**eMethods**

A. Dose-Hold Criteria

Due to the known effects of lofexidine on blood pressure and heart rate, study medication was to be held if predose vital signs met any of the criteria listed below.

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

* Systolic blood pressure <90 mm Hg and >20% below screen value
* Diastolic blood pressure <50 mm Hg and >20% below screen value
* Heart rate <50 beats per min and >20% below screen value
* Symptoms of hypotension and/or bradycardia (eg, lightheadedness, dizziness, syncope)

Orthostatic (after standing for 3 minutes)

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

**B. Study Discontinuation Criteria**

1. Cardiovascular events (see below)
2. Serious medical problem, whether related or unrelated to study medication
3. Intercurrent illness or medical complications that, in the opinion of the site investigator, precluded safe administration of study medication
4. Evidence of illicit drug use while participating in the study during days 1 to 7
5. Alcohol or other sedative/hypnotic withdrawal signs and symptoms developing following enrollment into the study
6. Required therapy with an exclusionary drug
7. Lack of compliance with protocol and/or unit procedures
8. Systolic blood pressure <70 mm Hg and >20% below screen value
9. Diastolic blood pressure <40 mm Hg and > 20% below screen value
10. Heart rate <40 beats per min and >20% below screen value
11. QTcF >500 msec or >25% above screen value for both males and females
12. Syncope
13. Subjects who missed more than 2 doses in 24 hours during days 1 to 7 prior to meeting “completer” criteria (ie, received at least 1 dose of study medication on day 7 and completed the 3.5-hour postdose SOWS-Gossop assessment on day 7)
14. Subjects who missed more than a total of 6 doses during days 1 to 7 prior to meeting “completer” criteria (ie, received at least 1 dose of study medication on day 7 and completed the 3.5-hour postdose SOWS-Gossop assessment on day 7)
15. Concomitant medication use other than allowed drugs specified in the protocol

A subject could withdraw his/her consent for participation in the study at any time without prejudice. The site investigator also had the discretion to discontinue a subject.

C. Cardiovascular Events Requiring Subject Discontinuation from the Study

Since lofexidine is associated with bradycardia and hypotension, the protocol specified that subjects be discontinued for certain cardiovascular events in addition to the criteria for vital sign assessments noted above. For the cardiovascular events listed below, subjects were to be discontinued from the study and the event reported and followed up as an AE or SAE as determined by the site investigator.

1. New onset of clinically significant abnormal ECG (eg, second- or third-degree heart block or uncontrolled arrhythmia, prolonged QTcF interval)
2. Persistent symptomatic hypotension (eg, hypotension not responding to bed rest or fluids)
3. Single occurrence of symptomatic bradycardia (as assessed by the site investigator, regardless of blood pressure) associated with chest pain, shortness of breath, or decreased level of consciousness
4. Persistent hypertension, defined as blood pressure ≥185/110 mm Hg recorded on 3 separate occasions taken at least 5 minutes apart AND within a 1-hour time period. If all 3 readings were ≥185/110 mm Hg (either systolic ≥185 mm Hg or diastolic ≥110 mm Hg), the subject was discontinued from the study
5. Medical Intervention for Cardiovascular Event: Any medical intervention (nonmedication or medication inclusive) used for the treatment of any cardiovascular event, except for a positional intervention in subjects displaying hypotension
6. Any other clinically significant cardiovascular signs or symptoms that placed the subject at risk

| D. Vital Sign Values Required to Be Reported as an AE |
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| Vital Sign Parameter | Observed Value |  | Change in Value from Screening |
| Systolic blood pressure | ≥180 mm Hg≤90 mm Hg | AND | Increase of ≥20 mm HgDecrease of ≥20 mm Hg |
| Diastolic blood pressure | ≥105 mm Hg≤50 mm Hg | AND | Increase of ≥15 mm HgDecrease of ≥15 mm Hg |
| Pulse | ≥120 beats per min≤50 beats per min | AND | Increase of ≥15 beats per min Decrease of ≥15 beats per min |

**E. Tertiary Efficacy Outcomes Reported in Supplemental Results**

1. Objective Opiate Withdrawal Scale-Handelsman (OOWS-Handelsman)

The OOWS-Handelsman was performed by a trained observer during screening, twice on day 1 (during baseline to confirm final eligibility for randomization [a score of ≥2 was required per inclusion criterion number 4] and 3.5 hours after the first dose of study medication, after completion of the SOWS-Gossop), once daily at 3.5 hours after the first dose of study medication on days 2 to 7 (after completion of the SOWS-Gossop).

The subject was observed for 5 minutes, and the presence or absence of 13 physical signs of opioid withdrawal were recorded. The presence of a sign was assigned 1 point, yielding a possible total score ranging from 0 to 13. Lower observed values in OOWS‑Handelsman scores indicated a more favorable clinical outcome. A copy of the OOWS‑Handelsman assessment form is in Appendix 2 of the clinical study protocol.

1. Modified Clinical Global Impressions Scale (MCGI)

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

In the original scale, Question 1 (severity of illness) evaluated the subject using a severity scale from 0 (not assessed), 1 (normal, not at all ill) to 7 (among the most extremely ill subjects). The language of this question was modified in this study for the subject assessment to make the scale more appropriate to opioid withdrawal. The original Question 2 referred to “global improvement” and was omitted from this study, since all subjects were treated (ie, underwent opioid withdrawal), and there was no untreated screen withdrawal to serve as a baseline for global improvement. Question 3 (efficacy index) recorded responses on a factorial grid – side effects on one side and therapeutic effects on the other side. Since there were no untreated screen withdrawal data, the therapeutic effect could not be assessed; therefore, only the side effect responses were examined.

The MCGI scale was used to estimate the overall clinical benefit of lofexidine treatment. The MCGI was completed once daily at 3.5 hours after the first dose of study medication on days 1 to 7 (after completion of the SOWS-Gossop). Lower observed values in MCGI scores indicated a more favorable clinical outcome. A copy of the rater and subject MCGI assessment forms are in Appendix 3 of the clinical study protocol.

1. Visual Analogue Scale for Efficacy (VAS-E)

The effectiveness of lofexidine in alleviation of withdrawal sickness was assessed by subjects using the VAS-E, which was completed once daily on days 1 to 7, 3.5 hours after the first dose of study medication (after completion of the SOWS-Gossop). Subjects made a mark on a 100-mm VAS scale to reflect the effectiveness of lofexidine in relieving withdrawal sickness from Not Effective at All (0 mm) to Completely Effective (100 mm). Greater observed values in VAS‑E scores indicated a more favorable clinical outcome. A copy of the VAS-E assessment form is in Appendix 4 of the clinical study protocol.

**F. Other Safety Procedures**

1. Standard Laboratory Tests

Standard clinical laboratory safety evaluations were performed for all subjects at screening, as needed at the physician’s discretion throughout the study, at the end of double‑blind dosing, and at discontinuation from the study. For this multicenter study, a central laboratory (PRL Central Laboratory Services) was used.

1. Infectious Disease Panel and Syphilis Tests

The infectious disease panel and syphilis tests were assayed at screening only. Qualitative analysis reporting positive/negative results was 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 purified protein derivative (PPD) skin test for tuberculosis and/or a chest x-ray was performed on all subjects. If the PPD was positive, a chest x-ray was required to assess the possibility of active tuberculosis. If the subject reported that he or she had been previously positive for the PPD test, the PPD test was not performed and only a chest x-ray was required. Syphilis antibody testing was performed, using an automated enzyme immunoassay (EIA). If the EIA was positive, a confirmatory rapid plasma reagin (RPR) test was performed. If the RPR test was non-reactive, a confirmatory treponema pallidum particle agglutination assay (TPPA) test was performed.

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

1. Urine Toxicology Screening

Qualitative urine drug screening (UDS) was performed at screening for all subjects, at baseline, and at least every other day for the following drugs: amphetamines/methamphetamines, cocaine, barbiturates, opioids, benzodiazepines, cannabinoids, methadone, and buprenorphine. The central laboratory provided standard sets of UDS “dipsticks” for use across all sites.

1. Pregnancy Test

A “dipstick” pregnancy test to measure human chorionic gonadotropin was performed on the first day of screening, at baseline, and at study discontinuation for all female subjects, regardless of their childbearing capacity. The central laboratory provided study sites with a supply of pregnancy dipsticks.

1. Physical Examination

A complete physical examination was performed at screening for all subjects.

An update of the physical examination was required at baseline (before randomization on day 1) and then a complete physical examination was performed 3 to 4 hours after randomization on day 1, and at the end of double-blind dosing. Height was recorded at screening only.

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

The C-SSRS measured both suicidal ideation and suicidal behavior and was completed at baseline (before dosing on day 1), 3.5 hours after the first dose (8 AM) on days 1 to 7 or, if applicable, at discontinuation from the study. The baseline version of the C-SSRS (Appendix 9 of the protocol) was used to assess lifetime suicidality on day 1 (before dosing). At all other protocol-specified time points, the C‑SSRS – Since Last Visit version (Appendix 10 of the protocol) was used to assess the subject’s suicidality since the last assessment.

1. Drug Concentration Measurements (Pharmacokinetic [PK] Sampling)

A fingerstick blood sample for PK analysis was collected concurrently with each scheduled ECG during days 1 to 7 only. In addition, fingerstick blood samples were collected on days 3 and 6 at 9 PM and 10 PM (3 and 4 hours, respectively, after the 6 PM dose).