

PATIENT INFORMATION SHEET

AND

INFORM CONSENT FORM

INFORM PATIENT SHEET

Title: "Doravirine concentrations and antiviral activity in genital fluids in HIV-1 infected individuals ("DORAGEN Study")

Sponsor: Fundació Lluita contra la SIDA

The Infectious Diseases Service - HIV Unit of the University Hospital of Bellvitge through Dr. Daniel Podzamczer (Principal Investigator of the study) is conducting a clinical research study to which he is invited to participate. (Contact: 93 260 7667)

The male and female genital tract act as reservoirs for HIV and also contribute to the transmission of the virus sexually due to the presence of HIV in semen and cervical fluid. Effective antiretroviral treatment (ART) for people with human immunodeficiency virus (HIV) infection significantly lowers the risk of sexually transmitted infection among patients treated with their sexual partners. Transmission of HIV through sexual intercourse is intimately related to the presence of virus with infective capacity in genital secretions and rectal tissue/fluid and the effectiveness of ART in preventing new sexually transmitted infections is associated with reduction of viral load in these compartments. Therefore, the ability of different antiretroviral drugs to reach genital secretions and reach sufficient concentrations to suppress viral replication in this compartment is of particular importance in the prevention of new HIV infections. The levels of each antiretroviral drug and its antiviral activity in the genital tract and rectum may vary depending on the characteristics of each drug. On the other hand, higher or lower concentrations of drugs and their antiviral activity may influence the time needed to achieve viral suppression, which may also be important in reducing the risk of sexual transmission of HIV.

Doravirine is a new drug in the family of non-nucleoside reverse transcriptase inhibitors (ITINN) which is active against viruses with resistance to other ITINN and which, due to its pharmacokinetic properties, can be administered once a day. Doravirine in combination with 2 nucleoside/nucleotide analog reverse transcriptase inhibitors (ITIAN) has been shown to be no less effective than another ITINN (efavirenz) and a protease inhibitor drug (darunavir), both also in combination with 2 ITIAN (tenofovir/emtricitabine oabacavir/lamivudine), as well as a good safety profile and tolerable, in phase III clinical trials, in adult patients with type 1 HIV infection who had not previously received treatment.

Therefore, Doravirine is a new option for the treatment of HIV infection, effective and with a favorable safety profile. However, as it is a newly introduced drug, there is no information about Doravirine concentrations and its effectiveness in maintaining viral suppression in genital fluids in patients with HIV infection.

This study can provide information on these issues, which will allow a better understanding of the drug and its potential both for the treatment of HIV infection and to prevent its transmission.

Objectives

The objectives of this study are::

- 1- To determine the concentrations of Doravirine in seminal plasma and cervicovaginal fluid in men and women with HIV-1 infection who modify their antiretroviral treatment to Doravirine in combination with tenofovir alafenamide and emtricitabine (Descovy®).
- 2- Study the viral load of HIV in seminal plasma and cervical fluid in men and women with HIV-1 infection who modify their antiretroviral treatment to Doravirine in combination with tenofovir alafenamide and emtricitabine (Descovy®).

Details of the study

This study will involve 15 men and 15 women over the age of 18, with HIV-1 infection, who are already receiving antiretroviral treatment and maintain undetectable plasma viral load for at least the previous 6 months. Participants will be offered to change their treatment to Doravirine + Tenofovir Alafenamide/Emtricitabine. At 8 weeks of treatment with Doravirine + Tenofovir Alafenamide/Emtricitabine concentrations of Doravirine and viral load of HIV in blood plasma and seminal plasma in male participants and in blood plasma and cervical fluid in the women participants. All study procedures will be developed at the University Hospital of Bellvitge.

The duration of the study shall be 3 months.

In accordance with the current legal regulations of clinical trials in our country, RD 1090/2015, this study has been approved by the Spanish Agency for Medicines and Medical Devices (AEMPS) and by a Clinical Research Ethics Committee with medicines (CEIm), an independent committee that oversees the rights, safety and well-being of people involved in clinical trials. This study will be carried out following the guidelines and standards of Good Clinical Practice, in accordance with Spanish legislation and the Declaration of Helsinki.

Discomforts and risks arising from the study:

Patients participating in the study will follow a stricter control than usual, with clinical controls at the baseline visit, week 4 and week 8, and analytical in the baseline visit and week 8. In addition, an additional follow-up visit will be performed one month after the end of the study.

Before starting the study:

Screening visit:

If you decide to participate in the study, we will ask you to sign this informed consent before being included.

In this visit we will make:

- A review of your medical history
- A physical examination
- A review of your medication
- Signature of consent

During the study:

Study visits:

At the baseline visit and week 8 visit of the study, a blood draw will be done to determine the viral load of HIV. In addition, other tests, similar to those carried out for the follow-up of patients with HIV infection in routine clinical practice (blood count, basic biochemistry and CD4 lymphocyte count)

Male patients will be asked at baseline and at week 8 to provide a semen sample, which should be delivered within 2 to 4 hours of collection.

In the case of female patients, a sample of cervical vaginal fluid will be obtained at each of these visits (baseline and week 8).

Collection of blood samples:

It consists of obtaining a blood sample from the vein in the anterior area of the elbow.

Risks associated with a blood draw are pain, bruising, bleeding, or other discomfort at the location of the prick. In rare cases anemia, fainting or infection of the spot of the prick may appear. Precautions will be taken to avoid or minimize these problems.

The blood extractions will be carried out by the nursing staff of the HIV and STI Unit of the University Hospital of Bellvitge. The amount of blood to be drawn at each of the study visits shall be 30 mL.

Obtaining the cervical fluid samples:

A speculum (commonly used for gynaecological examinations) will be used to obtain cervical fluid to locate the vaginal fornix (located in the deepest part of the vaginal wall) and a small amount of flow is aspirated through a syringe.

These procedures will be performed by doctors experienced in the use of these techniques.

*In compliance with the Biomedical Research Act 14/2007, it is noted that the storage of biological samples (blood, semen and cervical fluid) is planned in existing freezers in the HIV and STI Unit and/or the Microbiology Service of the University Hospital of Bellvitge, for the purpose of possible further analysis, either within the study or for other studies (in this case always requesting your consent again) which in no case will include genetic analysis.

Study medication

Doravirine is approved by the European Medicines Agency (EMA) for the treatment of HIV-1 infection, under the trade name Pifeltro, although it is not yet marketed in Spain.

In previous clinical trials Doravirine has been well tolerated serious adverse reactions were very rare.

The most commonly reported adverse reactions (5% or higher) are:

- Nausea (7%)
- Headache (6%)
- Fatigue (6%)
- Diarrhea (5%)
- Abdominal pain (5%)
- Dizziness (3%)

(Source: Datasheet of Doravirina (Pifeltro®)

Medication Not allowed during the study

The use of some other drugs is contraindicated or should be performed with caution when administered simultaneously with Doravirine/FTC/TAF. For this reason, the following drugs are not allowed during the study:

- Androgen receptor inhibitors: enzalutamide.
- Anticomycials: carbamazepine, oxcarbazepine, phenobarbital, phenytoin.
- Antimycobacterians: rifampicin, rifapentine.
- Cytotoxic: mitotane.
- Antiretrovirals: efavirenz, nevirapine, etravirin.
- Herbalist products: San Juan herb (Hypericum perforatum).

Do not use medicines (both over-the-counter and over-the-counter) without consulting the study doctor. The study physician will explain the need to avoid certain medications during the study, including contraindications. New drugs may be identified later that need to be added to the list of drugs not to be taken during the study

After the study

Once the study is completed, your doctor will decide on the most appropriate antiretroviral treatment regimen for you, either Doravirine + FTC/TAF or another combination in the event that Doravirine is not yet commercially available in Spain or at our center.

What are the expected benefits and potential risks of this study?

Possible benefits:

By participating in this study, you will receive antiretroviral treatment that has demonstrated high efficacy and excellent tolerability in different clinical trials. It is expected that with this treatment its plasma viral load is reduced and the objective of the treatment is to achieve a plasma viral load level lower than the limits of detectability of the techniques used in clinical practice (<40 copies/mL). In this sense, it is possible that Doravirine does not provide a clinical benefit superior to that achieved with other combinations of antiretrovirals.

Their participation in this study will allow to know if the drug Doravirine reaches adequate concentrations in semen and cervical fluid and if the combination of Doravirine with TAF/FTC allows to achieve an adequate suppression of the viral load of HIV in these reservoirs, which may benefit other people infected with HIV in the future.

Possible risks:

The derivatives of procedures for extracting blood samples from rectal tissue samples. According to the selection criteria for the study, in which the possibility of resistance to the study drugs should be ruled out, a failure of treatment with Doravirine and TAF/FTC due to lack of efficacy is not foreseeable. However, if this happens, your doctors will decide which treatment is best for you in that situation.

Costs:

This study does not cost you anything.

Compensation:

Financial compensation is foreseen for their participation in the study of €175.

Confidentiality

The confidentiality of the personal information of the participants will be guaranteed in accordance with current legal regulations (EU Regulation 2016/679 General Data Protection (GDPR) of the European Parliament and of the Council of 27 April 2016).

During this study, study physicians will record information about you, your health, and your participation in the study in forms called data collection notebooks.

In order to ensure that the data collected during the study is treated confidentially, your data shall be identified by a code, your name and any other information which allows you to be identified directly in the data collection logbooks.

Only your study doctors/collaborators will be able to relate such data to you and your medical history.

Moreover, as stipulated in current legal regulations, you can exercise your rights of access, rectification, cancellation or opposition (ARCO rights) with respect to your personal data collected, for which you must contact your study doctor. Likewise, you can exercise your rights of access, rectification, cancellation, opposition, limitation of the processing of data that are incorrect, request a copy or be transferred to a third party (portability) of the patient on the data you have provided for the study (PARSOL rights). To exercise their rights, the participant may contact the researcher or the data protection officer of the institution (josue.sallent@ticsalutsocial.com).

In case the study data are transferred to third countries outside the EU or EEA (European Economic Area), the promoter guarantees a level of data protection at least equivalent to that granted by European legislation.

Civil liability:

We inform you that if you have a health insurance policy, it may not cover participation in a clinical trial.

Likewise, it is possible that your participation in this clinical trial may modify the general and individual conditions (coverage) of your insurance policies (life, health, accident) and, therefore, we recommend that you contact your insurance company and inform you of your participation in it to determine could affect your current insurance policy or in the event that you will contract a new policy.

The promoter of the study has signed a civil liability insurance policy with the company Zurich Insurance PLC branch in Spain in accordance with the requirements set out in RD 1090/2015, which covers any damages they may experience as a result of their participation in the trial. Policy No: 00000105553366.

Study participation:

To participate in the study you do not need to make the decision at this time, you can take this Information Sheet home and meditate on it long enough and consult your participation with your family or regular doctor.

You participate in this study on a voluntary basis and may withdraw from the study at any time without having to explain or be affected by your subsequent attendance at our Consultation.

Once you have signed the Informed Consent, you will keep a copy of this document.

There is the possibility of exclusion from the trial by the sponsor or the researchers, in case of safety problems or non-compliance with the procedures established in the study.

In the event of cancellation of the trial by the sponsor, participants shall be informed of the reasons.

Any new information regarding drugs used in the study that may affect your decision to continue the study will be communicated to your doctor as soon as possible and, if necessary, a new consent will be signed.

Contact for information:

In case of any questions or problems related to your infection or the treatment administered, outside of working hours, you can contact the principal investigator of the study: (Please insert name and telephone of the investigator)

Dr.

Tel.:

If you agree to participate in this study, please express your consent by signing on the appropriate site:

INFORM CONSENT

Me, (name and surname)....., after having read the information sheet that has been given to me, about the study "Concentrations of Doravirine and antiviral activity in genital fluids in patients with HIV-1 infection (DORAGEN Study)" and ask the clarifying questions about it to the Dr..... from Hospital.....

I agree with everything related to this study and freely agree to participate in it and that my

data can be used for research purposes as stated in the patient information sheet.

Comprendo que mi participación es voluntaria.

I understand that I can withdraw from the studio:

Anytime.

Without having to explain.

Without any impact on my medical care.

Patient signature

Date

Investigator signature

Date

You will receive a copy of this document, once you have signed it, to keep with your records.