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

Internal reference: IMIMFCTL/OXY_1

Development Phase: Phase I

NCT number: NCT07223450

Protocol Summary

(version 2.0, March 2024)

PROTOCOL SUMMARY

Clinical trial title	[redacted] **pharmacokinetic modelling of oral and intranasal formulations of oxycodone in healthy volunteers.**
Protocol internal reference	HMRIFCTL/OXY_1
NCT number	NCT07223450
EudraCT number	2024-515461-34-00
Version/date	2.0/24th March 2025
Sponsor identification	[redacted]
Request type	Request for authorization of a clinical trial on a medicinal product for human use to the competent authorities and for opinion of the ethics committees in the community. The Investigational Medicinal Product (IMP) to be used in the clinical trial has a marketing authorization in the EU member state concerned.
Principal Investigator (PI)	[redacted]
Institution	[redacted]
Research Ethics Committee	The clinical protocol will be approved by the Ethics Committee for Drug Research [redacted]
Clinical phase	Phase I
Disease or disorder	Healthy volunteers
Inclusion criteria	• Healthy male or female volunteers according to physical examination, vital signs, ECG and safety laboratory parameters and

	results should be within normal ranges or considered as non-clinically relevant by the investigator. • Age ≥ 18 and ≤ 55 years. • Body weight up to 90 kg. • Body mass index (BMI) ≥ 18 and ≤ 30. • Able/willing to be compliant with the study restrictions. • Able to read Spanish and adhere to study requirements. • Signed informed consent prior to any study-mandated procedure. • Prior therapeutic or recreational experience with opioids (i.e., tramadol, oxycodone, or buprenorphine)
Exclusion criteria	• Life-time (current and/or history of) substance use disorders (SUD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). • Use of any illegal drug within 30 days of screening and throughout participation in the study. • History of smoking or use of nicotine containing products within 3 months of screening and throughout participation in the study. • Presence of acute, chronic, or allergic rhinitis. • Ongoing gastrointestinal diseases or history of gastrointestinal surgery affecting absorption. • History of severe bronchial asthma or chronic obstructive pulmonary disease, • Any anatomical abnormality or pathological condition of the nasal cavity based on medical history. • History of hypothyroidism. • Subjects with a clinically relevant disease or condition that in the judgment of the investigator might interfere with the safety or subject's ability to comply with study procedures or requirements and/or bias the interpretation of the study results and/or jeopardize the subject's safety. • Current mental diseases that require prescription drugs. • Any ophthalmologic condition that could interfere with pupillometry • Being under any administrative or legal supervision. • Pregnancy and breastfeeding • Positive blood or urine test for drugs of abuse or alcohol breath test prior to study drug administration. • Current and/or history of anxiety or depression not completely recovered within 12 months prior to study drug administration, as assessed by the Dual Diagnosis Screening Interview (DDSI). • CYP2D6 poor or ultrarapid metabolizers. • Any clinically relevant findings in physical examination, vital signs, 12-lead ECG and safety laboratory parameters. • Positive hepatitis or HIV tests (Ag VHB, IgG VHC, Ac VIH). • Known hypersensitivity to any drug or drug excipients. • Use of drugs known to induce or inhibit hepatic drug metabolism within one month prior to study administration or during the study and use of citrus juice during the study. • Use of sedative medicines such as benzodiazepines or related drugs in the last 3 months. • Any prescription or over-the-counter (OTC) product, not including oral contraceptives but including analgesics (paracetamol), aspirin,

	herbal, homeopathic, vitamins, minerals and nutritional supplements within one week prior to study drug administration. • Intake of foods or beverages containing xanthine (more than 5 cups of coffee, tea or 5 bottles/cans cola drinks) per day. • Donation of blood or plasma within two months prior to study drug administration • Transfusion of blood or plasma for medical/surgical reasons in the past 120 days. • Current or history of inadequate venous access and/or experience of difficulty donating blood. • Subject included in a clinical trial within 3 months prior to study drug administration.
Study Design	A single-dose, 2-period, 2-sequence, fasting, open label, crossover randomized design, comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal (IN) and oral (OR) oxycodone solutions.
Study Drugs	• Oral solution of oxycodone (OXYNORM CONCENTRADO 10 mg/ml) • Oxycodone (OXYNORM 10 mg/mL solution for IV/perfusion) administered intranasally • Nasal delivery system of Aluneb or similar.
Doses	OR oxycodone: In the absence of a significant bioavailability difference between oral and IN administration of oxycodone solution, it is proposed to administer oxycodone orally (oral solution) 0.1 mg/kg, in the range of 5-9 mg. IN administration of oxycodone solution: 0.1 mg/kg (subjects weighing approximately 70 kg, the total volume of the oxycodone chloride solution which will be sprayed intranasally will be 0.70 mL in total) with a total dose of 7 mg. The volume of one spray will be 0.1 mL. The nurse will administer the spray alternately in both nostrils while the subject is in a supine position to minimize dripping. If the subject begins coughing, sneezing or reports needing to swallow the solution, we will wait 2–3 minutes before proceeding with another sequence of applications. The IN doses will be administered over a period of 5 minutes. Subjects will be trained in intranasal administration prior to receiving the drug products. Doses in OR or IN administration will follow rounding down rule for body weight-based dosing.
Number of subjects / groups	A total of 8 healthy male/female subjects will be randomly assigned to one of two sequences in the crossover study. All subjects will receive the same dosage of oxycodone IN or OR and the sequence will be determined following randomization.
General Objective	The aim will be to characterize the PK and PD of two formulations of oxycodone (IN and OR) in healthy subjects, which will be used to verify/validate nasal- CNS-PBPK (Physiologically Based Pharmacokinetic) model predictions following IN dosing.

Specific objectives:	**1. Pharmacokinetics objectives:** To calculate plasma PK parameters listed below using a non-compartmental model: • Observed maximum concentration: C_{max}. • Observed minimum concentration: C_{last}. • Time to observed maximum concentration: t_{max}. • Time lag (time to first measurable plasma concentration): t_{lag}. • Area under the concentration-time curve (AUC_{0-24h}, AUC_{0-t}, $AUC_{0-\infty}$) where t is the latest observed timepoint. • Terminal elimination half-life: $t_{1/2}$. • Apparent clearance: Cl/F. • Apparent volume of distribution: Vd/F. • Elimination rate constant (λz). **2. Safety objectives** To evaluate drug safety focusing on: • Treatment-emergent AEs from Day 1 to end of study (EOS). • Treatment-emergent potentially clinically significant abnormalities (PSCAs) in vital signs, ECG and safety laboratory parameters from Day 1 to EOS. **3. Pharmacodynamic exploratory objectives:** To assess the effects of oxycodone on Pupil size.
Schedule and expected completion date	All adverse events and concomitant medications will be assessed, reviewed and recorded from the informed consent signature to the EOS visit. **Screening period: Visit 1 (Up to 28 days)** Following a signed informed consent, subjects will be screened for eligibility. Subjects will undergo a complete demographics, medical history, neuropsychiatric exploration (Dual Diagnosis Screening Instrument-DDS),and Hospital Anxiety and Depression Scale-HADS), medication history, physical examination, height, weight, vital sign evaluation (blood pressure, pulse rate, and body temperature), resting 12-lead ECG, CYP2D6 genotyping, clinical laboratory tests (chemistry, hematology, coagulation profile, urinalysis, HIV, hepatitis B & C diagnostic profile, thyroid hormones), urine pregnancy test, hair drug analysis, an alcohol breath test and urine drug screen within 28 days prior to receiving study medication. **First Treatment period:** **Visit 2 (Day 1):** • Subjects will be admitted to the [redacted] Research Unit (CRU) on Day 1, after a fasting period of at least 8 hours. All eligibility criteria will be confirmed. • On Day 1, before study drug dosing, the following assessments will be performed: (i) fasting body weight, (ii) fasting blood collection for clinical safety laboratory tests, (iii) ECG, (iv) vital signs (blood pressure, heart rate, body temperature), (v) physical examination, (vi) urinalysis, (vii) a urine caffeine test, (viii) an alcohol breath test, (ix) a EtG/EtS urine test, (x) urine drug test (xi) concomitant medications, (xii) urine pregnancy test (females), (xiii) pupil diameter.

	• Each subject will be assigned randomly to one of the sequences once the eligibility is reconfirmed. • Study drug dosing will take place around 08:00 in the morning. After drug dosing, the following assessments will be performed (± 5 minutes time window if needed at 0.25h and ±10 min for 24 hr. time-point if needed would be acceptable): • Blood PK sampling Intranasal and oral routes: pre-dose, and at 10, 20, 30, 40, 50, 60, 80, 100, 120 min and 3, 4, 6, 8, 12 h • 12-lead ECG pre-dose, 3h, 6h. • Vital signs (blood pressure, heart rate and body temperature) at pre-dose, 15min, 30min, 1h, 1.5h, 2h, 4h, 6h post-dose. • Pupil size at pre-dose, and at 10, 20, 30, 40, 50, 60, 80, 100, 120 min and 3, 4, 6, 8, 12h • Adverse events (AE) will be assessed and reviewed all along the day. • Subjects will be discharged from the CRU on Day 1 in the evening (after the 12h blood sampling) unless they present clinically significant drug-related AE impairing daily activities at the time of the discharge. **Visit 3: Day 2 (24h post-dose)** • Reviewing adverse events and concomitant medication. • 24 h blood PK sampling **Wash out period:** At least 3 days with a maximum of 2 weeks.) [redacted]
[redacted]	Indication: Oxycodone is a semisynthetic opioid used in the management of moderate to severe pain. Mechanism of action: Oxycodone's action appears to work through stimulating the opioid receptors found in the central nervous system that activate responses ranging from analgesia to respiratory depression to euphoria. Metabolism: Oxycodone's hepatic metabolism is extensive and completed by 4 main reactions. CYP3A4 and 3A5 regulate N-demethylation to noroxycodone, CYP2D6 regulates O-demethylation to oxymorphone (an active metabolite, deemed undetectable in many instances) and noroxymorphone (from noroxycodone), less characterized enzymes regulate 6-keto-reduction, and unknown enzymes perform conjugation. Oxycodone and its metabolites are eliminated in the urine The apparent elimination half-life of oxycodone PO is 3.2 hours for immediate release formulations and 4.5 hours for extended release formulations. Noroxycodone has a halflife of 5.8 hours, oxymorphone has a half-life of 8.8 hours, noroxymorphone has a halflife of 9 hours For OxyNorm 10 mg/ml in oral solution, the mean oral bioavailability is 87%. The estimated half-life of oral oxycodone is 4,5 hours and the peak concentrations is achieved at 1 hour.

	A solution for injection was administered intranasally by Takala et al (1997). The estimated half-life of intranasal oxycodone was 2.5 hours and the peak concentrations after the intranasal administration were achieved at 25 min (95% CI: 20-250 min). The mean bioavailability of intranasal administration was 46% (95% CI 25%-67%; min-max: 16%-90%). Pharmacodynamics: Oxycodone acts directly on a number of tissues not related to its analgesic effect. These tissues include the respiratory center in the brain stem, the cough center in the medulla, muscles of the pupils, gastrointestinal tract, cardiovascular system, endocrine system, and immune system. Oxycodone's effect on the respiratory center is dose dependent respiratory depression. The action on the cough center is suppression of the cough reflex. Pupils become myopic or decrease in size, peristalsis of the gastrointestinal tract slows, and muscle tone in the colon may increase causing constipation. In the cardiovascular system histamine may be released leading to pruritis, red eyes, flushing, sweating, and decreased blood pressure. Endocrine effects may include increased prolactin, decreased cortisol, and decreased testosterone. It is not yet known if the effects of opioids on the immune system are clinically significant. Adverse events: Very common: Somnolence, dizziness, headache, constipation, nausea, vomiting, itching Common adverse events: anxiety, confusion, depression, insomnia, restlessness, abnormal flow of thought, tremor, dyspnea, bronchospasm (especially in asthmatic patients), abdominal pain, diarrhea, dry mouth, dyspepsia, rash, ample sweating, faintness Overdose: Symptoms: Large doses depress the respiratory center considerably and circulation to a lesser extent. Overdose may lead to complete respiratory depression (apnea), bradycardia, hypotonia, miosis, hypotension, somnolence, which may lead to coma or intense grogginess, and death.
Statistical methodology	This is a Phase I study to assess the PK and PD of oxycodone intranasal vs oral administration. Given the nature of this Phase I study, the sample size was not based on power calculations and therefore statistical analyses will be mainly descriptive. Subjects will be randomized in two sequences: • Intranasal-washout period-oral (n=4) • Oral-washout period- intranasal (n=4)