CLINICAL TRIAL PROTOCOL WITH MEDICINAL PRODUCTS

Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD) : Roll-over study of the RALAM clinical trial (NCT02284035)

Protocol code: RALAM-Roll Over

Version and date: version 1.2 dated 04 Mayo 2017

EudraCT No.: 2017-000986-60

NCT Number: NCT03311945

Sponsor: Fundació Clinic per a la Recerca Biomédica

Principal Investigator: [redacted]

Abbreviations

3TC	Lamivudine
AE	Adverse event
AR	Adverse reaction
CREC	Clinical Research Ethics Committee
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CTU	Clinical Trials Unit
DSMB	Data and Safety Monitoring Board
DXA	Dual energy X-ray absorptiometry
HDL	High-density lipoprotein
HLA-DR	Human Leukocyte Antigen - antigen D Related
HOMA-IR	Insulin resistance index
IL-6	Interleukin-6
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LOCF	Last-Observation-Carried-Forward
PBMC	Peripheral mononuclear blood cells
PSQI	Pittsburgh Sleep Quality Index
QD	Once a day
QoL	Quality of Life
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TG	Triglyceride
UAR	Unexpected adverse reaction
ULN	Upper limit of normal
VL	Viral load

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PROTOCOL SYNOPSIS

TITLE: Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD) : Roll-over study of the RALAM clinical trial (NCT02284035)

SITES: National single center study: Hospital Clínic de Barcelona

Clinical phase: Phase IIIb

HYPOTHESIS: Patients from RALAM study who have been under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) for at least 24 weeks will be able to maintain sustained virological efficacy and to have good overall tolerability (more specifically reflected on metabolic parameters, body composition, renal function, sleep quality and QoL) for at least 48 weeks after switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD)

OBJECTIVES:

PRIMARY:

- efficacy assessed with standard plasma HIV-1 RNA detection (limit of detection 50 copies/mL) at 48 weeks

SECONDARY:

- efficacy assessed with standard plasma HIV-1 RNA detection (limit of detection 50 copies/mL) at 24 weeks
- efficacy assessed with ultrasensitive HIV-1 RNA detection (limit of detection 1 copy/mL) at 48 weeks
- change in peripheral mononuclear blood cells HIV-1 reservoir at 48 weeks
- changes in metabolic parameters including fasting plasma lipids and insulin resistance (HOMA-IR) at 24 and 48 weeks
- change in body fat distribution at 48 weeks
- change in lumbar and femoral bone mineral density at 48 weeks
- change in plasma 25-OH vitamin D levels at 48 weeks
- change in estimated glomerular filtration rate (CKD-EPI), urine protein/creatinine ratio and urine beta-2-microglobulin at 48 weeks
- changes in immune activation markers including CD38 and HLA-DR at 48 weeks

- changes in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163) at 48 weeks
- change in sleep quality (Pittsburgh Sleep Quality Index) at 48 weeks
- change in quality of life (QoL) at 48 weeks
- overall tolerability at 48 weeks

STUDY DESIGN AND DURATION: Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD): Roll-over study of the RALAM clinical trial (NCT02284035)

The study treatment period will be 48 weeks.
SAMPLE SIZE: A total of 50 patients, 18 years or older, will be included in the study.

TREATMENTS, DOSE, POSOLOGY:

Raltegravir + 3TC

DOSE: RAL + 3TC (1200mg+300mg)

POSOLOGY: QD 2 pills 600 mg Raltegravir and 1 pill 300 mg Lamivudine

EFFICACY MEASUREMENTS: Plasma viral load (HIV-RNA) will be measured at weeks 0, 24 and 48.

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

DATA ANALYSIS: All 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 fulfil the inclusion/exclusion criteria or withdrawing from the study or discontinuing study treatment for reasons other than virological failure or adverse event.

STATICAL METHODS: The primary variable, therapeutic failure at week 48, includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death. It will be analysed also at 24 weeks.

Virological failure is defined as two consecutive measurements of plasma viral load above 50 copies/ml separated at least by 2 weeks during the assigned treatment, using the FDA snapshot method. It will be assessed at 24 and 48 weeks.

The following items will be described and compared between arms at each post baseline time point as well as the change versus baseline values in:

- Laboratory parameters including CD4 cells, hematology, lipid profile, creatinine (and estimated glomerular filtration rate, CKD-EPI), urinary protein/creatinin, and vitamin D levels
- Body fat distribution
- Spine/femur bone mineral density

- QoL (EQ-5D-5L)
- Biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation SD-14 and SD-163
- HIV Reservoir

Descriptive analyses will be performed for those treatment-emergent adverse events (that means starting after baseline visit), for the possibly or probably related to the study drug treatment-emergent adverse events and for serious adverse event. A table will be performed with the proportion of patients reporting at least one adverse event described previously.

SAMPLE SIZE: RALAM switch arm has included 50 patients. We expect that at least 90% of the patients (n=45) will accept participating into this roll-over study with a maximum of 50 patients.

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.

STUDY TIMETABLE

WEEK	0 Baseline	24	48
Clinical assessment	√	√	√
Physical examination	√	√	√
Informed consent	√		
Pregnancy test	√		
Hematology	√	√	√
Biochemistry[1]	√	√	√
Plasma viral load (HIV-RNA)	√	√	√
Ultrasensitive viral load in plasma	√		√
HIV-1 reservoir in peripheral mononuclear blood cells	√		√
Immunology[2]	√		√
QoL (EQ-5D-5L Spanish)	√		√
DXA	√		√
Stored samples[3]	√		√
Adverse events	√	√	√

1 including lipid profile (total cholesterol, HDL, LDL and TG), creatinine (and estimated glomerular filtration rate, CKD-EPI), urine protein/creatinine ratio and beta-2-microglobulin, and 25OH vitamin D levels

2 including CD4, CD38 and HLA-DR

3 stored samples will be taken for potential future determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation SD-14 and SD-163 and reservoirs

Patients will end the roll-over study when the new formulation of Raltegravir QD will be commercially available in Spain (expected November 2017)

General Information

Trial identification

Title: Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD) : Roll-over study of the RALAM clinical trial (NCT02284035)

Protocol code: RALAM-Roll Over

Version and date: version 1.2 dated 04 May 2017

EudraCT No.: 2017-000986-60

Identification of sponsor and monitor

Sponsor: Fundació Clinic per a la Recerca Biomédica – Fiscal Identity No.: G59319681
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: dgarcia@clinic.cat

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]

Identification principal investigators of the participating sites

Dr. [redacted]

Hospital Clínic

Villarroel, 170

08036 Barcelona

E-mail: [redacted]

Phone: [redacted]

Fax. +34 93 451 55 38

Information on other departments involved

Clinical research ethics committees

The trial has been submitted for approval to the Clinical Research Ethics Committee (CREC) of Hospital Clínic.

No patient association has been involved in the design of the study.

Low-intervention clinical trial

It is considered a low-intervention clinical trial because fulfills all the following conditions:

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

(b) according to the protocol of the clinical trial,

(i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or

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

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

Rationale

Antiretroviral drugs have improved over time, becoming more effective, simpler and better tolerated. However, for some patients current ART may still be challenging. Patients living longer with HIV infection may develop comorbidities as they get older that may be negatively influenced by some antiretrovirals (e.g. cardiovascular ischemic events with abacavir, bone fractures with tenofovir, etc) and these comorbidities require them to take additional medications that may increase the risk of significant interactions with some antiretrovirals (mainly, ritonavir and cobicistat boosters with many agents metabolized through cytochrome P450, but also rilpivirine with omeprazole or dolutegravir with metformin, among others). Despite better tolerability, some patients may experience direct toxicities with contemporary antiretrovirals (e.g. digestive and metabolic with boosted protease inhibitors, renal and bone with tenofovir, etc.). Standard antiretroviral therapy contains three drugs, but decreasing the number of antiretrovirals represents a strategy aimed to avoid the negative impact of drug exposure.

RALAM-Roll Over study is a phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD) : Roll-over study of the RALAM clinical trial (NCT02284035)

RALAM study was a 24-week open-label randomized study in which virologically suppressed HIV-infected patients under combination antiretroviral therapy were switched to Dutrebis® (fixed-dose combination of 3TC/Raltegravir) (switch arm, n=50) or maintained under the same therapy (control arm, n=25). The trial ended the 28th of February 2017. As Dutrebis® is not clinically available, patients from the switch arm after completion of the 24 weeks have been offered to keep the same regimen in the commercially available forms of 3TC 150 mg BID plus Raltegravir 400 mg BID.

By March 2017, all patients of the RALAM patients have finished the 24 weeks of the trial follow-up. There have been no virological failures in the switch arm, while there has been 1 virological failure in the control arm. All patients in the switch arm have remained virologically suppressed and have not had any major adverse effects. Patients in the switch arm have been offered to maintain the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) and all of them have accepted which allows for a unique cohort of patients on dual therapy with 3TC plus Raltegravir.

A new, more convenient formulation of Raltegravir QD has become available. Raltegravir QD development has been exclusively focused to antiretroviral-naïve patients. Therefore, it will be of paramount importance to have data of the new Raltegravir QD formulation in antiretroviral-experienced patients. Because of the uniqueness of the RALAM study arm cohort, this will be an excellent opportunity to have preliminary data on efficacy, tolerability, and satisfaction of the new Raltegravir QD as well as longer follow-up data on the dual therapy strategy.

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Objective and Purpose of the Trial

General objective:

Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD): Roll-over study of the RALAM clinical trial (NCT02284035)

Primary objective:

- efficacy assessed with standard plasma HIV-1 RNA detection (limit of detection 50 copies/mL) at 48 weeks

Secondary objectives:

- Efficacy assessed with ultrasensitive HIV-1 RNA detection (limit of detection 1 copy/mL) at 48 weeks
- Change in peripheral mononuclear blood cells HIV-1 reservoir at 48 weeks
- Changes in metabolic parameters including fasting plasma lipids and insulin resistance (HOMA-IR) at 48 weeks
- Change in body fat distribution at 48 weeks
- Change in lumbar and femoral bone mineral density at 48 weeks
- Change in plasma 25-OH vitamin D levels at 48 weeks
- Change in estimated glomerular filtration rate (CKD-EPI), urine protein/creatinine ratio and urine beta-2-microglobulin at 48 weeks
- Changes in immune activation markers including CD38 and HLA-DR at 48 weeks
- Changes in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163) at 48 weeks
- Change in sleep quality (Pittsburgh Sleep Quality Index) at 48 weeks
- Change in quality of life (QoL) at 48 weeks
- Overall tolerability at 48 weeks

Trial Design

Primary and secondary endpoints

Primary variable:

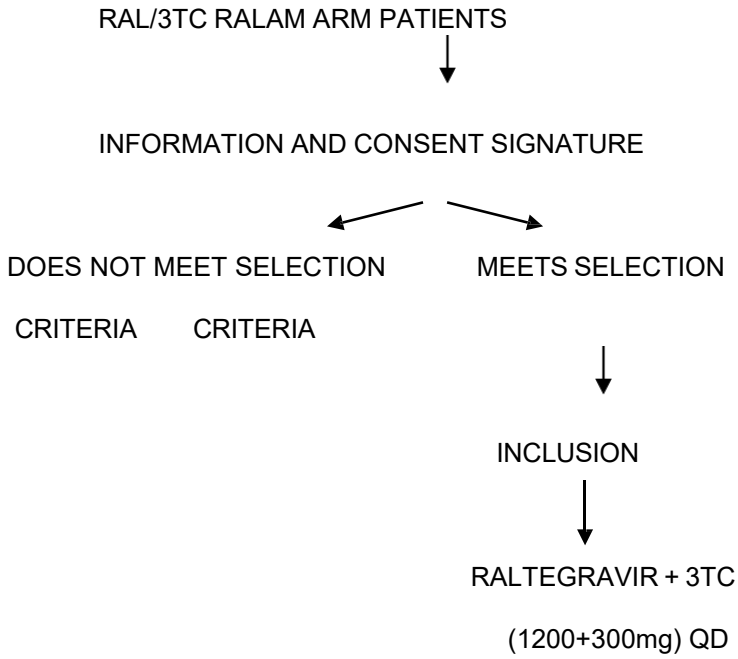
therapeutic failure at week 48, includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death Secondary variables:

