Removal of Doravirine by Hemodialysis in HIV-Infected Patients with End-Stage Renal Disease (ESRD)

Code: Dora-HD

Version 1.0, 0.6th October 2020

EudraCT: 2020-004454-30

Sponsor:

Fundació FLS de Lluita contra la SIDA, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
Hospital Universitari Germans Trias i Pujol
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Co-Investigators:
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SIGNATURES

The coordinating investigator/ Principal Investigator and the sponsor of the study:
Removal of Doravirine by Hemodialysis in HIV-Infected Patients with End-Stage Renal Disease (ESRD)

Declare that this study will be conducted in compliance with the protocol, Good Clinical Practices (GCP) published by the International Conference of Harmonization Guideline (ICH), and the applicable regulatory requirements.

Modifications to this protocol must be submitted prior agreement of the coordinating / principal investigator and sponsor.

Principal / Coordinating Investigator: José Moltó Marhuenda, MD, PhD

Signature and Date: 

Sponsor: Bonaventura Clotet, PhD, MD
Fundació Lluita contra la SIDA

Signature and Date: 

1 GENERAL INFORMATION

1.1 TITLE

Removal of Doravirine by Hemodialysis in HIV-Infected Patients with End-Stage Renal Disease (ESRD)

1.2 CODE

Dora-HD

1.3 PROTOCOL VERSION AND DATE

Version 1.0, 06th October 2020
Any modification of the protocol must also bear the amendment number and date.

1.4 SPONSOR

Fundació FLS de Lluita contra la SIDA, les Malalties Infeccioses i la Promoció de la Salut i La Ciència
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Person authorized by the sponsor to sign the protocol and amendments:
Bonaventura Clotet Sala, president of *Fundació FLS de Lluita contra la SIDA*

1.5 PRINCIPAL / COORDINATING INVESTIGATOR

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1.6 CLINICAL RESEARCH ORGANIZATION

The Sponsor will delegate the study monitoring, regulatory submission to EC and other study tasks to the following Clinical Research Organization (CRO):

FLS-Research Support
Fundació FLS de Lluita contra la SIDA
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1.7 SITES AND INVESTIGATORS

Multicentric trial.
The trial will be performed at:

Hospital	PI	Co- Investigators
H. U. Germans Trias i Pujols	José Moltó Marhuenda	Lucia Bailón Álvarez, Fredzzia Amada Graterol Torres, Jordi Soler Majoral
H. Vall d'Hebron	Adrià Curran Fàbregas	Natalia Ramos, Paula Suanzes
H. U. Bellvitge	Arkaiz Imaz Vacas	Sofía Scévola, Ana Coloma López

1.8 TECHNICAL SERVICES AND INSTITUTIONS INVOLVED

Biochemistry, blood count and dialysis session will be performed in the local facilities of participating sites.

Doravirine concentrations in plasma and dialysate fluid will be determined using high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS), at the Department of Molecular and Clinical Pharmacology of the University of Liverpool, according to a validated method.

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2 BACKGROUND INFORMATION

Progressive improvement in life expectancy of people living with HIV (PLWH) after the introduction of combined antiretroviral therapy (cART) has been accompanied by an increase in the prevalence of other non-AIDS defining comorbidities, including chronic kidney disease (CKD).[1, 2] Nowadays, CKD may be considered epidemic among PLWH, being present in 4.7 to 38% of patients. Similarly, PLWH have a 2- to 20-fold greater risk of end stage renal disease (ESRD) compared with the general population,[3-6] and the number of patients requiring hemodialysis as renal replacement therapy is increasing, especially among those with older age.[1] Patients on dialysis are subject to extracorporeal clearance of small molecules, including many drugs, and management of dosing of antiretrovirals in PLWH undergoing hemodialysis may be challenging.[7-9] Moreover, hemodialysis is intermittent and it has the potential for relatively rapid drug clearance. The extent to which dialysis removes a particular compound from plasma varies across different drugs, and it is dependent on drug properties including water solubility, molecular weight, protein binding and volume of distribution.[10]

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor that has demonstrated good efficacy, tolerability, and safety for the treatment of patients with HIV infection in phase III clinical trials. Doravirine achieved non-inferiority when compared with efavirenz- and darunavir/ritonavir-based regimens.[11, 12] Doravirine is mainly metabolized and eliminated by the liver, with only 6% of the drug being excreted unchanged through the urine.[13] In a study comparing 8 subjects with severe renal disease to 8 subjects without renal impairment, the single dose exposure of doravirine was 43% higher in subjects with severe renal function impairment.[14] However, according to prescribing information, no dosage adjustment of doravirine is required in patients with mild, moderate, or severe renal impairment. On the other hand, data on doravirine pharmacokinetics in patients with ESRD on dialysis are lacking.[15] This may be of special interest because doravirine has a relatively low molecular weight and it is only 76% bound to proteins in plasma.[13] These characteristics could make possible for hemodialysis to remove doravirine from plasma, potentially leading to subtherapeutic concentrations of doravirine after the dialysis sessions. On the contrary, doravirine volume of distribution is about 60 liters,[15] what could limit extraction of doravirine by hemodialysis. Since data on doravirine pharmacokinetics in PLWH with ESRD on dialysis are lacking, our aim is to evaluate the effect of intermittent hemodialysis on doravirine concentrations in HIV-infected patients with ESRD.

Clinical hypotheses:
Doravirine pharmacokinetics in HIV-infected patients with ESRD is not affected by intermittent hemodialysis.

2.1 REFERENCES

1.- Ando M, Yanagisawa N. Epidemiology, clinical characteristics, and management of chronic kidney disease in human immunodeficiency virus-infected patients. World J Nephrol 2015;4:388-95.

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3 TRIAL OBJECTIVE AND PURPOSE

3.1 PRIMARY OBJECTIVE

- To assess the hemodialysis extraction ratio of doravirine in HIV-infected patients with ESRD undergoing intermittent hemodialysis.

3.2 SECONDARY OBJECTIVE

- To evaluate the safety of doravirine in HIV-infected participants with ESRD on hemodialysis.

- To evaluate the effect of a hemodialysis session on doravirine concentrations in plasma in HIV-infected participants with ESRD.

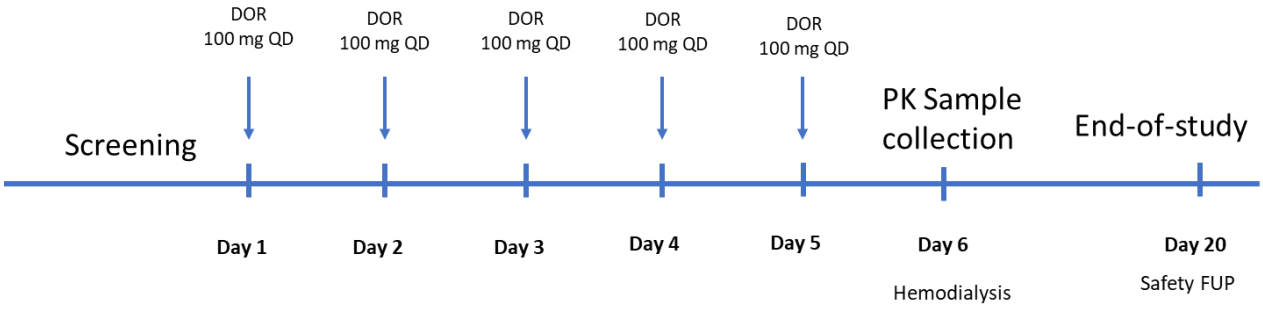
4 TRIAL DESIGN

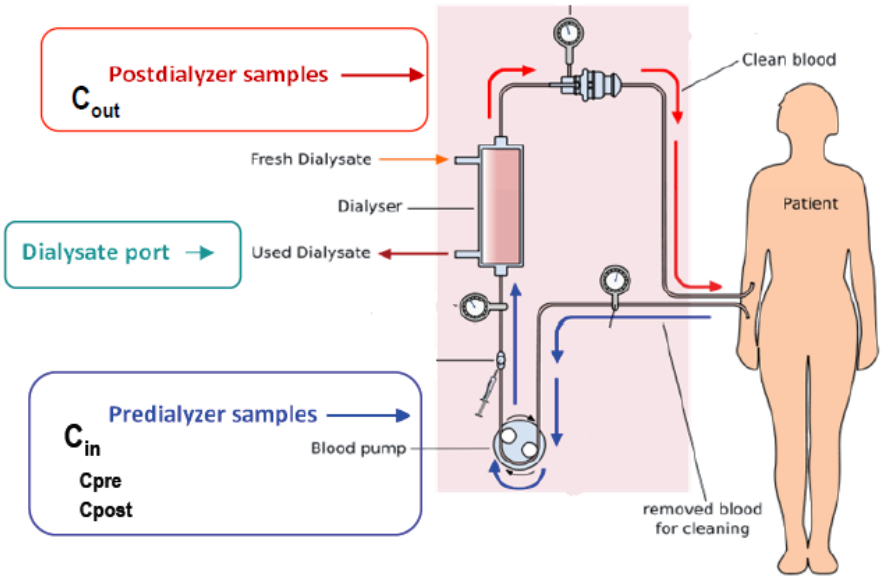
4.1 TYPE OF TRIAL

This is a multi-centre, single-arm, open-label, pilot study in HIV-infected participants with ESRD undergoing routine hemodialysis

4.2 DESCRIPTION OF THE DESIGN

After enrolment (on day 1), doravirine (Pifeltro, MSD) will be added to participant's cART (100 mg once daily) for 5 days. On day 6, blood samples from the pre-dialyzer line ('in') will be collected from each participant at the beginning ('C_{pre}') and at the end ('C_{post}') of a dialysis session. Additionally, paired samples of blood entering ('C_{in}') and leaving ('C_{out}') the dialyzer and resulting dialysate fluid will be collected during the dialysis session, approximately one hour after the start of the session.





5 ENDPOINTS

5.1 ENDPOINTS

5.1.1 Primary endpoint(s)

- To calculate the hemodialysis extraction ratio for doravirine in HIV-infected participants with ESRD

5.1.2 Secondary endpoints

- To assess the safety (adverse events grade 3-4) of doravirine in HIV-infected patients with ESRD undergoing hemodialysis

- To assess changes in concentrations of doravirine in plasma from the beginning to the end of a dialysis session

5.2 MEASURES TO AVOID BIAS

5.2.1 Randomization

Not applicable since it is an open clinical trial.

5.2.2 Stratification

Not applicable since it is an open clinical trial.

5.2.3 Blinding

Not applicable since it is an open clinical trial.

5.3 FORESEEN CALENDAR

- First subject first visit: January 2021
- Inclusion period: 2 months
- Follow-up period: 20 days
- Last subject last visit: March 2021 (End of study)
- Final report submission: March 2022

5.4 END OF TRIAL

The date of the end of the trial will be the last subject's last visit.

If the study had to be interrupted prematurely, all non-used materials should be returned to the sponsor, at the *Lluita Contra la SIDA Foundation.* The principal investigator will keep the investigator file and a copy of the completed CRF.

In case there were no subjects included in the study, the sponsor will take care of all materials.

5.5 SOURCE DATA

The source data are the subject's electronic health records including the results from blood test.

Study data will be collected through a study-specific Case Report Form (see annex 1).

6 TRIAL INVESTIGATIONAL PRODUCT(S)

6.1 EXPERIMENTAL AND CONTROL TREATMENTS

The investigational treatment will be doravirine. Open-label supplies of doravirine (100mg) will be required from MSD.

There is not control treatment in this trial.

6.2 SUPPLY, PACKAGING, LABELING AND STORAGE

Doravirine will be supplied by MSD on its marketed format.

Doravirine will be sent to the study staff of each participating site, where reception, units, batch number and expiration date will be confirmed. The labeling will be performed by the sponsor

Drug conditioning is not required.

All study medication will be stored in a safe place during the study. Storage shall be in accordance with the conditions defined conservation in the summary of products characteristics. Being marketed medication, specific temperature control for the study will not be performed, but the usual procedures of the custody and traceability of medication will be done by study staff of each participating sites.

6.3 DOSE, INTERVAL, ROUTE AND METHOD OF ADMINISTRATION

After enrolment, doravirine 100mg once daily will be added to participant's stable cART for 5 days.

Participants will be told to take one tablet of doravirine (Pifeltro, MDS) once daily, with or without food, approximately at the day time that they usually finish the hemodialysis sessions. The rest of their antiretroviral regimen and concomitant medications will remain unchanged.

6.4 DRUG ACCOUNTABILITY

The drug accountability will be performed on day 6. Participant will return the study medication to study staff, who will check the numbers of tablets taken.

6.5 ARM DESCRIPTION

This a single-arm study. All participants will receive doravirine 100 mg once daily during the study (5 days).

Participants will be instructed to take doravirine orally once a day, with or without food, plus their antiretroviral treatment and concomitant medications.

6.6 MODIFICATION OF THE TREATMENT REGIMEN

No changes in treatment regimens are foreseen during the study period.

In case of adverse reactions, the investigator will consider the interruption of the related medication and the subject will withdraw the study.

6.7 CONCOMITANT TREATMENTS

All other treatments apart from antiretroviral medication administered during the study period will be considered concomitant treatments and should be documented in the CRF.

Participants who participate in the study will be remembered that they should not start any new or continue any concomitant treatment without the knowledge and permission of the investigator.

In the SmPC of experimental drug (appendix II), detail on pharmacological interacions and dose recomendations with other drugs are specified.

Concomitant use of the following therapies is disallowed during the study and within 4 weeks before inclusion:

- Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- Androgen receptor inhibitor: enzalutamide
- Antimycobacterials: rifampin, rifapentine
- Cytotoxic agent: mitotane
- St. John's wort (Hypericum perforatum)

Participants will be told to avoid intake of products containing grapefruit or Seville orange from 48 hour before inclusion to day 6.

6.8 COMPLIANCE

Study drug accountability will be performed on day 6, when the participants will return the study medication to study staff.
Pill count will be performed to assess compliance.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 INCLUSION CRITERIA

1. Males and females* aging ≥ 18 years.
2. Documented HIV infection).
3. Stable antiretroviral treatment for at least 2 weeks prior to enrolment.
4. Optimal adherence to antiretroviral treatment, defined as less than 2 missed doses within the previous week.
5. End-stage renal disease in renal replacement therapy with periodic hemodialysis.
6. Agree with the study procedures and signature of the informed consent.

* Women of childbearing potential must have a negative pregnancy test prior to randomization into the study and commitment to use at least one of these birth control methods: male or female condom with or without spermicide, cap, diaphragm or sponge with or without spermicide, intrauterine device, bilateral tubal occlusion, vasectomized partner, sexual abstinence during the study. Condom use is considered as an additional method of contraception only and cannot be the only method of contraception used as not been considered an effective method by the Clinical Trial Facilitation Group (CTFG) guidelines.
Based on ICH, M3 (R2) 2009 a woman is considered of childbearing potential: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include tubal ligation, hysterectomy, bilateral oophorectomy.

7.2 EXCLUSION CRITERIA

1. Evidence or clinical suspicion that the patient will not be able to comply with the study protocol.
2. Hypersensitivity to doravirine
3. Concomitant therapy within the previous 4 weeks with any of the following drugs:
   - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
   - Androgen receptor inhibitor: enzalutamide
   - Antimycobacterials: rifampin, rifapentine
   - Cytotoxic agent: mitotane
   - St. John's wort (Hypericum perforatum)
4. Females who are pregnant or breastfeeding.
5. ALT and/ or AST ≥ 4 times the upper limit of normal (ULN) at screening.

6. Hemoglobin < 7,5 g/dL at screening.

7.3 SUBJECT WITHDRAWAL CRITERIA

7.3.1 Early subject withdrawal

Participants will complete the clinical study before the stipulated time in the following circumstances:

- Interruption of treatment due to adverse events, intolerance or poor adherence during the study.
- Concurrent process or illness which in the opinion of the investigator requires the withdrawal of the patient.
- Protocol deviation which in the opinion of the sponsor requires the withdrawal of the patient.
- The patient does not wish to continue in the study.
- Other

7.3.2 Medical approach to withdrawal

In all cases, a 'end of study form' needs to be filled. Detailed information will be given about the date and reasons of the discontinuation to the sponsor. The investigator will facilitate the necessary medical support.

7.3.3 Follow-up alter early withdrawal

As a general rule, participants who discontinue treatment prematurely will undergo a clinical examination and all tests specified in the visit.

In case early withdrawal happens while subject is participating in the present study a follow-up performs, in case of safety or until resolution of adverse events.

7.3.4 Replacement of participants

Participants withdrawn by protocol deviation will be replaced by new participants, if additional candidates are identified, until the expected number of participants will be met. Participants withdrawn by other reasons will not be replaced.

7.4 PRE-RANDOMIZATION / PRE-BASELINE LOSSES

Participants that do not meet the selection criteria after completing the screening visit will be considered screening failures. The reason for not inclusion of participant will be recorded in the CRF. Data from participants that do not meet the selection criteria will be recorded in the screening log form.

8 TRIAL CONDUCTION AND RESPONSE EVALUATION

8.1 CRITERIA FOR RESPONSE EVALUATION

8.1.1 Primary parameter

- Doravirine hemodialysis extraction ratio

8.1.2 Secondary parameters

- Adverse events grade 3-4 related to doravirine
- Doravirine concentrations in plasma at the beginning and at the end of a dialysis session

8.2 TRIAL DEVELOPMENT

After accepting the participation and meeting selection criteria, participants would be assessed the screening visit. Study visits would be at screening visit and on days 1, 6 and 20. All visit are mandatory.

For each visit, the procedures indicated in the schedule will be followed.

8.3 STUDY VISITS

8.3.1 Screening visit (day -14 to 0)

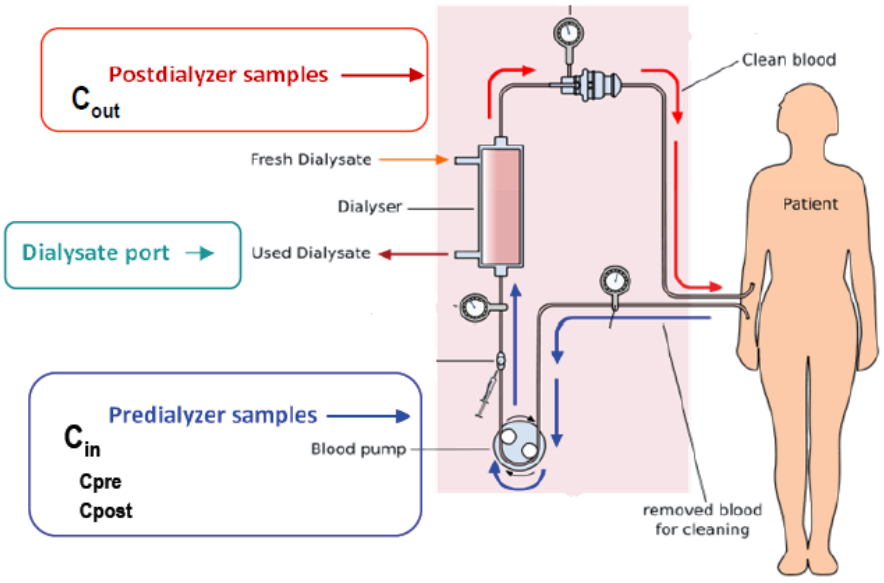
- Signed informed consent will be obtained from each participant.
- Review of inclusion/exclusion criteria.
- Record of demographic and clinical variables including gender, age, significant medical conditions, last HIV viral load in plasma, last CD4+ T lymphocytes count.
- Physical exam, including vital signs, body weight and height
- Blood test, including blood cell count and biochemistry. (This determination may be avoided if results within 2 weeks before the screening visit are available)
- Evaluation of Adverse events and concomitant therapy review (the participant will be asked about all medication, antiretroviral or not).
- Women of childbearing potential must have a pregnancy test.

8.3.2 Day 1

- Medical interview and a physical exam
- The investigator will provide each participant with one bottle containing 30 tablets of Pifeltro (doravirine 100 mg). Participant will be instructed to take one pill once-daily for 5 days, approximately at the same day-time when they usually finish the dialysis sessions.
- Blood test, a complete biochemistry and hematology (This determination may be avoided if results within 2 weeks before the Day 1 visit are available)
- Evaluation of adverse events and concomitant therapy review (the participant will be asked about all medication, antiretroviral or not).

8.3.3 Day 6

- Medical interview and physical exam
- Adverse events
- Concomitant treatments
- Adherence
- Dialysis parameters (type of dialysis, dialyzer, membrane, blood flux, begging and end of the session)
- Blood samples from the pre-dialyzer line ('in') will be collected from each participant at the beginning ('Cpre') and at the end ('Cpost') of a dialysis session. Additionally, paired samples of blood entering ('Cin') and leaving ('Cout') the dialyzer and resulting dialysate fluid will be collected during the dialysis session, approximately one hour after the start of the session.



8.3.4 Day 20 (+/- 4 days): Safety follow-up / End-of-study visit (Remote visit is accepted)

- Adverse events follow-up

8.4 STUDY ASSESMENTS

8.4.1 Clinical record and physical exam

Demographic and clinical variables will be recorded at screening visit.

Participants will be asked for all medications taken within the 4 weeks prior to the screening visit and during the study, antiretroviral or not, with special emphasis in prohibited medications (see section 6.7).

A complete physical examination will be performed at the screening visit. In the follow-up, a symptom-directed physical exam will be performed.

8.4.2 Laboratory tests

A blood test will be performed, in the points specified in the flow chart of the study (section 8.5). The following parameters will be quantified, as needed:

- **Hematology:**
  - Hematocrit
  - Red blood cell count
  - Hemoglobin
  - Leucocytes
  - Lymphocyte
  - Platelet count

- **Blood biochemistry:**
  - Glucose
  - Urea
  - Creatinine
  - Ionogramme: sodium, potassium
  - Total protein
  - Albumin
  - Liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT),

- **Pregnancy test in women (urine test strip or blood test in anuric women)**

Note: Before the beginning of the study, all labs will facilitate to the sponsor and to the investigator a list of the reference normal values of the parameters assessed.

- **Specific Lab Procedures:**

  - Doravirine concentrations in plasma:

  Blood samples for the determination of the plasma concentration of doravirine shall be collected in 5 ml EDTA tubes. The plasma will be separated by centrifugation (3,200 g during 15 minutes), and stored at -80ºC until analysis. The concentration of total doravirine in plasma will be determined by liquid chromatography with mass spectrometry (LC-MS/MS), according to a validated method.

8.5 ASSESSMENTS FLOW-CHART

Parameter	SCR	Day 1	Day 6	End-of-visit Day 20
Window	Day -14 to 0			+/- 4 days
Inclusion/ exclusion criteria	√			
Informed consent	√			
Pregnancy test [a]	√	√		
Clinical visit	√	√	√	
First dose of doravirine		√		
Cell count and chemistry	√[b]	√[b]	√[c]	
Adverse Events	√	√	√	√
Concomitant medication	√	√	√	√
Plasma sample (PK)			√	

[B] Women of childbearing potential, within 10 days prior to inclusion
[b] Cell count, glucose, urea, creatinine, Na, K, AST, ALT. Parameters performed within 2 weeks will be accepted.
[c] Total protein and albumin will be determined in C_{in} and C_{out} samples

9 ADVERSE EVENTS

9.1 DEFINITION

Adverse event (AE): Medical event presented by a patient or clinical research subject administered a pharmaceutical product, and which does not necessarily have a causal relation to the treatment.

Serious adverse event (SAE): Medical event classified as such and which, regardless of the dose involved:

- Causes patient death.
- Produces a life-threatening situation for the patient.
- Requires or prolongs in hospital admission.
- Produces important or persistent incapacitation/handicap or constitutes a congenital defect or anomaly.
- Needs action to prevent any of above situations.
- Is considered medically significant (examples of such events are intensive care in an Emergency Service or at home in a patient with allergic bronchospasm; blood dyscrasias or seizures not giving rise to hospital admission, or the development of drug dependency or abuse).

Unexpected adverse event (UAE): AE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

Serious Unexpected Adverse Reaction (SUSAR): SAE related to the product in investigation the nature or intensity of which does not coincide with the information available on the product administered (IB or SmPC).

9.2 DESCRIPTION OF THE IMPUTABILITY CRITERIA

The causal relation will be established according to the algorithm of the Spanish Pharmacovigilance System, which contemplates the following categories:

Definitive:

- A plausible time sequence exists in relation to administration of the drug or its plasma or tissue concentrations.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.
- The event cannot be explained by the concurrent disease or by other drugs or chemical substances.
- Response to withdrawal must be clinically plausible, i.e., the condition improves on discontinuing administration of the drug.
- A positive response to repeat exposure is observed.

Probable:

- A reasonable time sequence exists in relation to administration of the drug.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.
- The event is unlikely to be explained by the concurrent disease or by other drugs or chemical substances.
- Response to withdrawal is clinically plausible, i.e., the condition improves on discontinuing administration of the drug.
- No repeat exposure is required to complete this definition.

Possible:

- A reasonable time sequence exists in relation to administration of the drug.
- The observed manifestation coincides with the known adverse reactions profile of the implicated drug.
- The event might be attributable to the clinical condition of the patient or to other concomitantly administered drugs or chemical substances.
- Information concerning drug withdrawal may be unavailable or confusing.

Improbable:

- A clinical event, including anomalous laboratory test findings, with a time relation to administration of the drug which makes a causal association unlikely, and where other drugs, chemical substances or intercurrent disease afford plausible explanations for the observed event.

Unrelated:

- None of the above criteria are met.

9.3 ADVERSE EVENTS GRADING

Grading will be performed using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017].

Citation: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [March 2017]. Available from:
https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf

In case of events or laboratory abnormalities not included in the table, the following scale will be used:

Grade 1 (mild): Symptoms causing no or minimal interference with usual social & functional activities

Grade 2 (moderate): Symptoms causing greater than minimal interference with usual social and functional activities

Grade 3 (severe): Symptoms causing inability to perform usual social & functional activities

Grade 4 (potentially life-threatening): Symptoms causing inability to perform basic self-care functions or Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

Grade 5 (death): Any AE where the outcome is death.

9.4 PROCEDURE FOR REPORTING ADVERSE EVENTS

9.4.1 Investigator

The investigator will immediately notify the study sponsor of any serious and/or unexpected adverse events.

The report will be realized during the first 24 hours since the start of the serious adverse event. Notification will be made by means of the adverse events reporting form contained in Appendix V of this protocol.

Contact details for Sponsor

Fundació Lluita contra la SIDA
e-mail: safety@fls-rs.com
Fax. +34 93 465 76 02

All adverse events will be recorded, regardless of the imputability (i.e., causal) relationship involved, in the corresponding adverse events description form. The latter is found in the CRF of each participant in the study (see Appendix I).

Depending on the nature of the condition, each adverse event is to be classified as:

- serious / not serious
- unexpected / expected

The recording of adverse events is the responsibility of the trial investigator team, which should indicate the time of appearance of the event (expressed in the shortest time unit possible), its serious / not serious status, and in case it is considered related to investigational products, whether it was expected or unexpected. The intensity of the event (grade 1 to 5) is to be specified, along with the measures adopted (none, treatment, temporal or permanent discontinuation of investigational product), course (complete remission, partial remission, persistence) and imputability based on the criteria indicated in section 9.2.

9.4.2 Sponsor

The sponsor will inform the Spanish Drug Agency (Ministry of Health), the competent authorities of the autonomous region and the Ethics Committees implicated in the clinical trial about any important information of security of the investigational medicinal product.

The sponsor will inform the Spanish Drug Agency (Ministry of Health) of any SUSAR which may be related to the study treatment.

The sponsor will inform competent authorities of the implicated autonomous region of any SUSAR which may be related to the study treatment, and that have been happened in participants in its autonomous region.

The deadlines to notify suspect adverse reaction are, from the moment the SUSAR is known by the Sponsor:

- 15 days
- 7 days if the SUSAR has resolved in death or has been life-threatening. The information will be completed in 8 further days.

If the notification is sent in electronic form, it is not necessary to notify the competent authorities of the autonomous region.

The sponsor will keep a detailed register of all the adverse events notified by the investigators.

All adverse events will be notified in table form in the final report of the clinical trial.

9.5 HOSPITALIZATION AND FORESEEN PROCEDURES

If a subject has to be hospitalized or undergone a procedure (i.e, Elective surgery) scheduled before he/she was included in the trial (i.e, before the subject [or representative Legal thereof] signed informed consent) for any event / pre-trial disease, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event / disease worsens during the test should be reported as an AE (SAE or if the event / disease ends in a serious situation such as hospitalization).

9.6 ABNORMAL LABORATORY PARAMETERS

An abnormal laboratory parameter shall be considered an AE if the abnormality:

- results in withdrawal from the study
- requires treatment, dose modification or investigational drug interruption or any other therapeutically intervention

- is considered clinically important

Regardless of their severity, only laboratory abnormalities that meet criteria of seriousness should be recorded as SAE.

If the laboratory abnormality is part of a diagnosis or syndrome, only the syndrome or diagnosis will be included as AE or SAE. If the laboratory abnormality is not part of a diagnosis or syndrome, it shall be recorded as AE or SAE.

Clinically significant changes in safety parameters that are associated with the disease under study will not be rated as AE or SAE unless the investigator judges that are more severe than expected given the patient's condition.

9.7 DOCUMENTATION RELATED TO AE AND SAE

Each AE and SAE to take place during the study should be documented in the medical records of the patient in accordance with standard clinical practice of the investigator, and in the CRF. For each SAE, an independent set of SAE form will be used independently. Only if there are multiple SAE at the time of the initial report and these are temporary and / or clinically interrelated can be registered on the same set of SAE form.

The investigator should try to make a diagnosis of the event based on the signs, symptoms and / or other clinical information. An AE diagnosis has to be recorded per line or a sign/symptom if the diagnosis is not available. If a diagnosis subsequently becomes available, this then should be entered and the sign/symptom crossed out, initialed and dated by the investigator.

SAE pages found in the investigator's file shall be completed as precisely as possible, printed and shall be signed by the investigator before being sent to the sponsor. It is very important that the initial page SAE investigator provide its opinion in regard to the relationship of the event to the investigational product.

9.8 SAE FOLLOW-UP

The investigator must record all AE occurring from the moment the patient signs the informed consent until the last study visit.

AE will be followed-up until last visit or resolution.

SAE will be followed preferably until:

- Resolution of the event;
- Stabilization of the event; or
- Resetting the baseline situation of the event, in case baseline situation is available.

Otherwise, they will continue until:

- The event can be attributed to products other than the investigational product or factors unrelated to the study; or

- It is unlikely to obtain further information.

The investigator should ensure that follow-up reports include any additional information to enable a full assessment of the nature and/or the cause/effect of SAE, including any other laboratory test, pathology report and examination by a specialist.

9.9 PREGNANCY

The cases of pregnancy shall be recorded as AE and should only be considered as SAE only if they meet any seriousness criteria. Pregnancy is also a protocol deviation requiring premature termination of the patient. The investigator will provide medical support to the pregnant patient.

The Investigator will follow the female subject until completion of the pregnancy and must notify to the Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (i.e., spontaneous, or therapeutic abortion), the investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

9.9.1 Male subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10 STATISTICS

Statistical analysis will be conducted by the study investigators in collaboration the CRO FLS-Research. A computerized database for the study will be created, which will be used for data analysis.

Descriptive statistics (number of participants, proportions, median and range) will be performed.

The hemodialysis extraction ratio (ER) for doravirine will be calculated as:

$$ER(\%) = \frac{C_{in} - C_{out}}{C_{in}} \times 100$$

where C_{in} is predialyzer doravirine concentration in plasma (i.e., blood entering the dialyzer), and C_{out} is postdialyzer doravirine concentration in plasma (i.e., blood leaving the dialyzer).

Doravirine postdialyzer concentrations (C_{out}) will be corrected for hemoconcentration by a factor F based on total protein (TP) concentration pre- and postdialyzer:

$$F = \frac{TP_{in}}{TP_{out}}$$

Doravirine concentrations in plasma after the dialysis session (Cpost) will be numerically compared with those before entering the dialysis session (Cpre) as well as with doravirine trough concentrations in plasma in HIV-infected patients with normal renal function (KL Yee, A Ouerdani, A Claussen, R Greef, L Wenning. Population Pharmacokinetics of Doravirine and Exposure-Response Analysis in Individuals with HIV-. Antimicrob Agents Chemother. 2019 Mar 27;63(4):e02502-18). No formal statistical comparisons are envisioned.
The number/proportion of participants with doravirine concentrations at the end of a dialysis session above the protein binding-adjusted EC50 (>238 ng/mL) will be assessed.

Adverse events related to doravirine will be listed and graded according to DAIDS grading scale.

10.1 SAMPLE SIZE DESCRIPTION

Inclusion of 8 participants will allow detecting differences in doravirine concentrations in plasma (Cin vs Cout) of at least 30%, with an alpha risk of 0.05 and a beta risk of 0.2 in a one-sided comparison. Smaller changes in doravirine concentrations are not deemed as clinically significant.

10.2 DEVIATION OF STATISTICAL PLAN

Any deviation from that presented statistical plan will be described and justified in the final report.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Investigators and institutions will allow the monitoring, and audits by the Health Authorities or the Sponsor giving direct access to data and original source documents.

Access to personal patient information will be restricted to the Study physician / staff. To allow monitoring, audits and inspections, access to data to Health Authorities (Spanish Agency for Medicines and Health Products), the Ethics Committee and personnel authorized by the Sponsor, is guaranteed while maintaining the confidentiality thereof according to current legislation.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 STUDY MONITORING

In accordance with applicable regulations and Good Clinical Practice (GCP), the monitor will visit or contact the center on a regular basis. The duration, nature and frequency of visits / contacts depend on the monitoring plan.

During these contacts, the monitor shall:

- monitor and evaluate the progress of the study;
- examining the data collected;
- carry out a verification of the source documents;
- identify any problems and find solutions;

The goal of the monitoring activity is to verify that:

- the rights and welfare of subjects are respected;
- survey data are accurate, complete and verifiable with the help of original documents;
- the study is performed according to the protocol and any amendment adopted, GCPs and regulations.

The investigator must agree to:

- grant to monitor direct access to all relevant documentation;
- devote part of his/her time and staff time to the monitor to discuss the results of the monitoring, as well as any other possible aspect.

The monitor should also contact the center before starting the study with the aim to discuss with staff the Protocol and procedures for data collection.

12.2 AUDITS AND INSPECTIONS

Sponsor can carry out an audit of quality control at its sole discretion. In this case, the investigator should agree to grant the auditor direct access to all relevant documentation and devote part of his/her time and staff time to the auditor in order to discuss the results of the monitoring, as well as any other possible aspect.

Moreover, regulatory authorities may also inspect the study. In this case, the investigator should agree to give the inspector direct access to all relevant documentation and devote part of his/her time and staff time to the inspector in order to discuss the results of the supervision, as well as any other possible aspect.

12.3 CASE REPORT FORM

Data collection will be done through an electronic CRF with a system of access by username and password. The application includes track changes monitoring (recording the changes that have been made and details of the user that has made these changes).

Accurate and reliable data collection is ensured by checking and cross checking the CRF front site records conducted by the study monitor (verification of source documents). The data collected will be added to a computer database which will be reviewed for possible inconsistencies to be resolved by the research team of the study in each site.

Accurate and reliable data collection is ensured by checking and cross checking the eCRF front site records conducted by the study monitor (verification of source documents).

13 ETHICS

13.1 GENERAL CONSIDERATIONS

The clinical trial will be conducted according to the principles of the Declaration of Helsinki, Fortaleza, Brazil, October 2013.

This study will be conducted according to Spanish regulations regarding clinical trials (Royal Decree 1090/2015) and biomedical investigations (Organic Law 14/2007 of biomedical investigation and the Royal Decree 1716/2011), which develop the Clinical Trial Regulation (Regulation EU No 536/2014). The required documentation prior to the start will be:

- Protocol acceptance by the sponsor and the coordinating investigator
- Protocol approval by the Ethics Committee.
- Protocol authorization from the Spanish Drug Agency (Ministry of Health)

All subjects will be guaranteed continued medical and nursing supervision throughout the duration of the study.

This study will conform to the standards of GCP published by ICH (E6 R2), as required by Directive 2001/20/EC. Confidentiality requirements will follow the required Data Protection legislation (see section 13).

13.2 PATIENT INFORMATION SHEET AND INFORMED CONSENT

Informed consent will be obtained before including the patient in the trial (Appendix III). The investigator is to inform the patient of the nature, duration and purpose of the study, as well as of all the obstacles and inconveniences which – within reason – may be expected from it. Furthermore, the patient is to receive information in writing. The participating subjects must be legally competent to give informed consent, with the possibility of taking decisions at his/her own free will. The patient has the right to leave the study at any time.

12.3 PAYMENT TO RESEARCH PARTICIPANTS

Participants will be reimbursed for their time, effort and time travels to study site due to study participation. Reimbursement amounts will be documented.
A payment of €100 for meals, transfers and lost in productivity is foreseen. It will be paid after completing the follow-up visit (day 20). No payment will be offered in case of premature withdrawals before day 6 visit.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA HANDLING

The processing of the data to be compiled by the study sponsor during the study will be subject to current legislation as regards data protection (LOPD, The Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights complementary to the Regulation (EU) 2016/679 of the European Parliament and of 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).
The participant will be identified in the records by the corresponding unique code number. The participant is to be guaranteed anonymity and is to be informed that all communication will take place between him/her and the investigator and not the sponsor of the study.

It is not expected to transmit data to third parties.

14.2 RECORD KEEPING

14.2.1 Investigator file and document retention

The investigator must keep the investigator file with the proper and accurate records to enable the study to be fully documented and data subsequently verified.

The Investigator's study file will contain the protocol and its amendments, CRFs, questionnaires' forms, EC approval and authorization from the health authorities, samples of the participant information sheet and informed consent, staff curriculum, signatures' delegation log and listing of subjects, as well as other appropriate documents and correspondence.

Clinical source documents from subjects (usually predefined by the project to record key efficacy and safety parameters or documents that are not in the clinical record of the hospital) will be filed indicating the number of subject without personal data.

The investigator should retain these documents at least twenty-five years, according to Royal Decree 1090/2015, provided that the sponsor does not express another period.

14.2.2 Source documents and basic data

Patient participation in the study will be included on medical records, including assigned code number and identification of the different study visits that will take place throughout the study. At the end of the study, a copy of the CRF will be placed on the site.

15 FINANCING AND INSURANCE

15.1 SOURCE OF FINANCING

The funding source is the Lluita contra la SIDA Foundation.
This study is partially funded through a research grant from Initiated studies Program by researcher Merck Sharp & Dohme Corp.

15.2 INSURANCE POLICY

In accordance with the Royal Decree 1090/2015, of 4th December, the trial sponsor has a policy of liability insurance with Zurich Insurance Company PLC Branch in Spain established in Barcelona. The sponsor shall extend this policy or another with equivalent coverage until the end of the trial. The policy will cover the damages to the people that could be set as a result of the trial by an insured amount of € 600.000,00 per subject tested to a maximum of € 6.000.000,00 per year and clinical trial. This policy also covers the responsibilities of the sponsor, the principal, and his/her collaborators, as well as the hospital or site where they carry out the clinical trial.

The sponsor agrees to pay the premiums to cover the liability pertaining to the trial. It is presumed, unless proven otherwise, that damage affecting the health of the person subject to testing during implementation and in the following year the completion of treatment, have occurred as a result of the trial. However, once the year ended, the test subject is required to prove the link between the trial and damage.

The site and the principal investigator undertake to inform the sponsor of any claim or legal, real or potential action if known, linkable to trial.

16 PUBLICATION POLICY

The publication of the trial results shall meet the requirements set out in Article 42 of Royal Decree 1090/2015.

APPENDIX I: CASE REPORT FORM (CRF)

APPENDIX II: INVESTIGATOR'S BROCHURE

APPENDIX III: PATIENT INFORMATION AND WRITTEN INFORMED CONSENT

APPENDIX IV: INSURANCE

APPENDIX V: SERIOUS ADVERSE EVENT REPORT

APPENDIX VI: DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS