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

Internal reference: IMIMFCTL/ZOL_1

Development Phase: Phase I

NCT number: NCT06074016

Protocol Summary

(version 2.0, 14th JUNY 2023)

PROTOCOL SUMMARY

Clinical trial title	[redacted] **Pharmacokinetic-pharmacodynamic modelling of oral and intranasal formulations of zolmitriptan in healthy volunteers.**
Protocol internal reference	HMRIFCTL/ZOL_1
NCT number	NCT06074016
EudraCT number	2023-504492-24-00
Version/date	2.0/14th Juny 2023
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 mass index (BMI) ≥ 18 and ≤ 30. • Able/willing to accept restrictions regarding diet, physical exercise, and consumption of alcohol and/or xanthine containing items when out of URC. • Able to read Spanish and adhere to study requirements. • Signed informed consent prior to any study-mandated procedure.
Exclusion criteria	• Smoking. • History of or ongoing clinically relevant diseases or conditions, included a history of myocardial infarction, cerebrovascular accident (CVA) or transient ischaemic attack (TIA). • Being under any administrative or legal supervision. • Pregnancy and breastfeeding • Life-time substance use disorders (SUD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). • Positive blood or urine test for drugs of abuse or alcohol breath test prior to study drug administration. • Life-time history of mental diseases. • 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). • Any other clinically relevant disease or condition that in the judgment of the investigator might interfere with the 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. • Ongoing gastrointestinal diseases or history of gastrointestinal surgery affecting absorption. • Subjects with a clinically significant disease within one month prior to study drug administration. • Any clinically relevant findings in physical examination, vital signs, 12-lead ECG and safety laboratory parameters. • Clinically relevant abnormalities in 12-lead ECG determined by the Investigator (e.g., conduction pathway disorders). • Positive hepatitis or HIV test. • Known hypersensitivity to any triptan drug or drug excipients. • Use of drugs known to induce or inhibit hepatic drug metabolism (e.g., cimetidine) within one month prior to study administration or during the study and use of citrus juice during the study. • Use of ergot-containing drugs and 5-HT1B/1D agonists (e.g., dihydroergotamine and methysergide) or 5-HT1B/1D agonists within 24 h of using zolmitriptan nasal spray. • Use of known monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B) inhibitors within one month prior to study administration or during the study. • Any prescription or over-the-counter (OTC) product including herbal, homeopathic, vitamins, minerals and nutritional supplements within 2 weeks prior to study drug administration. • Intake of foods or beverages containing xanthine (more than 5 units of coffee, tea or cola drinks per day).

	• Donation of blood or plasma within one month prior to study drug administration or transfusion of blood or plasma for medical/surgical reasons or intention to donate blood or plasma within one month after study drug administration. • History of inadequate venous access and/or experience of difficulty donating blood. • Not able/not willing to accept restrictions regarding diet, physical exercise, and consumption of alcohol and/or xanthine containing items when out of URC. • Subject included in a clinical study 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) tablets of zolmitriptan.
Study Drugs	OR zolmitriptan (Zolmitriptán Normon 5 mg comprimidos bucodispersables EFG, Normon laboratories) and zolmitriptan nasal spray (Zomig 5 mg solución para pulverización nasal, Grünenthal Health).
Number of subjects / groups	Approximately 8 healthy male and female subjects will be randomly assigned to one of two sequences in the crossover study. All subjects will receive the same dose of zolmitriptan intranasally or orally and the sequence will be determined following randomization.
General Objective	The aim will be to characterize the PK and PD of two formulations of zolmitriptan (IN and OR) in healthy subjects, which will be used to verify/validate nasal-CNS-PBPK (Physiologically Based Pharmacokinetic) model predictions following IN dosing.
Schedule and expected completion date	All adverse events and concomitant medications will be assessed, reviewed and recorded from the informed consent signature to the end of study (EOS) visit. **Screening period: Up to 28 days** Following a signed informed consent, subjects will be screened for eligibility. Subjects will undergo a complete demographics, medical history, medication history, physical examination, height, weight, vital sign evaluation (blood pressure, pulse rate, and body temperature), resting 12-lead ECG, clinical laboratory tests (chemistry, hematology, coagulation profile, urinalysis, HIV, hepatitis B & C diagnostic profile), urine pregnancy test, an alcohol breath test and urine drug screen within 28 days prior to receiving study medication. **First Treatment period:** **VISIT 1 (DAY 1) AND VISIT 2 (DAY 2):** Subjects will be admitted to the IMIM URC on Day 1, after a fasting period of at least 8 hours. All eligibility criteria will be reviewed. 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, (iii) ECG, (iv) vital signs (blood pressure, heart rate, body temperature), ((v) physical examination, (vi) urinalysis,

	(vii) a caffeine test, (viii) an alcohol breath test, (ix) a EtG/EtS urine test, (x) urine drug test (xi) concomitant medications, (xii) urine pregnancy test. Each subject will be assigned randomly to one of the sequences. Study drug dosing will take place around 08:00 in the morning. An interval between subjects of up to 15 minutes is allowed. After study 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 o Oral route: at pre-dose, 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 4.5h, 5h, 5.5h, 6h, 8h, 12h and 24h post-dose. o Intranasal route: pre-dose, 5, 10, 15, 30, 45 minutes, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 5h, 6h, 8h, 12h and 24h post-dose. • Blood PD sampling at pre-dose, 0.25h, 0.5h, 1h, 2h, 4h, 8h, 12h and 24h post-dose. • 12-lead ECG pre-dose, 3h, 6h, 12h, 24h post-dose (±10 min) • Vital signs (blood pressure, heart rate and body temperature) at 0.25h, 0.5h, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 4h, 5h, 6h, 8h, 12h, 24h post-dose (±10 min). • Fasting blood collection for clinical safety laboratory 24h post dose. • Body weight on day 2 (24h). • Physical examination on day 2 (24h). • Concomitant medications on day 2 (24h). • Adverse events (AE) will be assessed and reviewed all along the day. Subjects will be discharged from the URC on Day 1 in the afternoon unless they present clinically significant drug-related AE impairing daily activities at the time of the discharge. **Wash out period: At least 7 days** **SECOND TREATMENT PERIOD:** **VISIT 3 (DAY 8) AND VISIT 4 (DAY 9):** Subjects will be admitted to the URC on Day 8. All assessments described in Period 1 will be performed during Period 2. **THE EOS VISIT** will be on Visit 5 (Day 9 (+2 days)) The following assessment will be performed: (i) Body weight (ii) Fasting clinical safety laboratory (chemistry, hematology, coagulation profile, urinalysis), (iii) Urine pregnancy test (females only), (iv) alcohol tests and urine drug screen, (v) 12-lead ECG, (vi) vital signs (Blood pressure, Heart Rate, Body temperature), (vi) physical examination, (vii) EtG/EtS test, (viii) review of adverse events and (ix) concomitant medications. The blood PK sampling at 24h post-dose will be collected at the same time as safety laboratory sampling if EOS it's performed on Day 9.

Expected completion date	This study is expected to last approximately 3 months from the First Subject First Visit to the Last Subject Last Visit.
Duration of subject participation	The total study duration for an individual subject will be between 2 to 5 weeks. All visits will be on an out-patient basis, but Day 1 and Day 8 will be long visits (12 hours approx.) [redacted].
[redacted]	[redacted] selective serotonin receptor agonists and is used to treat the symptoms of migraine headaches (severe, throbbing headaches that sometimes are accompanied by other symptoms such as nausea and sensitivity to sound and light). Study drugs (zolmitriptan nasal spray and zolmitriptan orally disintegrating tablets) will be administered in 8 subjects in two sequences under fasting conditions 10 hours predose and 4 hours post dose. An orodispersible (e.g., orally disintegrating) formulation of zolmitriptan is helpful in patients who experience migraines along with nausea and vomiting. This formulation was demonstrated to be bioequivalent with the conventional tablet in terms of AUC and Cmax for zolmitriptan and its active metabolite desmethylzolmitriptan. And, there was no statistically significant difference for AUC or Cmax values between nasal spray and oral formulations. Clinical pharmacology data show that the tmax for zolmitriptan for the orally dispersible tablet (range 0.6 to 5h, median 3h) is similar to intranasal administration (range 0.5 to 5h, median 2h). Almost 80% of the Cmax value is obtained in the first hour, and plasma concentrations are sustained for 4 to 6 hours. For the active metabolite, N-desmethyl-zolmitriptan, the median tmax is slightly later (approximately 5 hours after 5 mg) (Yates, 2002, zolmitriptan oral, zolmitriptan intranasal). Plasma protein binding is low and zolmitriptan is metabolized in the liver through the P450 cytochrome system and 3 metabolites are detected: indole-acetic acid, zolmitriptan N-Oxide and N-desmethyl-zolmitriptan (2-6 times more potent than zolmitriptan). MAOA enzymes have also been found to be related to its metabolic clearance. Comparison of AUC after IN administration of 2.5 mg (22.4 ng.hr/ml) relative to the corresponding value after OR administration of 2.5 mg (22.0 ng.hr/ml) showed that the bioavailability of IN zolmitriptan with respect to administration oral is 102%. Plasma concentrations and PK of zolmitriptan and the three major metabolites for the nasal spray and conventional tablets are similar. Some instructions will be followed for the administration: • Orally disintegrating tablet of zolmitriptan in the 5 mg strength will be taken without liquids. For oral administration, each tablet will be placed on the top of the tongue without any liquid and will be dispersed within seconds, and then swallowed with the saliva.

	• Zolmitriptan nasal spray comes in a ready-to-use spray unit for single use. Administration is in one nostril. How to use the device will be explained in the full protocol. Following drug administration, study subjects will continue in the fasting condition for a minimum of 4h and the snacks and standard meals might be served at scheduled times after drug administration (snack: +4h; lunch: +7h; snack: +10h). No fluid intake will be allowed from 2h before until 2h after drug administration.
Targets/ analyses/ variables	**Pharmacokinetics endpoints** Plasma PK parameters will be calculated using a non-compartmental model: • Observed maximum concentration: Cmax. • Observed minimum concentration: Clast. • Time to observed maximum concentration: tmax. • Time lag (time to first measurable plasma concentration): tlag. • Area under the concentration-time curve (AUC0-24h, AUC0-t, AUC0-∞) where t is the latest observed timepoint. • Terminal elimination half-life: t1/2. • Apparent clearance: Cl/F. • Apparent volume of distribution: Vd/F. • Elimination rate constant (λz). **Primary Pharmacodynamic endpoints** Effects of zolmitriptan on Heart Rate (HR) and Blood pressure (BP) **Secondary Pharmacodynamic endpoints** Effects of zolmitriptan on vasoactive intestinal polypeptide (VIP) in plasma on Day 1. **Safety endpoints** • Treatment-emergent adverse events (AEs) from Day 1 to EOS. • Treatment-emergent potentially clinically significant abnormalities (PSCAs) in vital signs, ECG and safety laboratory parameters from Day 1 to EOS.
Statistical methodology	This is a Phase I study to assess the PBPK of zolmitriptan 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)