Official Protocol Title:	Switching from regimens consisting of a RTV-boosted protease inhibitor plus TDF/FTC to a combination of RAltegravir plus NevIrapine and lAmivudine in HIV patients with suppressed viremia and impaired renal function (RANIA Study) (Pilot study) Protocol MK-0518-284-03
NCT number:	NCT02116660
Document Date:	16-April-2015

Abbreviated Title	***RANIA Study***
Title	Switching from regimens consisting of a RTV-boosted protease inhibitor plus TDF/FTC to a combination of RAltegravir plus NevIrapine and lAmivudine in HIV patients with suppressed viremia and impaired renal function (RANIA Study) (Pilot study) Protocol MK-0518-284-03
Sponsor	MSD Italia s.r.l.
Trial Physician	PPD [redacted]
Date of Finalization of This Current Version of the Protocol	APRIL 16th 2015

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PPD [redacted]

Name and Degree of Sponsor Representative
Department of Sponsor Representative

dd MMM yyyy

I have read Protocol No. MK-0518-284-03 dated 16-APRIL-2015, including all appendices, and agree to conduct the trial in accordance with the protocol. The protocol and trial documents must also be approved by the IRBs/IECs and regulatory authorities as appropriate, before implementation at the site. I agree to implement the protocol and trial documents only after all necessary approvals have been obtained and the sponsor has confirmed that it is acceptable to do so.

Name, Degree, full mailing address of Investigator ***Site Number*** ***dd MMM yyyy***

1.0 TITLE PAGE

Abbreviated Title	***RANIA Study***
Title	Switching from regimens consisting of a RTV-boosted protease inhibitor plus TDF/FTC to a combination of RAltegravir plus NevIrapine and lAmivudine in HIV patients with suppressed viremia and impaired renal function (RANIA Study). (Pilot study) Protocol MK-0518-284-03
Sponsor	MSD Italia s.r.l.
Sponsor's Address	Via Vitorchiano, 151 00189 Roma
EudraCT No.	2013-001637-40
Trial Physician	PPD
Phase	2b
Date of Finalization of This Current Version of the Protocol	APRIL 16th 2015
Protocol Template Approval Date	30-Jan-2013

C O N F I D E N T I A L

TRIAL PROTOCOL

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SUMMARY OF CHANGES

This amendment is to provide the most updated information on drug-drug interactions from the latest SmPCs. The remaining revisions are to provide more clarity on the procedures (administrative in nature). The following provides an overview of the changes made to the protocol:

- update to the list of drug-drug interactions according to the most updated SmPC for raltegravir and nevirapine. The most significant modification of which is for aluminum and magnesium antacids listed as an excluded/prohibited medication;
- update to text for consistent wording relating to the study subject participation/study duration;
- addition of the protocol overdose language from the SmPC for raltegravir, lamivudine, nevirapine which was previously inadvertently omitted;
- update to the pharmacokinetics text to further clarify sampling requirements (regarding drug/food intake) the clarify the subset of patients eligible for intensive PK.

Below is a summary table of the sections affected, with the description of the changes and rationale.

Section Numbers	Section Titles	Description of Changes	Rationale
Sections 2.0, 7.2	Study subject participation	Clarified the study duration participation of each subject including the 2 weeks of follow-up post therapy (104 weeks).	For consistency.
Section 2.0	Study duration	Clarified the study duration including the 2 weeks of follow-up post therapy (128 weeks).	For consistency.
Sections 2.0, 7.3.1	Inclusion Criteria	Inclusion Criteria #10 was updated to add a specification about genotype testing timelines.	For completeness.
Sections 2.0, 7.7.3	Pharmacokinetics	Added clarity regarding the pharmacokinetics sampling requirements (regarding drug/food intake) and the subset of patients eligible for intensive PK.	Update made for clarity.
Section 2.1	Trial Design Diagram	Added in the Trial Design Diagram footnotes, a box specifying the study duration including the 2 weeks of follow-up post therapy.	For completeness.

Section 2.2	Trial Flow Chart	Footnote on PK updated to remain consistent with the Synopsis and Section 7.7.3.	Footnotes updated for procedural clarity.
Section 2.2	Trial Flow Chart	For "Visit 11" cell added the abbreviation "EOT" (End-of-Treatment) and for "Visit 99" "EOS" (End-of-study).	For completeness.
Section 2.2	Trial Flow Chart/Footnote 6 and Appendix 1	The footnote was updated to clarify that blood samples for viral resistance will be collected only at virologic failure confirmation visit. Only genotype testing will be performed.	For consistency.
Section 2.2	Trial Flow Chart	"Footnote 11" formatting issue	Formatting issue
Sections 7.2, 7.7.2.3.1	Monitoring Adverse Events	Text which describes the period of AE monitoring was clarified. Based on recent guidance added additional protocol language to describe the AEs to be reported in the pre-randomization phase.	Update made for clarity and based on recent guidance.
Section 7.3.3	Subject Discontinuation Criteria	Updated list to include criteria # 7, 8 and re-worded criteria #4.	For completeness.
Section 7.4.1.1	Treatments	Formatting issue "daily" deletion.	Formatting issue
Section 7.4.2.1.1	Medications, Supplements, and Other Substances prohibited Prior to baseline and During the Trial	Updated the lists of drug-drug interactions according to the most updated SmPC for raltegravir and nevirapine. The most significant modification of which is for aluminum and magnesium antacids listed as an excluded/prohibited medication.	To update according to the most updated SmPC for raltegravir, nevirapine and lamivudine.
Section 7.4.3	Procedures for Monitoring Subject Compliance With Administration of Trial Treatments	Added a specification about the patient questionnaire provided to monitor the treatment compliance.	For completeness.
Section 7.6	Trial Procedures	For "Laboratory Tests" added a specification according to the Trial Flow Chart	To further clarify.
Section	Overdose	Removed reference to the product's	Previously inadvertently

7.7.2.2.4		Investigator's brochure and added overdose information from the SmPC for raltegravir, lamivudine, nevirapine. Specified that an overdose of the control arm does not need to be reported as an ECI or SAE.	omitted.
Section 7.7.2.5.1	Clinical complaint reporting	Updated to align with the standard process for commercial drugs	To align with Merck standard process.
Section 11	References	Reference n. 17 updated to support IC #10	For completeness.

2.0. SYNOPSIS

TITLE OF TRIAL: Switching from regimens consisting of a RTV-boosted protease inhibitor plus TDF/FTC to a combination of RAltegravir plus NevIrapine and lAmivudine in HIV patients with suppressed viremia and impaired renal function (RANIA Study) (Pilot, Phase 2b study - Protocol No. MK-0518-284-03)

ABBREVIATED TITLE: *RANIA Study*

OBJECTIVES: To assess the change in renal function, efficacy and the safety of a switch from a regimen consisting of PI/r (LPV/r, ATV/r, DAR/r) plus TDF/FTC to a combination of Raltegravir plus Nevirapine plus Lamivudine in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months with no documentation of HIV RNA ≥ 50 copies/mL during this time, without a change in antiretroviral therapy from at least 6 months and with an eGFR (MDRD-6 variables) between 60 and 90 mL/min/1.73 m^2 at screening.

Primary Trial Objective:

- To assess the changes in renal function (e.g. estimated GFR measured by MDRD formula with 6 variables that is MDRD 4 variables plus blood urea nitrogen and albumin) from baseline to 48 weeks.

Secondary Trial Objectives:

a) To assess the efficacy (stable suppressed HIV-RNA <50 copies/ml) after switch from PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
b) To evaluate the changes in T-lymphocyte CD4 cell count during 48 and 96 weeks of treatment
c) To assess laboratory alterations (liver enzymes, lipid profile) after switch from PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
d) To assess the safety (e.g. skin rash, GI disturbances) after switch from PI/r+ TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
e) To assess the alterations of the tubular kidney injury markers: b2-microglobulin (b2M) and retinol-binding protein (RBP) and N-acetyl-b-D-glucosaminidase (NAG) during 48 and 96 weeks of treatment.
f) To assess metabolic bone markers changes: Serum Bone Specific Alkaline Phosphatase (s-BSAP), C-telopepdides of type I Collagen (s-CTx) during 48 and 96 weeks of treatment.
g) To assess bone mineral density modifications during 48 and 96 weeks of treatment.
h) To evaluate pharmacokinetics of RAL and NVP.
i) To assess the development of genotypic resistance at virologic failure
j) To evaluate the adherence during 48 and 96 weeks of treatment.
k) To assess the Fracture Risk (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment
l) To assess the VACS Risk Index during 48 and 96 weeks of treatment
m) The frequency of experiencing a decline of renal function in HIV-infected patients with an eGFR (MDRD-6 variables) < 60 mL/ min/1.73 m2 at 48 weeks of treatment
n) To evaluate the changes in eGFR-MDRD at 96 weeks of treatment

Trial Design

Overview:
This is a pilot multicenter randomized, open-label, active-controlled, parallel-group, in patients with persistently (previous 12 months) suppressed plasma HIV viremia (< 50 copies/mL) after switch from PI/r plus TDF/FTC to a combination of Raltegravir 400 mg BID, plus 3TC 150 mg BID plus Nevirapine 200 mg BID.

This study is a pilot switch study with a comparator used as internal control. No comparisons will be made

between the groups. This study is designed as an estimation study only and no formal comparison between the two regimens is planned. The control arm will be not directly compared with the experimental arm and will act as a check to assess the internal validity of the study.

Number of Trial Centers: Approximately 15 Italian centers.

Duration of Participation: Each subject will participate in the trial for 104 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 6 weeks, each subject will be receiving assigned treatment for 96 weeks with 2 additional weeks of follow-up post therapy.

Duration of Trial*:* The trial will require approximately 128 weeks from the beginning to the end of the overall trial (first subject signing informed consent to last contact with last subject, considering a screening phase of 6 weeks, 24 weeks for enrollment, 96 weeks for treatment and 2 weeks of follow-up post therapy).

Key Inclusion Criteria:

1. Each subject must be willing and able to provide written informed consent for the trial
2. Each subject must be ≥ 18 years of age
3. Each subject must be male or non-pregnant, non-breastfeeding female
4. Each subject must have diagnosis of HIV infection
5. Each subject must have no history of previous virological failure (defined as 2 consecutive plasma HIV-1 RNA >200 copies/mL at least two weeks apart while on previous or current ARV therapy)
6. Each subject must have no history of previous exposure to NNRTIs or INIs prior to entering the study
7. Each subject must have no history of previous intolerance to Lamivudine
8. Each subject must have at least 2 documented plasma HIV-1 RNA <50 copies/mL and no HIV-1 RNA >50 copies/mL in the 12 months prior to the screening visit
9. Each subject must be taking the same PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC based ARV combination for at least 6 months before screening
10. Each subject mustn't have major IAS-USA mutations on genotypic testing performed before starting ARV treatment (genotype testing done before starting the first line therapy)
11. Each subject must have results of clinical laboratory tests (CBC, blood chemistries, and urinalysis) within normal limits or clinically acceptable to the investigator
12. Each subject must have results of a physical examination, including blood pressure, within normal limits or clinically acceptable limits to the investigator
13. Each subject must be able to adhere to dose and visit schedules
14. Each subject should have Creatinine Clearence between 60 and 90 mL/min/1.73 m^2 calculated according to MDRD 6 variables
15. Each sexually active subject and subject's partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception 2 weeks prior to Day 1 and at least 6 months after last dose of study drug

Key Exclusion Criteria:

1. The subject has HBsAg+ or anticipated need for HCV-treatment
2. The subject has grade 2-4 laboratory abnormality of liver transaminases (ALT and AST)
3. The subject has experiencing liver cirrhosis
4. The subject has history of diabetes mellitus (defined as initiation of antidiabetic treatment or verification of diabetes in a case report form)
5. The subject has any cancer (excluding stable Kaposi Sarcoma)
6. The subject has an allergy/sensitivity to investigational product or its/their excipients.
7. The female subject is nursing.
8. The female subject is pregnant or intending to become pregnant.
9. The subject has any clinically significant condition or situation, other than the condition being studied

that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial. The subject in the opinion of the investigator has an excessive intake of alcohol and substances.

10. The subject has active AIDS-defining event (CDC-C), exception for stable Kaposi Sarcoma, HIV Wasting Syndrome.
11. The subject has used any investigational drugs within 30 days of screening.
12. A subject who has participated in any other clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial.
13. The subject or a family member is among the personnel of the investigational or sponsor staff directly involved with this trial

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION

Investigational Product:

Raltegravir, 400 mg BID taken PO without regard to food + Lamivudine 150 mg BID PO without regard to food + Nevirapine 200 mg QD for 14 days followed by Nevirapine 200 mg BID PO without regard to food, for 96 weeks.

Non investigational Product:

Continuing the previous regimen PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC, for 96 weeks

STATISTICAL METHODS:

This is a pilot phase 2b, multicenter, randomized, open-label, active controlled, parallel group design.
Patients meeting all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following two treatment groups:

- **Regimen A**: switching to a regimen containing Raltegravir 400 mg BID PO+ Lamivudine 150 BID PO + Nevirapine 200 mg QD for 14 days followed by Nevirapine 200 mg BID PO
- **Regimen B (control arm)**: continue with the current regimen containing PI/r (LPV/r, ATV/r, DAR/r) +TDF/FTC

The primary endpoint of this study is the eGFR (MDRD) change from baseline to Week 48.

This randomized phase 2 study is mainly designed as an estimation study without a planned formal comparison between the two regimens. The control arm, not directly compared with the experimental arm, will be considered for assessing the internal validity of the study. A safety monitoring with more frequently visits will be ensured for the control arm only.

Data Set(s) to be Analyzed:

The primary analysis on primary and secondary endpoints will be performed on the Full Analysis Set (FAS) which includes all randomized subjects who received at least one dose of study medications, and have both a baseline assessment and at least one post-baseline assessment of any primary or secondary endpoints, irrespective of compliance with the study protocol and procedures.

In addition, a Per Protocol Set is defined as all FAS subjects who meet key eligibility criteria. Sensitivity analyses will be based on this Per Protocol Set. A supportive analysis using the Per-Protocol population will be performed for the primary endpoint only in case more than 10% of patients are identified as protocol violators.

Other safety analyses will be performed on the All Treated Set. The All Treated Set consists of all randomized patients who received at least one dose of study treatment.

Sample Size:

Patients to screen: 148; Patients evaluable: 100 (50 in each group).

It is expected that Regimen A is generally safe and well tolerated and can cause an improvement of the renal

function. A pre vs post design will be used to examine changes in eGFR (MDRD) in the Regimen A arm.

For sample size calculation our data and results from a pilot tenofovir switching study recently published (1) were used.

Sample size calculation was based on the primary endpoint of the study, defined as the change from baseline to week 48 in eGFR (MDRD), with the following assumptions:

Test: One group Student's t-test (two-sided).

Null hypothesis (H0): Expected mean change from baseline to week 48 is 0.0 ml/min.

Alternative hypothesis (H1): Expected mean change from baseline to week 48 is 15 ml/min.

Expected SD = 31.5 ml/min

Alpha = 0.05; Power = 90%;

When the sample size is 50, a single group Student's t-test with a 0.05 two-sided significance level will have 90% power to detect a difference between a null hypothesis mean of 0.0 ml/min and an alternative hypothesis mean of 15.0 ml/min, assuming that the standard deviation is 31.5 ml/min.

Overall 100 subjects (50 per arm) need to be evaluated. In order to obtain 50 subjects and assuming a 20% rate of non evaluable subjects the required set of patients will be approximately 63 per arm and considering a screen failure rate of 15%, such number should be increased to 74. Overall, approximately 148 subjects (74 per arm) will need to be screened to obtain 100 subjects valuables (50 per arm).

Calculations were made by using nQuery Advisor® 7.0.

Analysis of primary end-point:

The primary endpoint of this study is the eGFR (MDRD) change from baseline to Week 48.

The primary analysis will be conducted on the Full Analysis Set. An additional sensitivity analysis will be based on the Per Protocol Set.

The Primary Endpoint will be analyzed using a one-group (two-sided) Student's t test on the Regimen A group.

For the Regimen B group, the difference from baseline to week 48 will be estimated together with its pertinent 95% Confidence Interval. No formal comparison between the two arms will be carried out.

If missing data on primary end-point will be ≤ 5%, a LOCF approach (Last Observation Carried Forward procedure) will be used. In that case, if a patient permanently discontinues the treatment during the 48-week treatment period or does not have an eGFR (MDRD) value at week 48, the last post-baseline eGFR (MDRD) measurement during the on-treatment period will be used as the eGFR (MDRD) value at week 48. Otherwise, missing data will be imputed by using a multiple imputation method considering the previous trend and/or the baseline covariates.

Analysis of main secondary end-point:

The main secondary efficacy end-point will be the proportion of subjects with HIV-RNA < 50 copies/ml at 48 week. Based on the above criteria, patients will be classified as responders or not responders (failures). If a patient permanently discontinues the treatment during the 48-week treatment period or does not have an HIV-RNA assessment at week 48, a conservative approach will be used: all missing values due to premature discontinuations will be considered failures, regardless of the reason for discontinuation. Counts and percentages of "Responders" and "Not Responders" and their 95% two-sided exact confidence intervals will be presented for both arms.

Analysis of the main secondary end-points will be based on the Full Analysis Set.

Analysis of other secondary end-points:

Other secondary endpoints will be:

a) Proportion of subjects with HIV-RNA < 50 copies/mL at 96 weeks of treatment.
b) Time to virologic failure (HIV-1 RNA > 50 copies/mL).
c) Changes of HIV-RNA absolute values at different time points.
d) Changes of absolute CD4+ T-lymphocyte count at 48 and 96 weeks of treatment.

e) Proportion of subjects with laboratory alterations (liver enzymes, lipid profile).
f) Proportion of subjects with alterations of the tubular kidney injury markers.
g) Proportion of subjects with metabolic bone markers changes
h) Proportion of patients with bone mineral density modifications
i) Pharmacokinetics determination (only for RAL and NVP) (see PK paragraph).
j) Proportion of subjects with genotypic resistance at virologic failure.
k) Incidence of mutations associated to resistance to NRTIs, NNRTIs, PI and INI, at virological failure.
l) Proportion of subjects with adherence to therapy during 48 and 96 weeks of treatment.
m) Changes in the Bone disease Risk assessment (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment.
n) Changes in the VACS Index during 48 and 96 weeks of treatment.
o) Proportion of subjects experiencing a decline of renal function defined as eGFR (MDRD-6 variables) < 60 mL/min/1.73 m2 at 48 weeks of treatment.
p) Changes in eGFR-MDRD at 96 weeks of treatment

Analysis of the secondary end-points will be based on the Full Analysis Set.

Continuous data will be summarized by treatment group using the number of observations available n, mean, SD, minimum, median, and maximum at each time point.

Categorical data will be summarized by treatment group using counts and percentages at each time point. Missing data will not be categorized in the summaries. In general, descriptive statistics of quantitative efficacy and safety endpoints (result and change from baseline) by scheduled visit will be provided on observed cases, i.e., the inclusion of only patients having non-missing assessments at a specific visit.

Safety Analysis:

Safety analyses will be descriptive, based on the safety population.

Interim Analysis No formal interim analysis are planned.

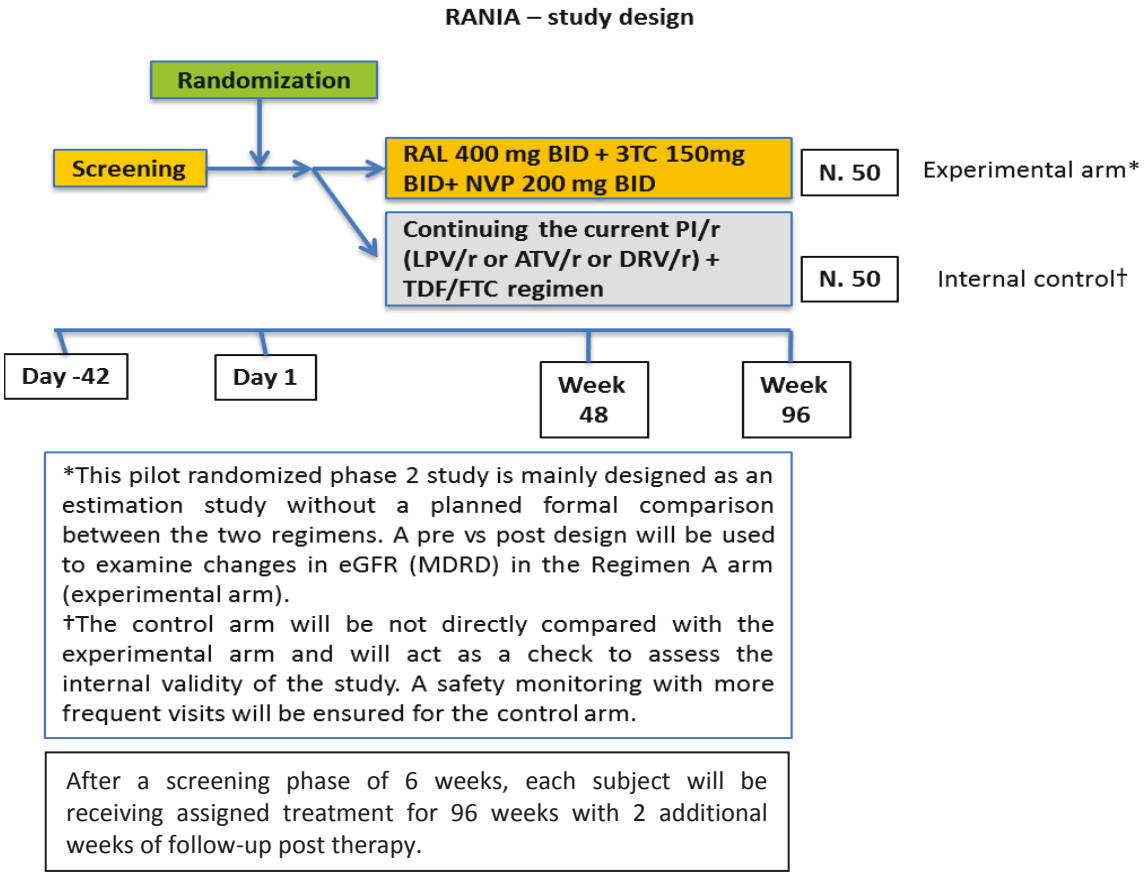
Pharmacokinetics:

Determination of raltegravir and nevirapine AUCs (areas under the curve) will be carried out at steady state according to the dosing interval with blood sampling taking place at the end of dosing interval at time 0 (fasted state), and 1, 2, 3, 6 and 12 h after drug intake (regardless food) in a subset of enrolled patients with available data in the experimental arm at week 12 (~ the first 10 patients). The remaining 40 patients in the experimental arm will undergo Ctrough sampling (at the end of dosing interval at 12 h) at week 12 and 48. Adequate documentation of drug and food intake will be required.

Blood will be collected into 7 ml lithium heparin and plasma obtained by centrifugation (3000 rpm for 10 minutes at 4 °C) will be stored in two criovials at -20 °C. Plasma concentrations will be analyzed by a validated HPLC-PDA method at the Clinical Pharmacology and Pharmacogenetics Laboratory of the University of Torino, Torino, Italy.

In Torino centre, CYP2B6 single nucleotide polymorphisms (SNPs) will be screened in both patients undergoing AUC determination and those being sampled for Ctrough.

2.1 Trial Design Diagram



2.2 Trial Flow Chart

Visit Title		Timing of Evaluation and Procedures (Relative to Initiation of Product)											
	Screening	Baseline	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Discontinuation Visit	Viral Failure Confirmation	Fasting 14 days post-therapy Follow-up
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOT	Visit U	Visit 99 EOS
Scheduled Week	Days -42 to day 1	Day 1	Week 2[5]	Week 4	Week 6[5]	Week 8[5]	Week 12	Week 24	Week 48	Week 72	Week 96		
Scheduling Window			±2days	±2 days	±2days	±2days	±6days	±6days	± 12 days	±12days	±12 days		
Informed Consent	X												
Subject Identification Card- Dispensed	X												
Subject Identification Card-Returned											X		
Medical History	X												
Pregnancy Test[1]	X	X					X	X	X	X	X		
Inclusion/esclusion Criteria	X	X											
Review prior/Concomitant Medications	X	X					X[2]	X	X	X	X		
CYP 2B6 SNP[3]		X											
PK intensive blood sampling (AUC subgroup)[4]							X						

Visit Title		Timing of Evaluation and Procedures (Relative to Initiation of Product)											
	Screening	Baseline	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Discontinuation Visit	Viral Failure Confirmation	Fasting 14 days post-therapy Follow-up
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOT	Visit U	Visit 99 EOS
Scheduled Week	Days -42 to day 1	Day 1	Week 2[5]	Week 4	Week 6[5]	Week 8[5]	Week 12	Week 24	Week 48	Week 72	Week 96		
Scheduling Window			±2days	±2 days	±2days	±2days	±6days	±6days	± 12 days	±12days	±12 days		
PK C_{trough} sampling (experimental arm)[4]							X		X				
Review Adverse Events	X	X	X[5]	X	X[5]	X[5]	X	X	X	X	X		X
Blood for HIV-RNA	X	X		X			X	X	X	X	X	X	
Blood for CD4 cell count, for CD8 cell count and for CD4/CD8 ratio		X		X			X	X	X	X	X		
Plasma for viral resistance[6]												X	
Adherence Questionnaire evaluation	X	X					X	X	X	X	X		
Physical Examination[7]	X	X					X	X	X	X	X		
Blood for hepatic Safety[8]	X	X	X[5]	X	X[5]	X[5]	X	X	X	X	X		
Blood for safety[8]-	X	X		X			X	X	X	X	X		

Visit Title		Timing of Evaluation and Procedures (Relative to Initiation of Product)											
	Screening	Baseline	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Discontinuation Visit	Viral Failure Confirmation	Fasting 14 days post-therapy Follow-up
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOT	Visit U	Visit 99 EOS
Scheduled Week	Days -42 to day 1	Day 1	Week 2[5]	Week 4	Week 6[5]	Week 8[5]	Week 12	Week 24	Week 48	Week 72	Week 96		
Scheduling Window			±2days	±2 days	±2days	±2days	±6days	±6days	± 12 days	±12days	±12 days		
[9]													
MDRD-6 assessment	X	X					X	X	X	X	X		
Urine Kidney Tubular Markers ( )[8]		X					X	X	X	X	X		
Test for renal safety (control arm)[11]		X					X	X and 36 weeks	X and 60 weeks	X and 84 weeks	X		
Metabolic bone markers		X					X	X	X	X	X		
Perform BMD measurement (DXA scan-Total Hip and Lumbar spine)[10]	X								X		X		
Dispense Trial Medication		X					X	X	X	X			
Fracture Risk Assessment (FRAX® score in persons > 40 years)		X							X		X		

		Timing of Evaluation and Procedures (Relative to Initiation of Product)											
Visit Title	Screening	Baseline	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring	Discontinuation Visit	Viral Failure Confirmation	Fasting 14 days post-therapy Follow-up
Visit Number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11 EOT	Visit U	Visit 99 EOS
Scheduled Week	Days -42 to day 1	Day 1	Week 2[5]	Week 4	Week 6[5]	Week 8[5]	Week 12	Week 24	Week 48	Week 72	Week 96		
Scheduling Window			±2days	±2 days	±2days	±2days	±6days	±6days	± 12 days	±12days	±12 days		
VACS Risk index assessment		X							X		X		
Investigational Product Accountability		X					X	X	X	X	X		

[1]Serum pregnancy test

[2] Concomitant Medications from day 0 to Week 12

[3]CYP2B6 single nucleotide polymorphisms (SNPs) will be screened in both patients undergoing AUC determination and those being sampled for Ctrough [4]Procedures for collection of samples are described in the protocol. Determination of raltegravir and nevirapine AUCs (areas under the curve) will be carried out at steady state according to the dosing interval with blood sampling taking place at the end of dosing interval at time 0 (fasted state), and 1, 2, 3, 6 and 12 h after drug intake (regardless food) in a subset of enrolled patients with available data in the experimental arm at week 12 (~ the first 10 patients). The remaining 40 patients in the experimental arm will undergo Ctrough sampling (at the end of dosing interval at 12 h ± 2h) at week 12 and 48. Adequate documentation of drug and food intake will be required.

[5]only for the patients enrolled in the experimental arm

[6]If viral failure or relapse is confirmed (with a confirmatory HIV RNA at least two week apart) defined as 2 consecutive plasma HIV-1 RNA >200 copies/mL plasma for genotype resistance testing will be collected and sent to a local qualified hospital laboratory for testing.

[7] Full physical exam including vital signs (blood pressure, heart rate, temperature, breathing rate). At investigator discretion a chest x-ray and/or an ECG could be obtained if felt necessary

[8]see Appendix 1

[9]Fasting for at least 12 hours

[10] Perform BMD only in patients already qualifies by medical history, kidney function evaluation and medication review

[11]A safety monitoring with more frequently visits will be ensured for the control arm. Visits each 3 months according to the international and national guidelines for monitoring TDF safety profile have been planned. Test for renal safety planned each months are creatinine clearance evaluation and serum phosphate. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) renal function should be re-evaluated within one week including measurement of blood glucose, blood potassium, urine glucose concentrations and proteinuria.

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4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
3TC	Lamivudine
AE	Adverse Event
AIDS	Acquired Immune Deficiency Sindrome
AKI	Acute Kidney Injury
ALT	Alanine aminotransferase (SGPT)
APTT	Activated Partial Thromboplatin Time
AST	Aspartate aminotransferase (SGOT)
ATV/r	Atazanavir/ritonavir
AUC	Area Under the Curve
AV (block)	Atrio Ventricular
b2M	Beta-2 microglobuline
BID, b.i.d.	Bis in Die
BL	Baseline
BMD	Bone Mineral Density
cART, ART	Current Antiretroviral Therapy, Antiretroviral Therapy
CBC	Complete Blood Count
CCR5	Cysteine-Cysteine Chemokine Receptor 5
CD4 cell	Cluster of Differentiation 4 cell
CD8 cell	Cluster of Differentiation 8 cell
CDC, CDC-C	United States Centers for Disease Control and Prevention, CDC-Classification
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CRF	Case Report Form
CSR	Clinical Study Report
CTC	Clinical Trial Coordinator
CTD	Clinical Trial Directive
CVD	Cardiovascular Disease
CYP	Cytochrome P
DAIDS	Division of AIDS (National Institutes of Health, USA)
DAR/r	Darunavir/ritonavir
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board

Term	Definition
DXA	Dual-Energy X-Ray Absorptiometry
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration, USA
FRAX	Fracture Risk Assessment Tool
FTC	Emtricitabine
Global Safety Intake Form	The sponsor's collection form used to report serious adverse events (SAE) or other events to Global Safety
GCP	Good Clinical Practice
GFR, eGFR	Glomerular Filtration Rate, estimated GFR
GGT	Gamma-glutamyl-transpeptidase
GI	Gastrointestinal
HAART	Highly Active Antiretroviral Therapy
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein - Cholesterol
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HIVAN	HIV - Associated Nephropathy
HPLC	High Performance Liquid Chromatography
IAS-USA (mutation)	International AIDS Society
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
INI	Integrase Inhibitor

Term	Definition
INR	International Normalized Ratio
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
IUD	Intrauterine Device
IV	Intravenous
IVRS	Interactive Voice Response System
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LDL-C	Low-Density Lipoprotein Cholesterol
LPV/r	Lopinavir/ritonavir
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT, ITT	Modified ITT, Intention To Treat
NA, N/A	Not applicable
NAG	N-acetyl-b-D-glucosaminidase
ND	Not determined
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
NRTI	Nucleoside/ Nucleotide Reverse Transcriptase Inhibitor
OT	Observed Treatement
PCP	Pneumocystis carinii Pneumonia
PCR	Polymerase Chain Reaction
PDA	Photo Diode Array
PDF	Portable Document Format
PGt	Pharmacogenetics
PGx	Pharmacogenomics
pH	pH (/piː eɪtʃ/ or /piː heɪtʃ/) is a measure of the acidity or basicity of an aqueous solution
PI, PI/r	Protease Inhibitor, PI/ritonavir
PK	Pharmacokinetics
PO	Per Os
PQC	Product Quality Complaint
PT	Prothrombin test
PTH	Parathyroid Hormone
PTT	Partial Thromboplastin Time
QD, q.d.	quaque die (every day/once daily)
RAL	Raltegravir

Term	Definition
RBC	Red Blood Cell
RBP	Retinol-Binding Protein
RNA	Ribonucleic Acid
rpm	revolutions per minute
RSI	Reference Safety Information
RTV	Ritonavir
SAE	Serious Adverse Event
(S)AE	All Adverse Events, including Serious Adverse Events
s-BSAP	Serum Bone Specific Alkaline Phosphatase
s-CTx	C-telopepdides of type I Collagen
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SmPC	Summary of Product Characteristics
SNP	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedure
TDF	Tenofovir Disoproxyl Fumarate
TID	Ter in Die (three times a day)
UDP	Uridine diphosphatase
UGT, UGT1A1	UDP-glucuronosyltransferases; UDP-glucuronosyltransferases 1 (family) polypetdide A1
ULN	Upper Limit of Normal
USA	United States of America
User ID	User Identification
VACS	Veterans Aging Cohort Study
WBC	White Blood Cell

5.0 INTRODUCTION

5.1 Background and Therapeutic Rationale

Persistency in treatment and stable virological suppression are main driven factors associated to long-term cART efficacy. However a saving toxicity profile of regimen may improve tolerability and minimize drug discontinuation. The use of antiretroviral drugs has been associated with a number of toxicities, including those affecting the kidney. The kidney plays a major role in the metabolism and excretion of antiretroviral drugs and this makes it vulnerable to various types of injuries from some of these agents, including acute kidney injury (AKI), tubulopathies, chronic kidney disease (CKD), and end-stage renal disease requiring renal replacement therapy. As the population of HIV-infected patients ages and remains on HAART for longer periods of time, age-, HIV- and HAART-related metabolic disorders are increasingly being encountered by clinicians looking after these patients. HIV can cause direct injury to the kidneys as manifested by HIV-associated nephropathy (HIVAN). This entity was described before the era of HAART but continues to be a significant problem despite the advent of HAART. HAART has also been associated with CKD. The major drugs implicated in this include indinavir, atazanavir and tenofovir (1). NRTI-sparing strategies may protect from long-term renal and bone toxicity, and boosted PI-sparing regimens may have favorable impact on GI tolerance and potential reduction of CVD risk as well as reduce the challenges of drug to drug interactions. Preclinical studies with tenofovir identified renal and bone toxicities as potential issues with this agent, however, the incidence of nephrotoxicity in the pivotal clinical studies, which excluded subjects with low estimated glomerular filtration rate (eGFR), was relatively low. Subsequently, case reports have described serious renal toxicity, including acute renal failure requiring dialysis, progressive decline in renal function, proximal renal tubular dysfunction, and Fanconi syndrome. Further studies have suggested in older age, more advanced HIV-1 infection, lower body mass, impaired renal function, and coadministration of protease inhibitors or additional nephrotoxic drugs as possible risk factors for tenofovir-associated nephrotoxicity (2). Data from Eurosida cohort implicated concomitant use of ATV and TDF with a 41% increased incidence of CKD per year of exposure and a significantly increased risk of CKD was implicated also with lopinavir. In a recent study a significantly increased risk of developing renal impairment associated with atazanavir and lopinavir independent of exposure to tenofovir has also been demonstrated (3). In the PROGRESS study, a pilot study on NRTI-sparing regimen, the renal function as estimated by changes from baseline in eGFR showed a greater mean decrease for the LPV/r + TDF/FTC group versus the LPV/r + RAL group (4). These findings may provide a rationale for the use of a TDF-sparing ART approach given the recent findings from the EuroSIDA Study Group. This cohort study of 6,843 HIV-infected persons with a median follow-up duration of 3.7 years demonstrated that 3.3% of the cohort progressed to chronic kidney disease (CKD) during 21,482 person-years follow-up resulting in an incidence of 1.05 per 100 person-years follow-up. After adjusting for traditional factors associated with CKD and confounding factors, increasing cumulative exposure to tenofovir with an incidence rate ratio (IRR) per year of 1.16 (95% CI: 1.06–1.25, P<0.0001) was associated with a significantly increased rate of CKD (5). The improvement of renal function in subjects on the LPV/r + RAL regimen in PROGRESS could be related to the absence of tenofovir in that arm, even when LPV/r itself may be associated with a worsening of renal function itself (4). The switch to raltegravir-based regimens has been investigated in several trials, with different results. SWITCHMRK 1 and 2 compared substitution of RAL for LPV/r with continuation of LPV/r in those with viral suppression on LPV/r-based therapy. A total of 707 patients were randomized in this multicenter, double-blind, double-dummy trial. Switching to RAL resulted in significant improvement in lipid profile (the primary endpoint) but inferior virological efficacy compared to continuation of LPV/r therapy (84.4% with VL < 50 copies/ml vs 90.6%, respectively) and the studies were terminated. Of note, 84% (27 of 32) of patients with confirmed virological failure in the RAL group were on at least their second ART regimen and 66% (18 of 27) reported a history of prior virological failure. The SPIRAL study was a similarly designed randomized, multicenter, open-label trial of 273 patients with HIV RNA < 50 copies/ml (for at least 6 months) on a PI/r-based regimen. Switching to RAL was non inferior to continuing PI/r-based treatment at 48 weeks (89.2 vs 86.6% free of treatment failure, respectively), with an improvement in plasma lipids. Early evidence suggests that RAL may have anti-inflammatory properties, and data have shown improvement in inflammatory biomarkers and T-cell activation when PI/r are switched to RAL. (6).

A pilot study, Rasta Study (The Raltegravir Switch for Toxicity or Adverse Events) explored the safety and efficacy at 48 weeks of a treatment switch to raltegravir associated with tenofovir/emtricitabine or abacavir/lamivudine in patients with regimens with optimal virological control. The investigated switch strategy was associated with rare virological failure. Improvements in lipid levels, quality of life measures, neuropsychological performance, and bone composition suggest good tolerability of raltegravir-based regimens. (7) Also a retrospective study in a cohort of 263 HIV-1 infected patients attended in routine daily practice with sustained virological suppression confirms that switching to raltegravir due to toxicity, convenience or interactions was well-tolerated and secured virological suppression in the large majority of patients. (8). Switch to NRTI and PI-sparing regimen with RAL plus NVP, considering their renal tolerability, it could be a good therapeutic option for patients with risk factors for development of renal alterations. The combination of RAL based regimen to Nevirapine may have an additional favorable impact on lipid changes and allow marked viral suppression under threshold and control of HIV reservoirs, especially CNS compartment. Indeed, NVP has shown during the last years that patients switching from other regimen with undetectable viral load did not have a significantly higher risk of hepatotoxicity or rash when stratified by gender and CD4 cell count (9-10). More recently these results where strengthened showing a safe lipid profile with reduced hepatoxicity in a cohort of 508 patients through 9 years follow-up (11). NRTI and PI-sparing regimens may be useful to some HIV-infected patients and raltegravir and nevirapine are both potent antiretrovirals with good long-term safety profiles and may allow a durable suppression and a sustained improvement in renal function. Raltegravir, the first available INSTI, has demonstrated good tolerability over 5 years. Neither of these two antiretrovirals are associated with drug-limiting adverse events in the long-term, such as increased cardiovascular risk, lipid elevations, renal, bone or central nervous system toxicity. Furthermore, Raltegravir is metabolized primarily via uridine diphosfate glucuronosyltransferase (UGT) 1A1, instead of cytochrome P-450; therefore, no clinically meaningful drug-to-drug interaction is expected between raltegravir and nevirapine. The low genetic barrier of resistance of representatives of these classes could present a limitation to this combination, although their use in the setting of long-term virological suppression and good adherence might be less of an issue. Reliquet has published an experience of the use of this combination in 39 patients with long-term virological suppression on antiretroviral therapy throughout 36 months of follow-up, shown that this dual therapy was effective and had acceptable tolerance (median values of serum creatinine and lipids significantly improved after switch) and may provide an alternative strategy for those unable to tolerate NRTI or PI/r agents. (12).

Dual therapy based on raltegravir and nevirapine has been also recently proposed as a possible switching strategy in selected patients, by different italian groups. 75 patients on RAL and NVP since at least 3 months were retrospectively evaluated at 6 Italian HIV clinics. Switch to RAL/NVP regimen in patients with long-lasting virological suppression showed to be highly effective over a 2-years follow up (failure only in 2.7% of patients and limited to subgroup administered with RAL once-daily schedule). No patients discontinued the regimen due to tolerability issues and a significant decrease in abnormal triglycerides was reported. (13).

Lamivudine is an NRTI administered once daily or twice daily with optimal tolerability. Despite a low genetic barrier to resistance, the rapid development of the M184V mutation, conferring a high level of lamivudine resistance in vitro, has been associated with slower development or prevention of thymidine analogue mutations and increased susceptibility to tenofovir, zidovudine and other NRTIs. (14).

On these bases, a combination of raltegravir, nevirapine and lamivudine could be a suitable option for treatment simplification in stable suppressed patients.

5.2 Subject Population Rationale

The risk of experiencing CKD/ESRD/renal death is high only in patients with baseline eGFR ≤ 60 mL/min. The EuroSIDA study on 18295 HIV-positive patients reported that during a median follow-up period of 5.0 years, 58 persons experienced advanced CKD/ESRD/renal death. The median baseline eGFR in those with and without advanced CKD/ESRD/renal death was 59 and 98 mL/min,

respectively (p < 0.0001). Of those experiencing the endpoint, 51.7% had a baseline eGFR ≤ 60 mL/min compared with 3.2% of those not experiencing the endpoint. At 6 years after baseline, 0.83% were estimated to have experienced advanced CKD/ESRD/ renal death; in those with baseline eGFR ≤ 60 mL/min this was 11.26%, with much lower proportions in the eGFR 61–90 and > 90 mL/min groups (15).

The italian guidelines recommend that in patients treated with regimens including tenofovir, especially if associated with PI/r, physicians should reevaluate ongoing therapy only if the glomerular filtration rate is <60 mL/min or in the case of rapid decline of the same, taking into account the incomplete reversibility of the damage once instituted. No other recommendations are made for patients treated with TDF + PI/r with eGFR 61–90 mL/min, therefore these patients can continue on the current regimen (16)

In case of progressive impairment of renal function (measured by eGFR-MDRD 6 variables), the recommendations indicated in the TDF/FTC's IMP should be followed.

So according to these considerations HIV-infected patients without a history of virological failure, with stable suppressed HIV-1 RNA at < 50 copies/mL from at least 12 months and with a current stable ARV regimen based on TDF/FTC + PI/r (LPV/r, ATV/r, DAR/r) from at least 6 months will be enrolled No previous exposure to NNRTI or INI drug-classes and no previous intolerance to Lamivudine will be allowed, with a GFR estimated with MDRD formula with 6 variables between 60 and 90 mL/min/1.73 m^2 at baseline. This study is considered a pilot switch study with a comparator used as internal control without the aim to compare the two treatment groups.

The rationale of this study is to evaluate the feasibility of the experimental combination based on Raltegravir + Nevirapine + Lamivudine in virological suppressed patients, since the data in the clinical setting under this therapeutic approach are limited.

The hypothesis is that patients, stable suppressed, without any virological failure, switching to a regimen containing Raltegravir 400 mg BID + Lamivudine 150 mg BID + Nevirapine 200 mg QD for 14 days followed by 200 mg BID, will have an improvement in renal safety from the baseline (> or equal to 15 ml/min is expected).,

5.3 Dose and Administration Rationale

Patients in **Regimen A** switch to a regimen containing Raltegravir 400 mg BID (PO without regard to food) + Lamivudine 150 mg BID (PO without regard to food) + Nevirapine 200 mg QD for 14 days followed by 200 mg BID (PO without regard to food). All the drugs of the investigational arm are marketed in Italy and doses used correspond to the current approved dosing for regulatory purpose. According to the label indication of nevirapine into the IMP the lead-in period for nevirapine is mandatory (200 mg tablet daily for 14 days, followed by one 200 mg tablet twice daily).

Patients in **Regimen B** continue with the current regimen containing PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC. All the drugs of the non investigational arm are marketed in Italy and doses used correspond to the current approved dosing for regulatory purpose.

6.0 TRIAL OBJECTIVES

6.1 Primary Trial Objectives

To assess the changes in renal function (e.g. estimated GFR measured by MDRD formula with 6 variables that is MDRD 4 variables plus blood urea nitrogen and albumin) from baseline to 48 weeks.

6.2 Secondary Trial Objectives

a) To assess the efficacy (stable suppressed HIV-RNA <50 copies/ml) after switch from PI/r (LPV/r, ATV/r, DR/r) + TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
b) To evaluate the changes in T-lymphocyte CD4 cell count during 48 and 96 weeks of treatment
c) To assess laboratory alterations (liver enzymes, lipid profile) after switch from PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
d) To assess the safety (e.g. skin rash, GI disturbances) after switch from PI/r+ TDF/FTC to RAL + NVP + 3TC in patients with a stable HIV-1 RNA < 50 copies/mL in the previous 12 months during 48 and 96 weeks of treatment.
e) To assess the alterations of the tubular kidney injury markers: b2-microglobulin (b2M) and retinol-binding protein (RBP) and N-acetyl-b-D-glucosaminidase (NAG) during 48 and 96 weeks of treatment.
f) To assess metabolic bone markers changes: Serum Bone Specific Alkaline Phosphatase (s-BSAP), C-telopepdides of type I Collagen (s-CTx) during 48 and 96 weeks of treatment.
g) To assess bone mineral density modifications during 48 and 96 weeks of treatment.
h) To evaluate pharmacokinetics of RAL and NVP.
i) To assess the development of genotypic resistance at virologic failure
j) To evaluate the adherence during 48 and 96 weeks of treatment.
k) To assess the Fracture Risk (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment
l) To assess the VACS Risk Index during 48 and 96 weeks of treatment
m) The frequency of experiencing a decline of renal function in HIV-infected patients with an eGFR (MDRD-6 variables) < 60 mL/ min/1.73 m2 at 48 weeks of treatment
n) To evaluate the changes in eGFR-MDRD at 96 weeks of treatment

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

This is a pilot multicenter randomized, open-label, active-controlled, parallel-group, in patients with persistently (previous 12 months) suppressed plasma HIV viremia (< 50 copies/mL) after switch from PI/r plus TDF/FTC to a combination of Raltegravir 400 mg BID, plus 3TC 150 mg BID plus Nevirapine 200 mg BID. This study is a pilot switch study with a comparator used as internal control. No comparisons will be made between the groups. This study is designed as an estimation study only and no formal comparison between the two regimens is planned. The control arm will be not directly compared with the experimental arms and will act as a check to assess the internal validity of the study.

7.2 Beginning and End of the Trial

Each subject is considered to be enrolled in the trial when the subject (or the subject's legal representative) has provided written informed consent.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (e.g.,, visits or telephone contacts) or prematurely discontinues from the trial.

A subject is considered to have been a completer of the trial after he/she has completed all of the protocol-specified visits and activities.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in **Section 7.3.3**.

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

The overall trial begins when the first subject is enrolled (i.e., signs the informed consent form). The overall trial ends when the last remaining subject has ended participation in the trial, by completing the trial, being discontinued from the trial, or being lost to follow-up.

Each subject will be monitored for the occurrence of any AEs immediately after the subject has signed informed consent and until the last protocol specified visit (14 days post therapy follow-up) or discontinued the study.

Adverse events that are to be reported in the pre-randomization phase are limited to:

– Events that cause the subject to be excluded from the trial

– Events that are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Follow-up procedures related to pregnancy or SAEs may continue beyond the end of the clinical trial.

Once a subject has ended participation in the trial, the investigational product from the trial will no longer be available to the subject and any future care will be provided according to the subject's clinical site.

Each subject will participate in the trial for approximately 104 weeks, from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 6 weeks, each subject will receive assigned treatment (**Section 7.4.1.1**) for approximately 96 weeks and will be followed for 2 additional weeks post therapy.

7.3 Trial Population

HIV-infected adult subjects with stable suppressed HIV-1 RNA (< 50 copies/mL) from at least 12 months prior to the screening visit and with a current stable ARV regimen from at least 6 months (PI/r + TDF/FTC) and GFR measured by MDRD formula between 60 and 90 mL/min/1.73 m^2 will be selected to participate in the trial.

7.3.1 Subject Inclusion Criteria

A subject must meet all the criteria listed below to participate in the trial.

1. Each subject must be willing and able to provide written informed consent for the trial
2. Each subject must be ≥ 18 years of age
3. Each subject must be male or non-pregnant, non-breastfeeding female
4. Each subject must have diagnosis of HIV infection
5. Each subject must have no history of previous virological failure (defined as 2 consecutive plasma HIV-1 RNA >200 copies/mL at least two week apart while on previous or current ARV therapy)

6. Each subject must have no history of previous exposure to NNRTIs or INIs prior to entering the study
7. Each subject must have no history of previous intolerance to Lamivudine
8. Each subject must have at least 2 documented plasma HIV-1 RNA <50 copies/mL and no HIV-1 RNA > 50 copies/mL in the 12 months prior to the screening visit
9. Each subject must be taking the same PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC based ARV combination for at least 6 months before screening
10. Each subject mustn't have major IAS-USA mutations on genotypic testing performed before starting ARV treatment (genotype testing done before starting the first line therapy)
11. Each subject must have results of clinical laboratory tests (CBC, blood chemistries, and urinalysis) within normal limits or clinically acceptable to the investigator
12. Each subject must have results of a physical examination, including blood pressure, within normal limits or clinically acceptable limits to the investigator
13. Each subject must be able to adhere to dose and visit schedules
14. Each subject should have Creatinine Clearance between 60 and 90 mL/min/1.73 m^2 calculated according to MDRD 6 variables
15. Each sexually active subject and subject's partner(s) of child-bearing potential must agree to use each a medically acceptable method of contraception 2 weeks prior to Day 1 and at least 6 months after last dose of study drug

Medically accepted methods of contraception include condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, medically prescribed IUD, inert or copper-containing IUD, hormone-releasing IUD, systemic hormonal contraceptive, and surgical sterilization (e.g., hysterectomy or tubal ligation).

Postmenopausal women are not required to use contraception. Postmenopausal is defined as at least 12 consecutive months without a spontaneous menstrual period.

Each sexually active male subject with a female partner(s) of child-bearing potential must also provide written informed consent to provide information regarding any pregnancy.

7.3.2 Subject Exclusion Criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial:

1 The subject has HBsAg+ or anticipated need for HCV-treatment
2 The subject has grade 2-4 laboratory abnormality of liver transaminases (ALT and AST)
3 The subject has experiencing liver cirrhosis
4 The subject has history of diabetes mellitus (defined as initiation of antidiabetic treatment or verification of diabetes in a case report form)
5 The subject has any cancer (excluding stable Kaposi Sarcoma)
6 The subject has an allergy/sensitivity to investigational product or its/their excipients
7 The female subject is nursing
8 The female subject is pregnant or intending to become pregnant
9 The subject has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial. The subject in the opinion of the investigator has an excessive intake of alcohol and substances
10 The subject has active AIDS-defining event (CDC-C), exception for stable Kaposi Sarcoma, HIV Wasting Syndrome
11 The subject has used any investigational drugs within 30 days of screening

12 A subject who has participated in any other clinical trial within 30 days, inclusive, of signing the informed consent form of the current trial

13 The subject or a family member is among the personnel of the investigational or sponsor staff directly involved with this trial

7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason.

It is the right and the duty of the investigator or subinvestigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or subinvestigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results. If a subject discontinues prior to completion of the study, the reason for the discontinuation will be obtained. The date of the last dose of study medication and the date of the last assessment and/or contact will be obtained. This information will be documented in the appropriate section of the case report form (CRF). A follow-up contact (telephone or visit) will be arranged as appropriate. At the time of discontinuation, every effort should be made to ensure that all procedures and evaluations scheduled for the final treatment visit are performed. For all discontinued subjects, AEs should be recorded and medication compliance should be assessed.

Discontinuation from treatment is “permanent”: once a subject is discontinued, he/she shall not be allowed to enroll again.

At a minimum collect the following information when a subject discontinues:

1. The reason the subject discontinued
2. The date of the last dose of test products from the trial
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
4. Serious and non serious adverse events;
5. Compliance with the test product administration as specified in this protocol;
6. Final Assessments:

   Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed (**Section 2.2**, Trial Flow Chart)
7. Retrieve all IMPs from the subject.

A subject must be discontinued from the trial for any of the following reasons:

1. The subject or legal representative (such as a parent or legal guardian) withdraws consent;
2. Any patient who becomes pregnant during the course of the study must immediately be discontinued from all study medication. All pregnancies must be reported immediately to the SPONSOR and must be followed to the completion/termination of the pregnancy. The outcome of all pregnancies must be reported to the SPONSOR. Patients who become pregnant will be asked to join a pregnancy registry which collects information about the outcome of the pregnancy.

3. Patients who are compliant to therapy and who have virologic relapse, defined as: HIV RNA > 50 copies/mL (on 2 consecutive measurements at least 1 week apart.)
4. The subject requires any study drug dose and administration modifications.
5. Any other severe organ dysfunction/impairment treatment related and that require switching
6. In case of continuous deterioration of renal function (measured by eGFR-MDRD 6 variables), especially in patients assigned to continue baseline therapy (PI and TDF containing regimen) if creatinine clearance < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).
7. Subject requires use of a prohibited medication (see Section 7.4.2.1.1).
8. Subject experiences a severe toxicity due to nevirapine (see Section 7.7.2.3.2).

7.3.4 Replacement of Subjects

A subject who discontinues from the trial will not be replaced.

7.4 Treatments

7.4.1 Trial Treatments

7.4.1.1 Treatments Administered in the Experimental arm (Investigational Product, Dose, mode of Administration) - Regimen A

- Raltegravir 400 mg tab., 400 mg b.i.d. PO plus Nevirapine 200 mg tab., 200 mg QD for 14 days followed by 200 mg b.i.d. PO plus Lamivudine 150 mg tab., 150 mg b.i.d. PO

  (The choice to use nevirapine and lamivudine BID is to propose a symmetric therapy since Raltegravir should be administered twice)

7.4.1.2 Treatments Administered in the Non Experimental arm/control arm (Product, Dose, mode of Administration) - Regimen B

- Tenofovir Disoproxil Fumarate/Emtricitabine 300/200 mg tab., 300/200 mg q.d. PO plus Lopinavir/ritonavir 200/50 mg tab., 400/100 mg b.i.d., PO or 800 mg/200 mg q.d. PO

  or

- Tenofovir Disoproxil Fumarate/Emtricitabine 300/200 mg tab., 300/200 mg q.d. PO plus Atazanavir + Ritonavir 300 mg + 100 mg tab., 300 mg + 100 mg q.d., PO

  or

- Tenofovir Disoproxil Fumarate/Emtricitabine 300/200 mg tab., 300/200 mg q.d. PO plus Darunavir + Ritonavir 400 mg + 100 mg tab., 800 mg + 100 mg q.d., PO or 600 mg + 100 mg tab., 600 mg + 100 mg b.i.d. PO

7.4.1.3 Method of Treatment Assignment, Randomization, and/or Stratification

For identification purposes during the screening period (Visit 1 – Screening) , each eligible patient will be sequentially assigned by eCRF to a unique identification screening number with the format XXX-S-YYY, where "XXX" is the site number, "S" stands for "Screening" and "YYY" is the progressive patient number within each site. If a subject discontinues from the study, the subject number will not be re-used, and the subject will not be allowed to re-enter the study. The screening failure patients will be registered in the eCRF collecting only the demographic data and the reason for screening failure.

The subjects must meet all the inclusion criteria and none of the exclusion criteria to receive treatment assignment. All drugs will be dispensed to all subjects in an open-label manner. At Visit 2 (Baseline), patients meeting all the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio, via e-CRF, to one of the following two treatment groups:

- Regimen A: switching to a regimen containing Raltegravir 400 mg BID PO+ Lamivudine 150 BID PO, + Nevirapine 200 mg QD for 14 days followed by 200 mg BID PO

- Regimen B: continue with the current regimen containing PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC

The principal investigator will receive a notification via the e-CRF assigning the treatment group ("REGIMEN A" or "REGIMEN B") and the randomization number to the patients. Each randomized patient, will be sequentially assigned to a unique 3-digits randomization number (starting from 001 up to 100). It is the responsibility of the Investigator (or designee) to explain, and make sure patient fully understands any appropriate treatment related information. Before dispensing the treatment kit to the patient, the investigator must report on the label the site number, the Investigator name, the randomization number and the treatment group assigned.

The randomization list will be generated using PROC PLAN procedure (SAS® System version 9.2). No stratification factors based on age, sex, or other patient characteristics will be performed.

Recruitment will be competitive among the study sites, until the planned number of patients is enrolled. Competitive recruitment has been chosen to increase the speed of recruitment.

Treatment should be started as close as possible to the date in which randomized treatment is assigned, preferably on the same day.

7.4.1.4 Selection and Timing of Dose for Each Subject

7.4.1.3.1. Selecting the Dose for Each Subject

The rationale for the selection of doses to be used in this trial is presented in **Section 5.3**.

7.4.1.3.2. Determining the Timing of Dose Administration for Each Subject

- **Regimen A**: Switching to a regimen containing Raltegravir 400 mg BID PO+ Lamivudine 150 BID PO + Nevirapine 200 mg QD for 14 days followed by 200 mg BID PO
- **Regimen B (control arm):** continue with the current regimen containing PI/r (LPV/r, ATV/r, DAR/r) PO + TDF/FTC 300 mg/200 mg QD PO.

7.4.1.5 Blinding Trial Treatments

All drugs will be dispensed to all subjects in an open-label manner.

7.4.1.6 Investigational Medicinal Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, handling, storage, distribution, and usage of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.6.1 Identity of Investigational Medicinal Product(s)

- Raltegravir 400 mg
- Nevirapine 200 mg
- Lamivudine 150 mg

7.4.1.6.2 Source

MSD will provide all supplies as follows:

- Raltegravir 400 mg film-coated tablets
- Nevirapine 200 mg tablets
- Lamivudine 150 mg film-coated tablets

All the above listed supplies will be locally sourced.

For this study MSD will provide the branded drugs of Nevirapine - Viramune® - and Lamivudine - Epivir® - . No generic forms of 3TC and NVP will be provided.

7.4.1.6.3 Labeling

Raltegravir, Lamivudine and Nevirapine, will be provided open label with commercial labels. A secondary label specifying study number, Labeling Request number, investigational use statement, appropriate caution statement, instructions to take as directed and Sponsor details will be applied. Secondary label will also contain a space for the subject number, site number and investigator name that will be written in at the study center.

7.4.1.6.4 Packaging

Raltegravir 400 mg tablets will be supplied as single bottles with child-resistant closure containing 60 tablets or multi-pack containing 3 bottles of 60 tablets, depending on country availability.

Nevirapine 200 mg tablets will be supplied as cartons containing 6 or 12 blister cards (60 or 120 tablets), depending on country availability.

Lamivudine 150 mg tablets will be supplied as bottles with child resistant closure or blister packs each containing 60 tablets, depending on country availability.

7.4.1.6.5 Storage

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

7.4.1.6.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in **Section 2.2** for a schedule of when clinical supplies are to be dispensed to the subjects.

Subjects should be dispensed a quantity of drugs that will allow them to have an adequate supply until their next visit plus one week extra supply in case their visit is delayed.

The principal investigator agrees neither to dispense study drugs from nor store them at any site(s) other than the study site(s). The principal investigator agrees that study drugs will be dispensed by the site's designee. The principal investigator and site personnel also agree that study drugs will be dispensed only to study subjects who have provided written informed consent and have met all entry criteria. Study drugs may not be used for any purpose other than that stated in the protocol. Study drugs should be dispensed as appropriate based on the subject's treatment visit schedule.

7.4.1.6.7 Replacement of Investigational Product

Lost or damaged supplies of Raltegravir, Nevirapine and Lamivudine will be replaced by the study center as needed.

7.4.1.6.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational product(s) will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal product(s) dispensed to each site will be recorded in the trial-specific Site Investigational Medicinal Product (IMP) Accountability Log (or equivalent document approved by the sponsor);
- Investigational medicinal product(s) dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document approved by the sponsor).

The Site IMP Accountability Log and Subject IMP Accountability Log will be verified by the sponsor's trial monitor or sponsor's designee. The original Site IMP Accountability Log and Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the sponsor or designee when the trial is complete.

Each subject will be instructed by the investigator or designee to return all unused and partially used IMPs to the site at all protocol-specified visits. In the event the investigational product destruction is arranged by the site (only under instructions from the sponsor), copies of the destruction records should be returned to the sponsor. The sponsor's trial monitor or its designee will instruct the site on the return of all investigational product(s) supplies. A final inventory of the total amount of investigational product(s) received at each trial site against the amount used and returned must be

recorded in the Site IMP Accountability Log. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Trial Treatments

7.4.2.1 Prior and Concomitant Medications

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited Prior to Baseline and During the Trial

The prohibited Substances are listed in the drug-drug interactions section into the drugs SmPC.. It is responsibility of the investigator to check on potential drug-drug interactions, before placing a patient on a specific therapy.

The list of drug-drug interactions for each drug reported below is referring to the SmPC in force at the time of finalization of Amendment 03. For any future updates to the SmPC it is the responsibility of the investigator to check on potential drug-drug interactions, before placing a patient on a specific therapy.

The drug-drug interaction profiles of the experimental IMP are:

- Raltegravir

In vitro studies indicate that raltegravir is not a substrate of cytochrome P450 (CYP) enzymes, does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A, does not induce CYP3A4 and does not inhibit P glycoprotein mediated transport. Based on these data, raltegravir is not expected to affect the pharmacokinetics of medicinal products that are substrates of these enzymes or P-glycoprotein. Based on in vitro and in vivo studies, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. Although in vitro studies indicated that raltegravir is not an inhibitor of the UDP glucuronosyltransferases (UGTs) 1A1 and 2B7, one clinical study has suggested that some inhibition of UGT1A1 may occur in vivo based on effects observed on bilirubin glucuronidation. However, the magnitude of the effect seems unlikely to result in clinically important drug drug interactions. Considerable inter- and intra-individual variability was observed in the pharmacokinetics of raltegravir. The following drug interaction information is based on Geometric Mean values; the effect for an individual patient cannot be predicted precisely.

In interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of etravirine, maraviroc, tenofovir, hormonal contraceptives, methadone, or midazolam.

Given that raltegravir is metabolised primarily via UGT1A1, caution should be used when co administering raltegravir with strong inducers of UGT1A1 (e.g., rifampicin). Rifampicin reduces plasma levels of raltegravir; the impact on the efficacy of raltegravir is unknown. However, if co administration with rifampicin is unavoidable, a doubling of the dose ofraltegravir can be considered. The impact of other strong inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown. Less potent inducers (e.g., efavirenz, nevirapine, etravirine, rifabutin, glucocorticoids, St. John's wort, pioglitazone) may be used with the recommended dose of raltegravir.

Co administration of raltegravir with medicinal products that are known to be potent UGT1A1 inhibitors (e.g., atazanavir) may increase plasma levels of raltegravir. Less potent UGT1A1 inhibitors (e.g., indinavir, saquinavir) may also increase plasma levels of raltegravir, but to a lesser extent compared with atazanavir. In addition, tenofovir may increase plasma levels of raltegravir, however, the mechanism for this effect is unknown (see Table 1). From the clinical trials, a large proportion of patients used atazanavir and / or tenofovir, both agents that result in increases in raltegravir plasma levels, in the optimised background regimens. The safety profile observed in patients who used

atazanavir and / or tenofovir was generally similar to the safety profile of patients who did not use these agents. Therefore no dose adjustment is required. In healthy subjects, co administration of raltegravir with omeprazole increases raltegravir plasma levels. As the effects of increasing gastric pH on the absorption of raltegravir in HIV-infected patients are uncertain, use raltegravir with medicinal products that increase gastric pH (e.g., proton pump inhibitors and H2 antagonists) only if unavoidable.

In the pharmacokinetic Interaction Data table are listed the recommendations concerning the co-administration of raltegravir with the others drugs and the drugs contraindicated with raltegravir and not allowed during the study.

Pharmacokinetic Interaction Data

Medicinal products by therapeutic area	**Interaction** (mechanism, if known)	**Recommendations concerning co-administration**
ANTI-RETROVIRAL		
Protease inhibitors (PI)		
atazanavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 41 % raltegravir C_{12hr} ↑ 77 % raltegravir C_{max} ↑ 24 % (UGT1A1 inhibition)	No dose adjustment required for ISENTRESS.
tipranavir /ritonavir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 24 % raltegravir C_{12hr} ↓ 55 % raltegravir C_{max} ↓ 18 % (UGT1A1 induction)	No dose adjustment required for ISENTRESS.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
efavirenz (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 36 % raltegravir C_{12hr} ↓ 21 % raltegravir C_{max} ↓ 36 % (UGT1A1 induction)	No dose adjustment required for ISENTRESS.
etravirine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 10 % raltegravir C_{12hr} ↓ 34 % raltegravir C_{max} ↓ 11 % (UGT1A1 induction) etravirine AUC ↑ 10 % etravirine C_{12hr} ↑ 17 % etravirine C_{max} ↑ 4 %	No dose adjustment required for ISENTRESS or etravirine.
Nucleoside/tide reverse transcriptase inhibitors		

tenofovir (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 49 % raltegravir C_{12hr} ↑ 3 % raltegravir C_{max} ↑ 64 % (mechanism of interaction unknown) tenofovir AUC ↓ 10 % tenofovir C_{24hr} ↓ 13 % tenofovir C_{max} ↓ 23 %	No dose adjustment required for ISENTRESS or tenofovir disoproxil fumarate.
CCR5 inhibitors		
maraviroc (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 37 % raltegravir C_{12hr} ↓ 28 % raltegravir C_{max} ↓ 33 % (mechanism of interaction unknown) maraviroc AUC ↓ 14 % maraviroc C_{12hr} ↓ 10 % maraviroc C_{max} ↓ 21 %	No dose adjustment required for ISENTRESS or maraviroc.
HCV ANTIVIRALS		
NS3/4A protease inhibitors (PI)		
boceprevir (raltegravir 400 mg Single Dose)	raltegravir AUC ↑ 4 % raltegravir C_{12hr} ↓ 25 % raltegravir C_{max} ↑ 11 % (mechanism of interaction unknown)	No dose adjustment required for ISENTRESS or boceprevir.
ANTIMICROBIALS		
Antimycobacterial		
rifampicin (raltegravir 400 mg Single Dose)	raltegravir AUC ↓ 40 % raltegravir C_{12hr} ↓ 61 % raltegravir C_{max} ↓ 38 % (UGT1A1 induction)	Rifampicin reduces plasma levels of ISENTRESS. If co-administration with rifampicin is unavoidable, a doubling of the dose of ISENTRESS can be considered (see section 4.4). NOTE: Doubling of the raltegravir dose is not permitted in P284. Patients who require use of rifampicin will need to be discontinued from the study.
SEDATIVE		

midazolam (**raltegravir** 400 mg Twice Daily)	midazolam AUC ↓ 8 % midazolam C_{max} ↑ 3 %	No dosage adjustment required for ISENTRESS or midazolam. These results indicate that raltegravir is not an inducer or inhibitor of CYP3A4, and raltegravir is thus not anticipated to affect the pharmacokinetics of medicinal products which are CYP3A4 substrates.
METAL CATION ANTACIDS		
aluminium and magnesium hydroxide antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 49 % raltegravir $C_{12\ hr}$ ↓ 63 % raltegravir C_{max} ↓ 44 % 2hoursbeforeraltegravir raltegravir AUC ↓ 51 % raltegravir $C_{12\ hr}$ ↓ 56 % raltegravir C_{max} ↓ 51 % 2 hours after raltegravir raltegravir AUC ↓ 30 % raltegravir $C_{12\ hr}$ ↓ 57 % raltegravir C_{max} ↓ 24 % 6hoursbeforeraltegravir raltegravir AUC ↓ 13 % raltegravir $C_{12\ hr}$ ↓ 50 % raltegravir C_{max} ↓ 10 % 6 hours after raltegravir raltegravir AUC ↓ 11 % raltegravir $C_{12\ hr}$ ↓ 49 % raltegravir C_{max} ↓ 10 % (chelation of metal cations)	Aluminium and magnesium containing antacids reduce raltegravir plasma levels. Co-administration of ISENTRESS with aluminium and/or magnesium containing antacids is not recommended.
calcium carbonate antacid (raltegravir 400 mg Twice Daily)	raltegravir AUC ↓ 55 % raltegravir $C_{12\ hr}$ ↓ 32 % raltegravir C_{max} ↓ 52 % (chelation of metal cations)	No dose adjustment required for ISENTRESS.
H2 BLOCKERS AND PROTON PUMP INHIBITORS		
omeprazole (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 37 % raltegravir $C_{12\ hr}$ ↑ 24 % raltegravir C_{max} ↑ 51 % (increased solubility)	No dose adjustment required for ISENTRESS.

famotidine (raltegravir 400 mg Twice Daily)	raltegravir AUC ↑ 44 % raltegravir $C_{12\ hr}$ ↑ 6 % raltegravir C_{max} ↑ 60 % (increased solubility)	No dose adjustment required for ISENTRESS.
HORMONAL CONTRACEPTIVES		
Ethinyl Estradiol **Norelgestromin** (raltegravir 400 mg Twice Daily)	Ethinyl Estradiol AUC ↓ 2 % Ethinyl Estradiol C_{max} ↑ 6 % Norelgestromin AUC ↑ 14 % Norelgestromin C_{max} ↑ 29 %	No dosage adjustment required for ISENTRESS or hormonal contraceptives (estrogen- and/or progesterone-based).
OPIOID ANALGESICS		
methadone (raltegravir 400 mg Twice Daily)	methadone AUC ↔ methadone C_{max} ↔	No dose adjustment required for ISENTRESS or methadone.

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- Nevirapine

Nevirapine is an inducer of CYP3A and potentially CYP2B6, with maximal induction occurring within 2-4 weeks of initiating multiple-dose therapy. Compounds using this metabolic pathway may have decreased plasma concentrations when coadministered with nevirapine. Careful monitoring of the therapeutic effectiveness of P450 metabolised medicinal products is recommended when taken in combination with nevirapine. The absorption of nevirapine is not affected by food, antacids or medicinal products which are formulated with an alkaline buffering agent.

The interaction data is presented as geometric mean value with 90% confidence interval (90% CI) whenever these data were available in the below table 2. ND = Not Determined, ↑ = Increased, ↓ = Decreased, ↔ = No Effect

Pharmacokinetic Interaction Data

Medicinal products by therapeutic areas	**Interaction**	**Recommendations concerning co-administration**
ANTI-INFECTIVES		
ANTIRETROVIRALS		
NRTIs		
Didanosine 100-150 mg BID	Didanosine AUC ↔ 1.08 (0.92-1.27) Didanosine C_{min} ND Didanosine C_{max} ↔ 0.98 (0.79-1.21)	Didanosine and Viramune can be co-administered without dose adjustments.
Emtricitabine	Emtricitabine is not an inhibitor of human CYP 450 enzymes.	Viramune and emtricitabine may be coadministered without dose adjustments.
Abacavir	In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms.	Viramune and abacavir may be coadministered without dose adjustments.

Lamivudine 150 mg BID	No changes to lamivudine apparent clearance and volume of distribution, suggesting no induction effect of nevirapine on lamivudine clearance.	Lamivudine and Viramune can be co-administered without dose adjustments.
Stavudine: 30/40 mg BID	Stavudine AUC ↔ 0.96 (0.89-1.03) Stavudine C_{min} ND	Stavudine and Viramune can be co-administered without dose
	Stavudine C_{max} ↔ 0.94 (0.86-1.03) Nevirapine: compared to historical controls, levels appeared to be unchanged.	adjustments.
Tenofovir 300 mg QD	Tenofovir plasma levels remain unchanged when co-administered with nevirapine. Nevirapine plasma levels were not altered by co-administration of tenofovir.	Tenofovir and Viramune can be co-administered without dose adjustments.
Zidovudine 100-200 mg TID	Zidovudine AUC ↓ 0.72 (0.60-0.96) Zidovudine C_{min} ND Zidovudine C_{max} ↓ 0.70 (0.49-1.04) Nevirapine: Zidovudine had no effect on its pharmacokinetics.	Zidovudine and Viramune can be co-administered without dose adjustments Granulocytopenia is commonly associated with zidovudine. Therefore, patients who receive nevirapine and zidovudine concomitantly and especially paediatric patients and patients who receive higher zidovudine doses or patients with poor bone marrow reserve, in particular those with advanced HIV disease, have an increased risk of granulocytopenia. In such patients haematological parameters should be carefully monitored.
NNRTIs		
Efavirenz 600 mg QD	Efavirenz AUC ↓ 0.72 (0.66-0.86) Efavirenz C_{min} ↓ 0.68 (0.65-0.81) Efavirenz C_{max} ↓ 0.88 (0.77-1.01)	It is not recommended to co-administer efavirenz and Viramune (see section 4.4), because of additive toxicity and no benefit in terms of efficacy over either NNRTI alone (for results of 2NN study, see section 5.1).

Delavirdine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
Etravirine	Concomitant use of etravirine with nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of etravirine.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
Rilpivirine	Interaction has not been studied.	The concomitant administration of Viramune with NNRTIs is not recommended (see section 4.4).
PIs		
Atazanavir/ritonavir 300/100 mg QD 400/100 mg QD	Atazanavir/r300/100mg: Atazanavir/r AUC ↓ 0.58 (0.48-0.71) Atazanavir/r C_{min} ↓ 0.28 (0.20-0.40) Atazanavir/r C_{max} ↓ 0.72 (0.60-0.86) Atazanavir/r400/100mg: Atazanavir/r AUC ↓ 0.81 (0.65-1.02) Atazanavir/r C_{min} ↓ 0.41 (0.27-0.60) Atazanavir/r C_{max} ↔ 1.02 (0.85–1.24) (compared to 300/100mg without nevirapine) Nevirapine AUC ↑ 1.25 (1.17-1.34) Nevirapine C_{min} ↑ 1.32 (1.22–1.43) Nevirapine C_{max} ↑ 1.17 (1.09-1.25)	It is not recommended to co-administer atazanavir/ritonavir and Viramune (see section 4.4).
Darunavir/ritonavir 400/100 mg BID	Darunavir AUC ↑ 1.24 (0.97-1.57) Darunavir C_{min} ↔ 1.02 (0.79-1.32) Darunavir C_{max} ↑ 1.40 (1.14-1.73) Nevirapine AUC ↑ 1.27 (1.12-1.44) Nevirapine C_{min} ↑ 1.47 (1.20-1.82) Nevirapine C_{max} ↑ 1.18 (1.02-1.37)	Darunavir and Viramune can be co-administered without dose adjustments.

Fosamprenavir 1,400 mg BID	Amprenavir AUC ↓ 0.67 (0.55-0.80) Amprenavir C_{min} ↓ 0.65 (0.49-0.85) Amprenavir C_{max} ↓ 0.75 (0.63-0.89) Nevirapine AUC ↑ 1.29 (1.19-1.40) Nevirapine C_{min} ↑ 1.34 (1.21-1.49) Nevirapine C_{max} ↑ 1.25 (1.14-1.37)	It is not recommended to co-administer fosamprenavir and Viramune if fosamprenavir is not co-administered with ritonavir (see section 4.4).
Fosamprenavir/ritonavir 700/100 mg BID	Amprenavir AUC ↔ 0.89 (0.77-1.03) Amprenavir C_{min} ↓ 0.81 (0.69-0.96) Amprenavir C_{max} ↔ 0.97 (0.85-1.10) Nevirapine AUC ↑ 1.14 (1.05-1.24) Nevirapine C_{min} ↑ 1.22 (1.10-1.35) Nevirapine C_{max} ↑ 1.13 (1.03-1.24)	Fosamprenavir/ritonavir and Viramune can be co-administered without dose adjustments
Lopinavir/ritonavir (capsules) 400/100 mg BID	Adultpatients: Lopinavir AUC ↓ 0.73 (0.53-0.98) Lopinavir C_{min} ↓ 0.54 (0.28-0.74) Lopinavir C_{max} ↓ 0.81 (0.62-0.95)	An increase in the dose of lopinavir/ritonavir to 533/133 mg (4 capsules) or 500/125 mg (5 tablets with 100/25 mg each) twice daily with food is recommended in combination with Viramune. Dose adjustment of Viramune is not required when co-administered with lopinavir.
Lopinavir/ritonavir (oral solution) 300/75 mg/m2 BID	Paediatric patients: Lopinavir AUC □ 0.78 (0.56-1.09) Lopinavir Cmin □ 0.45 (0.25-0.82) Lopinavir Cmax □ 0.86 (0.64-1.16)	For children, increase of the dose of lopinavir/ritonavir to 300/75 mg/m2 twice daily with food should be considered when used in combination with Viramune, particularly for patients in whom reduced susceptibility to lopinavir/ritonavir is suspected.
Ritonavir 600 mg BID	Ritonavir AUC□ 0.92 (0.79-1.07) Ritonavir Cmin □ 0.93 (0.76-1.14) Ritonavir Cmax □ 0.93 (0.78-1.07) Nevirapine: Co-administration of ritonavir does not lead to any clinically relevant change in nevirapine plasma levels.	Ritonavir and Viramune can be co-administered without dose adjustments.

Saquinavir/ritonavir	The limited data available with saquinavir soft gel capsule boosted with ritonavir do not suggest any clinically relevant interaction between saquinavir boosted with ritonavir and nevirapine	Saquinavir/ritonavir and Viramune can be co-administered without dose adjustments.
Tipranavir/ritonavir 500/200 mg BID	No specific drug-drug interaction study has been performed. The limited data available from a phase IIa study in HIV-infected patients have shown a clinically non significant 20% decrease of TPV Cmin.	Tipranavir and Viramune can be co-administered without dose adjustments.
ENTRY INHIBITORS		
Enfuvirtide	Due to the metabolic pathway no clinically significant pharmacokinetic interactions are expected between enfuvirtide and nevirapine.	Enfuvirtide and Viramune can be co-administered without dose adjustments.
Maraviroc 300 mg QD	Maraviroc AUC ↔ 1.01 (0.6 -1.55) Maraviroc C_{min} ND Maraviroc C_{max} ↔ 1.54 (0.94-2.52) compared to historical controls Nevirapine concentrations not measured, no effect is expected.	Maraviroc and Viramune can be co-administered without dose adjustments.
INTEGRASE INHIBITORS		
Elvitegravir/ cobicistat	Interaction has not been studied. Cobicistat, a cytochrome P450 3A inhibitor significantly inhibits hepatic enzymes, as well as other metabolic pathways. Therefore coadministration would likely result in altered plasma levels of cobicistat and Viramune.	Coadministration of Viramune with elvitegravir in combination with cobicistat is not recommended (see section 4.4).
Raltegravir 400 mg BID	No clinical data available. Due to the metabolic pathway of raltegravir no interaction is expected.	Raltegravir and Viramune can be co-administered without dose adjustments.

ANTIBIOTICS		
Clarithromycin 500 mg BID	Clarithromycin AUC ↓ 0.69 (0.62-0.76) Clarithromycin C_{min} ↓ 0.44 (0.30-0.64) Clarithromycin C_{max} ↓ 0.77 (0.69-0.86) Metabolite 14-OH clarithromycin AUC ↑ 1.42 (1.16-1.73) Metabolite 14-OH clarithromycin C_{min} ↔ 0 (0.68-1.49) Metabolite 14-OH clarithromycin C_{max} ↑ 1.47 (1.21-1.80) Nevirapine AUC ↑ 1.26 Nevirapine C_{min} ↑ 1.28 Nevirapine C_{max} ↑ 1.24 compared to historical controls.	Clarithromycin exposure was significantly decreased, 14-OH metabolite exposure increased. Because the clarithromycin active metabolite has reduced activity against *Mycobacterium avium-intracellulare complex* overall activity against the pathogen may be altered. Alternatives to clarithromycin, such as azithromycin should be considered. Close monitoring for hepatic abnormalities is recommended
Rifabutin 150 or 300 mg QD	Rifabutin AUC ↑ 1.17 (0.98-1.40) Rifabutin C_{min} ↔ 1.07 (0.84-1.37) Rifabutin C_{max} ↑ 1.28 (1.09-1.51) Metabolite 25-O-desacetylrifabutin AUC ↑ 1.24 (0.84-1.84) Metabolite 25-O-desacetylrifabutin C_{min} ↑ 1.22 (0.86-1.74) Metabolite 25-O-desacetylrifabutin C_{max} ↑ 1.29 (0.98-1.68) A clinically not relevant increase in the apparent clearance of nevirapine (by 9%) compared to historical data was reported.	No significant effect on rifabutin and Viramune mean PK parameters is seen. Rifabutin and Viramune can be co-administered without dose adjustments. However, due to the high interpatient variability some patients may experience large increases in rifabutin exposure and may be at higher risk for rifabutin toxicity. Therefore, caution should be used in concomitant administration.
Rifampicin 600 mg QD	Rifampicin AUC ↔ 1.11 (0.96-1.28) Rifampicin C_{min} ND Rifampicin C_{max} ↔ 1.06 (0.91-1.22) Nevirapine AUC ↓ 0.42 Nevirapine C_{min} ↓ 0.32 Nevirapine C_{max} ↓ 0.50 compared to historical controls.	It is not recommended to co-administer rifampicin and Viramune (see section 4.4). Physicians needing to treat patients co-infected with tuberculosis and using a Viramune containing regimen may consider co-administration of rifabutin instead.
ANTIFUNGALS		
Fluconazole	Fluconazole AUC ↔ 0.94 (0.88-	Because of the risk of increased

200 mg QD	1.01) Fluconazole C_{min} ↔ 0.93 (0.86-1.01) Fluconazole C_{max} ↔ 0.92 (0.85-0.99) Nevirapine: exposure: ↑100% compared with historical data where nevirapine was administered alone.	exposure to Viramune, caution should be exercised if the medicinal products are given concomitantly and patients should be monitored closely.
Itraconazole 200 mg QD	Itraconazole AUC ↓ 0.39 Itraconazole C_{min} ↓ 0.13 Itraconazole C_{max} ↓ 0.62 Nevirapine: there was no significant difference in nevirapine pharmacokinetic parameters.	A dose increase for itraconazole should be considered when these two agents are administered concomitantly.
Ketoconazole 400 mg QD	Ketoconazole AUC ↓ 0.28 (0.20-0.40) Ketoconazole C_{min} ND Ketoconazole C_{max} ↓ 0.56 (0.42-0.73) Nevirapine: plasma levels: ↑ 1.15-1.28 compared to historical controls.	It is not recommended to co-administer ketoconazole and Viramune (see section 4.4).
ANTIVIRALS FOR CHRONIC HEPATITIS B AND C		
Adefovir	Results of *in vitro* studies showed a weak antagonism of nevirapine by adefovir (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Adefovir did not influence any of the common CYP isoforms known to be involved in human drug metabolism and is excreted renally. No clinically relevant drug-drug interaction is expected.	Adefovir and Viramune may be coadministered without dose adjustments.

Boceprevir	Boceprevir is partly metabolized by CYP3A4/5. Co-administration of boceprevir with medicines that induce or inhibit CYP3A4/5 could increase or decrease exposure. Plasma trough concentrations of boceprevir were decreased when administered with an NNRTI with a similar metabolic pathway as nevirapine. The clinical outcome of this observed reduction of boceprevir trough concentrations has not been directly assessed.	It is not recommended to coadminister boceprevir and Viramune (see section 4.4).
Entecavir	Entecavir is not a substrate, inducer or an inhibitor of cytochrome P450 (CYP450) enzymes. Due to the metabolic pathway of entecavir, no clinically relevant drug-drug interaction is expected.	Entecavir and Viramune may be coadministered without dose adjustments.
Interferons (pegylated interferons alfa 2a and alfa 2b)	Interferons have no known effect on CYP 3A4 or 2B6. No clinically relevant drug-drug interaction is expected.	Interferons and Viramune may be coadministered without dose adjustments.
Ribavirin	Results of *in vitro* studies showed a weak antagonism of nevirapine by ribavirin (see section 5.1), this has not been confirmed in clinical trials and reduced efficacy is not expected. Ribavirin does not inhibit cytochrome P450 enzymes, and there is no evidence from toxicity studies that ribavirin induces liver enzymes. No clinically relevant drug-drug interaction is expected.	Ribavirin and Viramune may be coadministered without dose adjustments.

Telaprevir	Telaprevir is metabolised in the liver by CYP3A and is a P-glycoprotein substrate. Other enzymes may be involved in the metabolism. Co-administration of telaprevir and medicinal products that induce CYP3A and/or P-gp may decrease telaprevir plasma concentrations. No drug-drug interaction study of telaprevir with nevirapine has been conducted, however, interaction studies of telaprevir with an NNRTI with a similar metabolic pathway as nevirapine demonstrated reduced levels of both. Results of DDI studies of telaprevir with efavirenz indicate that caution should be exercised when co-administering telaprevir with P450 inducers.	Caution should be exercised when co-administering telaprevir with nevirapine. If co-administered with Viramune, an adjustment in the telaprevir dose should be considered.
Telbivudine	Telbivudine is not a substrate, inducer or inhibitor of the cytochrome P450 (CYP450) enzyme system. Due to the metabolic pathway of telbivudine, no clinically relevant drug-drug interaction is expected.	Telbivudine and Viramune may be coadministered without dose adjustments.
ANTACIDS		
Cimetidine	Cimetidine: no significant effect on cimetidine PK parameters is seen. Nevirapine C_{min} ↑ 1.07	Cimetidine and Viramune can be co-administered without dose adjustments.
ANTITHROMBOTICS		
Warfarin	The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly.	Close monitoring of anticoagulation levels is warranted.
CONTRACEPTIVES		
Depo-medroxyprogesterone acetate (DMPA) 150 mg every 3 months	DMPA AUC ↔ DMPA C_{min} ↔ DMPA C_{max} ↔ Nevirapine AUC ↑ 1.20 Nevirapine C_{max} ↑ 1.20	Viramune co-administration did not alter the ovulation suppression effects of DMPA. DMPA and Viramune can be co-administered without dose adjustments.

Ethinyl estradiol (EE) 0.035 mg	EE AUC ↓ 0.80 (0.67 - 0.97) EE C_{min} ND EE C_{max} ↔ 0.94 (0.79 - 1.12)	Oral hormonal contraceptives should not be used as the sole method of contraception in women taking Viramune (see section 4.4). Appropriate doses for hormonal contraceptives (oral or other forms of application) other than DMPA in combination with Viramune have not been established with respect to safety and efficacy.
Norethindrone (NET) 1.0 mg QD	NET AUC ↓ 0.81 (0.70 - 0.93) NET C_{min} ND NET C_{max} ↓ 0.84 (0.73 - 0.97)	
ANALGESICS/OPIOIDS		
Methadone Individual Patient Dosing	Methadone AUC ↓ 0.40 (0.31 - 0.51) Methadone C_{min} ND Methadone C_{max} ↓ 0.58 (0.50 - 0.67)	Methadone-maintained patients beginning Viramune therapy should be monitored for evidence of withdrawal and methadone dose should be adjusted accordingly.
HERBAL PRODUCTS		
St. John's Wort	Serum levels of nevirapine can be reduced by concomitant use of the herbal preparation St. John's Wort (*Hypericum perforatum*). This is due to induction of medicinal product metabolism enzymes and/or transport proteins by St. John's Wort.	Herbal preparations containing St. John's Wort and Viramune must not be co-administered (see section 4.3). If a patient is already taking St. John's Wort check nevirapine and if possible viral levels and stop St. John's Wort. Nevirapine levels may increase on stopping St. John's Wort. The dose of Viramune may need adjusting. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's Wort.

(19)

- Lamivudine

The likelihood of metabolic interactions is low due to limited metabolism and plasma protein binding and almost complete renal clearance.

Administration of trimethoprim/sulfamethoxazole 160 mg/800 mg results in a 40 % increase in lamivudine exposure, because of the trimethoprim component; the sulfamethoxazole component did not interact. However, unless the patient has renal impairment, no dosage adjustment of lamivudine is necessary. Lamivudine has no effect on the pharmacokinetics of trimethoprim or sulfamethoxazole. When concomitant administration is warranted, patients should be monitored clinically. Co-administration of lamivudine with high doses of co-trimoxazole for the treatment of Pneumocystis carinii pneumonia (PCP) and toxoplasmosis should be avoided.

The possibility of interactions with other medicinal products administered concurrently should be considered, particularly when the main route of elimination is active renal secretion via the organic cationic transport system e.g. trimethoprim. Other medicinal products (e.g. ranitidine, cimetidine) are

eliminated only in part by this mechanism and were shown not to interact with lamivudine. The nucleoside analogues (e.g. didanosine) like zidovudine, are not eliminated by this mechanism and are unlikely to interact with lamivudine.

A modest increase in Cmax (28 %) was observed for zidovudine when administered with lamivudine, however overall exposure (AUC) is not significantly altered. Zidovudine has no effect on the pharmacokinetics of lamivudine.

Lamivudine metabolism does not involve CYP3A, making interactions with medicinal products metabolised by this system (e.g. PIs) unlikely (20).

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the Medications, Supplements, and Other Substances Prohibited Prior to Baseline and During the Trial section. It is responsibility of the investigator to check on potential drug-drug interactions, before placing a patient on a specific therapy. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

7.4.2 Other Treatments

None.

7.4.3 Procedures for Monitoring Subject Compliance With Administration of Trial Treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval. If not, the date(s) and reason for each dosing non compliance must be recorded. A specific adherence questionnaire in Italian language will be completed (appendix 3).

7.5 Trial Schedules

An overview of the study is provided in the Study Design Diagram (see section 2.1), and the study schedule is shown in the Study Flow Chart (see section 2.2). All treatment visits must be scheduled based on the Day 1 visit date, which is defined as the day of switch.

All visits should be performed within the windows specified in Section 2.2, the Trial Flow Chart. Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not miss a protocol-specified visit due to scheduling difficulties.

7.6 Trial Procedures

The Trial Flow Chart in Section 2.2 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below. In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site.

METHODS USED

DEMOGRAPHIC INFORMATION

Date of birth, sex, race, ethnicity.

MEDICAL HISTORY

Any relevant medical history and/or current medical conditions

MAIN PROTOCOL ASSESSMENTS

Clinical and physical assessment
Clinical and biological safety and tolerability (specific untoward effects in the setting of renal and bone metabolism and functions)
Metabolic changes, renal function (by MDRD 6 variables), tubular cell damage markers and bone mineral density modifications
Change in CD4 cell count and in viral load
Pharmacokinetics
Genotypic resistance at virologic failure
Adherence questionnaire
Bone mineral density assessed by DXA
Fracture Risk assessment with the FRAX® score in persons > 40 years
VACS index assessment

1. **Explain Trial and Obtain Written Informed Consent**

   The investigator or qualified designee will explain the trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure. A copy of the informed consent will be given to the subject (see Section 9.1.2 for further description of the Informed Consent).

2. **Obtain Medical History**

   A medical history will be obtained by the investigator or qualified designee. Subject history should include information on personal history.

3. **Review Inclusion/Exclusion Criteria**

   The inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

4. **Review Prior Medications**

   Review of appropriate prior medications, including the necessary washout times, with the subject.

   A record of prior medication taken by the subject within 30 days before starting the trial is to be obtained.

5. **Record Concomitant Medications**

   A record of medication taken by the subject during the trial is to be obtained.

6. **Record Adverse Events and Serious Adverse Events**

   See **Section 7.7.2.3**, for instructions on the assessment and reporting of Adverse Events and Serious Adverse Events and **Section 7.7.2.4** for instructions on the reporting of Adverse Events and Serious Adverse Events to the sponsor.

7. **Physical Examination**

   A complete physical examination will be performed, including vital signs (blood pressure, heart rate, temperature, breathing rate). If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

8. **List Other Assessments/Procedures**

see **section 7.7.3**

9. **Pregnancy Assessment**

Assess whether a subject is pregnant with a medically acceptable test, serum hCG test.

10. **Laboratory Tests**

Laboratory tests for hematology, blood chemistry, and urinalysis are specified in Appendix 1. Blood samples for laboratory tests are to be taken prior to investigational product(s) administration at day 1 and at visits specified into Trial Flow Chart (section 2.2).

11. **Alcohol/Substance Abuse**

Patients should be questioned about their estimated daily intake of alcohol and about substance abuse during the screening evaluation of eligibility. Any patient who in the opinion of the investigator has an excessive intake of any of these substances must be excluded from the study.

7.7 Assessments

7.7.1 Efficacy and Safety Assessments

7.7.1.1 Primary endpoint

The primary endpoint of this study is the eGFR (MDRD) change from baseline to Week 48.

No formal comparison between the two arms will be carried out.

7.7.1.2 Secondary Endpoint(s)

The main secondary efficacy end-point will be the proportion of subjects with HIV-RNA < 50 copies/ml at 48 week.

Other secondary endpoints will be:

a) Proportion of subjects with HIV-RNA < 50 copies/mL at 96 weeks of treatment.

b) Time to virologic failure (HIV-1 RNA > 50 copies/mL).

c) Changes of HIV-RNA absolute values at different time points.

d) Changes of absolute CD4+ T-lymphocyte count at 48 and 96 weeks of treatment.

e) Proportion of subjects with laboratory alterations (liver enzymes, lipid profile).

f) Proportion of subjects with alterations of the tubular kidney injury markers.

g) Proportion of subjects with metabolic bone markers changes

h) Proportion of patients with bone mineral density modifications

i) Pharmacokinetics determination (only for RAL and NVP) (see PK paragraph).

j) Proportion of subjects with genotypic resistance at virologic failure.

k) Incidence of mutations associated to resistance to NRTIs, NNRTIs, PI and INI, at virological failure.

l) Proportion of subjects with adherence to therapy during 48 and 96 weeks of treatment.

m) Changes in the Bone disease Risk assessment (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment.

n) Changes in the VACS Index during 48 and 96 weeks of treatment.

o) Proportion of subjects experiencing a decline of renal function defined as eGFR (MDRD-6 variables) < 60 mL/min/1.73 m2 at 48 weeks of treatment.

p) Changes in eGFR-MDRD at 96 weeks of treatment

7.7.1.3 Other Efficacy Endpoint(s)

No other efficacy endpoint(s) are planned.

7.7.2 Safety Monitoring And Assessments

7.7.2.1 Safety Endpoints

- To assess the changes in renal function (eGFR -MDRD-6 variables) during 48 and 96 weeks of treatment, and the frequency of experiencing a decline of renal function with an eGFR< 60 mL/min/1.73 m2 during 48 weeks of treatment
- To assess laboratory alterations (liver enzymes, lipid profile) after switch from PI/r (LPV/r, ATV/r, DAR/r) + TDF/FTC to RAL + NVP + 3TC during 48 and 96 weeks of treatment
- To assess the alterations of the tubular injury markers: b2-microglobulin (b2M), and retinol-binding protein (RBP) and N-acetyl-b-D-glucosaminidase (NAG) during 48 and 96 weeks of treatment
- To assess metabolic bone markers changes: Serum Bone Specific Alkaline Phosphatase (s-BSAP), , C-telopepdides of type I Collagen (s-CTx) during 48 and 96 weeks of treatment.
- To assess bone mineral density modifications during 48 and 96 weeks of treatment.
- To assess the safety (e.g. skin rash, GI disturbances)
- To assess the Fracture Risk (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment
- To assess the VACS Risk Index during 48 and 96 weeks of treatment

7.7.2.2 Definition of Terms

7.7.2.2.1 Adverse Event

According to the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

The onset and end dates, severity and relationship to study drug will be recorded for each adverse event. The severity of the adverse event will be assessed according to specific guidelines (DAIDS). Any action or outcome (e.g., hospitalization, discontinuation of therapy, etc.) will also be recorded for each adverse event. All lab abnormalities considered as clinically significant by the Investigator will be recorded as AEs on the CRF.

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

1. Results in death
2. Is life-threatening
3. Requires hospitalization or prolongation of existing inpatients' hospitalization
4. Results in persistent or significant disability or incapacity and/or
5. Is a congenital anomaly or birth defect
6. Is a cancer
7. Is associated with an overdose
8. Is an Other Important Medical Event

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered "Other Important Medical Events".

7.7.2.2.3 Events of Clinical Interest

An "Event of Clinical Interest" (ECI) is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as though it were a serious adverse event – as described in **Section 7.7.2.4.1**.

The following events are considered events of clinical interest for this trial:

1. An overdose of Sponsor's product, as defined in Section 7.7.2.1.4, Overdose, that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."
2. An elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing is to be reported as a non-serious ECI.

   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.7.2.2.4 Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product. In this current trial an overdose of the investigational products is any dose higher than the dose specified in Section 7.4.1.1 of this protocol or any dose specified in the SmPC of the products of the experimental arm (Raltegravir dose higher than 400 mg BID, Lamivudine dose higher than 150 mg BID, Nevirapine dose higher than 200 mg BID). The overdose of the control arm does not need to be reported as an ECI or SAE. Any overdose, whether or not associated with an adverse experience, must be reported within 24 hours to the SPONSOR.

7.7.2.2.5 Clinical Supply Complaint

A clinical supply complaint is defined as any communication concerning manufacturing, packaging, labeling or distribution (including adverse storage at depots) of a clinical supply that describes a potential defect related to its identity, strength, quality or purity after it is released and left the control of a Merck-approved packaging facility for distribution. A clinical supply GCP inquiry is defined as any communication of an event taking place at a trial site after the product was satisfactorily received at the trial site, which puts product disposition in question. Examples include adverse storage of product at the trial site and dosing past expiration. The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. This responsibility includes reporting of all clinical supply complaints and/or clinical supply GCP inquiries to the Sponsor.

Clinical supplies complaints and GCP inquiries, as defined above, must be reported to the Sponsor within 1 business day of first becoming aware of the issue. Sponsor Contact information and related reporting details can be found in the Investigator Trial File Binder.

7.7.2.2.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

Each subject will be monitored for the occurrence of any AEs immediately after the subject has signed informed consent and until the last protocol specified visit (14 days post therapy follow-up) or discontinued the study.

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects.

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

AEs, actions taken as a result of AEs, and follow-up results must be recorded in the electronic Case Report Forms (eCRF; **Section 9.2**), as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.3.2 Monitoring Laboratory Assessments

All laboratory assessments will be performed in the local laboratory. The clinical laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance and consideration as an AE(s).

a. Safety concerns related to experimental arm: RAL-3TC-NVP about NVP related toxicity.

Clinical care of patients randomized to experimental arm would follow recommendations stated on NVP label.

Patients should be instructed that a major toxicity of nevirapine is rash. They should be advised to promptly notify their physician of any rash and avoid delay between the initial symptoms and medical consultation. The majority of rashes associated with nevirapine occur within the first 6 weeks of initiation of therapy. Therefore, patients should be monitored carefully for the appearance of rash during this period. Nevirapine must be permanently discontinued in any patient experiencing severe rash or a rash accompanied by constitutional symptoms (such as fever, blistering, oral lesions, conjunctivitis, facial edema, muscle or joint aches, or general malaise), including Stevens-Johnson syndrome, or toxic epidermal necrolysis. Nevirapine must be permanently discontinued in any patient experiencing hypersensitivity reaction (characterized by rash with constitutional symptoms, plus visceral involvement, such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction).

Monitoring of hepatic tests should be done every two weeks during the first 2 months of treatment, and, then regularly thereafter. Liver test monitoring should be performed if the patient experiences signs or symptoms suggestive of hepatitis and/or hypersensitivity.

If AST or ALT > 2.5 ULN before or during treatment, then liver tests should be monitored more frequently during regular clinic visits. If AST or ALT increase to > 5 ULN during treatment, nevirapine should be immediately stopped. If clinical hepatitis occurs, characterized by anorexia, nausea, vomiting, icterus and laboratory findings (such as moderate or severe liver function test abnormalities (excluding GGT), nevirapine must be permanently stopped and should not be readministered

b. Renal Safety concerns.

MDRD 6 variables will be used to calculate the renal function in patient throughout the study period.

According TDF/FTC's IMP the patients treated with FTD/FTC + PI/r have to manage closely and the renal function (creatinine clearance and serum phosphate) should be monitored every three months.

A safety monitoring with more frequently visits will be ensured for the control arm. Visits each 3 months according to the international and national guidelines for monitoring TDF safety profile have been planned. Test for renal safety planned each months are creatinine clearance evaluation and serum phosphate. If serum phosphate is < 1.5 mg/dl (0.48 mmol/l) renal function should be re-evaluated within one week including measurement of blood glucose, blood potassium, urine glucose concentrations and proteinuria

In case of continuous deterioration of renal function (measured by eGFR-MDRD 6 variables), especially in patients assigned to continue baseline therapy (TDF containing regimen) we suggested to follow these recommendations:

- The dose and administration to any subject may not be modified. If necessary, a subject must be discontinued.

- treatment with tenofovir disoproxil fumarate should be stopped in adult patients with creatinine clearance decreased to < 50 ml/min or decreases in serum phosphate to < 1.0 mg/dl (0.32 mmol/l).

7.7.2.4 Assessment of Adverse Events

7.7.2.4.1 Assessment of Severity

Where the determination of adverse event severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically-qualified investigator.

The severity of (S)AEs will be graded according to the following definitions:

MILD: awareness of sign, symptom, or event, but easily tolerated;

MODERATE: discomfort enough to cause interference with usual activity and may warrant intervention;

SEVERE: incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention.

7.7.2.4.2 Assessment of Causality

A medically-qualified investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product using the guidelines listed below:

- Yes, there is reasonable possibility of drug relationship. There is evidence of exposure to test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause.
- No, there is not a reasonable possibility of drug relationship. Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.7.2.4.3 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

The expectedness of an adverse reaction shall be determined according to the reference document. The reference document for this current study is to be the Investigator's Brochure (Raltegravir), Summary of Product Characteristics (Lamivudine, Nevirapine, tenofovir/emtricitabine, lopinavir/ritonavir, darunavir, ritonavir, atazanavir).

7.7.2.4.4 Known Potential Toxicities of Investigational Products

Refer for the drugs to the Summary of Product Characteristics for additional information on AEs expected toxicity of the study drug.

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting of Safety Observations by the Investigator to the Sponsor

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor's Global Safety representative or designee using the Global Safety Intake Form provided by the sponsor/designee – or a sponsored-approved equivalent form – **within 1 working day of becoming aware of the event, sending it to MSD Italy (Pharmacovigilance Office** PPD **).**

1. SAE (including SAEs associated with overdose, pregnancy, exposure during pregnancy or lactation – including the pregnancy of a male subject's female partner who has provided written informed consent to provide information regarding pregnancy)
2. Death
3. Planned hospitalizations (not previously reported in the medical history)
4. Events of clinical interest
5. Cancer

Any occurrence of a product quality complaint in the trial must be reported expeditiously (within 1 working day) by the investigator or qualified designee to the sponsor's Designated Point of Contact in MSD Italy, either by telephone or by sending the form named "Product Quality Complaint Reporting Form" filed in the ITF. Contact data are: PPD PPD .

Any occurrence of pregnancy, exposure during pregnancy or lactation NOT associated with an SAE in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor or designee using the Global Safety Intake Form **within 5 working days of becoming aware of the event**. In this trial the pregnancy of a male subject's female partner who has provided written informed consent to provide information regarding pregnancy must be reported using the Global Safety Intake Form **within 5 working days of becoming aware of the event**.

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported to the sponsor or designee using the Global Safety Intake Form within 1 working day.

Any observation reported to the sponsor or designee via the Global Safety Intake Form that is also an AE, is to be recorded in the CRF (**Section 9.2**), as well as in the subject's source documentation along with any actions taken as a result of AE and follow-up results.

If an autopsy is performed, the de-identified autopsy report must be provided to the sponsor within 1 working day of the results being available.

The investigator must assess causality of the event as relative to the investigational product administered in the trial as describes in **Section 7.7.2.3.2**.

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

Global Safety will monitor data for safety. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations, with reference to the guideline "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')".

7.7.2.6 Discontinuation, Treatment Interruption, and Unblinding of Blinded Treatment Due to Safety Observations

7.7.2.6.1 Discontinuation

See **Section 7.3.3** for the criteria by which a subject must be discontinued. Should a subject be discontinued from the trial, complete the visit activities as specified for discontinuation in the Trial Flow Chart in **Section 2.2**.

7.7.2.6.2 Temporary Interruption of Treatment for a Subject

A Subject may not temporarily interrupt and then restart treatment. The investigator is to discontinue a subject as necessary according to the criteria provided in **Section 7.3.3**.

7.7.2.6.3 Modification of Dose and/or Administration of Investigational Product for a Subject

The dose and administration to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in **Section 7.3.3**.

7.7.2.6.4 Unblinding Treatment for a Subject During the Trial

No treatments in this current trial are blinded.

7.7.3 Other Endpoints

Although no clinically relevant drug-to-drug interactions are expected according to the drugs metabolic pathways, no data is currently available on the pharmacokinetic compatibility of the raltegravir/nevirapine combination. The rather wide intra and inter-patient variability of Raltegravir exposure, along with the recent appraisal of its pharmacokinetic/pharmacodynamics profile, and the rather different elimination half-lives of the three drugs here concerned, make the development of a pharmacokinetic substudy of relevance in order to fully evaluate the properties of such new three-drug regimen.
Determination of raltegravir and nevirapine AUCs (areas under the curve) will be carried out at steady state according to the dosing interval with blood sampling taking place at the end of dosing interval at time 0 (fasted state), and 1, 2, 3, 6 and 12 h after drug intake (regardless food) in a subset of enrolled patients with available data in the experimental arm at week 12 (~ the first 10 patients). The remaining 40 patients in the experimental arm will undergo Ctrough sampling (at the end of dosing interval at 12 h) at week 12 and 48. Adequate documentation of drug and food intake will be required.
Blood will be collected into 7 ml lithium heparin and plasma obtained by centrifugation (3000 rpm for 10 minutes at 4 °C) will be stored in two criovials at -20 °C. Plasma concentrations will be analyzed by a validated HPLC-PDA method at the Clinical Pharmacology and Pharmacogenetics Laboratory of the University of Torino, Torino, Italy.
CYP2B6 single nucleotide polymorphisms (SNPs) will be screened in both patients undergoing AUC determination and those being sampled for Ctrough.

7.7.4 Criteria For Early Termination Of The Trial

The clinical trial may be stopped if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable.

In addition, further recruitment in the trial or at (a) particular site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high.

8.0 STATISTICAL AND ANALYTICAL PLAN

8.0 STATISTICAL AND ANALYTICAL PLAN

This section outlines the statistical analysis strategy and procedures for the study. The following is an outline of the statistical methodology that will be used to report and analyze this study. A more detailed description will be provided in a separate statistical analysis plan that may include additional exploratory analysis not explicitly mentioned in the following sections. A Statistical Analysis Plan (SAP) will be produced before the database lock and will contain full details of all planned summaries, listings and analyses.
All analyses will be performed using SAS System software (version 9.2 or later).

8.1 Hypotheses / Estimation

The primary objective of the study is stated in Section 6.1.
This randomized phase 2 study is mainly designed as an estimation study without a planned formal comparison between the two regimens. The control arm, not directly compared with the experimental arm, will be considered for assessing the internal validity of the study.

It is expected that Regimen A is generally safe and well tolerated and can cause an improvement of the renal function. A pre vs post design will be used to examine changes in eGFR (MDRD) in the Regimen A arm.
The primary endpoint of this study will be the eGFR (MDRD) change from baseline to Week 48.

The secondary trial objectives are stated in section 6.2.

8.2 Analysis Endpoints

8.2.1 Primary Endpoint

The primary endpoint is the eGFR (MDRD) change from baseline to week 48.

8.2.2 Main Secondary Endpoint

The main secondary efficacy endpoint is the proportion of subjects with HIV-RNA < 50 copies/ml at 48 week.

8.2.3 Other Secondary Endpoints

a) Proportion of subjects with HIV-RNA < 50 copies/mL at 96 weeks of treatment.

b) Time to virologic failure (HIV-1 RNA > 50 copies/mL).

c) Changes of HIV-RNA absolute values at different time points.

d) Changes of absolute CD4+ T-lymphocyte count at 48 and 96 weeks of treatment.

e) Proportion of subjects with laboratory alterations (liver enzymes, lipid profile).

f) Proportion of subjects with alterations of the tubular kidney injury markers.

g) Proportion of subjects with metabolic bone markers changes

h) Proportion of patients with bone mineral density modifications

i) Pharmacokinetics determination (only for RAL and NVP) (see PK paragraph).

j) Proportion of subjects with genotypic resistance at virologic failure.

k) Incidence of mutations associated to resistance to NRTIs, NNRTIs, PI and INI, at virological failure.

l) Proportion of subjects with adherence to therapy during 48 and 96 weeks of treatment.

m) Changes in the Bone disease Risk assessment (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment.

n) Changes in the VACS Index during 48 and 96 weeks of treatment.

o) Proportion of subjects experiencing a decline of renal function defined as eGFR (MDRD-6 variables) < 60 mL/min/1.73 m2 at 48 weeks of treatment.

p) Changes in eGFR-MDRD at 96 weeks of treatment

8.2.4 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including:

- Occurrence of Adverse experiences (AEs)
- Laboratory tests
- Vital signs

8.3 Analysis Populations

8.3.1 Full Analysis Set (FAS)

The primary analysis on primary and secondary end-points will be performed on the Full Analysis Set (FAS) which includes all randomized subjects who received at least one dose of study medications, and have both a baseline assessment and at least one post-baseline assessment of any primary or secondary endpoints, irrespective of compliance with the study protocol and procedures.

In addition, a Per Protocol Set is defined as all FAS subjects who meet key eligibility criteria. Sensitivity analyses will be based on this Per Protocol Set. A supportive analysis using the Per-Protocol population will be performed for the primary endpoint only in case more than 10% of patients are identified as protocol violators.

The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made and documented prior to the Data Base Lock at the Data Review Meeting.

8.3.2 Safety Analysis Populations (SAF)

The All Treated Set will be used for the analysis of safety data in this study.
The All Treated Set consists of all randomized patients who received at least one dose of study treatment.

8.4 Statistical Methods

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events. Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication).
If the date of the event is on or after the reference date then: Study Day = (date of event – reference date)+1.
If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the endpoint value, or best/ worst case value where required (e.g. shift table).
For quantitative measurements, change from baseline will be calculated as: Test Value at Visit X – Baseline Value.

8.4.1 Statistical Methods for Primary Endpoint

The primary endpoint for this trial is the eGFR (MDRD) change from baseline to week 48.
The primary analysis will be conducted on the Full Analysis Set. An additional sensitivity analysis will be based on the Per Protocol Set.
The primary endpoint will be analyzed using a one-group (two-sided) Student's t test on the Regimen A group. Assumption of normality distribution will be checked and in case of strong deviation from normality, the non parametric Wilcoxon test will be used.
For the Regimen B group, the difference from baseline to week 48 will be estimated together with its pertinent 95% Confidence Interval.
No formal comparison between the two treatment arms will be carried out.

If missing data on primary end-point will be ≤ 5%, a LOCF approach (Last Observation Carried Forward procedure) will be used. In that case, if a patient permanently discontinues the treatment during the 48-week treatment period or does not have an eGFR (MDRD) value at week 48, the last post-baseline eGFR (MDRD) measurement during the on-treatment period will be used as the eGFR (MDRD) value at week 48. Otherwise, missing data will be imputed by using a multiple imputation method considering the previous trend and/or the baseline covariates.

8.4.2 Statistical Methods for the main secondary endpoint

The main secondary efficacy end-point is the proportion of subjects with HIV-RNA < 50 copies/ml at week 48.
Based on the above criteria, patients will be classified as responders or not responders (failures). If a patient permanently discontinues the treatment during the 48-week treatment period or does not have an HIV-RNA assessment at week 48, a conservative approach will be used: all missing values due to premature discontinuations will be considered failures, regardless of the reason for discontinuation. Counts and percentages of "*Responders"* and "*Not Responders"* and their 95% two-sided exact confidence intervals will be presented for both arms.
Analysis of the main secondary end-point will be based on the Full Analysis Set.
No formal comparison between the two arms will be carried out.

8.4.3 Statistical Methods for other secondary endpoints

Analysis of the secondary end-points will be based on the Full Analysis Set. No formal comparison between the two arms will be carried out.
Continuous data will be summarized by treatment group by using the number of observations available (n), mean, SD, minimum, median, and maximum
Categorical data will be summarized by treatment group by using counts and percentages at each time points. Missing data will not be categorized in the summaries. In general, descriptive statistics of quantitative efficacy and safety endpoints (result and change from baseline) by scheduled visit will be provided on observed cases, i.e., the inclusion of only patients having non-missing assessments at a specific visit.

The secondary endpoints will be analyzed as follow:

- Proportion of subjects with HIV-RNA < 50 copies/mL at 96 weeks of treatment.
  Based on the above criteria, patients will be classified as responders or not responders. Counts and percentages of "*Responders"* and "*Not Responders"* and their 95% two-sided exact confidence intervals will be presented for both arms.

- Time to virologic failure (HIV-1 RNA > 50 copies/mL).
  Time to virologic failure will be calculated as the difference between the date of randomization and the date in which HIV-1 RNA > 50 copies/mL. Summary statistics will be presented for both arms.

- Changes of HIV-RNA absolute values at different time points.
  Actual values and changes from baseline to each time point will be presented for each arm. Moreover, pertinent 95% Confidence Intervals at week 48 and 96 will be also presented.

- Incidence of mutations associated to resistance to NRTIs, NNRTIs, INI, at virological failure.
  Counts and percentages of patients classified as "*Mutated"* and "*Not Mutated"* and their 95% two-sided exact confidence intervals will be presented for both arms.

- Changes of absolute CD4+ T-lymphocyte count at 48 and 96 weeks of treatment.
  Actual values and changes from baseline to each time point will be presented for each arm. Moreover, pertinent 95% Confidence Intervals at week 48 and 96 will be also presented.

- Proportion of subjects with laboratory alterations (liver enzymes, lipid profile).
  Counts and percentages of patients classified as "*Having Normal value"* and "*Having Abnormal value"* will be presented at each time point for both arms.

- Proportion of subjects with alterations of the tubular kidney injury markers.
  Counts and percentages of patients classified as "*Having Normal value"* and "*Having Abnormal value"* will be presented at each time point for both arms.

- Proportion of subjects with metabolic bone markers changes and change in the bone mineral density modifications.
  Counts and percentages of patients classified as "*Having markers changes"* and "*Not-having markers changes"* will be presented at each time point for both arms.
  Actual values and changes from baseline to each time point will be presented for each arm.

- PK determination (only for RAL and nevirapine).
  AUC[0-t] , c-through will be calculated using the trapezoidal method and summary statistics will be presented.

- Proportion of subjects with genotypic resistance at virologic failure.
  Counts and percentages of patients classified as "*Showing genotypic resistance"* and "*Not-showing* genotypic resistance*"* will be presented for both arms.

- Proportion of subjects with adherence to therapy during 48 and 96 weeks of treatment.
  Adherence to therapy will be evaluated by using the Adherence Questionnaire. Summaries statistics will be presented for each item at each time interval for both arms.

- Changes in the Bone disease Risk assessment (FRAX® score in persons > 40 years) during 48 and 96 weeks of treatment.
  Actual values and changes from baseline to each time point will be presented for each arm. Moreover, pertinent 95% Confidence Intervals at week 48 and 96 will be also presented.

- Changes in the VACS Index during 48 and 96 weeks of treatment.

Actual values and changes from baseline to each time point will be presented for each arm. Moreover, pertinent 95% Confidence Intervals at week 48 and 96 will be also presented.

- Proportion of subjects experiencing a decline of renal function defined as eGFR (MDRD-6 variables) < 60 mL/min/1.73 m^2 at week 48 and 96.
  Based on the above criteria, patients will be classified as failures or not failures. Counts and percentages of "Failures" and "Not Failures" and their 95% two-sided exact confidence intervals will be presented for both arms.

Missing data on secondary endpoints will be handled as described for the primary and main secondary endpoint, where applicable.

8.4.4 Statistical Methods for Safety Analyses

AEs will be coded using MedDRA dictionary (using the most updated version). Adverse events (AEs) will be reported on a per subject basis. If a patient has more than one AE for a treatment that coded to the same preferred term (PT), the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE for a treatment within a system organ class (SOC) category, the patient will be counted only once in that system organ class category. A patient with multiple CTCAE grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Any Adverse Events which started at or after the first administration of study treatment will be considered a treatment Emergent Adverse Event (TEAE). If the start date is missing for an AE, the AE will be considered to be treatment emergent.
An overview of AEs including the number of subjects with at least one AE, at least one TEAE, at least one drug-related TEAE, at least one serious TEAE, any SAE, any AE leading to death, any TEAE leading to death, any TEAE leading to drug discontinuation, at least one grade ≥ 3 TEAE, will be presented.
The following AE frequency tables will be also provided:

- incidence of TEAEs by primary SOC and PT;
- incidence of drug-related TEAEs by primary SOC and PT;
- incidence of TEAEs by maximum severity, primary SOC and PT;
- incidence of TEAEs by strongest relationship maximum severity, primary SOC and PT;
- incidence of TESAEs by primary SOC and PT;
- incidence of TEAEs leading to study drug discontinuation by primary SOC and PT;
- incidence of TEAEs leading to dose modification by primary SOC and PT.

Other safety data including laboratory evaluations and vital signs assessments will be summarized at each time point. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. In addition, a shift table describing out of normal range shifts (low/normal/high values) will be provided for clinical laboratory results.

8.4.5 Subject disposition, Demographics and Other Baseline Characteristics

The number and percentage of patients screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed.
Demographic variables (e.g., age, gender, weight, BMI), baseline characteristics and medical history will be summarized by treatment arm using summary statistics.
Continuous data will be summarized by treatment group using the number of observations available (n), mean, SD, minimum, median, and maximum.
Categorical data will be summarized by treatment group using counts and percentages. Missing data will not be categorized in the summaries.
Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (using the most updated version) and will be presented by SOC and PT.

8.4.6 Prior and Concomitant Medications

Prior medications are defined as those starting and ending prior to the first administration of investigational study drug.
Concomitant medications are defined as those started at or after first administration of study drug and include those started prior to the first administration of investigational study drug but continued during the study.
Prior and concomitant medications will be classified according to active drug substance using the WHO-DRL drug dictionary (using the most updated version). Frequency tabulations will be presented for prior and concomitant medication by primary therapeutic subgroup (3rd level ATC code), and generic name.

8.5 Sample size and power calculation

Patients to screen: 148; Patients evaluable: 100 (50 in each group).
It is expected that Regimen A is generally safe and well tolerated and can cause an improvement of the renal function. A pre vs post design will be used to examine changes in eGFR (MDRD) in the Regimen A arm.
For sample size calculation our data and results from a pilot tenofovir switching study recently published (21) were used.
Sample size calculation was based on the primary endpoint of the study, defined as the eGFR (MDRD) change from baseline to week 48 with the following assumptions:

Test: One group Student's t-test (two-sided).
Null hypothesis (H0): Expected mean change from baseline to week 48 is 0.0 ml/min.
Alternative hypothesis (H1): Expected mean change from baseline to week 48 is 15 ml/min.
Expected SD = 31.5 ml/min
Alpha = 0.05; **Power** = 90%;

When the sample size is 50, a single group Student's t-test with a 0.05 two-sided significance level will have 90% power to detect a difference between a null hypothesis mean of 0.0 ml/min and an alternative hypothesis mean of 15.0 ml/min, assuming that the standard deviation is 31.5 ml/min.
Overall 100 subjects (50 per arm) need to be evaluated. In order to obtain 50 subjects and assuming a 20% rate of non evaluable subjects the required set of patients will be approximately 63 per arm and considering a screen failure rate of 15%, such number should be increased to 74. Overall, approximately 148 subjects (74 per arm) will need to be screened to obtain 100 subjects valuables (50 per arm).

Calculations were made by using nQuery Advisor® 7.0.

8.6 Subgroup analyses and effect of baseline factors

Not applicable for this study.

8.7 Multiplicity

Not applicable for this study.

8.8 Interim Analyses

No formal interim analyses are planned.

8.9 Data Safety Monitoring Board

Not applicable for this study.

9.0 ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the trial is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. In obtaining informed consent, the information must be provided in language and terms understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent form must be given to the subject. The consent form must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent form identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s)are not completely

known. The consent form must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent form must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Registration of the Trial

The trial will be registered by the sponsor on a publicly accessible database. The results will be disclosed by the sponsor on a publicly accessible database.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (e.g., CRFs, diaries; EDC screens), electronic database entries, etc, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

For a Trial Using Electronic Signatures

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. The investigator will attest in writing at the beginning of the trial that his/her electronic signature is the legally binding equivalent of a written signature and will

acknowledge by entering his/her electronic signature that he/she has verified the accuracy of the recorded data.

9.2.3 Preparing Case Report Forms for Subjects Who Fail Screening

Data are to be collected from the time the informed consent form is signed until the subject is determined to have failed screening. A CRF with a minimum of the following information must be completed for subjects who fail screening: (1) demographics, (2) subject status, (3) reason for screen failure and (4) serious adverse events.

9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this **Section 9.3** of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, e.g., any computer access system such as the Internet, World Wide Web, etc.) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. Proprietary information that is protected by the provisions contained in **Section 9.3.2**;
2. The accuracy of the information contained in the publication; and
3. To ensure that the presentation is fairly balanced and in compliance with FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or manuscript submitted for review, the sponsor shall promptly identify such subject

matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.
2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

10.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this trial is indicated in **Section 1**, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with raltegravir are selected. The sponsor will contact and select all investigators (i.e., the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(ies) (e.g., subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(ies) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the

CSR is to be called the CSR Coordinating Investigator. The sponsor is to select the CSR Coordinating Investigator and using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;
2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

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APPENDICES

Appendix 1

Laboratory Analyses for Admission to Study and for Safety Assessment

Hematology Laboratory Test

Blood hemoglobin test

Whole blood hematocrit

Red blood cell count

White blood cell count

White blood cell differential:

- blood neutrophil count
- blood monocyte count
- blood eosinophilic leukocyte count
- blood basophilic leukocyte
- blood lymphocyte count

Blood platelet count

Mean corpuscular volume

Blood helper/inducer cell lymphocyte count (absolute and %) (blood CD4 count)

Blood suppressor/cytotoxic cell lymphocyte count (absolute and %) (blood CD8 count)

Blood helper cell/suppressor cell lymphocyte ratio (blood CD4/CD8 ratio)

Blood Chemistry Test

Serum aspartate aminotransferase test (AST or SGOT)*

Serum alanine aminotransferase test (ALT or SGPT)*

Serum alkaline phosphatase test

Serum gamma-glutamyl transferase (GGT) test*

Serum lactate dehydrogenase (LDH) test

Serum creatine kinase test

Total serum bilirubin test *

Direct serum bilirubin test*

Indirect serum bilirubin test*

Uric acid test

Amylase

Lipase

Serum creatinine test

Serum blood urea nitrogen test

Total serum protein test

Serum albumin test

Serum glucose test

Serum sodium test

Serum potassium test

Serum phosphate test

Serum chloride test

Serum bicarbonate test

Serum calcium test

PTH test

25-hydroxyvitamin D test

*test for hepatic safety

Fasting Lipids

Fasting lipid profile (CDC lipids):

serum low-density lipoprotein cholesterol test (serum LDL-C)

serum high-density lipoprotein cholesterol test (serum HDL-C)

serum cholesterol test

serum triglyceride test

Pregnancy Test

Serum beta-human chorionic gonadotropin test

Hemostatic Function Test

Prothrombin test (PT)

Activated partial thromboplastin time (APTT)

International Normalized Ratio (INR)

Kidney function

Estimated GFR measured by MDRD formula with 6 variables that is MDRD 4 variables plus blood urea nitrogen and albumin

Urine test

Urine Tubular Kidney Injury Markers (24h urine collection): b2-microglobulin (b2M), and N- Tubular Kidney Injury Markers: retinol-binding protein (RBP)

Urine Tubular Kidney Injury Markers (urine test) : acetyl-b-D-glucosaminidase (NAG)

Bone Evaluation

Metabolic bone formation markers: s-BSAP (Serum Bone Specific Alkaline Phosphatase)
Metabolic bone resorption markers: s-CTx (C-telopepdides of Type I Collagen)

Clinical Serology Test
To be done at Screening for all patients prior to randomization.

Serum hepatitis B surface antigen test

Serum hepatitis B surface antibody test

Serum hepatitis Be antigen test

Serum hepatitis C antibody test[a]

1 If results is positive, then hepatitis C virus PCR quantitative test should also be perfomed

Virology Test

Plasma HIV-RNA quantification test

Viral Resistance Tests

Blood samples for genotypic assay will be collected at virologic failure confirmation visit to assess resistance to the drugs. The viral resistance tests are carried out by local qualified hospital laboratories.

Pharmacokinetic Analysis

Pk Intensive Blood sampling: determination of raltegravir and nevirapine AUCs

Pk Ctrough sampling: at the end of the dose interval 12 ± 2 hours

Pharmacogenomic Analysis

CYP2B6 single nucleotide polymorphisms (SNPs) will be screened in both patients undergoing AUC determination and those being sampled for Ctrough.

Appendix 2:
Guidelines For Grading Severity Of Laboratory Adverse Experiences For Toxicity Management

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pla

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Appendix 3: Adherence Questionnaire

Appendix 4: Merck Code Of Conduct For Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these studies in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical studies will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to studies which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated studies (eg, Medical School Grant Program), which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation studies, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, studies to assess or validate various endpoint measures, or studies to determine patient preferences, etc.

The design (ie, subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate patients, adequacy of facilities and staff, previous performance in Merck studies, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

D. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of studies it conducts. Some early phase or pilot studies are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC Review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck studies. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck studies will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an attachment to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp, which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."