CLINICAL TRIAL PROTOCOL WITH MEDICINAL PRODUCTS

A pilot 24-week open-label, randomized, controlled clinical trial to assess the safety, tolerability and efficacy of dual therapy with Raltegravir/Lamivudine combination when replacing standard combination therapy in HIV-infected patients with prolonged virological suppression. RALAM Study

Protocol code: RALAM

Version and date: version 2.0 dated 7 November 2014

EudraCT No.: **2014-003142-27**

NCT Number: NCT02284035

Sponsor: Fundació Clinic per a la Recerca Biomédica
Dr. Josep Maria Gatell Artigas

Principal Investigator: [redacted]

Abbreviations

3TC	Lamivudine
AE	Adverse event
AR	Adverse reaction
BID	Twice daily (“bis in die”)
CKD-EPI	Change in estimated glomerular filtration rate
CREC	Clinical Research Ethics Committee
CT	Computed tomography
CTU	Clinical Trials Unit
DSMB	Data and Safety Monitoring Board
DXA	Dual energy X-ray absorptiometry
FTC	Emtricitabine
HOMA-IR	Homeostasis model assessment-estimated insulin resistance (fasting insulin (µU/L) x fasting glucose (nmol/L)/22.5)
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LOCF	Last-Observation-Carried-Forward
LPV/r	Lopinavir/ritonavir.
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PBMC	Peripheral mononuclear blood cells
PI/r	ritonavir-boosted Protease Inhibitor
PSQI	Pittsburgh Sleep Quality Index
QD	Once a day
RAL/3TC	Raltegravir/Lamivudine
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
UAR	Unexpected adverse reaction
ULN	Upper limit of normal
VL	Viral load

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PROTOCOL SYNOPSIS

A pilot 24-week open-label, randomized, controlled clinical trial to assess the safety, tolerability and efficacy of dual therapy with Raltegravir/Lamivudine combination when replacing standard combination therapy in HIV-infected patients with prolonged virological suppression. RALAM Study

SITES: National single center study: Hospital Clínic de Barcelona

Clinical phase: Phase III

HYPOTHESIS: Raltegravir /Lamivudine in patients with prolonged virological suppression will be able to maintain virological efficacy, while being overall well tolerated and specifically able to improve metabolic parameters, body composition, renal function and sleep quality

OBJECTIVES:

Primary:

- efficacy in virological suppression assessed with standard plasma HIV-1 RNA detection (limit of detection 37 copies/mL).

Secondary:

- efficacy in virological suppression assessed with ultrasensitive HIV-1 RNA detection (limit of detection 1 copy/mL)
- changes in peripheral mononuclear blood cells HIV-1 reservoir
- changes in metabolic parameters including fasting plasma lipids and insulin resistance (HOMA-IR)
- changes in body fat composition and bone mineral density
- changes in plasma 25-OH vitamin D levels
- changes in estimated glomerular filtration rate (CKD-EPI) and urine beta-2-microglobulin
- changes in immune activation markers including CD38 and HLA-DR
- changes in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163)
- changes in sleep quality (Pittsburgh Sleep Quality Index)
- changes in adherence in both treatment arms (Morisky-Green Test) overall tolerability

STUDY DESIGN AND DURATION: This is a single center, national, phase III, prospective, open-label, randomized, and controlled, 24-week pilot study.

SAMPLE SIZE: A total of 75 patients, 18 years or older, will be included in the study, 50 in the study arm and 25 in the control arm (randomized 2:1).

TREATMENTS, DOSE, POSOLOGY:

Group 1 (study): Raltegravir / 3TC (MK0518B) (50 patients)

Group 2 (control): Continue current treatment (25 patients)

DOSE: RAL/3TC (300mg/150mg)

POSOLOGY: BID single pill

EFFICACY MEASUREMENTS: Plasma viral load (HIV-RNA) will be measured at weeks 0, 4, 12 and 24.

SAFETY ASSESSMENTS: At each visit, a physical examination and a blood test will be performed.

DATA ANALYSIS: All randomized patients will be included in the intent-to-treat (ITT) population. The per protocol population will include all patients from the ITT population except those who did not fulfill the inclusion/exclusion criteria or withdrawing from the study or discontinuing study treatment for reasons other than virological failure or adverse event.

Statistical Methods: The baseline patients' characteristics of the ITT population will be described. Continuous variables will be described by their means, standard deviations,medians, Interquartile ranges, minimums and maximums. Categorical variables, figures and percentages per class will be presented per arm.

The primary analysis will be done when all patients have reached 24 weeks. Analysis of the primary endpoint will be performed on both ITT and per protocol populations. The 95% two sided confidence interval of the of the difference in percentage of patients in therapeutic success (RAL/3TC – Current regimen) will be calculated.

The percentage and absolute changes in continous variables between week 4, 12 and 24 versus baseline will be compared between arms in the ITT population (LOCF of other imputation method to be defined in the statistical analysis plan) using a two-sided non parametric Mann WhitneyTest.

The categorical endpoints will be compared using Fisher's exact test or chi-squared test.

Two sided p-values will be reported. The level of significance will be tested at 0.05.

Power/Sample Size:

A total of 75 patients will be included in the study with a randomization 2:1 (RAL/3TC and Current treatment). The study is not a noninferiority study, in which case the delta should be -15% or less. It is a pilot study which tries to see the feasibility of the pattern and to generate data with which to design a larger study with a noninferiority design. However, there are security measures in the primary end-point is the virologic efficacy. The DSMB will review the data if 4 episodes of treatment failure are detected, and then every 4 additional failures detected. The study will be interrupted as early as 5 episodes of virological failure in experiemental branch are detected (10%).

The DSMB will meet not when 8 cases of treatment failure but 4 patients occur. Treatment failure may be due to virological failure, but also for other reasons (discontinuation due to toxicity, loss to follow rupture of consent, etc).

However, we are committed to make a thorough study and monitoring of each failure by independent researchers to study team to discover the possible reason for it.

This pilot study is exploratory, and must serve to see whether it is feasible, if the results are good enough, to make a large-scale study.

STUDY TIMETABLE

WEEK	-2 / -4 Screening	0 Randomization	4	12	24
Clinical assessment	√	√	√	√	√
Physical examination	√	√	√	√	√
Informed consent	√				
Pregnancy test	√				
Hematology	√	√	√	√	√
Biochemistry[1]	√	√	√	√	√
Beta-2-microglobulin (urine)		√	√	√	√
Plasma viral load (HIV-RNA)	√	√	√	√	√
Ultrasensitive viral load in plasma		√	√	√	√
Immunology[2]		√	√	√	√
Insulin		√			√
Vitamin D		√			√
DXA		√			√
Stored samples[3]		√			√
Validated Spanish PSQI		√			√
Morisky-Green test		√	√	√	√
Genotypic resistance test	In case of virological failure				
Adverse events		√	√	√	√

[1] including lipid profile (total cholesterol, HDL, LDL and TG), creatinine, glucose and vitamin D levels

[2] including CD4 and CD8

[3] stored plasma samples will be taken for the determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein). Stored cell samples will be taken for the determination of biomarkers of mononuclear activation SD-14 and SD-163 and immunology (CD38 and HLA-DR)

1. General Information

1.1 Trial identification

Title: A pilot 24-week open-label, randomized, controlled clinical trial to assess the safety, tolerability and efficacy of dual therapy with Raltegravir/Lamivudine combination when replacing standard combination therapy in HIV-infected patients with prolonged virological suppression. RALAM Study

Protocol code: RALAM

Version and date: version 1.0 dated 17 July 2014

EudraCT No.: 2014-003142-27

1.2 Identification of sponsor and monitor

Sponsor: Fundació Clinic per a la Recerca Biomédica – Fiscal Identity No.: G59319681
Dr. José Mª Gatell Artigas
Address: C/ Villarroel, 170
Town/City: Barcelona (Spain)
Zip Code: 08036

Monitor: [redacted]
CTU (Clinical Trials Unit)
Department of Clinical Pharmacology
Hospital Clínic C/Villarroel 170, 08036 Barcelona (Spain).
Phone: [redacted]
Fax: [redacted] E-mail: [redacted]

1.3 Identification of applicant

Applicant: [redacted]
Address: CTU (Clinical Trials Unit). Clinical Pharmacology
Hospital Clínic C/Villarroel 170, 08036 Barcelona (Spain).
Phone: [redacted]
Fax: [redacted] E-mail: [redacted]

1.4 Identification principal investigators of the participating sites

Dr. [redacted]z
Hospital Clínic
Villarroel, 170
08036 Barcelona
E-mail: [redacted]
Phone: [redacted]
Fax. [redacted]

1.5 Information on other departments involved

Clinical research ethics committees
The trial has been submitted for approval to the CREC of Hospital Clínic.

2. Rationale

Treatment of HIV infection typically consists of a combination of antiretroviral drugs. Normally, it is a combination of three drugs which are both inhibitors of nucleoside analogue reverse transcriptase and the third is a drug of another family. However, there have been treatment options with two drugs where one of them is usually a protease inhibitor boosted with low dose ritonavir; these dual patterns have shown similar efficacy to standard triple patterns not only in naive patients but in patients already treated with sustained suppression of viral replication as are the patients be targeted by the study RALAM. These dual patterns are contained in the "Recommendations for Antiretroviral Therapy GESIDA 2014". In real life, there are also patients treated with the monotherapy, which in this case are provided with an inhibitor boosted protease, but these patterns have a suboptimal efficacy and therefore patients on monotherapy are not considered candidates for RALAM study.

Effective antiretroviral therapy leads not only to undetectable plasma HIV-1 RNA, but to a decrease in the body HIV-1 burden. The longer virological suppression in HIV-infected patients, the more likely virological suppression will persist. This may be particularly evident in therapeutically suboptimal ritonavir-boosted protease (PI/r) monotherapy studies, in which initial PI/r monotherapy (Monark Study[1]) of HIV infection performed worst, induction-maintenance (613 Study[2], triple PI/r-based therapy followed by PI/r monotherapy) performed better, and simplification (OK Study[3], PI/r monotherapy in virologically suppressed patients) performed best out of these three possibilities.

We are guiding therapy of HIV infection based on studies in antiretroviral-naïve subjects. Triple therapy including two nucleoside reverse transcriptase inhibitors plus a third drug is the standard therapy for initial HIV infection. Follow-up of studies in antiretroviral-naïve patients is usually two years and very few up to five years. Many patients in our clinical units are virologically suppressed and virological suppression may have been lasting for years, as we saw in the SPIRAL study[4]. For these patients, triple antiretroviral therapy may not be needed. In fact, a subanalysis of SPIRAL[5] study looking back at patients with previous resistance failure and genotypic resistance tests available in their history database showed than a proportion of patients were on functional dual or even monotherapy both in the PI/r and raltegravir arm. A subanalysis of the BENCHMRK[6] study also suggested that some patients in the raltegravir arm had no other drugs active as shown by the genotypic sensitivity score.

Until now, regimens containing less than 3 drugs should have a PI/r included[7]. However, preliminary data[8] suggests that dual combinations of a non-nucleoside reverse transcriptase inhibitor such as etravirine or nevirapine plus raltegravir in virologically suppressed patients may maintain virological efficacy while improving tolerability[9]. In addition, the Latte study[10] has recently shown the capability of 744 (an integrase inhibitor) plus rilpivirine (a low genetic barrier non-nucleoside reverse transcriptase inhibitor) to maintain virological suppression after only 6 months induction therapy.

Lamivudine is probably the safest antiretroviral drug. It is now available as a generic drug, and therefore its cost is relatively low. It has shown potentially useful data when combined with a PI/r in

both naive and experienced HIV patients. Raltegravir is also a well-tolerated antiretroviral drug. Because a co-formulation of raltegravir plus lamivudine is already planned meaning that it will be available in the near future, it will represent a very convenient regimen (a BID single pill) that will prevent selective lack of adherence.

2.1 Name and description of the investigational drugs

Patients will be randomized 2:1 to:

1. Switch to MK0518B (Raltegravir/3TC) (50 patients)
2. Continue current treatment (25 patients)

The study treatment period will be 24 weeks.

The study medication MK0518B (Raltegravir/3TC) will be supplied by Merck for 24 weeks. After the study, MSD will provide MK0518B (RAL/3TC) until it is available commercially. If not possible, RAL/3TC will be switched to RAL + 3TC or any other antiretroviral regimen considered appropriate for the patient at the discretion of the investigator.

The rest of antiretroviral medication will be obtained through the standard prescription and dispensing route in which antiretroviral drugs are dispensed on an outpatient basis by the pharmacy service of the center.

Raltegravir/3TC (MK0518B)

Integrase inhibitor/nucleoside analogue reverse transcriptase inhibitor
Therapeutic group: JO5AE10
Manufacturing laboratory: MSD (Merck Sharp & Dohme)
The main characteristics of Raltegravir/3TC are detailed in the summary of product characteristics (see Appendix VIII: Summary of product characteristics of investigational products)

Raltegravir/3TC will be supplied by Merck as a fixed-dose combination for the whole duration of the study. The medication will be packed and labeled by Merck in accordance with European regulations.

2.2 Summary of known and potential risks and benefits

The potential risks of a clinical trial with drugs include the possible occurrence of adverse events attributable to the study drugs. However, this simplification study does not add a new drug but withdraws or not one of them from the current regimen, and therefore an increase in potential toxicity is not expected.

The risk of virological failure in patients with inclusion criteria similar to those in the study who are switched to dual therapy are subjected is actually very small, similar to that expected with triple standard combinations (references 8 y 9). In addition, virological monitoring in this study will be more frequent than in clinical practice and the results of HIV RNA measurements in plasma will be available one or two days after blood sampling.

The reduction in the number of drugs could be associated with improved tolerability and less toxicity, as well as improved treatment compliance, which could result in superior effectiveness.

2.3 Route of administration, dose, dosing regimen and treatment period

A randomization list will be generated with a computer program according to a 2:1 allocation scheme. The randomization procedure will result with a code that will allow the treatment of each patient (patient code) to be identified. Randomization will be performed using the electronic case report form for the study.

1. Study group : MK0518B (Raltegravir/3TC) (300mg/150mg) twice daily

   it will be administered orally in the 300/150 mg film-coated tablets according to instructions in the prescribing information.

2. Control group: All drug products included in the antiretroviral regimen will be part of the standard prescription and will be used according to the prescribing information.

The study treatment period will be 24 weeks.

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

The trial will be conducted in accordance with the principles of the Declaration of Helsinki, and according to applicable regulations (Royal Decree 223/2004). The study will not start until obtaining the favorable opinion of the reference CREC, authorization from the Spanish Agency for Medicinal Products and Medical Devices, and approval from the Management of the site.

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

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

2.5 Description of study population

The study will be conducted in HIV-1 infected patients with virological suppression.

A total of 75 patients will be included in the study, 50 in the study arm and 25 in the control arm.

2.6 References

1. Delfraissy JF, Flandre P, Delaugerre C et al. Lopinavir/ritonavir monotherapy or plus zidovudine and lamivudine in antiretroviral-naïve HIV-infected patients. AIDS 2008; 22: 385–93.
2. Cameron DW, da Silva BA, Arribas JR, Myers RA, Bellos NC, Gilmore N, et al. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. J Infect Dis 2008; 198: 234-240
3. Arribas JR, Pulido F, Delgado R, et al. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). J Acquir Immune Defic Syndr 2005; 40: 280-287
4. Martínez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS 2010; 24: 1697-1707
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6. Gatell JM, Katlama C, Grinsztejn B, et al. Long-term efficacy and safety of the HIV integrase inhibitor raltegravir in patients with limited treatment options in a phase II study. J Acquir Immune Defic Syndr 2009; 53(4):456-463
7. Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral Treatment of Adult HIV Infection2014 Recommendations of the International Antiviral Society–USA Panel. JAMA 2014; 312: 410-425
8. Reliquet V, Chirouze C, Allavena C, et al. Nevirapine-raltegravir combination, an NRTI and PI/r sparing regimen, as maintenance antiretroviral therapy in virologically suppressed HIV-1-infected patients. Antivir Ther 2014; 19:117-123
9. Monteiro P, Perez I, Laguno M, et al. Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study. J Antimicrob Chemother 2014; 69: 742-748
10. Margolis D, Brinson CC, Eron JJ, et al. 744 and rilpivirine as two-drug oral maintenance therapy: LAI116482 (LATTE) week 48 results. 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014). March 3–6, 2014. Boston. Abstract 91LB.

3. Objective and Purpose of the Trial

General objective:

A pilot 24-week open-label, randomized, controlled clinical trial to assess the safety, tolerability and efficacy of dual therapy with Raltegravir/Lamivudine combination when replacing standard combination therapy in HIV-infected patients with prolonged virological suppression.

Randomization:

1. to simplify to MK0518B (Raltegravir / 3TC) (50 patients)
2. to continue current treatment (25 patients)

Primary:

- efficacy in virological suppression assessed with standard plasma HIV-1 RNA detection (limit of detection 37 copies/mL).

Secondary:

- efficacy in virological suppression assessed with ultrasensitive HIV-1 RNA detection (limit of detection 1 copy/mL)
- changes in peripheral mononuclear blood cells HIV-1 reservoir
- changes in metabolic parameters including fasting plasma lipids and insulin resistance (HOMA-IR)
- changes in body fat composition and bone mineral density
- changes in plasma 25-OH vitamin D levels
- changes in estimated glomerular filtration rate (CKD-EPI) and urine beta-2-microglobulin
- changes in immune activation markers including CD38 and HLA-DR
- changes in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163)
- changes in sleep quality (Pittsburgh Sleep Quality Index)
- changes in adherence in both treatment arms (Morisky-Green Test)
- overall tolerability

4. Trial Design

4.1 Primary and secondary endpoints

Primary variable:

- The primary variable is the proportion of patients free of therapeutic failure at week 24. Therapeutic failure includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death.

  Virological failure is defined as two consecutive measurements of plasma viral load above 37 copies/ml (current detection limit in hospital lab) separated at least by 2 weeks during the assigned treatment, using the FDA snapshot method.

Secondary variables:

- Proportion of patients with viral load below 37copies/ml at 24 weeks
- Proportion of patients with viral load below ultrasensitive HIV-1 RNA detection limit (limit of detection 1 copy/mL) at 24 weeks
- Changes from baseline in peripheral mononuclear blood cells HIV-1 reservoir at 24 weeks
- Changes from baseline in metabolic parameters including fasting plasma lipids (cholesterol total, LDL, HDL and triglycerides) and insulin resistance (HOMA-IR) at 24 weeks
- Changes from baseline in body fat composition at 24 weeks
- Changes from baseline in lumbar and femoral bone mineral density at 24 weeks
- Changes from baseline in plasma 25-OH vitamin D levels at 24 weeks
- Changes from baseline in estimated glomerular filtration rate (CKD-EPI) and urine beta-2-microglobulin at 24 weeks
- Changes from baseline in immune activation markers including CD38 and HLA-DR at 24 weeks
- Changes from baseline in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163) at 24 weeks
- Changes from baseline in sleep quality (Pittsburgh Sleep Quality Index) at 24 weeks
- Incidence of adverse events in both treatment arms
- Proportion of patients discontinuing study treatment due to adverse events related to medication
- Proportion of patients with serious adverse events related to study medication
- Changes in treatment adherence during all the study duration (Morisky-Green test)

4.2 Type of design

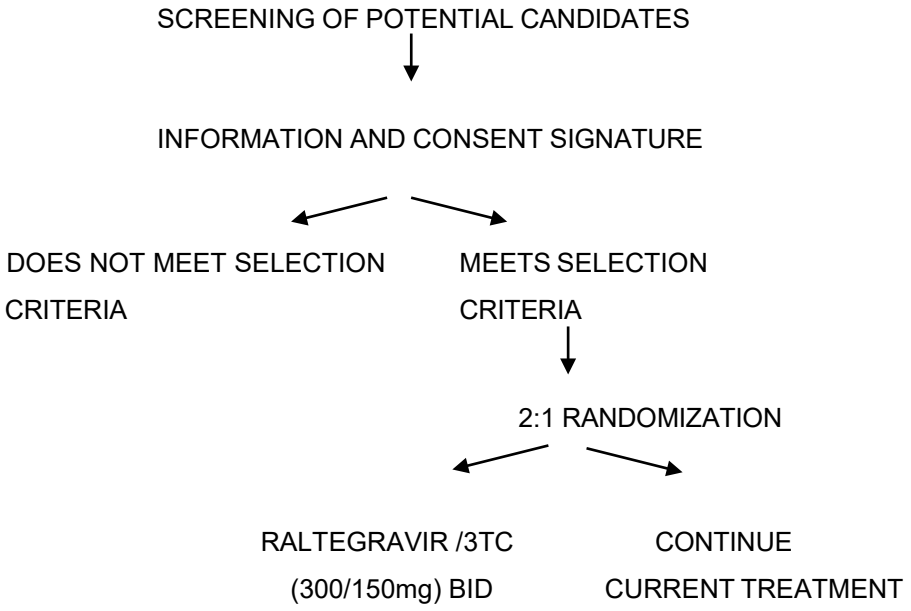
This is a single center, national, phase III, prospective, open-label, randomized, controlled, 24-week pilot study.

Eligible participants will be randomized (2:1) to one of the following arms:

1. to simplify to to switch to Raltegravir / 3TC (MK0518B) (50 patients)
2. to continue current treatment (25 patients)

The study treatment period will be 24 weeks.

A randomization list will be generated with a computer program according to a 2:1 allocation scheme. The randomization procedure will result with a code that will allow the treatment of each patient (patient code) to be identified. Randomization will be performed using the electronic case report form for the study.



Patients will attend the selection and randomization visit (baseline) and visits 4, 12 and 24 weeks.

A total of 75 patients will be included in the study, 50 in the study arm and 25 in the control arm.

4.3 Description of measures taken to minimize or prevent bias

A randomization list will be generated with a computer program according to a 2:1 allocation scheme. The randomization procedure will result with a code that will allow the treatment of each patient (patient code) to be identified. The same randomization procedure will result in the generation of a

code that will allow the treatment of each patient (patient code) to be identified. Randomization will be performed centralised at Coordinating Center (CTU).

4.4 Description of trial treatments

Patients will be randomized 2:1 to:

1. to simplify to Raltegravir / 3TC (MK0518B) 300/150mg BID
2. to continue current treatment

The study treatment period will be 24 weeks.

The study medication (Raltegravir/3TC) will be supplied by Merck as a fixed-dose combination for 24 weeks. The medication will be packed and labeled by Merck in accordance with European regulations.

After the study, MSD will provide RAL/3TC until it is available commercially. If not possible, RAL/3TC will be switched to RAL + 3TC or any other antiretroviral regimen considered appropriate for the patient at the discretion of the investigator

The study medication for the control group will be obtained through the standard prescription and dispensing route in which antiretroviral drugs are dispensed on an outpatient basis by the pharmacy department of the hospital. There are no plans to re-label the samples of this group. Patients will continue under the same treatment that they are already receiving.

The study will assure the traceability of samples by recording the lot number and expiry date of the antiretroviral drugs. In addition, treatment adherence will be assessed at each visit through Morisky-Green test.

4.5 Trial duration

The total duration of the study will be 24 weeks. The recruitment period will be 6 months followed by a follow-up period of 24 weeks.
End of study will coincide with the last follow-up visit of the last patient included in the study.

4.6 Criteria for termination and/or discontinuation

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

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

The DSMB will review the data if 4 episodes of treatment failure are detected, and then every 4 additional failures detected. The study will be interrupted as early as 5 episodes of virological failure in experiemental branch are detected (10%).

The DSMB will meet not when 8 cases of treatment failure but 4 patients occur. Treatment failure may be due to virological failure, but also for other reasons (discontinuation due to toxicity, loss to follow rupture of consent, etc).

4.7 Drug accountability

Drug accountability will not be performed.

4.8 Allocation participant identification codes

A randomization list will be generated with a computer program according to a 2:1. allocation scheme.

As this is an open-label study, unblinding of the randomization codes is not necessary.

The randomization procedure will result with a code that will allow the treatment of each patient (patient code) to be identified. The same randomization procedure will result in the generation of a code that will allow the treatment of each patient (patient code) to be identified

4.9 Source data identification

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

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

4.10 End of trial

End of trial will coincide with the date of the last follow-up visit of the last patient included in the study.

5. Subject Selection and Withdrawal

5.1 Subject inclusion criteria

1. Inclusion criteria

The study population will consist of 75 adults who meet the following selection criteria:

a. Eligible patients will be males or females at least 18 years of age. Women of childbearing potential must have a negative pregnancy test within 10 days prior to randomization into the study.

b. Patients seropositive for HIV-1 using standard diagnostic criteria.

c. Patients virologicaly suppressed during at least 12 months prior to inclusion (viral load <50 copies/mL).

d. Patients on combination antiretroviral therapy (at least 2 antiretroviral drugs) for at least 12 months before being randomized in this study.

e. Patients who are clinically stable in the opinion of the investigator at study entry (clinical status and chronic medication must not have not been modified at least 14 days prior to randomization).

f. Patients who have signed informed consent to participate in the study.

*Women of childbearing potential must agree to sexual abstinence or use of barrier contraceptive methods during the study.

5.2 Subject exclusion criteria

The study population must not meet the following exclusion criteria:

a. Pregnancy, lactation, or planned pregnancy during the study period.

b. Previous failure to an integrase inhibitor-containing regimen.

c. Previous failure to a 3TC or FTC-containing regimen.

d. Resistance mutations to 3TC or integrase inhibitor if any resistance test had been previously performed.

e. Any disease or history of disease which, in the opinion of the investigator, might confound the results of the study or pose additional risk to patient treatment.

f. Chronic hepatitis B.

g. Current therapy with RAL+3TC

5.3 Withdrawal criteria

Treatment discontinuation

If a clinical or laboratory adverse event requiring an interruption in the antiretroviral regimen occurs, all drugs may be stopped or one of the drugs may be discontinued selectively if there is a clear causal relationship to the event.

Discontinuation of therapy will be at the discretion of the investigator or the patient. If so, the reasons for discontinuing treatment will be recorded both in the medical records and the case report form and

patient follow-up will be continued. If the medication is discontinued permanently, the investigator will start the treatment judged appropriate in his opinion and maintain the planned follow-up according to the study.

Study withdrawal

The patient may discontinue study participation if he/she is unwilling or unable to meet the protocol requirements in terms of the visit schedule or if the patient or the investigator considers it best to end his/her participation in the study. All patients have the right to withdraw their consent at any time during the study without prejudice to them.

If a female participant becomes pregnant along study, she will discontinue the study, but will be asked for consent for the pregnancy and delivery follow up (Appendix III).

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

Should this prematurely terminated patient withdraw the study more than 2 months apart previous visit, a termination visit would need to be completed following w24 procedures as termination visit.

6. Subject Treatment

6.1 Treatment arms

Patients who meet all inclusion criteria and no exclusion criteria will be randomized to one of the two treatment arms:

1. to simplify to to switch to Raltegravir / 3TC (MK0518B) (50 patients)
2. to continue current treatment (25 patients)

The study treatment period will be 24 weeks.

6.2 Concomitant, rescue and nonpermitted medication

Concomitant medication

Any concomitant medication used during the study will be duly recorded in case report form for that purpose. The data to be recorded will be the name of the drug, dose, and date of dosing as well as the reason or indication for administration.

Rescue medication

Rescue medication will be at the investigator's discretion.

Nonpermitted medication

Investigational drugs.

Cytotoxic systemic chemotherapy.

Administration of the drugs formally contraindicated in the prescribing information of the investigational

6.3 Monitoring of compliance

Compliance will be monitored by the Morisky-Green test (Appendix IX).

7. Efficacy Assessment

7.1 Efficacy parameters

Primary endpoint

- The primary variable is the proportion of patients free of therapeutic failure at week 24. Therapeutic failure includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death.

  Virological failure is defined as two consecutive measurements of plasma viral load above 37 copies/ml (current detection limit in hospital lab) separated at least by 2 weeks during the assigned treatment, using the FDA snapshot method.

Secondary variables:

- Proportion of patients with viral load below 37copies/ml at 24 weeks
- Proportion of patients with viral load below ultrasensitive HIV-1 RNA detection limit (limit of detection 1 copy/mL) at 24 weeks

Screening visit

The visit will be performed within 2-4 weeks prior to study start.

At the screening visit, the principal investigator or designated collaborator will obtain written informed consent from each patient before tests and assessments specific to the protocol are started.

Demographic data, medical history, complete physical examination, and laboratory tests (including hematology, biochemistry and plasma viral load) will be obtained and assessed to confirm the eligibility of the patient.

Women of childbearing age will undergo a pregnancy rest (urine test) within 10 days prior to study start and will only be able to participate in the study if they obtain a negative result. If a female participant become pregnant along study, she will discontinue the study, but will be asked for consent for the pregnancy and delivery follow up (Appendix III).

Baseline visit (randomization)

During the randomization visit, the investigator will ensure that all subject selection procedures were performed and the results confirm that the patient is eligible for participation in the study.

After sign informed consent, eligible patients will be allocated to the study treatment according to the randomization list which will be by blocks. Randomization will be performed using the electronic case report form for the study.

During the visit, a complete physical exam, measurement of viral load, ultrasensible viral load, CD4 and CD8, a laboratory test (including hematology, biochemistry, lipid profile, glucose, creatinine, insulin and 25-OH vitamin D levels) and an urine sample (for the determination of Beta-2-microglobulin) will be obtained.

In addition, a DXA examination will be performed to determine body composition. Also the Morisky-Green test and PSQI will fulfilled by the patient (see Appendices IX and X).

Follow-up visits

Patients will return to the center in weeks 4, 12 and 24 of the study.

At each follow-up visit, a complete physical examination, measurement of viral load, ultrasensible viral load, CD4 and CD8 and laboratory tests (including hematology, biochemistry, lipid profile, and creatinine) will be performed.

Viral load controls will be made at baseline, 4, 12, and 24 weeks. This frequency of controls is greater than that corresponding to a stable patient with undetectable viral load (currently performed controls viral load every 6 months): However, control after 4 weeks is a reasonable practice and recommended in the "Antiretroviral Treatment recommendations 2014 GESIDA" for any patient changes medication in real life. Antiretroviral medication is dispensed with a frequency of 3 months or less, so that the control after 12 weeks, not constitute an additional visit (and therefore an additional expense) for the patient to participate in the study.

At each follow-up visit, tolerability of antiretroviral therapy and the presence of potential adverse events will be assessed.

At the visit in week 24 insulin and 25-OH vitamin D levels and urine sample (for the determination of Beta-2-microglobulin) will be obtained.

In addition, a DXA examination will be performed to determine body composition. Also the Morisky-Green test and PSQI will fulfilled by the patient (see Appendices IX and X).

Stored samples

During the baseline visit and week 24 visits, a plasma sample will be taken and stored frozen for determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein). In addition, a PBMC sample will be taken and stored frozen for determination of biomarkers of mononuclear activation SD-14 and SD-163 and immunology (CD38 and HLA-DR).

If a patient experiences a plasma viral load above 37 copies/mL, the patient will need to repeat the test within 2 weeks. If viral load remains above 37 copies/mL the patient will be considered a virological failure: Genotypic resistance tests will be done in this case.

The investigator will freely decide the most appropriate therapeutic option. Any change in antiretroviral therapy must be recorded in the case report form.

All patients will continue follow-up according to the protocol during 24 weeks as planned in the study timetable.

Table 1. Study timetable

WEEK	-2 / -4 Screening	0 Randomization	4	12	24
Clinical assessment	√	√	√	√	√
Physical examination	√	√	√	√	√
Informed consent	√				
Pregnancy test	√				
Hematology	√	√	√	√	√
Biochemistry[1]	√	√	√	√	√
Beta-2-microglobulin (urine)		√	√	√	√
Plasma viral load (HIV-RNA)	√	√	√	√	√
Ultrasensitive viral load in plasma		√	√	√	√
Immunology[2]		√	√	√	√
Insulin		√			√
Vitamin D		√			√
DXA		√			√
Stored samples[3]		√			√
Validated Spanish PSQI		√			√
Morisky-Green test		√	√	√	√
Genotypic resistance test	In case of virological failure				
Adverse events		√	√	√	√

[1] including lipid profile (total cholesterol, HDL, LDL and TG), creatinine, glucose and vitamin D levels

[2] including CD4 and CD8

[3] stored plasma samples will be taken for the determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein). Stored cell samples will be taken for the determination of biomarkers of mononuclear activation SD-14 and SD-163 and immunology (CD38 and HLA-DR)

7.2 Assessment of efficacy parameters

- Blood tests will be performed for the determination of viral load, ultrasensible viral load, CD4 and CD8.
- The laboratory test will be performed during the screening and baseline and visits in week 4, 12, and 24.
- Resistance determination in patients with virological failure.

8. Safety Assessment

8.1 Safety parameters

The investigator is responsible for detecting and documenting any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE) per this protocol.

8.2 Assessment of safety parameters

During the conduct of the study, the presence of adverse events, whether or nonserious, will be verified according to the adverse event definitions given in this section of the protocol.

Minimum information

Definitions:

An **adverse event (AE)** is any untoward occurrence to the health of a patient or clinical trial subject treated with a medicinal product and which does not necessarily have a causal relationship with this treatment.

It may be a new concomitant disease, a worsening of a concomitant disease, an injury, or any concomitant deterioration in the patient's health status, including laboratory values, regardless of etiology. Any medical condition that was present before the study treatment and that remains unchanged or improves should not be considered or recorded as an AE. A worsening of that medical condition will be considered as an AE.

An **adverse reaction (AR)** is any noxious and unintended reaction to an investigational drug, regardless of the dose administered.

A **serious adverse event (SAE)** is any adverse event that, at any dose, results in death, is life-threatening, requires or prolongs hospitalization of the subject, causes persistent or significant disability or incapacity, or gives rise to a congenital anomaly or birth defect. Life-threatening is defined as the situation in which, in the opinion of physician, the patient would have died if it had not been for a timely therapeutic intervention.

For reporting purposes, any suspected adverse events considered medically important will be classified as serious even if they do not meet the above criteria.

Medically important events are defined as those events that may not be immediately life-threatening or cause death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias or convulsions not requiring hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be used to decide if other situations that have resulted in one of the outcomes listed in the above definitions should be reported as a SAE.

Hospitalization or prolongation of an existing hospitalization are a criterion for considering that an AE is serious. Only admission when the patient stays overnight in the hospital should be considered hospitalization. The following situations do not meet the criteria for a SAE:

- if hospitalization or prolongation of hospitalization is required for completing a procedure required by the protocol (for instance day or night visits are performed for biopsies or surgery required by the protocol).

- if hospitalization or prolongation of hospitalization is part of the routine procedure at the site (such as withdrawal of a stent after surgery)

- if hospitalization was scheduled prior to patient entry in the study

- if hospitalization was scheduled for a preexisting condition that has not worsened

An **unexpected adverse reaction (UAR)** is defined as any adverse reaction whose nature or severity is not consistent with product information (e.g., Investigator's Brochure for an unapproved investigational drug or the summary of product characteristics for an approved medicinal product).

A **suspected unexpected serious adverse reaction (SUSAR)** is an adverse reaction that is both serious and unexpected.

Attributability criteria

The causal relationship of the investigational product to the occurrence of the AE/SAE will be established based on a clinical judgment. For this, other causes will be considered and studied, such as the natural history of underlying diseases, concomitant treatment, other risk factors, and temporal relationship of the event to the investigational product. In addition, the summary of product characteristics of the products will be reviewed.

To analyze the possible cause-effect relationship, the temporal relationship between drug administration and the AE, possible alternative explanations, the outcome (complete remission, partial recovery, death, sequelae, persistence), persistence or not after discontinuation of the study drug,

recurrence on drug rechallenge, or previous knowledge of the event consistent with the known or expected pattern of response to the study drug will be considered.

The causal relationship of an AE to the study drug will be described according to the following definitions:

Unlikely related: The adverse event does not occur after a plausible temporal sequence from administration of the study product and/or can be reasonably explained by other factors such as the patient's clinical state, toxic or environmental factors, or other concomitant therapies. In addition, it does not follow the known or expected pattern of response to the drug.

Possible relationship: The adverse event occurs after a plausible temporal sequence from administration of the study product, but can also be explained by the patient's clinical state, toxic or environmental factors, or other concomitant therapies. In addition, it does not follow the known or expected pattern of response to the drug.

Probable relationship: The adverse event occurs after a plausible temporal sequence from administration of the study product, cannot be reasonably explained by the patient's clinical state, toxic or environmental factors, or other concomitant therapies, and after withdrawal or dose reduction of the suspect drug, the event follows a logical clinical sequence. In addition, it follows the known or expected pattern of response to the drug.

Clear relationship: The adverse event occurs after a plausible temporal sequence from administration of study product, cannot be reasonably explained by the patient's clinical state, toxic or environmental factors or other concomitant therapies, after withdrawal or dose reduction of the suspect drug, the event follows a logical clinical sequence, and the adverse event recurs after reintroduction of the suspect drug. In addition, it follows the known or expected pattern of response to the drug.

No relationship: The adverse event is clearly due to causes unrelated to the study drug, and the criteria for another causal relationship are not met.

Nonassessable relationship: Any report suggesting an adverse effect which cannot be judged because the information is insufficient or contradictory, and which cannot be supplemented or verified.

8.3 Adverse event detection and recording

AEs will be recorded at each visit based on careful clinical observation of the patient, laboratory tests, spontaneous reports by the patient and also by open-ended questioning by the investigator.

All AEs (serious or not) occurring during the study must be noted in the medical history and recorded in the CRF. The investigator will also decide whether the adverse event is, based on his/her judgment, related or not to the study drug—this decision should also be noted in the medical history and CRF.

At each visit, all AEs experienced by the patient since the previous visit should be recorded in the specific adverse event form of the CRF.

The following will be recorded for each event: description, severity (grade 1, 2, 3, 4 and 5), duration (start and end dates), causal relationship with the drug (according to the previously attributability

criteria) and study drug(s) for which this causal relationship is suspected, need for treatment (if applicable) or the actions taken, possible alternative explanations, predisposing factors, and outcome. For a preexisting AE that has worsened in terms of severity or frequency, the meaning of the change should be specified.

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

The severity of an AE will be rated based on the Division of AIDS toxicity table (AppendixVII)

8.3.1 Procedures for expedited reporting of serious adverse events by the investigator

The principal investigator will report immediately to the Coordinating Center (CTU Clinic: telephone 93 227 5400 ext 4386, fax 93 227 9877, e-mail jcamacho@clinic.ub.es) all serious adverse events regardless of their degree of causal relationship with the study drug. All SAEs occurring from signing of informed consent and up to 30 days after receiving the last dose of the study drug should be reported. The initial report of SAE should be written and as complete as possible including details of the current disease and SAE and assessment of the causal relationship between the AE and the investigational product. Reporting will be made using the Serious Adverse Event Report Form included in Appendix V of this protocol within 24 hours from first knowledge by the investigator, completing all information on the form in the following two days.

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

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

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

In the event of death, the investigator must provide the sponsor and/or Coordinating Center, the Ethics Committee, and the relevant regulatory authorities with all additional information requested by them.

8.3.2 Procedures for expedited reporting of serious and unexpected adverse reactions by the sponsor

The study sponsor will report any events that are serious and unexpected that may be related to the investigational products (i.e., suspected unexpected serious adverse reactions, SUSARs) to the Spanish Regulatory Agency, the competent bodies of the Autonomous Communities involved (the communities in whose territory the trial is being conducted) and to the EC involved (EC of the site where the SUSAR occurred).

Reporting will be made using Suspected Adverse Reaction Report Form.

The maximum deadline for reporting will be 15 calendar days from the time the sponsor is aware of the SUSAR. For SUSARs causing death or that are life-threatening for the subject, the maximum reporting time will be 7 calendar days from the time the sponsor is aware of them. This information will be completed, when possible, in the following 8 days (Appendix VI).

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

The Coordinating Center will keep a record of all AEs reported by investigators. These records will be submitted to the Spanish Regulatory Agency when requested.

