Clinical trial results:
A PHASE II STUDY TO EVALUATE THE EFFICACY AND SAFETY OF PLASMA EXCHANGE WITH 5% ALBUMIN IN BETA-AMYLOID PEPTIDE CLEARANCE IN CEREBROSPINAL FLUID, AND ITS EFFECTS IN PATIENTS WITH MILD-MODERATE ALZHEIMER'S DISEASE

Summary

EudraCT number	2007-000414-36
Trial protocol	ES
Global end of trial date	07 March 2011

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	IG0602

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00742417
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols S.A.
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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 March 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 March 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether plasma exchange with 5% human albumin is able to modify the concentration of beta-amyloid peptide in cerebrospinal fluid (CSF) in the treatment group of patients with Alzheimer's disease (AD).

Protection of trial subjects:

The study characteristics will be duly described to all subjects amenable to participation in the trial (or to the legal representatives in the case the patient is unable) - followed by the request for free and voluntary authorization. The subject and the accepted legal representative of the subject will be informed of the nature, purpose and procedures of the study, with a description of the possible risks involved.

Background therapy:

Receiving stable treatment with acetylcholine esterase inhibitors (AChEIs) for the previous three months prior to starting the trial.

Evidence for comparator:

No comparators were used in this study. The control group was subjected to simulated plasma exchanges (without invasive procedures).

Actual start date of recruitment	20 July 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Spain: 33
Worldwide total number of subjects	42
EEA total number of subjects	33

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)	17
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

2 weeks for screening and randomization of treatment and control group. Subjects were randomized in a 1:1 proportion.
After screening and randomization, followed:
3 weeks of intensive treatment with 2 PE/week
Followed by a 1,5 months (6 weeks) of maintenance treatment with 1 PE/week, and
3 months (12 weeks) of treatment with 1 PE/2weeks

Pre-assignment

Screening details:

After obtaining informed consent, there was a screening period of 2 weeks of 1 or more visits for each patient.

Pre-assignment period milestones

Number of subjects started	48[1]
Number of subjects completed	39

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening Failure: 4
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Withdrawal by Legal Representative: 1
Reason: Number of subjects	Consent withdrawn by subject: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 48 patients from 4 different centres were enrolled in the study, 42 of them were finally randomised: 21 patients were randomized to treatment and 21 patients to control. Of those, 39 subjects received at least 1 treatment. The overall study population has been considered to be the safety population (39 subjects) for age and gender purposes information.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[2]
Roles blinded	Subject, Carer

Blinding implementation details:

Neuropsychologists were also blinded.

The control group was subjected to simulated plasma exchanges (without invasive procedures). A gauze dressing was placed on the subclavicular region, affixing a catheter of characteristics similar to the catheters used in the treatment group, and procedures simulating plasma exchange were carried out.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Group (Sham)

Arm description:

The control group was subjected to simulated plasma exchanges (without invasive procedures).

Arm type	Sham group

No investigational medicinal product assigned in this arm

Arm title	Treatment Group

Arm description:

18 Plasma Exchanges using Albutein 5%:
• three weeks of intensive treatment with two plasma exchanges per week
• six weeks of maintenance treatment with one weekly plasma exchange
• three months of maintenance treatment with one plasma exchange every two weeks

Arm type	Experimental
Investigational medicinal product name	Albutein 5%
Investigational medicinal product code	B05AA01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The volume of each replacement was approximately that of the plasma volume of the subject as calculated from body weight, height and hematocrit (approximately 35-45 mL/kg, corresponding to a volume of 2500-3000 mL).

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This study is blind for patients, caregivers and raters.

Number of subjects in period 1[3]	Control Group (Sham)	Treatment Group
Started	20	19
Intensive Period	20	19
Maintenance I Period	19	16
Maintenance II Period	19	16
Completed	19	16
Not completed	1	3
Consent withdrawn by subject	1	2
Adverse event, non-fatal	-	1

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Thirty nine (39) started the treatment while only 35 completed all the study procedures (Per protocol population). The overall study population has been considered to be the safety population (39 subjects).

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description:

There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.

Reporting group values	Overall Study	Total	
Number of subjects	39	39	
Age categorical			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	22	22	
Age continuous			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: years			
arithmetic mean	67.7		
standard deviation	± 7.9	-	
Gender categorical			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: Subjects			
Female	30	30	
Male	9	9	

Subject analysis sets

Subject analysis set title	FAS Population - Control Group
Subject analysis set type	Full analysis

Subject analysis set description:

The efficacy analyses were performed with the FAS population which was defined as the set of subjects who were randomized and received at least three plasma exchange sessions during the intensive treatment phase (the three first weeks of treatment).

Subject analysis set title	FAS Population - Treatment Group
Subject analysis set type	Full analysis

Subject analysis set description:

The efficacy analyses were performed with the FAS population which was defined as the set of subjects who were randomized and received at least three plasma exchange sessions during the intensive treatment phase (the three first weeks of treatment).

Reporting group values	FAS Population - Control Group	FAS Population - Treatment Group	
Number of subjects	19	18	

Age categorical			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: Subjects			
Adults (18-64 years)	10	6	
From 65-84 years	9	12	
Age continuous			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: years			
arithmetic mean	66.8	67.7	
standard deviation	± 9	± 6.6	
Gender categorical			
There were 42 enrolled subjects and 3 out of them did not start the Intensive Period (treatment period) because were withdrawn due to the following reasons: Withdrawal by legal representative, Withdrawal by Subject and Physician Decision.			
Units: Subjects			
Female	14	15	
Male	5	3	

End points

End points reporting groups

Reporting group title	Control Group (Sham)

Reporting group description:

The control group was subjected to simulated plasma exchanges (without invasive procedures).

Reporting group title	Treatment Group

Reporting group description:

18 Plasma Exchanges using Albutein 5%:
• three weeks of intensive treatment with two plasma exchanges per week
• six weeks of maintenance treatment with one weekly plasma exchange
• three months of maintenance treatment with one plasma exchange every two weeks

Subject analysis set title	FAS Population - Control Group
Subject analysis set type	Full analysis

Subject analysis set description:

The efficacy analyses were performed with the FAS population which was defined as the set of subjects who were randomized and received at least three plasma exchange sessions during the intensive treatment phase (the three first weeks of treatment).

Subject analysis set title	FAS Population - Treatment Group
Subject analysis set type	Full analysis

Subject analysis set description:

The efficacy analyses were performed with the FAS population which was defined as the set of subjects who were randomized and received at least three plasma exchange sessions during the intensive treatment phase (the three first weeks of treatment).

Primary: Change from baseline in AB42 Cerebrospinal Fluid (CSF) Levels

End point title	Change from baseline in AB42 Cerebrospinal Fluid (CSF) Levels

End point description:

Change in levels of Aβ1-42 in CSF in the period between baseline lumbar puncture (before the start of treatment) and lumbar puncture immediately after the end of the last plasma exchange (whenever this may be). Separate assays of Aβ1-42 were performed with Innotest and The Genetics Company commercial kits.

End point type	Primary

End point timeframe:

Baseline up to week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: pg/mL				
least squares mean (confidence interval 95%)				
Innotest	-45.5 (-135.1 to 44.2)	75.3 (-20 to 170.5)		
The Genetics Company	-283 (-441.1 to -125)	-86.2 (-253.9 to 81.5)		

Statistical analyses

Statistical analysis title	Statistical hypothesis testing

Statistical analysis description:

The analysis of the primary efficacy variable (change in Aβ1-42 levels in CSF) was carried out by an analysis of covariance (ANCOVA), with the change from baseline in Aβ1-42 in CSF at the last available measurement as dependent variable, treatment group as factor and the baseline level of Aβ1-42 in CSF as a covariate. The model assessed was the following: Yi = μ + Ti + Xi BASELINE + eit.

Comparison groups	FAS Population - Control Group v FAS Population - Treatment Group
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - A calculation was made of the confidence intervals of the fitted means for each treatment group, and of the differences between them, based on the above analytical model.
[2] - The statistical tests were performed with a 5% significance level and were two-sided. In addition to the tests, two-sided 95% confidence intervals (95% CI) were reported.

Secondary: P-Tau and Tau CSF Levels Throughout the Study.

End point title	P-Tau and Tau CSF Levels Throughout the Study.

End point description:

Levels of Tau and P-tau in CSF throughout the treatment phase and the follow-up phase (week 44).

End point type	Secondary

End point timeframe:

Baseline, week 02, week 08, week 20, week 33 and week 44

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: pg/mL				
arithmetic mean (standard deviation)				
P-Tau (baseline) (Albutein n=18; Control n=19)	79 (± 35.1)	87.7 (± 51.4)		
P-Tau (week 02) (n=16; n=19)	94.1 (± 46.7)	87.5 (± 43.8)		
P-Tau (week 08) (n=15; n=18)	78 (± 41.3)	78.9 (± 46.3)		
P-Tau (week 20) (n=15; n=18)	84.1 (± 36.8)	88.4 (± 42)		
P-Tau (week 33) (n=14; n=15)	78.7 (± 40.4)	91.9 (± 57.6)		
P-Tau (week 44) (n=14; n=14)	85.1 (± 46.5)	89.9 (± 54.5)		
Tau (baseline) (n=18; n=19)	589.6 (± 344.2)	571.2 (± 354.4)		
Tau (week 02) (n=16; n=19)	711 (± 388.8)	669.8 (± 496.8)		

Tau (week 08) (n=15; n=18)	526.3 (± 326.9)	482.2 (± 307.4)		
Tau (week 20) (n=15; n=18)	555.6 (± 308.3)	537.1 (± 253.5)		
Tau (week 33) (n=14; n=15)	483.5 (± 318.5)	539.5 (± 309.6)		
Tau (week 44) (n=14; n=14)	544.1 (± 347.4)	544.3 (± 299.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aβ1−40 Plasma Levels Before and After Each Study Period (The Genetics Company)

End point title	Aβ1−40 Plasma Levels Before and After Each Study Period (The Genetics Company)

End point description:

Plasma levels of Aβ1−40 before and after the Intensive period, Maintenance period I, Maintenance period II and the
Follow-up phase (using The Genetics Company commercial kits).

End point type	Secondary

End point timeframe:

Baseline, pre-plasma exchange 1 (PRE-PE1), post-plasma exchange 6 (POST-PE6), pre-plasma exchange 7 (PRE-PE7), post-plasma exchange 12 (POST-PE12), pre-plasma exchange 13 (PRE-PE13), post-plasma exchange 18 (POST-PE18), week 33 and week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: pg/mL				
arithmetic mean (standard deviation)				
Aβ1−40 Baseline (Albutein n=18; Control n=18)	126.7 (± 43.2)	121.3 (± 52.6)		
Aβ1−40 PRE-PE1 (Intensive) (n=18; n=19)	105.8 (± 47.7)	120.3 (± 57.1)		
Aβ1−40 POST-PE6 (Intensive) (n=15; n=19)	123.9 (± 53.7)	255.7 (± 98.4)		
Aβ1−40 PRE-PE7(Maintenance I) (n=14; n=17)	139.7 (± 41.8)	150.7 (± 51.3)		
Aβ1−40 POST-PE12 (Maintenance I) (n=14; n=18)	150.4 (± 54.4)	287.1 (± 98.6)		
Aβ1−40 PRE-PE13 (Maintenance II) (n=15; n=19)	129.6 (± 40.3)	150 (± 66)		
Aβ1−40 POST-PE18 (Maintenance II) (n=14; n=18)	135.4 (± 50.2)	245.9 (± 102)		
Follow up (33 week) (n=14; n=15)	136.9 (± 37.3)	153.3 (± 50.6)		
Follow up (44 week) (n=15; n=14)	147.1 (± 23.4)	146.7 (± 41.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aβ1−42 Plasma Levels Before and After Each Study Period (The Genetics Company).

End point title	Aβ1−42 Plasma Levels Before and After Each Study Period (The Genetics Company).

End point description:

Plasma levels of Aβ1−42 before and after the Intensive period, Maintenance period I, Maintenance period II and the Follow-up phase (using The Genetics Company commercial kits).

End point type	Secondary

End point timeframe:

Baseline, pre-plasma exchange 1 (PRE-PE1), post-plasma exchange 6 (POST-PE6), pre-plasma exchange 7 (PRE-PE7), post-plasma exchange 12 (POST-PE12), pre-plasma exchange 13 (PRE-PE13), post-plasma exchange 18 (POST-PE18 and week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: pg/mL				
arithmetic mean (standard deviation)				
Aβ1−42 Baseline (Albutein n=18; Control n=18)	33.7 (± 81.4)	2.8 (± 9.3)		
Aβ1−42 PRE-PE1 (Intensive) (n=18; n=19)	20.9 (± 58.4)	6.6 (± 16.3)		
Aβ1−42 POST-PE6 (Intensive) (n=15; n=19)	4.9 (± 11.8)	9.8 (± 15.6)		
Aβ1−42 PRE-PE7 (Maintenance) (n=14; n=17)	4.5 (± 12.9)	0 (± 0)		
Aβ1−42 POST-PE12 (Maintenance I) (n=14; n=18)	5.9 (± 14.3)	10.7 (± 15.9)		
Aβ1−42 PRE-PE13 (Maintenance II) (n=15; n=19)	8.2 (± 17.2)	6.9 (± 11.8)		
Aβ1−42 POST-PE18 (Maintenance II) (n=14; n=18)	7.1 (± 14.3)	8 (± 16.7)		
Follow up (44 week) (n=15; n=14)	10.2 (± 18.2)	1.7 (± 6.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aβ1−42 Plasma Levels Before and After Each Study Period (Innotest).

End point title	Aβ1−42 Plasma Levels Before and After Each Study Period (Innotest).

End point description:

Plasma levels of Aβ1−42 before and after the Intensive period, Maintenance period I, Maintenance period II and the Follow-up phase (using Innotest commercial kits).

End point type	Secondary

End point timeframe:

Baseline, pre-plasma exchange 1 (PRE-PE1), post-plasma exchange 6 (POST-PE6), pre-plasma exchange 7 (PRE-PE7), post-plasma exchange 12 (POST-PE12), pre-plasma exchange 13 (PRE-PE13), post-plasma exchange 18 (POST-PE18), week 33 and week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: pg/mL				
arithmetic mean (standard deviation)				
Aβ1−42 Baseline (Albutein n=18; Control n=18)	49.5 (± 43.7)	40.1 (± 77.1)		
Aβ1−42 PRE-PE1 (Intensive) (n=18; n=19)	33.4 (± 29.1)	20.4 (± 21.5)		
Aβ1−42 POST-PE6 (Intensive) (n=15; n=19)	45.4 (± 31.3)	29.1 (± 23.2)		
Aβ1−42 PRE-PE7 (Maintenance I) (n=14; n=17)	58.5 (± 68.1)	29.5 (± 30.9)		
Aβ1−42 POST-PE12 (Maintenance I) (n=14; n=18)	41.4 (± 35.5)	25.1 (± 21)		
Aβ1−42 PRE-PE13 (Maintenance II) (n=15; n=19)	51.2 (± 48.3)	36.4 (± 35.9)		
Aβ1−42 POST-PE18 (Maintenance II) (n=14; n=18)	45.3 (± 42.4)	37.1 (± 40.9)		
Follow up (33 week) (n=14; n=15)	10.2 (± 16.7)	10.1 (± 12.9)		
Follow up (44 week) (n=15; n=14)	11.7 (± 20.8)	11.3 (± 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 44 in Cognitive, Functional and Neuropsychiatric Scores (MMSE, ADAS-Cog, NPS

End point title	Change From Baseline to Week 44 in Cognitive, Functional and Neuropsychiatric Scores (MMSE, ADAS-Cog, NPS

End point description:

Change in the cognitive, functional and neuropsychiatric scores and overall development.
• MMSE: Mini Mental State Examination Score (range = 0 to 30, with lower values indicating impairment)
• ADAS-Cog: Alzheimer's Disease Assessment Scale, Cognitive Subscale (range = 0 to 70, with higher values indicating impairment)
• NPS (Neuropsychological battery): •SDMT (Symbol Digit Modalities Test, range = 0 to 110, with lower values indicating impairment), •SVF(Semantic Verbal Fluency Test, with a maximum of 44 words in 60 seconds), •PVF F, A and S (Phonetic Verbal Fluency Test, with a maximum of 44 words in 60 seconds),

•BNT (Boston Naming Test, with a maximum of 15 pictures), •RAVLT (Rey Auditory Verbal Learning Test, with 15 words the patient should listen and remind)
• CSDD (Cornell Scale for Depression in Dementia, 0 = none; 1 =mild or intermittent; 2 = severe)

End point type	Secondary

End point timeframe:

Change from baseline at week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: units on a scale				
arithmetic mean (standard deviation)				
MMSE (Albutein n=15; Control n=14)	-3.8 (± 5.9)	-1.7 (± 3.2)		
ADAS-Cog (n=15; n=14)	6.6 (± 10.5)	3.9 (± 6.2)		
NPS (SDMT) (n=15; n=14)	-0.5 (± 2.5)	1.3 (± 11.2)		
NPS (SVF) (n=15; n=14) (n=15; n=14)	-0.4 (± 3.8)	2.5 (± 3.2)		
NPS (PVF(F)) (n=15; n=14)	0.6 (± 3.8)	-0.2 (± 2.6)		
NPS (PVF(A)) (n=15; n=14)	0.2 (± 3.2)	0.2 (± 3.4)		
NPS (PVF(S)) (n=15; n=14)	-0.6 (± 3.3)	1.1 (± 1.8)		
NPS (BNT) (n=15; n=14)	0.3 (± 4.1)	1.7 (± 2.5)		
NPS (RAVLT Intermediate 1) (n=15; n=14)	-0.1 (± 2)	1.1 (± 1.9)		
NPS (RAVLT Intermediate 2) (n=15; n=14)	-1 (± 1.5)	0.3 (± 1.6)		
NPS (RAVLT Intermediate 3) (n=15; n=14)	-0.3 (± 2)	0.1 (± 2.1)		
NPS (RAVLT Intermediate 4) (n=15; n=14)	-0.9 (± 2.5)	-1.1 (± 1.8)		
NPS (RAVLT Intermediate 5) (n=15; n=14)	-1.4 (± 1.8)	-0.3 (± 2.1)		
NPS (RAVLT Delayed) (n=15; n=14)	0.1 (± 1)	0.5 (± 1.6)		
CSDD (patient) (n=10; n=7)	-2.1 (± 5.6)	-0.8 (± 2.9)		
CSDD (caregiver) (n=13; n=11)	1.8 (± 3.7)	1 (± 4.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 44 in Cognitive, Functional and Neuropsychiatric Scores (ADCS-ADL, NPI, CDR-Sb and

End point title	Change From Baseline to Week 44 in Cognitive, Functional and Neuropsychiatric Scores (ADCS-ADL, NPI, CDR-Sb and

End point description:

Change in the cognitive, functional and neuropsychiatric scores and overall development.
• ADCS-ADL: Alzheimer's Disease Cooperative Study/Activities Of Daily Living (23 questions describing daily activity of the subject and requests the informer to describe the actions or behaviors observed. Increased autonomy associated with higher scores, maximum of 78 points)
• NPI: Neuropsychiatric Inventory Questions (12 symptom domains scored by frequency [range=0 to 4, higher values being more frequent] and severity [range=1 to 3, higher values being more severe], total

score is sum of frequency x severity of all domains)
• CDR-Sb: Clinical Dementia Rating (range=0 to 3, higher values being more severe)
• ADCS-CGIC: Alzheimer's Disease Cooperative Study/Clinical Global Impression of Change (7-point Likert scale, 0=not assessed, 1=marked improvement, 2=moderate improvement, 3=minimal improvement, 4=no change, 5=minimal worsening, 6=moderate worsening and 7=marked worsening)

End point type	Secondary

End point timeframe:

Change from baseline at week 44.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	18		
Units: units on a scale				
arithmetic mean (standard deviation)				
ADCS-ADL (Albutein n=15; Control n=14)	-4.9 (± 10.9)	-7.1 (± 11.4)		
NPI (total score) (n=15; n=14)	-4 (± 13.7)	-1.7 (± 14.1)		
NPI (total distress) (n=15; n=14)	3.6 (± 6.4)	-2.1 (± 7.8)		
CDR Sb score (n=15; n=14)	1.4 (± 3.3)	1.7 (± 1.5)		
ADCS-CGIC (n=15; n=14)	1.2 (± 1.1)	1.5 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Magnetic Resonance Imaging (MRI) Structural Changes Variations Versus Baseline

End point title	Magnetic Resonance Imaging (MRI) Structural Changes Variations Versus Baseline

End point description:

Structural changes in volume of the hippocampus, posterior cingular area, and other associated areas by Magnetic Resonance Imaging (MRI). Three measurements were made (week -2 or -1, 20 and 44). It was measured the variations versus the baseline.

End point type	Secondary

End point timeframe:

Week 00 (baseline), week 20 and week 44

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[3]	20[4]		
Units: cubic centimeters (cc)				
arithmetic mean (standard deviation)				
Hippocampus L (week 00)	1.91 (± 0.48)	1.9 (± 0.41)		

Hippocampus L (week 20)	1.85 (± 0.4)	1.76 (± 0.45)		
Hippocampus L (week 44)	1.76 (± 0.39)	1.64 (± 0.43)		
Hippocampus R (week 00)	2.14 (± 0.38)	2.04 (± 0.41)		
Hippocampus R (week 20)	2.07 (± 0.32)	1.98 (± 0.41)		
Hippocampus R (week 44)	1.96 (± 0.34)	1.88 (± 0.35)		
Post Cingulate (week 00)	10.38 (± 0.8)	10.6 (± 1.34)		
Post Cingulate (week 20)	10.39 (± 0.8)	10.22 (± 1.58)		
Post Cingulate (week 44)	10.23 (± 1.06)	10.6 (± 1.48)		
Total Intracranial Volume (week 00)	1064.38 (± 130.29)	1034.38 (± 99.77)		
Total Intracranial Volume (week 20)	1042.7 (± 119.93)	990.31 (± 83.42)		
Total Intracranial Volume (week 44)	1026.51 (± 148.43)	985.43 (± 86.1)		

Notes:

[3] - 2 groups of patients analysed, treatment and control group, of 20 each group.

[4] - 2 groups of patients analysed, treatment and control group, of 20 each group.

Statistical analyses

No statistical analyses for this end point

Secondary: Variations in Hypoperfusion Based on Single Photon Emission Computed Tomography (SPECT)

End point title	Variations in Hypoperfusion Based on Single Photon Emission Computed Tomography (SPECT)

End point description:

Percentage of patients with improved perfusion at the end of the study compared to their initial perfusion. Frontal, parietal and temporal lobes were evaluated from the quantified NeuroGam images. This rendered parametric images showed brain alterations with more than 2 standard deviations with respect to a normal data base. Initial parametric images were compared to the final ones and it was considered perfusion improvement those patients that showed less stretch and/or defect intensity.

End point type	Secondary

End point timeframe:

End of study.

End point values	FAS Population - Control Group	FAS Population - Treatment Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[5]	20[6]		
Units: percentatge of improvement				
number (not applicable)				
Parietal	20	25		
Temporal	10	25		
Frontal	5	5		

Notes:

[5] - 2 groups of patients analysed, treatment and control group, of 20 each group.

[6] - 2 groups of patients analysed, treatment and control group, of 20 each group.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Primary criterion of safety was % of plasma exchange (PE) associated with at least one adverse event (AE) that may be related to the study procedure (adverse reaction).

Adverse event reporting additional description:

In addition, global consideration will be made of the percentage PE involving some AE, whether or not related to the procedure. Vital signs, anxiety and restlessness tests and the criterion of the investigator were also used to evaluate patient safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Control Group

Reporting group description:

Control group followed the same schedule; however, they did not undergo plasma replacement (it was subjected to simulated plasma replacements)

Reporting group title	Treatment Group

Reporting group description:

18 Plasma Exchanges using Albutein 5%:
• three weeks of intensive treatment with two plasma exchanges per week
• six weeks of maintenance treatment with one weekly plasma exchange
• three months of maintenance treatment with one plasma exchange every two weeks

Serious adverse events	Control Group	Treatment Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	3 / 19 (15.79%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Medical device complication			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Control Group	Treatment Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 20 (70.00%)	18 / 19 (94.74%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Bunion operation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Urinary cystectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Catheter site haemorrhage			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	2 / 20 (10.00%)	4 / 19 (21.05%)	
occurrences (all)	2	4	
Confusional state			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Depressive symptom			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Disinhibition			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 20 (10.00%)	2 / 19 (10.53%)	
occurrences (all)	2	2	
Procedural dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Dementia Alzheimer's type			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 20 (10.00%)	7 / 19 (36.84%)	
occurrences (all)	2	7	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Vomiting			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 20 (10.00%)	1 / 19 (5.26%)	
occurrences (all)	2	1	
Muscle haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Periarthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Device related infection			
subjects affected / exposed	1 / 20 (5.00%)	5 / 19 (26.32%)	
occurrences (all)	1	5	
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Upper respiratory tract infection			

subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Hypercalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 October 2007	(Spanish amendment only) 1. Increase of the sample size from 40 to 42 subjects to have 36 evaluable subjects. 2. To clarify the procedures and the simulation of the plasmapheresis and to detail the tests done at each study visit. 3. To summarize the secondary biomarkers for AD to be determined in each study period. 4. To detail the specific methodology for the neuropsychological tests. The RAV Learning Test has been detailed as well as the order and the scales at each visit. It has been also clarified the paper of the blinded evaluators who should administer the neuropsychological tests to the patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes: