.

- Incomplete dates

All incomplete dates will be included in the clinical database as they were entered in the eCRF. Thereafter for calculation purposes, the incomplete dates will be completed using pre-defined rules. If a day or month is not recorded it will be replaced by the first day of the month or January respectively, provided this does not contradict any other dates recorded. For missing adverse events and medications dates/times during the trial, the worst-case date will be used (e.g. the end of the month for a stop date and 23:59 for the stop time, the date/time of initial dose for start of AE i.e. all events with missing start dates will be assumed to be treatment emergent).

- Ambiguous values

In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x”, then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken.

- Questionnaire Data

In the event that component items used to calculate total scores for questionnaire data e.g. SOWS Gossop score are missing then the total scores will also be set to missing.

6.3 Analysis populations

The Enrolled Population includes all subjects screened into the study irrespective of whether they received the study medication.

The Safety Population includes all subjects who received at least one dose of study medication.

With the exception of the disposition table all outputs will use the Safety Population.

6.4 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2.

6.5 Data Summaries

The data will be summarized in tabular form by treatment (Lofexidine).

Graphical presentations of the data will also be provided where appropriate.

6.6 Disposition of Subjects

The following will be summarized:

- The number of subjects who are included in the Enrolled Population,
- The number of enrolled subjects that enrolled but failed to be dosed along with the reasons,
- The number of subjects that completed the inpatient treatment period and the number of subjects who transitioned to outpatient at Day 4, 5, 6 and 7 (each day will be displayed separately).
- The number of enrolled subjects that completed the study (took one dose on Day 7). Additionally, the reason for withdrawal will be summarized as follows:
    - Lack of effectiveness
    - AE related to study drug
    - Withdrew consent
    - Lost to Follow-Up
    - AE unrelated to the study drug or withdrawal symptoms (e.g. concomitant illness)
    - There is evidence of contraband drug use while participating in the study
    - Requires treatment with an exclusionary drug
    - Lack of compliance with protocol and/or unit procedures
    - Other, specify

6.7 Baseline Comparability

6.7.1 Study Population

Subject demographics and baseline characteristics will be presented for all subjects within the Safety Population.

Co-administration categories will include the following:

- Any co-administration of Buprenorphine
- Any co-administration of Methadone
- Other (no co-administration of buprenorphine or methadone)

6.7.2 Variables Considered

Standard continuous or categorical variable summaries will be presented for the following variables:

Demography

- Site number
- Age at screening visit as recorded on the study database (years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other). If more than one race is selected then race will be "Other".
- Height (cm) at Screening visit
- Body weight (kg) at Screening visit
- BMI (kg/m^2), at Screening visit, calculated as weight (kg) divided by height (m^2) rounded to one decimal place.

Medical History

Separate tabulations will be produced for previous and ongoing conditions with all conditions coded using MedDRA Version 18.0 (primary system organ class and preferred term).

Smoking & Alcohol History

- Ever smoked cigarettes (Yes, No). If yes,
    - Number of years used
    - Average number of times used/day
    - Whether currently smoking (Yes, No)

Alcohol History

- Was Alcohol ever used? (Yes, No). If yes,
    - Number of years alcohol was used (Yes, No)
    - Currently using (Yes, No)
    - Average number of times consumed/week

Opioids Abuse

- Primary Opioid of Abuse (data recorded on the concomitant medication eCRF)
- Duration of substance abuse (years).
- Average number times taken per day.
- IV Use (Yes/No)

Infectious Disease Panel and Syphilis Tests at Screening

- Syphilis Antibody (Positive, Negative)
- HBsAg (Reactive, Non-reactive)
- Anti-HBc, Total (Reactive, Non-reactive)
- Hep B Surface Ab (IU/L)
- Anti-HCV (Reactive, Non-reactive)

Urine Drug Screen at Screening

- Result, positive for:
    - Amphetamines (Yes, No)
    - Methamphetamines (Yes, No)
    - Cocaine (Yes, No)
    - Barbiturates (Yes, No)
    - Opiates (Yes, No)

- Benzodiazepines (Yes, No)
- Cannabinoids (Yes, No)
- Methadone (Yes, No)
- Buprenorphine (Yes, No)
- Oxycodone (Yes, No)
- Phencyclidine (Yes, No)
- MDMA (Yes, No)

Prior medications

Verbatim terms (as recorded on the CRFs) of medications that ceased prior to the time of the initial dose of study medication will be mapped to Anatomical Therapeutic Chemical (ATC) Level 2 and Drug Reference Names using the World Health Organization (WHO) dictionary (Version 6.2015 Enhanced). Prior medications will be listed in Appendix 16.2.

Measurement of Treatment Compliance

Details of compliance will be tabulated overall and for each co-administration category by study day.

Additionally, lofexidine concentration data will be summarized by descriptive statistics for each study day.

6.8 Effectiveness Endpoints

Treatment Goal

Number and proportion of subjects' baseline treatment goal will be presented overall and for each co-administration category.

Status of Pre-defined Withdrawal Treatment Goal as Assessed by the Site Investigator

Number and proportion of subjects successfully completing their pre-defined withdrawal treatment goal as assessed by the Site Investigator at Day 7 or early termination (last assessment) and Day 14 will be presented overall and for each co-administration category. The number and proportion of subjects who relapsed during the study will be presented overall by study day.

Questionnaires

Summary statistics will be provided overall and for each co-administration category by study day for Days 1-14:

- SOWS-Gossop

- COWS

Concomitant Medications

For each of Days 1 to 14, each subject's number of concomitant medication taken will be treated as a continuous variable. Descriptive statistics will be provided on the as-observed data on each study day and also overall study days.

Details of the Day 30 Follow-Up

- Lost to Follow-up
- Whether subject entered one of the following programs:
    - None
    - Methadone
    - Buprenorphine
    - Naltrexone
    - Other
- Whether subject relapsed to drug use after exiting the study (Yes, No)

6.9 Safety analysis

Safety measures will be summarized for the following:

- Safety Population
- Co-administered Buprenorphine;
- Co-administered Methadone
- Other (no co-administration of buprenorphine or methadone)
- and
- Any other identifiable co-administration categories not otherwise noted.

Extent of exposure

Extent of exposure will be described by whether the subject took the trial medication and the number of days' exposure (last date of medication minus first date of medication + 1). Average daily dose of study medication will also be calculated. No allowance will be made for breaks in therapy in the exposure calculations. If the date of last dosing is completely missing for the trial medication then the date of last dosing will be taken for analysis purposes as the date the medication was last dispensed. If only the month of the last dose is recorded, the first day of the month will be assumed as the last dosing date.

Additionally, the number and percentage of subjects with a dose reduction from 3.2 mg/day to 2.4 mg/day will be presented overall and for each co-administration category by study day.

Adverse Events

All AEs will be listed and tabulated by severity, relationship to study medication, primary system organ class and preferred term according to MedDRA Version 18.0. In counting the number of events reported, a continuous event, i.e., an event reported more than once and which did not cease, will be counted only once with the worst recorded severity; non-continuous AEs reported several times by the same subject will be counted as multiple events. Events present immediately prior to the first dose of study medication that do not worsen in severity, will not be regarded as treatment emergent. Events with start dates more than 30 days after the administration of the last dose of study medication will not be considered treatment emergent and will be listed separately. In deriving the tabulation relating to preferred term reporting, the severity of a recurrent AE will be taken to be the most severe and the relationship to study medication as the highest probable. Missing or incomplete TEAE start dates will be imputed to correspond with the date of dosing.

The following will be summarized and presented for the overall study, for the inpatient phase and for the outpatient phase over and for each co-administration category:

- The number and percentage of subjects experiencing at least 1 TEAE by MedDRA preferred term and SOC.
- The number and percentage of subjects experiencing an opioid withdrawal related TEAE as determined by the investigator by MedDRA preferred term and SOC.
- The number and percentage of subjects experiencing a TEAE of special interest (Table 2).
- The number and percentage of subjects experiencing TEAEs by severity of event
- The number and percentage of subjects experiencing treatment-related TEAEs (i.e. Possibly Related, Probably Related, Definitely Related)
- The number and percentage of subjects experiencing at least 1 treatment emergent SAE by MedDRA preferred term and SOC
- The number and percentage of subjects experiencing SAEs by severity of the event by MedDRA preferred term and SOC
- The number and percentage of subjects experiencing SAEs by relatedness to IP

Table 2: TEAEs of Special Interest

Hypotension	Rebound Hypertension	Bradycardia
	agitation	chest pain, tightness in chest
	anxiety, nervousness	
dizziness	chest pain, tightness in chest	

Table 2: TEAEs of Special Interest

Hypotension	Rebound Hypertension	Bradycardia
hypotension	epistaxis	confusion
	fatigue	hypotension
orthostatic hypotension	flushing, warm feeling	
palpitations	headache	dizziness
presyncope	hypertension	pallor
	hypertensive encephalopathy	shortness of breath
	lightheadedness	
syncope	nausea	
tachycardia	pallor	
	perspiration	
	shortness of breath	
	stroke/CVA	
	syncope	
	tachycardia	
	tremor	
	vision changes	

Narratives of deaths, serious and other significant AEs will be provided in the relevant section of the CSR.

A complete subject listing of all AEs will be provided in Appendix 16.2 to the study report. This listing will include AE verbatim, MedDRA primary system organ class and preferred term, the time of onset and cessation of event relative to first dosing of study medication, duration of AE (for ongoing AEs use the date of investigator signature as the cessation date for calculation purposes), whether serious, severity, relationship to study medication, action taken and outcome.

Treatment emergent and non-treatment emergent events will be listed separately.

Vital Signs Measurements

Summary statistics for observed and changes from baseline in sitting and standing vital signs, separately, will be tabulated at each follow-up for each vital sign parameter and at post-baseline endpoint for each variable overall and for each co-administration category. All values will be included in the summary of potentially clinically significant vital signs. However, post-baseline repeat/unscheduled assessments will be excluded for the other tabulations.

In addition the number and proportion of subjects having PCS will be tabulated:

- Systolic blood pressure ≥180 mmHg and an increase of ≥ 20 mmHg from baseline
- Systolic blood pressure ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline;
- Diastolic blood pressure ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline;

- Diastolic blood pressure ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline; or

Additionally, the number and proportion of subjects having a dose-hold due to a VS measurement will be tabulated as follows:

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.

In addition, the number and proportion of subjects meeting the discontinuation Vital Signs criteria will be tabulated as follows:

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

All of the above will be summarized overall and for each co-administration category at each study day.

The incidence of missed standing vital signs will be counted for those subjects with a resting blood pressure measurement and a missing standing blood pressure measurement. The count of unique subjects and number of events will be tabulated. Consecutive missing measurements will be counted as one event. Additionally, the number of missed doses and the reason for each missed dose will be presented for each subject and study day.

The number and percentage of subjects with a reduced dose that still met each of the above criterion after the dose reduction will be presented overall and for each co-administration category by study day.

Mean profiles by study day will be presented for sitting and standing blood pressure and pulse rate.

ECG

For ECG data collected during this study, a separate SAP will be used for the analysis and the results will be presented separately in a stand-alone report.

In addition, PI overall interpretation of the ECG (Normal, Abnormal NCS, and Abnormal CS) will be listed in Appendix 16.2.

Clinical Laboratory Evaluations

Descriptive statistics will be calculated for the baseline values, study discontinuation values and for the changes from baseline for each continuous hematology, coagulation, chemistry and urinalysis parameter. Each measurement will be categorized as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to study discontinuation will be presented. For post-baseline laboratory values, only scheduled values will be tabulated. Post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed in the relevant appendices to the report; in particular all clinically significant values will be noted in a table or a separate listing.
Details of clinically warranted clinical laboratory tests and microscopic urinalysis will be provided in Appendix 16.2 of the report.

C-SSRS

The C-SSRS will be completed 3.5 hours after the first dose (8 AM) during in-clinic treatment, and once daily before an in-clinic dose of lofexidine during outpatient treatment, or, if applicable, at discontinuation from the study;

The following will be summarized for the study overall and by inpatient or outpatient phase**:**

1. To assess safety:
    a. **Suicidality:** The number and percentage of subjects reporting any suicidal ideation or behavior throughout the assessment period.
    b. **Suicidal behavior only:** The number and percentage of subjects reporting any type of suicidal behavior throughout assessment period.
    c. **Suicidal ideation only:** The number and percentage of subjects reporting any type of suicidal ideation throughout assessment period.

    In addition, taking into account baseline data regarding suicidal ideation to determine if suicidal ideation or behavior has worsened:

    d. **Emergence of suicidal ideation:** The number and percentage of subjects reporting no suicidal ideation at baseline and any type of ideation during the assessment period.
    e. **Emergence of serious suicidal ideation:** The number and percentage of subjects reporting no suicidal ideation at baseline and had serious suicidal

ideation (as defined above; score of 4 or 5 on suicidal ideation severity rating) during the assessment period.

f. **Worsening of suicidal ideation:** The number and percentage of subjects whose most severe suicidal ideation rating is more severe than it was at baseline.
g. **Emergence of suicidal behavior:** The number and percentage of subjects who had no suicidal behavior at baseline and any type of behavior during the assessment period.

Physical Examination

Complete physical examination will be assessed 3 to 4 hours after first dose on Day 1, as clinically warranted, and at discontinuation from the study. Each body system within the physical examination be summarized (Normal; Abnormal NCS, Abnormal CS) for each visit collected. For body weight, descriptive statistics will be tabulated for baseline, end of study and the changes from baseline to end of the study.

Concomitant medications

Concomitant medication verbatim terms (as recorded on the CRFs) after the initial dose of study drug will be mapped to Anatomical Therapeutic Chemical (ATC) Level 2 and Drug Reference Names using the World Health Organization (WHO) dictionary (Version 6.15 Enhanced) and tabulated overall.

6.10 Change to Planned Protocol Analysis

The following changes have been made to the planned protocol analyses sections:

Section 6.10 Subject Cohorts

Change: Addition of cohort for subjects undergoing methadone-assisted withdrawal.

Reason: This cohort should have been included in the protocol.

Section 6.10 Adverse Events

Change: Addition of adverse event summaries by inpatient and outpatient phase.

Reason: There is interest in the difference between inpatient and outpatient events.

Section 6.10 Vital Signs Measurements

Change: Addition of the incidence of missing standing vital signs measurements.

Reason: There is interest in determining the number of subjects who could not stand.

6.11 References

(1) SAS Institute Inc. The SAS System, Version 9.3. Cary, NC, SAS Institute Inc. 2012.

7. TABLES TO BE INCLUDED IN THE CLINICAL STUDY REPORT

Table number	Table Title

8. FIGURES TO BE INCLUDED IN THE CLINICAL STUDY REPORT

Figure number	Figure Title

9. APPENDIX 16.2 LISTINGS

Listing number	Listing Title

Approval for implementation of
Statistical Analysis Plan

Title: **A Phase 3, Open-Label, Safety Study of Lofexidine**

Reference: **USWM-LX1-3003-2/SAP**

Version: **Final 1.0**

Date effective: **07-APR-2016**

Author:

Author's signature:

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Approver:

Position:

Signature for

Name of Approver:

Position:

Signature for