

## INFORMATION PATIENT SHEET

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**Title:** “Doravirine concentrations and antiviral activity in Cerebrospinal fluid in HIV-1 Infected individuals (“DORACENES Study”)

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Sponsor: Fundació Lluita contra la SIDA

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

The introduction of highly active antiretroviral treatment (HAART) has contributed significantly to improving the rate of HIV infection, with a drastic reduction in morbidity and mortality.

However, currently available treatments are not capable of eradicating the infection and therefore need to be administered indefinitely to achieve permanent viral suppression. In some cases, in order to improve adherence or reduce drug toxicity, it is proposed to simplify antiretroviral treatment, within the new antiretroviral drugs, to Doravirina. Although this drug is not yet commercialized is approved by the American and European agencies, in previous studies it has been shown to have a confirmed efficacy and a very favorable toxicity profile. It is also important to note that this drug is coformulated (in the same pill) with lamivudine (3TC) and tenofovir (TDF) which would constitute a single pill regimen very important when maintaining good adherence and that does not interfere with daily activities.

Despite the effectiveness of current treatments in terms of survival of HIV-infected patients, neurological diseases associated with HIV are still relatively common even in patients with suppressed plasma viral load. The penetration of antiretroviral drugs into the central nervous system is known to be associated with better control of HIV replication in this compartment and a lower incidence of neurocognitive problems. The drugs currently considered of choice for the treatment of HIV infection have shown great efficacy in reducing the viral load in the plasma, however, not all of them penetrate well into the central nervous system. Thus, while simplification strategies may have the advantage of reducing or avoiding the toxicity of some drugs, it is necessary to know whether they are able to maintain control of HIV replication in the central nervous system.

The efficacy of treatment within the nervous system reservoir depends on good penetration as well as confirmation of virus suppression at that level.

With new drugs these data are obviously limited and that is why we propose to carry out a study in order to know this information.

### **Objective**

The aim of this study was to determine the pharmacological concentrations of Doravirine as well as the viral load of HIV in cerebrospinal fluid in patients with HIV-1 infection who receive Doravirine+Emtricitabine/Tenofovir alafenamide.

### **Study details**

This study will be conducted at the University Hospital of Bellvitge and will involve 15 patients over 18 years of age, with HIV-1 infection with undetectable plasma viral load for at least the previous 6 months. Participants will be offered to change their treatment to a single pill containing Doravirine +Emtricitabine/Tenofovir Alafenamide and after 1 month of treatment they will have a Lumbar Puncture to obtain Cerebrospinal Fluid.

The duration of the study shall be 4 months.

This study has been approved by the Ethics Committee of Drug Research (CEIm) of its hospital and by the Spanish Agency for Medicines and Medical Devices (AEMPS) in accordance with the current legal regulation of clinical trials in our country, RD 1090/2015. This study will be carried out following the guidelines and standards of Good Clinical Practice, in accordance with Spanish legislation and in accordance with the Declaration of Helsinki.

## **Study medication**

Doravirina 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®))

### ***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:**

A blood test will be performed to determine the viral load of HIV and other parameters of clinical utility for monitoring HIV infection and complications of antiretroviral treatment. 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), will be performed with the blood samples obtained. After 4

weeks with the new treatment, a lumbar puncture will be performed to obtain CSF as detailed below.

There is the possibility that it may not be included in the study, because it did not meet some or all of the inclusion criteria defined in the study, or that even if it was included in the study, it might be decided to exclude it from the study. The possible causes of exclusion from the study are:

- their voluntary withdrawal
- failure on the part of the investigator to comply with the procedures laid down
- Grade III or IV laboratory anomalies or adverse events related to the pattern of the study which, in the opinion of the researcher, suggest not to continue with the same pattern
- lack of effectiveness of study pattern
- decision to cancel the trial by the study promoter.

In all the above cases, the study doctor will tell you the reason personally.

In the event that during their participation in the study, any new information regarding the drugs used in the study that could affect their decision to continue participating in the study, such information shall be communicated to you as soon as possible by the study physician and, if necessary, you shall be asked to sign a new consent to document it.

\*In compliance with the Biomedical Research Act 14/2007, it is established that biological samples (blood and CSF) are to be stored in existing freezers in the HIV Unit of the University Hospital of Bellvitge, with the aim of possible further analysis, either within the study or for other studies (in this case always requesting their consent again) which in no case will include genetic analysis. No further studies shall be conducted without prior approval of the Clinical Research Committee.

These samples may be kept for a period of 10 years before being destroyed.

These samples will be processed in accordance with Spanish law 14/07 of July 3 on Biomedical Research and Royal Decree RD 1716/2011 on biobanks. The samples will be stored with a code, that is, a number specific to you. Only study physicians or collaborators will have the code key needed to link the data to you.

If samples are used for purposes other than those described in this study, you will be informed of the purpose of the investigation and asked for your consent to use your samples. Its results shall be analysed for research purposes only and may not be used to diagnose other diseases or ailments.

You have the right to revoke your consent to the preservation of the samples, including the destruction of the samples. If you wish to request it, contact the study physician. You may also revoke your consent to participate in the study.

### ***After 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?**

#### **Potential benefits:**

It is expected that the study treatment will keep the status of your HIV infection and/or its complications stable. It is expected that with this treatment the plasma viral load will be maintained below the limits of detectability of the techniques used in clinical practice (<40 copies/mL). However, we cannot guarantee that you will get any clinical benefit from participating in the study. The information you get in this study can help others in the future.

Your participation in this study will allow to know the concentrations of the new drug (Doravirine) and if the treatment with Doravirine+ Emtricitabine/Tenofovir Alafenamide allows to achieve an adequate suppression of the viral load of HIV in the CSF, which may benefit other people infected with this virus in the future.

#### **Discomforts and risks arising from the study:**

Patients participating in the study will follow a stricter control than usual, with clinical and analytical controls at the selection visit, baseline visit (start of treatment with Doravirine+Emtricitabine/Tenofovir Alafenamide) and visit in week 4 and week 12 of treatment. From this moment on, the usual routine of visits in clinical practice will be followed.

#### **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 amount of blood extracted will be 20 mL at each of the baseline visits, week 4 and week 12 and 10 mL on the day that the lumbar puncture is also performed.

### *Performing a lumbar puncture*

After 4 weeks of treatment, you will have a lumbar puncture to obtain a sample of CSF. CSF is the fluid that surrounds the brain and spinal cord.

In this case the lumbar puncture will be performed solely and exclusively for the fact of participating in this clinical trial, and it is not part of the routine procedures in which they are performed in the usual clinical practice.

The main complication that may occur after a lumbar puncture is headache or nausea. In some cases, a post-lumbar puncture syndrome may occur. It results in headaches, ringing, or neck pain. These clinical signs usually go away when lying down and usually last for 3-5 days at most.

The fluid that is collected is known as "cerebrospinal fluid (CSF)" CSF circulates through the brain and spinal cord area. During a lumbar puncture, fluid samples are taken and sent to the lab. This test will evaluate the presence of HIV and levels of antiretroviral drugs in the CSF. This research could be very useful to learn more about the pharmacological concentrations and efficacy of the antiretroviral treatment regimen under study.

### *How do I prepare for a lumbar puncture procedure?*

It is advisable to drink plenty of fluid the night before to make sure you are well hydrated for the procedure. No further preparation is necessary.

### *During the lumbar puncture procedure*

The lumbar puncture will be performed in the Day Hospital of the HIV Unit of the hospital. You will be asked to lie on your side with your knees bent to your chest or sit on a bed and lean against a raised table in front of you. Pillows may be placed to help you maintain posture. The study doctor will clean an area of the skin on your lower back (lumbar area) with a special antibacterial soap.

A narrow hollow needle (to reduce the risk of headache after the procedure) will be inserted between two lumbar vertebrae. You may feel pressure on your back during part of the procedure. A small amount of cerebrospinal fluid (approximately 9 mLs, two teaspoons) will be collected. The needle is then removed.

### *After the lumbar puncture procedure*

The area where the puncture was done will be covered with an adhesive bandage. You may feel discomfort in this area. After the lumbar puncture procedure, you will stay in the Day Hospital for approximately 1 hour. You will be asked to lie on your back and will not be able to get up. After the procedure you will be able to eat and drink. You will

not be able to drive home. You will be given medication to relieve pain if necessary after the procedure and also to take home if necessary.

#### *After the lumbar puncture*

Care at the puncture point: The adhesive bandage can be removed from the back at night.

Headache: Headache, which occurs in 10% to 30% of patients, is the most common complication of the lumbar puncture and is the result of a leakage of cerebrospinal fluid (CSF). It's a headache that can appear when you sit or walk, but goes away when you lie down. To relieve it, lie down and drink plenty of fluids. If the headache persists and does not improve with bed rest, fluid intake, or pain-relieving medication, then call your doctor.

Back discomfort: Some people feel discomfort in their back after a lumbar puncture.

Toilet: On the day of the procedure you can shower but not immerse in a bath.

Limitations on your activities: Rest as much as possible on the day of the procedure.

Do not participate in strenuous activities on the day or night of the procedure.

Diet: Go back to your usual diet and fluid intake.

Ask your doctor for more information about this procedure.

In the event of evidence of treatment failure you will receive a new antiretroviral treatment that is considered effective based on the results of resistance studies conducted.

#### **Medication not allowed during the study**

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 study***

Participating patients will be offered the same treatment as they were taking prior to starting the study or discussing other options based on the opinion of the investigating physician.

#### **Costs:**

This study does not cost you anything.

**Compensation:**

A compensation of 100 euros per participant is provided for the loss of time involved in participation, travel and other unforeseen events.



## **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](mailto: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.

## **Study results**

The results of the study may be communicated to the health authorities and the scientific community through congresses and/or publications.

In none of the publications that are generated at the root of the study results will any data identifying the patients participating in the study appear.

You have the right to request your test results after the study is completed. To do this, you need to tell your doctor about the study.

If during the study, and as part of the research, any information about your medical situation that may be relevant to you or your family members arises, the study physician will let you know. At that time, you will be advised if any additional tests are required if confirmation of such information is required.

Also, if you do not wish to be informed of the results of the investigations, your right to do so will be respected.

**Civil liability:**

In case of injury or prejudice, please contact the principal investigator of the study (Dr. Daniel Podzamczer, HIV-Infectious Diseases Unit of the University Hospital of Bellvitge as the first contact person.

The promoter of the study has signed a civil liability policy with the company Zurich Insurance PLC Branch in Spain, with the number 00000106148950 according to the requirements set out in RD 1090/2015, which covers any damages they may experience as a result of their participation in the trial.

If you have a health insurance policy, it may not cover participation in a clinical trial.

**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.

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.

Daniel Podzamczer

Tel.: 649 630 408

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 “Doravirine concentrations and antiviral activity in Cerebrospinal fluid in HIV-1 Infected individuals (“DORACENES 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

- I agree that my blood and/or CSF samples will be kept for future research outside the main research study, in accordance with Spanish law 14/07 of 3 July on Biomedical Research

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