- Therapeutic failure at week 24, includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death
- Proportion of patients with viral load below ultrasensitive HIV-1 RNA detection limit (limit of detection 1 copy/mL) at 48 weeks
- Change from baseline in peripheral mononuclear blood cells HIV-1 reservoir to week 48
- Changes from baseline in metabolic parameters including fasting plasma lipids (cholesterol total, LDL, HDL and triglycerides) and insulin resistance (HOMA-IR) at 24 and 48 weeks
- Change from baseline in lumbar and femoral bone mineral density to week 48
- Change from baseline in plasma 25-OH vitamin D levels to week 48
- Change from baseline in estimated glomerular filtration rate (CKD-EPI), urine protein/creatinine ratio and urine beta-2-microglobulin to week 48
- Changes from baseline in biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation (SD-14, SD-163) at 48 weeks
- Changes from baseline in sleep quality (Pittsburgh Sleep Quality Index) at 48 weeks
- Change from baseline in quality of life (QoL) at 48 weeks
- Incidence of adverse events

Type of design

Phase 3b, single arm, single site simplification study of HIV-1 infected patients with virological suppression under the combination of 3TC (150 mg BID) plus Raltegravir (400 mg BID) switching to 3TC (300 mg QD) plus Raltegravir (1200 mg QD): Roll-over study of the RALAM clinical trial (NCT02284035)

The study treatment period will be 48 weeks.



Patients will attend the selection/baseline visit and visits 24 and 48 weeks.

A maximum of 50 patients will be included in the study.

Description of trial treatments

The study treatment period will be 48 weeks.

Raltegravir will be supplied by Merck as a fixed-dose combination for 48 weeks. The medication will be packed and labeled by Merck in accordance with European regulations.

After the study, MSD will provide raltegravir 600 mg until it is available commercially.

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.

Trial duration

The total duration of the study will be 48 weeks. The recruitment period will be 6 months followed by a follow-up period of 48 weeks.

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

It is expected to begin the recruitment in July of 2017 and end the study 18 months later at December of 2018.

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.

A Data Safety Monitoring Board (DSMB) will review the data if 4 episodes of treatment failure are detected andsubsequently every 4 new episodes of treatment failure. Study will be interrupted as soon as 5 episodes (10%) of confirmed virological failure are detected

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, patients questionnaires, hospital reports, patient progress notes, 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.

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.

Measures taken to minimize bias

No other measures are taken to minimize the bias than described before.

Subject Selection and Withdrawal

Description of study population

The study will be conducted in the RAL+3TC arm patients

Subject inclusion criteria

The study population will consist of a maximum of 50 adults who meet the following selection criteria:

a. Patients in the switch arm who have completed the 24-week follow-up of RALAM (NCT02284035) study and remain virologically suppressed (viral load <50 copies/mL) on dual therapy with 3TC plus Raltegravir

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

Subject exclusion criteria

The study population must not meet the following exclusion criteria:

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

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

c. Hepatitis B co-infection

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 w48 procedures as termination visit.

Subject Treatment

Treatment arms

Patients who meet all inclusion criteria and no exclutsion criteria will be included to the study and will begin the study treatment:

- to simplify to switch to Raltegravir + 3TC (50 patients)

The study treatment period will be 48 weeks.

Name and description of the investigational drugs

DOSE: RAL+3TC (1200mg+300mg)

POSOLOGY: QD 2 pills 600 mg Raltegravir and 1 pill 300 mg Lamivudine (3TC)

The study medication Raltegravir 600 mg will be supplied by Merck for 48 weeks.

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

Integrase inhibitor

Therapeutic group: J05AX08

Manufacturing laboratory: MSD (Merck Sharp & Dohme)

The main characteristics of Raltegravir are detailed in the investigator brochure (see Appendix VIII: Summary of product characteristics of investigational products)

Lamivudine

Nucleoside reverse transcriptase inhibitor

Therapeutic group: J05AF05

Manufacturing laboratory: ViiV Healthcare

The main characteristics of Lamivudine are detailed in the Summary of product characteristics of investigational products (see Appendix VIII: Summary of product characteristics of investigational products)

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.

Route of administration, dose, dosing regimen and treatment period

It is a single arm study:

(Raltegravir+3TC) (1200 mg+300mg) <u>one daily</u>

it will be administered orally two 600 mg film-coated tablets of Raltegravir and one 300 mg film-coated tablet of Lamivudine according to instructions in the prescribing information.

The study treatment period will be 48 weeks.

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.

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

Monitoring of compliance

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

Drug accountability

Drug accountability will not be performed.

Drug traceability

The raltegravir will be stored at the clinical trials pharmacy of Hospital Clínic, the pharmacy will maintain a record of the storage times and conditions, the supply of the raltegravir of the patients, and file the receipt of the raltegravir. At the end of the study the it will be filed a record of the destruction of raltegravir.

The investigator team will ask the patients to inform them about the batch number and expiration date of the Lamivudine taken during the study in order to maintin the drug traceability

Efficacy Assessment

Selection/baseline visit

For patient's convenience, selection and baseline will be done in the same visit. The visit will be performed at Week 0.

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

Women of childbearing age will undergo a pregnancy rest (urine test) and will only be able to participate in the study if they obtain a negative result.

During the visit, a complete physical exam will be performed, and adequate samples for measurement of viral load, ultrasensible viral load, HIV-1 reservoir in peripheral mononuclear blood cells, CD4 cells, HLA-DR and CD38 cells and laboratory tests (including hematology, biochemistry, lipid profile, creatinine (and estimated glomerular filtration rate, CKD-EPI), urine protein/creatinin ratio and beta-2-microglobulin, and vitamin D levels) will be taken.

In addition, the following tests will be done:

1. DXA examination to determine body composition and spine/femur bone density.
2. Pittsburgh Sleep Quality Index to assess sleep quality
3. Quality of Life assessment through EQ-5D-5L (http://www.euroqol.org/eq-5d-products/eq-5d-5l.html)

During the baseline visit, a plasma sample will be taken and stored frozen for potential future determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein), biomarkers of mononuclear activation SD-14 and SD-163, and reservoirs.

Follow-up visits

Patients will return to the center at weeks 24 and 48 of the study.

At each follow-up visit, a complete physical examination and laboratory tests (including plasma HIV RNA, CD4 cells, hematology, biochemistry, lipid profile, creatinine (and estimated glomerular filtration rate, CKD-EPI), urine protein/creatinin ratio and beta-2-microglobulin, and vitamin D levels) will be performed. Also, at each follow-up visit, tolerability of antiretroviral therapy and the presence of potential adverse events will be assessed.

At the 48-week visit, measurement of ultrasensible viral load, HIV-1 reservoir in peripheral mononuclear blood cells, HLA-DR and CD38 cells will be also performed. In addition, DXA examination to determine body composition and spine/femur bone density, Pittsburgh Sleep Quality Index to assess sleep quality, and Quality of Life assessment through EQ-5D-5L will be also performed. Futhermore, a plasma sample will be taken and stored frozen for determination of

biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation SD-14 and SD-163.

If a patient has a result of a plasma viral load above 50 copies/mL, the patient will return to the center to repeat the test within 2 weeks. If viral load remains above 50 copies/mL the patient will be considered to have had a virological failure and a plasma sample will be collected for genotyping resistance test.

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 48 weeks foreseen in the study timetable.

The clinical trial will be conducted in accordance with the principles contained in the Declaration of Helsinki, ICH/GCP Guidelines, and according to applicable regulations (EU Clinical Trial Directive and Royal Decree 223/2004) and local regulations. The study will be started once approval from the reference EC, authorization from the Spanish Regulatory Agency, and approval by the Director of each participating Institution are obtained.

Stored samples

During the baseline visit and week 48 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 50 copies/mL, the patient will need to repeat the test within 2 weeks. If viral load remains above 50 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 48 weeks as planned in the study timetable.

STUDY TIMETABLE

WEEK	0 Baseline	24	48
Clinical assessment	√	√	√
Physical examination	√	√	√
Informed consent	√		
Pregnancy test	√		
Hematology	√	√	√
Biochemistry[1]	√	√	√
Plasma viral load (HIV-RNA)	√	√	√
Ultrasensitive viral load in plasma	√		√
HIV-1 reservoir in peripheral mononuclear blood cells	√		√
Immunology[2]	√		√
QoL (EQ-5D-5L Spanish)	√		√
DXA	√		√
Stored samples[3]	√		√
Adverse events	√	√	√

1 including lipid profile (total cholesterol, HDL, LDL and TG), creatinine (and estimated glomerular filtration rate, CKD-EPI), urine protein/creatinine ratio and beta-2-microglobulin, and 25OH vitamin D levels

2 including CD4, CD38 and HLA-DR

3 stored samples will be taken for potential future determination of biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation SD-14 and SD-163 and reservoirs

Patients will end the roll-over study when the new formulation of Raltegravir QD will be commercially available in Spain (expected November 2017)

Safety Assessment

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.

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.

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.

Adverse events 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.

Procedures for expedited reporting of serious adverse events by the investigator

The principal investigator will report immediately to the Coordinating Center 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 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 (EC) involved, and the relevant regulatory authorities with all additional information requested by them.

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).

These reports will also be communicated simultaneously to the Pharmacovigilance responsibles at MSD within the 24 hr of uncknowledgement of the SAE in order to have the affiliate reporting it internally to its headquarters. 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 lifethreatening 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.

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.

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 regardless of age) occurring during the study or within 28 days after the end of the study.

Statistics

Methods

The statistical analysis will be performed by the statistician of Infectious Disease and HIV Unit using Stata version 14.0.

Assignment of patients to subsets and identification of protocol, violations will be reviewed and approved before the statistical analysis.

Variables/Time Points of Interest

The primary variable, therapeutic failure at week 48, includes virological failure, change in treatment for any reason, consent withdrawal, loss to follow-up or death. It will be analysed also at 24 weeks.

Virological failure is defined as two consecutive measurements of plasma viral load above 50 copies/ml separated at least by 2 weeks during the assigned treatment, using the FDA snapshot method. It will be assessed at 24 and 48 weeks.

The following items will be described and compared between arms at each post baseline time point as well as the change versus baseline values in:

- Laboratory parameters including CD4 cells, hematology, lipid profile, creatinine (and estimated glomerular filtration rate, CKD-EPI), urinary protein/creatinin, and vitamin D levels
- Body fat distribution
- Spine/femur bone mineral density
- QoL (EQ-5D-5L)
- Biomarkers of inflammation (IL-6, high sensitivity C-reactive protein) and biomarkers of mononuclear activation SD-14 and SD-163
- HIV Reservoir

Descriptive analyses will be performed for those treatment-emergent adverse events (that means starting after baseline visit), for the possibly or probably related to the study drug treatment-emergent adverse events and for serious adverse event. A table will be performed with the proportion of patients reporting at least one adverse event described previously.

Sample size

RALAM switch arm has included 50 patients. We expect that at least 90% of the patients (n=45) will accept participating into this roll-over study.

.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.

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.

Management of missing data

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

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.

Analysis population

All 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 fulfil the inclusion/exclusion criteria or withdrawing from the study or discontinuing study treatment for reasons other than virological failure or adverse event.

DSMB

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.

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, study auditors and members of the Ethics Committee or the Spanish competent authority- Agencia Espñola del Medicamento y Productos Sanitarios), to regulatory authorities and to CRECs if they request to inspect the study.

Ethics

General considerations and Statement that the trial will be conducted in compliance with legal requirements

The clinical trial will be conducted in accordance with the principles contained in the Declaration of Helsinki, according to the principles of Good Clinical Practice, and according to applicable regulations (European Union Regulation 536/2014 and Royal Decree 1090/2015) 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 1090/2015 on Clinical Trials.

By signing this protocol, 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 Union, 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.

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.

Storage samples

The samples will be stored according to the Spanish law 14/2007. No future use of the biological samples are planned for this study. The investigator team will maintain a record of the collection and storage of the samples of this study.

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.

Study data will be collected and managed using REDCap electronic data capture instance hosted at Eurecat Foundation for the CONNECARE EU project.

Funding and Insurance

The study was financed by a grant provided by Merck.

In accordance with Royal Decree 1090/2015, the sponsor has taken out civil liability insurance for this study (see Appendix XII).

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.

Appendix I. Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly,
Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd
WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added
by the WMA General Assembly, Washington 2002

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protectionsfor human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision ofa clinically competent medical person. The responsibility for the human subject must
always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17.
Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged inthe investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it isnot possible to obtain consent, including proxy or advance consent, should be done only if
the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH OMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (See footnote*)
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

***FOOTNOTE:**
Note of Clarification on Paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may beethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review

Appendix II. Morisky Green test

Answer the following questions:

1.Some people forget to take their medication as prescribed.

How often does it happen to you?

ALWAYS OFTEN SOMETIMES RARELY NEVER

2. Some people forget to take some medication or change the prescribed schedule/intake to suit their own needs.

How often do you do it?

ALWAYS OFTEN SOMETIMES RARELY NEVER

3. Some people stop taking their medicines as prescribed when they feel better. How often do you do it?

ALWAYS OFTEN SOMETIMES RARELY NEVER

4. Some people stop taking their medicines as prescribed when they feel worse. How often do you do it?

ALWAYS OFTEN SOMETIMES RARELY NEVER

Total score (sum of score of all questions = _____points

Appendix III. Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions. During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. When have you usually gotten up in the morning? _____
4. How many hours of actual sleep do you get at night? (This may be different than the number of hours you spend in bed) _____

5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, including how often you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Component 1	#9 Score	C1_____
Component 2	#2 Score (≤15min=0; 16-30 min=1; 31-60 min=2, >60 min=3) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)	C2_____
Component 3	#4 Score (>7=0; 6-7=1; 5-6=2; <5=3)	C3_____
Component 4	(total # of hours asleep)/(total # of hours in bed) x 100 >85%=0, 75%-84%=1, 65%-74%=2, <65%=3	C4_____
Component 5	Sum of Scores #5b to #5j (0=0; 1-9=1; 10-18=2; 19-27=3)	C5_____
Component 6	#6 Score	C6_____
Component 7	#7 Score + #8 Score (0=0; 1-2=1; 3-4=2; 5-6=3)	C7_____

Add the seven component scores together _____ **Global PSQI Score** _____

Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Journal of Psychiatric Research, 28*(2), 193-213.

Appendix IV. EQ-5D-5L

Health Questionnaire

Spanish version for Spain

(translated into English)

Under each statement, check ONE box, the one that best describes your health TODAY.

MOBILITY

I have no trouble walking ☐
I have mild trouble walking ☐
I have moderate trouble walking ☐
I have serious trouble walking ☐
I can't walk ☐

CARE

I have no problem washing or dressing ☐
I have mild problems washing or dressing ☐
I have moderate problems washing or dressing ☐
I have serious problems washing or dressing ☐
I can't wash or get dressed ☐

DAILY ACTIVITIES *(e.g., working, studying, doing household chores, family activities, or leisure activities)*

I have no problem doing my daily activities ☐
I have mild problems doing my daily activities ☐
I have moderate trouble doing my daily activities ☐
I have serious problems doing my daily activities ☐
I can't do my daily activities ☐

PAIN / DISCOMFORT

I have no pain or discomfort ☐
I have mild pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY/DEPRESSION

I'm not anxious or depressed ☐
I'm mildly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am very anxious or depressed ☐
I am extremely anxious or depressed ☐

- We'd like to know how good or bad your health is TODAY.
- The scale is numbered from 0 to 100.
- 100 represents the best health you can imagine.
  0 represents the worst health you can imagine.
- Mark with an X on the scale to indicate your status health TODAY.
- Now, in the box that you will find below, write the number you have marked on the scale.

YOUR HEALTH TODAY = ☐