Clinical trial results:
Pilot study to evaluate the effect of plasma exchange in motor and cognitive function in patients with amyotrophic lateral sclerosis

Summary

EudraCT number	2013-004842-40
Trial protocol	ES
Global end of trial date	03 June 2016

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018
Summary attachment (see zip file)	IG1309 CSR Synopsis (2-Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	IG1309

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02479802
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols S.A.
Sponsor organisation address	Can Guasch 2, Parets del Vallés, Spain, 08150
Public contact	Miquel Barceló, Instituto Grifols S.A., 34 935712368, miquel.barcelo@grifols.com
Scientific contact	Miquel Barceló, Instituto Grifols S.A., 34 935712368, miquel.barcelo@grifols.com

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	15 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2016
Global end of trial reached?	Yes
Global end of trial date	03 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the disease progression using the Amyotrofic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score and the Forced Vital Capacity (FVC) of subjects affected by Amyotrophic Lateral Sclerosis (ALS) and treated with Plasma Exchange (PE) with Albutein 5%.

Protection of trial subjects:

The Investigator obtained a freely given written informed consent from each subject (or his/her legal representative if he/she was disabled) participating in this study, after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study relevant to the subject's decision to participate prior to initiating any study-related procedure to the subject. Subjects were informed of the advantages, risks and constrains of the study and of their right to withdraw at any time. The informed consent form was signed, with name and date noted by the subject, before the subject (or his/her representative) was exposed to any study-related procedure, including screening tests for eligibility.
The Investigator ensured that the subject's anonymity was preserved. On CRFs or any other documents submitted to the Sponsor, the subjects were not identified by their names, but by an identification code. Documents not for submission to the Sponsor, i.e. the confidential subject identification code, original consent forms and source records were maintained by the Investigator in strict confidence.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2014
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: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	12
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The enrolled population, that is, all recruited subjects who provided written informed consent to participate, was composed of 13 (100%) subjects. Originally, the planned enrollment was 10 subjects, but 3 additional subjects were recruited to achieve 10 fully eligible subjects.

Pre-assignment

Screening details:

Subjects of both gender, older than 18 and younger than 70 years of age, who had an ALS diagnosis and FVC >70% and who gave their signed written consent to participate were included in the study. 13 subjects were screened and enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Overall study

Arm description:

Plasma exchange with Albumin

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

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 0 (Week 0)

Arm description:

Baseline visit

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

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 1 (Week 4)

Arm description:

Evaluation visit at end of Intensive treatment period

Arm type	Experimental

Investigational medicinal product name	Albutein 5%
Investigational medicinal product code	
Other name	Human Albumin 5%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 2 (Week 12)

Arm description:

Evaluation vist in the middle of treatment phase

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

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 4 (Week 25)

Arm description:

Evaluation visit one week after the end of treatment phase, start of follow-up phase

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

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 5 (Week 36)

Arm description:

Evaluation visit in the middle of Follow-up phase

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

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Arm title	Visit 6 (Week 48)

Arm description:	
Final visit - end of follow-up phase or early withdrawal visit	
Arm type	Experimental
Investigational medicinal product name	Albutein 5%
Investigational medicinal product code	
Other name	Human Albumin 5%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

27 plasma exchange procedures using Albumin 5% (estimated 3000 mL per plasma exchange) as replacement solution:
- three weeks of intensive treatment with two plasma exchanges per week
- twenty-one weeks of maintenance treatment with one weekly plasma exchange

Number of subjects in period 1	Overall study	Visit 0 (Week 0)	Visit 1 (Week 4)
Started	13	13	13
Completed	10	13	13
Not completed	3	0	0
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	1	-	-
Lost to follow-up	1	-	-

Number of subjects in period 1	Visit 2 (Week 12)	Visit 4 (Week 25)	Visit 5 (Week 36)
Started	12	11	10
Completed	12	11	10
Not completed	0	0	0
Adverse event, serious fatal	-	-	-
Adverse event, non-fatal	-	-	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Visit 6 (Week 48)
Started	11
Completed	11
Not completed	0
Adverse event, serious fatal	-
Adverse event, non-fatal	-
Lost to follow-up	-

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	13	13	
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)	12	12	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	48.9		
standard deviation	± 9.86	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	9	9	
Race Units: Subjects			
White or Caucasian	13	13	
Black or African American	0	0	
Asian	0	0	
Other	0	0	
Body part first affected by the disease Units: Subjects			
Bulbar	5	5	
Left Upper Extremity	1	1	
Right Upper Extremity	4	4	
Trunk	0	0	
Left Lower Extremity	2	2	
Right Lower Extremity	1	1	
Respiratory	0	0	
Revised El Escorial-Arlie Criteria Units: Subjects			
Definite	6	6	
Probable	7	7	
Possible	0	0	

End points

End points reporting groups

Reporting group title	Overall study
Reporting group description: Plasma exchange with Albumin	
Reporting group title	Visit 0 (Week 0)
Reporting group description: Baseline visit	
Reporting group title	Visit 1 (Week 4)
Reporting group description: Evaluation visit at end of Intensive treatment period	
Reporting group title	Visit 2 (Week 12)
Reporting group description: Evaluation vist in the middle of treatment phase	
Reporting group title	Visit 4 (Week 25)
Reporting group description: Evaluation visit one week after the end of treatment phase, start of follow-up phase	
Reporting group title	Visit 5 (Week 36)
Reporting group description: Evaluation visit in the middle of Follow-up phase	
Reporting group title	Visit 6 (Week 48)
Reporting group description: Final visit - end of follow-up phase or early withdrawal visit	

Primary: Changes From Baseline in the ALS Functional Rating Scale Revised (ALSFRS-R)

End point title	Changes From Baseline in the ALS Functional Rating Scale Revised (ALSFRS-R)[1]
End point description:	
End point type	Primary
End point timeframe: Weeks 4, 12, 25, 36, and 48	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, a statistical analysis is only present from baseline and final visit.

End point values	Visit 0 (Week 0)	Visit 1 (Week 4)	Visit 2 (Week 12)	Visit 4 (Week 25)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	12	11
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 0.0)	-1.0 (-1.0 to 0.0)	-1.5 (-4.0 to 0.0)	-4.0 (-8.0 to -3.0)

End point values	Visit 5 (Week 36)	Visit 6 (Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))	-5.5 (-9.0 to -3.0)	-10.0 (-14.0 to -7.0)		

Statistical analyses

Statistical analysis title	Change from Baseline at Week 48
Comparison groups	Visit 6 (Week 48) v Visit 0 (Week 0)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	t-test, 1-sided

Primary: Change From Baseline in Forced Vital Capacity (FVC)

End point title	Change From Baseline in Forced Vital Capacity (FVC)[2]

End point description:

End point type	Primary

End point timeframe:

Weeks 4, 12, 25, 36, and 48

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, a statistical analysis is only present from baseline and final visit.

End point values	Visit 0 (Week 0)	Visit 1 (Week 4)	Visit 2 (Week 12)	Visit 4 (Week 25)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	12	11
Units: Percentage of predicted value				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 0.0)	-6.0 (-9.0 to 2.0)	-3.5 (-12.5 to 0.0)	-9.0 (-23.0 to -6.0)

End point values	Visit 5 (Week 36)	Visit 6 (Week 48)		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	11		
Units: Percentage of predicted value				
median (inter-quartile range (Q1-Q3))	-12.0 (-22.0 to -12.0)	-23.0 (-38.0 to -9.0)		

Statistical analyses

Statistical analysis title	Change from Baseline at Week 48
Comparison groups	Visit 6 (Week 48) v Visit 0 (Week 0)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0006
Method	t-test, 1-sided

Secondary: Changes From Baseline in ALS Cognitive Function Determined by the ALS-Cognitive Behavioral Screen (ALS-CBS) Test

End point title	Changes From Baseline in ALS Cognitive Function Determined by the ALS-Cognitive Behavioral Screen (ALS-CBS) Test[3]

End point description:

End point type	Secondary

End point timeframe:

Weeks 25 and 48

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, a general assessment was performed only at Visit 4 (Week 25) and Visit 6 (Week 48), so not all the arms (time points) have results data.

End point values	Visit 4 (Week 25)	Visit 6 (Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))				
Behaviour Status	0.0 (-3.0 to 2.0)	-1.0 (-6.0 to 1.0)		
Symptom Status	0.0 (-1.0 to 1.0)	0.0 (-1.0 to 1.0)		
Cognitive Screening	0.0 (-2.0 to 1.0)	-1.0 (-3.0 to 2.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Motor Evoked Potential in Thenar and Hypothenar Eminence, and Anterior Tibialis Muscle

End point title	Motor Evoked Potential in Thenar and Hypothenar Eminence, and Anterior Tibialis Muscle[4]

End point description:

End point type	Secondary

End point timeframe:

Weeks 0, 4, 12, 25, 36, and 48

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, overall study arm had not result data.

End point values	Visit 0 (Week 0)	Visit 1 (Week 4)	Visit 2 (Week 12)	Visit 4 (Week 25)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	13	12	11
Units: millivolt				
median (inter-quartile range (Q1-Q3))				
Right Tibialis Anterior	2.6 (0.5 to 6.2)	4.9 (1.5 to 7.1)	3.1 (0.6 to 5.5)	1.9 (0.4 to 4.5)
Left Tibialis Anterior	3.2 (1.2 to 6.6)	3.1 (0.4 to 5.3)	3.3 (0.1 to 5.2)	2.6 (0.1 to 4.3)
Right Thenar Eminence (APB)	4.0 (0.6 to 9.4)	4.4 (0.6 to 7.3)	3.0 (0.9 to 4.1)	2.6 (0.4 to 3.7)
Left Thenar Eminence (APB)	6.4 (1.4 to 8.7)	2.6 (0.9 to 6.2)	3.1 (0.6 to 6.4)	1.9 (0.2 to 6.0)
Right Hypothenar Eminence (ADM)	6.4 (0.6 to 8.1)	7.4 (6.3 to 7.9)	5.8 (2.7 to 8.1)	5.1 (2.6 to 5.8)
Left Hypothenar Eminence (ADM)	6.2 (3.3 to 8.8)	5.5 (3.5 to 8.2)	4.4 (2.1 to 7.4)	3.8 (1.1 to 6.5)

End point values	Visit 5 (Week 36)	Visit 6 (Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	11		
Units: millivolt				
median (inter-quartile range (Q1-Q3))				
Right Tibialis Anterior	2.1 (0.3 to 5.5)	1.2 (0.0 to 3.2)		
Left Tibialis Anterior	2.1 (0.2 to 4.1)	1.0 (0.0 to 3.7)		
Right Thenar Eminence (APB)	1.2 (0.4 to 3.4)	0.6 (0.1 to 3.1)		
Left Thenar Eminence (APB)	0.6 (0.2 to 2.7)	0.5 (0.2 to 1.2)		
Right Hypothenar Eminence (ADM)	5.0 (2.8 to 6.1)	3.2 (0.6 to 6.9)		
Left Hypothenar Eminence (ADM)	4.0 (0.2 to 7.0)	2.4 (0.4 to 7.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in ALS Assessment Questionnaire 40 (ALSA-Q40).

End point title	Changes From Baseline in ALS Assessment Questionnaire 40 (ALSA-Q40).[5]

End point description:

The transformed scores are presented that use an index from 0 to 100 for each dimension to allow for straightforward interpretation of the results.

End point type	Secondary

End point timeframe:

Weeks 25 and 48

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, a general assessment was performed only at Visit 4 (Week 25) and Visit 6 (Week 48), so not all the arms (time points) have results data.

End point values	Visit 4 (Week 25)	Visit 6 (Week 48)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Units on a scale				
median (inter-quartile range (Q1-Q3))				
Physical Mobility	10.0 (0.0 to 20.0)	32.5 (7.5 to 50.0)		
ADL/Independence	12.5 (-2.5 to 45.0)	25.0 (7.5 to 45.0)		
Eating and Drinking	0.0 (0.0 to 25.0)	8.3 (0.0 to 58.3)		
Communication	0.0 (0.0 to 28.6)	0.0 (0.0 to 35.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Plasma Exchange Sessions Associated With One Adverse Event or Adverse Reaction, Including Clinically Significant Changes in Vital Signs or Lab Parameters

End point title	Percentage of Plasma Exchange Sessions Associated With One Adverse Event or Adverse Reaction, Including Clinically Significant Changes in Vital Signs or Lab Parameters[6]

End point description:

End point type	Secondary

End point timeframe:

During the Treatment Phase (24 weeks)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a single arm study, arm reported in the Overall study period are different time points where assessments were made. For this particular endpoint, a general assessment was performed at the end of treatment phase, so not all the arms (time points) have results data.

End point values	Overall study			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage of Plasma Exchange Sessions				
arithmetic mean (standard deviation)	0.9 (± 2.22)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected throughout the study (48 weeks).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Plasma exchange with Albumin	

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Surgical and medical procedures			
Mechanical ventilation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Presyncope			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Toothache			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Nasal ulcer			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Depression			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 13 (46.15%)		
occurrences (all)	6		
Upper respiratory tract infection			

subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2014	This amendment included the following changes relevant to the conduct of the study: Modification of Secondary efficacy variables: - Neuropsychological tests and clinical criteria such as the Neary criteria for frontotemporal dementia were removed from the protocol. Therefore, each subject's cognitive function would be evaluated solely with the ALS-CBS (Amyotrophic Lateral Sclerosis - Cognitive Behavioral Screen) test to better align with standard clinical practice procedures of the site. - The motor evoked potential variable determined by electromyography was redefined to follow the standard clinical practice procedures of the site. - The study visit dates for biomarker measurements (oxidative stress, inflammation and functional capacity of plasma albumin) were changed from Visit 4 (Week 25) to Visit 3 (Week 24 coinciding with PE#27). This way, biomarker samples could be obtained prior and after PE#27. The numbers of laboratory tests were reduced following the medical criteria of the site's apheresis experts. Therefore, safety blood count and coagulation tests were no longer included in each PE and only scheduled at Baseline visit (before the first PE), at Visit 1 (Week 4 coinciding with PE#7, which is the evaluation visit after the end of the intensive phase of treatment [PE#1 to PE#6]), at Visit 5 (Week 36 during Follow-up) and at Final visit 6 (Week 48). Additionally, a lipid profile test was added, as it is routine clinical practice in the Multidisciplinary Unit ELA Bellvitge University Hospital
17 October 2014	This amendment included the following changes relevant to the conduct of the study: - Some discrepancies between protocol section 6.2.1 Study Chronogram and Appendix 1 Study Procedure Flow-Chart were detected. Therefore, coagulation tests and blood count from V5 visit were eliminated. In addition, metabolomics biomarkers assessments were removed from Visit 5 and Visit 6 and metabolomics biomarkers tests were limited to visits V0, V2 and V3. - The minimum blood volume extracted for biomarker analysis was added. Total blood volume to be extracted was increased in order to be able to analyze all planned biomarkers (oxidative stress, inflammation and non-directed metabolomic profile).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported