**PRODUCT:** Lofexidine granules for reconstitution (oral)

**INFORMED CONSENT FORM**

**PROTOCOL NUMBER:** USWM-LX2-1001

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

**TITLE:**
A Study to Evaluate the Relative Bioavailability of a Test Formulation of Lofexidine Granules for Reconstitution and the Effect of Food on the Bioavailability of the Test Formulation in Healthy Adult Subjects

**DOCUMENT DATE:** February 2, 2021
**IND NUMBER:** 47857
**NCT NUMBER:** NCT04188730

The information being provided below is some of the most important information about this study. **More details about the study are explained later in this consent form.**

Taking part in this research project is voluntary. You do not have to participate, and you can stop at any time. Please take time to read this entire form and ask questions before deciding whether to take part in this research project.

## Key Information

**Drugs being studied:** Lofexidine in a liquid form and a tablet form are being compared. The liquid form is new and investigational (meaning not approved by the FDA). The tablet form (LUCEMYRA®) is already FDA-approved. Lofexidine is used in adults to help lessen symptoms of opioid withdrawal when opioid medications are stopped suddenly.

**Purpose:** To see how quickly and to what extent the body absorbs and gets rid of the liquid form of lofexidine compared to the tablet form of lofexidine.

**Who is being asked to participate:** About 16 healthy volunteers, ages 18 to 50. Females must not be pregnant or breastfeeding and must be using an effective birth control method before and during the study.

**Medical benefits to participating in this study:** This is a healthy volunteer study. There are no direct medical benefits to you by participating in this study.

**Time commitment:** 3 study periods lasting about 3½ days (3 overnights) each. Your total participation in this study will be about 2½ weeks. This does not include your screening visit.

**Restrictions:** During confinement you will eat/drink only the food and beverages given to you. You won't be allowed to eat/drink/use certain products before and during the study, such as caffeine, alcohol, grapefruit, and tobacco/nicotine. You will have to fast (not eat anything) for at least 10 hours before each dosing.

**Procedures:** If you are eligible and decide to participate, you will receive one dose of the tablets in one period and one dose of the liquid form in the other two periods (either on an empty stomach or after eating a high-fat, high-calorie breakfast). You will be asked to remain lying down in bed for 8 hours after dosing. Study staff will monitor your health and perform various safety tests while you are in the clinic, such as taking your blood pressure, pulse, and ECG (measurement of the electrical activity of the heart).

**Blood draws each period:** About 17 blood samples. Total of about 1½ cups of blood, including blood taken to check your health and 1 sample for a genetic test to see how your body metabolizes [breaks down] the study drug(s).

**Common Side Effects:** Low blood pressure or symptoms of low blood pressure, slow heartbeat, dizziness, lightheadedness, and feeling faint at rest or when standing up. The complete list can be found later in the form. For your safety, you should be honest about your medical and social history.

**Risks associated with blood draws:** Pain, bruising, swelling and/or numbness of the arm, fainting, and infections (rarely).

**Privacy Risks:** Accidental breach of confidential information collected from you as part of this study.

"A study to evaluate the relative bioavailability of a test formulation of lofexidine granules for reconstitution and the effect of food on the bioavailability of the test formulation in healthy adult subjects"

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| **STUDY DRUG(S):** | Lofexidine granules for reconstitution (oral), [redacted], final strength lofexidine 90 µg/mL [redacted]<br>LUCEMYRA® (lofexidine) tablets, EQ 0.18 mg base (US WorldMeds, LLC) | **SPONSOR PROTOCOL NO.:** USWM-LX2-1001 |
| **SPONSOR:** | **USWM, LLC**<br>4441 Springdale Rd.<br>Louisville, KY 40241 | |
| **INVESTIGATOR:** | [redacted] | |
| **SUBJECT'S RIGHTS ADVOCATE:** | [redacted] | |

***What is informed consent?***

You are being asked to take part in a clinical research study. It is important that you understand the potential risks and benefits of participating in the study to make an informed decision. This process is known as informed consent.