8.4 Follow-up of adverse events

The investigator must also follow up SAEs and similarly report information related to the event until it has subsided, returned to baseline, can be attributed to products other than the study medication or to factors unrelated to conduct of the study, it is unlikely to obtain additional information, or in case of permanent impairment, until the condition stabilizes.

Although not considered an adverse event, it is the responsibility of the investigator and his/her coinvestigators to report immediately any pregnancy or suspected pregnancy (including positive pregnancy tests) occurring during the study or within 28 days after the end of the study.

9. Statistics

9.1 Methods

The baseline patients' characteristics of the ITT population will be described. Continuous variables will be described by their means, standard deviations,medians, Interquartile ranges, minimums and maximums. Categorical variables, figures and percentages per class will be presented per arm.

The primary analysis will be done when all patients have reached 24 weeks. Analysis of the primary endpoint will be performed on both ITT and per protocol populations. The 95% two sided confidence interval of the of the difference in percentage of patients in therapeutic success (RAL/3TC – Current regimen) will be calculated.

The percentage and absolute changes in continuous variables between week 4, 12 and 24 versus baseline will be compared between arms in the ITT population (LOCF of other imputation method to be defined in the statistical analysis plan) using a two-sided non parametric Mann WhitneyTest.

The categorical endpoints will be compared using Fisher's exact test or chi-squared test.

Two sided p-values will be reported. The level of significance will be tested at 0.05.

DSMB will review the data if 4 episodes of treatment failure are detected and subsequently every 4 new episodes of treatment failure. Study will be interrupted as soon as 5 episodes (10%) of confirmed virological failure are detected in the experimental arm.

9.2 Sample size

A total of 75 patients will be included in the study with a randomization 2:1 (RAL/3TC and Current treatment).

This study is not a noninferiority study, in which case the delta should be -15% or less. It is a pilot study which tries to see the feasibility of the pattern and to generate data with which to design a larger study with a noninferiority design. However, there are security measures in the primary end-point is the virologic efficacy. The DSMB will review the data if 4 episodes of treatment failure are detected, and then every 4 additional failures detected. The study will be interrupted as early as 5 episodes of virological failure in experiemental branch are detected (10%).

This pilot study is exploratory, and must serve to see whether it is feasible, if the results are good enough, to make a large-scale study.

9.3 Statistical significance and adjustments for multiplicity

In all cases, all tests will be performed with a two-sided type I error of 5%. For the primary endpoint, adjustment is not necessary to preserve the type I error.

9.4 Criteria for discontinuation

The study will be completed when these two premises are met:

- Inclusion of the number of patients needed for the sample size in each randomized group

- End of clinical monitoring

No interim analyses are planned.

9.5 Management of missing data

In case of missing values, the Last Observation Carried forward (LOCF) method will be used.

9.6 Deviations from statistical plan

A statistical analysis plan will be prepared during the course of the study and before closing the database and unblinding which will describe in detail the statistical methods to be used, the approach to be followed in case of missing values and the tables and charts to be included in the statistical report. In addition, a data blind review will be made to define the subjects who will enter each study population.

Any deviation from the original statistical plan must be reported and justified in the final report, if necessary.

9.7 Analysis population

Study analysis will be performed in the per protocol population (PP). In addition the primary endpoint will also be assessed in the intent-to-treat population (ITT), including all randomized subjects who have been administered study medication.

10. Direct Access to Source Data/Documents

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

11. Ethics

General considerations

The clinical trial will be conducted in accordance with the principles contained in the Declaration of Helsinki, and according to applicable regulations (Royal Decree 223/2004) and will be started once approval is obtained from the reference CREC, authorization from the Spanish Agency for Medicinal Products and Medical Devices, and approval by the Director of the Institution.

The investigator agrees to comply with the rules set forth in the applicable clinical trial regulations: Medicines Act 29/2006 (Official State Journal No. 178, 27-07-06) and Royal Decree 223/2004 on Clinical Trials.

Subject information

Patients will be informed verbally and in writing and all relevant information will be reported to the participants adapted to their level of understanding.

(See Appendix II: Patient Information Sheet and Patient Informed Consent)

Confidentiality

Patient will be informed that their participation in the trial will be treated with the same confidentiality as their clinical documentation, but, if necessary, a member of the site Ethics Committee, an inspector designated by the health authorities, or the clinical trial monitor may have access to those records.

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

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

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

Duly authorized persons by the sponsor and the health authorities and the Clinical Research Ethics Committee may audit or inspect the trial. Personal information will not be publicly available, in compliance with Organic Act 15/1999, of 13 December, on Personal Data Protection.

Participants may exercise their right to processing, reporting, and transfer of the personal data pursuant to Organic Act 15/1999, of 13 December (Spanish Royal Decree 1720/2007, of 21 December), on Personal Data Protection. According to the above law, patients can exercise their rights to data access, rectification, opposition, and cancellation, for which they must contact the study doctor.

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

12. Data Management and Record Retention

The processing, reporting, and transfer of personal data from all participating subjects will comply with the provisions in Organic Act 15/1999, of December 13 (Spanish Royal Decree 1720/2007, of 21 December), on Personal Data Protection.

According to this regulation, all data collected in the case report form should be verifiable against the source documents. In addition, the sponsoring investigator will have a file that will contain all case report forms, data correction forms, templates, source documents, monitoring records and visit scheduling, regulatory filings (e.g. signed protocol, amendments, correspondence with Ethics Committee, approval, approved version of patient information sheet, signed patient consents, investigator agreement, regulatory agency authorization, etc.). These files must be kept as established by regulations.

13. Funding and Insurance

The study was financed by a grant provided by Merck.

In accordance with Royal Decree 223/2004, the sponsor has taken out civil liability insurance for this study (see Appendix XII).

14. Publication Policy

The investigators, in agreement with the Coordinating Center for the study, will publish the results of the trial in internationally indexed journals. Authorship will take into account members of the study management, participating investigators and persons responsible for coordination, data analysis and article writing.