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*CLINICAL STUDY PROTOCOL*

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**Doravirine concentrations and antiviral activity in genital fluids in  
HIV-1 infected individuals  
(“DORAGEN Study”)**

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Protocol ID: DORAGEN

Version: 1.2 (06/05/2019)

EudraCT Number: 2018-003921-27

Promoter: Lluita contra la SIDA Foundation

Principal Investigator: Daniel Podzamczer Palter. Hospital Universitari de Bellvitge

Source of financing: Lluita contra la SIDA Foundation in collaboration with Merck Sharp & Dome.

## **1. PROTOCOL SYNOPSIS**

### **1.1. Promoter Identification:**

Lluita contra la SIDA Foundation (Fundació Lluita contra la SIDA); Hosp. Univ. Germans Trias i Pujol. Badalona Barcelona, Spain

### **1.2. Study Title:**

Doravirine concentrations and antiviral activity in genital fluids in HIV-1 infected individuals (“DORAGEN Study”).

### **1.3. Protocol ID:**

EudraCT Number: 2018-003921-27

### **1.4. Principal Investigator:**

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Department of Infectious Diseases.

Hospital Universitari de Bellvitge. L’Hospitalet de Llobregat. Barcelona. Spain

### **1.5. Study Center:**

HIV and STI Unit. Department of Infectious Diseases.

Hospital Universitari de Bellvitge. L’Hospitalet de Llobregat. Barcelona. Spain

### **1.6. Responsible for monitoring**

HIV Unit monitoring team

HIV and STI Unit. Department of Infectious Diseases.

Hospital Universitari de Bellvitge. L’Hospitalet de Llobregat. Barcelona. Spain

### **1.7. Referral Ethics Committee:**

Clinical Investigation Ethics Committee of the Hospital Universitari de Bellvitge

### **1.8. Test Product, Dose, and Mode of Administration:**

- Doravirine (MK-1439) 100 mg administered orally once daily in combination with Tenofovir alafenamide (TAF) and emtricitabine (FTC) coformulated as single tablet (Descovy® TAF/FTC 25/200 mg) and administered orally once daily.

**1.9. Objectives:**

- To determine Doravirine concentrations in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals receiving ART with Doravirine plus TAF/FTC.

-To evaluate HIV-1 viral load in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals receiving ART with Doravirine plus TAF/FTC.

**1.10. Study Phase:**

Phase II

**1.11. Study Design:**

Open label, single arm, single center, prospective study.

**1.12. Study Disease:**

HIV-1 infection

**1.13. Study Endpoints:**

- Concentration of Doravirine in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals, respectively, 8 weeks after switching to Doravirine plus TAF/FTC.  
-HIV-1 RNA in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals, respectively, 8 weeks after switching to Doravirine plus TAF/FTC.

**1.14. Target Population:**

Male and female adult HIV-1 infected patients receiving standard ART with TAF/FTC, tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudina , plus an non-nucleoside reverse transcriptase inhibitor, a boosted protease inhibitor or an integrase inhibitor during at least 3 months, with plasma HIV-1 RNA suppression (<40 copies/mL) during at least 6 months.

**1.15. Number of Subjects Planned:**

15 male and 15 female individuals.

**1.16 Study duration:**

16 weeks

**1.17. Anticipated Study Calendar**

Anticipated Start Date: May 2019

Recruiting Period: 4 weeks. Anticipated end date of the Recruiting Period: June 2019

Anticipated end date: September 2019

Analysis: October and November 2019

Final Inform: January 2020

***These dates are yet to be confirmed.***

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## APPENDIX

### Appendix A GRADING SCALE FOR SEVERITY OF ADVERSE EVENTS AND LABORATORY ABNORMALITIES

### **3. GENERAL INFORMATION**

#### ***3.1. Protocol ID***

Study ID: DORAGEN

EudraCT Number: 2018-003921-27

**Study Title:** Doravirine concentrations and antiviral activity in genital fluids in HIV-1 infected individuals (“DORAGEN Study”).

#### ***3.2. Study Type***

Phase II, open label, single arm, single center, prospective study.

#### ***3.3. Description of the Investigational medicinal products***

Doravirine (MK-1439) 100 mg administered orally once daily.

Doravirine will be administered in combination with Tenofovir alafenamide (TAF) and emtricitabine (FTC) coformulated as single tablet (Descovy® TAF/FTC 25/200 mg) and administered orally once daily.

Doravirine and TAF/FTC tablets are capsule-shaped, film-coated tablets

#### ***3.4. Promoter Identification***

Fight AIDS Foundation (Fundació Lluita contra la SIDA). Hosp. Univ. Germans Trias i Pujol. Badalona • Barcelona, Spain

#### ***3.5. Technical services involved in the study***

The HIV-1 RNA analyses will be performed in the Microbiology Department of the Hospital Universitari de Bellvitge.

The analysis of tenofovir-diphosphate (TFV-DP) concentrations in SMC and PBMC as well as tenofovir (TFV) concentrations in SP and BP will be performed at the laboratory of the Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill (Chapel Hill, NC, USA).

Haematological and biochemical parameters will be determined in the Clinical Analysis Department of the Hospital Universitari de Bellvitge, following the routine clinical practice.

### ***3.6. Study medication supplier***

- Doravirine 100 mg tablets will be provided by Merck Sharp & Dome, the product manufacturer.
- Descovy® (TAF/FTC 25/200 mg) will be provided by the Pharmacy of the Hospital Universitari de Bellvitge.

### ***3.7. Monitoring***

HIV and STI Unit – Monitoring Team, Infectious Diseases Department  
Hospital Universitari de Bellvitge.

Tel: +34 93 260 76 67 or +34 93 260 76 68. Fax: +34 93 260 76 69

### ***3.8. Principal investigator***

Daniel Podzamczer, MD, PhD.

HIV Unit -Infectious Diseases Department. Hospital Universitari de Bellvitge.

### ***3.8. Co-investigators***

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HIV and STI Unit - Infectious Diseases Department. Hospital Universitari de Bellvitge.

### ***3.9. Study center***

Hospital Universitari de Bellvitge

### ***3.10. Referral Ethics Committee***

Clinical Investigation Ethics Committee of the Hospital Universitari de Bellvitge

### ***3.11. Study timeline***

16 weeks

Recruitment: 4 weeks

Study period: 8 weeks

Follow-up after the study end: 4 weeks

## 4. BACKGROUND

### 4.1. *Background and justification*

The HIV-1/AIDS epidemic remains a global health problem of unprecedented dimensions, with approximately 37 million people living with HIV-1 in 2015 [1].

The advent of potent combined antiretroviral therapy (ART) led to a substantial mortality reduction in HIV infected patients, transforming HIV-1 infection into a chronic disease in those patients who have access to treatment and who achieve durable virologic suppression [2]. In addition, the more favourable safety profile and simpler dosage of modern antiretroviral (ARV) drugs and combinations, have contributed to improve the efficacy of ART and the quality of life of HIV-infected individuals.

The treatment of HIV-infected patients with currently available cART reduces the risk of HIV acquisition by their sexual partners [3-4]. However, the number of new infections has continued stable and even increased in particular groups such as men who have sex with men [5]. HIV transmission during unprotected sexual intercourse is associated with the presence of HIV in genital fluids, and the efficacy of ART in preventing new infection is based on the ability to reduce HIV viral load in these fluids [6-10]. On the other hand HIV suppression in cervicovaginal fluid (CVF) is also a key factor to prevent mother-to-child transmission during childbirth, which is extremely important taking into account that women represent more than half of all people living with HIV-1 worldwide, and nearly 60% of HIV-1 infections in sub-Saharan Africa [1].

Furthermore, HIV persistence in reservoirs constitutes a barrier for HIV eradication [11] and the male and female genital tract constitutes separate reservoirs for HIV [12].

Therefore, the capability of antiretroviral (ARV) drugs to penetrate in the male and female genital tract is a key factor for achieving HIV suppression in these reservoirs, as well as for preventing sexual transmission of the virus [13-14]

and also, in the case of the female genital tract, to prevent mother-to-child transmission, and also to control.

All ART regimens currently used in clinical practice have demonstrated high efficacy in terms of HIV-1 RNA suppression in blood plasma. However, the activity of certain ARV drugs in the male and female GT may be limited by the presence of natural barriers to drug penetration into these compartments. The ability of drugs to penetrate into the genital fluids depends on many variables including molecular size, lipophilicity, electric charge, plasma protein binding and active transport [13-14].

Doravirine is a new NNRTI with activity against common NNRTI-resistant mutants that has demonstrated non-inferior efficacy compared to efavirenz (both in combination with tenofovir/emtricitabine) and boosted darunavir (both in combination with tenofovir/emtricitabine or abacavir/lamivudine) as well as good tolerability profile in randomized, double-blind, phase III studies in ART-naïve HIV-1-positive adult patients [15-16].

However, a number of key issues regarding the capability of Doravirine to suppress HIV replication in male and female genital tract remain to be addressed, including:

1. The pharmacokinetic (PK) profile of Doravirine given orally in stable, undetectable HIV-1 infected individuals in male and female genital fluids (semen and cervicovaginal)
2. Maintenance of HIV suppression in male and female genital fluids.
3. The correlation between blood plasma and male and female genital fluids Doravirine drug levels.

This study will address these unknowns and provide additional evidence for the scientific rational for the use of Doravirine in treatment and prevention strategies.

## 4.2 References

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## 5. STUDY DESIGN

Open label, single arm, single center, prospective study.

### 5.1. STUDY PHASE

Phase II

### 5.2. Objectives

- To determine Doravirine concentrations in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals receiving ART with Doravirine plus TAF/FTC.
- To evaluate HIV-1 viral load in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals receiving ART with Doravirine plus TAF/FTC.

## 6. SUBJECT POPULATION

### 6.1. *Subjects selection*

Male and female HIV-1 infected adults receiving an antiretroviral therapy ART. Subjects will be selected from the routine control visits in the outpatient clinic of the HIV and STD Unit at the Bellvitge University Hospital.

### 6.2. *Inclusion Criteria*

1. Asymptomatic, HIV-1 infected individuals  $\geq$  18 years of age.
2. Be on a stable ART consisting of TAF/FTC, tenofovir disoproxil fumarate/emtricitabine or abacavir/lamivudina, plus an non-nucleoside reverse transcriptase inhibitor, a boosted protease inhibitor or an integrase inhibitor, continuously for at least 3 consecutive months preceding the screening visit.
3. Plasma HIV-1 RNA  $<40$  copies/mL for at least 6 months at the Screening visit.
4. Signed and dated written informed consent prior to inclusion.
5. Female Subjects of Childbearing Potential\* must agree to utilize a highly effective\*\* method of contraception during heterosexual intercourse from the screening visit throughout the duration of the study.

(\*) A woman of Childbearing Potential is considered following menarche and until becoming postmenopausal<sup>a</sup> unless permanently sterile<sup>b</sup>.

a) A postmenopausal state is defined as amenorrhea for 12 months without an alternative medical cause.

d) Permanent sterility is defined as Documented hysterectomy, bilateral salpingectomy or bilateral oophorectomy

(\*\*) Highly effective methods of contraception as defined by the Clinical Trial Facilitation Group (CTFG) ("Recommendations related to contraception and pregnancy testing in clinical trials", version 15/09/2014): 1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); 2. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable); 3. Intrauterine device (IUD); 4. Intrauterine hormone-releasing system (IUS); 5. Bilateral tubal occlusion; 6. Vasectomised partner; 7. Sexual abstinence.

### **6.3. Exclusion Criteria**

1. Severe hepatic impairment (Child-Pugh Class C)
2. Ongoing malignancy
3. Active opportunistic infection
4. Resistance to any of the ARV included in the study or history of virologic failure with risk of resistance selection to any of the study drugs.
5. Any verified Grade 4 laboratory abnormality
6. ALT or AST  $\geq 3 \times \text{ULN}$  and/or bilirubin  $\geq 1.5 \times \text{ULN}$
7. Severe renal impairment (Estimated creatinine filtration rate  $<50 \text{ mL/min}$ ).
8. Females who are pregnant (as confirmed by positive serum pregnancy test) or breastfeeding.

### **6.4 Sample size**

Fifteen male and fifteen female individuals will be included in the study. This is a study designed to obtain information about doravirine concentrations and HIV viral suppression in seminal plasma and cervicovaginal fluid. The study design is similar to other studies evaluating PK and PD of antiretroviral drugs in these compartments.

### **6.5. Study duration**

The study will have a recruitment period of 4 weeks.

The study treatment period will be of 8 weeks.

A follow up visit will be performed 4 weeks after the end of the study treatment period.

## **6.6. Treatment of patients at the end of the study**

If at the end of the study doravirine is marketed in Spain, and the study treatment has resulted effective and safe, participants will be offered to continue the same study treatment.

If at the end of the study, participants refuse to continue taking the same treatment or doravirine is not yet marketed in Spain, participants will be offered to return to their previous treatment or to discuss other treatment options.

## **6.7. Criteria for discontinuation of study treatment**

1. Grade III or IV laboratory abnormalities or Adverse Events related to the study drug, or that in the investigator's opinion, advise against continuing taking the study drugs.
2. Subject request to discontinue for any reason (withdrawal of consent).
3. Protocol non compliance.
4. Lost of follow up or death

### **6.7.1. Managing of a study patient withdrawal**

In case of any study withdrawal, the information must be recorded in the Case Report Form.

Detailed information about the date and reasons for discontinuation will be recorded.

As a general rule, for all the premature discontinued patients, a clinical examination and all the tests specified in the final visit will be performed.

The investigator will provide the appropriated medical care to the premature discontinued patient for any reason.

## 7. INVESTIGATIONAL MEDICINE PRODUCT

### 7.1. Study regimen

Study patients will receive Doravirine (MK-1439) 100 mg administered in combination with Tenofovir alafenamide (TAF) and emtricitabine (FTC) orally once daily.

Doravirine 100 mg will be administered as a film-coated tablet, orally, once daily, without regard to food.

TAF/FTC will be administered co-formulated as single tablet (Descovy® TAF/FTC 25/200 mg). Each film-coated tablet contains 25 mg of tenofovir alafenamide and 200 mg of emtricitabine. TAF/FTC will be administered orally, once daily, without regard to food.

#### 7.1.1. Packaging and labelling

The Promoter will register the study medication lot and expiry date to guarantee the traceability, collecting this information in the Case Report Form of each participant.

The study medication (Doravirine) will be provided by the manufacturer, Merck Sharp & Dome, and will be sent to the Pharmacy of the Hospital University de Bellvitge.

Descovy® (TAF/FTC 25/200 mg) will be provided by the Pharmacy of the Hospital Universitari de Bellvitge.

Study medication (Doravirine) will be relabelled by the HIV and STI Unit monitoring team once received at the hospital pharmacy. The label will be in Spanish, as requested by the applicable Spanish Law.

The information in the label will be:

Study. EudraCT: 2018-003921-27

Sponsor: Fight AIDS Foundation (Fundació Lluita contra la SIDA).

Investigator: Dr. Daniel Podzamczer

Content: Doravirine 100 mg.

Oral administration

Patient number: XXXXXX

Lot number: XXXXXX

Expiry date: XXXXXX

To be stored in the original package in order to protect from moisture. Keep the bottle tightly closed.

Keep away from children

USE FOR CLINICAL TRIAL

### **7.1.2. Criteria for changing the treatment regimen during the study**

No changes in the ARV treatment regimen are expected during the study period.

In case of virological failure, the appropriated treatment will be given to the patient in base to the genotypical resistance study.

In case of Adverse Reactions related to the study drugs, the investigator will provide the patient with the treatment that he considers appropriate for the patient, and the patient will be discontinued from the study.

At the end of the study, if doravirine is marketed in Spain, and the study treatment has resulted effective and safe, participants will be offered continue the same study treatment. If participants refuse to continue taking the same treatment or doravirine is not yet marketed in Spain, participants will be offered to return to their previous treatment or to discuss other treatment options.

### **7.1.3 Prior and concomitant medications**

Concomitant medication should only be used during patient participation in the study only when medically necessary.

All the concomitant medications should be listed in the Case Report Form.

### **MEDICATION DISALLOWED WITH DORAVIRINE**

- Androgen Receptors inhibitors: enzalutamide.
- anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin.
- antimycobacterials: rifampicin, rifapentine.
- Cytotoxic Agents: mitotane.
- HIV Antiviral Agents: efavirenz, nevirapine, etravirine.

- herbal products: St. John's wort (*Hypericum perforatum*).

#### **7.1.4 Investigational Medicinal Product Management**

Doravirine will be stored at controlled room temperature. It will be stored in the original package in order to protect from moisture. The bottle should be tightly closed. Until dispensed to the subjects, all bottles of study drugs should be stored in a secure area, accessible only to authorized site personnel.

#### **7.1.5. Compliance assessment test**

Adherence to the study treatment will be assessed at each study visit by the study investigators.

### **8. STUDY DEVELOPMENT AND EVALUATION OF THE RESPONSE**

#### **8.1. Evaluation criteria**

##### *Primary study endpoints:*

- Concentration of Doravirine in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals, respectively, 8 weeks after switching to Doravirine plus TAF/FTC.
- HIV-1 RNA in seminal plasma and cervicovaginal fluid in HIV-1 infected male and female individuals, respectively, 8 weeks after switching to Doravirine plus TAF/FTC.

#### **8.2. Procedures**

Eligibility criteria will be evaluated in a screening visit before the inclusion of patients in the study.

Patients will be evaluated at baseline, weeks 4 and 8 (end of the study), and 4 weeks after the end of the study (follow up visit).

##### **8.2.1. Clinical records and physical examination**

At baseline, demographic data of interest related to HIV infection will be collected to characterize the study population: gender, date of birth, HIV diagnosis date, HIV

risk factor, CDC stage, opportunistic infections, malignancies or previous diseases, concomitant treatments).

At baseline a complete physical examination will be performed. At the following visits, a physical examination oriented to symptoms will be performed.

### ***8.2.2. Laboratory Procedures***

#### ***HIV-1 RNA quantification***

At baseline and week 8 visits HIV-1 RNA will be determined in paired blood plasma and seminal plasma samples in male participants, and paired blood plasma and cervicovaginal fluid samples in female participants. HIV-1 RNA will be assessed by real-time PCR assay (Abbott Real Time HIV-1) with a quantification limit of 40 copies/mL.

#### ***Doravirine concentrations***

At week 8 visit doravirine concentrations will be determined in paired blood plasma and seminal plasma samples in male participants, and paired blood plasma and cervicovaginal fluid samples in female participants.

Drug concentrations will be determined at the end of the dosing interval ( $C_{24h}$ ).

Doravirine concentrations (total and protein-unbound) will be quantified using a validated liquid chromatography-tandem mass spectrometry ('LC-MS/MS') method. Drug concentrations analyses will be performed at the laboratory of the Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

#### ***General laboratory parameters***

As part of the routine clinical follow up of HIV-infected patients and also for safety surveillance during the study, at baseline and week 8 visits the following parameters will be also determined:

- Haematology: red blood cells, hemoglobin, hematocrit, white blood cells, platelets.

- Biochemistry: Glucose, urea, creatinine, bilirubin, alkaline phosphatase, gamma glutamyl transferase, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides.
- T CD4 lymphocytes.

Pregnancy test will be performed in all women at each study visit.

#### **8.2.4 Biological samples management**

##### *Blood samples:*

Blood samples will be obtained by venopuncture. Samples will be processed in the Microbiology laboratory within 2 hours after collection (centrifugation and plasma separation) and stored at -80°C until analysis.

##### *Semen samples:*

Semen samples will be obtained by self-collection in a sterile, pre-labelled urine sample pot (study name, number, initials, date of birth, date of collection, visit number and type of sample) and kept on wet ice while being transferred to the Microbiology laboratory, where they will be processed within 2 hours after collection (centrifugation and plasma separation) and stored at -80°C until analysis.

##### *Cervicovaginal fluid samples:*

Cervicovaginal fluid samples will be collected via intra-vaginal aspiration using a sterile volumetric aspiration device (CarTika Medical INC ([www.cartikamedical.com](http://www.cartikamedical.com))). Specimens will be kept on wet ice while being transferred to the Microbiology laboratory, where they will be processed within 2 hours after collection (centrifugation and plasma separation) and stored at -80°C until analysis.

The study samples will be stored in -80°C freezers, in the HIV and STI Unit and the Microbiology Department of the Hospital Universitari de Bellvitge. Samples will be stored with a numeric code. Only the site staff will have access to stored

samples. Only the principal investigator and delegated personnel will have access to the list where the patients and samples are identified.

HIV-1 RNA analyses will be performed at the Microbiology Department of the Hospital Universitari de Bellvitge.

Doravirine concentrations analyses will be performed at the Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill (Chapel Hill, NC, USA.)

### **8.3. Clinical Trial Management**

- The study will take place in the Bellvitge Hospital – HIV and STI Unit
- For each of the study participants a selection visit will be performed, where the signed informed consent form will be obtained, the investigators will review the inclusion / exclusion criteria and the patients will be informed about the study procedures and the study flowchart.

At the study visits the procedures indicated in the below flowchart will be followed

#### **8.3.1. Study Flowchart**

Procedures	Screening visit (-2 to -4 weeks )	Day 0	W 4	W8	Follow up visit
Inclusion / exclusion criteria	X				
Informed Consent	X				
Medical History	X				
Physical Examination	X	X	X	X	X
Haematology, Biochemistry, CD4 count		X		X	
BP HIV-1 RNA		X		X	
SP HIV-1 RNA		X		X	
CVF HIV-1 RNA		X		X	

Doravirine concentrations in BP, SP and CVF				X	
AEs and concomitant medication	X	X	X	X	X
Adherence assessment		X	X	X	X
Medication dispensation		X	X	X	

BP: blood plasma; CVF: cervicovaginal fluid; SP: seminal plasma.

## 9. ADVERSE EVENTS AND TOXICITY MANAGEMENT

### 9.1 Definition Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after screening (before the administration of study investigational medicinal product).
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.
- Complications and termination of pregnancy
- All AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.
- Uncomplicated pregnancy.
- An induced elective abortion to terminate a pregnancy without medical reason.

## 9.2 Assessment of Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. During the study, in case of a safety evaluation, the investigator or site staff will be responsible for reporting AEs and SAEs, as detailed in this section of the protocol.

Severity of AEs will be assessed according to “Division of AIDS table for grading the severity of adult and pediatric adverse events”, version 2.0 of November 2014. Patients will be asked to report all AEs as part of the procedures performed at each study visit. The site personnel will document all AEs in the patient’s medical record. All AEs subsequently must be recorded in the appropriate eCRF sections.

The following points must be recorded for each event:

- A description of the event in medical terms
- Date of onset (start date);
- Date of resolution (stop date);
- The time of onset with respect to administering the investigational product;

- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC AE Classification;
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered.
  - **No:** Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
  - **Yes:** A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.
- Action taken regarding the investigational product:
  - o No action;
  - o Temporary discontinuation;
  - o Permanent discontinuation;
  - o Patient's outcome:
    - o Recovered without sequelae
    - o Resolved with sequelae;
    - o Recovering/Resolving;
    - o On-going;
    - o Fatal (for SAEs only).

### 9.3 Serious Adverse Events

Throughout the study, the reporting of SAEs to the Sponsor or its designee will be done through the SAE forms in the eCRF.

It is the investigator's responsibility to ensure that the SAE report is reported within 24 hours after knowledge of the event(s). The SAE forms or paper report forms should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. An assessment of causality should always be provided at the time of the initial report.

A **serious adverse event** (SAE) is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death. NOTE: Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome.
- Life-threatening situation. NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs).
- Persistent or significant disability/incapacity. NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product.
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as “serious” when it meets one of the predefined outcomes described above in Section.

The HIV and STD Unit monitoring team will inform about all the Suspected Unexpected Serious Adverse Reactions (SUSARs) to the applicable authorities in accordance the the applicable law in Spain regarding Clinical Trials.

## 10. ETHICAL ASPECTS

The study be conducted in compliance with the study protocol and will follow the International Conference on Harmonization, ICH guidelines, Declaration of Helsinki and its amendments and the Royal Decree 1090/2015 and will be initiated once obtained the hospital Clinical Research Ethics Committee and Spanish MOH (*Agencia Española de Medicamentos y Productos Sanitarios*) corresponding approvals.

The signed Informed Consent will be obtained for all the study participants previously to perform any study related procedure.

Before the study ICF signature, the patients will have enough time to read the Patient Information Sheet and to perform all the questions they need.

It is the responsibility of the investigator to give, to each patient, full and adequate verbal and written information regarding the aims, methods, anticipated benefits and potential hazards. The patient must be informed that participation is voluntary, and that they are free to withdraw from the study at any time without any

disadvantages for their subsequent care. Although a patient is not obliged to give her/his reason(s) for withdrawing prematurely from the trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Written consent (signed and dated by the patient and the investigator) must be obtained prior to admission. The patient must be provided with a copy of the patient information and informed consent.

The data collected in this study will be processed anonymously.

The patient must be informed of and consent in writing that personal data relating to the trial may be subject to audits by Health Authorities and the sponsor. However, personal data will be kept strictly confidential and will not be made publicly available

## **10.1 Responsibilities and Study Management**

The investigator will ensure that the study is conducted in accordance with the approved protocol. All protocol modifications must be submitted to the EC for approval if necessary. The Investigator will ensure that this study is conducted in accordance with the principles of the “Declaration of Helsinki”, International Conference on Harmonisation (ICH) guidelines, and with the laws and regulations applicable in Spain

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an EC approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

The Investigator and the Promoter must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. At least the following documents will be kept: the

protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, and other appropriate documents and correspondence. Study documents will be retained until a

The Principal Investigator will ensure that all the study collaborators will be informed about the study procedures and about their responsibilities.

#### Drug Handling

The Investigator or designee is responsible for ensuring adequate accountability of all used and unused investigational medicinal product. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) at the hospital pharmacy and subject dispensing records and returned or destroyed study product. Dispensing records will document quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, and the initials of the person dispensing the medication. The medication will be dispensed individually to each patient subject after being relabelled with the study information and patient's number. See section 7.1.1

#### Confidentiality

Study subjects will be informed that their participation in the study will be treated with the same confidentiality than their clinical records.

Patients' participation in the study will be reflected in their clinical records.

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties.

Personal information will be treated following the Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (Implementation date 25 May 2018).

Also according to the current European Regulation participants will Possibility of exercising the rights of access, rectification, cancellation and objection regarding their personal data (ARCO rights) contacting with the study investigators.

In case of that cession of the study data to third countries, this will be only according to the study purposes and guaranteeing the data confidentiality. There will only be transmitted to third parts or other countries the study collected data dissociated and without information that could identify directly the patient. In case of the study data would be transferred to other countries out of the EU and EEA (European Economic Area) the study promoter will warrantee the protection of personal data at less at the same level as required by European regulation.

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The investigator will keep a coded list that will allow to identify to all the study patients (subject name study number). This list will be kept at the site.

#### Condiciones de publicación

A clinical study report will be prepared and provided to the regulatory agency and the EC.

The study results will be published in internationally indexed publications.

## **12. STATISTICAL ANALYSIS**

The statistical analysis will be performed by using SPSS 21.0 software.

1. A descriptive analysis of the baseline characteristic will be performed. Quantitative variable will be described as median and range. Qualitative variables will be described as frequencies and percentages.
2. The study endpoints will be expressed as mean and standard deviation or median and range for quantitative variables and as frequencies and percentages for qualitative variables. For comparisons, Chi Square or Fisher exact test were used for quantitative variables and the non-parametric Mann

Whitney U test for qualitative variables. For intra-group comparisons McNemar and Wilcoxon tests were used when appropriate.

3. All adverse events will be listed and analyzed

## Appendix A

### **Division of AIDS table for grading the severity of adult and pediatric adverse events**

The severity of adverse events will be assessed using the division of AIDS table for grading the severity of adult and pediatric adverse events, version 2.0 of November 2014. A copy can be downloaded from the internet web site below

[http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS\\_AE\\_Grading\\_Table\\_v2\\_NOV2014.pdf](http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf)