[redacted] pharmacokinetic modelling of oral and intranasal formulations of oxycodone in healthy volunteers

Internal reference: IMIMFCTL/OXY_1

Development Phase: Phase I

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Informed Consent Form

(version 2.0, 03rd February 2025)

[redacted]

PROSPECTIVE PARTICIPANT INFORMATION SHEET

STUDY TITLE: [redacted] pharmacokinetic modeling of oral and intranasal formulations of oxycodone in healthy volunteers

Code: IMIMFCTL/OXY_1
Version and date: vs 2.0; 03 FEB 2025
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Sponsor
[redacted]

Principal Investigator
[redacted]

Co-principal
[redacted]

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

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INTRODUCTION

We are writing to inform you about a research study in which you are invited to participate. The study has been approved by the Comitè Ètic d'Investigació amb medicaments [redacted], in accordance with current legislation, Royal Decree 1090/2015 of December 4 and European Regulation 536/2014 of April 16, regulating clinical trials with medicinal products.

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

VOLUNTARY PARTICIPATION

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

OXYCODONE IS AN ANALGESIC DRUG

Oxycodone is a semi-synthetic opioid used to treat moderate to severe pain. It acts as a full agonist of opioid receptors (mu, μ) in the CNS, leading to its analgesic effect and the induction of other effects such as euphoria, relaxation, and anxiety. There are formulations for oral or intravenous administration. Its formulation for intranasal administration is not commercialized, although the pharmacokinetics (the evolution of plasma concentrations in the organism) of oxycodone by this route has been studied by administering crushed tablets or injectable solutions.

[redacted]

PURPOSE OF THE STUDY

The drug administered intranasally can reach the brain by two main routes: systemic circulation and through the membrane lining the nasal passages. Drug transport through these routes depends on the physicochemical properties of the drug, formulation, physiological condition, type of delivery device, among other factors.

The aim of this study is to obtain more data on plasma concentrations over time of intranasal administration of an injectable solution compared to the administration of an oral solution. Both presentations are commercially available and have been used in previous studies.

GENERAL INFORMATION ABOUT THE STUDY
1. Type of Study

If you decide to participate in this study you should understand that this is a single-center (conducted at a single center), randomized (a process by which participants are randomly assigned to separate groups receiving different treatments or other interventions), crossover (a study in which subjects receive a sequence of different treatments) study. That is, you will receive one of the two formulations for oral or intranasal administration but the selection of the route of administration you will receive in the first session will be randomized; thus, in the second session you will receive the drug by the route of administration you have not received.

If you choose to participate, you will receive oxycodone by both routes of administration:

1. Intranasal administration of oxycodone solution: 0.1 mg/kg dose (e.g., 7 mg if you weigh 70 kg); 2. intranasal administration of oxycodone solution: 0.1 mg/kg dose (e.g., 7 mg if you weigh 70 kg).
2. Oral oxycodone:

    If your weight < 70 kg: dose of 5 mg

    If your weight > 70 kg: 10 mg dose

You will receive these doses in two separate sessions.

2. Participants and treatments

A total of 8 healthy subjects between 18 and 55 years of age are planned to participate in the study. As explained above, you will receive both formulations, for this one of the following administration sequences will be randomly assigned:

- Oral - Intranasal (4 participants).

- Intranasal - Oral (4 participants).

The doses used in this study will never exceed the maximum therapeutic doses recommended by the Spanish Medicines Agency for this product.
You will be given an attached copy of the package insert for this drug, which is also included at the end of this information document.

[redacted]

[redacted]

3. Methodology used

Selection criteria

In order to participate, you must be in good health and have been a consumer on some occasion of opiates or opioids (semi-synthetic opiates such as oxycodone) for the treatment of pain or recreational consumption, but we will rule out the abuse of this type of substance. To verify this and, before starting the study, you must come to our center on an empty stomach to undergo a medical check-up.

You should know that you will be able to participate in the study if in the 14 days prior to the medical examination you do not present symptoms compatible with potentially infectious respiratory disease such as cough, choking sensation, 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 above 37ºC. Before coming to our center, the investigator will have conducted a telephone questionnaire beforehand, if at any time you present any of these symptoms please inform the investigator. Please note that it is your individual responsibility to answer truthfully to the investigator.

The medical examination in our center consists of a review of your medical history (medical history), a physical examination, an electrocardiogram, a general analytical control in blood and urine, as well as specific tests (serology of hepatitis B / C and the test to know if you have antibodies against the HIV virus or AIDS virus), also the presence of drugs in urine will be determined. Additionally, we will collect a sample of your hair to check your drug use retrospectively.

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

[redacted]

General rules and regulations

If you have been selected to participate in this study, you must agree to comply with the following requirements.

Please answer truthfully to the investigators' questions about your medical history, current illnesses and treatments you are taking. Report any medications you are taking chronically, those you have taken in the last month and last few weeks. If you hide this information you are taking an unnecessary risk. Think that the most important thing is your health. You must undertake to abstain from the consumption of alcoholic beverages and energy drinks from 48 hours before the administration of the drug until the end of the study. The consumption of methylxanthine beverages (coffee, tea, chocolate, cola) is allowed only one drink per day.

[redacted]

You must not take any type of drug or drug of abuse during your participation in the study. To this end, urine drug screens will be performed.

You will also be asked to avoid strenuous physical activities (if any, e.g. jogging or running, fast swimming, fast cycling, climbing stairs, sports such as soccer, rugby and field hockey, jumping rope, aerobics, gymnastics or martial arts) during the study, as they may affect some of your blood parameters.

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

Development of the study

The SELECTION VISIT will take place within 4 weeks prior to the start of the study. During this visit, a medical 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) and caffeine will be performed to verify that they meet the inclusion criteria and do not meet any exclusion criteria.

The general analysis will include a biochemical profile, hemogram, coagulation, serology (hepatitis B and C, HIV), thyroid hormones and pregnancy test; and qualitative elemental urinalysis .

For inclusion, the values of the analytical tests must be within the limits of the population reference values. Minor or punctual variations of these limits will be admitted if, in the opinion of the Principal Investigator, considering the state of science, they do not have clinical significance, do not pose a risk for the subjects and/or do not interfere in the assessment of the treatments. These variations and their non-relevance will be specifically justified in writing.

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

For this study, on the day of the EXPERIMENTAL SESSION (day 1) you will have to come to the Unit early in the morning (07:45 am) on fasting conditions. An exhaled breath alcohol test and a urine drug test will be performed prior to administration. After verifying that you continue to meet the inclusion criteria and none of the exclusion criteria, vital signs will be taken, a basal blood sample will be drawn for safety biochemistry, and a blood sample and an isolated urine sample will be collected for analysis of drug concentrations prior to administration. A single dose of oral oxycodone of 5 to 10 mg will be administrated, depending on the patient's weight greater than or equal to or less than 70 kg, or 0.1 mg/kg by the intranasal route, respectively, and according to the order to which it has been previously and randomly assigned (intranasal-oral or oral-intranasal).

The patient must remain in the Clinical Research Unit (CRU) until the end of the evaluations. For both routes of administration, 12 hours after administration (approximately 13 hours in the CRU). Afterwards, if you are in condition, you will be able to leave the Unit.

[redacted]

Throughout the session, vital signs will be determined: systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR) and oral temperature (T°) by means of specific monitors (Dinamap® Pro Care, GE® or similar).

Throughout the study, the patient will be constantly asked about the occurrence of possible adverse events and the need to take additional medication to the clinical trial will be assessed.

Once the drug under study is administered, blood extractions will be performed during day 1, in the CRU, prior to the administration of the drug and at 5, 10, 15, 20, 30, 45, and 60 minutes and at 2, 3, 4, 5, 6, 8, 12 and 24 hours later. To perform these extractions, a catheter will be placed to avoid the discomfort that direct blood extractions could cause.

Approximately 270 mL will be drawn by adding the samples from the screening visit and those after drug administration (note that up to 450 mL can be drawn from one person in a single blood donation).

Your pupil diameter will also be determined with a digital ruler at 10, 20, 30, 45, 60 min, and at 2, 4, 6, 8, and 12 h.

Vital signs (blood pressure and heart rate) will also be measured prior to the study medication and at 15min, 30min, 1h, 1.5h, 2h, 4h, 6h post-dose.

It will be at least 72 hours after the first dose before you return for the second session. At this session you will be given the medication by the missing route of administration and the first day's procedures will be repeated. The next day we will make a phone call to check that everything is fine.

After the drug administration you will need to continue fasting for 4 hours. We will provide you with snacks and a menu with first and second dishes after this time.

Duration of the study

The duration of participation per subject in the study is approximately 6 weeks, considering a first screening visit, two experimental sessions with collection of biological samples and a final visit at least the day after of the second 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 come to our center on several occasions (information, entry review, experimental sessions, follow-up visits and final visit). In addition to the possible (mild) discomforts from vein stripping such as: bleeding, fainting or feeling dizzy, bruising, multiple punctures to locate veins or infection, the study medication may have some possible adverse effects described below.

POSSIBLE ADVERSE EVENTS

[redacted]

In this section we will inform about the possible adverse events induced by oxycodone, which are summarized in this sheet and in the package insert of the drug for oral solution administration.

Oxynorm® is authorized for oral administration for the treatment of severe pain in patients over 12 years of age, in repeated doses at intervals of 4 to 6 hours. In oral administration for the treatment of pain, possible adverse events were described:

Very frequent (≥1/10): drowsiness, dizziness, headache, constipation, nausea, vomiting, pruritus [at single doses as in the case of the study in which you will participate].

At repeated doses (which is not the case in the present study) other adverse effects that may occur are listed in the package insert enclosed.

In intranasal administration of an injectable solution, used in a 1998 study by Takkala published in Acta Anaesthesiol Scand 1997; 41: 309-312, no changes in either heart rate or blood pressure were observed after single-dose intranasal administration. In all ten volunteers who participated, it caused drowsiness. One of the volunteers experienced dysphoria and vomiting, but his drug concentrations were similar to those of the rest of the study participants and the event resolved.

In general, any drug can 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] promoter 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 the Organic Law 3/2018 of 5 December on the Protection of Personal Data 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 the data, for which you should contact your study doctor.

As of May 25, 2018, new legislation in the EU on personal data, specifically Regulation (EU) No. 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection

[redacted]

(GDPR), is fully applicable. Therefore, it is important that you are aware of the following information:

All data about 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 the researchers for scientific purposes. Only one code will be included in the data collection notebooks, which may be inspected by the sponsor (or persons authorized by the sponsor, e.g. auditors), [redacted] or by the Health Authorities. In this way your identity will not be revealed with these inspections. In the final report of the study or in case of communicating these results to the scientific community, your identity will be kept anonymous using a code. The coded data may be transmitted to third parties and to other countries, but in no case will it contain information that can directly identify you. In the event that this transfer occurs, it will be for the same purposes of the study described or for use in scientific publications, but always maintaining the confidentiality of the same in accordance with current legislation.

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

In addition to the rights you already know (access, modification, opposition and cancellation of data) you can now also limit the processing of data that are incorrect and request (once the trial ends) a copy or that the data you have provided for the study be transferred to a third part. [redacted] We remind you that the data cannot be deleted, even if you stop participating in the study to ensure the validity of the study results and to comply with legal duties and drug authorization requirements. You also 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. Thereafter, your personal information will only be retained by the Center for your health care and by the Sponsor for other scientific research purposes if you have given your consent to do so, or if permitted by law to comply with pharmacovigilance regulations.

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

[redacted]

For your safety, the Clinical Research Unit is equipped with video surveillance cameras so that during your stay in our facilities you will be monitored at all times.

COMPENSATION

[redacted] This compensation is graded so that full participation in the study is rewarded. If you do not complete the study according to the instructions provided to you, you will not receive the full compensation. Remember that your health does not benefit directly from participating in the study.

OTHER RELEVANT INFORMATION

Any new information concerning the drug used in the study that is discovered during your participation that may affect your willingness to participate in the study will be communicated to you by your physician as soon as possible.

If you decide to withdraw consent to participate in this study, no new data will be added to the database and, you may require the destruction of all identifiable samples previously retained to prevent further analysis.

You should also be aware that you may be withdrawn from the study at the Principal Investigator's discretion in the event of:

1) Significant protocol transgression.
2) Undesirable effects due to the drug under study.
3) Intercurrent diseases that could increase the risk or invalidate the results.
4) Ingestion of medications, alcohol or use of illegal drugs.

If you have any doubts about any aspect of the study or would like to comment on any aspect of this information, please do not hesitate to let the members of the research team know.
For this purpose, you will be provided with a card containing the study code, contact telephone numbers and the responsible physician. You must undertake to carry the card with you at all times from the beginning of the study until the end of the study. [redacted]

CONSENT

If, after reading this information and clarifying any doubts that may have arisen, you decide to participate, you must sign a "written consent form" based on the model proposed by the Coordinating Center for Clinical Research Ethics Committees (CC-CEIC) of the Ministry of Health and Consumer Affairs.