Clinical trial results:
IMPACTO DE LA INTENSIFICACIÓN CON RALTEGRAVIR EN LA LATENCIA VIRAL DE VIH-1 EN PACIENTES CON SUPRESIÓN VIRAL COMPLETA (IMPACT OF RALTEGRAVIR INTENSIFICATION ON HIV-1 VIRAL LATENCY IN PATIENTS WITH PREVIOUS COMPLETE VIRAL SUPPRESSION).

Summary

EudraCT number	2007-003801-28
Trial protocol	ES
Global end of trial date	30 September 2009

Results information

Result version number	v1 (current)
This version publication date	05 January 2018
First version publication date	05 January 2018

Trial information

Trial identification

Sponsor protocol code	INTEGRAL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00554398
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	CRA, Fundació Lluita contra la SIDA, +34 93 497 84 14, rescrig@flsida.org
Scientific contact	CRA, Fundació Lluita contra la SIDA, +34 93 497 84 14,

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	30 September 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2009
Global end of trial reached?	Yes
Global end of trial date	30 September 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Change at 48 weeks in the slope of decay of integrated and unintegrated viral DNA in PBMCs (peripheral blood mononuclear cells).

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2007
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: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 69 subjects were randomized 2:1 ratio
HIV-1-infected subjects were eligible if they were 18 years of age or older, received a HAART regimen composed of two nucleoside/nucleotide reverse transcriptase inhibitors and a protease inhibitor or a nonnucleoside/nucleotide transcriptase inhibitor, and were naive to integrase inhibitors.

Pre-assignment

Screening details:

A total of 67 subjects were enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control arm

Arm description:

continue their HAART

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Intensifying HAART group (+raltegravir group)

Arm description:

HAART plus raltegravir

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

Dosage and administration details:

400mg twice daily

Number of subjects in period 1	Control arm	Intensifying HAART group (+raltegravir group)
Started	22	45
Completed	20	41
Not completed	2	4
Consent withdrawn by subject	-	4
Adverse event, non-fatal	1	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Control arm
Reporting group description: continue their HAART	
Reporting group title	Intensifying HAART group (+raltegravir group)
Reporting group description: HAART plus raltegravir	

Reporting group values	Control arm	Intensifying HAART group (+raltegravir group)	Total
Number of subjects	22	45	67
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	45	67
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45	46	
standard deviation	± 8	± 9	-
Gender categorical Units: Subjects			
Female	6	6	12
Male	16	39	55

End points

End points reporting groups	
Reporting group title	Control arm
Reporting group description: continue their HAART	
Reporting group title	Intensifying HAART group (+raltegravir group)
Reporting group description: HAART plus raltegravir	

Primary: changes in total HIV-1 DNA	
End point title	changes in total HIV-1 DNA
End point description:	
End point type	Primary
End point timeframe: from baseline to week 48	

End point values	Control arm	Intensifying HAART group (+raltegravir group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	45		
Units: copies per million PMBCs				
median (inter-quartile range (Q1-Q3))				
baseline	14.1 (3.1 to 61.3)	10.3 (4.5 to 38.3)		
week 48	54.6 (11.5 to 367.1)	19.6 (1.4 to 104.9)		

Statistical analyses

Statistical analysis title	Comparing medians between groups
Comparison groups	Control arm v Intensifying HAART group (+raltegravir group)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.043
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Comparison at week 48

Primary: changes in integrated HIV-1 DNA

End point title	changes in integrated HIV-1 DNA

End point description:

End point type	Primary

End point timeframe:

from baseline to week 48

End point values	Control arm	Intensifying HAART group (+raltegravir group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	45		
Units: copies per million PBMCs				
median (inter-quartile range (Q1-Q3))				
baseline	1.9 (0 to 41.7)	0 (0 to 7.4)		
week 48	0.4 (0 to 19.3)	0 (0 to 3.3)		

Statistical analyses

Statistical analysis title	Comparing medians between groups
Comparison groups	Control arm v Intensifying HAART group (+raltegravir group)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	= 0.061
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Comparison at week 48

Secondary: Effect of RAL intensification on the decay of residual HIV-1 replication (assessed by an ultrasensible tecnique)

End point title	Effect of RAL intensification on the decay of residual HIV-1 replication (assessed by an ultrasensible tecnique)

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	Control arm	Intensifying HAART group (+raltegravir group)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	45		
Units: copies/ml				
median (inter-quartile range (Q1-Q3))				
baseline	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.6)		
week 48	0.5 (0.2 to 2.7)	0.4 (0.01 to 2.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from baseline to week 48	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	DAIDS AE GRADING TAB
Dictionary version	1.0

Reporting groups	
Reporting group title	Intensifying HAART group (+raltegravir group)
Reporting group description: -	
Reporting group title	Control arm
Reporting group description: -	

Serious adverse events	Intensifying HAART group (+raltegravir group)	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	2 / 22 (9.09%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
anal carcinoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Pancreatitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
bacteraemic pneumoccocal pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 22 (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: 1 %

Non-serious adverse events	Intensifying HAART group (+raltegravir group)	Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 45 (0.00%)	4 / 22 (18.18%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
cerebral meningioma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
hypernephroma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Renal and urinary disorders			
uterine cervical carcinoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2007	1. exclusion criteria number 6 deleted 2. PBMCs week 2 and 4 storage added 3. ultrasensible viral load technique modified
25 October 2007	typographical error corrected
25 February 2008	1. lymphocyte subset and T-cell activation determination in baseline, week 2, week 4, week 12, week 24 and week 48 added. 2. sample size increased. 3. viral load determination modified.
16 April 2008	inclusion criteria number 2 and 3 deteled from protocol and inclusion criteria number 5 modified.
26 June 2008	1. sample size adjusted 2. stratification deleted 3. secondary objective added
12 January 2009	week 48 and week 60 apoptosis study in lymphocytes added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported