CLINICAL TRIAL PROTOCOL

Protocol Title**:** Evaluation of (doravirine / lamivudine / tenofovir disoproxil fumarate) (Delstrigo®) as a New Strategy for non-occupational Post Exposure Prophylaxis, a Prospective Open Label Study.

Protocol Code: DORAVIPEP

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EudraCT No: 2019-004140-30

Sponsor: Fundació Clinic per a la Recerca Biomèdica. Barcelona, Spain Chief Investigator: Dr. Josep Mallolas. Hospital Clínic de Barcelona, Spain

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SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable local laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (ICH GCP), the ethical principles that have their origin in the Declaration of Helsinki and applicable privacy laws.

Name of person who signs on behalf of the sponsor: Signature:

Date:

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I have thoroughly read and reviewed the trial protocol. I agree:

- To conduct the trial in accordance with GCP and the applicable regulatory requirements and with the approved protocol.

- That I am thoroughly familiar with the appropriate use of the investigational medicinal products, as described in the Investigator's Brochure and any other information provided by the Sponsor.

- To comply with the procedures for data recording /reporting.

- To ensure that all persons assisting me with the study are adequately informed about the study and of their study-related duties and functions.

- To permit monitoring, auditing and inspection and to retain the trial related essential documents for the period of time required according to ICH-GCP and local regulatory requirements.

Name of Principal Investigator: Signature:

Date:

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ABBREVIATIONS

3TC	Lamivudine
ABIC	Age, serum Bilirubin, INR, and serum Creatinine score
ADR	Adverse Drug Reaction
ABsup	Superficial Antibody
ABcore	Core Antibody
Agup	Superficial Antigen
AgE	E antigen
AE	Adverse Event
ALT	Alanine aminotransferase
AP	Alcaline phosphatase
AR	Adverse reaction
AST	Aspartate aminotransferase
ATZ/r	Atazanavir boosted ritonavir
AZT	Zidovudine
CI	Confidence Interval
CK	Creatin Kinase
CRP	C Reactive Protein
CYP3A4	Cytochrome P450 3A4
DSMB	Data Safety Monitoring Board
DRV/r	Darunavir boosted ritonavir
EFV	Efavirenz
EKG	Electrocardiogram
EMA	European Medicines Agency
eNOS	endotelial Nitric Oxide Synthase
EVG/c	Elvitegravir boosted cobicistat
FTC	Emtricitabine
GCP	Good Clinical Practice
HVB	Hepatitis B virus
HCV	Hepatitis C Virus
HIV	Human immunodeficency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDIBAPS	Institut d'Investigacions Biomèdiques August Pi i Sunyer
IMP	Investigational Medicinal Products
IQR	Interquartile range
ISF	Investigator Site File
NEV	Nevirapine
LOP/r	Lopinavir boosted ritonavir

RAL	Raltegravir
RIL	Rilpivirine
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMAQ	Simplified medication adherence questionary
SMT	Standard Medical Therapy
STis	Sexually transmitted diseases
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDF	Tenofovir disoproxil fumarate
PEP	Post exposure prophylaxis
TMF	Trial master file
UAR	Unexpected Adverse Reaction
WHO	World Health Organization

PROTOCOL SYNOPSIS

Protocol code	Evaluation of (doravirine / lamivudine / tenofovir disoproxil fumarate) (Delstrigo®) as a New Strategy for non-occupational Post Exposure Prophylaxis, a Prospective Open Label Study.
Title of the study	DORAVIPEP
EudraCT No.	2019-004140-30
Sites	Multicenter clinical trial: - Hospital Clínic de Barcelona, Barcelona, Spain - Hotel-Dieu de France University Hospital, Nantes, France
Study period	The study is expected to begin, once authorizations are obtained, in February 2020. The recruitment period will be 6-12 months, and the follow-up will last up to 4 months after the inclusion of the last subject. The study is expected to end by March 2022.
Primary objective	To estimate the proportion of subjects who correctly complete (for 28 days) the entire antiretroviral treatment proposed in the study.
Secondary objectives	Incidence and description of adverse effects (clinical and laboratory) that appear during cART. Description of adherence to cART, including the time until loss of adherence . Proportion of patients that maintain follow-up at 1 and 3 months. Rate of HIV Seroconversion
Study population	Adult individuals eligible for post exposure HIV prophylaxis using
Study Design	A Phase 4, prospective, open, multi-center study on subjects outcomes (efficacy and safety) following post exposure prophylaxis.
Number of subjects	400 subjects

Study population	Inclusion Criteria Subjects attending ER due to potential HIV exposition of either sex: 1. Aged 18 years or more. 2. Who have been exposed to non-occupational HIV and who meet the prerequisites for the current recommendations to begin PEP with three antiretroviral drugs. 3. Who after being fully informed, give their written consent to participate in the study and undergo the tests and examinations required. 4. Individuals able to do follow up correctly. Exclusion Criteria 1. Pregnant women or nursing mothers or women trying to conceive during the study period. 2. Patients in whom it is known or suspected that the source case has a resistance to one of the drugs from the study treatment regimens. 3. Treatment with drugs that are contraindicated in the study or products that are in the investigational phase. 4. Allergic reactions or intolerance to the compounds of the study treatment regiments
Investigational Product	Doravirine, Lamivudine and tenofovir disoproxil fumarate (Delstrigo®)
Route and dosage form	Oral administration dosage: 1 covered tablet every day (QD)
Dosage	Doravirine / lamivudine / tenofovir disoproxil fumarate (Delstrigo®) 100 mg doravirine, 300 mg lamivudine,300 mg tenofovir disoproxilo fumarate equivalen t to 245 mg de tenofovir disoproxilo. 1 covered tablet for day .(will be administered 28 days maximum)
Duration of treatment	The duration of the study treatment will be 28 days.
Outcome measures	Primary outcome will be defined as : Proportion of subjects with treatment completion at day 28. PEP non-completion is considered in cases: 1. If the subject dies. 2. Does not go to visits (loss of follow-up) 3. Change or suspend the treatment under study for any

Secondary and exploratory outcome measures	1. Assess the baseline characteristics associated to non-completion. 2. Incidence and description of adverse effects (clinical and laboratory) that appear during cART. 3. Description of adherence to cART, including the time until loss of adherence. 4. Proportion of subjectsthat maintain follow-up at 1 and 3 months
Statistical Methods and Planned Analyses:	A sample size of 400 individuals from a population of 1400 produces a two-sided 95% confidence interval with a precision of 0.04 when the actual proportion of non-completion is near 40%. The population size considered corresponds to the yearly number of individuals receiving post-exposure profilaxis in our hospital. Summary statistics will be performed using absolute frequency and percentages for qualitative variables and mean and SD or median and IQR for quantitative characteristics, at each visit. The primary outcome will be reported as absolute frequency and percentage along with the 95%CI. The secondary objectives will be assessed as follow: 1. Baseline characteristics associated to treatment non-completion will be identified using logistic regression model. 2. The incidence of adverse effects (AEs) will be reported as number of AEs per 100/person-time and its 95%CI, differentiating those leading to discontinuation or to study withdrawal, those caused by laboratory abnormalities (grade 1-2 and 3-4) during study treatment and also until week 12 of follow-up. 3. Absolute frequency and percentage of individuals who showed non-adherence at each follow-up visit. Median (IQR) time until loss of adherence. 4. Absolute frequency and percentage of individuals who performed week 4 assessment and week 12 (retention rate). 5. The rate of HIV seroconvertion will be reported as the number of individuals newly diagnosed of HIV per 100/person-time and its 95%CI.

1. INTRODUCTION AND RATIONALE

According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), in 2017 there were 2.1 million new HIV infections worldwide, adding up to a total of 36.7 million people living with HIV1. In this scenario, the use of antiretroviral therapy (ART) has been proposed as a secondary prevention to avoid infection. This strategy is known as Post-exposure prophylaxis (PEP), which is used after either occupational contact or non-occupational contact.

PEP was initially used in the occupational context 2. Data available from animal transmission models, perinatal clinical trials, and studies of health-care workers receiving prophylaxis after occupational exposures and observational studies indicate that PEP administered within 48-72 hours and continued for 28 days might reduce the risk for HIV infection3-6. The sooner PEP is administered after exposure, the more likely is the interruption of transmission.

The recommended guidelines in Spain and Europe for PEP consist of two nucleoside reverse Transcriptase Inhibitors (NRTI) that can be combined with either an integrase or a protease inhibitor7,8. PEP toxicity is the main reason for poor adherence and the high rate of discontinuation in the treatment9. The side effects of PEP that mostly appear with the use of three-drug regimens are mainly attributed to protease inhibitors and cause irregular compliance and dropouts which ultimately lead to worsen treatment completion10-14.

This hospital attended in 2018 1,596 cases of Post Exposure Prophylaxis and the evaluation of new PEP regimens would be welcome.

NNRTIs based triple therapy could qualify for PEP regimens, however, DDI potential, treatment associated toxicities and lack of convenience (i.e. bedtime dosing or calorie intake requirements) have prevented the currently existing NNRTIs to become so. Current guidelines recommend the use of integrase inhibitors with raltegravir as core treatment as standard of care.

Guidelines for PEP's treatment suggest a triple treatment with the aim of avoiding the development of resistance. Drugs are chosen for their pharmacodynamic characteristics (potency), pharmacokinetics (dosage and potential interactions) and convenience of administration (single tablet). Among the options is raltegravir, but in this case the dosage is not comfortable since it is twice a day. There is elvitegravir, which allows a daily dose but presents multiple potential drug interactions, and there is dolutegravir, which is administered in a single tablet a day and includes abacavir, which requires a previous test before use and therefore invalidates it as PEP. Our proposal is doravirin, a potent, well-tolerated NNRTI that allows dosing in a single tablet once a day.

Doravirine, is novel non nucleotide transcriptase inhibitor that has recently arrived on the market as an STR in combination with (Lamivudine and tenofovir disoproxil fumarate) (Delstrigo®) and in studies in HIV infected patients have shown a very good toxicity profile [15,16)]

Doravirine has an in vitroresistance profile that is distinct from other NNRTIs retaining activity against viruses containing the most frequently transmitted NNRTI mutations, K103N, E138K,

Y181C and G190A. Recent studies show that the prevalence of doravirine resistance associated mutations in HIV-1-infected ARV-treated patients in the Mediterranean was low(17)

The emerging of Integrase resistance mutations during Initial therapy containing dolutegravir is reminder that, despite a high barrier to resistance (18), no agent as initial therapy for HIV-1 is impervious to resistance, doravirine as a novel agent has a role for HIV prevention.

Doravirine may be as good a choice as a PEP given its excellent tolerance profile, mechanism of action, its potency, the lack of interactions due to mostly being unboosted and also its single tablet administration. It is likely that a much better dosage pill and BID to QD could improve adherence to medication (19). Current guidelines recommend the use Raltegravir as first line regimen,Data available from previous studies show that a 32% of patients occasionally missed the second dose of raltegravir (20). Doravirina as a STR regimen might Improve the perception of illness and, therefore, its compliance.

2. OBJECTIVES OF THE CLINICAL TRIAL

Primary objective

To estimate the proportion of subjects who correctly complete (for 28 days) the entire antiretroviral treatment proposed in the study.

Secondary objectives

1. Assess the baseline characteristics associated to non-completion.
2. Incidence and description of adverse effects (clinical and laboratory) that appear during cART.
3. Description of adherence to cART, including the time until loss of adherence.
4. Proportion of patients that maintain follow-up at at 4 at 12 weeks.
5. Rate of HIV Seroconversion.

3. TRIAL DESIGN

a. Primary and secondary endpoints

Primary endpoint:

Primary outcome will be defined as:

Proportion of subjects that achieved treatment completion at day 28. PEP non-completion is considered in cases:

1. If subject dies
2. Does not go to visits (loss of follow-up)
3. Changes or suspends the treatment under study for any reason.
4. Consent withdrawal.

Secondary endpoints:

1. Assess the baseline characteristics associated to non-completion.
2. Incidence and description of adverse effects (clinical and laboratory) that appear during cART.
3. Description of adherence to cART, including the time until loss of adherence .
4. Proportion of subjects that maintain follow-up at 1 and 3 months.
5. Rate of HIV Seroconversion

b. Study design

This is a phase 4, multicenter, open, prospective, on subjects outcomes (efficacy and safety) following post exposure prophylaxis.

The study will be developed at two tertiary care centers:

- Hospital Clínic de Barcelona, Barcelona, Spain
- Hotel-Dieu de France University Hospital, Nantes, France

Subjects attending emergency room due to a potential HIV exposition of either sex who meet inclusion criteria and none of the exclusion criteria will be included in this trial.

A total of 400 subjects will receivea regimen consisted **of (doravirine / lamivudine / tenofovir disoproxil fumarate) (Delstrigo®) 1 covered tablet for day** (will be administered 28 days maximum).

Subjects **will receive the study medication for 28 days.** Follow-up will be performed at 1 to 7 days after starting PEP and week 4 and 12.visit consisting in telemedicine, in those sites which it is the current clinical practice,evaluation and analysis assessment will be done.

For PEP treatment in some sites the follow up evaluation the clinical practice consist on a telemedicine visit. This visit is carried out through a digital platform used in other patients evaluations. If the normal clinical practice is by telemedicine in the site, the clinical evaluation can be done by telemedicine.

Figure 1. Flow-chart of the study

	Day 0 (Treatment initiation)	**Day 7 after start PEP**	**Week 4 (End of treatment)**	**Week 12 (after start PEP)**
Compliance with inclusion and exclusion criteria	x			
Clinical evaluation	x	x	x	x
Biochemistry, liver and CBC	x (1)	x	x	x
HIV, HAV, HBV, HCV and syphilis serology (**)	x (1)	X, Syphilis serology(2)	x	x
Cholesterol, HDL and LDL cholesterol, triglycerides	x (1)	x	x	x
Pregnancy test	x		x	x
Questionnaire on adherence to ART(3)		x	x	
Pill Count		x	x	
Adverse events	x	x	x	x

(1) This analysis can be performed within the first 10 days after exposure

(2) Lues serology will only be performed in sexual exposures until day 28

(3) Evaluated with a Simplified Medication Adherence Questionnaire SMAQ

c. Trial duration

The duration of the trial will be of 28 days of daily treatment plus 3 follow-up visits at 1-7 days after PEP initiation, between day 28 and 60 after PEP initiation, and another visit between 12 and 16 weeks after stopped the treatment.

d. Criteria for termination and/or discontinuation

The participants will discontinue study participation if they are unwilling or unable to meet the protocol requirements in terms of the visit schedule or if the patient or the investigator considers it is best to end their participation in the study. All participants have the right to withdraw their consent at any time during the study without prejudice to them.

All follow-up terminations of study subjects and the reasons for them must be reported immediately to the study monitor and be duly documented both in the medical records and the case report form.

Premature termination of the study will occur if subjects are considered to be exposed to an unacceptably high risk in the investigators decision. Premature termination will be reported to the local Ethics Committee and competent authorities within 15 days in accordance with country- specific requirements.

See section 4.4 *Withdrawal criteria* for specific criteria for treatment discontinuation.

e. Drug accountability.

The study treatment will be administered to patients who are admitted to the hospital from the Pharmacy Service of each participating hospital, but adherence to treatment will be evaluated by the medical researcher.

f. Allocation participant identification code

All participants will be assigned with a subject number that will allow the patient to be identified. Subjects will be identified only by subject number in order to protect confidentiality. Each site investigator will keep its own patient log to match the identification number with the patient's personal data, in accordance with applicable regulatory and country-specific data protection requirements.

The subject number will be done through an electronic case report form (eCRF) that will be created using RedCap. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive).

g. Source data verification

Source documents are defined as all observations or notes recorded on the clinical interventions, and all reports and notes required for assessment and reconstruction of the research study. Accordingly, source documents include but are not limited to laboratory reports, EKG tracings, hospital reports, patient progress notes, radiologist reports, or any other reports or records of any procedure according to this protocol.

Whenever possible the original document should be kept as the source document; however, provision of a photocopy which is clear, legible and an exact duplicate of the original document and signed by the principal investigator is acceptable.

h. End of the trial

The end of the trial is defined as the date of the last visit of last subject undergoing the trial (LVLP).

i. Statement that the trial will be conducted in compliance with legal requirements

The trial will be conducted in accordance with the principles of the Declaration of Helsinki, and according to applicable regulations in each country.

By signing the investigator's agreement, the investigator undertakes to comply with the provisions contained in applicable legislation on clinical trials and agrees to conduct the study in an efficient and diligent manner in accordance with good clinical practice guidelines, applicable European and local regulations, as well as the guidelines or regulations relating to clinical trial management.

The investigator must prepare and keep adequately study documentation according to good clinical practice, and applicable local and national regulations.

4. SUBJECT SELECTION AND WITHDRAWAL

a. Description of study population

Patients eligible for this study will be subjects post HIV exposure prophylaxis attended from the hospital participating in the study.

b. Subject inclusion criteria

Patients included into the study must meet all the following criteria:

1. Patients attending emergency room due to potential HIV exposition of either sex:
2. Aged 18 years or more.
3. Who have been exposed to non-occupational HIV and who meet the prerequisites for the current recommendations to begin PEP with three antiretroviral drugs.
4. Who after being fully informed, give their written consent to participate in the study and undergo the tests and examinations required.
5. Individuals able to do follow up correctly.

c. Subject exclusion criteria

1. Pregnant women or nursing mothers or women trying to conceive during the study period.
2. Patients in whom it is known or suspected that the source case has a resistance to one of the drugs from the study treatment regimens.
3. Treatment with drugs that are contraindicated in the study or products that are in the investigational phase.
4. Allergic reactions or intolerance to the compounds of the study treatment regiments
5. Sexual assault victims
6. Past history of PEP use in several occasions without accomplishing Follow-up testing.

d. Withdrawal criteria

Study withdrawal

All patients have the right to withdraw their consent at any time during the study without prejudice to them.

The patient may also discontinue study participation in the following instances:

1. If the investigator considers in the interest of the subject (i.e intercurrent illness, occurrence of adverse events) that it is best for them to stop study medication.
2. The subject fails to comply with the protocol requirements or fails to cooperate with investigator.
3. The individual move to another country being unable to do the follow up.

   All follow-up terminations of study patients and their reasons must be reported immediately to monitor and sponsor and be duly documented in both the subject's CRF and source document. All patients who discontinue study medication will be asked to do the follow up and requested to attend for study visits up until 28 days of treatment. If this is not possible or acceptable to the subject or Investigator, the subject may be withdrawn from the study and the reason for withdrawal recorded in the CRF. The Early Termination Visit (ETV) form in the CRF should be completed.
4. If a female subject becomes pregnant along the study, she will discontinue the study treatment.

Specific criteria for study treatment withdrawal

1. If the subject has HIV positivity against HIV .
2. Bad tolerance or appearance of serious adverse events related to study medication.
3. Patient decision: Risk reconsideration.
4. If the source of the exposure had a HIV negative test by a 4th generation test.

5. TREATMENT OF SUBJECTS

A cohort of 400 subjects will recive (doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, for oral use , (will be administered for 28 days)

a. Name and description of the investigational products

Farmaceutical form

DELSTRIGO™: Covered Tablets: 100 mg of doravirine, 300 mg of lamivudine, and 300 mg of tenofovir disoproxil fumarate

b. Storage conditions

Store in the original bottle and keep the bottle tightly closed to protect it from

humidity. Do not remove the desiccant. This medication does not require any special temperature of conservation.

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in in double LDPE liners within a fiberboard container for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The results for three additional primary commercial stability batches for 12 months at 25°C/60%RH and 6 months at 40°C/75%RH showed comparable results to prior stability studies.

c. Summary of known and potential risks and benefits Undesirable effects

- Most common adverse reactions (incidence greater than or equal to 5%, all grades) are dizziness, nausea, and abnormal dreams.

Others:

-Severe acute exacerbations of hepatitis B (e.g., liver decompensated and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV and have discontinued products containing lamivudine and/or TDF, and may occur with discontinuation of DELSTRIGO

- Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of TDF, a component of DESLTRIGO

-The concomitant use of DELSTRIGO and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to.

Loss of therapeutic effect of doravirine, lamivudine, and tenofovir disoproxil fumarate and possible development of resistance.

Possible clinically significant adverse reactions from greater exposures of a component of doravirine, lamivudine, and tenofovir disoproxil fumarate

- Bone Loss and Mineralization Defects

d. **Contraindications**

DELSTRIGO is contraindicated when co-administered with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers as significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DELSTRIGO. (4) DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine

Renal impairment, including cases of acute renal failure and Fanconi syndrome, have been reported with the use of TDF. DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple NSAIDs). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in patients with risk factors for renal dysfunction who appeared stable on TDF.

DELSTRIGO is contraindicated in patients with a previous hypersensitivity reaction to lamivudine.

Renal impairment, including cases of acute renal failure and Fanconi syndrome, have been reported with the use of TDF. DELSTRIGO should be avoided with concurrent or recent use of a nephrotoxic agent (eg, high-dose or multiple NSAIDs). Cases of acute renal failure after initiation of high-dose or multiple NSAIDs have been reported in patients with risk factors for renal dysfunction who appeared stable on TDF.

e. **Drug interactions**

Co-administration of DELSTRIGO with a CYP3A inducer decreases doravirine plasma concentrations, which may reduce DELSTRIGO efficacy [see Contraindications (4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]. Co-administration of DELSTRIGO and drugs that are inhibitors of CYP3A may result in increased plasma concentrations of doravirine.

f. Adverse events

The focus of this safety section is the safety outcomes in the phase 3 studies. Potential risks include possible adverse effects due to the trial medication. Specifically, these include the renal effects associated with tenofovir. Doravirine is well tolerated drug but can cause side effects. The most commonly observed adverse drug reactions during clinical trials as long term treatment in HIV individuals were: headache (13%), diarrhea (14%), sleep disorders (12%), nausea (10%), Nasopharyngitis (10%) dizziness (8%), vomiting, fatigue (8%), rash (5%) . Severe adverse events were observed in the minority of cases (< 0,01%) as; acute kidney injury, genital wards, appendicitis, Pneumonia.

Laboratory abnormalities

In general, treatment with DOR and DOR/3TC/TDF was well tolerated in the phase 2 and 3 studies. Few Grade 3 or 4 lab abnormalities were reported. Around 5% de los patients have grade I and grade II elevations of bilirubin. The majority of elevations in the laboratory test were Grade 1, single, transient elevations, with no pattern of the elevation occurring early or late relative to dosing. The duration of treatment limits the possibility of adverse effects that appear in the long term.

g. Labeling of investigational products

Ther are complet IMPD In the Investigator file to consult

Delstrigo ®will be distributed to each Hospital Pharmacy Service labeled according to the current legislation by Pharmacy Service of the study sites.

h. Concomitant, non permitted and permitted medication

Co-administration with drugs that are strong cytochrome P450 (CYP)3A enzyme inducers should be avoided:

- Carbamazepine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Enzalutamide
- Rifampin
- Rifapentine
- Mitotane.

- St. John’s wort (Hypericum perforatum))

Co-administration with drugs that are strong cytochrome P450 (CYP)3A enzyme inhibitors should be avoided:

- Clarithromycin
- Telithromycin
- Nefazodone
- Itraconazole
- Ketoconazole

A closer patient follow up of the investigator team will be needed for patients in treatment with moderate and weak CYP3A inhibitors and inducers.

All the medication listed above had a significant decrease in doravirine plasma concentrations, which may decrease the effectiveness of DELSTRIGO.

i. Monitoring of compliance

The researcher's health staff will be in charge

Assessment of compliance by a health staff will be performed in the first and second follow-up consultation at day 7 and 4- 8 weeks, with the SMAQ questionnaire.

The SMAQ questionnaire was developed as a modification of the Morisky-Green questionnaire to measure adherence to antiretroviral treatment in patients with acquired immunodeficiency syndrome (AIDS). The questionnaire provides good levels of validity and interobserver agreement. An enhanced sensitivity is advantageous to better detect non-adherent patients for a better follow-up.

This questionnaire consists of six questions that evaluate different aspects of patient compliance with treatment: forgetfulness, routine, adverse effects, and a quantification of omissions. A patient is classified as non-compliant if he/she responds to any of the questions with a non-adherence answer, and in terms of quantification, if the patient has lost more than two doses during the last week or has not taken medication during more than two complete days during the last three months.

This validated questionnaire for HIV compliance is written as follows.

“SIMPLIFIED MEDICATION ADHERENTE QUESTIONNARIE (SMAQ)

This questionnaire refers to the level of compliance that you hold with the post exposure prophylaxis treatment prescribed by your doctor please answer the entire question, indicating the correct response in each case. Please remember that you answers are confidential, and that you should respond to the question in as truthful a manner as possible. THANK YOU.

1. - Do you always take your medication at the appropriate time?

YES ____

NO ____

2. - When you feel bad, have you ever discontinued taking your medication?

YES _____

NO _____

3.- Have you ever forgotten to take your medication?

YES _____

NO_____

4. - Have you ever forgotten to take your medications during the weekend?

YES _____

NO_____

5. - In the last week, how many times did you fail to take you prescribed dose?

Never _____

1-2 times_____

3-5 times _____

6-10 times _____

More than 10 times _____

6. - Since your last visit, how many whole days have gone by in which you did not take your medication?

Days _____ “

Continuation of treatment after the end of the trial

At day 28, the study medication will be stopped and the investigator will decide the best management for each patient.

6. VISIT SCHEDULE AND STUDY PROCEDURES

a. Assessment at each visit

Table 1 shows the summary of visits and procedures that will take place during the study.

Day 0.

After providing informed consent, all subjects will undergo screening assessments:

- Risk assessment, establishing better PEP should be indicated (high, intermediate, low)
- Review inclusion and exclusion criteria.
- Obtain written informed consent.
- Medical history and physical examination (including vital signs). Demographics: Age, Sex (male, female, no binary), Sexual orientation (heterosexual, homosexual, Transexual), Origin (North America, Latin America, Europe, Asia, Africa, Oceania)
- Register comorbidities. (ICD-10)
- Register concomitant medication.
- Register allergies
- Previous Hep B vaccination.
- Previous PEP episodes (yes/no). Regimen: Back bone (TDF/FTC or AZT/3TC), third agent (EVG, LOP/r, RAL, ATZ/r, RIL, EFV, NEV), other. When (year).
- Previous PREP use (yes/no).
- Previous STIs (yes/no). Type: Herpes, Gonococal uretritis, Clamidia uretritis, Unknow uretritis, Sifilis, Linfrogranulom venereum. When (year of diagnosis).
- Last HIV test performed (date)
- Use of abuse drugs (cocaine, GHB, ketamine, Tina, mefedrone, Speed, Extasis, MDMA, Poppers, Viagra, Cannabis).
- Hours from the exposure.
- HIV status of the source (HIV+, HIV -, Unknown)
- Anal sex (yes/no), vaginal sex (yes/no), oral sex (yes/no).
- Condom less sex (yes/no), Blood (yes/no), Semen (yes/no), broken condom.
- Adverse events.
- Antimicrobial prophylaxis (yes/no).
- Hepatitis B prophylaxis (yes/no).
- Counseling.

- Blood tests for (further detailed in 6.2.1):
    - Hematology.
    - Creatinine levels, glomerular filtration rate, sodium and potassium levels.
    - Liver tests: ALT, AST, Bilirubin, AP, albumin.
    - Leukocyte count.
    - Serologies: HIV antibody.

- Evaluation of other activities (HBV prophylaxis, STDs).
- Pregnancy test in urine will be performed in all fertile women.
- Recommendations on contraception methods during participation in the clinical trial will be provided.

Total required amount of blood at Day 0 visit: 70mL. Total required amount of urine at Day 0 visit (applies only to women with childbearing potential): 100mL.

Day 7 after PEP initiation (day 1-7)

The following procedures will be completed:

- Complete physical examination, vital signs.
- Register of comorbidities.
- Register concomitant medications.
- Investigation of PEP tolerance and initial adherence.
- Adverse events
- Blood tests for (further detailed in 6.2.1):
    - Hematology
    - Creatinine levels, glomerular filtration rate, sodium and potassium levels
    - Liver tests: ALT, AST, Bilirubin, AP, albumin.
    - Leukocyte count
    - Serologies: HIV antibody, HCV, HAV, HBV, Syphilis.
- Simplified Medication Adherence Questionnaire (should be expressed as a percentage) and the level of tolerance, with the questioning directed towards body changes and changes in daily routines. These parameters will be graded on a 0 to 10 analog scale.

- Pill Count

- Baseline laboratory testing with kidney and liver function, hemogram, lipids (cholesterol, fractions and triglycerides).
- Simplified Medication Adherence Questionnaire.

Total required amount of blood for Day 7 visit: 70mL.

Study follow-up visit: Week 4 (4-8 weeks). End of treatment

- Medical history and physical examination (including vital signs).
- Register comorbidities.
- Register concomitant medication.
- Counseling.
- Assesment of development of adverse Events
- Blood tests for (further detailed in 6.2.1):
    - Hematology and coagulation tests.
    - Creatinine levels, glomerular filtration rate, sodium and potassium levels
    - Liver tests: ALT, AST, Bilirubin, AP, albumin.
    - Leukocyte count and CRP.
    - Serologies: HIV antibody. Syphilis Test
- Simplified Medication Adherence Questionnaire.
- Pill Count
- Evaluation of other activities (HBV prophylaxis, tetanus, STDs, gynecological evaluation in cases of sexual assault.
- Pregnancy test in urine will be performed in all fertile women.
- Recommendations on contraception methods during participation in the clinical trial will be provided.

Total required amount of blood at week 4 visit: 70 mL. Total required amount of urine at week 4 visit (applies only to women with childbearing potential and amenorrea): 100 mL.

- Clinical interview, investigating treatment adherence using Simplified Medication Adherence Questionnaire (should be expressed as a percentage) and the level of tolerance, with the questioning directed towards body changes and changes in daily routines. These parameters will be graded on a 0 to 10 analog scale.

Study follow-up visit: Week 12 (weeks 12-16)

- Medical history and physical examination (including vital signs).
- Register comorbidities.
- Register concomitant medication (incluiding LVP).
- Assesment of development of adverse Events
- Blood tests for (further detailed in 6.2.1):
    - Hematology Creatinine levels, glomerular filtration rate, sodium and potassium levels
    - Live r tests: ALT, AST, Bilirubin, , albumin.
    - Leukocyte count..
    - Serologies: HIV antibody. Syphilis test, HCV antibodies
- Evaluation of other activities (HBV prophylaxis, tetanus, STDs, gynecological evaluation in cases of sexual assault
- Pregnancy test in urine will be performed in all fertile.

Total required amount of blood at week 12 visit: 70mL. Total required amount of urine (applies only to women with childbearing potential and amenorrea): 100mL.

Early termination

In case of early termination of a participant, a termination should be done. The evaluations and procedures will be the same as the Standard of Care.

6.2.1 Blood and urine samples for laboratory assessments during the study

Blood samples to determine hematology, biochemistry and coagulation and serology tests will be analyzed at the local laboratory of each participating center. After analysis the samples will be destroyed locally.

The following parameters will be evaluated:

- Hematology: Hemoglobin (g/L), Hematocrit 0.48 L/l, Platelets 10^9L, White cell count10^9L, Lymphocytes10^9L, Neutrophils10^9L. Total required amount of blood: 5mL
- Biochemistry: Glucose mg/dl, Bilirubin mg/dl, Direct bilirubin mg/dl, Indirect bilirubin mg/dl, AST U/l, ALT U/L, Alkaline phosphatase U/L, GGT U/L, Creatinine mg/dl, Na mg/dl, K

mg/dl, Total cholesterol mg/dl, High density cholesterol mg/dl, low density cholesterol mg/dl,Total required amount of blood: 5mL.

-HIV test: Total required amount of blood: 5 mL

-Hepatitis A, Hepatitis B IgM, IgG, Asup, ABsup, ABcore AgE, and hepatitis C antibodies and Syphilis test (VDRL, IgM, IgG): total required amount of blood: 10 mL

-Pregnancy test (applies to women with childbearing potential in case of amenorrea): Total required amount of urine: 13.5 mL

Samples for analysis at the end of the study (stored samples)

No samples will be stored for the study

7. STATISTICAL ANALYSIS

General remarks

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9 (CPMP / ICH / 363/96) (1).

Data analysis will be performed using the statistical software: Stata version 15 (2).

A summary of the overall approach to statistical analysis is presented hereafter.

Sample size

A sample size of 400 individuals from a population of 1400 produces a two-sided 95% confidence interval with a precision of 0.04 when the actual proportion of non-completion is near 40%. The population size considered corresponds to the yearly number of individuals receiving post-exposure profilaxis in our hospital.

The sample size calculation was performed using PASS 15 (3).

Criteria for evaluation Analysis populations

The population considered for this study will be the ITT (intention-to-treat): all patients who have received the first dose of the investigational product after signing the informed consent will be included in the ITT population.

Statistical Methods

Summary statistics will be performed using absolute frequency and percentages for qualitative variables and mean and SD or median and IQR for quantitative characteristics, at each visit.

The primary outcome, proportion of subjects who achieved treatment completion at day 28, will be reported as absolute frequency and percentage along with the 95%CI.

The secondary objectives will be assessed as follow:

1. Baseline characteristics associated to treatment non-completion will be identified using logistic regression model selecting variables in a stepwise fashion.
2. The incidence of adverse effects (AEs) will be reported as number of AEs per 100/person-time and its 95%CI, differentiating those leading to discontinuation or to study withdrawal, those caused by laboratory abnormalities (grade 1-2 and 3-4) during study treatment and also until week 12 of follow-up.
3. Absolute frequency and percentage of individuals who showed non-adherence at each follow-up visit. Median (IQR) time until loss of adherence.

4. Absolute frequency and percentage of individuals who performed week 4 assessment and week 12 (retention rate).
5. The rate of HIV seroconvertion will be reported as the number of individuals newly diagnosed of HIV per 100/person-time and its 95%CI.

Subgroups

No subgroup analyses are planned in the protocol. In case of any post-hoc subgroup analysis, they will be justified and identified as data-driven.

Inferential Analysis

No inferential analyses are planned in the protocol.

Multiplicity adjustment and interim analysis

No multiplicity adjustment neither interim analysis are planned in the protocol.

Procedures to account for missing data

The primary outcome includes the missing value in the non-completer category. No formal imputations will be performed for the rest of variables and the analyses will be based on the Available Data Only (ADO) approach.

Data Review (DR) will be performed before lock of database. Data will be examined for compliance with the trial protocol by the monitor and the data manager. Deviations will be sent to the project statistician to plan listings for the Data Review. The objective is to carry out the population selection and definition of the final study populations as well as a preliminary assessment of the quality of the trial data.

Statistical references

(1) (1) European Medicines Agency. International Conference on Harmonisation (ICH) Topic E9 (CPMP/ICH/363/96)
(2) (2) StataCorp. 2017. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC
(3) (3) PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

8. SAFETY ASSESSMENT

Definitions

Adverse event (AE): an AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonization [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious adverse event (SAE): an SAE is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important (according to the treating physician), other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following: hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility), surgery or procedure planned before entry into the study.

Adverse reaction: An AR is an AE suspected to be causally related to a medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (i.e. the relationship cannot be ruled out). Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include overdose, misuse, abuse and medication errors. [Sources EMA GVP Annex I, and ICH E2A].

Unexpected Adverse Reaction (UAR): Any adverse reaction, whose nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product).

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both serious and unexpected.

Assessment of intensity

An assessment of intensity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale (see Appendix 4). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

Assessment of causality

- Possible: An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- Probable: An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).
- Very Likely: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).
- AE related: The relationship in time of the AE with the study drug indicates a possible causal relationship and it cannot be explained by factors such as the patient's clinical condition or therapeutic interventions.
- AE unrelated: The relationship in time of the AE with the study drug indicates an unlikely causal relationship, or other factors (concomitant medication or conditions) or other therapeutic interventions provide a satisfactory explanation for the AE.

Collection and follow up of adverse events

AEs may be recorded at each visit based on careful clinical observation of the patient, laboratory tests or spontaneously reports by the participant discovered as a result of general questioning by the study staff. All AEs will be recorded on the medical history and in the CRF. The investigator will also decide whether the adverse event is, based on his/her judgment, related or not to the study drug—this decision should also be noted in the medical history and CRF.

The following will be recorded for each event: description, severity (grade 1, 2, 3, 4 and 5), duration (start and end dates), intensity, causal relationship with the drug (according to the previously attributability criteria) and study drug(s) for which this causal relationship is suspected, actions taken and outcome, using choices given on the patient's medical history. The investigator should report the underlying condition when a surgical or medical procedure is required as the event term, and the procedure as an action taken. For a preexisting AE that has worsened in terms of severity or frequency, the meaning of the change should be specified.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as a serious adverse event (SAE) requiring immediate notification (see section 8.3). Follow-up of the AE is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

The degree of severity of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event elicited by the investigator or reported by the patient. Severity does not reflect the clinical seriousness of the event, only the grade or extent of the complaint or incidence.

Adverse events (including pre-treatment adverse events) must be recorded on an *Adverse Event Report Form*. The investigator must provide information on the adverse event, preferably with a diagnosis, or at least with signs and symptoms; start and stop dates (and start and stop time if the adverse event lasts less than 24 hours); intensity; causal relationship to IMP; action taken; and outcome. If the adverse event is an overdose, the nature of the overdose must be stated (for example, medication error, accidental overdose, or intentional overdose) and the investigator shall notify sponsor or whoever assumes the tasks delegated by the sponsor, within 24 hours from the time of knowing about the event. The reporting circuit and form will be the same as for the SAE.

In order to avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology using MedDRA dictionary, rather than the patient's own words. The SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs: the event resolves, the event stabilizes, the event returns to baseline, if a baseline value/status is available, the event can be attributed to agents other than the study drug or to factors unrelated to study conduct, it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Information on adverse events that are not serious or unexpected and on those considered unrelated to the study treatment will be collected in tabular form at the end of the clinical trial or at the time of interim analyses when these are planned.

The sponsor will keep a record of all AEs reported by investigators. These records will be submitted to the competent authorities when requested.

Pregnancy

Subjects will be instructed to notify the investigator if the subject or partner becomes pregnant.

If any pregnancy occurs during the course of the study, the investigator shall notify the sponsor or whoever assumes the tasks delegated by the sponsor within 24 hours of knowing about the event. Also, a follow-up of the pregnancy will be performed to document its outcome and the state of health of the newborn. If the pregnancy outcome meets the SAE.

criteria or if the newborn presents a serious event, the procedures for reporting an SAE will be followed.

The report shall be made using the specific form for the notification of pregnancy, which must be sent by fax or email to the same contact who receives the SAE notifications .

Procedure for expedited reporting of serious adverse events and serious unexpected adverse reactions

Phamacovigilance activities will be delegated by the sponsor to Pharmacovigilance center (PV center) located at Hospital Clínic Barcelona CTU (Clinical Trial Unit),Barcelona , Spain.

8.3.1 Serious Adverse Events (SAEs)

The principal investigator or delegates will report immediately any SAE occurring during the study to the PV center regardless of their degree of causal relationship with the study drug. Any such serious adverse event due to any cause, whether or not related to the study medication, occurring from signing of informed consent and up to 30 days after receiving initiating the study, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event.

The initial report of SAE should be written and as complete as possible including details of the current disease and SAE and assessment of the causal relationship between the AE and the investigational product. Reporting will be made using the Serious Adverse Event Report Form included in Appendix 3 of this protocol within 24 hours from first

knowledge by the investigator, completing all information on the form in the following two days.

The information missing at the time of the initial report must be reported in the SAE follow-up form.

SAEs forms should be sent immediately by fax or email to: CTU)clinical Trial Unit) . Farmacologia Clínica.Hospital Clínic Barcelona

Fax number: 93 2279877

Email address: cencinas@clinic.cat and copy acruceta@clinic.cat/

For SAEs, the investigator will provide the PV center with all documentation related to the event (additional laboratory tests, discharge reports, etc.).

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study

medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

In the event of fatal or life-threatening, the investigator should be required to provide with all additional information requested by the study coordinator, the EC and regulatory authorities to PV center..

The PV center shall keep detailed records of all the SAEs or the events of special interest which are notified by the investigators.

In the case of a medication error or if the investigational medicinal product is used outside the provisions of the protocol, while conducting the study, the investigator shall notify the PV center within 24 hours from the time of knowing about the event. The reporting circuit and form will be the same as for the SAE.

In the case of documenting medication errors or overdose, the sponsor will carry out the necessary actions for its management and prevention (specify when necessary).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The PV center will report any events that are serious and unexpected that may be related to the investigational products to the competent authorities in accordance with local regulations.

Reporting will be made using the SAE form

The maximum deadline for reporting will be 15 calendar days from the time the sponsor is aware of the SUSAR. For SUSARs causing death or that are life-threatening for the subject,

the maximum reporting time will be 7 calendar days from the time the sponsor is aware of them. This information will be completed, when possible, in the following 8 days.

Expedited reporting of other relevant safety information:

The FV center shall notify regulatory authorities, as soon as possible and no later than 15 days after having knowledge of it, any information that could alter the benefit/risk relationship of the investigational medicinal product (e.g. an increase in the rate of occurrence of the expected SAR, SUSARs that occur after the completion of a clinical trial, new events related to the conduct of the trial or the development of the investigational medicinal product, etc.).

Annual safety report

During the course of the study, the FV center will prepare periodic safety reports annually following the recommendations outlined in the ICH E2F guidelines, and they must be submitted to the regulatory authorities and the ECs involved following the timetable established in the legislation.

Opening of the blind and unmasking: Not Aplicable

8.6 Report to the invest igators

The sponsor shall present the safety information that could affect the safety of the patients included in the study to the investigators as soon as possible.

The SUSAR information will be sent annually through a line listing, together with a summary of the data analysis. For masked studies, the SUSAR line listing will present worldwide SUSAR information, rather than by investigational medicinal product, in order not to break the blind for the investigator.

In addition, the investigator will be informed throughout the study about all safety aspects, including amendments to the protocol due to safety reasons.

9. DATA HANDLING

Recording of data

Data generated and/or collected will be registered in participating centers using an electronic data management system with remote data entry. Completeness and plausibility checks will ensure the collection of high quality data. An electronic case report form (eCRF) will be designed, validated and implemented with REDCap electronic data capture tools (1,2) hosted at Hospital Clinic and will provide electronic data capture functionality (EDC) to the investigators. The system complies with the relevant international standards and provides the capability to perform all major data management activities within a consistent, auditable and integrated electronic environment (query management, data entry, data validation, report generation). An e-CRF for each patient will be completed by authorized personnel.

Each centre will have access to their patients, and access will be secured by the use of unique personal logins. Each data recording or editing event will be logged in the database to allow better monitoring and database coordination.

The Sponsor or his delegates must ensure that data are recorded in the eCRF correctly and completely by authorized personnel. The investigator has to confirm the integrity of the data transferred to the eCRF by signature.

Direct access to source data/documents

Investigators will ensure access to the source documents of the staff responsible for guaranteeing data quality and data analysis. In addition, access to documentation will be provided, if necessary, to the staff duly authorized by the sponsor (study monitors), to regulatory authorities and to Ethics Committee if they request to inspect the study.

Source documents will be stored in the Investigators´s File. These documents will be kept for a minimum period of 25 years by the PI, after which they will be destroyed.

Data management

The Investigator must ensure the accuracy, completeness, legibility and timelines of data reported in the CRF and all required reports. Any change or correction to the CRF must be dates, initialled and explained (if necessary).

All documentation derived from this study must be stored for 25 years.

Archiving and storage of data

The investigator is responsible for maintaining all records which enable the conduct of the clinical trial at the site to be fully documented, in compliance with ICH GCP filing standard. Timeliness and completeness of the documentation will be regularly checked by

the clinical monitor. The documentation of the clinical trial including all the relevant correspondence should be kept by the investigator for the minimum period required by applicable regulatory and country-specific requirements.

All completed study related documents (e.g. eCRF, Informed consent forms, drug accountability logs, staff signature lists, Subject identification log, …) must be archived by 25 years.

9.5 Audit and inspection

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

According to ICH/GCP guidelines, the sponsor should ensure that the trial is adequately monitored.

The purpose of monitoring is to verify that the rights and wellbeing of human subjects are protected; that the trial is accurate, complete and verifiable with source data and that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements. A monitoring plan will be designed by the lead CTU. The monitoring plan will establish the guideline for conducting all the monitoring activities.

To ensure homogeneity and the same quality standards, monitors in all study countries will be trained with the same procedures.

Source data will be verified during on-site monitoring visits. During the visits, the monitor will compare the data entered into the eCRF with the source documents. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the monitor and study-site personnel and are accessible for verification. During monitoring visits, the relevant study-site personnel should be available, the source documentation accessible, and a suitable environment provided for review of suty- related documents. The monitor will meet the investigator The number of visits will be described in detail in the monitoring plan.

A close-out visits will be performed before the final closure of each centre. During this visit, medication accountability will be checked and arranged according to the indications of the final version of the protocol. Besides, a general overview and a final revision of pending queries will be implemented, ensuring that all data and corresponding source documents are in place before the site closure.

11. ETHICAL AND REGULATORY CONSIDERATIONS

Ethics approval

This study will be conducted in accordance with the protocol and ethical principles stated in the Declaration of Helsinki or the applicable guidelines on GCP, and all applicable local laws, rules, and regulations.

Requirements for ethical review as set forth in Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations.

and administrative provisions of the Member States relating to the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use or other relevant local regulations for institutional review will be followed. The Protocol, informed consent form, Investigator's Brochure and other required documents must be approved by the Ethics Committee before enrolment of subjects in the study. The letter of approval from the Ethics Committee, as well as a list of documents reviewed, will be filed in the Investigator Site File (ISF) and a copy will be filed in the trial master file (TMF) held by the Sponsor.

The Sponsor and his delegates, in collaboration with the investigator, will be responsible for reporting to the Ethics Committee all changes in research activity, including protocol amendments, updates of Investigator's Brochures, annual safety reports, all unanticipated problems involving risks to human subjects, and study termination.

Regulatory considerations

In parallel to the submission to the Ethics Committee, the Sponsor has to obtain an authorization from the appropriate competent authority to conduct the clinical study. Subjects must not be entered into the study until the relevant Ethics Committee has issued its opinion and the CA has given authorization to conduct the study.

All substantial amendments must be submitted to the Ethics Committee and/or to the Competent authorities for approval.

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior Ethics Committee approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the Ethics Committee and relevant competent authority.

Documentation of amendment approval by the investigator and Ethics Committee must be provided to the sponsor. During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative. Except in emergency situations, this

contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any

departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Responsibilities of the investigators

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki (and updated according to its last version, Fortaleza, Brazil, 2013), and that the study data are credible.

In addition, the investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, before and during the course of the study.

The investigator is also responsible for ensuring the privacy, health, and welfare of the subjects during and after the study. The investigator(s) must be familiar with the background and requirements of the study and with the properties of the investigational product as described in the Investigator's Brochure.

Before the start of the study, the investigator (or sponsor where required) will provide the Ethics Committee with current and complete copies of the following documents (as required by local regulations).

Informed consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing Ethics Committee and be in a language that the patient can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki (updated according to its last version, Fortaleza, Brazil, 2013), current ICH and GCP guidelines, applicable regulatory and country-specific requirements, and sponsor policy. Before enrollment in the study, the investigator or an authorized member of the study- site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort that the participation in the study may entail.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will

not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

Patient confidentiality

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. Patient data will be under a patient code to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

Subjects will be codified with a study code that prevents their identity from being deduced.

The PI and duly authorized collaborators will compromise to maintain personal data strictly confidential, according to the corresponding country-specific requirements. The link between the numeric code and real personal data from subjects will be rigorously kept by the PI. The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review, and regulatory inspection.

In the case report form, the patient will only be identified by the assigned study code. The name of patients will not appear in any publication or report of the study results.

The participation of the patient in the trial will be noted in their medical records.

The investigator will complete a list which will include the names of the patients participating in the trial, the number of inclusion in the study, and their medical history. Only investigators and the staff responsible for guaranteeing data quality and data analysis will have access to the clinical documentation of the participants.

Duly authorized persons by the sponsor and the health authorities and the Ethics Committee may audit or inspect the trial. Personal information will not be publicly available, in compliance with Personal Data Protection regulation.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete pursuant to European requirements (EU Directive 2016/679, on data protection). According to the above law, patients can exercise their rights to data access, rectification, opposition, cancellation, request a copy and portability, for which they must contact the study doctor.

In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

Only data collected for the study that does not bear any information that could directly identify the patient will be transferred to third parties or other countries. Should this transfer occur, it will be for the same purposes as the study and guarantee confidentiality with at least the level of protection afforded by applicable regulations in Spain.

Patients will be informed that their clinical data will be incorporated into an automated study- specific file after and the results of the clinical trials and different studies conducted with samples can be communicated at scientific meetings, medical conferences or publications. However, patient's identity or identifiable data will never be disclosed.

12. FINANCING AND INSURANCE

Financing

This study is funded by a grant received from MSD Sponsored Research grants

Insurance

It is considered a low-intervention because complies with the following conditions:

a) the investigational medicinal products, excluding placebos, are authorised;

b) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and

c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

13. PUBLICATION

The main results will be published according regulatory Spanish requirements.

14. REFERENCES

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Appendix I. World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added) 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2- Consistent with the mandate of the WMA, the Declaration is ad- dressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3- The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4- It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5- Medical progress is based on research that ultimately must include studies involving human subjects.

6- The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and

therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7- Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8- While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9- It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self- determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10- Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11- Medical research should be conducted in a manner that minimises possible harm to the environment.

12- Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13- Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14- Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15- Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16- In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be con- ducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17- All medical research involving human subjects must be pre- ceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non- vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, ani- mal experimentation. The welfare of animals used for research must be respected.

22- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23- The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the re- searcher, the sponsor and any other undue influence and must be duly qualified. It must

take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24- Every precaution must be taken to protect the privacy of re- search subjects and the confidentiality of their personal information.

Informed Consent

25- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the re- searcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the in- formation, the physician or another appropriately qualified individual must then seek the potential subject's freely-given in- formed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27- When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed con- sent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28- For a potential research subject who is incapable of giving in- formed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot in- stead be performed with persons capable of providing in- formed consent, and the research entails only minimal risk and minimal burden.

29- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30- Research involving subjects who are physically or mentally in- capable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the re- search may be done only after consideration and approval of a research ethics committee.

Useof Placebo

33- The benefits, risks, burdens and effectiveness of a new inter- vention must be tested against those of the best proven inter- vention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be sub- ject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34- Inadvanceofaclinicaltrial, sponsors,researchersandhostcoun- try governments should make provisions for post-trial access for all participants who still need an intervention identified as ben- eficial in the trial. This information must also be disclosed to par- ticipants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly avail- able. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of re- search not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37- In the treatment of an individual patient, where proven inter- ventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with in- formed consent from the patient or a legally authorised repre- sentative, may use an unproven intervention if in the physi- cian's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subse- quently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be re- corded and, where appropriate, made publicly available.