**Title :** A multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat).

**NTC number:** NCT02735863

**Approval date:** November 7th 2016

# CLINICAL STUDY PROTOCOL
# ABX464-004

| | |
|---|---|
| Sponsor: | ABIVAX<br>5, rue de la Baume<br>75008 Paris<br>FRANCE |
| Investigational product: | Not Available |
| Product code: | ABX464 |
| Therapeutic indication: | A multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat). |
| EudraCT number: | 2015-004195-30 |
| Study code: | ABX464-004 |
| Version number: | 4.0 |
| Release date: | November 7th 2016 |

**CLINICAL STUDY PROTOCOL**

| | |
|---|---|
| **Study code** | ABX464-004 |
| **Investigational product code** | ABX464 |
| **EudraCT number** | 2015-004195-30 |
| **Detailed Title** | A multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat). |
| **Study Phase** | Phase IIa |
| **Coordinating Investigator** | **Professor Jacques REYNES**<br>Hospital Gui de Chauliac<br>80, avenue Augustin Fliche<br>34 295 Montpellier cedex 5<br>Tél: 04 67 33 72 14/77 14<br>Fax: 04 67 33 77 09<br>E-mail: j-reynes@chu-montpellier.fr<br><br>***Investigational sites will be initiated in France, in Spain, in Belgium.*** |
| **Sponsor** | **ABIVAX**<br>5 rue de la Baume<br>75008 Paris<br>Tel: +33 (0) 1 53 83 08 41<br>Fax: +33 (0) 1 53 83 07 48 |
| **Date/Version** | November 7, 2016 / V4.0 |

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|---|---|---|
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| **Coordinating investigator** | **Professor Jacques REYNES**<br>Hospital Gui de Chauliac<br>80, avenue Augustin Fliche<br>34 295 Montpellier cedex 5 - France<br>Tel: + 33 (0) 4 67 33 72 14/77 14<br>Fax: + 33 (0) 4 67 33 77 09<br>E-mail: j-reynes@chu-montpellier.fr | |
| **Statistical Analysis** | **SIMBEC ORION**<br>Simbec-Orion Group Limited<br>Orion Santé SARL<br>Centre d'Affaires La Boursidière<br>Bâtiment le Jura, BP 141<br>92357 Le Plessis- Robinson - France | |
| **Central Laboratory (HIV reservoir)** | **Prof. Linos Vandekerckhove**<br>University Hospital Ghent<br>De Pintelaan 185<br>De Pintepark 1<br>tav HTRU Karen Vervisch/Prof. Linos Vandekerckhove<br>9000 Ghent - Belgium | |
| **Pharmacovigilance** | **SIMBEC ORION**<br>pharmacovigilance@orioncro.com<br>Fax: +44 (0) 1753 695 101 | |
| **miRNA determination** | **THERADIAG**<br>9, avenue de l'Europe<br>34830 Clapiers -France | |
| **Pharmacokinetics** | **PhinC Development**<br>Eric EVENE<br>Pharmacometrician<br>5 rue Henri Auguste Desbruères<br>91000 Evry – France | **ATLANBIO (Bioanalyses)**<br>ZI de Brais<br>1 Rue Graham Bell<br>BP 40309<br>44605 Saint-Nazaire - France |

## INVESTIGATOR AGREEMENT PAGE

**EudraCT number** 2015-004195-30

**Detailed Title:** A multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat).

I have carefully read all the pages of this clinical study protocol and I agree to the following:

- To conduct the study as outlined in the protocol, any mutually agreed future protocol amendments and with all the terms and conditions set out by ABIVAX.
- Not to implement any changes in the procedures described in the protocol without the prior approval of the sponsor and prior to review and written approval by the Ethics Committee and/or Regulatory Authorities, unless instructed otherwise by the Regulatory Authorities or the wellbeing of patients is jeopardized.
- To conduct the study in accordance with the ICH GCP guidelines, US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations), the European Union Clinical Trials Directive 2001/20/EC, the provisions of the Helsinki Declaration, and relevant legislation in force.
- I am thoroughly aware of the study drug specifications and adverse events as described in the protocol and the current Investigator's Brochure and any other information provided by the Sponsor.
- To ensure that sub-investigator(s) and other relevant members of my staff involved in the study are fully aware of their responsibilities regarding this study and will conduct the study according to the protocol.

**Investigator's Name:** _____

**Investigator's Signature:** _____

**Date:** _____

# TABLE OF CONTENTS

## ABBREVIATIONS

| Abbreviation or Term | Definition |
|---|---|
| AE | adverse event |
| ALT/SGPT | alanine aminotransferase/serum glutamic pyruvate transaminase |
| ART | Antiretroviral Therapies |
| AST/SGOT | aspartate aminotransferase/serum glutamic oxaloacetic transaminase |
| $AUC_{0-24}$ | area under the plasma concentration-versus-time curve from zero to 24 hours |
| $AUC_{0-\infty}$ | area under the plasma concentration-versus-time curve from zero to infinity |
| $AUC_{0-\tau}$ | area under the plasma concentration-versus-time curve from time zero to the dosing interval |
| $AUC_{0-t}$ | area under the plasma concentration-versus-time curve from time zero to the time of the last quantifiable concentration |
| BMI | body mass index |
| CBC | Cap Binding Complex |
| CI | confidence interval |
| $C_{max}$ | peak plasma concentration |
| CRF | case report form |
| CTC-AE | Common Terminology Criteria for Adverse Events, version 4.0 |
| CTFG | Clinical Trial Facilitation Group |
| COBI | Cobicistat |
| DBP | Diastolic Blood Pressure |
| DSMB | Data and Safety Monitoring Board |
| DRV | Darunavir |
| ECG | electrocardiogram |
| EDTA | ethylenediaminetetraacetic acid |
| $F_{rel}$ | relative bioavailability |
| GCP | good clinical practice |
| GGT | gamma-glutamyl transferase |
| GM | geometric mean |
| H | hours |
| HAART | Highly Active Anti-Retroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonization |
| IMP | Investigational Medicinal Product |
| IEC | Independent Ethics Committee |
| Max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | milligram |
| Min | minimum |
| mL | milliliter |
| mmHg | millimeters of mercury |
| NOAEL | No Observed Adverse Effect Level |
| o.d. | Once Daily |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PT | preferred term |
| PCSA | potentially clinically significant abnormalities |
| QTc | heart-rate–corrected QT interval (time between the start of the Q wave and the end of the T wave in the heart's electrical cycle) using Bazett's formula |
| R | Accumulation ratio |
| RTV | Ritonavir |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SEM | standard error of the mean |
| SOC | system organ class |
| TEAE | treatment emergent adverse event |
| $t_{lag}$ | interval between administration time and the sampling time preceding the first concentration above the limit of quantification |
| $t_{1/2}$ | terminal half-life |
| $t_{max}$ | time to peak plasma concentration |
| Vd/F | volume of distribution |
| vs. | versus |

# SYNOPSIS

| | |
|---|---|
| **Study n°** ABX464-004 | **Clinical Phase** IIa<br>**Type of Study** Safety Study |
| **Study title** | A multi-center, randomized, double-blind, placebo-controlled Phase IIa trial to compare the safety of ABX464 given at a fixed dose to placebo in fully controlled HIV infected patients treated with boosted protease inhibitor treatment (darunavir/ritonavir or darunavir/cobicistat). |
| **Short title** | Safety study of ABX464 in HIV controlled patients treated with boosted protease inhibitor treatment. |
| **Investigators and study centers** | 8 sites will be initiated in France, in Spain and in Belgium. |
| **Study Duration** | Recruitment period: Q1 2016 – Q2 2016<br>Overall Study period: Q4 2015 – Q3 2016 |
| **Investigational product** | |
| **Study Design and Methodology** | This study is a placebo-controlled study aimed at assessing the safety of ABX464 administered at 50 mg o.d. (or potentially at 150 mg o.d.) versus placebo in HIV infected patients who are treated with darunavir + ritonavir (DRV/RTV) or darunavir + cobicistat (DRV/COBI). Eligible patients should be treated with darunavir + ritonavir or darunavir + cobicistat as monotherapy for at least 8 weeks prior to baseline. Patients should be fully suppressed (< 50 copies/mL) at least during the last 6 months prior to enrolment.<br><br>Upon screening visit, eligible patients will continue DRV/RTV or DRV/COBI single regimen given respectively at 800 mg of darunavir with 100 mg of ritonavir or 150 mg of cobicistat once a day with food in the morning.<br><br>At Day 0, study drug (ABX464 or its matching placebo) will be added on top of this background therapy for the next 28 days. ABX464 or its matching placebo will be given once a day at the fixed dose of 50 mg (or potentially at 150 mg o.d.).<br><br>A 3:1 randomization ratio will be applied meaning that, per treatment block, 3 patients will receive ABX464 on top of DRV/RTV or DRV/COBI and 1 patient will receive placebo on top of DRV/RTV or DRV/COBI.<br><br>The original fixed dose (i.e. 50mg o.d.) of the study drug has been selected in November 2015 based on the reassuring safety data accumulated on the 50 mg o.d. and the concentrations in ABX464-N-glucuronide, the active metabolite of ABX464. However, in January 2016, the results of first phase IIa study conducted in treatment-naïve HIV infected patients with high viral load upon enrolment (5,000-500,000 copies/mL) confirmed the antiviral activity of ABX464 at higher doses. A reduction of viral load > 0.5 log was observed in 3/12 patients in the 75 and 100 mg cohorts and 4/6 patients in the 150 mg cohort, demonstrating a dose relationship effect of ABX464.<br><br>In case the first 8 patients treated for 28 days at 50mg o.d. in the present study (i.e. two first randomization blocks) do not show a DLT, the study protocol plans to study the 150 mg dose. The DSMB will specifically meet once the first 8 patients have been treated for 28 days in order to recommend, if appropriate, a dose increase to 150mg o.d.<br><br>At 150mg, the DSMB will meet every 4 patients in order to review on a regular basis the safety profile of this dose level and to recommend, if appropriate, the continuation of the study.<br><br>The sample size at a dose level will not be changed (i.e. 28 patients will need to be randomized receiving the same dose).<br><br>Dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the "Division of AIDS table for grading the severity of adult and pediatric adverse events" (including signs/symptoms, lab toxicities and/or clinical events) considered by the Data Safety Monitoring Board as probably or definitely related to study treatment.<br><br>If more than 2 DLTs occur during the treatment period of the first four treated patients |

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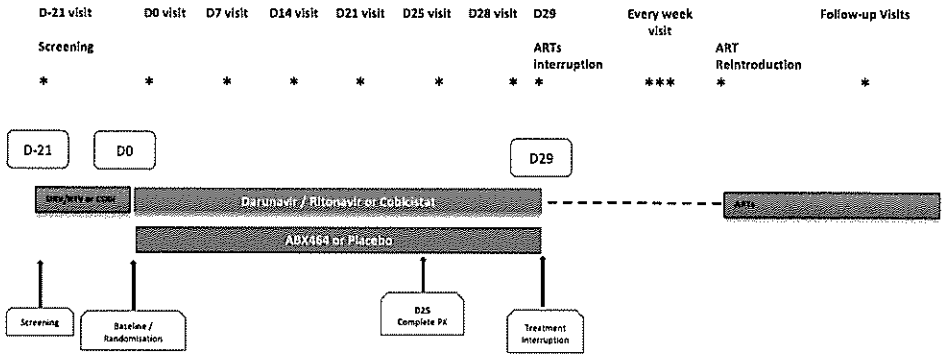
|---|---|
| | (regardless of the dose), then the enrolment of additional patients will be stopped. In addition, in case of a life threatening (grade 4) adverse reaction enrolment and treatment of ongoing patients will be immediately discontinued. In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.<br><br>At day 29, DRV/RTV or DRV/COBI and ABX464 or its matching placebo (i.e. all treatments) will be stopped. The viral load will be monitored twice a week during the first three weeks and weekly during the next weeks. In case of Viral Rebound (VR; defined below), ART will be resumed.<br><br>Thorough pharmacokinetics analysis will be performed to characterize potential drug-drug interactions between ABX464 and DRV/RTV-COBI.<br><br>The study design is summarized below in this chart.<br><br>  <br><br><br>Safe sex counseling will be offered at every study visit in order to inform the patient about potential infectiousness since the viral load can rebound.<br><br>Study visits will be performed every week until study completion (i.e. reintroduction of ARTs and follow-up visits performed after ARTs reintroduction). A viral load and a CD4+ count will be assessed weekly during the course of the study. However, these testings will be performed twice a week during the first three weeks following treatment stop (i.e. Day 29) in order to capture as early as possible a potential early relapse.<br><br>A Viral Rebound (VR) is defined as HIV viral load > 1000 copies mL-1. If a patient meets this criterion, then ARTs should be reintroduced. The patient should be withdrawn from the study and should perform some follow-up visits every 14 days after ARTs reintroduction until the viral load has returned to undetectable levels. |
| **Study Objectives** | **Primary objective:**<br>▪ To evaluate the **safety of ABX464** versus placebo when administered on top of darunavir/ritonavir or darunavir/cobicistat monotherapy.<br><br>**Secondary objectives**<br>▪ To evaluate the long-lasting effect of ABX464 on the viral load after treatment stop (i.e. Day 29) using the **Time to Viral Rebound** versus placebo;<br>▪ To compare the **viral load (HIV RNA)** versus placebo from Day 0 to Viral Rebound;<br>▪ To compare the **CD4+ T cell counts** versus placebo from Day 0 to Viral Rebound;<br>▪ To compare the **CD4+/CD8+ T cells ratio** versus placebo from Day 0 to Viral Rebound;<br>▪ To evaluate **HIV reservoir (pro-viral DNA in PBMC)** versus placebo from Day 0 to Viral Rebound.<br>▪ To assess the **Pharmacokinetics parameters** of ABX464 given on top of darunavir/ritonavir/cobicistat and ABX464;<br>▪ To compare **miRNA modulations** and tropism of HIV versus placebo from Day 0 to Viral Rebound. |
| **Main Selection Criteria** | **Inclusion criteria:** |

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|---|---|
| | **A patient will be eligible for inclusion in this study only if ALL of the following criteria apply:**<br>▪ Patients infected with HIV;<br>▪ Patients with HIV plasma viral load ≤ 50 copies mL-1 during the 6 months prior to screening with a maximum of 2 blips during this period;<br>▪ Patients treated by DRV/RTV or DRV/COBI as a monotherapy for at least 8 weeks prior to baseline;<br>▪ Patients' HIV plasma viral load ≤100,000 copies mL-1 at any time (apart from primary infection if recorded);<br>▪ Patients' CD4+ T cells count ≥ 250 cells per $mm^3$ at any time since diagnosis;<br>▪ Patients with CD4+ T cells count ≥ 600 cells per $mm^3$ at screening;<br>▪ Man or woman aged 18-65 years;<br>▪ Patients with hematological and biochemical laboratory parameters as follows and within 7 days of baseline:<br>o Hemoglobin > 9.0 g dL-1;<br>o Absolute neutrophil count ≥ 750 mm-3;<br>o Platelets ≥ 100,000 mm-3;<br>o Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);<br>o Creatinine clearance > 50 mL min-1 by the Cockcroft-Gault equation within 60 days of entry;<br>o Total serum bilirubin < 2.0 x ULN;<br>o Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN;<br>o Serum lipase less than or equal to 2.0 x ULN;<br>▪ Patients should be able and willing to comply with study visits and procedures as per protocol;<br>▪ Patients should understand, sign and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures being performed;<br>▪ Patients should be affiliated to a social security regimen (for French sites only);<br>▪ Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 3 months after end of study or early termination. Contraception should be in place at least 2 weeks prior to study participation. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception associated with inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle.<br><br>**Exclusion Criteria:**<br><br>**The following criteria should be checked at the time of screening. If ANY exclusion criterion applies, the subject will not be included in the study:**<br>▪ Patient displaying any HIV protease inhibitor resistance mutation as listed in the current version of the HIV drug resistance database (Stanford University);<br>▪ Patient having had previously a viral load ≥ 500 copies $mL^{-1}$ confirmed by a second measure since the initiation of the current ART;<br>▪ History of an AIDS-defining clinical illness;<br>▪ Concomitant AIDS-related opportunistic disease;<br>▪ History of allergic disease, anaphylaxis or reactions likely to be triggered or exacerbated by any component of the study drug;<br>▪ Acute or chronic infectious disease other than HIV infection (include but not limited to viral hepatitis such as hepatitis B, active tuberculosis, active syphilis [i.e. currently treated], HTLV-1, HTLV-2). *Of note co-infection with hepatitis C is allowed as long as their liver function parameters are within the following ranges: platelet > 150.000/mm3; γGT ≤ 2.5 ULN; Albumin > 40 g/L and providing that they are not receiving specific treatment during the study that could interfere with the study objectives;*<br>▪ Acute, chronic or history of clinically relevant pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology, angina or cardiac arrhythmias, or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history;<br>▪ Uncontrolled dyslipidemia;<br>▪ Acute, chronic or history of immunodeficiency or autoimmune disease other than HIV |

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|---|---|
| | infection;<br>▪ Unstable asthma (defined as sudden acute attacks occurring in less than three hours without an obvious trigger, hospitalization for asthma in the last two years); food or wine induced asthma;<br>▪ History of malignancy unless there has been surgical excision that is considered to have achieved cure;<br>▪ Active malignancy that may require chemotherapy or radiation therapy;<br>▪ Seizure disorder or any history of prior seizure;<br>▪ Serious illness requiring systemic treatment and/or hospitalization within 7 days prior to baseline;<br>▪ Pregnant or breast-feeding woman;<br>▪ Active drug or alcohol abuse or dependence;<br>▪ Use of any investigational or non-registered product within 3 months preceding baseline;<br>▪ Any condition, which in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol. |
| **Medications** | **Mandatory treatment:**<br>▪ Patients must be treated with darunavir/ritonavir or darunavir/cobicistat for at least 8 weeks prior to baseline and during the course of this study until Day 28 at following doses:<br>o 800 mg of darunavir and 100 mg of ritonavir once a day with food or,<br>o 800 mg of darunavir and 150 mg of cobicistat once daily with food.<br>▪ ABX464 or its matching placebo should be administered once daily at a fixed dose of 50 mg (or potentially at 150 mg o.d.) from Day 1 to Day 28.<br><br>**Prohibited prior or Concomitant treatments:**<br>▪ Other antiretroviral therapies than those part of the study treatments (e.g. NRTIs, NNRTIs,...)<br>▪ Drug therapy with immunomodulators or immunosuppressive drugs (such as IL-2, IL-7, intravenous immunoglobulin-IVIG- or IFN) within one month preceding Day 0;<br>▪ Drugs that could interact either with darunavir/ritonavir, darunavir/cobicistat or ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix#2). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (Clozapine, theophylline, ropinirol, warfarin and methadone);<br>▪ Use of any investigational or non-registered product within 3 months preceding baseline. |
| **Premature trial discontinuation** | Patient's premature trial discontinuation could occur for the following reasons:<br>▪ Investigator's decision;<br>▪ An Adverse Event or an intercurrent condition that preclude continuation of treatment;<br>o Specifically, an increase ≥ 2.0 x ULN in liver transaminases (AST/SGOT and/or ALT/SGPT) or in Alkaline phosphatase should be considered a treatment and study discontinuation criterion.<br>▪ Major protocol violation;<br>▪ Patient's decision;<br>▪ Withdrawal of consent. |
| **Patient Follow-up** | Patients will be followed up twice a week during the first three weeks after ART interruption and then weekly until Viral Rebound and ART reintroduction. The patient should be withdrawn from the study and should perform some follow-up visits, every 14 days after ARTs reintroduction, until the viral load has returned to undetectable levels. |
| **Data Safety Monitoring Board (DSMB)** | A Data Safety Monitoring Board with expertise and experience in the management in HIV will review the safety of the trial on an on-going basis. |
| **Number of subjects planned Sample Size calculation** | The endpoint considered for the sample size calculation is the Time To Viral Rebound defined as the time between treatment stop (i.e. day 29) and viral rebound detection.<br>According to published studies, the expected median Time To Viral Rebound (calculated from treatment stop) is expected to be 7 days in the 'DRV/RTV or COBI + placebo' group while it should be at least 28 days in the 'DRV/RTV or COBI + ABX464 group' in order to continue the clinical development of this new drug.<br>According to these hypotheses, the corresponding power was calculated using the PROC POWER of the SAS software (version 9.4). Thus, the enrolment of 28 evaluable patients at a dose level (21 in the ABX464 at 50 mg or 150 mg and 7 in the group placebo) will permit to have 80% power to detect a significant difference, at 0.05 level, between groups using the Time To Viral Rebound as end point. |

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|---|---|
| | Thus, the overall sample size can vary from 28 patients (in case the dose escalation procedure is not recommended) to 36 patients in case the dose escalation to 150 mg o.d. is recommended (ie 8+28 patients). |
| **Statistical Methods** | **Safety:**<br>Analysis of safety will be performed on the safety data set consisting in all patients who received at least one dose of ABX464 in the study. The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the "Division of AIDS table for grading the severity of adult and pediatric adverse events" (Version 2.0 November 2014) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations].<br><br>Adverse events will be tabulated (counts and percents) by group and dose. All adverse events will be listed and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment and dose level.<br><br>Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of patients with at least one abnormal values will be tabulated (counts and percents) for each parameter in summary shift tables, by group and dose.<br><br>**Efficacy:**<br>All efficacy endpoints will be summarized descriptively. Time to virological failure, time to treatment failure, HIV reservoirs, etc. will be analyzed by dose versus placebo. Kaplan-Meier estimates will be calculated for these variables (median time to virological failure, viral rebound and estimation of response duration).<br><br>**Pharmacokinetics:**<br>Considering that DRV/RTV or DRV/COBI is a chronic treatment and that ABX464 is planned to be used as a complement of ART and thus as a chronic treatment too, it is more relevant to determine the possible PK interaction at steady-state.<br><br>As a result, the $t_{1/2}$ of each drug must be considered to set the optimum days for PK assessment:<br>• DRV $t_{1/2}$ is around 15 h, steady-state is expected to be reached after 5 times the $t_{1/2}$ of a given drug, DRV should be reached around 75 h after the first administration, i.e. between the 3rd and the 4th day of administration.<br>• RTV has a low $t_{1/2}$ (about 5 h), this means that following a twice daily administration, steady-state could be considered as reached from the second or third day of administration with a negligible drug accumulation.<br>• COBI terminal plasma half-life is approximately 3 to 4 h which is slightly lower than ritonavir. Likewise RTV, following a twice daily administration, steady-state of COBI could be considered as reached from the second or third day of administration with a negligible drug accumulation.<br>• ABX464 has a very short $t_{1/2}$ (1 to 2 h) and generally no drug could be quantified after 10 h post-dose, so steady-state is virtually reached at the second administration.<br>• NGlcABX464 (main ABX464 metabolite) has a $t_{1/2}$ of 90 to 110 h, meaning that steady-state is reached after 19 to 22 days of administration.<br><br>The drug with the longest $t_{1/2}$ drives the decision, thus blood collection for PK purpose should be done at least 22 days after initiation of ABX464 administration.<br>To prevent individual patient exhibiting slightly slower NGlcABX464 elimination, the PK blood collection will be done on Day 25 +/- 4 days (From Day 21 to Day 28 days after initiation of ABX464 administration).<br>Collection of sparse pre-dose samples from Day 1 to Day 25 will allow to control that NGlcABX464 is at steady-state at the time of PK assessment and to check if steady-state pre-dose levels of DRV and RTV are maintained with co-administration of ABX464.<br><br>PK analysis being done at steady-state, overall drug exposure is expressed through determination of $AUC_{0-\tau}$ (i.e. limited to $\tau$=24 h post-dose for ABX464 and NGlcABX464 and 12 h post-dose for DRV and RTV/COBI). |

# 1. INTRODUCTION AND STUDY RATIONALE

## 1.1. HIV Infection

### 1.1.1. Disease

### 1.1.2. Management of patients

## 1.2. ABX464 rationale

### 1.2.1. Investigational treatment description

### 1.2.2. Investigational product description

### 1.2.3. Investigational product mode of action

### 1.2.4. Rationale for the development of ABX464

### 1.2.5. Preclinical data of ABX464

#### 1.2.5.1. Non-clinical background information

### 1.2.6. Previous clinical experience with ABX464

## 1.3. Rationale for the clinical study and study design

# 2. STUDY OBJECTIVES

## 2.1. Primary Objective

The primary objective of the study is to evaluate the safety of ABX464 versus placebo when administered on top of darunavir/ritonavir or darunavir/cobicistat.

## 2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the long-lasting effect of ABX464 on the viral load after treatment stop (i.e. Day 29) using the Time to Viral Rebound versus placebo;
- To compare the effect of ABX464 on viral load (HIV RNA) versus placebo from Day 0 to Viral Rebound;
- To compare the effect of ABX464 on the CD4+ T cell counts versus placebo from Day 0 to Viral Rebound;
- To compare the effect of ABX464 on the CD4+/CD8+ T cells ratio versus placebo from Day 0 to Viral Rebound;
- To evaluate the effect of ABX464 on HIV reservoir (pro-viral DNA in PBMC) versus from Day 0 to Viral Rebound.
- To assess the Pharmacokinetics parameters of ABX464 given on top of darunavir/ritonavir/cobicistat and ABX464.
- To compare miRNA modulations and tropism of HIV versus placebo from Day 0 to Viral Rebound.

# 3. INVESTIGATIONAL PLAN

## 3.1. Study design

### 3.1.1. Design and methodology

This study is a placebo-controlled study aimed at assessing the safety of ABX464 administered at 50 mg o.d. (or potentially at 150 mg o.d.) versus placebo in HIV infected patients who are treated with darunavir + ritonavir (DRV/RTV) or darunavir + cobicistat (DRV/COBI). Eligible patients should be treated with darunavir + ritonavir or darunavir + cobicistat as monotherapy for at least 8 weeks prior to baseline. Patients should be fully suppressed (< 50 copies/mL) for at least 6 months prior to enrolment.

Upon screening visit, eligible patients will continue DRV/RTV or DRV/COBI single regimen given respectively at 800 mg of darunavir with 100 mg of ritonavir or 150 mg of cobicistat once a day with food in the morning.

At Day 0, study drug (ABX464 or its matching placebo) will be added on top of this background therapy for the next 28 days. ABX464 or its matching placebo will be given once a day at the fixed dose of 50 mg (or potentially at 150 mg o.d.).

A 3:1 randomization ratio will be applied meaning that, per treatment block, 3 patients will receive ABX464 on top of DRV/RTV or DRV/COBI and 1 patient will receive placebo on top of DRV/RTV or DRV/COBI.

The original fixed dose (i.e. 50mg o.d.) of the study drug has been selected in November 2015 based on the reassuring safety data accumulated on the 50 mg o.d. and the concentrations in ABX464-N-glucuronide, the active metabolite of ABX464. However, in January 2016, the results of first phase IIa study conducted in treatment-naïve HIV infected patients with high viral load upon enrolment (5,000-500,000 copies/mL) confirmed the antiviral activity of ABX464 at higher doses. A reduction of viral load > 0.5 log was observed in 3/12 patients in the 75 and 100 mg cohorts and 4/6 patients in the 150 mg cohort, demonstrating a dose relationship effect of ABX464.

In case the first 8 patients treated for 28 days at 50mg o.d. in the present study (i.e. two first randomization blocks) do not show a DLT, the study protocol plans to study the 150 mg dose. The DSMB will specifically meet once the first 8 patients have been treated for 28 days in order to recommend, if appropriate, a dose increase to 150mg o.d.

At 150mg, the DSMB will meet every 4 patients in order to review on a regular basis the safety profile of this dose level and to recommend, if appropriate, the continuation of the study.

The sample size at a dose level will not be changed (i.e. 28 patients will need to be randomized receiving the same dose).

Dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the "Division of AIDS table for grading the severity of adult and pediatric adverse events" (including signs/symptoms, lab toxicities and/or clinical events) considered by the Data Safety Monitoring Board as probably or definitely related to study treatment.

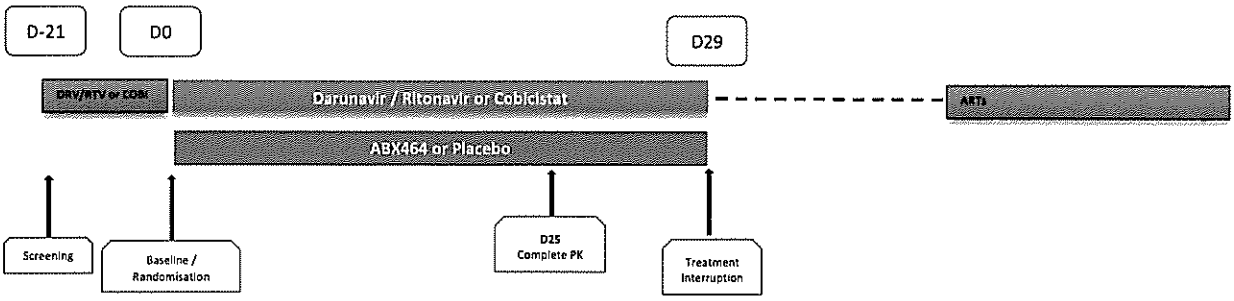
If more than 2 DLTs occur during the treatment period of the first four treated patients (regardless of the dose), then the enrolment of additional patients will be stopped. In addition, in case of a life threatening (grade 4) adverse reaction enrolment and treatment of ongoing patients will be immediately discontinued. In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.

At day 29, DRV/RTV or DRV/COBI and ABX464 or its matching placebo (i.e. all treatments) will be stopped. The viral load will be monitored twice a week during the first three weeks and weekly during the next weeks. In case of Viral Rebound (VR; defined below), ART will be resumed.

Thorough pharmacokinetics analysis will be performed to characterize potential drug-drug interactions between ABX464 and DRV/RTV-COBI.

The study design is summarized below in this chart.

| D-21 visit | D0 visit | D7 visit | D14 visit | D21 visit | D25 visit | D28 visit | D29 | Every week visit | | Follow-up Visits |
|---|---|---|---|---|---|---|---|---|---|---|
| Screening | | | | | | | ARTs interruption | | ART Reintroduction | |
| * | * | * | * | * | * | * | * | *** | * | * |




Safe sex counseling will be offered at every study visit in order to inform the patient about potential infectiousness since the viral load can rebound.

In this open-ended study, the study visits will be performed every week until Viral Rebound and then reintroduction of ARTs.

A viral load and a CD4+ count will be assessed weekly during the course of the study. However, these testings will be performed twice a week during the first three weeks following treatment interruption in order to capture as early as possible a potential early relapse.

A Viral Rebound (VR) is defined as HIV viral load > 1000 copies mL-1. If a patient meets this criterion, then ARTs should be reintroduced. The patient should be withdrawn from the study and should perform a follow-up visits every 14 days after ARTs reintroduction until the viral load has returned to undetectable levels.

### 3.1.2. Dose limiting toxicity (DLT)

A dose limiting toxicity (DLT) is defined as a grade 3 or higher adverse event as defined by the Division of AIDS Toxicity Table for Severe Adult and Pediatric Adverse Events (including signs/symptoms, lab toxicities and/or clinical events) considered by a safety review board as probably or definitely related to study treatment. The first four patients (regardless of the dose) will be enrolled first and followed up for at least 2 weeks of treatment. If more than 2 DLTs occur of the first four treated patients, then the enrolment of additional patients will be stopped, otherwise the enrolment of planned patients will be confirmed.

In addition, in case of a life threatening (grade 4) adverse reaction enrolment and treatment of ongoing patients will be immediately discontinued.

In both cases, enrolment will only be resumed upon the decision of the sponsor if the Data Safety Monitoring Board can conclude that the causality of the event was unrelated or unlikely related to study treatment.

### 3.1.3. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (iDSMB), with expertise and experience in the pathology, and without direct involvement in the conduct of the trial, will be set up specifically to guarantee effective protection of patients, insure the ethical conduct of the trial, benefit/risk ratio of the trial, and to ensure the independent review of the scientific results during the trial and at the end of the trial.

The DSMB will meet first after the 4 first patients are enrolled and treated for at least 2 weeks and then every group of 4 patients. Besides, the DSMB may recommend the early termination of the trial at any time if an unacceptable toxicity occurs.

In addition, the DSMB will meet specifically once the first 8 patients are treated with the 50mg o.d. for 28 days. If none of these patients experience a DLT, then the DSMB can recommend a dose escalation to 150mg o.d.

The DSMB has only a consultative role; it will inform the sponsor who will decide whether the DSMB recommendation will be followed. A DSMB charter must be available upon submission of the trial (initial protocol) to the respective competent authorities.

## 3.2. Duration of study participation

From a patient standpoint, the study participation is defined as

- Two to four weeks of screening period;
- Four weeks as combination treatment period (DRV/RTV or DRV/COBI + ABX464/placebo);
- A treatment interruption period that will last until the viral load rebounds.
- Some follow-up visits, every 14 days, after ARTs reintroduction until the viral load has returned to undetectable levels. In any case, the liver function testings should be peformed during these visits for at least 28 days after treatment interruption or premature study discontinuation.

Overall, the minimal study duration will be 49 days.

In case of no Viral Rebound then the end of study will be 3 months after treatment interruption with the possibility for the patient to be enrolled in long term-observational follow-up study.

# 4. STUDY POPULATION

## 4.1. Number of Patients/Centers

28 to 36 patients overall will be enrolled in this study. These patients will be enrolled in up to 8 sites located in France, Belgium and Spain.

## 4.2. Eligibility Criteria

### 4.2.1. Inclusion Criteria

A patient will be eligible for inclusion in this study only if ALL of the following criteria apply:

1. Patients infected with HIV;
2. Patients with HIV plasma viral load ≤ 50 copies $mL^{-1}$ during the 6 months prior to screening with a maximum of 2 blips during this period;
3. Patients treated by DRV/RTV or DRV/COBI for at least 8 weeks prior to baseline;
4. Patients' HIV plasma viral load ≤ 100,000 copies $mL^{-1}$ at any time (apart from primary infection if recorded);
5. Patients' CD4+ T cells count ≥ 250 cells per $mm^3$ at any time since diagnosis;
6. Patients with CD4+ T cells count ≥ 600 cells per $mm^3$ at screening;
7. Man or woman aged 18-65 years;
8. Patients with hematological and biochemical laboratory parameters as follows and within 7 days of baseline:
   - Hemoglobin > 9.0 g $dL^{-1}$;
   - Absolute neutrophil count ≥ 750 $mm^{-3}$;
   - Platelets ≥ 100,000 $mm^{-3}$;
   - Total serum creatinine ≤ 1.3 x ULN (upper limit of normal);
   - Creatinine clearance > 50 mL $min^{-1}$ by the Cockcroft-Gault equation within 60 days of entry;
   - Total serum bilirubin < 2.0 x ULN;
   - Alkaline phosphatase, AST (SGOT) and ALT (SGPT) < 1.5 x ULN;
   - Serum lipase less than or equal to 2.0 x ULN;
9. Patients should be able and willing to comply with study visits and procedures as per protocol;
10. Patients should understand, sign and date the written voluntary informed consent form at the screening visit prior to any protocol-specific procedures being performed;
11. Patients should be affiliated to a social security regimen (for French sites only);
12. Females and males receiving the study treatment and their partners must agree to use a highly effective contraceptive method during the study and for 3 months after end of study or early termination. Contraception should be in place at least 2 weeks prior to study participation. Women must be surgically sterile or if of childbearing potential must use a highly effective contraceptive method. Women of childbearing potential (WOCBP) will enter the study after confirmed menstrual period and a negative pregnancy test. Highly effective methods of contraception include true abstinence, intrauterine device (IUD) or hormonal contraception associated with inhibition of ovulation, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomized partner. True abstinence is defined when this is in line with the preferred and usual lifestyle of the patient. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is required. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycle.

### 4.2.2. Exclusion Criteria

The following criteria should be checked at the time of screening. If ANY exclusion criterion applies, the subject will not be included in the study:

1. Patient displaying any HIV protease inhibitor resistance mutation as listed in the current version of the HIV drug resistance database (Stanford University);
2. Patient having undergone virological failure as defined by a viral load ≥ 500 copies mL-1 confirmed by a second measure since initiation of the ART;
3. History of an AIDS-defining clinical illness;
4. Concomitant AIDS-related opportunistic disease;
5. History of allergic disease, anaphylaxis or reactions likely to be triggered or exacerbated by any component of the study drug;
6. Acute or chronic infectious disease other than HIV infection (include but not limited to viral hepatitis such as hepatitis B, active tuberculosis, active syphilis [i.e. currently treated], HTLV-1, HTLV-2). Of note co infection with hepatitis C is allowed providing their liver function parameters are within the following ranges: platelet > 150.000/mm3; γGT ≤ 2.5 ULN; Albumin > 40 g/L and providing that they are not receiving specific treatment during the study that could interfere with the study objectives;
7. Acute, chronic or history of clinically relevant pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic or renal functional abnormality, encephalopathy, neuropathy or unstable CNS pathology, angina or cardiac arrhythmias, or any other clinically significant medical problems as determined by physical examination and/or laboratory screening tests and/or medical history;
8. Uncontrolled dyslipidemia;
9. Acute, chronic or history of immunodeficiency or autoimmune disease other than HIV infection;
10. Unstable asthma (defined as sudden acute attacks occurring in less than three hours without an obvious trigger, hospitalization for asthma in the last two years); food or wine induced asthma;
11. History of malignancy unless there has been surgical excision that is considered to have achieved cure;
12. Active malignancy that may require chemotherapy or radiation therapy;
13. Seizure disorder or any history of prior seizure;
14. Serious illness requiring systemic treatment and/or hospitalization within 7 days prior to baseline;
15. Pregnant or breast-feeding woman;
16. Active drug or alcohol abuse or dependence;
17. Use of any investigational or non-registered product within 3 months preceding baseline;
18. Any condition, which in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.

# 5. STUDY ASSESSMENTS AND PROCEDURES

## 5.1. Study Flow Chart

A detailed study flow chart (with all assessments) is displayed hereafter.

| | Screening | Days | | | | | | Treatment interruption - Follow-up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Window | ± 7 days | ± 2 days (except D25 ± 4) | | | | | | ± 2 days | | | |
| Days | D-21 | D0 | D7 | D14 | D21 | D25 | D28 | Twice weekly for 3 weeks | Every week till VR | ARTs reintroduction visit | FU visit(s)*** |
| Obtained Inform Consent | X | | | | | | | | | | |
| Check of IN/EX Criteria | X | X | | | | | | | | | |
| Physical Examination | X | X | X | X | X | X | X | | X | X | X |
| Body Weight (kg) | X | X | X | X | X | X | X | | X | X | X |
| Height Measurement (cm) | X | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Medical Calls to patients | | Day 3 & 5 | | | | | | | | | |
| Serology: HBV, HCV, HIV | X | | | | | | | | | | |
| Hematology + Biochemistry | X | X | X | X | X | X | X | | X | X | X**** |
| CD4 and CD8 count | X | X | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | X | X | X | X | X | | X | X | |
| Blood Pregnancy test | X | | | | | | | | | | |
| Urine pregnancy test | X | X | X | X | X | X | X | | X | X | |
| Vital signs | X | X | X | X | X | X | X | | X | X | |
| ECG (12 lead) | X | X | X | | | | X | | | X | |
| DRV/RTV-COBI prescription | X | X | X | X | X | X | X | | | X | X |
| ABX464/placebo treatment dispensation and patient diary review | | X | X | X | X | X | X | | | | |
| Blood samples drug pK | | X* | X* | X* | X* | X** | | | | | |
| Blood samples for viral load /miRNA | X | X | X | X | X | X | X | X | X | X | X |
| Genotyping | | | | | | | | | | X | |
| Leukopheresis (optional) | X | | | | | | | | | X | |
| Blood samples for reservoir assessment<br>• Viral DNA<br>• TILDA | <br><br>X | <br>X | | | | | <br>X | | | <br>X<br>X | |
| Adverse Events recording | | X | X | X | X | X | X | | X | X | X |

* pre DRV/RTV or DRV/COBI morning dose

** pre DRV/RTV or DRV/COBI morning dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and 24 h post-dose (hospitalization is not required)

*** Every 14 days till undetectable VL

**** only bioschemistry required and for at least 28 days after treatment interruption

## 5.2. Study conduct

It is the investigator's responsibility to ensure that all the assessments are carried out during each visit and that the intervals between visits/follow-ups are adhered to.

### 5.2.1. Screening Visit (21 ± 7 days prior to baseline)

The patient will be informed about the general aspects of the study and will sign the screening informed consent form. The patient number will be allocated once the patient will be created in the eCRF. Only when consent has been given may further study procedures be carried out. During the screening phase, the following assessments will be performed:

- Signed informed consent form;
- Demographic data: date of birth and gender;

- Medical history, including Peak Viral Load and Nadir from patient's medical file (if available);
- Physical examination and vital signs;
- Hematology;
- Biochemistry and urinalysis including pregnancy test for all women of childbearing potential;
- Serology (HIV, HBV, HCV) – Previous HIV serology results are accepted;
- Viral Load, CD4/CD8 count;
- Blood collection for HIV reservoir assessment;
- 12 leads ECG;
- Leukopheresis (Optional);
- Record all medications received within 3 months prior to baseline and note if the medication is continuing;
- Inclusion/exclusion criteria will be verified globally.

#### 5.2.2. Randomization Visit / Day 0 - Baseline

- Physical examination and vital signs;
- Hematology;
- Biochemistry and urinalysis;
- 12 leads ECG;
- Viral Load, CD4/CD8 count;
- Urine pregnancy test for all women of childbearing potential;
- Adverse Events reporting;
- Perform Pk blood sample (pre DRV/RTV or COBI morning dose);
- Blood collection for HIV reservoir assessment;
- Only patients who meet all of the inclusion and randomization criteria and none of the exclusion criteria will be randomized;
- Complete e-CRF to register patient;
- Adverse event assessment;
- Dispense study treatment (allocated by SODIA) to patient and instruct how to take them.

#### 5.2.3. D7, D14, D21 Visits (± 2 days)

- Physical examination and vital signs;
- Medical calls to patient (on Day 3 and Day 5);
- Hematology;
- Biochemistry and urinalysis;
- Viral Load, CD4/CD8 count;
- 12 leads ECG (only at Day 7);
- Perform Pk blood sample (pre DRV/RTV or COBI morning dose);
- Urine pregnancy test for all women of childbearing potential;
- Adverse Events reporting;
- Dispense study treatment at each study visit to patient and instruct how to take them.

#### 5.2.4. D25 Visit (± 4 days)

- Physical examination and vital signs;

- Perform Pk blood samples (pre DRV/RTV or COBI morning dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h post-dose);
- Adverse Events reporting.

*Of note, according to the time-window allowed, this visit could be performed on Day 21 or Day 28 if needed.*

### 5.2.5. Day 28 Visit (± 2 days)

- Physical examination and vital signs;
- Hematology;
- Biochemistry and urinalysis;
- Viral Load, CD4/CD8 count;
- Urine pregnancy test for all women of childbearing potential;
- 12 leads ECG,
- Blood collection for HIV reservoir assessment;
- Check treatment compliance;
- Adverse Events reporting;
- Stop all treatments (DRV/RTV or COBI + ABX464/placebo);
- Schedule next patient visits.

### 5.2.6. Treatment interruption period Visits (± 2 days)

During the treatment interruption period study visits should be performed weekly until viral load rebounds. The following examination should be performed during these visits.

- Physical examination and vital signs;
- Hematology;
- Biochemistry and urinalysis;
- Viral Load, CD4/CD8 count;
- Blood collection for HIV reservoir assessment;
- Urine pregnancy test for all women of childbearing potential;
- Adverse Events reporting.

However, during the first three weeks (after treatment interruption), the Viral Load and the CD4/CD8 count should be controlled twice a week.

### 5.2.7. Viral Rebound – ART reintroduction Visit

This visit should be performed in all patients who experienced a viral rebound or who have been prematurely discontinued from the study (before the treatment interruption phase- End of Study visit).

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Hematology;
- Biochemistry and urinalysis;
- Viral Load, CD4/CD8 count;
- 12 lead ECG;
- Leukopheresis (Optional);
- Urine pregnancy test for all women of childbearing potential;

- Blood collection for HIV reservoir assessment;
- Adverse Events reporting;
- HIV genotyping (if ARTs have been stopped);
- Resume ARTs (if applicable).

#### 5.2.8. Follow-up Visits – HIV control restauration (± 2 days)

For patients who have stopped ARTs (DRV/RTV or COBI + ABX464/placebo) and have experienced a viral rebound, some follow-up visits, every 14 days, after ARTs reintroduction will be performed until the viral load has returned to undetectable levels. The last follow up will be considered the End of Study visit.

Following examinations/procedures should be performed:

- Physical examination and vital signs;
- Biochemistry;
- Viral Load, CD4/CD8 count;
- Adverse Events reporting;

### 5.3. Detail of the study assessments

#### 5.3.1. Physical Examination and Vital Signs

A routine physical examination (including body weight) will be done at each study visit. Physical examinations will cover eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculo-skeletal system, and, if applicable, others. Any new clinically relevant finding compared to baseline must be documented as adverse event.

Measurements of vital signs will be done at each visit (Blood pressure, Heart Rate, Body temperature). The patient should rest for at least 15 minutes prior to measurements. The measurements can be performed either in sitting or supine position of the patient. The right or left arm may be used. However, the position and the arm used for measurement should be kept constant throughout the trial for an individual patient.

The investigator should ensure that each parameter outside the normal range is assessed for clinical significance. For any deviation assessed clinically significant, the investigator has to document the change as an AE in the CRF.

In addition, it is at the discretion of the investigator to document any change or trend over time in vital signs as an AE if he considers the change to be clinically significant, even if the absolute value is within the alert limit or reference range.

#### 5.3.2. Pregnancy

For all female patients of childbearing potential, a blood pregnancy test (beta human chorionic gonadotropin [HCG]) will be performed at Day 0. In addition, a urine pregnancy test will be performed at each of the study visit until Viral Rebound.

In case of positive pregnancy testing, detailed procedures can be found in section 8.3.2.

#### 5.3.3. ECG

Electrocardiograms have to be done at Screening, Day 0, Day 7, Day 28 and ART reintroduction visit and, if clinically indicated, at follow-up. At least a 12-lead ECG with recordings of at least 6 action potentials in lead II (paper speed 25mm/s, amplitude 10mm/mV) has to be done in a resting position. Prior to the recording the patient should be at rest for at least five minutes. Resting ECG should be performed before any examinations.

The ECG printout will be reviewed by the investigator and a signed and dated copy of the ECG will be attached to the medical file. The original ECG printouts are considered as source data and should be stored at site. In case thermal paper is used, a copy of the original ECG must be kept as well. All abnormal findings must be

documented in the CRF. Any clinically relevant findings compared to Visit V0 must be documented as adverse events.

### 5.3.4. Hematology and biochemistry

For hematology and biochemistry local laboratories will be used. All laboratory results and reference ranges for safety parameters must be entered in the eCRF. Each laboratory value that is outside of the institution's normal range will be identified. The investigator will be responsible for assessing the clinical significance of laboratory abnormalities. If the investigator is uncertain about the clinical significance of a laboratory abnormality, he/she will consult with the Sponsor medical monitor. The investigator should follow any clinically significant laboratory abnormalities until resolution.

Table 1 displays the clinical laboratory parameters that must be measured.

**Table 1: Laboratory Tests**

| HEMATOLOGY | BIOCHEMISTRY |
|---|---|
| Hemoglobin | Sodium |
| Hematocrit | Potassium |
| WBC | Chloride |
| Neutrophils | Calcium |
| Lymphocytes | Phosphate |
| Monocytes | Glucose |
| Eosinophils | BUN or urea |
| Basophils | Creatinine |
| Platelet count | AST |
| | ALT |
| | GLDH |
| | Alkaline phosphatase |
| | gGT |
| | Total bilirubin |
| | Total protein |
| | Albumin |
| | LDH |
| | CRP |

At each biochemistry timepoint, a tube containing the remaining sera (at least 1 mL) should be kept and stored at -20°C for potential further liver function parameters such as soluble caspase-cleaved keratin 18 (M30 Elisa) and/or miRNA22 as a marker of early hepatotoxicity.

### 5.3.5. Viral load and HIV Reservoirs assessment

Regarding HIV viral load, local laboratories will be used as this is done in routine for HIV infected patients and as method is standardized so that comparisons between laboratories can be performed.

The total HIV-DNA level quantified in blood cells is an indirect marker of HIV reservoir. It is predictive of disease progression, to progression to CD4+ T cells count lower than 300 cells per $mm^3$ and to death.

Total and integrated HIV-DNA will be quantified at Day -21, Day 0 and then at the pre-specified visits (cf. flowchart).

30 ml of blood for Viral DNA assays and 60ml for the TILDA assays will be withdrawn at the pre-specified visits (cf. flowchart). PBMC will be prepared and frozen at study site according a study specific procedure. Frozen PBMC will be sent to the Department of Internal Medicine and Infectious Diseases Ghent University and Ghent University Hospital De Pintelaan 185 9000 Ghent, Belgium.

Total HIV DNA will be quantified using HIV DNA assay. This assay is based on real time PCR technology with the amplification of the LTR gene. To differentiate total cell-associated HIV-DNA from integrated HIV-DNA levels, different mode of DNA extraction will be used on identical aliquots of frozen PBMC (previously separated by Ficoll-Hypaque). Both markers will be quantified within the same technique and the same standard of quantification. Results will be expressed as the number of HIV-DNA copies/millions of PBMC; using the blood formula and CD4+ T cells count, the frequency per million of CD4+ T cells will be estimated.

In addition, depending on the number of PBMC collected using a stepwise approach the following assays could be performed: integrated DNA, Full length CA RNA, Spliced CA RNA, 2LTR circles, Tilda, VOA and the integration sites of the HIV.

Sub and optional study on the reservoir: molecular identity of the earliest rebounding virus and the T cells that harbor this virus.

Should ABX464 delay rebound in some but not all treated patients we will be able to examine how the source of rebound virus has been altered by the treatment in order to guide the design of future studies.

Given the possibility that the ABX 464 treatment arm will rebound over a more prolonged period, we will be able to study the T cells that are the source of the early or late rebound and compare them to T cells that rebound in the control arm. This data may help identify the characteristics of a latently infected T cell that ABX 464 is most likely to maintain in a prolonged quiescent state.

Specific Aims:

1. Determine the sequence of the rebounding founder virus.
2. Determine the T cell receptor and viral integration site of the T cells harboring the rebounding virus.

We will use an assay to detect HIV infected cells in order to pair the sequence of the rebounding virus with a specific T cell clonotype containing matching integrated pro-viral DNA. We will accomplish this by pairing high sensitivity sequencing of plasma viremia and sorting of latently infected T cells. This assay to determine the HIV integration site, genome wide HIV proviral sequence and TCR alpha/beta sequence at a single cell level has been developed at the Institute for Immunology and Infectious Diseases, Perth, Australia, directed by Prof. Simon Mallal.

In order to optimally carry out these studies, we will require leukopheresis specimens to obtain at least 5 billion PBMC. We will anticipate sorting 200 latently infected cells per subject. This will assure that we capture not only CD4+ T cells that are only making transcript, but also the replication competent virus that is contributing to rebound. Assuming a conservative estimate of one HIV infected cell per million CD4+ T cells, we would need to process 200 million CD4+ T cells.

The leukopheresis prior to the initiation of the study (screeninig visit), will enable us to catalogue the identity (based on TCR sequence and integration site) of latently infected T cells prior to study drug and treatment interruption. The second leukopheresis at or shortly after rebound (ART reintroduction visit) will allow discrimination of newly infected cells associated with viremia and other infected cells coming out of the reservoir. This opt-in ancillary study will be performed after receiving informed consent of the patients.

### 5.3.6. miRNA modulation

ABX464 up-regulates miRNA in non-infected and infected PBMCs, making of this micro-RNA a potentially useful biomarker for ABX464 treatment monitoring. The miRNA assays will be performed from the remaining plasma collected for viral load determination. No specific blood sample are therefore needed. Determination of miRNA level in plasma will be performed in order to assess treatment effect by comparing before and after treatment. Assays for miRNA determination and tropism test will be conducted by Theradiag, 9 avenue de l'Europe, Cap Alpha, 34830 Clapiers, France.

Blood collected in EDTA tubes should be store at room temperature (20-22°C) and processed within 4 hours after collection. Plasma isolation consist in a centrifugation at 500 G during 10 min at room temperature followed by the storage of 900 µL de plasma in an eppendorf tube at -80°C (or -20°C) until the end of the study. The plasma should be collected from all viral load samples.

### 5.3.7. Pharmacokinetics

**Darunavir**

The pharmacokinetic (PK) properties of DRV, co-administered with RTV, have been evaluated in healthy adult volunteers and in HIV-1 infected patients. Exposure to DRV was higher in HIV-1 infected patients than in healthy subjects. The increased exposure to DRV in HIV-1 infected patients compared to healthy subjects may be explained by the higher concentrations of α1-acid glycoprotein (AAG) in HIV-1 infected patients, resulting in

higher DRV binding to plasma AAG and, therefore, higher plasma concentrations. DRV is primarily metabolized by CYP3A. RTV inhibits CYP3A, thereby increasing the plasma concentrations of DRV considerably.

*Absorption*

DRV was rapidly absorbed following oral administration. Maximum plasma concentration (Cmax) of DRV in the presence of low dose RTV is generally achieved within 2.5-4.0 hours (h). The absolute oral bioavailability of a single 600 mg dose of DRV alone was approximately 37% and increased to approximately 82% in the presence of 100 mg twice daily RTV. The overall PK enhancement effect by RTV was an approximate 14-fold increase in the systemic exposure of DRV when a single dose of 600 mg DRV was given orally in combination with RTV at 100 mg twice daily. When administered without food, the relative bioavailability of DRV in the presence of low dose RTV is lower as compared to intake with food. The type of food does not affect exposure to DRV.

*Distribution*

DRV is approximately 95% bound to plasma protein. DRV binds primarily to plasma AAG. Following intravenous administration, mean (± SD) the volume of distribution of DRV alone was 88 (± 59) L and increased to 131 (± 50) L in the presence of 100 mg twice-daily RTV.

*Biotransformation*

In vitro experiments indicate that DRV primarily undergoes extensive oxidative metabolism by the hepatic cytochromes (CYP) system and almost exclusively by CYP3A4. At least 3 oxidative metabolites of DRV have been identified in humans; all showed activity that was at least 10-fold less than the activity of DRV against wild type HIV.

*Elimination*

After a 400/100 mg 14C-DRV with RTV dose, approximately 79.5 and 13.9% of the administered dose of 14C-DRV could be retrieved in feces and urine, respectively. Unchanged DRV accounted for approximately 41.2 and 7.7% of the administered dose in feces and urine, respectively. The terminal elimination half-life (t1/2) of DRV was approximately 15 h when combined with RTV. The intravenous clearance (CL) of DRV alone (150 mg) and in the presence of low dose RTV was 32.8 L/h and 5.9 L/h, respectively.

**Ritonavir**

PK of RTV have been studied in healthy volunteers and HIV-1 infected patients.

*Absorption*

The absolute bioavailability of RTV has not been determined.

After a single 600 mg dose, total system exposure was 13% higher when administered with a meal.

*Metabolism*

Nearly all of the plasma radioactivity after a single oral 600 mg dose of 14C-RTV oral solution was attributed to unchanged RTV. Five (5) RTV metabolites have been identified in human urine and feces. The isopropylthiazole oxidation metabolite (M-2) is the major metabolite and has antiviral activity similar to that of parent drug; however, the concentrations of this metabolite in plasma are low. In vitro studies utilizing human liver microsomes have demonstrated that CYP3A is the major isoform involved in RTV metabolism, although CYP2D6 also contributes to the formation of M-2.

*Elimination*

In a study of 5 subjects receiving a 600 mg dose of 14C-RTV oral solution, about 11% of the dose was excreted into the urine, with about 2 to 5% of the dose excreted as unchanged parent drug. In that study, more than 80% of the dose was excreted in the feces with about 20 to 40% of the dose excreted as unchanged parent drug. Upon multiple dosing, RTV accumulation is less than predicted from a single dose possibly due to a time and dose-related increase in clearance.

**Cobicistat**

COBI is a mechanism-based CYP3A inhibitor and pharmacokinetic (PK) enhancer. COBI chemical structure is closely related to ritonavir and, as a result, it shares some of its characteristics.

*Absorption*

In a trial where subjects were instructed to take co-administered COBI and darunavir with food, median COBI peak plasma concentrations was observed 3.5 hours (h) post-dose.

Steady-state COBI Cmax, $AUC_{0-\tau}$ and $C\tau$ (mean ± SD), values were 0.99 ± 0.3 µg/mL (n=60), 7.6 ± 3.7 µg.h/mL (n=59), and 0.03 ± 0.1 µg/mL (n=59), respectively.

A food effect trial was not conducted for COBI since it is coadministered with other antiretroviral agents under fed conditions, in accordance with the prescribing information for these agents. It is recommended that COBI coadministered with atazanavir or darunavir be administered with food.

*Metabolism*

COBI is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation. COBI 150 mg provides near-maximal inhibition of CYP3A, as assessed using midazolam. These results were roughly in agreement with those obtained with ritonavir (in vitro studies utilizing human liver microsomes have demonstrated that CYP3A is the major isoform involved in RTV metabolism, although CYP2D6 also contributes to its biotransformation.

Overall, COBI a lower potential for off-target drug interactions than the standard boosting agent ritonavir, due to its more selective inhibition of CYP3A and lower likelihood for enzymatic induction, and is devoid of anti-HIV activity.

*Elimination*

The terminal plasma half-life of cobicistat following administration of COBI is approximately 3 to 4 h which is slightly lower than ritonavir (3 to 5 h). With single dose administration of 14C COBI after multiple dosing of COBI for 6 days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.

**ABX464**

After single oral administration of 50 to 200 mg ABX464, ABX464 is relatively quickly absorbed and undergoes a very extensive biotransformation into its N-glucuronide metabolite, NGlc.

In most of the subjects, regardless of the dose, ABX464 plasma concentrations is generally not measured after 8 to 10 h post-dose. Cmax is generally observed within the first 2 h post-dose and then ABX464 plasma concentrations decreased with a t1/2 of about 1 to 2 h.

NGlcABX464 plasma concentrations were markedly higher than those of the parent drug with mean Cmax about 200 to 300-fold higher than ABX464 Cmax. Cmax was observed around 4 h post-dose with a very limited variability thereafter ABX464NGlc was slowly eliminated and had a t1/2 of 90 to 110 h.

Relationship between rate and extent of absorption of ABX464 and ABX464 dose is quite erratic with a reduced increase with the dose up to 150 mg and a saturation like behavior at 200 mg.

NGlcABX464 exposure-dose relationship is somehow comparable to that of ABX464 although increase of Cmax and AUCs tend to be dose proportional between 50 and 150 mg.

Since ABX464 undergoes a high level of biotransformation, ratios between metabolite and parent drug appear to be unchanged across the studied dose range but inter-individual variability prevented from definite conclusions.

Therefore, ABX464 should rather be considered as a pro-drug with regard to its short t1/2. Its metabolite, ABX464NGlc exhibits markedly higher blood concentrations and has a much longer t1/2 which could be of pharmacological interest. Last, dose-exposure relationship appears erratic between 50 and 200 mg but tends to linearity up to 150 mg.

**PK Study Design**

The main objective of the PK analysis is to evaluate the impact of concomitant administration of ABX464 on DRV and RTV/COBI PK characteristics.

Considering that DRV/RTV or DRV/COBI is a chronic treatment, it is deemed more relevant to evaluate the possible drug-drug interaction at steady-state.

With regard to the relatively short $t_{1/2}$ of DRV (15 h), steady-state is expected to be reached between the 3rd and the 4th day of administration. RTV and COBI have a lower $t_{1/2}$ and thus will not require a longer treatment duration to be at steady-state.

ABX464 was shown to have a very short $t_{1/2}$ (1 to 2 h), so steady-state is virtually reached at the second administration, while NGlcABX464 has a $t_{1/2}$ of 90 to 110 h, meaning that steady-state is reached after 19 to 22 days of administration. Therefore, PK blood collection is planned to be done on Day 25 (25 days after initiation of ABX464 administration). Collection of sparse pre-dose samples from Day 1 o Day 25 will allow to control that NGlcABX464 is at steady-state at the time of PK assessment and to check if steady-state pre-dose levels of DRV and RTV are maintained with co-administration of ABX464.

Since PK analysis is done at steady-state, PK blood sampling will be limited to the higher dosing interval and expression of the extent of exposure of each compound will be determined by $AUC_{0-\tau}$ (with $\tau$=24 h for ABX464 and NGlcABX464 and 12 h for DRV and RTV).

A first blood sample (reference) for DRV and RTV/COBI will be collected on the first day of treatment before any drug administration then blood samples will be collected for PK purpose at the following days:

Day 0 pre DRV/RTV-COBI morning dose*;

Day 7 pre DRV/ RTV-COBI morning dose;

Day 14 pre DRV/ RTV-COBI morning dose;

Day 21 pre DRV/ RTV-COBI morning dose;

Day 25** pre DRV/ RTV-COBI morning dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h post-dose;

* reference for DRV and RTV-COBI;
** could be performed at Day 21 or Day 28 according to the allowed time window

A total of 17 blood samples per patient will be collected for PK purpose and sent to ATLANBIO for Bioanalyses.

Blood samples for determination of ABX464, NGlcABX464, and/or DRV and RTV-COBI blood levels will be collected from all patients using direct venipuncture or an indwelling catheter.

Then, the following PK parameters will be derived for ABX464, NGlcABX464, DRV, and RTV-COBI Day 25 for each patient:

- Cmax, tmax: the maximum plasma concentration (Cmax) and the time taken to reach Cmax (tmax) will be obtained directly from the concentration-time data.
- $AUC_{0-\tau}$: the area under the concentration-time curve from time zero to the time of dosing interval $\tau$ (24 h post-dose for ABX464 and NGlcABX464, and 12 h post-dose for DRV and RTV). If no concentration can be measured at this time point, AUC0-last (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

Moreover, evaluation of steady-state will be made by visual inspection of the pre-dose concentration measurement collected over the study duration.

## 5.4. Summary of blood samples

The Table 2 below summarizes the volume of blood to be sampled at each study visit.

| Summary of Maximal Blood Volume (mL) | |
|---|---|
| **Day - 21** | 26 mL + 60 ml (TILDA) |
| **Day 0** | 23 mL + 30 ml (reservoirs) |
| **Day 7** | 24 mL |
| **Day 14** | 24 mL |
| **Day 21** | 24 mL |
| **Day 25** | 52 mL |
| **Day 28** | 24 mL + 30 ml (reservoirs) |
| **TOTAL** | **317 mL** |
| **Follow-up (every week) – Reservoir and genotyping at Viral Rebound only** | 20 ml + 90 ml (TILDA and reservoirs) + 2 ml genotyping |
| **Follow-up visit post ARTs reintroduction** | 15 mL |

| Laboratory testing | Tube | Volume (ml) |
|---|---|---|
| Glucose | Fluoride (2 cc) | 2 |
| Biochemistry | Heparin blood (6 cc) | 6 |
| Hematology | EDTA (3 cc) | 3 |
| HBV, HCV, HIV screen | Clotted blood (6 cc) | 6 |
| HIV RNA | EDTA (6 cc) | 6 |
| HIV Reservoir / TILDA | EDTA tube (7 cc) for PBMC collection | 30 / 60 |
| CD4 and CD8 | EDTA (3 cc) | 3 |
| PK (per time point) | Heparin blood (4 cc) | 4 |

# 6. INVESTIGATIONAL PRODUCT(S)

All investigational products to be used in this study have been manufactured, packaged and labelled by contract manufacturers for ABIVAX, according to GMP standards and are supplied to investigators free of charge.

## 6.1. Description of investigational treatment

The study treatment that will be administrated to patients enrolled in this Phase IIa study consists of capsules containing ABX464 or its matching placebo given orally once daily for 28 days.

## 6.2. Description of investigational Product

### 6.2.1. Active investigational product (ABX464)

The ABX464 investigational medicinal product (IMP) is a hard gelatin capsule intended for oral administration.

For the proposed clinical trial, the IMP consists of size 00 capsules containing 50 mg of ABX464 drug substance in the form of a granulate prepared with a number of common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica). It is supplied in high-density polyethylene bottles closed with high-density screw caps.

ABX464 will be manufactured by SEPS Pharma (Belgium) and distributed to the sites by SODIA.

| | |
|---|---|
| SEPS Pharma CTM | SODIA |
| Technologiepark 4 | Avenue Robert Schuman |
| 9052 Gent | 51100 REIMS Cedex |
| Belgium | France |

The study drug has to be stored at ambient temperature (< 25°C). The capsule or combination of capsules to be used depends on the dose-level to be administered as per the clinical study protocol.

### 6.2.2. Placebo

The matching placebo consists of the same hard gelatin, powder-filled capsules (size 00) filled with only the same common excipients (microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate and colloidal silica) as the active IMP, supplied in high-density polyethylene bottles closed with high-density screw caps.

ABX464 matching placebo will be manufactured by SEPS Pharma (Belgium) and distributed to the sites by SODIA.

| | |
|---|---|
| SEPS Pharma CTM | SODIA |
| Technologiepark 4 | Avenue Robert Schuman |
| 9052 Gent | 51100 REIMS Cedex |
| Belgium | France |

The study drug has to be stored at ambient temperature (< 25°C). The capsule or combination of capsules to be used depends on the dose-level to be administered as per the clinical study protocol.

## 6.3. Administration and Dosing

### 6.3.1. Administration of the investigational product

Patients will be dosed with a fixed daily dose of 50 mg that is respectively 1 capsule of 50 mg. In case of dose escalation to 150 mg is recommended then patients will be dosed with 3 capsules of 50 mg every day.

Patients will be orally dosed in fed condition (regular breakfast) with 240 mL of water.

A patient diary, in which the patient should report the number of capsules taken and the intake time, will be given to the patient at baseline. Moreover, this diary will enable the patient to report also potential discomfort or side effects s/he could experience.

### 6.3.2. Guidelines for treatment postponement and dose modifications

No intra-patient dose escalation/dose adjustment are allowed.

## 6.4. Method of Assigning Patients to Treatment Arms

All patients will be assigned a unique and incremental patient Identification (ID) number. Patient IDs will be unique (i.e. reallocation of the ID will not be permitted). The format will be a seven-digit number as follows: ABX-country/site number (4 digits) – patient number (3 digits). The latter 3-digit patient number will be assigned according to the patient's order of inclusion in the center.

Patients will be randomized in the ratio 3:1 to either an ABX464 or the placebo arm at Day 0 if s/he fulfils all inclusion exclusion criteria.

Randomization will be performed via e-CRF. The e-CRF will allocate treatment number assignment. Treatment bottles will be allocated at once at Day 0 by SODIA and send by e-mail or fax.

However, depending on the bottles/strength used, the study treatment dispensation will be performed either only once at Day 0 (30-capsule bottles) or at every site visit (5-capsule bottles). In all cases, patient should return his/her used and unused bottles at each study visit for a compliance check.

## 6.5. Blinding and breaking the study blind

Study drug will be packaged in blinded label bottles. Bottles will be numbered according to a randomized treatment number list. The content of the labeling is in accordance with the required references listed in the Good Manufacturing Practices.

The investigator, study personnel, and study participants are blinded with respect to treatment (i.e., active ABX464 or placebo). Sponsor or delegate will generate the random code list and the corresponding treatment number list.

Investigator could have access to unblinding only in case of medical emergency via specific envelopes. However, as there is no antidote it is highly unlikely that knowledge of treatment would affect the clinical management of the patient.

## 6.6. Packaging

The IMP consists in hard gelatin, powder-filled capsules (size 00) containing 50 mg of ABX464, supplied in high-density polyethylene bottles closed with high-density screw caps.

## 6.7. Storage

ABX464/Placebo capsules will be shipped to the investigational site at ambient temperature. ABX464/Placebo capsules should not be stored above 25°C. DO NOT FREEZE OR REFRIGERATE.

The IMP should not be used beyond the expiration date. Drug supplies are to be stored in a secure, limited-access location under the storage conditions required by GCP/GMP guidelines.

## 6.8. Product Accountability

An accurate and current accounting of the dispensing and return of IMP(s) will be maintained on an ongoing basis by the pharmacist and a member of the study site staff in the Accountability Log and case report form and will be verified by the study's monitor.

## 6.9. Prior and Concomitant Medication

### 6.9.1. Background and allowed concomitant treatment

All Patients must be treated by darunavir/ritonavir or darunavir/cobicistat given as a monotherapy for at least 8 weeks prior to baseline. Ritonavir boosted protease inhibitor treatment should be given at the following doses:

- 800 mg of darunavir and 100 mg of ritonavir once a day with food or
- 800 mg of darunavir and 150 mg of cobicistat once daily with food.

This ritonavir boosted protease inhibitor treatment should be continued during the study period until Day 28.

### 6.9.2. Prohibited prior or concurrent medications

The following drugs are prohibited during the course of the study.

- Other antiretroviral therapies than those part of the study treatments (e.g. NRTIs, NNRTIs,...);
- Drug therapy with immunomodulators or immunosuppressive drugs (such as IL-2, IL-7, intravenous immunoglobulin-IVIG- or IFN) within one month preceding Day 0;
- Drugs that could interact either with darunavir/ritonavir, darunavir/cobicistat or ABX464 should be avoided especially the CYP1A2 substrates (cf. Appendix#2). The following CYP1A2 substrates with a narrow therapeutic margin are prohibited during the whole course of the study (Clozapine, theophylline, ropinirol, warfarin and methadone).
- Use of any investigational or non-registered product within 3 months preceding baseline.

Potential concomitant medications should be kept at constant dose during the course of the study and properly reported in the medical file of the patient and the eCRF.

This information should include the name of the medication (international nonproprietary name), daily dosage, duration, indication and the time of last intake before all PK samplings.

# 7. PATIENT COMPLETION AND WITHDRAWAL

## 7.1. Patient Completion

Treatment with ABX464/Placebo shall continue until Day 28, except if a patient fulfils a premature discontinuation criterion (defined below). After ARTs interruption (Day 28), patients will be followed up twice weekly during the first three weeks and then weekly until Viral Rebound/ART resumption criteria are met. Afterwards, specific follow-up visits should be performed every 14 days after ARTs reintroduction until the viral load has returned to undetectable levels.

## 7.2. Premature trial discontinuation

A patient can be withdrawn at any time from the study for the following reasons:

- Investigator's decision;
- An Adverse Event or an intercurrent condition that preclude continuation of treatment;
- Major protocol violation;
- Patient's decision;
- Withdrawal of consent

A patient who prematurely exits the study before Day 28, for a non-drug related reason, will be replaced (i.e. an additional patient will be randomized and receive the next treatment allocation. This may or may not be the same treatment as the withdrawn patient).

In addition, a patient must be withdrawn from the study, at any time, if s/he presents an increase in transaminases (AST/SGOT and/or ALT/SGPT) or in Alkaline phosphatase ≥ 2.0 x ULN.

## 7.3. Study Discontinuation

All patients, regardless of the completion or premature discontinuation, should perform the ART reintroduction Visit according to the study flow-chart.

## 7.4. Screen and Baseline Failures

A patient is considered to be a baseline failure if the patient signs the informed consent but withdraws before the screening visit. All potential patients who are screened for enrolment in this study will be listed on the Patient Screening Log/Identification List. Reasons for exclusion will be recorded for potential patients who do not enter the study.

A patient who does not fulfil the randomization criteria at Day 0 will be considered as screen failure. All patient data should be entered in the eCRF including the screen failure data.

# 8. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

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

During the screening period, only adverse event related to the screening procedures will be collected. Adverse events related to the antiretroviral treatments will be reported directly to the concerned pharmaceutical company according to the local process.

Any disease progression will not be reported in the eCRF as an adverse event, but will be documented in the efficacy section.

## 8.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Note:** The official definition also extends to AEs occurring in the placebo arm. Because of regulatory requirements, events occurring during pre-and post-treatment periods will also be designated as AEs. Therefore, reporting of such events, AEs and SAEs, will commence when the patient is enrolled into the study (date of signature of the informed consent) up until 4 weeks after the end of the treatment visits. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

## 8.2. Definition of a SAE

A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose:

a) Results in death

NOTE: Death is an outcome of an AE, and not an AE in itself. Event which led to death should be recorded with fatal outcome.

b) Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization means that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen after informed consent was given is not considered an AE.

d) Results in persistent or significant disability/incapacity,

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as

uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Is another medically important condition: This refers to an AE that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Based on medical and scientific judgment this should usually be considered serious.

If there is any doubt about whether or not an AE is serious, the investigator should contact the sponsor.

#### 8.2.1. Events and/or Outcomes Not Qualifying as SAEs

Any hospitalization, or prolongation of hospitalization due to the circumstances listed below, will not be reported as SAE:

- planned medical/surgical procedure;
- planned medical/surgical admission (planned prior to entry into study, appropriate documentation required), for the disease under study;
- Administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances).

### 8.3. Events or Outcomes Qualifying as AEs or SAEs

#### 8.3.1. Clinical laboratory parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g. vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definitions of sections 8.1 and 8.2 respectively. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at informed consent and significantly worsen during the study will be reported as AEs or SAEs. Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, and are present at the start of the study but do not worsen, will **not** be reported as AEs or SAEs. However, if these findings or assessments are judged by the investigator to be more severe than expected considering the patient's condition, then they may be reported as AEs or SAEs.

#### 8.3.2. Pregnancy report

Patients who become pregnant at any time will be immediately withdrawn from participation in the study. All appropriate withdrawal assessments may be performed at the discretion of the investigator.

The investigator will collect pregnancy information on any woman patient or partner of a male patient, who becomes pregnant and their partner while participating in this study. The investigator will record pregnancy information and submit it to ABIVAX or its designee within 24 hours after knowledge of a patient's or partner's pregnancy. The patient or partner will also be followed to determine the outcome of the pregnancy, be it full-term or prematurely terminated. Information on the status of the mother and child will be forwarded to ABIVAX or its designee. Follow-up will normally end 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

The time period for collecting pregnancy information is identical to the time period for collecting AEs, as stated in Section 8.4, Time Period, Frequency, and Method of Detecting AEs and SAEs. Pregnancy information is collected from the signing of informed consent to 4 weeks after the last dose.

### 8.4. Time Period, and Frequency of Detecting AEs and SAEs

All AEs and SAEs occurring from the time a patient consents to participate in the study until 4 weeks after he or she has completed or discontinued the investigational product must be recorded in the patient's eCRF. Importantly, SAEs will have to be reported, either by email or by Fax, to SIMBEC- ORION within 24 hours of awareness of an SAE.

SIMBEC ORION

**pharmacovigilance@orioncro.com**

**Fax: +44 (0) 1753 695 101**

Legislative guidance requires also reporting any **related** SAEs to be reported after the patient finished the study if the investigator becomes aware of them.

## 8.5. Recording AEs and SAEs

Severity of AEs will be assessed according to "Division of AIDS table for grading the severity of adult and pediatric adverse events", version 2.0 of November 2014.

Patients will be asked to report all AEs as part of the procedures performed at each study visit. The site personnel will document all AEs in the patient's medical record. All AEs subsequently must be recorded in the appropriate eCRF sections.

The following points must be recorded for each event:

- A description of the event in medical terms, not as reported by the patient;
- Date of onset (start date);
- Date of resolution (stop date);
- The time of onset with respect to administering the investigational product;
- The severity of the sign/symptom or clinically significant abnormal laboratory value according to CTC AE Classification;
- The causal relationship between the investigational product and the occurrence of each AE. This will be assessed by each investigator using clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant medications, other risk factors and the temporal relationship of the event to the investigational product will have to be considered. The causality of all AEs should be assessed by the investigator with the following question: Is there a reasonable possibility that the AE may have been caused by the investigational product? And answered "NO" (if not related) and "YES" (if related);
- Action taken regarding the investigational product:
    - No action;
    - Temporary discontinuation;
    - Permanent discontinuation;
    - Patient's outcome:
    - Recovered without sequelae / resolved without sequelae;
    - Recovered with sequelae / resolved with sequelae;
    - Recovering/Resolving;
    - On-going;
    - Fatal (for SAEs only).

If in any one patient, the same AE occurs on several occasions, the AE in question must be documented and assessed anew each time.

## 8.6. Reporting of SAEs to ABIVAX or its designee

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

It is the investigator's responsibility to ensure that the SAE report is submitted to SIMBEC- ORION **within 24 hours after knowledge of the event(s).** The SAE forms or paper report forms should be completed as thoroughly as possible, with all the available details of the event and signed by the investigator or designee. An assessment of causality should always be provided at the time of the initial report. If the investigator or designee does not have all information regarding the SAE, he/she should not wait to receive additional information before completing the form and notifying SIMBEC- ORION.

Additional or follow-up information relating to the initial SAE report, will be requested, if necessary. Again, this information is to be completed and submitted through the SAE forms within 24 hours of receipt of the information.

In the rare occasion when the facsimile equipment does not work and in the absence of, the investigator should notify SIMBEC- ORION by telephone within the given timeframe, and send a copy of the SAE report form by email.

## 8.7. Reporting of SAEs to Regulatory Authorities

ABIVAX has a legal responsibility to notify, as appropriate, both the local regulatory authorities and other regulatory agencies about the safety of the investigational product. It is therefore important that the investigator notifies promptly ABIVAX or designee of any SAEs, in order for legal obligations and ethical responsibilities towards other patients to be met.

In addition, the investigator or designee, will comply with the local regulatory requirements (when applicable) in reporting of SAEs to the ethics committee and, if required, to the relevant government authority.

Safety reports on adverse events that are serious AND unexpected AND associated with the investigational product are prepared according to ABIVAX's policy and applicable regulations and are forwarded to the investigators. These reports are filed with the investigator brochure or other appropriate study documentation. It is the Sponsor or its designee and/or investigator's responsibility to notify the IRB or IEC of these reports, if applicable according to local requirements.

# 9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

A summary of the principal features of the statistical analysis of the data will be described here, in the statistical section of the protocol. A more technical and detailed elaboration of the principal features stated in the protocol will be given in the first version of the statistical analysis plan (SAP).

Any amendments to the SAP will be clearly documented and signed prior to the final database lock including justifications and details of their potential impact on the interpretation of the study results.

## 9.1. Statistical and Analytical Plans

No interim analysis is planned.

The study analysis will be performed following database lock upon the completion of the last patient or upon its early discontinuation whichever occurs first.

### 9.1.1. Protocol deviations

Protocol deviations will be reviewed and classed as major or minor during the blind-review meeting. Major protocol deviations are defined as deviations liable to bias the evaluation of the main efficacy endpoint. The following deviations will be considered as major (non-exhaustive list):

- Non compliance with the inclusion or exclusion criteria;
- Non compliance with the study treatment;
- Intake of prohibited medication;
- Noncompliance with time window.

### 9.1.2. Definition of study analysis sets

The following datasets will be defined and used for the analyses:

- The **Safety dataset (SAF population)** is defined as those patients included in the study, who have received at least one dose of the study treatment.
- The **Full Analysis dataset (FAS population)** is defined as those patients included in the study, who have received at least one dose of the study treatment, and who have at least one baseline data.
- The **Per Protocol dataset (PP population)** is defined as those patients of the FAS population without any major protocol deviation.

### 9.1.3. Patients/Subjects disposition

The number and the percentages of patients enrolled and included in each of the populations will be tabulated. The reason for patient exclusions from each of the populations will also be listed. In addition, the number of discontinued patients with their reason for discontinuation will be tabulated.

### 9.1.4. Demographic and other baseline characteristics

Demographics and other baseline characteristics will be summarized by treatment arm. This analysis will be conducted on the FAS population.

### 9.1.5. Treatment compliance

Number of injections will be presented on the FAS population.

## 9.2. Efficacy Analysis

All efficacy analysis will be conducted on both FAS population and PP population except if otherwise specified.

Descriptive statistics will be presented by treatment arm and include:

- Quantitative variables: mean, standard deviation, minimum and maximum, 95% confidence intervals, median and quartiles will be presented when considered relevant. Number of filled and missing values will also be presented.
- Qualitative variables: count, percentage for each modality and 95% confidence intervals when relevant. Number of missing values will also be presented.

Comparison between treatment and placebo will include the following inferential statistics:

- For Time-to-event analyses Kaplan-Meier estimates will be used.
- Categorical variables: the Fisher exact test or Pearson Chi-2 test, as appropriate, will be used to compare rates of categorical variables between the active group and the placebo arm. When stratification or adjustment of the comparisons will be needed, the Cochran-Mantel Haenszel procedure will be used.
- Continuous variables: parametric ANOVA (or non-parametric ANOVA or an appropriate transformation of the data if the assumptions for parametric ANOVA are not met) will be used to compare continuous variables between the dose group and the placebo arm. When stratification or adjustment of the comparisons will be needed, parametric or non-parametric ANCOVA (or data-transformation) will be used.

### 9.2.1. Pharmacokinetics

A total of 22 blood samples per patient will be collected for PK purpose.

Individual plasma concentrations of ABX464, NGlcABX464, DRV, and RTV or COBI will be presented by treatment and time points. Descriptive statistics for the plasma concentrations will be presented as number of available data (N), mean, standard deviation (SD) and will be calculated if at least 2/3 of the plasma values per time-point are above LOQ (i.e. N ≥ 10 if 15 patients are available for a given group). For descriptive statistics calculations, BLQ concentrations below the limit of quantification will be set to zero (0) if they are reported before the first quantifiable sample or considered as missing data if they are reported after the first quantifiable data.

Then, the following PK parameters will be derived for ABX464, NGlcABX464, DRV, and RTV Day 53 for each patient:

$C_{max}$, $t_{max}$: the maximum plasma concentration ($C_{max}$) and the time taken to reach $C_{max}$ ($t_{max}$) will be obtained directly from the concentration-time data.

$AUC_{0-\tau}$ : the area under the concentration-time curve from time zero to the time of dosing interval $\tau$ (24 h post-dose for ABX464 and NGlcABX464, and 12 h post-dose for DRV and RTV). If no concentration can be measured at this time point, AUC0-last (from time zero to the last quantifiable concentration) will be calculated. Both parameters will be presented independently. For both parameters, a linear trapezoidal method will be used.

Individual derived PK parameters will be presented by treatment and day of PK assessment when appropriate. Descriptive statistics of the PK parameters will be presented as N, mean, SD, coefficient of variation (CV %), median, minimum (Min), maximum (Max) values, and geometric mean (GM).

In the tables of individual PK parameters, all the deviations from planned analysis will be mentioned by flagging the abnormal results.

Possible exclusion of flagged PK parameters could be performed if, in the judgment of the pharmacokineticist, they are deemed not to be "pharmacokinetically relevant". Exclusion of PK parameters will be discussed in the PK results section. If data are excluded from the PK dataset, all subsequent statistical analyses will be performed twice, once using the complete available PK dataset and once using the final PK dataset as defined by the pharmacokineticist. Study conclusion will be based on the final dataset as defined by the pharmacokineticist.

For each compound, plasma concentration vs. time curves will be presented on a log-linear scale:

- mean plots showing the data of both treatments (administration alone and co-administration with ABX464);
- by patient plots with the treatments on separate plots (spaghetti plots).

*Formal PK Statistics*

It is assumed that all PK data of DRV and RTV/COBI obtained with co-administration of placebo will be gathered in a placebo group accounting for a theoretical total of a minimum of 7 patients.

Evaluation of drug-drug interaction

The relative bioavailability ($F_{rel}$) after multiple dose administration with either co-administration of ABX464 or of placebo will be evaluated on PK parameters determined on Day 25.

The comparison will be performed on Cmax and $AUC_{0-\tau}$ using a 1-way ANOVA model with treatment as main effect on logarithmically transformed data. For each parameter, a point estimate for the ratio of geometric means (DRV/RTV or COBI with 50 mg ABX464 / DRV/RTV-COBI with placebo) will be obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation with the exponential function. Likewise, 90% confidence interval for the ratios will be obtained by back transforming the 90% confidence intervals of least square mean differences on log-transformed PK parameters.

Moreover, evaluation of steady-state will be made by visual inspection of the pre-dose concentration measurement collected over the study duration.

## 9.3. Safety Analyses

Adverse events will be coded using the standard dictionary (MedDRA) down to the lower level term (LLT).

An overall summary table will be presented (Any adverse event, any treatment emergent adverse event (TEAE), any serious adverse event (SAE), death, any grade 3 or higher adverse events from baseline to the end of Study. This analysis will be conducted on SAF population.

Two periods will be defined for TEAE:

- Any adverse event which occurs or worsens from first dosing to Day 28;
- Any adverse event which occurs after Day 28.

Adverse events will be described by primary system organ class and preferred term. Numbers and percentage of patients, and number of occurrence of adverse event will be presented for:

- TEAE;
- Serious TEAE;
- TEAE leading to drug discontinuation;
- TEAE of grade 3 or 4;
- TEAE for which relationship with the study drug is recorded as possible or probable.

The assessment of safety will be based on the frequency of adverse events (with and without regard to causality) graded according to the "Division of AIDS table for grading the severity of adult and pediatric adverse events" (December 2004) and also, the review of individual values for clinical laboratory data, vital signs and ECG focusing on the detection of abnormal values and PCSAs [potentially clinically significant abnormalities (PCSAs) determined upon investigator considerations].

Adverse events will be tabulated (counts and percents) by group. All adverse events will be listed and the data will be tabulated by body system/organ class. Adverse event tabulations will include all treatment emergent adverse events, which will be further classified by severity, and relationship to treatment and dose level.

Clinical laboratory parameters, vital signs, ECG will be summarized by using descriptive statistics (n, mean, SD, SEM, median, minimum and maximum). Number of patients with at least one abnormal values will be tabulated (counts and percents) for each parameter in summary shift tables, by group and dose.

### 9.3.1. Clinical laboratory evaluation

Descriptive statistics for laboratory parameters will be computed at each scheduled assessment. If relevant for some parameter, change from baseline will also be tabulated.

In addition, shift tables from baseline will be presented.

## 9.4. Determination of Sample Size

The endpoint considered for the sample size calculation is the Time To Viral Rebound defined as the time between treatment stop (i.e. day 29) and viral rebound detection. According to published studies, the expected median Time To Viral Rebound (calculated from treatment stop) is expected to be 7 days in the 'DRV/RTV or COBI + placebo' group while it should be at least 28 days in the 'DRV/RTV or COBI + ABX464 group' in order to continue the clinical development of this new drug.

According to these hypotheses, the corresponding power was calculated using the PROC POWER of the SAS software (version 9.4). Thus, the enrolment of 28 evaluable patients at a dose level (21 in the ABX464 at 50 mg or 150 mg and 7 in the group placebo) will permit to have 80% power to detect a significant difference, at 0.05 level, between groups using the Time To Viral Rebound as end point.

Thus, the overall sample size can vary from 28 patients (in case the dose escalation procedure is not recommended) to 36 patients in case the dose escalation to 150 mg o.d. is recommended.

# 10. STUDY CONDUCT CONSIDERATION

## 10.1. Regulatory and Ethical Considerations

### 10.1.1. General Requirements

The study will be conducted in compliance with the study protocol, ABIVAX Standard Operating Procedures and in accordance with any local regulatory requirements, to ensure adherence to Good Clinical Practice (GCP) as described in the following documents:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use and its guidance.
- Declaration of Helsinki and its amendments.

Upon signing the protocol, the investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Written informed consents will be obtained for each patient before he or she can participate in the study.

ABIVAX will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agencies in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

### 10.1.2. Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the study protocol and amendments if applicable as well as other appropriate study-related documents will be submitted to an independent Institutional Review Board (IRB) or independent Ethics Committee (IEC), respectively.

For each center it will be individually specified, who (investigator or sponsor) will be responsible for informing the IRB or IEC, respectively of any protocol amendments or new relevant information that require an ethical reconsideration of the study protocol.

If the investigator is responsible for obtaining approval, he/she should also obtain a statement from the IRB or IEC, respectively that it is organized and operates according to GCP and applicable laws and regulations.

### 10.1.3. Patient Informed Consent

It is the responsibility of the investigator to give each patient full and adequate verbal and written information regarding the aims, methods, anticipated benefits and potential hazards. The patient must be informed that participation is voluntary, and that they are free to withdraw from the study at any time without any disadvantages for their subsequent care. Although a patient is not obliged to give her/his reason(s) for withdrawing prematurely from the trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Written consent (signed and dated by the patient and the investigator) must be obtained prior to admission. The patient must be provided with a copy of the patient information and informed consent.

The data collected in this study will be processed anonymously at ABIVAX. Patients should be informed about the purpose of the planned computer data processing and the publication of the data (e.g. at scientific meetings). The patient must give consent to the computer processing and to the publishing of anonymous data.

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

### 10.1.4. Compensation to Patients

Insurance coverage will be provided for all patients enrolled in the study from the time of the patient's inclusion in the study (i.e. date of signing the ICF). The insurance coverage will be provided by the Sponsor and will be in line with GCP guidance and legal requirements, but also in accordance with local regulations. Depending on the local policies and the services/availabilities of the insurance providers, different such providers may be used in individual countries. A confirmation of insurance and corresponding insurance conditions should be archived in the Investigator File.

# 11. STUDY MANAGEMENT

## 11.1. Remote Data Entry

An electronic case report form (eCRF) will be used to record all data required by the protocol. Remote Data Entry (RDE) will be used for data collection, *i.e.* the patient's information pertaining to the study, will be entered into the eCRF via a computer at the investigational site.

Prior to the start of the study, the investigator will complete a "*Delegation of significant study-related duties*" form, showing the signatures and initials of any person who is authorized to make or change entries in the eCRF and any person authorized to electronically sign the eCRF.

The eCRF used for this study is validated and fulfils the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) requirements, European and FDA (21 CFR Part 11) regulations.

Training sessions will be held for all the participants who will use this tool (*e.g.* investigators, ABIVAX staff and contract research organization [CRO] staff, including project managers, CRAs and data managers).

Several supports are available to help all users with this tool including eCRF user manuals (CRA and site manuals) and five days a week / working hours helpdesk (support line).

All of the information will be recorded through transcription from source documents into the eCRF by an authorized person.

The investigator is responsible for the management and accuracy of the information in the eCRF. At each monitoring visit, the patient medical files should be at the clinical research associate's (CRA) disposal for review.

## 11.2. Data management

Data management will be outsourced to a Contract Research Organization (CRO). The data managers will issue electronic edit checks via EDC, and modification of the data will be permitted by the investigator to achieve accuracy with source documents and eliminate all inconsistencies in the data.

The data will be reviewed for completeness and logical consistency. Automated validation programs will identify missing data, out of range data and other data inconsistencies at the time of entry.

All new/updated information will be reviewed and verified by the appointed monitor.

## 11.3. Data coding

Adverse events, concomitant diseases, medical/surgical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded using the WHO-DRUG dictionary.

## 11.4. Randomization

Randomization will be centrally managed by block of 4 patients (3 ABX464/1 placebo). It will be performed via the eCRF. The bottle numbers to be used for a specific patient will assign according to a pre-defined randomization list by SODIA. This information will be provided to the site by fax.

## 11.5. Study Monitoring

The study will be conducted in accordance with the ICH Note for Guidance on GCP (ICH, Topic 6, 1996). The appointed monitor will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ABIVAX requirements. Throughout the study, the monitor will arrange visits to the study center at appropriate intervals to assess the progress of the study and review the completed eCRFs.

During the monitoring visits, the monitor will:

- Ensure that the safety and the rights of patients are being protected;
- Check that the data are authentic, accurate, and complete and discuss any inconsistencies;
- Ensure that all study materials are correctly stored and dispensed with particular emphasis to the investigational product;
- Verify that the site staff and facilities continue to be adequate for the proper conduct of the study;
- Ensure that the study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements;
- Help resolve any problems that may have arisen.

In line with ICH GCP guidelines, monitoring will include verification of data entered in the CRF against the original patient records. Therefore, for the purpose of monitoring review, direct access to all study-related site and source documents is mandatory. Data items for which the eCRF will serve as the source document will be identified, agreed upon and documented. The investigator must also ensure provision of sufficient time, space and qualified personnel for the monitoring visits.

## 11.6. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff.

ABIVAX will inform the investigator/institution of the required time period for retaining these records in order to be compliant with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study site, as dictated by ICH GCP E6 Section 4.9, any institutional requirements or local laws and regulations, or ABIVAX standards/procedures; otherwise, by default the retention period will be 15 years.

The investigator must notify ABIVAX of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. In addition, the investigator should seek the written approval of the Sponsor prior to disposing any of the archived records.

## 11.7. Quality Assurance and Inspection by Authorities

To ensure compliance with GCP and all applicable regulatory requirements, ABIVAX may conduct quality assurance audits. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. By signing the protocol agreement page, the investigator agrees to permit drug regulatory agencies and ABIVAX audits. If an audit or inspection occurs, the investigator and institution will allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues. Items of particular interest in case of an audit are, but not limited to, the following:

- IRB/IEC and regulatory authority approvals;
- Informed consent forms of the patients;
- Approved study protocol and amendments and investigator brochure;
- Treatment accountability;
- Safety reporting;
- Study file;
- Study personnel;

- Log of monitoring visits and monitoring process;
- Medical records and other source documents;
- Site facilities;
- Reports to the IRB/IEC and the sponsor;
- Record retention.

## 11.8. Study and Site Closure

If the study is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients

ABIVAX reserves the right to temporarily suspend or prematurely discontinue this study, at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites. If such action is required, the Sponsor will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action, at that time. Advance notification will be provided to the site(s) when feasible, on the impending action prior to it taking effect.

All investigators and/or medical institutions conducting the study will be informed in writing should the Sponsor decide to suspend or prematurely discontinue the study for safety reasons. The regulatory authorities will also be informed of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by local regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

Upon premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and ABIVAX procedures. All data must be returned to ABIVAX. Arrangements will be made for any unused investigational product based on the relevant ABIVAX procedures for the study.

## 11.9. Study report and Publication

Upon conclusion of the study, an integrated clinical and statistical study report will be written by the Sponsor in consultation with the Coordinating Investigator. This report will be based on the items detailed in this study protocol. When the clinical study report is completed, ABIVAX will provide the investigators with a full summary of the study results. The investigators are encouraged to share the summary results with the patients, as appropriate.

The first resulting publication will be a full publication of all data from all participating sites, coordinated by ABIVAX. Any secondary publications by the investigators (abstracts in journals, oral presentations etc.) will reference the original publication and will require pre-submission review by the Sponsor. Note that the Sponsor is entitled to delay any proposed secondary publication, in order to obtain patent protection, if required.

The Coordinating Investigator as well as other members of the study committee will be authors on the first publication. The principal investigator of the trial will be the first author. Authorship for other investigators will be assigned on the basis of their recruitment contribution, as well as intellectual and administrative input. Ranking will be according to the number of patients randomized as well as contribution to the study conduct and preparation of final manuscript.

## 11.10. Ownership and Confidentiality

All information provided by ABIVAX and all data and information generated by the sites, as parts of the study (excluding the patients' medical records) are property of ABIVAX.

All potential investigators must be aware of and agree in writing (confidentiality agreement) to the confidential nature of the information pertaining to this study. Furthermore, all information provided by ABIVAX and all data and information generated by the sites during the study must be kept confidential by the investigator and other site staff, and may not be used for any purpose other than conducting this study.

# 12. REFERENCES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# 13. APPENDICES

Appendix 1: Division of AIDS table for grading the severity of adult and pediatric adverse events

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

http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf

Appendix 2: CYPIA2 substartes (in bold: prohibited concomitant medications)

| |
|---|
| Amitriptyline, Clomipramine, Imipramine, Agomelatine, Fluvoxamine, **Clozapine**, Olanzapine, Haloperidol, Ropivacaine, **Theophylline,** Zolmitriptan, Tamoxifen, Erlotinib, Cyclobenzaprine, Mexiletine, Naproxen, Ondansetron, Phenacetin, Paracetamol, Propranolol, Tacrine, Tizanidine, Verapamil, **Warfarin**, Zileuton, **Ropinirole, Methadone** |