Clinical trial results:
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)

Summary

EudraCT number	2013-001637-40
Trial protocol	IT
Global end of trial date	10 July 2017

Results information

Result version number	v1 (current)
This version publication date	29 June 2018
First version publication date	29 June 2018

Trial information

Trial identification

Sponsor protocol code	0518-284

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02116660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective was to evaluate changes in renal function, efficacy, and safety when switching from a combination of tenofovir/emtricitabine (TDF/FTC) plus a protease inhibitor/ritonavir (PI/r) to a combination of raltegravir (MK-0518) plus nevirapine plus lamivudine in human immunodeficiency virus (HIV)-1 infected participants with suppressed viremia and impaired renal function.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Human immunodeficiency virus (HIV) infected adults with stable suppressed HIV-1 ribonucleic acid (RNA) from at least 12 months prior to the screening visit, and with a current stable anti-retroviral (ARV) regimen were enrolled in this trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Raltegravir plus Nevirapine plus Lamivudine

Arm description:

Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks

Arm type	Experimental
Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	MK-0518
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg tablet orally twice daily, for 96 weeks

Investigational medicinal product name	Nevirapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg tablet orally once daily, for 14 days; followed by 200 mg tablet orally twice daily for 96 weeks

Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

150 mg tablet orally twice daily, for 96 weeks

Arm title	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine

Arm description:

Tenofovir/emtricitabine 300/200 mg orally once daily plus 1) lopinavir/ritonavir 400/100 mg orally twice daily or 800/200 mg orally once daily, or 2) atazanavir/ritonavir 300/100 mg orally once daily, or 3) darunavir/ritonavir 800/100 mg orally once daily or 600/100 mg orally twice daily for 96 weeks

Arm type	Active comparator

Investigational medicinal product name	Tenofovir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablet orally once daily for 96 weeks

Investigational medicinal product name	Emtricitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg tablet orally once daily for 96 weeks

Investigational medicinal product name	Lopinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg tablet orally twice daily or 800 mg tablet orally once daily for 96 weeks

Investigational medicinal product name	Ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg tablet orally once or twice daily or 200 mg tablet orally once daily for 96 weeks

Investigational medicinal product name	Atazanavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg tablet orally once daily for 96 weeks

Investigational medicinal product name	Darunavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

800 mg tablet orally once daily or 600 mg tablet orally twice daily for 96 weeks

Number of subjects in period 1	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine
Started	6	5
Completed	4	1
Not completed	2	4
Deteriorating renal function	-	1
Consent withdrawn by subject	-	2
Adverse event, non-fatal	1	1
Organization reason	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Raltegravir plus Nevirapine plus Lamivudine
Reporting group description:	
Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks	
Reporting group title	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine
Reporting group description:	
Tenofovir/emtricitabine 300/200 mg orally once daily plus 1) lopinavir/ritonavir 400/100 mg orally twice daily or 800/200 mg orally once daily, or 2) atazanavir/ritonavir 300/100 mg orally once daily, or 3) darunavir/ritonavir 800/100 mg orally once daily or 600/100 mg orally twice daily for 96 weeks	

Reporting group values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine	Total
Number of subjects	6	5	11
Age Categorical Units: Subjects			
Adults (18-64 years)	6	5	11
Age Continuous Units: years			
arithmetic mean	49.83	54.00	
standard deviation	± 6.21	± 5.92	-
Gender Categorical Units: Subjects			
Female	2	2	4
Male	4	3	7
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	6	4	10
More than one race	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	5	11
Unknown or Not Reported	0	0	0
eGFR			
Estimated Glomerular Filtration Rate			
Units: mL/min			
arithmetic mean	87.5	87.7	
standard deviation	± 7.32	± 6.52	-

End points

End points reporting groups

Reporting group title	Raltegravir plus Nevirapine plus Lamivudine

Reporting group description:

Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks

Reporting group title	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine

Reporting group description:

Tenofovir/emtricitabine 300/200 mg orally once daily plus 1) lopinavir/ritonavir 400/100 mg orally twice daily or 800/200 mg orally once daily, or 2) atazanavir/ritonavir 300/100 mg orally once daily, or 3) darunavir/ritonavir 800/100 mg orally once daily or 600/100 mg orally twice daily for 96 weeks

Subject analysis set title	Raltegravir
Subject analysis set type	Full analysis

Subject analysis set description:

Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks

Subject analysis set title	Nevirapine
Subject analysis set type	Full analysis

Subject analysis set description:

Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks

Primary: Change from Baseline in estimated Glomerular Filtration Rate (eGFR)

End point title	Change from Baseline in estimated Glomerular Filtration Rate (eGFR)[1]

End point description:

Glomerular Filtration Rate (eGFR) was estimated from the Modification of Diet in Renal Disease (MDRD) -6 equation. The MDRD-6 equation = 198 × [serum creatinine(mg/dL) ^−0.858 × [age]−0.167 × [0.822 if patient is female] × [1.178 if patient is black] × [serum urea nitrogen concentration (mg/dL)]^−0.293 × [urine urea nitrogen excretion (g/d)]^0.249. The population analyzed is all randomized participants who received at least one dose of study medications and who had both a baseline assessment, and at least one post-baseline assessment.

End point type	Primary

End point timeframe:

Baseline and Week 48

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses were neither planned nor performed for this primary endpoint.

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	3		
Units: mL/min				
arithmetic mean (standard deviation)	-1.1 (± 4.65)	-5.5 (± 11.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with suppressed viremia (<50 copies/mL HIV-1 Ribonucleic Acid [RNA]) at Week 48

End point title	Percentage of participants with suppressed viremia (<50 copies/mL HIV-1 Ribonucleic Acid [RNA]) at Week 48

End point description:

Plasma was to be collected at Week 48 in order to quantify HIV-1 RNA. and identify the percentage of participants with <50 copies/mL HIV-1 RNA.

End point type	Secondary

End point timeframe:

Week 48

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[2] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[3] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with suppressed viremia (<50 copies/mL HIV-1 RNA) at Week 96

End point title	Percentage of participants with suppressed viremia (<50 copies/mL HIV-1 RNA) at Week 96

End point description:

Plasma was to be collected at Week 96 in order to quantify HIV-1 RNA. and identify the percentage of participants with <50 copies/mL HIV-1 RNA.

End point type	Secondary

End point timeframe:

Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[4] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[5] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with decline in renal function at Week 48

End point title	Percentage of participants with decline in renal function at Week 48

End point description:

Decline in renal function was to be assessed by evaluating MDRD-6, creatinine clearance and serum phosphate.

End point type	Secondary

End point timeframe:

Week 48

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[6] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[7] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with virologic failure (HIV-1 RNA > 50 copies/mL)

End point title	Percentage of participants with virologic failure (HIV-1 RNA > 50 copies/mL)

End point description:

Plasma was to be collected up to Week 96 in order to quantify HIV-1 RNA, and identify the percentage of participants with >50 copies/mL HIV-1 RNA.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[8] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[9] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline of HIV-RNA absolute values

End point title	Change from baseline of HIV-RNA absolute values

End point description:

Plasma was to be collected at baseline and Week 96 in order to determine the change from baseline in HIV-1 RNA.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Copies/mL				
arithmetic mean (standard deviation)	()	()		

Notes:

[10] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[11] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with mutations associated with resistance to NRTIs, NNRTIs, INI, at virological failure.

End point title	Percentage of participants with mutations associated with

	resistance to NRTIs, NNRTIs, INI, at virological failure.

End point description:

Participants were to be identified with mutations associated with Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Integrase Inhibitor (INI). Virological failure is defined as 2 consecutive plasma HIV-1 RNA >200 copies/mL at least two weeks apart while on previous or current ARV therapy.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[12] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[13] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in absolute CD4+ T-lymphocyte count

End point title	Change from baseline in absolute CD4+ T-lymphocyte count

End point description:

Cluster of Differentiation 4 + (CD4+) T-lymphocyte cell counts were to be determined at baseline and Week 96, in order to determine the change from baseline.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Cells/mm^3				
arithmetic mean (standard deviation)	()	()		

Notes:

[14] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[15] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with altered liver enzymes and lipid profile

End point title	Percentage of participants with altered liver enzymes and lipid profile

End point description:

Values of liver enzymes and lipids were to be determined from laboratory tests, in order to identify the percentage of participants classified with altered values.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[16] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[17] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with altered values of tubular kidney injury markers

End point title	Percentage of participants with altered values of tubular kidney injury markers

End point description:

Values of tubular kidney injury markers. were to be determined, in order to identify the percentage of participants classified with altered values.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: Percentage of participants				

number (not applicable)				

Notes:

[18] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected..

[19] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants having changes from baseline in metabolic bone markers

End point title	Percentage of participants having changes from baseline in metabolic bone markers

End point description:

Changes from baseline in metabolic bone markers, serum Bone Specific Alkaline Phosphatase (s-BSAP) and C-telopeptides of type 1 Collagen (s-CTx), were to be determined, in order to classify the percentage of participants with changes.

End point type	Secondary

End point timeframe:

Baseline and up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[20] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[21] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration time curve from time 0 the last measurement time t (AUC0-t) for Raltegravir and Nevirapine

End point title	Area under the concentration time curve from time 0 the last measurement time t (AUC0-t) for Raltegravir and Nevirapine

End point description:

Blood samples were to be collected in Week 12 in order to use the trapezoidal method to determine the AUC0-t of Raltegravir and Nevirapine

End point type	Secondary

End point timeframe:

Week 12: Fasted state (0 hr) and 1, 2, 3, 6 and 12 hr post-dose

End point values	Raltegravir	Nevirapine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[22]	0[23]		
Units: mmol/L*hr				
arithmetic mean (standard deviation)	()	()		

Notes:

[22] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[23] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough concentration (Ctrough) for Raltegravir and Nevirapine

End point title	Trough concentration (Ctrough) for Raltegravir and Nevirapine

End point description:

Blood samples were to be collected in Weeks 12 and 48 in order to use the trapezoidal method to determine the Ctrough, the lowest concentration reached by the drug before the next dose is administered, of Raltegravir and Nevirapine.

End point type	Secondary

End point timeframe:

Weeks 12 and 48: at the end of dosing interval at 12 hr

End point values	Raltegravir	Nevirapine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[24]	0[25]		
Units: nM				
arithmetic mean (standard deviation)	()	()		

Notes:

[24] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[25] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with genotypic resistance at virologic failure

End point title	Percentage of participants with genotypic resistance at virologic failure

End point description:

Genotypic resistance measures the presence of particular HIV-1 mutations that give rise to drug resistance. Virological failure is defined as 2 consecutive plasma HIV-1 RNA >200 copies/mL at least two weeks apart while on previous or current ARV therapy.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[26]	0[27]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[26] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[27] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected..

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with adherence to study therapy

End point title	Percentage of participants with adherence to study therapy

End point description:

An Adherence Questionnaire was to be given in order to determine the percentage of participants who adhered to study therapy.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[28]	0[29]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[28] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[29] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in bone disease risk assessment

End point title	Change from baseline in bone disease risk assessment

End point description:

Bone disease risk assessment was to be based on a Fracture Risk Assessment Tool (FRAX®) score in participants >40 years old, and the change from baseline determined.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[30]	0[31]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[30] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected..

[31] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the VACS Index

End point title	Change from baseline in the VACS Index

End point description:

The Veterans Aging Cohort Risk Index (VACS Index) combines various clinical biomarkers into a cumulative index weighted according to the risk of all-cause mortality.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[32]	0[33]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[32] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[33] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants experiencing a decline of renal function

End point title	Percentage of participants experiencing a decline of renal

	function

End point description:

Decline in renal function was to be assessed by evaluating MDRD-6, creatinine clearance and serum phosphate.

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[34]	0[35]		
Units: Percentage of participants				
number (not applicable)				

Notes:

[34] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[35] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in eGFR at Week 96

End point title	Change from Baseline in eGFR at Week 96

End point description:

eGFR was estimated from the MDRD-6 equation. The MDRD-6 equation = 198 × [serum creatinine(mg/dL) ^−0.858 × [age]−0.167 × [0.822 if patient is female] × [1.178 if patient is black] × [serum urea nitrogen concentration (mg/dL)]^−0.293 × [urine urea nitrogen excretion (g/d)]^0.249.

End point type	Secondary

End point timeframe:

Baseline and Week 96

End point values	Raltegravir plus Nevirapine plus Lamivudine	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[36]	0[37]		
Units: mL/min				
arithmetic mean (standard deviation)	()	()		

Notes:

[36] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

[37] - Poor enrollment led to early termination of the study; so data for this endpoint was not collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 98

Adverse event reporting additional description:

All randomized participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine

Reporting group description:

Tenofovir/emtricitabine 300/200 mg orally once daily plus 1) lopinavir/ritonavir 400/100 mg orally twice daily or 800/200 mg orally once daily, or 2) atazanavir/ritonavir 300/100 mg orally once daily, or 3) darunavir/ritonavir 800/100 mg orally once daily or 600/100 mg orally twice daily for 96 weeks

Reporting group title	Raltegravir plus Nevirapine plus Lamivudine

Reporting group description:

Raltegravir 400 mg orally twice daily for 96 weeks; plus nevirapine 200 mg orally once daily for 14 days followed by nevirapine 200 mg orally twice daily, plus lamivudine 150 mg orally twice daily for 96 weeks

Serious adverse events	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine	Raltegravir plus Nevirapine plus Lamivudine	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Protease Inhibitor/Ritonavir plus tenofovir/emtricitabine	Raltegravir plus Nevirapine plus Lamivudine	
Total subjects affected by non-serious			

adverse events subjects affected / exposed	2 / 5 (40.00%)	3 / 6 (50.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Lichen planus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gonorrhea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypophosphataemia			

subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2	0 / 6 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2014	Amendment 2: Clarified the rationale of study: a pilot study that involves a transition from the standard therapeutic regimen to an experimental regimen with the use of an internal control comparator to evaluate the full validity of the study. Better defined the primary endpoint as change of eGFR from the baseline to week 48. Excluded participants with anamnesis of diabetes mellitus and those with any type of cancer. Added more frequent renal safety monitoring assessments for the control arm. The statistical plan was reviewed to better define the sample size.
06 July 2015	Amendment 3: Update of the list of drug-drug interactions according to the last Summary of Product Characteristics (SmPc) updated for raltegravir and nevirapirine. Updated the text for consistent wording related to the study participation/study duration. Added to protocol the definition of overdose, previously inadvertently omitted. Updated the pharmacokinetic (PK) test to further clarify sampling requirements (regarding drug food intake).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 July 2017	Due to poor enrollment the study was terminated early.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to poor enrollment the study was terminated early; therefore data for secondary outcome measures were not collected, and were not analyzed.

Notes: