Clinical trial results:
CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY AND ECONOMIC IMPACT OF REDUCING DOSES OF DARUNAVIR IN PATIENTS INFECTED WITH HIV TREATED WITH DARUNAVIR / RITONAVIR ONCE A DAY

Summary

EudraCT number	2011-006272-39
Trial protocol	ES
Global end of trial date	26 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	DRV600

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	Ensayos Clínicos, Fundació Lluita contra la Sida, +34 934978849, sgel@flsida.org
Scientific contact	Ensayos Clínicos, Fundació Lluita contra la Sida, +34 934978849, jmolto@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	30 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2014
Global end of trial reached?	Yes
Global end of trial date	26 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the proportion of patients maintaining HIV viral load in plasma <50 copies / mL after 48 weeks of follow-up.

Protection of trial subjects:

No specific measures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 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: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	96
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at four hospitals in the urban area of Barcelona, Spain. Eligible participants were HIV-infected patients aged ≥18 years who were on ART including 800/100 mg of darunavir/ritonavir once daily plus two NRTIs and who had had HIV-1 RNA levels in plasma ,50 copies/mL for at least 12 weeks.

Pre-assignment

Screening details:

Out of 105 patients screened from May 2012 to February 2013, a total of 100 fulfilled eligibility criteria and were enrolled and randomized (50 to each arm).

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	DRV600

Arm description:

Darunavir (Prezista600®)/ ritonavir (Norvir®): 1 tablet 600mg/1 tablet 100mg QD

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

Dosage and administration details:

Darunavir (Prezista600®) 1 tablet of 600mg daily

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

Dosage and administration details:

Ritonavir (Norvir®): 1 tablet 100 mg daily

Arm title	DRV800

Arm description:

Darunavir (Prezista400®)/ ritonavir (Norvir®): 2 tablets 800mg/1 tablet 100mg QD

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

Dosage and administration details:

Darunavir (Prezista 800®) 2 tablets of 400mg daily

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

Dosage and administration details:

Ritonavir (Norvir®): 1 tablet 100 mg daily

Number of subjects in period 1	DRV600	DRV800
Started	50	50
Completed	45	47
Not completed	5	3
Adverse event, serious fatal	1	-
Lost to follow-up	1	1
Lack of efficacy	3	2

Baseline characteristics

Reporting groups	
Reporting group title	DRV600
Reporting group description:	
Darunavir (Prezista600®)/ ritonavir (Norvir®): 1 tablet 600mg/1 tablet 100mg QD	
Reporting group title	DRV800
Reporting group description:	
Darunavir (Prezista400®)/ ritonavir (Norvir®): 2 tablets 800mg/1 tablet 100mg QD	

Reporting group values	DRV600	DRV800	Total
Number of subjects	50	50	100
Age categorical			
Date of birth			
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)	47	49	96
From 65-84 years	3	1	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	45.6	44.8	
standard deviation	± 10.8	± 10.5	-
Gender categorical			
Units: Subjects			
Female	10	9	19
Male	40	41	81
HIV transmission route			
Units: Subjects			
homosexual/bisexual contact	21	25	46
heterosexual contact	18	16	34
intravenous drug user	8	6	14
other/unknown	3	3	6
Hepatitis C virus coinfection			
Hepatitis C virus coinfection			
Units: Subjects			
Hepatitis C virus coinfection	13	7	20
Hepatitis C virus non coinfection	37	43	80
NRTI backbone			
NRTI backbone			
Units: Subjects			
TDF/FTC (tenofovir/emtricitabine)	32	34	66

ABC/3TC (abacavir/lamivudine)	17	16	33
Non NRTI backbone	1	0	1

Time since HIV infection diagnosis			
Units: Years			
arithmetic mean	8.2	8.9	
standard deviation	± 6.8	± 7.2	-
Number of prior ART regimens			
Units: number			
arithmetic mean	1.5	1	
inter-quartile range (Q1-Q3)	0 to 3.75	0 to 2.75	-
CD4+ T cell count			
Units: cells/mm3			
arithmetic mean	523	591	
standard deviation	± 331	± 272	-
Nadir CD4+ T cell count			
Units: cells/mm3			
arithmetic mean	197	201	
standard deviation	± 157	± 136	-
Time since last HIV-1 RNA<50 copies/mL			
Units: weeks			
median	106.9	107.4	
inter-quartile range (Q1-Q3)	40.3 to 252.4	55.4 to 219	-
Body mass index			
Units: Kg/m2			
arithmetic mean	25.3	24.9	
standard deviation	± 3.4	± 3.5	-

End points

End points reporting groups	
Reporting group title	DRV600
Reporting group description:	
Darunavir (Prezista600®)/ ritonavir (Norvir®): 1 tablet 600mg/1 tablet 100mg QD	
Reporting group title	DRV800
Reporting group description:	
Darunavir (Prezista400®)/ ritonavir (Norvir®): 2 tablets 800mg/1 tablet 100mg QD	

Primary: Absence of treatment failure	
End point title	Absence of treatment failure
End point description:	
Compare the proportion of patients maintaining HIV viral load in plasma <50 copies / mL after 48 weeks of follow-up. Absence of treatment failure was achieved by 45/50 (90%) and by 47/50 (94%) patients in the DRV600 and DRV800 groups, respectively (difference –4%; 95% CI lower limit, –12.9%).	
End point type	Primary
End point timeframe:	
48 weeks	

End point values	DRV600	DRV800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Percentatge				
Absence of treatment failure	45	47		
No absence of treatment failure	5	3		

Statistical analyses

Statistical analysis title	ITT comparative analysis
Statistical analysis description:	
The primary efficacy endpoint (absence of treatment failure) was evaluated considering all the patients randomized (ITT analysis).	
Comparison groups	DRV600 v DRV800
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	> 0.05
Method	comparing proportions

Notes:

[1] - Proportion of absence of treatment failure per group and confidence interval 95% of the difference between groups was reported

Secondary: Incidence of adverse events

End point title	Incidence of adverse events

End point description:

Compare the incidence of adverse events after 4, 12, 24, 36 and 48 weeks follow up

End point type	Secondary

End point timeframe:

4, 12, 24, 36 and 48 weeks follow up

End point values	DRV600	DRV800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Number of patients	5	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Darunavir plasma concentration

End point title	Darunavir plasma concentration

End point description:

The mean of DRV trough concentration

End point type	Secondary

End point timeframe:

4, 12, 24, 36 and 48 weeks follow up

End point values	DRV600	DRV800		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: mg/L				
number (not applicable)	2.19	2.21		

Statistical analyses

Statistical analysis title	Pharmacokinetic study

Statistical analysis description:

For the pharmacokinetic substudy, individual darunavir pharmacokinetic parameters [Cmax, AUC 0–24 and concentration at the end of the dosing
interval (Ctrough)] were calculated using non-compartmental analysis (Winnonlin version 2.0; Pharsight, Mountain View, CA, USA) and the two
study arms were compared with the geometric mean ratio and its 90% CI.

Comparison groups	DRV800 v DRV600

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence[2]
P-value	> 0.05
Method	geometric mean ratio and its 90% CI.

Notes:

[2] - Full darunavir plasma concentration–time curves were determined in 15 patients in each arm

Adverse events

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

Dictionary used	
Dictionary name	DAIDS AE Grading Tab
Dictionary version	2.0

Reporting groups	
Reporting group title	DRV600
Reporting group description: Darunavir (Prezista600®)/ ritonavir (Norvir®): 1 tablet 600mg/1 tablet 100mg QD	
Reporting group title	DRV800
Reporting group description: Darunavir (Prezista400®)/ ritonavir (Norvir®): 2 tablets 800mg/1 tablet 100mg QD	

Serious adverse events	DRV600	DRV800	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 50 (10.00%)	2 / 50 (4.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Headache	Additional description: Hospitalisation for headache post lumbar punction		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection	Additional description: Hospitalisation for respiratory infection with bronchial hiperreactivity		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Hospitalization for right pneumonia (basal)		
alternative assessment type: Systematic			

subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Died of refractory septic shock	Additional description: Patient with liver cirrhosis developed spontaneous Escherichia coli bacteraemia during the trial and died of refractory septic shock		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal	Additional description: Hospitalization due to hepatic decompensation		
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erisipela facial	Additional description: Erisipela facial		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Autolitic fact by pharmacologic ingest	Additional description: Autolitic fact by pharmacologic ingest		
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	
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: 0 %

Non-serious adverse events	DRV600	DRV800	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)	11 / 50 (22.00%)	
Cardiac disorders			
Lipids increased			
subjects affected / exposed	0 / 50 (0.00%)	5 / 50 (10.00%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Gastrointestinal disturbances grade 2			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4	6 / 50 (12.00%) 6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported