CLINICAL STUDY PROTOCOL

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

Protocol ID: DORACeNeS
Version: 2.4 (26/06/2019)

EudraCT Number: 2018-003915-24

Promoter: Fundació LLuita contra la SIDA

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

1. PROTOCOL SYNOPSIS

1.0. Study type:

Pilot study, Phase III, prospective, open label, single arm, single center.

1.1. Promoter Identification:

Fundació Lluita contra la SIDA
Hospital Germans Trias I Pujol, 2ª planta maternal
Carretera del Canyet s/n
Badalona 08916

1.2. Study Title:

Doravirine concentrations and antiviral activity in Cerebrospinal fluid in HIV-1 infected Individuals.

1.3. Protocol ID:

EudraCT Number: 2018-003915-24

1.4. Principal Investigador:

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Department of Infectious Diseases.
Hospital Universitari de Bellvitge. L´Hospitalet de Llobregat. Barcelona. Spain

1.5. Study Center:

HIV and STD Unit. Department of Infectious Diseases.
Bellvitge University Hospital. L´Hospitalet de Llobregat. Barcelona. Spain

1.6. Responsible for monitoring

HIVand STD Unit monitoring team
HIV and STD Unit. Department of Infectious Diseases.
Bellvitge University Hospital. L´Hospitalet de Llobregat. Barcelona. Spain

1.7. Referral Ethics Committee:

Research Ethics Review Committee of the Bellvitge University Hospital

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

Doravirine will be administered in combination with a emtricitabine and tenofovir alafenamide (FTC/TAF, Descovy®). Each Doravirine tablet contains 100 mg of the drug. Descovy® contains 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. Doravirine+Descovy® will be administered orally, once daily, without regard to food.

1.9. Study Phase:

Phase III

1.10. Objectives:

The primary objectives of this study are:

- To assess Doravirine concentrations in CSF and to estimate penetration into the CNS.
-To evaluate antiviral activity of a combination of Doravirine+FTC/TAF in CSF.

1.11. Study Design:

Pilot study, Phase III, prospective, open label, single arm, single center.

1.12. Study Disease:

HIV-1 infection

1.13. Primary Endpoints:

- To determine total and unbound Doravirine concentrations in cerebrospinal fluid in HIV-1 infected individual receiving ART with Doravirine+FTC/TAF.
-Total Doravirine concentrations in blood plasma.
-Doravirine CSF/plasma ratio.
-HIV-1 RNA in cerebrospinal fluid.
-HIV-1 RNA in blood plasma.

1.14. Target Population:

HIV-1 infected male and female adults on stable ART.

1.15. Number of Subjects Planned:

15 HIV infected individuals.

1.16 Study duration:

4 months

1.17. Anticipated Study Calendar (dates will be confirmed later)

Anticipated Start Date: 10/09/2019.

Recruiting Period: 3 months. Anticipated End date of the Recruiting Period: 10/11/2019.

Anticipated end date: 10/02/2020

Analysis: 1/04/2020

Final Inform: 01/06/2020

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

3. GENERAL INFORMATION

3.1. Protocol ID

Study ID: DORACeNeS

EudraCT Number: 2018-003915-24

Study Title: Doravirine concentrations and antiviral activity in Cerebrospinal fluid in HIV-1 infected individuals.

3.2. Study Type

Pilot study, Phase III, prospective, open label, single arm, single center.

3.3. Description of the Investigational medicinal products

Doravirine 100 mg will be administered in combination with emtricitabine and tenofovir alafenamide (Doravirine+FTC/TAF). Each Doravirine tablet contains 100 mg of Doravirine and Descovy contains 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. Doravirine+FTC/TAF will be administered orally, once daily, without regard to food.

3.4. Promoter Identification

Fundació Lluita contra la SIDA
Hospital Germans Trias I Pujol, 2ª planta maternal
Carretera del Canyet s/n
Badalona 08916
Phone: 649893921

3.5. Technical services involved in the study

- For this trial, we will work the Microbiology Department of the Bellvitge University Hospital for the determination of the microbiologic parameters.
- Haematological and biochemical parameters will be determined in the Clincal Analisys Department of the the Bellvitge University Hospital, following the normal practice routine.
- Laboratory sampling managing and storage will be done at the Bellvitge University Hospital HIV and STD Unit and Microbiology Department,

- Doravirine concentrations will be measured at the University of Liverpool, UK

3.6. Study medication supplier

Doravirine will be provided by MSD, S.L, the product manufacturer.

Descovy will not be provided by MSD, which is a commercial medication that will be dispensed through the Hospital Pharmacy Service.

3.7. Monitoring

HIV and STD Unit – Monitoring Team, Infectious Diseases Department

Bellvitge University Hospital.

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3.8. Principal investigator

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3.8. Co-investigators

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Bellvitge University Hospital.

Arkaitz Imaz, M.D, PhD.

HIV and STD Unit -Infectious Diseases Department

Bellvitge University Hospital.

3.9. Study center

Bellvitge University Hospital.

3.10. Referral Ethics Committee

Research Ethics Review Committee of the Bellvitge University Hospital

3.11. Study timeline

Estudy duration: 2 months

Recritment period: 3 months

Treatment period: 8 weeks

Follow up period: 4 weeks

Anticipated Start Date: 10/092019.

Recruiting Period: 3 months. Anticipated End date of the Recruiting Period: 10/11/2019.

Anticipated end date: 10/02/2020Analysis: 1/04/2020

Final Inform: 01/06/2020

These dates are yet to be confirmed.

4. BACKGROUND

4.1. Backgroung and justification

Combination antiretroviral therapy (cART) has markedly reduced the morbidity and mortality of HIV-1 infection, transforming a generally lethal infection into a chronic disease amenable to medical management. Treatment has not only reduced systemic disease, but also the various neurological complications, including both central nervous system opportunistic infections and AIDS dementia complex associtaed with HIV-1 encephalitis. Direct therapeutic effects on HIV replicationm within the CNS may have contributed to achieve these goals and it might be crucial in some cases. These effects requier of suppressive levels of drug reach infected cells within the CNS to inhibit local virus propagation. The blood-brain barrier reduces delivery of antiretrovirals to the brain. Most antiretroviral drugs penetrate the CNS but the levels of penetration for different ARV drugs may vary.

Doravirine is a new HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) that has demonstrated a good efficacy and safety profile in clinical trials [3-5]. It functions by inhibiting viral replication of both wild-type virus and most common NNRTI variants [6]. It is dosed orally once daily and always given in combination with other HIV-1 active agents as part of highly active antiretroviral therapy (HAART). Initial pharmacokinetic studies demonstrated a time to maximal oncentration of 1–5 h, not extensive binding to plasma proteins, major CYP3A metabolism, low renal excretion (< 10%), and an apparent terminal half-life of 12–21 h [6, 7]. Doravirine is not a strong inhibitor or inducer of cytochrome nzymes but may be prone to drug interactions as a substrate of CYP3A [7].

These two physicochemical characteristics are crucial determinants of CSF drug penetration.

Thus two key issues in the use of Doravirine remain to be addressed:

1. The pharmacokinetic (PK) profile of Doravirine in CSF when given orally in stable, undetectable HIC-1 infected individuals.
2. Maintenance of HIV suppression in CSF.

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

4.2 REFERENCES

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4.3. Objetives

Primary objectives:

-To assess Doravirine concentrations in CSF and to estimate penetration into The CNS.

- To evaluate antiviral activity of a combination of Descovy®+Doravirine in CSF.

5. STUDY DESIGN

Pilot study, Phase III, prospective, open label, single arm, single center.

5.1. STUDY PHASE

Phase III

5.2. Randomization process

NA.

6. SUBJECT POPULATION

6.1.Subjects selection

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

6.2. Inclusión Criteria:

1. Asymptomatic, HIV-1 infected individuals ≥ 18 years of age
2. Be on a stable ART continously or ≥3 consecutive months preceding the screening visit. Patients already receiving TAF/FTC+DoravirineC for at least three consecutive months will be eligible.
3. Plasma HIV-1 RNA at screening <40 copies/mL for at least 3 months at the Screening visit.
4. Signed and dated written informed consent prior to inclusion.

5. Subjects must agree to utilize a highly effective method of contraception during heterosexual intercourse from the screening visit throughout the duration of the study.

* 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.
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.

6.3. Exclusion Criteria

1. Severe hepatic impairment (Child-Pugh Class C)
2. Ongoing malignancy
3. Active opportunistic infection
4. Primary resistance to any of the ARV included in the study or history of virologic failure with risk of resistance selection to any of the study drugs.
5. Any verified Grade 4 laboratory abnormality
6. ALT or AST ≥ 3xULN and/or bilirubin ≥ 1.5xULN
7. Adequate renal function: Estimated glomerular filtration rate ≥ 50 mL/min
8. Females who are pregnant (as confirmed by positive serum pregnancy test) or breastfeeding.
9. Current treatment with antiaggregant or anticoagulant therapy.
10. History of any neurologic disease/condition/treatment may alter the blood brain barrier permeability.

6.4 Sample size

Fifteen individuals will be included in the study. This is a pilot study designed to obtain information about Doravirine concentrations and HIV viral suppression in CSF. The study design is similar to other studies evaluating ARV PK and PD in this compartment.

6.5. Study duration

The study will have a recruitment period of 12 weeks The treatment period will be of 2 months.

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

6.6. Treatment of patients at the end of the study

At the end of the study, participants will be offered to return to their previous treatment or to discuss other treatment options depending on investigator´s opinion.

6.7. Criteria for discontinuation of study treatment

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

6.7.1. Managing of a study patient withdrawal

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

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

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

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

7. INVESTIGATIONAL MEDICINE PRODUCT

7.1. Study regimen

Study patients will receive one tablet of Doravirine 100 mg administered in combination with FTC and TAF (Descovy®)).

Each film-coated tablet contains contains 100 mg of Doravirine. Each tablet of Descovy® contains 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. Doravirine+ Descovy® will be administered orally, once daily, without regard to food.

7.1.1. Packaging and labelling

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

Medication will be provided by the manufacturer, MSD; and will be sent to the Pharmacy of the Bellvitge Hospital.

Study medication will be re-labelled by the HIV Unit monitoring team once received at the hospital pharmacy. The lable will be in Spanish, as requested by the applicable Spanish Law.

The information in the label will be:

DORACeNeS Study. EudraCt: 2018-003915-24
Sponsor: Fight AIDS Foundation (Fundació Lluita contra la SIDA).
Investigator: Dr. Daniel Podzamczer, 649630408
(Doravirine) Content: Doravirine 100 mg
30 film-coated tablets
Oral administration
Patient number: XXXXXX
Lot number: XXXXXX
Expiry date: XXXXXX
To be stored in the original package in order to protect from moisture. Keep the bottle tightly closed.
Keep away form children

USE FOR CLINICAL TRIAL

Estudio DORACeNeS . EudraCt: 2018-003915-24
Promotor: Fundació Lluita contra la SIDA.
Investigador principal: Dr. Daniel Podzamczer 649630408
Doravirina 100 mg
30 cápsulas
Administracion oral
Numero de paciente: XXXXXX
Lote : XXXXXX
Fecha de caducidad: XXXXXX
Mantener el envase bien cerrado para protegerlo de la humedad. Mantener lejos del alcance de los niños
USO EXCLUSIVO PARA ENSAYO CLINICO

7.1.2. Criteria for changing the treatment regimen during the study

No changes in the ARV treatment regimen are expected during the study period.
In case of virological failure, the appropiated treatment will be given to the patient in base to the genotypical resistence study.
In case of Adverse Reactions related to the study drugs, the investigator will provide the patient with the treatment that he considers appropiate for the patient, and the patient will be discontinued from the study.
At the end of the study, participants will be offered to return to their previous treatment or to discuss other treatment options depending on investigator´s opinion.

7.1.3 Prior and concomitant medications

Concomitant medication should only be used during patient participation in the study only when medically necessary.
All the concomitant medications should be listed in the Case Report Form.

MEDICATION DISALLOWED WITH Doravirine+FTC/TAF

Drug Class	**Agents Disallowed**	**Use Discouraged and To Be Used With Caution**
Acid Reducing Agents Antacids Buffered medications		Concentration of study drug may decrease with antacids. Subjects may not take antacids (eg, Tums or Rolaids); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 2 hours before and 6 hours after any dose of study drug.
Antiarrhythmic Agent	Dofetilide	
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifampin, Rifapentine	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinaccea	
Oral Hypoglycemic Agent		Metformin: close monitoring is recommended. A dose adjustment of Metformin may be necessary. Limit total daily doses of Metformin to 1000mg when initiating study medication or if initiating metformin while on study drug.

7.1.4 Investigational Medicinal Product Management

Stribild does not have special precautions for storage.

Following the instructions from de manufacturer Doravirine+FTC/TAF will be stored at controlled room temperature of 25°C. It will be stored in the original package in order to protect from moisture. The bottle sould be tightly closed. Until dispensed to the subjects, all bottles of study drugs should be stored in a secure area, accessible only to authorized site personnel.

7.1.5. Compliance assessment test

To assess the treatment adherence, a validated adherence questionnaire, routinely used in the clinical practice (SMAQ questionnaire) will be provided to the participants at each study visit.

8. STUDY DEVELOPMENT AND EVALUATION OF THE RESPONSE

8.1. Response evaluation citeria

8.1.1.Primary endpoinst:

- To determine total and unbound Doravirine concentrations in cerebrospinal fluid in HIV-1 infected individual receiving ART with TAF/FTC+Doravirine.

-Total Doravirine concentrations in blood plasma.

- Doravirine CSF/plasma ratio.

-HIV-1 RNA in cerebrospinal fluid.

-HIV-1 RNA in blood plasma.

8.2. Procedures

8.2.1 Study visits

Eligibility criteria will be assessed in at Screening visit (week -4) before the inclusion of patients in the study.

Patients will be evaluated at baseline (treatment switch, week 0),

At week 4, clinical review and samples (blood and CSF) will be obtained.

At week 8 FU visit (end of the study).

8.2.2 Clinical records and physical examination

-At screening a complete physical examination will be performed. At the following visits, a physical examination oriented to symptoms will be performed.
-At baseline, demographic data of interest related to HIV infection will be collected to characterize the study population: gender, date of birth, HIV diagnosis date, HIV risk factor, CDC stage, opportunistic infections, malignancies or previous diseases, concomitant treatments). Antiretroviral treatment will be switched to FTC/TAF/Doravirine.
-At week 4: Inclusion/exclusion criteria review. Blood test and CSF sample will be taken.
-At week 8 (FU visit): A physical examination oriented to symptoms will be performed. AE and concomitant medications review.

At the end of the study, participants will be offered to return to their previous treatment or to discuss other treatment options depending on investigator´s opinion.

8.2.3 Laboratory Procedures

HIV-1 RNA quantification

At screening, baseline and week 4 visits HIV-1 RNA will be determined in blood plasma using a real-time PCR assay (Abbott RealTime HIV-1) with a quantification limit of 40 copies/mL.

CSF HIV-1 RNA will be assessed at baseline by real-time PCR assay (Abbott Real Time HIV-1) with a quantification limit of 40 copies/mL.

All determinations will be performed at the Microbiology lab, Bellvitge University Hospital.

Doravirine concentrations

At baseline visit Doravirine concentrations will be determined in blood plasma (BP), cerebrospinal fluid (CSF). In CSF Doravirine unbound concentrations will be also determined. Drug concentrations will be determined at the end of the dosing interval (C_{24h}).
Doravirine concentrations will be quantified using a validated liquid chromatography-tandem mass spectrometry ('LC-MS/MS') method. Drug concentrations will be performed at the Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK.

General laboratory parameters

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

- Haematology: red blood cells, haemoglobin, white blood cells, platelets; coagulation.
- Biochemistry: Glucose, urea, creatinine, bilirrubin, alkaline phosphatase, gamma glutamyl transferase, albumin, total cholesterol, HDL cholesterol. LDL cholesterol, triclycerides.
- T CD4 lymphocites (at baseline and week 8 visits)

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

8.3.4 Biological samples management

- Blood samples will be obtained by venipuncture.
- CSF samples will be taken through Lumbar Puncture using a Pencil Point Spinal Needle.

All samples will be stored at -80ºC in the HIV Unit of the Bellvitge Hospital until the end of the study.

Only the site staff will have access to them. Samples will be stored with a numeric code.

All the study analysis except CSF and plasma Doravirine concentrations will be performed at the Bellvitge Hospital,

Doravirine determinations in CSF and plasma will be performed at the Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Only the principal investigator and delegated personnel will have access to the list where the patients and samples are identified.

9. ADVERSE EVENTS AND TOXICITY MANAGEMENT

9.1 Definition Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

• Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g. such as venipuncture, biopsy) during or after screening (before the administration of study investigational medicinal product).

• Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial, will also be considered an AE.

• Complications and termination of pregnancy

• All AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study medication period should be recorded as an AE.

An AE does not include the following:

• Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event.

• Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.

• Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).

• Overdose without clinical sequelae.

· Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

· Uncomplicated pregnancy.

· An induced elective abortion to terminate a pregnancy without medical reason.

9.2 Assessment of Adverse Events

All AEs will be assessed by the Investigator or qualified designee and recorded on the CRF. The AE entry should indicate whether or not the AE was serious, the start date

(AE onset), the stop date (date of AE resolution), whether or not the AE was related to investigational medicinal product or to a study procedure, the action taken with investigational medicinal product due to the AE, and the severity of the AE. The Investigator is responsible for final review and confirmation of accuracy of events, relationship and severity confirmed by the signature on the eCRF book. The relationship to investigational medicinal product therapy should be assessed using clinical judgment and the following considerations:

• **No**: Evidence exists that the adverse event has an etiology other than the investigational medicinal product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

• **Yes**: A temporal relationship exists between the AE onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the AE abates or resolves and reappears upon rechallenge.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

9.3 Serious Adverse Events

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

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

- Death
- Life-threatening situation (subject is at **immediate** risk of death)

• In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs).

• Persistent or significant disability/incapacity.

• Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product.

• Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Examples of such events are as follows:

• Intensive treatment in an emergency room or at home for allergic bronchospasm

• Blood dyscrasias or convulsions that do not result in hospitalization

• Development of drug dependency or drug abuse

.

A distinction should be drawn between seriousness and severity of AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE.

Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as “serious” when it meets one of the predefined outcomes described above in Section.

The sponsor will inform about all the Suspected Unexpected Serious Adverse Reactions (SUSARs) to the applicable authorities in accordance the the applicable law in Spain regarding Clinical Trials.

The appendix A contains the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (“DAIDS AE Grading Table”), which is a descriptive terminology that will be utilized for Adverse Event (AE) reporting.

10. ETHICAL ASPECTS

The study will follow the Interrnational Conference on Harmonization, ICH guidelines and the Royal Decree 1090/2015 and will be initiated once obtained the EC and Spanish MOH (Agencia Española de Medicamentos y Productos Sanitarios) corresponding approvals.

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

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

An insurance policiy will be contracted for this study, covering the possible damages ocurred to the study as a result of the study

10.1 Responsabilities

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

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

The Investigator and the Promoter must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. At least the following documents will be kept: the protocol/amendments, CRF and query forms, IRB and governmental approval with correspondence, informed consent, drug records, and other appropriate documents and correspondence.

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

Drug Handling

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

Confidentiality

Study subjects will be informed that their participation in the study will be treated with the same confidentiality than their clinical records.
Patietns' participation in the study will be reflected in their clinical records.
The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth and an identification code (i.e., not names) will be recorded in the CRF or on any form or biological sample submitted to the external laboratory. The Investigator will keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study.
The study subjects will be informed about the confidentiality in the management of their personal data, and that only the study team and eventually, members of the hospital EC or an inspector would have access to their clinical records.

Personal information will be treated following the Organic Law 15/1999 of 13 December on the Protection of Personal Data.

Study participants would be able to exercise their rights in the treatment, communication and cesion of their personal data. Following that law, study

patients will have the possibility of exercising their rights of access, rectification, erasure and objection of data contacting with the study investigators.
There will only be transmitted to third parts or other countries the study collected data dissociated and without information that could identify directly the patient.
In case of that cesion of the study data to third countries the confiendality, this will be only with the study purposes and guaranteeing the data confidentiality.

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

Publication
A clinical study report will be prepared and provided to the regulatory agency and the EC.
The study results will be published in internationally indexed publications.
The intellectual property of the study design and results belongs to the Principal Investigator, Dr. Daniel Podzamczer Palter.

12. STATISTICAL ANALYSIS

The statistical analysis will be performed by using SPSS 18.0 IBM software.
- Data will be analysed with descriptive, statistics using standard methods: Categorical variables will be described as the number and percentage and continuous variables as the median and range or interquartile range (IQR).
- All adverse events will be listed and analyzed using descriptive statistics.

Appendix A

Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE Grading Table	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/ malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than emergency room visit) indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness
Injection site reaction (localized)				
Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm2 – 81cm2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
SKIN – DERMATOLOGICAL				
Alopecia	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities NA	NA
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention ndicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
HYPERTENSION				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
PROLONGED PR INTERVAL				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16	Years 1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
PROLONGED QTC				
Adult > 16 years	Asymptomatic, QTc interval 0.45-0.47 sec OR Increase interval <0.03 sec above baseline	Asymptomatic, QTc interval 0.48-0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years Life-threatening consequences, e.g.	Asymptomatic, QTc interval 0.450–0.464 sec	Asymptomatic, QTc intervalo 0.465-0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., nticoagulation, lysis filter, invasiveprocedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus
Vasovagal episode (associated with a procedure of any kind)	Present without loss of Consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation Indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea				
Adult and Pediatric ≥ 1 year	Transient or intermittent episodes of unformed stools OR Increase of 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences
Pediatric < 1 year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis
Proctitis (functional-symptomatic) Also see	Rectal discomfort AND No intervention indicated	Mucositis/stomatitis for clinical exam Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
NEUROLOGIC				
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤ 16 Years	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Headache	Symptoms causing no or minimal interference with usual social & unctional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset) – Adult ≥ 18 years See also Seizure: (known preexisting seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Seizure – Pediatric < 18 years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care Functions
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70-80%	FEV1 or peak flow 50–69%	FEV1 or peak flow 25–49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	Joint pain causing no or minimal nterference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care Functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic selfcare functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing lifethreatening Consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing lifethreatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary tract obstruction (e.g., stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on Exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY				
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days 1,250 –	1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤ 1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased 100 – 200 mg/dL	*1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62 – 5.23 mmol/L*	6.50 – 7.4 g/dL *4.03 – 4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 – 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 – 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL ≥ *2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 – 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤ 21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59 – 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES ***Standard International Units are listed in italics***				
Acidosis	NA	pH < normal, but ≥ 7.3	pH < 7.3 without lifethreatening consequences	pH < 7.3 with lifethreatening consequences
Albumin serum, low	3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase	1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis	NA	pH > normal, but ≤ 7.5	pH > 7.5 without lifethreatening consequences	pH > 7.5 with lifethreatening consequences
ALT (SGPT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum,	low 16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)				
Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
nfant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)				
Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low				
Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI) NA NA NA	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer Continued

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin T (cTnT)	NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)				
Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase	3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine	1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN †	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high				
Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low				
Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate	ULN - < 2.0 x ULN without acidosis	≥ 2.0 x ULN Without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH <7.3 with life-threatening consequences
LDL cholesterol (fasting)				
Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL ≥ *4.91 mmol/L*	NA
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN

1. ∗ Values are for term infants. Preterm infants should be assessed using local normal ranges.2. † Use age and sex appropriate values (e.g., bilirubin).