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

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Informed Consent Form

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Informed Consent Form

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

VERSION AND DATE OF PROTOCOL: Version 2; 05/29/2023

PROMOTER CODE: IMIMFCTL/ZOL_1

PROMOTER: [redacted]

PRINCIPAL INVESTIGATOR: [redacted]

INTRODUCTION

This document is to tell you about a research study in which you are invited to participate.

The study has received a favorable opinion from a Drug Research Ethics Committee [redacted] in accordance with current legislation: Royal Decree 1090/2015, of December 4, and European Regulation 536/2014, of April 16, which regulates clinical drug trials.

Our intention is that you receive correct and sufficient information so that you can evaluate and judge if you agree to participate in this study. Therefore, please read this information carefully and we will clarify any doubts you may have after reading it. In addition, you can consult with the people you consider appropriate.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw your consent at any time without altering your relationship with your doctor or causing any harm to your medical care.

STUDY DESCRIPTION

Context

The intranasal route may be an attractive mode of drug administration for rapid onset of action, direct delivery to the central nervous system, or avoidance of hepatic metabolism (first-pass effect). Administration by this route also helps to minimize the need for an intravenous catheter while achieving rapid and effective drug blood concentrations. Because of his efficacy in terms of drug delivery and benefits, this route of administration is increasingly being considered in adults and children. In general, intranasal administration of drugs is used to target local, systemic, and CNS effects.

Zolmitriptan is a medication that is authorized for the acute treatment of patients with migraine-type headaches, so it is advisable to administer it as soon as possible to achieve symptom remission. There are different presentations of zolmitriptan. In this project we will evaluate

zolmitriptan via two routes of administration (oral vs. nasal) and compare the observed plasma concentrations.

The data obtained in the study will be analyzed using physiologically based pharmacokinetic (PBPK) models. PBPK is a computational process that simulates the absorption, distribution, metabolism, and excretion of a substance in the body of an organism based on the interrelationships between key physiological, biochemical, and physicochemical factors using mathematical equations. PBPK models are also used to assess formulation differences and could be used to support the development of methodologies and tools to assess generic drug equivalence. PBPK should allow comparison of the two routes of administration and define whether nasal administration of zolmitriptan is a better alternative to oral administration.

Objectives

The objective of this trial is to characterize the pharmacokinetics (blood drug concentrations after a single dose) and pharmacodynamics (effects on vital signs and selected biomarkers) of two formulations (intranasal and oral) of zolmitriptan in healthy subjects.

Volunteers and study design

Approximately 8 eligible healthy men and women will receive zolmitriptan by two different routes. The sequences of administration (oral or nasal) will be randomized in a crossover study. That is, oral or nasal zolmitriptan will be administered on an empty stomach (fasting) during the first period, and then zolmitriptan will be administered in another way (oral or nasal) during the second period, according to the randomization sequence. In each period you will be given a single 5 mg dose of zolmitriptan. The two periods will be separated by a washout period (without taking any dose of zolmitriptan) of at least seven days. At the end of the study, you will have tried both oral and nasal formulations.

Your participation in the study has the following periods:

1. Initial screening phase. During this phase, you will receive detailed explanations of the study procedures and will be asked to read this form. You can ask any questions you have about the study, and once you feel that all of your questions have been answered and you feel that you would like to participate in the study, you will be asked to sign the informed consent form. You will receive a copy of the signed informed consent form. In the screening phase you can attend 2 to 3 times in our facilities spaced with a maximum of 28 days apart. During the screening visit, the health personnel in our group will assess whether you meet all the criteria to participate in the study. You will have a physical examination that will include vital sign measurements, an electrocardiogram (ECG) and blood tests (complete blood count, biochemistry, urinalysis, coagulation and some markers of hepatitis B and C infection and HIV antibodies), and you will be given details of your collected medical history. In addition, a urine drug test, alcohol tests, and pregnancy test (if applicable) will be requested. We want to make sure that you are in good health and that it is safe for you to be in the study.

You will be asked to avoid alcohol and drugs before participating in the study sessions (about 4 weeks into the screening period).

2. Experimental sessions.

Your urine will be tested for drugs and alcohol at the beginning of the screening phase and prior to drug administration to ensure that you have complied with any restrictions related to drug use. The consumption of stimulant beverages (i.e., coffee, tea, chocolate, or cola-type beverages) will not be allowed from 48 hours prior to entry until the end of the study (a caffeine test will verify compliance with this limitation).

Prior to the second experimental period, you will need to continue your abstinence from alcohol and drugs during the 7-day washout period, as well as refrain from stimulant beverages 48 hours prior to admission until the end of the study.

Your safety comes first, and you could be putting your health at risk if you do not refrain from using these substances.

First experimental period. You will be admitted to the Clinical Research Unit (ICU) on the morning of the experimental session (Visit 1) in which you will take zolmitriptan. You must come fasting, around 8 hours on an empty stomach. There will be water restrictions for one hour before dosing and one hour after dosing. The researchers will provide water and food during the experimental session. You cannot leave the UIC during the experimental session.

We will measure your vital signs, do an ECG and take a first blood sample. You will receive your dose around 8 a.m. Depending on the group you are randomly assigned to, you will take either oral or nasal medication. During the session, your blood will be drawn (up to 16 times) and your vital signs will be repeatedly measured, along with several ECGs. You will also be asked about any side effects, if any. You will leave the UIC 13 hours later and on the morning of the second day (Visit 2) you will have to return to the UIC and a blood sample will be taken 24 hours after drug administration.

After at least seven days of not receiving zolmitriptan, also known as washout, you will need to return to the UIC for the second treatment period.

In this second experimental period, on Day 8 (Visit 3) you will be admitted to the UIC around 8 a.m. and will take zolmitriptan and follow the same protocol as the first experimental period. You will leave the UIC 13 hours later and, on the morning of day 9 (Visit 4), you will have to return to the UIC and a blood sample will be taken 24 h after drug administration. The only difference is that you will now be taking a different formulation of zolmitriptan.

3. End of study.

During this visit (Visit 5) laboratory tests (blood and urine) will be carried out, vital signs will be taken, an ECG will be performed and a final blood sample will be taken for a complete blood count, biochemistry, urinalysis.

Visits 4 and 5 can be done on the same day. Otherwise, visit 5 could take place within a two-day time frame after Visit 4.

HOW LONG DOES YOUR PARTICIPATION LAST AND WHAT DOES IT CONSIST OF?

The total duration of the study for an individual participant will be 7 weeks.

All visits will be ambulatory. Visit 1 and Visit 3 will be long visits and Visits 2, 3 and 5 will be shorter.

If you experience any significant side effects before leaving the UIC, the investigator may ask you to

spend additional hours in the UIC.

Throughout the study you will be asked to avoid drugs, alcohol, stimulant drinks (i.e., coffee, tea, chocolate or cola-like drinks) until the end of the study.

Some fruits or fruit juices (grapefruits, Seville oranges, tangelos [a cross between tangerines and grapefruits]), may affect the way the drug is processed in the body and eliminated, thus biasing the results. Its consumption is prohibited during the entire study.

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

A total of 406 mL of blood will be collected during your participation in the study over a 7-week period. Please note that up to 450 ml of blood can be drawn from one person in a single blood donation.

COLLECTION AND USE OF BIOLOGICAL SAMPLES

The collection and use of biological samples are regulated by Law 14/2007, of July 3, on Biomedical Research and Royal Decree 1716/2011, of November 18, which guarantee respect for your rights.

To carry out the research, biological samples (blood) will be collected. They may be analyzed by various laboratories during the trial and will be kept for 2 years after the end of the trial in case it is necessary to repeat any analysis related to the objectives of the trial or use them for additional research related to the drug under study (such as, but not limited to: determination of blood biomarkers). These samples will be stored in the freezers of the cryopreservation systems [redacted]

The data obtained from the use of these samples will be processed in the same way as the other data collected during the test.

BENEFITS AND RISKS

This is a clinical trial with healthy participants, and we do not expect any direct benefit after zolmitriptan dosing. If the results are as expected, we will be able to contribute to the development of a useful PBPK model to guide the intranasal administration of drugs. For this reason, we thank you for your collaboration in the study.

Zolmitriptan is a treatment indicated in acute migraine. The benefit/risk ratio is favorable according to previous studies and post-marketing surveillance. Common side effects of zolmitriptan include: dysgeusia (altered sense of taste). Other side effects are: dizziness, drowsiness, hyperesthesia, jaw pain, nausea, neck pain, paresthesia, sore throat, flushing sensation, local pain and cold sensation.

During the study, the risks of blood draws include temporary discomfort from the needle stick, bruising, bleeding and, rarely, infection. Some adverse events may result from blood draws, such as fainting, minor bruising, phlebitis, dizziness, infection and/or pain at the puncture site.

It is your responsibility as a participant in a clinical research study to comply with study visits and activities, as well as to report any side effects and any medication you may have taken (including herbal medicines), without first consulting your study doctor.

ALTERNATIVE TREATMENTS

This is a study in healthy volunteers, so there are no alternative treatments.

CONTRACEPTIVE MEASURES

If you are a man, it is very important that your partner does not become pregnant during and for one month after this study. You also should not donate sperm during the study and one month after.

If you are a sexually active man and your partner can become pregnant, you should

- Use a condom from the moment of selection, throughout the study.

- tell the study doctor immediately if your partner becomes pregnant.

- do not donate sperm during this study and for 3 months after the last dose of study medication

- tell your partner to use a highly effective method of contraception.

A highly effective method of birth control is one that has a failure rate of less than 1% when used correctly. Highly effective contraceptive methods are

- non-hormonal intrauterine devices (IUDs)

- surgery (ligation) of the fallopian tubes

A male partner who has had a vasectomy (surgery to close the tubes that carry sperm from the

testicles), if he is your only male sexual partner, and if sperm absence has been confirmed; and

-Do not have sexual relations with a male partner.

The most effective methods of contraception for male participants with partners who may become pregnant include

- condom use

- the use by the couple of a highly effective contraceptive.

If your partner becomes pregnant during or in the month following study drug administration, we will ask your partner to provide us with information about this pregnancy and about the baby up to one month after birth. Your partner will be free to provide us with this information and, if they agree, they will have to sign a specific Informed Consent.

If you are a woman, it is very important that you do not become pregnant during and one month after this study.

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 in the event of deterioration of your health or injuries that may occur in connection with your participation in the study

ETHICAL ISSUES

Voluntary participation guarantee

Your participation in this study is completely voluntary and you must give your written consent to participate. If, after consideration, you decide not to participate in the study, or if you decide to participate and later change your mind, you may withdraw your consent at any time without explanation. In any case, your decision will not affect in any way the treatment you receive from your doctor or subsequent check-ups.

Confidentiality

The treatment, communication and transfer of personal data of all participating subjects will comply with the applicable legislation. The communication and transfer of personal data will comply with Organic Law 3/2018, of December 5, on the Protection of Personal Data and 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 know the following information: In accordance with the provisions of the aforementioned legislation, you can exercise the rights of access, rectification, opposition and cancellation of the data, for which you must contact the researcher of the study.

All data on 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. The data collected for the study will be identified by a unique code, so that no information

that could identify you is included, and only your doctor/study collaborators will be able to link such data to you and your medical record. Your identity will not be revealed to anyone other than the Health Authorities when necessary or in cases of medical emergency. The representatives of the Health Authorities, the Ethics Committee for Research with Medical Devices (CEIm), [redacted], and/or personnel authorized by the Sponsor (for example, study monitors, auditors) may have access to the data of your personal information only to verify the data and procedures of the clinical trial (maintaining confidentiality at all times).

In the final report of the study or if these results are communicated to the scientific community, your identity will be kept anonymous through the use of this code. The encrypted 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 as the study described or for use in scientific publications, but always maintaining the confidentiality of the data 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 data already collected will be used. In addition to the rights you already know (access, rectification, opposition and cancellation of data) you can now also limit the processing of data for research purposes other than those defined in this protocol and request (once the trial has finished) that the data you have provided for the study be transferred to a third party (for example, a primary care physician). [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 obligations 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 obligated to retain the data collected for the study for at least 25 years after its completion. Thereafter, your personal data 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. Both the Center and the Sponsor are responsible for the processing of your data and undertake to comply with current regulations on data protection.

The UIC is equipped with video surveillance cameras so that during your stay at our facilities you will be monitored at all times. Any video recording will be stored during your stay.

COMPENSATION

For your participation in this study, you will receive [redacted]. If you are unable to complete all required procedures, compensation will be prorated based on the procedures completed.

OTHER RELEVANT INFORMATION

Any new information regarding the study that may affect your willingness to participate in it, or that is discovered during your participation, will be communicated to you by the researchers as soon as possible.

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

You should also know that you may be withdrawn from the study at the discretion of the principal investigator if:

- non-compliance with protocol procedures
- any adverse event due to study drug for safety reasons
- consumption of other medicines, alcohol or illegal drugs

If you have any questions about any aspect of the study or wish to comment on any detail of this information, please do not hesitate to contact the members of the research team.

CONTACT IN CASE OF QUESTIONS

You will be given a card with the study code, contact telephone numbers and the responsible physician. You must agree to carry the card with you from the beginning of the study until its completion.

[redacted]

THANK YOU

The sponsor would like to thank you for considering participating in this study. We understand that your time is valuable and we appreciate your participation.