Clinical trial results:
Pharmacokinetic interactions between silymarin and Darunavir/Ritonavir

Summary

EudraCT number	2010-021159-25
Trial protocol	ES
Global end of trial date	20 July 2011

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	SILIDAR

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01346982
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, sgel@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	20 July 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2011
Global end of trial reached?	Yes
Global end of trial date	20 July 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the potential of silymarin to interact with a boosted protease inhibitor such as darunavir-ritonavir and to evaluate the risk associated of its joint intake in HIV-Infected patients.

Protection of trial subjects:	
not specific	
Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	28 March 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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 15 Caucasian HIV-infected males were enrolled.

Pre-assignment

Screening details:

All patients receiving antiretroviral therapy with darunavir-ritonavir (600/100 mg twice daily) for at least 4 weeks were enrolled.

Period 1

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

Arms

Arm title	Experimental arm

Arm description:

darunavir-ritonavir plus one capsule containing 150 mg of silymarin

Arm type	Experimental
Investigational medicinal product name	Darunavir/ritonavir (DRV/r)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600/100 mg twice daily

Investigational medicinal product name	silymarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg of silymarin every 8 h from days 1 to 14

Number of subjects in period 1	Experimental arm
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	overall

Reporting group description: -

Reporting group values	overall	Total	
Number of subjects	15	15	
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)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	48		
inter-quartile range (Q1-Q3)	44 to 50	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	15	15	

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: darunavir-ritonavir plus one capsule containing 150 mg of silymarin	

Primary: darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[1]
End point description:	
End point type	Primary
End point timeframe: week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: area under the time-concent (mg*h/l)				
geometric mean (confidence interval 90%)				
DRV/r	53.21 (46.03 to 61.38)			
DRV/r+silymarin	45.6 (39.54 to 52.72)			

Statistical analyses

No statistical analyses for this end point

Primary: darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[2]
End point description:	
End point type	Primary
End point timeframe: week 12	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: maximum concentration (mg/l)				
geometric mean (confidence interval 90%)				
DRV/r	7.08 (6.28 to 7.98)			
DRV/r+ silymarin	5.86 (5.2 to 6.61)			

Statistical analyses

No statistical analyses for this end point

Primary: darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	darunavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[3]

End point description:

End point type	Primary

End point timeframe:

week 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: concentration at the end (mg/l)				
geometric mean (confidence interval 90%)				
DRV/r	2.58 (2.17 to 3.07)			
DRV/r+silymarin	2.42 (2.04 to 2.87)			

Statistical analyses

No statistical analyses for this end point

Primary: ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[4]

End point description:

End point type	Primary

End point timeframe:

week 12

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: area under the time-concent (mg*h/l)				
geometric mean (confidence interval 90%)				
DRV/r+silymarin DRV/r	6 (5.19 to 6.93) 6.73 (5.82 to 7.8)			

Statistical analyses

No statistical analyses for this end point

Primary: ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[5]

End point description:

End point type	Primary

End point timeframe:

week 12

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: maximum concentration (mg/l)				
geometric mean (confidence interval 90%)				

DRV/r DRV/r+silymarin	0.95 (0.8 to 1.12) 0.86 (0.73 to 1.01)			

Statistical analyses

No statistical analyses for this end point

Primary: ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin

End point title	ritonavir pharmacokinetic parameters with and without coadministration of multiple doses of silymarin[6]

End point description:

End point type	Primary

End point timeframe:

week 12

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: one single arm study

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: concentration at the end (mg/l)				
geometric mean (confidence interval 90%)				
DRV/r DRV/r+silymarin	0.24 (0.21 to 0.28) 0.23 (0.19 to 0.26)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: week 12	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	DAIDS AE GRADING TAB
Dictionary version	1.0

Reporting groups	
Reporting group title	experimental group

Reporting group description: -

Serious adverse events	experimental group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	experimental group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		
Gastrointestinal disorders			
mild heartburn			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

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