Clinical trial results:
Exploratory Controlled Prospective Randomized Trial to Compare the Efficacy and Safety of Two Different Pharmacology Strategies on Neurocognitive Impairment in HIV Infection. TRIANT-TE Study

Summary

EudraCT number	2010-024510-57
Trial protocol	ES
Global end of trial date	19 March 2014

Results information

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

Trial information

Trial identification

Sponsor protocol code	TRIANT-TE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01348282
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 934978414 , j.toro@flsida.org
Scientific contact	CRA, Fundació Lluita Contra la SIDA, +34 934978414 ,

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	19 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of transdermal rivastigmine for the treatment of HIV-associated cognitive impairment.

Protection of trial subjects:

not specific

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Seventy-six subjects were screened, 29 were finally enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	lithium group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	oral lithium (Plenur®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg twice daily and was titrated progressively to ensure plasma drug concentrations of between 0.4 and 0.8 mEq/l.

Arm title	rivastigmine group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	transdermal rivastigmine (Prometax®)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

4.6mg daily and increased to 9.5 mg daily at week 4. This second dose was maintained throughout the follow-up.

Arm title	control group

Arm description: -

Arm type	participants who did not initiate a new treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	lithium group	rivastigmine group	control group
Started	11	10	8
Completed	6	5	6
Not completed	5	5	2
Adverse event, non-fatal	4	4	-
uncompleted assessments	-	-	2
voluntary withrawal	-	1	-
acute hepatitis B virus infection	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	lithium group
Reporting group description: -	
Reporting group title	rivastigmine group
Reporting group description: -	
Reporting group title	control group
Reporting group description: -	

Reporting group values	lithium group	rivastigmine group	control group
Number of subjects	11	10	8
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)	11	10	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	43	45	45
standard deviation	± 5	± 7	± 3
Gender categorical			
Units: Subjects			
Female	2	3	1
Male	9	7	7

Reporting group values	Total		
Number of subjects	29		
Age categorical			
Age			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	29		
From 65-84 years	0		

85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	6		
Male	23		

End points

End points reporting groups	
Reporting group title	lithium group
Reporting group description: -	
Reporting group title	rivastigmine group
Reporting group description: -	
Reporting group title	control group
Reporting group description: -	

Primary: change in a global cognitive score (NPZ-7)	
End point title	change in a global cognitive score (NPZ-7)
End point description:	
End point type	Primary
End point timeframe:	
From Baseline to 48 week	

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: NPZ-7 score				
arithmetic mean (standard deviation)	0.25 (± 0.4)	0.35 (± 0.14)	0.2 (± 0.44)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control
Statistical analysis description:	
Statistical significance was set at p<0.05	

Comparison groups	rivastigmine group v control group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.484 [2]
Method	t-test, 2-sided

Notes:

[1] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.
[2] - Cohen's effect size tests equal to 0.38

Statistical analysis title	Comparison between lithium group and control group
Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.849 [4]
Method	t-test, 2-sided

Notes:

[3] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.
[4] - Cohen's effect size tests equal to 0.12

Secondary: finances: Daily Functioning variables

End point title	finances: Daily Functioning variables

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	0.16 (± 0.4)	0.2 (± 0.83)	0 (± 0)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	rivastigmine group v control group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.568 [6]
Method	t-test, 2-sided

Notes:

[5] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.
[6] - Cohen's effect size tests equal to 0.36

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.34 [8]
Method	t-test, 2-sided

Notes:

[7] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[8] - Cohen's effect size tests equal to 0.57

Secondary: work: Daily Functioning variables

End point title	work: Daily Functioning variables

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	0 (± 0.63)	-0.2 (± 0.83)	0.5 (± 0.83)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	rivastigmine group v control group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[9]
P-value	= 0.2 [10]
Method	t-test, 2-sided

Notes:

[9] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[10] - Cohen's effect size tests equal to -0.84

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[11]
P-value	= 0.27 [12]
Method	t-test, 2-sided

Notes:

[11] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[12] - Cohen's effect size tests equal to -0.68

Secondary: Mental dimension: Quality of life variables

End point title	Mental dimension: Quality of life variables

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	0.16 (± 0.98)	0 (± 0.7)	0 (± 0.63)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v rivastigmine group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 1 [13]
Method	t-test, 2-sided

Notes:

[13] - Cohen's effect size tests equal to 0

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.734 [14]
Method	t-test, 2-sided

Notes:

[14] - Cohen's effect size tests equal to 0.19

Secondary: Global quality of life

End point title	Global quality of life

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	0 (± 1.26)	-0.2 (± 0.44)	0 (± 0)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v rivastigmine group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[15]
P-value	= 0.296 [16]
Method	t-test, 2-sided

Notes:

[15] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[16] - Cohen's effect size tests equal to -0.68

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[17]
P-value	= 1 [18]
Method	t-test, 2-sided

Notes:

[17] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[18] - Cohen's effect size tests equal to 0

Secondary: Depressive symptoms: Emotional status variables

End point title	Depressive symptoms: Emotional status variables

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	-0.2 (± 0.83)	-1.2 (± 4.14)	-1.2 (± 3.83)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	rivastigmine group v control group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[19]
P-value	= 1 [20]
Method	t-test, 2-sided

Notes:

[19] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[20] - Cohen's effect size tests equal to 0

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[21]
P-value	= 0.584 [22]
Method	t-test, 2-sided

Notes:

[21] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[22] - Cohen's effect size tests equal to 0.36

Secondary: Anxiety symptoms: Emotional status variables

End point title	Anxiety symptoms: Emotional status variables

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outcomes				
arithmetic mean (standard deviation)	0.6 (± 5.31)	-1.6 (± 2.88)	1.2 (± 5.54)	

Statistical analyses

Statistical analysis title	Comparison between rivastigmine group and control

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	rivastigmine group v control group
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	= 0.345 [24]
Method	t-test, 2-sided

Notes:

[23] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[24] - Cohen's effect size tests equal to -0.61

Statistical analysis title	Comparison between lithium group and control group

Statistical analysis description:

Statistical significance was set at p<0.05

Comparison groups	control group v lithium group

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	equivalence[25]
P-value	= 0.865 [26]
Method	t-test, 2-sided

Notes:

[25] - Cohen's effect size tests were additionally performed to quantify the magnitude of the differences found. Values were considered small when scores were less than 0.40, medium when they ranged between 0.40 and 0.75, and large when they were over 0.75.

[26] - Cohen's effect size tests equal to -0.11

Secondary: Total impaired areas: Daily Functioning

End point title	Total impaired areas: Daily Functioning

End point description:

End point type	Secondary

End point timeframe:

from baseline to week 48

End point values	lithium group	rivastigmine group	control group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	5	6	
Units: numerical outsomes				
arithmetic mean (standard deviation)	1 (± 4.64)	-0.6 (± 3.71)	0.66 (± 3.72)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 week follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	DAIDS AE GRADING TAB
Dictionary version	2.0
Reporting groups	
Reporting group title	lithium group
Reporting group description: -	
Reporting group title	rivastigmine group
Reporting group description: -	
Reporting group title	control group
Reporting group description: -	

Serious adverse events	lithium group	rivastigmine group	control group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	0 / 10 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	lithium group	rivastigmine group	control group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	5 / 10 (50.00%)	0 / 8 (0.00%)
Nervous system disorders			
rash and tremors			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Epistaxis			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
skin irritation			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Hepatitis B			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2011	amendment in order to ask Ethics Committee
01 April 2011	Protocol and PIS modification
28 June 2011	added week 1 follow up
02 November 2011	added new determinations: Vitamine B12, folic acid and T. Pllidum test (RPR)
17 April 2012	exclusion criteria changed

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported