Clinical trial results:
A multicenter randomised opened study to assess the efficacy and safety of the withdrawal of nucleos/tide analogues in HIV-1-infected subjects with complete or intermediate resistance to these analogues, multitreated with virological suppression

Summary

EudraCT number	2012-000198-21
Trial protocol	ES
Global end of trial date	15 October 2014

Results information

Result version number	v1 (current)
This version publication date	14 August 2016
First version publication date	14 August 2016

Trial information

Trial identification

Sponsor protocol code	NUKE-OUT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 93497 84 14, jtoro@flsida.org
Scientific contact	CRA, Fundació Lluita contra la SIDA, +34 93497 84 14, jtoro@flsida.org

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	15 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2014
Global end of trial reached?	Yes
Global end of trial date	15 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy at 48 weeks of withdrawing NRTIs with intermediate or complete resistance in subjects with previous virological failure and a suppressed viral load for > 6 months.

Protection of trial subjects:

No specific measures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2012
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: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	90
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 92 subjects screened, 90 were randomized and treated (experimental, n=45; and control, n=45)

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	experimental

Arm description:

stop NRTIs without complete activity, either one or both.

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

Dosage and administration details:

multidrug salvage regimen with at least two active drugs (one a boosted PI)

Arm title	control

Arm description:

maintain the treatment unchanged

Arm type	control
Investigational medicinal product name	NRTIs + PI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

multidrug salvage regimen with at least two active drugs (one a boosted PI)

Number of subjects in period 1	experimental	control
Started	45	45
Completed	44	44
Not completed	1	1
Adverse event, non-fatal	1	-
discontinued study drug due to other reasons	-	1

Baseline characteristics

Reporting groups	
Reporting group title	experimental
Reporting group description:	
stop NRTIs without complete activity, either one or both.	
Reporting group title	control
Reporting group description:	
maintain the treatment unchanged	

Reporting group values	experimental	control	Total
Number of subjects	45	45	90
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)	45	45	90
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52	49.2	
standard deviation	± 7.3	± 6.4	-
Gender categorical Units: Subjects			
Female	4	14	18
Male	41	31	72

End points

End points reporting groups	
Reporting group title	experimental
Reporting group description: stop NRTIs without complete activity, either one or both.	
Reporting group title	control
Reporting group description: maintain the treatment unchanged	

Primary: proportion HIV-1 RNA < 50 copies/mL

End point title	proportion HIV-1 RNA < 50 copies/mL
End point description:	
End point type	Primary
End point timeframe: week 48	

End point values	experimental	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: people	41	44		

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description: The primary efficacy analysis used the ITT-exposed population (patients who had received at least one dose of study medication). The trial was designed to show non-inferior efficacy of the experimental arm at week 48 (non-inferiority margin: -12%)	
Comparison groups	experimental v control
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.05 [1]
Method	confidence interval 95%

Notes:

[1] - adjusted treatment difference: 26.7%; 95% CI: -17.4, 4.1);

Secondary: rate of virological failure

End point title	rate of virological failure

End point description:

End point type	Secondary

End point timeframe:

week 48

End point values	experimental	control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	45		
Units: people	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

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

Dictionary used	
Dictionary name	DAIDS AE GRADING TAB
Dictionary version	2.0

Reporting groups	
Reporting group title	experimental
Reporting group description: -	
Reporting group title	control
Reporting group description: -	

Serious adverse events	experimental	control	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 45 (13.33%)	5 / 45 (11.11%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
lung carcinoma			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
uterine cervical carcinoma			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Giardia lamblia enterocolitis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cirrhotic ascite			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
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			
bacterial pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Death			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syphilis			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	experimental	control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 45 (55.56%)	20 / 45 (44.44%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Memory impairment			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Haematinuria			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
glycemia increase			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
iron deficiency anaemia			
subjects affected / exposed	0 / 45 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Social circumstances			
Anxiety			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			

subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal			
subjects affected / exposed	0 / 45 (0.00%)	3 / 45 (6.67%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Endocrine disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Tendinous contracture			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	2 / 45 (4.44%)	0 / 45 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
malar infection			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Respiratory disorder			
subjects affected / exposed	5 / 45 (11.11%)	0 / 45 (0.00%)	
occurrences (all)	5	0	
Hepatitis C			
subjects affected / exposed	1 / 45 (2.22%)	0 / 45 (0.00%)	
occurrences (all)	1	0	
Urinary infection			
subjects affected / exposed	0 / 45 (0.00%)	1 / 45 (2.22%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 March 2012	Protocol, Patient Information and Informed consent, protocol summary and first submission modifications
24 October 2012	Oral patient Informatio oral and witness informed consent
28 January 2013	inclusion of a new trial site
22 April 2013	inclusion of a new trial site

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported