Clinical trial results:
PROSPECTIVE, RANDOMISED, CROSSOVER, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO ASSESS THE LIPID-LOWERING EFFECT OF ADDING TENOFOVIR/EMTRICITABINE CO-FORMULATION VS PLACEBO TO HIV-1-INFECTED SUBJECTS WITH DYSLIPIDEMIA AND SUSTAINED VIRAL LOAD SUPPRESSION UNDER MONOTHERAPY WITH RITONAVIR-BOOSTED PROTEASE INHIBITORS.

Summary

EudraCT number	2011-002853-77
Trial protocol	ES
Global end of trial date	25 February 2014

Results information

Result version number	v1 (current)
This version publication date	30 July 2016
First version publication date	30 July 2016

Trial information

Trial identification

Sponsor protocol code	TULIP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01458977
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,
Public contact	CRA, Fundació Lluita Contra la SIDA, +34 934978414 , jtoro@flsida.org
Scientific contact	CRA, Fundació Lluita Contra la SIDA, +34 934978414 , 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	29 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2014
Global end of trial reached?	Yes
Global end of trial date	25 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the cholesterol-lowering ability of TDF/FTC co-formulation in HIV-1-infected subjects with high cholesterol levels.

Protection of trial subjects:

No specific measures

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2011
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: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	48
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible subjects included HIV-1–infected adults with hypercholesterolemia (TC level ≥200 mg/dL and/or LDL-c level ≥130 mg/dL) in the last 2 consecutive tests obtained at least 4 weeks apart before screening, receiving stable PI monotherapy with DRV/r or LPV/r and with HIV-1 RNA < 50 copies/mL during at least 6 months before screening.

Pre-assignment

Screening details:

Between November 2011 and May 2013, 48 subjects were randomized.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As it is a double-blind clinical trial, neither the treating physician nor the patient will know whether the patient is receiving TDF/FTC or placebo. The placebo will have the same appearance as TDF/FTC co-formulation.

Arms

Are arms mutually exclusive?	Yes
Arm title	group A

Arm description:

TDF/FTC was added for 12 weeks followed by 12 weeks of placebo (washout) and 12 additional weeks of placebo (placebo period)

Arm type	crossover placebo-controlled
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet/24 h

- Composition (excipients): Denatonium benzoate, Lactose Monohydrate, Pregelatinized Starch, Croscarmellose Sodium, Magnesium Stearate, Opadry II Blue Y-30-10701.
- Pharmaceutical form: Film-coated tablet. Blue, capsule-shaped tablets, debossed with “GILEAD” on one side and plain-faced on the other side.

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

Dosage and administration details:

1 tablet/24 h

Truvada® (300 mg tenofovir disoproxil fumarato/200 mg emtricitabine): It is a marketed antiretroviral drug used in general HIV management. The formulation of the active principal components corresponds to the marketed formulation.

Arm title	group B

Arm description:

Addition of placebo for 12 weeks (placebo period) followed by TDF/FTC for 12 weeks and placebo for 12 additional weeks (washout)

Arm type	crossover placebo-controlled
Investigational medicinal product name	TDF/FTC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet/24h

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

Dosage and administration details:

1tablet/24h

Number of subjects in period 1	group A	group B
Started	24	24
Completed	23	23
Not completed	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	group A
Reporting group description:	
TDF/FTC was added for 12 weeks followed by 12 weeks of placebo (washout) and 12 additional weeks of placebo (placebo period)	
Reporting group title	group B
Reporting group description:	
Addition of placebo for 12 weeks (placebo period) followed by TDF/FTC for 12 weeks and placebo for 12 additional weeks (washout)	

Reporting group values	group A	group B	Total
Number of subjects	24	24	48
Age categorical			
Age			
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)	24	24	48
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	44.9	42.6	
inter-quartile range (Q1-Q3)	34 to 64	26 to 56	-
Gender categorical			
Units: Subjects			
Male	16	16	32
Female	8	8	16

End points

End points reporting groups

Reporting group title	group A
Reporting group description:	
TDF/FTC was added for 12 weeks followed by 12 weeks of placebo (washout) and 12 additional weeks of placebo (placebo period)	
Reporting group title	group B
Reporting group description:	
Addition of placebo for 12 weeks (placebo period) followed by TDF/FTC for 12 weeks and placebo for 12 additional weeks (washout)	

Primary: Total cholesterol

End point title	Total cholesterol
End point description:	
Changes in median fasting total cholesterol levels during TDF/FTC co-formulation addition compared to placebo.	
End point type	Primary
End point timeframe:	
Baseline and week 12	

End point values	group A	group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
Baseline	235.9 (216.5 to 262.9)	234.7 (213.5 to 265.9)		
Week 12	204.9 (182.9 to 230.5)	232 (204.9 to 255.6)		

Statistical analyses

Statistical analysis title	Comparative Analysis week 12
Statistical analysis description:	
Longitudinal changes in cholesterol levels were analyzed using paired Student t test, Wilcoxon test, or Friedman t test when appropriate. The McNemar or Cochran test was used to compare proportions. All analyses were blinded and performed by intention to treat (ITT)	
Comparison groups	group A v group B

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Differences were considered statistically significant at P < .05

Secondary: CD4+

End point title	CD4+

End point description:

End point type	Secondary

End point timeframe:

baseline and week 12 follow up

End point values	group A	group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: cells/microlitre				
median (inter-quartile range (Q1-Q3))				
Baseline	610 (473.5 to 881.5)	631.5 (513 to 937.7)		
week 12	653.5 (484.3 to 854.7)	640 (478 to 960)		

Statistical analyses

No statistical analyses for this end point

Secondary: decrease trygliceride levels

End point title	decrease trygliceride levels

End point description:

End point type	Secondary

End point timeframe:

baseline and week 12

End point values	group A	group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
baseline	133.7 (106.3 to 194.9)	150.1 (124 to 192.6)		
week 12	137.3 (104.9 to 193.1)	141.7 (106.3 to 208.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: increase HDL-cholesterol

End point title	increase HDL-cholesterol

End point description:

End point type	Secondary

End point timeframe:

baseline and week 12

End point values	group A	group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))				
baseline	50.3 (38.7 to 58)	48.3 (39.7 to 57)		
week 12	44.5 (38.4 to 50.4)	47.8 (38.7 to 58.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: evaluate adverse events

End point title	evaluate adverse events

End point description:

End point type	Secondary

End point timeframe:

baseline and week 48

End point values	group A	group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: number	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 week follow up	
Adverse event reporting additional description: mild diarrhea	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	DAIDS AE grading Tab
Dictionary version	2.0

Reporting groups	
Reporting group title	LPV/r-based treatment
Reporting group description: -	
Reporting group title	DRV/r-based treatment
Reporting group description: -	

Serious adverse events	LPV/r-based treatment	DRV/r-based treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	LPV/r-based treatment	DRV/r-based treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
Gastrointestinal disorders			
mild diarrhea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2012	Addition of two more new sites: Bellvitge University Hospital and Vall d'Hebron Universitary Hospital

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported