Clinical trial results:
Pharmacokinetic study in HIV infected patient receiving 1 tenofovir disoproxil fumarate (TDF): Investigation of systemic and intracellular interaction between TDF and abacavir, lamivudine or lopinavir/ritonavir

Summary

EudraCT number	2004-000948-25
Trial protocol	ES
Global end of trial date	07 September 2005

Results information

Result version number	v1 (current)
This version publication date	04 April 2018
First version publication date	04 April 2018

Trial information

Trial identification

Sponsor protocol code	INTRANUCS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00335192
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,
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	07 September 2005
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 September 2005
Global end of trial reached?	Yes
Global end of trial date	07 September 2005
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if the co-administration of tenofovir disoxipropil fumarate (TDF) modifies intracelular levels of abacavir (ABC) and lamivudine

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 January 2005
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: 27
Worldwide total number of subjects	27
EEA total number of subjects	27

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)	27
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study enrolled subjects who had been receiving a triple HAART regimen for more than 42.2 months (±8.2) including TDF 300 mg once daily, taken with food, 3TC 300 mg once daily or ABC 300 mg twice daily and a NNRTI (NVP 400 mg once daily) or a PI (LPV/r, 400/100 mg twice daily).

Pre-assignment

Screening details:

Twenty seven patients were included in the cross-sectional part of the study. Fourteen of them also participated in the longitudinal study.

Period 1

Period 1 title	cross-sectional part
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: TDF + 3TC + LPV/r
Arm description: -	
Arm type	Experimental
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 once daily	
Investigational medicinal product name	lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg once daily	
Investigational medicinal product name	lopinavir/ritonavir (LPV/r)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400/100 mg twice daily	
Arm title	Group 2: TDF + 3TC + NVP
Arm description: -	
Arm type	Experimental

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 once daily	
Investigational medicinal product name	lamivudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg once daily	
Investigational medicinal product name	nevirapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400 mg once daily	
Arm title	Group 3: TDF + ABC + LPV/r
Arm description: -	
Arm type	Experimental
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 once daily	
Investigational medicinal product name	Abacavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg twice daily	
Investigational medicinal product name	lopinavir/ritonavir (LPV/r)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400/100 mg twice daily	
Arm title	Group 4: TDF + ABC + NVP
Arm description: -	
Arm type	Experimental

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 once daily	
Investigational medicinal product name	Abacavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg twice daily	
Investigational medicinal product name	nevirapine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400 mg once daily	

Number of subjects in period 1	Group 1: TDF + 3TC + LPV/r	Group 2: TDF + 3TC + NVP	Group 3: TDF + ABC + LPV/r
Started	7	8	7
Completed	7	8	7

Number of subjects in period 1	Group 4: TDF + ABC + NVP
Started	5
Completed	5

Period 2	
Period 2 title	longitudinal study
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes

Arm title	Group 1: 3TC + LPV/r
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	lamibudine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg/24 h	
Investigational medicinal product name	lopinavir/ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 133.3/33.3 mg, 3 tablets/12 h	
Arm title	Group 3: ABC + LPV/r
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	abacavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 300 mg/12 h	
Investigational medicinal product name	lopinavir/ritonavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 133.3/33.3 mg, 3 tablets/12 h	

Number of subjects in period 2[1]	Group 1: 3TC + LPV/r	Group 3: ABC + LPV/r
Started	7	7
Completed	7	7

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The study design was a cross sectional study followed by a longitudinal prospective study (after 4 weeks of TDF interruption).
TDF was withdrawn for 4 weeks to assess pharmacokinetic interactions between TDF and ABC or 3TC only in patients under LPV/r (group 1 and 3) in order to avoid viral rebound during the dual therapy. So,

patients starting the second period (longitudinal study) were less than those who were completed the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	cross-sectional part

Reporting group description: -

Reporting group values	cross-sectional part	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	27	27	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	43.8		
standard deviation	± 9.5	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	20	20	

End points

End points reporting groups

Reporting group title	Group 1: TDF + 3TC + LPV/r
Reporting group description: -	
Reporting group title	Group 2: TDF + 3TC + NVP
Reporting group description: -	
Reporting group title	Group 3: TDF + ABC + LPV/r
Reporting group description: -	
Reporting group title	Group 4: TDF + ABC + NVP
Reporting group description: -	
Reporting group title	Group 1: 3TC + LPV/r
Reporting group description: -	
Reporting group title	Group 3: ABC + LPV/r
Reporting group description: -	
Subject analysis set title	group A
Subject analysis set type	Sub-group analysis
Subject analysis set description: 3TC with LPV/r	
Subject analysis set title	group B
Subject analysis set type	Sub-group analysis
Subject analysis set description: 3TC with NVP	
Subject analysis set title	group C
Subject analysis set type	Sub-group analysis
Subject analysis set description: ABC with LPV/r	
Subject analysis set title	group D
Subject analysis set type	Sub-group analysis
Subject analysis set description: ABC with NVP	
Subject analysis set title	group E
Subject analysis set type	Sub-group analysis
Subject analysis set description: TFV with LPV/r	
Subject analysis set title	group F
Subject analysis set type	Sub-group analysis
Subject analysis set description: TFV with NVP	

Primary: Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: area under the curve

End point title	Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: area under the curve
End point description:	
End point type	Primary
End point timeframe: week 4	

End point values	group A	group B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		
Units: ng.h/ml				
median (inter-quartile range (Q1-Q3))	5748 (3932 to 7365)	4974 (3707 to 7414)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group A v group B
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.491
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: maximum concentration observed

End point title	Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: maximum concentration observed
End point description:	
End point type	Primary
End point timeframe: week 4	

End point values	group A	group B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	2241 (2014 to 2299)	1850 (1666 to 2599)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group A v group B
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.121
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval

End point title	Plasma pharmacokinetic parameters of lamivudine in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval
End point description:	
End point type	Primary
End point timeframe: week 4	

End point values	group A	group B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	161 (62.0 to 178)	84.3 (55.6 to 99.1)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group A v group B
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.232
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of abacavir in the presence of

lopinavir/ritonavir or nevirapine: area under the curve

End point title	Plasma pharmacokinetic parameters of abacavir in the presence of lopinavir/ritonavir or nevirapine: area under the curve

End point description:

End point type	Primary

End point timeframe:

week 4

End point values	group C	group D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	5		
Units: ng.h/ml				
median (inter-quartile range (Q1-Q3))	3630 (2248 to 3762)	5257 (3868 to 7802)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description:

Ratio of the geometric mean (GMR)

Comparison groups	group C v group D
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.048
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of abacavir in the presence of lopinavir/ritonavir or nevirapine: maximum concentration observed

End point title	Plasma pharmacokinetic parameters of abacavir in the presence of lopinavir/ritonavir or nevirapine: maximum concentration observed

End point description:

End point type	Primary

End point timeframe:

week 4

End point values	group C	group D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	5		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	1783 (954.9 to 1992)	2665 (2173 to 3718)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group C v group D
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.012
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of abacavir in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval

End point title	Plasma pharmacokinetic parameters of abacavir in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval
End point description:	
End point type	Primary
End point timeframe: week 4	

End point values	group C	group D		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	5		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	42.4 (32.7 to 181)	76.3 (56.5 to 135)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio

Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group C v group D
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.343
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of tenofovir in the presence of lopinavir/ritonavir or nevirapine: area under the curve: area under the curve

End point title	Plasma pharmacokinetic parameters of tenofovir in the presence of lopinavir/ritonavir or nevirapine: area under the curve: area under the curve
End point description:	
End point type	Primary
End point timeframe: week 4	

End point values	group E	group F		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: ng.h/ml				
median (inter-quartile range (Q1-Q3))	1006 (612 to 1344)	582.7 (456.7 to 811.7)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group E v group F
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.026
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of tenofovir in the presence of lopinavir/ritonavir or nevirapine: maximum concentration observed

End point title	Plasma pharmacokinetic parameters of tenofovir in the

	presence of lopinavir/ritonavir or nevirapine: maximum concentration observed

End point description:

End point type	Primary

End point timeframe:

week 4

End point values	group E	group F		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	349.5 (228.2 to 453.4)	252.1 (195.6 to 306.3)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group E v group F
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.033
Method	t-test, 2-sided

Primary: Plasma pharmacokinetic parameters of tenofovir in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval

End point title	Plasma pharmacokinetic parameters of tenofovir in the presence of lopinavir/ritonavir or nevirapine: residual concentration at the end of the dosing interval

End point description:

End point type	Primary

End point timeframe:

week 4

End point values	group E	group F		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	13		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	96.7 (54.6 to 119)	54.4 (33.5 to 62.1)		

Statistical analyses

Statistical analysis title	Geometric Mean Ratio
Statistical analysis description: Ratio of the geometric mean (GMR)	
Comparison groups	group E v group F
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.013
Method	t-test, 2-sided

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: from baseline to week 4	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	DAIDS AE GRADING TAB
Dictionary version	1.0

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

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 were reported

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 February 2005	TDF withdrawal period extended

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported