[redacted] pharmacokinetic modelling of intravenous and intranasal formulations of naloxone in healthy volunteers

Internal reference: IMIMFCTL/NLX_1

Development Phase: Phase I

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Informed Consent Form

(version 2.0, 15th December 2023)

This document may be publicly available on ClinicalTrials.gov in accordance with applicable regulations.

INFORMATION SHEET FOR THE POTENTIAL PARTICIPANT

STUDY TITLE: [redacted] pharmacokinetic modeling of intravenous and intranasal formulations of naloxone in healthy volunteers
Code: IMIMFCTL/NLX_1
Version and date: Version 2, date 15/12/2023
EU CT Number: 2023-506064-14-00

Sponsor
[redacted]

Principal Investigator and Coordinator
[redacted]

Co-Principal Investigator
[redacted]

This information sheet follows the recommendations of the Coordinating Center of Clinical Research Ethics Committees (CC-CEIC) of the Ministry of Health and Consumer Affairs.

INTRODUCTION

We are contacting you to inform you about a research study in which you are invited to participate. The study has been approved by the Research Ethics Committee with medicines [redacted], in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, which regulate clinical trials with medicines.

Our intention is only that you receive correct and sufficient information so that you can evaluate and judge whether or not you accept to participate in this study. For this purpose, read this information sheet carefully and we will clarify any doubts that may arise after the explanation. In addition, you may consult with the persons you consider appropriate.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary. You may decide not to participate or change your decision and withdraw your consent at any time, without this altering your relationship with your doctor or causing any prejudice to your healthcare.

INTRODUCTION

Naloxone is a medicine that rapidly reverses an opioid overdose. It is an opioid antagonist, that is, it attaches to opioid receptors reversing and blocking the effects of other opioids. Its effects begin within two minutes when administered intravenously and within five minutes when injected intramuscularly or intranasally. It blocks the effects of opioids between 30 and 90 minutes.

PURPOSE OF THE STUDY

The objective will be to carry out an excretion study of two formulations of naloxone (intranasal and intravenous) in healthy subjects.

Excretion studies provide us with information on variations in plasma and urine concentrations over time, allowing knowledge of the elimination of a drug when administered at a specific dose.

GENERAL INFORMATION OF THE STUDY

1. Type of study

If you decide to participate in this study, you must understand that it is a single-center study (carried out in a single center), randomized (process by which participants are assigned at random to separate groups receiving different treatments or other interventions), cross-over (study in which subjects receive a sequence of different treatments). That is, you will receive one of the two formulations (intravenous or nasal) randomly in the first session and then, in the second part of the study, you will receive the other. If you decide to participate, you will receive both routes of administration:

1. One intravenous dose of 1 mg.
2. One intranasal dose of 1.8 mg.

You will receive these doses in two different sessions. The selection of the route of administration you will receive in the first session will be done randomly; thus, in the second session you will receive the medicine by the route of administration that you have not received.

2. Participants and treatments

It is planned that a total of 8 healthy subjects between 18 and 55 years old will participate in each administration. As explained above, you will receive both formulations; for this, one of the following administration sequences will be randomly assigned:

- Intravenous – Intranasal (4 participants).
- Intranasal – Intravenous (4 participants).

The doses used in this study will never exceed the maximum therapeutic doses recommended by the Spanish Agency of Medicines for this product.

You will be given a copy attached of the package leaflet of this medicine, which is also included at the end of this information document.

Receiving one route of administration or another will be done randomly.

The administration will be carried out in the [redacted] in the morning.

3. Methodology used

Selection criteria

In order to participate, you must be in good health. To verify this, and before starting the study, you must come to our center fasting to undergo a medical examination.

You should know that you will be able to participate in the study if, in the 14 days prior to the medical examination, you have not presented symptoms compatible with a potentially infectious respiratory disease such as cough, sensation of shortness of breath, sore throat, chest pain when breathing in, chills, asthenia, joint and/or muscle pain, nausea, vomiting, diarrhea, headache, total loss or alteration of taste and/or smell, and body temperatures higher than 37ºC. For this reason,

the investigator will have carried out a prior telephone questionnaire; if at any time you present any of these symptoms, inform the investigator. Keep in mind that individual responsibility is essential to minimize the spread of the disease among the rest of the participants and the team.

The medical examination consists of the review of your medical history (clinical history), a physical examination, an electrocardiogram, a general analytical control in blood and urine, as well as specific tests (hepatitis B/C serology and the test to determine whether you have antibodies against the HIV virus or AIDS virus). Likewise, the presence of drugs in urine will be determined.

The results of all your blood analyses, as well as other analytical results, will be provided to the sponsor. These results are coded so that the sponsor does not know to whom they belong. Positive results for HIV and viral hepatitis will be communicated to the local health authorities as required by health legislation.

Biological samples will be analyzed in the laboratory [redacted]. Once the clinical trial is completed, the samples will be destroyed.

General rules
In the event that you have been selected to participate in this study, you must commit to complying with the requirements detailed below.

Please answer honestly the investigators' questions about your medical history, current illnesses, and treatments you are taking. Inform about medications you take chronically, those you have taken in the last month and recent weeks. If you hide this information, you are assuming an unnecessary risk. Keep in mind that the most important thing is your health. You must commit to abstaining from the consumption of alcoholic beverages and energy drinks from 48 hours before administration of the drug until the end of the study. The consumption of beverages with methylxanthines (coffee, tea, chocolate, cola) is allowed as one single drink per day.

You must not take any type of medication or drug of abuse during your participation in the study. For this purpose, urine drug tests will be performed.

You must also not perform strenuous exercise 48 hours before administration nor during your participation in the study (more than 2 hours per day or more than 3000 Kcal per day).

For the proper development of this study, it is essential that you follow at all times the instructions provided by the research team and that you are extremely punctual.

Study development
The SCREENING VISIT will take place within the 4 weeks prior to the start of the study. At this visit, a clinical history, general physical examination including weight, height and body mass index (BMI), 12-lead electrocardiogram (ECG), general blood and urine analysis, and urine screening for drugs of abuse (amphetamines, benzodiazepines, cocaine, morphine and THC, or similar) will be performed to verify that you meet the inclusion criteria and do not meet any exclusion criteria.

The general analysis will consist of a biochemical profile (glucose, urea, creatinine, uric acid, sodium, potassium, LDH, CPK, total and direct bilirubin, AST (GOT), ALT (GPT), gamma-GT (GGT), alkaline phosphatase, calcium, phosphorus, total proteins, cholesterol and triglycerides), blood count (red blood cells, hemoglobin, hematocrit, leukocyte count and differential), coagulation (platelets, PPT and PT), serologies (HBV, HCV, HIV); and qualitative elemental urine analysis (pH, glucose, ketone bodies, bilirubin, urobilinogen, proteins, red blood cells/hemoglobin, leukocytes and nitrites).

For inclusion, analytical values must be within the limits of population reference values. Minor or occasional variations may be accepted if, in the opinion of the Principal Investigator, considering the state of science, they have no clinical relevance, do not pose a risk to subjects and/or do not interfere with the evaluation of treatments. These variations and their non-relevance will be specifically justified in writing.

If you meet the inclusion criteria and do not incur in any exclusion criteria, you may participate in the study. Subsequently, and if you agree with the study conditions, you will be given the informed consent for you to sign.

For this study, on the day of the **EXPERIMENTAL SESSION (day 1)** you must come fasting early in the morning (07:45 h) to the Unit. A breath alcohol test and a urine drug test will be performed before administration. After verifying that you still meet the inclusion criteria and none of the exclusion criteria, vital signs will be taken, a baseline blood sample will be drawn for safety biochemistry, and a blood sample and a single urine sample will be collected for analysis of drug concentrations prior to administration.

You will receive a single dose of intravenous or intranasal naloxone of 1 mg and 1.8 mg, respectively, according to the order to which you have been previously and randomly assigned (intranasal-intravenous or intravenous-intranasal).

You must remain in the Unit until the evaluations are completed. For both routes of administration, this will be 6 hours after administration (approximately 7 hours in the Unit). Afterwards, if you are in adequate condition, you may leave the Unit.

Throughout the session, vital signs will be determined: systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), and oral temperature (T^a) using specific monitors (Dinamap® Pro Care, GE® or similar). Throughout the study, you will be constantly asked about the appearance of possible adverse events and the need to take medication additional to the clinical trial will be assessed.

Once the study drug has been administered, blood samples will be taken during day 1 in the Unit at 2, 5, 10, 15, 20, 25, 30, 35, and 45 minutes, and 1h, 1.5h, 2h, 4h and 6h afterwards. To perform these extractions, a catheter will be placed to avoid discomfort caused by direct blood draws.

Three days after the first dose, you will have to return for the second session. In this session, the medication will be administered by the remaining route of administration and the procedures of the first day will be repeated. The following day, a phone call will be made to check that everything is fine.

After administration of the drug, you must continue fasting for 4 hours. [redacted]

Duration of the study

The duration of participation per subject in the study is approximately 6 weeks, considering an initial screening visit, two experimental sessions with collection of biological samples, and a final visit 5 days after the first administration.

BENEFITS AND RISKS

Benefits: Your health does not directly benefit from your participation in this study.

Discomforts and risks: During the study you will have to attend our center on several occasions (information, screening visit, experimental sessions, follow-up visits, and final visit). In addition to possible (mild) discomfort from venous blood draws such as: bleeding, fainting or feeling dizzy, bruising, multiple punctures to locate veins, or infection.

POSSIBLE ADVERSE EVENTS

In this section we will refer to the possible adverse events induced by naloxone, which are included in the package leaflet of the medicine that is attached together with this document. The administration of this opioid antagonist is associated with very few side effects. In particular, if it is administered to a person who is not using opiates, it will not have any perceptible effect, but in very few cases it may cause:

- Intranasal:
    - Very common: feeling of illness (nausea).
    - Common: dizziness, headache, rapid heart rate (tachycardia), high blood pressure (hypertension), low blood pressure (hypotension) and vomiting.
    - Uncommon: tremor, slow heart rate, sweating, irregular heart rate, diarrhea, dry mouth and rapid breathing.
    - Very rare: allergic reactions such as swelling of the face, mouth, lips or throat, allergic shock, irregular and potentially life-threatening heartbeats, myocardial infarction, accumulation of fluid in the lungs, skin problems such as itching, rash, redness, swelling or severe peeling of the skin.
- Intravenous:
    - Very common: nausea.
    - Common: dizziness, headache, rapid heartbeat (tachycardia), increased or decreased blood pressure, vomiting.
    - Uncommon: involuntary tremors, sweating, changes in the way your heart beats, slow heart rate (bradycardia), diarrhea, dry mouth, excessive breathing (hyperventilation), irritation of the vessel walls, local irritation and inflammation.
    - Rare: seizures and tension.
    - Very rare: allergic reactions (hives, nasal discharge or cold, difficulty breathing, angioedema (severe swelling), allergic shock, fibrillation, cardiac arrest, fluid in the lungs (pulmonary edema), discoloration and skin lesions (erythema multiforme).

In general, any drug may cause adverse effects, although not all people experience them.

ALTERNATIVE TREATMENTS

Since this is a study with healthy volunteers, it is not appropriate to establish any alternative treatment.

INSURANCE

[redacted] sponsor of the study, has an insurance policy that complies with current legislation (Royal Decree 1090/2015) and that will provide you with compensation and indemnification in case of impairment of your health or injuries that may occur in relation to your participation in the study.

CONFIDENTIALITY

The processing, communication and transfer of personal data of all participating subjects will comply with the provisions of Organic Law 3/2018 of December 5 on Personal Data Protection and guarantee of digital rights, and the Royal Decree that develops it (RD 1720/2007). In accordance with the provisions of the aforementioned legislation, you may exercise your rights of access, modification, opposition and cancellation of data, for which you must contact your study doctor.

As of May 25, 2018, the new EU legislation on personal data is fully applicable, specifically Regulation (EU) No. 2016/679 of the European Parliament and of the Council of April 27, 2016 on Data Protection (GDPR). Therefore, it is important that you are aware of the following information:

All data regarding your participation in this study will be collected in a research file under the responsibility of the institution, will be considered confidential and will only be used by researchers for scientific purposes. In the data collection notebooks, which may be inspected by the sponsor (or persons authorized by it, for example auditors), [redacted] or the Health Authorities, only a code will appear. In this way, your identity will not be revealed during these inspections. In the final report of the study or if these results are communicated to the scientific community, your identity will be kept anonymous using a code.

The coded data may be transferred to third parties and to other countries, but in no case will they contain information that can directly identify you. In the event that such transfer occurs, it will be for the same purposes of the study described or for use in scientific publications, always maintaining confidentiality in accordance with current legislation.

If you decide to withdraw your consent to participate in this study, no new data will be added to the database, but those already collected will be used.

In addition to the rights you already know (access, modification, opposition and cancellation of data), you may now also limit the processing of incorrect data and request (once the trial has ended) a copy or that the data you have provided for the study be transferred to a third party. To exercise your rights, contact the principal investigator of the trial [redacted] We remind you that the data cannot be deleted, even if you stop participating in the study, in order to guarantee the validity of the results and comply with legal obligations and requirements for the authorization of medicines. Likewise, you have the right to contact the Data Protection Agency if you are not satisfied.

The Investigator and the Sponsor are obliged to keep the data collected for the study for at least 25 years after its completion. Subsequently, your personal information will only be kept by the center for your healthcare and by the sponsor for other scientific research purposes if you have given your consent for this, or if permitted by law to comply with pharmacovigilance regulations.

Both the Center and the Sponsor are responsible for the processing of your data and undertake to comply with current data protection regulations. The data collected for the study will be identified by means of a code (pseudonymized), so that no information that can identify you is included, and only your study doctor/collaborators will be able to link this data with you and your clinical history. Therefore, your identity will not be revealed to any other person except to health authorities when required or in cases of medical emergency. Research Ethics Committees, representatives of the Health Authority in inspection matters, and personnel authorized by the Sponsor may only access the data to verify personal data and clinical study procedures (always maintaining their confidentiality).

[redacted]

COMPENSATION

[redacted] This compensation is structured in such a way that full participation in the study is rewarded. If you do not complete the study while respecting the instructions that have been provided to you, you will not be able to receive the full amount of the compensation. Remember that your health does not directly benefit from participating in the study.

OTHER RELEVANT INFORMATION

Any new information regarding the drug used in the study that is discovered during your participation and that may affect your willingness to participate will be communicated to you by your doctor as soon as possible. If you decide to withdraw your consent to participate in this study, no new data will be added to the database and you may request the destruction of all previously retained identifiable samples to prevent further analyses.