This consent form describes the purpose, procedures, possible benefits, and risks of participating in the study. This form will also explain how your medical information will be used and who may see it. Once you have been informed about the study and had all questions answered to your satisfaction, you will be asked if you are willing to sign this form. By giving your consent, you are allowing your medical information to be collected, used, and shared with certain persons involved in the study. Signing this form will also show that this study has been sufficiently and appropriately explained to you and that you agree to participate in it.

You cannot be in this study if you have participated in any other study, at [redacted] or any other research facility, within the last 30 days. The study investigator is interested both in your health and in the conduct of this study. [redacted] is paid by USWM, LLC (the study sponsor) to conduct this study.

***What drug will be used in this study?***

Lofexidine in the form of granules that will be dissolved into an oral solution (liquid) and as tablets, of the same strength, will be used in this research study. Lofexidine is a drug approved by the United States Food and Drug Administration (FDA) to be used in adults to help with the symptoms of opioid withdrawal that may happen when someone stops taking an opioid suddenly. Lofexidine tablets (LUCEMYRA®) have been approved by the FDA for use in the U.S. for approximately 3 years; however, lofexidine tablets have been approved and prescribed by doctors in the United Kingdom (U.K.) for over 25 years.

The usual dose of lofexidine in adults is 0.54 mg (three tablets) taken by mouth 4 times a day, about 5 to 6 hours apart. The total daily dosage of LUCEMYRA® should not

exceed 2.88 mg (16 tablets) and no single dose should exceed 0.72 mg (4 tablets). A single 0.36 mg dose of lofexidine will be given in each period of this study.

***Why is this study being done?***
This study is being done to compare how the two forms (liquid and tablet) of the study drug are absorbed (passed from the gut into the blood stream) and eliminated (removed) from the body after taken on an empty stomach and taken after eating a high-fat, high-calorie breakfast. A new, **UNMARKETED** "investigational" version of lofexidine (dissolved granules) will be compared to an approved, **MARKETED** version of lofexidine (tablets) called LUCEMYRA®. "Investigational" means the formulation being tested has not been approved yet by the FDA.

***Who is being asked to take part in this study?***
You are one of about 16 non-tobacco, non-nicotine using adults who have been asked to participate in this study. To be in this study, you must be 18 to 50 years of age and be in good health. Since we usually sign up more eligible participants for the first study check-in than we need, you may be released from the study before dosing.

***How will I know if I am eligible to take part in this study?***
**Screening Visit (within 28 days of first dosing)**
The purpose of this visit is to obtain information about your current health status and to decide if you qualify for the study. The screening evaluation will include (but may not be limited to) the following:

- Review of your medical (including allergies) and social (drug, alcohol, tobacco, and caffeine use, etc.) history. **It is potentially dangerous to withhold information concerning your medical and social history.**
- Review of any medicines, vaccines, nutritional supplements, vitamins, and herbal products that you are taking or have taken recently.
- A general physical examination.
- Measurement of your vital signs in a sitting or supine (flat on your back) position (blood pressure, pulse, and body temperature), body weight, and height.
- A blood pressure assessment for orthostatic hypotension. Orthostatic hypotension is a form of low blood pressure that happens when you stand up from sitting or lying down.
- Measurement of heart rhythms (ECG or electrocardiogram).
- Collection of a blood sample (about 2½ teaspoonfuls) to verify you can safely enter the clinical study.
- Collection of a blood sample (about 3½ teaspoonfuls) to test for Hepatitis B, Hepatitis C, and HIV (the virus that causes AIDS).
- Collection of a blood sample (about 1 teaspoonful) for pregnancy testing (females).
- Females who are considered post-menopausal (meaning no menstrual period for at least 1 year) will have a sample of blood collected (about 1 teaspoonful) to confirm postmenopausal status.
- Collection of a urine sample to test for selected diseases and drugs of abuse.

- You will be given a "*Participant Handbook"* to read or have read to you. This handbook contains the [redacted] *Rules and Regulations.*

Some of these tests may be repeated for safety reasons before you begin the study, during the study, or at the end of the study.

Study Restrictions:

If you have taken any prescription medication (except hormonal contraceptives) within 14 days of the study start or plan to take them during the study, you can NOT participate in this study. If you are taking any over-the-counter medications (including vitamins and herbal products) or dietary supplements (for example, Cellucor®, Muscle Tech®), you will be asked to stop taking them within 7 days before dosing with study drug and throughout the blood collection portion of the study. You will not be allowed to take any of the following products within the following timeframes before dosing with study drug and throughout the blood collection portion of the study:

- Alcohol (beer, wine, liquor, etc.) – 3 days
- Caffeine (coffee, tea, chocolate, soda, cola, etc.) – 3 days
- Energy drinks (for example, Red Bull, 5-Hour Energy®, Monster Energy®) – 3 days
- Grapefruit containing products (grapefruit or grapefruit juice, Ruby Red, Fresca®, etc.) – 7 days

You will not be allowed to use tobacco or nicotine-containing products (patches, gum, etc.) for 30 days before the study start and throughout the entire study.

Since there may be other medicines or products that are not allowed prior to or during the study, it is very important for your safety that you tell the study staff about all medications or products you have taken or used. You will be given an information sheet that lists the dates and times of your clinic visits and study restrictions.

***What are the procedures of this study?***

This study consists of 3 study periods. Each study period will involve about a 3½ day (3 overnights) stay at the clinic. There will be about 3 days between study periods during which no procedures will be performed. Your total participation in this study will be about 2½ weeks. This does not include your screening visit.

At each check-in (the day before dosing), the following will occur:

- Your personal belongings will be searched to make sure you did not bring any restricted items, as listed in the *Participant Handbook*.
- A brief physical examination will be performed.
- You will be asked to complete the Columbia Suicidality Severity Rating Scale (C-SSRS), an assessment for your risk of suicide.
- You will be asked about your health and any medication/drug use.
- You will have a urine/saliva test for alcohol and drugs of abuse.
- Females will have a urine pregnancy test.
- Your blood pressure, temperature, and pulse rate will be measured.
- Your heart rhythms (ECG or electrocardiogram) will be measured at check-in Periods 2 and 3 only.

At check-in of Groups A and B (fasted periods):

- If you arrive before dinnertime, you will be provided a meal. You will not be able to eat anything past 10:00 pm (approved snacks may be allowed before this time) until lunch the next day.

At check-in of Group C (fed period):

- If you arrive before dinnertime, you will be provided a meal. You will not be able to eat anything past 10:00 pm (approved snacks may be allowed before this time) until breakfast the next day. You will be required to eat 100% of a high–fat, high-calorie breakfast within 30 minutes of dosing. The high-fat, high-calorie breakfast consists of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of milk.

**Day of Dosing**

If you are still eligible to be in the study, you will be required to drink about a 1¼ cup of water in the morning at 4, 3, 2, and 1 hours before dosing. You will receive one of the following:

**Group A:** A little less than 1 teaspoonful of lofexidine oral solution [redacted] 0.36 mg total dose – Administered following an overnight fast of at least 10 hours

**Group B:** 0.36 mg lofexidine (2 × 0.18 mg) tablets, LUCEMYRA® (US WorldMeds, LLC) – Administered following an overnight fast of at least 10 hours

**Group C:** A little less than 1 teaspoonful of lofexidine oral solution [redacted] 0.36 mg total dose – Administered 30 minutes after eating a high-fat, high-calorie breakfast

**Groups A and C:**

[redacted] You will then be required to drink about one cup of room temperature, distilled water. Immediately after dosing, a mouth check will be performed to confirm that the solution, mouth rinse, and additional water have been swallowed. Within 10 minutes after completing the dosing procedure, you will complete a Taste Assessment Questionnaire. It should take you less than 10 minutes to complete it.

**Group B:**

When lofexidine is given in tablet form, you will be required to drink one cup of room temperature, distilled water with the two tablets provided to you by study staff. You will be instructed to swallow the tablets whole without chewing or biting. Immediately after dosing, the study staff will perform a mouth check to ensure that the study drug and water have been swallowed. If you bite or chew the tablets, you will be discontinued from the study.

Over the course of the entire study, you will receive each of the study drugs listed above. The order that you receive the study drugs will be determined randomly (by chance).

Tests and Procedures during Your Stay

The following tests and procedures will also occur as follows:

- Blood samples (a little more than 1 teaspoonful each time) will be collected just before and frequently after dosing to measure the study drug.
- In Period 1 only, a blood sample (about 1 teaspoonful) will be collected to see if your body has limited ability to make a certain enzyme called CYP2D6. This enzyme is responsible for breaking down certain drugs in the body. People who have limited ability to make this enzyme are sometimes known as "slow metabolizers" and it may take them longer to break down and eliminate certain drugs from the body than other people. Whether or not you are a "slow metabolizer" is determined by your genetic makeup and is pre-determined at birth. This sample will only be analyzed, if needed, after review of your blood sample results.
- Your health will be monitored while you are in the clinic. You will be asked to report any side effects you are experiencing throughout the study. The study staff will monitor how well you follow study requirements throughout the study.
- Your blood pressure and pulse rate will be measured at least 2 times before each dosing, at least 2 times after each dosing, and before release from the clinical facility in Periods 1 and 2.
- Your heart rhythms (ECG or electrocardiogram) will be measured at least 1 time before each dosing, at least 1 time after dosing, and before release from the clinical facility in Periods 1 and 2.
- You will be restricted in the times that you may drink water or stand up. You will be asked to lie down flat on your back or in a reclined position for about 8 hours after dosing, except as required for study procedures or at the discretion of the study investigator. You will not be allowed to drink water or any other fluids starting 4 hours before dosing until 8 hours after dosing, with the exception of the scheduled water administrations and milk given with breakfast (fed study period only). At about 2, 4, 6, and 8 hours after dosing, you will be required to drink about 1 cup of room temperature water.
- You will not be permitted to participate in strenuous activity while you are in the clinic.
- You will be provided with food and drinks. You will be required to consume all food and drinks provided to you.
- A brief physical examination will be performed before you leave the clinical facility in Periods 1 and 2.
- You will be asked to complete the Columbia Suicidality Severity Rating Scale (C-SSRS) before you leave the clinical facility in Periods 1 and 2.

Additional procedures or laboratory tests may be performed to monitor your health.

**End of Study or Early Withdrawal from the Study**

- A blood sample (about 2 ½ teaspoonfuls) and a urine sample for laboratory testing will be collected. Your blood and urine will be tested to assess your general health.
- A blood sample (about 1 teaspoonful) will be collected to test for pregnancy (females).

- A complete physical examination (including weight) will be performed.
- Your heart rhythms (ECG or electrocardiogram) will be measured.
- Your blood pressure, pulse rate, and temperature will be measured.
- You will be asked to complete the Columbia Suicidality Severity Rating Scale (C-SSRS).

***How much blood and urine will be collected during this study?***

Blood samples will be collected from you using a sterile needle about 17 times over approximately a 54-hour period in each study period. About 9 of these samples will be collected within the first 7 hours after dosing. There may be more than 1 tube of blood collected at each collection time. Over the course of the entire study, a total of about 52 blood samples will be collected. This includes your screening visit.

About 1½ cups of blood will be collected from you during this study. For your comparison, when people donate blood, they give about 2 cups at once.

You should not give blood during this study and within **30 days** prior to check-in. You should not donate plasma for **14 days** prior to check-in. You should not donate blood until at least **30 days** after dosing.

A urine/saliva test will be collected at screening and at check-in of each study period. A urine test will also be collected at the end of the study or early withdrawal.

***What are the possible risks, side effects, and discomforts of this study?***

You may experience none, some, or all the side effects listed below. Some side effects may occur that may not be expected or predicted. The study drugs may have other risks that might include life-threatening reactions that are not yet known. Side effects should be reported to the study investigator or [redacted] medical staff as soon as possible.

The following **Side Effects** have been reported by people taking the marketed version of lofexidine (LUCEMYRA®). However, because the test formulation of lofexidine (granules dissolved in liquid) is “investigational” and not currently approved by FDA or available in the commercial market, it is possible that more or different side effects could occur.

**The most common side effects of LUCEMYRA® (lofexidine tablets) include:**

- Low blood pressure or symptoms of low blood pressure such as lightheadedness
- Slow heart rate
- Dizziness
- Sleepiness
- Dry mouth

You should be careful not to stand up too suddenly from lying down or sitting.

**Taking LUCEMYRA® (lofexidine) with opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.**

**Since LUCEMYRA® (lofexidine) can cause dizziness or sleepiness, you should take caution while participating in activities that require mental alertness and potentially hazardous activities, such as operating machinery, DRIVING a motor vehicle, or riding a bicycle until you feel fully awake.**

**This is not a complete list of side effects. Others may occur including serious or even life-threatening reactions. You should be aware that not being truthful about your medical history, the use of alcohol or any other drugs or medicines during the study (other than the study drugs), could lead to serious or even life-threatening reactions.**

**Allergic Reaction Risks**

As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash/hives.
- Difficulty breathing and wheezing.
- A sudden drop in blood pressure.
- Swelling around the mouth, tongue, throat, or eyes.
- A fast pulse.
- Sweating.

Please seek treatment immediately and tell the study investigator and study staff if you have any of these symptoms, or any other side effects, during the study.

**Side effects of blood collections:**

Pain, bruising, swelling and/or numbness of the arm, fainting, and infections (rarely) may result from the multiple blood collections taken during this study.

**NEW INFORMATION**

You will be given any new information about the study drug that becomes known during the course of the study that the study investigator or the study sponsor believes might reasonably affect your willingness to continue to take part in the study.

**CONTRACEPTION/PREGNANCY/BREASTFEEDING:**

There are no well-controlled studies in pregnant women with the drugs used in this study. There could be unknown, unforeseeable risks to an unborn child or breast-feeding infants. You cannot participate in this study if you are pregnant or become pregnant during the study or are breast-feeding a child. If you are a woman of child-bearing potential:

- You must take precautions to prevent pregnancy during this study.
- A pregnancy test will be done to confirm that you are not pregnant before you take part in this study. A pregnancy test will be done before the beginning of each study period. Even if the test result is negative, this does not guarantee that you are not pregnant.
- You must agree to use a reliable form of birth control (e.g., condom with spermicide, IUD, hormonal contraceptives), if you are sexually active, to avoid becoming pregnant from at least 30 days before the first dose of study drug and throughout the study.

The study investigator will decide if you are using an acceptable form of birth control. Please Note: Whichever method of birth control you choose, remember that aside from abstinence (not having sexual intercourse), all birth control methods sometimes fail, even if used properly and consistently.

You must tell the study investigator right away if you become pregnant during this study or within 30 days of completion of the study. The study investigator will follow you to the completion or termination of your pregnancy to collect information about the pregnancy and the health of the baby.

***Will I benefit from taking part in this study?***

There is no intended medical benefit to you from taking part in this study. However, you may indirectly benefit by having a physical examination, an electrocardiogram (ECG), and blood and urine tests.

***Will anyone know that I am taking part in this study?***

Certain people and organizations will need to see and copy your research records so that they can do their part in the study. Only authorized users will be given access to and may make copies of your research records. Your research records may or may not include your name and they may be traced back to you even if it does not include your name. Authorized users include:

- Representatives of [redacted]
- Representatives of the [redacted]
- Representatives of USWM, LLC.
- Representatives of the Food and Drug Administration (FDA) and other US governmental agencies.
- Governmental agencies of other countries.
- Labs working with the Sponsor and [redacted] on this study.

- State/Governmental agencies to whom certain diseases (like HIV, hepatitis) must be reported.

We cannot promise complete confidentiality of your research records and personal health information. However, sharing your research records will be guided by professional standards and the law. Information from this study may be presented at meetings or published in medical journals but will not include your name or information that can be traced back to you. Your records shall not be used for any other purpose or shown to any other third party, except as required by law.

For your safety, the study investigator should tell your regular health care provider that you are in this study. Please inform the study staff if you would like us to do so. If you would like us to send results from your physical examination and laboratory tests to your personal doctor, we will do so if you complete a release of information form. At your request, we can also supply those results to you.

***Will persons looking at my medical information be able to identify me?***
Records of your participation in this study will be held confidential except when sharing the information is required by law or as described in this form. Research records that are sent to the study sponsor do not identify you by name. The study investigator uses your initials and a code number on these records. However, authorized users may look at all of your research records at the study investigator's site that will identify you. The reason these persons may look at your research records is to make sure the study has been done properly and that study data have been collected correctly, or for other reasons allowed by law.

A description of this clinical trial will be available on **http://www.ClinicalTrials.gov**, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

***Will my information be used for future research?***
There is no future research planned for your provided samples (e.g., blood, urine). The research study results, including individual research results, **will not** be provided to you.

***Who will pay if I am injured during this study?***
If you have a medical emergency, illness or bodily injury that was caused by the administration of the research drug or any study procedures, medical care approved by the study investigator will be provided to you free of charge. The study investigator will arrange for medical treatment and any tests necessary to determine the cause of your illness or injury. Other than the payment for participation and free medical care for study-related illness and injury, you can expect no other payment or care from [redacted] or the sponsor.

To pay medical expenses, related to your participation in the study, [redacted] or the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier. This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

If a research-related adverse effect or injury occurs after you have left our facility, call our duty nurse at: [redacted]. If you are not in the [redacted] area, you may use our toll-free number: [redacted].

***How can I get more information about this study?***
For more information about this study you may contact the [redacted] medical staff at [redacted] or [redacted].

***Who do I call if I think my rights as a research subject have been violated?***
For information about your rights as a research subject call the subject's research advocate at [redacted].

***Is my participation in this study voluntary?***
Your participation in this study is purely voluntary. You may refuse to take part in it, or you may stop participating at any time, even after signing this form. If you stop, it is in your best interest to tell the study staff and follow any instructions they may give you. You will not be penalized or lose any medical benefits to which you are otherwise entitled. When you stop taking part in the study, you will be asked to go through the termination procedures the study investigator thinks are necessary for your safety. You may be asked to remain at the clinic until the study investigator considers it safe for you to leave. Any data or samples that have already been collected from you may still be used as described in this consent form.

The sponsor and the study investigator may stop the study or stop your participation at any time. This may be done for any of the reasons listed below and does not require your agreement.

- If you do not follow the study investigator's instructions
- If we find out you should not be in the study
- If the study is stopped
- If you have difficulties with blood collection
- If it becomes harmful to your health
- If you are female and become pregnant
- Adverse events/side effects

***What other treatments are available to me?***
This is not a study designed to provide treatment. Your alternative is to not take part in this study.

***How much will I be paid if I complete this study?***

If you complete the entire study, you will be paid [redacted].

You will be paid an appropriate amount based on your extent of participation if:

- You are unable to complete the study.
- You voluntarily leave the study.
- The study is stopped early.
- You are withdrawn because of side effects.
- You screened and qualified for the study but you were not chosen to participate.

[redacted]

[redacted]

## SIGNATURE PAGE

### SUBJECT

- I have read or have had read to me the consent form for this study and the contents were explained to me. All of my questions were answered to my satisfaction. I understand that I have the right to be provided with answers to any questions that may come up during the study.
- I understand that my participation in this study is voluntary and I may stop participating at any time.
- I agree to be in this research study.
- I will receive a copy of this consent form.

_____
Subject Name *(Print)*

_____ _____
Subject Name *(Sign)* Dated by Subject

### INFORMED CONSENT OBTAINED BY:

I have explained to the subject the nature and purpose of this study. There has been an opportunity for the subject to ask questions about this research study. I hereby verify the informed consent, the subject's signature and acknowledge that a copy of the consent was provided to the subject.

My signature verifies that the subject provided consent prior to participation in this research study.

_____ _____ _____
Investigator or Investigator's Designee *(Sign)* Title Date