Clinical trial results:
Study of the effect of atorvastatin for reducing “inflamaging” (aging-related complication) in HIV-infected patients older than 45 years receiving a protease inhibitor-based regimen versus a raltegravir-based regimen.

Summary

EudraCT number	2015-002682-30
Trial protocol	ES
Global end of trial date	01 July 2018

Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020

Trial information

Trial identification

Sponsor protocol code	RALATOR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02577042
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundació Lluita contra la SIDA
Sponsor organisation address	Crta de Canyet s/n, Badalona, Spain, 08916
Public contact	Fundació Lluita contra la SIDA, Fundació Lluita contra la SIDA, 34 93 497 84 14, jtoro@fls-rs.com
Scientific contact	Fundació Lluita contra la SIDA, Fundació Lluita contra la SIDA, 34 93 497 84 14, jtoro@fls-rs.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	27 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2018
Global end of trial reached?	Yes
Global end of trial date	01 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare changes in IL-6 between protease inhibitors and raltegravir, with or without atorvastatin.

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2015
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	Spain: 42
Worldwide total number of subjects	42
EEA total number of subjects	42

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)	42
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were stratified according to the baseline levels of LDL-cholesterol (cutoff value 160 mg/dL) and to the nucleoside drugs used, Truvada or Kivexa. Candidates to the study were chronically HIV-infected individuals, aged ≥ 40 years, Vreceiving a PI-based antiretroviral regimen including tenofovir/emtricitabine (Truvada) or abacavir/lamivudine

Pre-assignment

Screening details:

165 candidates were assessed for eligibility and 123 were excluded due to not meeting inclusion criteria (n= 86); declined to participate (n= 17); history of bad adherence (n=13) and prevision of treatment hepatitis C virus (n=7)

Period 1

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

Blinding implementation details:

not specific

Arms

Are arms mutually exclusive?	Yes
Arm title	PI group

Arm description:

Continue with the same PI-based regimen, plus Kivexa or Truvada. After that, atorvastatin, 20mg/day, has been added for 48 weeks

Arm type	Experimental
Investigational medicinal product name	Kivexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

abacavir 600 mg/ lamivudina 300 mg every 24h for 24 weeks

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

Dosage and administration details:

tenofovir 300mg/ emtricitabina 200mg every 24h for 24 weeks

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

Dosage and administration details:

20mg/day, added for 48 weeks

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

Dosage and administration details:

dosage according to guidelines

Arm title	Raltegravir Group

Arm description:

Switching the PI by raltegravir, plus Kivexa or Truvada for 24 weeks. After that, atorvastatin, 20mg/day has been added for 48 weeks.

Arm type	Active comparator
Investigational medicinal product name	Kivexa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

abacavir 600 mg/ lamivudina 300 mg every 24 hour for 24 weeks

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

Dosage and administration details:

tenofovir 300mg/ emtricitabina 200mg t every 24 hours, for 24 weeks

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

Dosage and administration details:

20mg/day has been added for 48 weeks

Investigational medicinal product name	Raltegravir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400mg/12 hours

Number of subjects in period 1	PI group	Raltegravir Group
Started	22	20
Completed	19	15
Not completed	3	5
Early subject withdrawal	-	1
Adverse event, non-fatal	1	1

Virological failure	-	1
Lost to follow-up	1	-
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	PI group
Reporting group description:	
Continue with the same PI-based regimen, plus Kivexa or Truvada. After that, atorvastatin, 20mg/day, has been added for 48 weeks	
Reporting group title	Raltegravir Group
Reporting group description:	
Switching the PI by raltegravir, plus Kivexa or Truvada for 24 weeks. After that, atorvastatin, 20mg/day has been added for 48 weeks.	

Reporting group values	PI group	Raltegravir Group	Total
Number of subjects	22	20	42
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	22	20	42
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	51.8	49.5	
standard deviation	± 8.2	± 3.5	-
Gender categorical Units: Subjects			
Female	5	2	7
Male	17	18	35

End points

End points reporting groups

Reporting group title	PI group
Reporting group description:	
Continue with the same PI-based regimen, plus Kivexa or Truvada. After that, atorvastatin, 20mg/day, has been added for 48 weeks	
Reporting group title	Raltegravir Group
Reporting group description:	
Switching the PI by raltegravir, plus Kivexa or Truvada for 24 weeks. After that, atorvastatin, 20mg/day has been added for 48 weeks.	

Primary: Changes in plasma soluble markers (IL-6)

End point title	Changes in plasma soluble markers (IL-6)
End point description:	
End point type	Primary
End point timeframe:	
baseline, 24 weeks and 72 weeks	

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))				
baseline	40.0 (36.9 to 53.7)	42.5 (34.5 to 50.1)		
week 24	41.1 (36.1 to 53.2)	39.3 (34.6 to 49.8)		
week 72	41.7 (34.7 to 51.5)	43.2 (36.8 to 52.9)		

Statistical analyses

Statistical analysis title	Comparing between groups
Comparison groups	PI group v Raltegravir Group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Changes in plasma soluble markers (D-dimer)	
End point title	Changes in plasma soluble markers (D-dimer)
End point description:	

End point type	Primary
End point timeframe:	
baseline, week 24 and week 72	

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
baseline	1990 (1574 to 2523)	1743 (1459 to 1894)		
week 24	1917 (1552 to 2244)	1844 (1547 to 2340)		
week 72	1868 (1438 to 2175)	2051 (1656 to 2414)		

Statistical analyses

Statistical analysis title	Comparing between groups
Comparison groups	PI group v Raltegravir Group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Changes in plasma soluble markers (sCD14)	
End point title	Changes in plasma soluble markers (sCD14)
End point description:	

End point type	Primary
End point timeframe:	
Baseline, week 24 and week 72	

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Baseline	7588 (7121 to 8419)	7579 (7039 to 8726)		
week 24	7736 (7307 to 8465)	7368 (7131 to 9056)		
week 72	8342 (7333 to 8856)	7658 (7039 to 8355)		

Statistical analyses

Statistical analysis title	Comparing between groups
Comparison groups	PI group v Raltegravir Group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Primary: Changes in plasma soluble markers (CRP)

End point title	Changes in plasma soluble markers (CRP)

End point description:

End point type	Primary

End point timeframe:

Baseline, week 24 and week 72

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))				
Baseline	8587 (6700 to 16735)	6744 (4461 to 15211)		
week 24	7531 (5056 to 15069)	7059 (4729 to 10868)		
week 72	10268 (5695 to 21228)	8334 (5134 to 17392)		

Statistical analyses

Statistical analysis title	Comparing between groups
Comparison groups	PI group v Raltegravir Group
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Wilcoxon (Mann-Whitney)

Secondary: Changes in lipid profile (total cholesterol)

End point title	Changes in lipid profile (total cholesterol)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week 24 and week 72

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	4.9 (± 0.9)	4.7 (± 0.8)		
week 24	4.7 (± 1.0)	4.4 (± 0.7)		
week 72	3.8 (± 0.9)	3.7 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in lipid profile (LDL cholesterol)

End point title	Changes in lipid profile (LDL cholesterol)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week 24 and week 72

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	2.8 (± 0.8)	2.7 (± 0.7)		
week 24	2.8 (± 0.8)	2.7 (± 0.6)		
week 72	1.9 (± 0.7)	2.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in lipid profile (Triglycerides)

End point title	Changes in lipid profile (Triglycerides)

End point description:

End point type	Secondary

End point timeframe:

Baseline, week 24 and week 72

End point values	PI group	Raltegravir Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: mmol/L				
arithmetic mean (standard deviation)				
Baseline	1.8 (± 1.2)	2.0 (± 1.5)		
week 24	1.4 (± 0.8)	1.2 (± 0.5)		
week 72	1.5 (± 0.7)	1.1 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

from baseline to week 72

Assessment type	Non-systematic

Dictionary used

Dictionary name	DAIDS AE GRADING TAB
Dictionary version	2.0

Reporting groups

Reporting group title	Raltegravir group

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non-serious adverse events occurred during the study

Serious adverse events	Raltegravir group		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
increments of creatine kinase	Additional description: 2 participants showed a grade 3 and grade 4 which improved without interrupting therapy		
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
increment of liver enzymes	Additional description: 1 participant showed a grade 4 that resolved after interrupting the atorvastatin		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Raltegravir group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2015	Inclusion criteria modification
03 May 2016	Inlcusion criteria modification

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported