Clinical trial results:
A multicenter, randomized, controlled study to evaluate the efficacy and safety of short-term plasma exchange followed by long-term plasmaphereses with infusion of human albumin combined with intravenous immunoglobulin in patients with mild-moderate Alzheimer's disease.

Summary

EudraCT number	2011-001598-25
Trial protocol	ES
Global end of trial date	06 March 2018

Results information

Result version number	v1 (current)
This version publication date	01 March 2020
First version publication date	01 March 2020

Trial information

Trial identification

Sponsor protocol code	IG1002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01561053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Poligono Levante, C/Can Guasc 2, Parets del Valles, Barcelona, Spain, 08150
Public contact	AMBAR Clinical Manager, Grifols, +34 935712200, AMBARclinical@grifols.com
Scientific contact	AMBAR Clinical Manager, Grifols, +34 935712200, AMBARclinical@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	31 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2018
Global end of trial reached?	Yes
Global end of trial date	06 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the changes in the cognitive, functional, behavioral and global domains based on the different applicable psychometric batteries and scales.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 151
Country: Number of subjects enrolled	Spain: 171
Worldwide total number of subjects	322
EEA total number of subjects	171

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)	94
From 65 to 84 years	224
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 41 sites in the US and Spain between 2012 and 2016.

Pre-assignment

Screening details:

The total number of screened subjects were 496 (264 in US and 232 in Spain) in this study. Among them, 347 subjects were randomized (162 in US and 185 in Spain), and from this population, 25 subjects were randomized but not treated. As a result, 322 subjects were evaluable subjects.

Period 1

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

Blinding implementation details:

The control group was subjected to simulated procedures (full plasma exchange and low volume plasma exchange) with no direct connection or fluid interchange during the same time as the treated subjects and followed the same schedule of assessments. The duration of the sham FPE and LVPE procedures was similar to the real procedures. These control subjects also received the same visits and procedures (blood draws and lumbar puncture) as the subjects in the treatment group.

Arms

Are arms mutually exclusive?	Yes
Arm title	High Albumin + Immunoglobulin

Arm description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with high dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)

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

Dosage and administration details:

Therapeutic plasma exchange with human albumin 5%

Investigational medicinal product name	Albumin 20%
Investigational medicinal product code	
Other name	Albutein 20%, Human Albumin Grifols 20%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Low volume plasma exchange with human albumin 20%

Investigational medicinal product name	Immunoglobulin
Investigational medicinal product code	
Other name	Flebogamma 5% DIF
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous human immunoglobulin 5%

Arm title	Low Albumin + Immunoglobulin

Arm description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)

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

Dosage and administration details:

Therapeutic plasma exchange with human albumin 5%

Investigational medicinal product name	Albumin 20%
Investigational medicinal product code	
Other name	Albutein 20%, Human Albumin Grifols 20%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Low volume plasma exchange with human albumin 20%

Investigational medicinal product name	Immunoglobulin
Investigational medicinal product code	
Other name	Flebogamma 5% DIF
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous human immunoglobulin 5%

Arm title	Low Albumin

Arm description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% (maintenance treatment period)

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

Dosage and administration details:

Therapeutic plasma exchange with human albumin 5%

Investigational medicinal product name	Albumin 20%
Investigational medicinal product code	
Other name	Albutein 20%, Human Albumin Grifols 20%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Low volume plasma exchange with human albumin 20%

Arm title	Control (Sham) Group

Arm description:

Simulated plasma exchange procedure. The simulated process did not involve fluid interchange.
The control group was subjected to simulated procedures (full plasma exchange and low volume plasma exchange) with no direct connection or fluid interchange .

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - 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: In this study, even though Subject, Carer, Assessor were blinded, the investigator team who were involved in the treatment were not blinded.

Number of subjects in period 1	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin
Started	78	86	78
Completed	51	56	61
Not completed	27	30	17
Consent withdrawn by subject	10	11	4
Adverse event, non-fatal	9	15	6
Allergic reaction	1	-	-
Poor venous access	2	1	2
Investigator decision	-	-	1
Sponsor decision	1	1	-
Lost to follow-up	1	-	2
Health problems	1	-	-
Protocol deviation	2	2	2

Number of subjects in period 1	Control (Sham) Group
Started	80
Completed	64
Not completed	16
Consent withdrawn by subject	12
Adverse event, non-fatal	1
Allergic reaction	-
Poor venous access	-
Investigator decision	-
Sponsor decision	-
Lost to follow-up	2
Health problems	-
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	High Albumin + Immunoglobulin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with high dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)	
Reporting group title	Low Albumin + Immunoglobulin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)	
Reporting group title	Low Albumin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% (maintenance treatment period)	
Reporting group title	Control (Sham) Group
Reporting group description:	
Simulated plasma exchange procedure. The simulated process did not involve fluid interchange. The control group was subjected to simulated procedures (full plasma exchange and low volume plasma exchange) with no direct connection or fluid interchange .	

Reporting group values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin
Number of subjects	78	86	78
Age categorical Units: Subjects			
Adults (18-64 years)	22	17	26
From 65-84 years	54	69	51
85 years and over	2	0	1
Age continuous Units: years			
arithmetic mean	69.54	69.47	68.47
standard deviation	± 7.895	± 6.924	± 7.476
Gender categorical Units: Subjects			
Female	47	48	43
Male	31	38	35
Severity of Alzheimer disease at Baseline Units: Subjects			
Mild (MMSE 22-26)	36	49	32
Moderate (MMSE 18-21)	42	37	46
APO E4 at Baseline Units: Subjects			
APO E4 Carrier at Baseline	33	40	47
APO E4 Non-carrier at Baseline	41	43	27
Missing	4	3	4
Baseline Mini-Mental State Examination total Score			
Mini-Mental State Examination (MMSE) is a widely used, brief 30-point questionnaire test of cognitive function among the elderly; it includes tests of orientation, registration, attention and calculation,			

memory (recall, naming and repetition), language (comprehension, reading and writing) and visual-spatial skills. The score ranges from 0 to 30 and is obtained by summing the points corresponding to each answer. Lower score indicates more impaired cognition.			
Units: Units on a scale			
arithmetic mean	21.41	22.09	21.24
standard deviation	± 2.616	± 2.633	± 2.408

Reporting group values	Control (Sham) Group	Total	
Number of subjects	80	322	
Age categorical			
Units: Subjects			
Adults (18-64 years)	29	94	
From 65-84 years	50	224	
85 years and over	1	4	
Age continuous			
Units: years			
arithmetic mean	68.44		
standard deviation	± 8.378	-	
Gender categorical			
Units: Subjects			
Female	36	174	
Male	44	148	
Severity of Alzheimer disease at Baseline			
Units: Subjects			
Mild (MMSE 22-26)	44	161	
Moderate (MMSE 18-21)	36	161	
APO E4 at Baseline			
Units: Subjects			
APO E4 Carrier at Baseline	34	154	
APO E4 Non-carrier at Baseline	43	154	
Missing	3	14	
Baseline Mini-Mental State Examination total Score			
Mini-Mental State Examination (MMSE) is a widely used, brief 30-point questionnaire test of cognitive function among the elderly; it includes tests of orientation, registration, attention and calculation, memory (recall, naming and repetition), language (comprehension, reading and writing) and visual-spatial skills. The score ranges from 0 to 30 and is obtained by summing the points corresponding to each answer. Lower score indicates more impaired cognition.			
Units: Units on a scale			
arithmetic mean	21.69		
standard deviation	± 2.559	-	

Subject analysis sets

Subject analysis set title	All Treated Subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All Treated group included all subjects treated in this study, including subjects from the High Albumin + Immunoglobulin group, Low Albumin + Immunoglobulin group, and Low Albumin group.

Reporting group values	All Treated Subjects		
Number of subjects	242		
Age categorical Units: Subjects			
Adults (18-64 years)	65		
From 65-84 years	174		
85 years and over	3		
Age continuous Units: years			
arithmetic mean	69.17		
standard deviation	± 7.410		
Gender categorical Units: Subjects			
Female	138		
Male	104		
Severity of Alzheimer disease at Baseline Units: Subjects			
Mild (MMSE 22-26)	117		
Moderate (MMSE 18-21)	125		
APO E4 at Baseline Units: Subjects			
APO E4 Carrier at Baseline	120		
APO E4 Non-carrier at Baseline	111		
Missing			
Baseline Mini-Mental State Examination total Score			
Mini-Mental State Examination (MMSE) is a widely used, brief 30-point questionnaire test of cognitive function among the elderly; it includes tests of orientation, registration, attention and calculation, memory (recall, naming and repetition), language (comprehension, reading and writing) and visual-spatial skills. The score ranges from 0 to 30 and is obtained by summing the points corresponding to each answer. Lower score indicates more impaired cognition.			
Units: Units on a scale			
arithmetic mean	21.60		
standard deviation	± 2.574		

End points

End points reporting groups

Reporting group title	High Albumin + Immunoglobulin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with high dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)	
Reporting group title	Low Albumin + Immunoglobulin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)	
Reporting group title	Low Albumin
Reporting group description:	
Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% (maintenance treatment period)	
Reporting group title	Control (Sham) Group
Reporting group description:	
Simulated plasma exchange procedure. The simulated process did not involve fluid interchange. The control group was subjected to simulated procedures (full plasma exchange and low volume plasma exchange) with no direct connection or fluid interchange .	

Subject analysis set title	All Treated Subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
All Treated group included all subjects treated in this study, including subjects from the High Albumin + Immunoglobulin group, Low Albumin + Immunoglobulin group, and Low Albumin group.	

Primary: Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) Total Score (Changes From Baseline to 14 Months)

End point title	Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) Total Score (Changes From Baseline to 14 Months)
End point description:	
ADAS-Cog total score as a change from baseline to 14 months The ADAS-Cog Scale is a questionnaire that assesses cognitive performance in 12 different domains. The domains are: word recall, commands, constructional praxis, delayed word-recall task, naming objects/figures, ideational praxis, orientation, word recognition, remembering test instructions, comprehension, word finding difficulty, and spoken language ability. The total score ranges from 0 to 80, where a higher score indicates more cognitive impairment.	
End point type	Primary
End point timeframe:	
Baseline and 14 months	

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	57	61	64
Units: Units on a scale				
least squares mean (standard error)	0.8 (± 1.28)	0.8 (± 1.09)	1.5 (± 1.02)	3.2 (± 0.95)

End point values	All Treated Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	168			
Units: Units on a scale				
least squares mean (standard error)	1.0 (± 0.64)			

Statistical analyses

Statistical analysis title	All Treated Subjects versus Control (Sham) Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.063
Method	Mixed model for repeated measures

Notes:

[1] - Statistical comparison of the combined active treatment groups to the Control (Sham) Group

Primary: Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score (Changes From Baseline to 14 Months)

End point title	Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) Total Score (Changes From Baseline to 14 Months)

End point description:

ADCS-ADL total score as a change from baseline to 14 months
The ADCS-ADL comprises 23 questions covering a wide array of activities of daily living. Many of the activities begin with an assessment of whether that activity is relevant and then, if yes, follow with an assessment of the difficulty. The total score over all activities ranges from 0 to 78, where a higher score indicates more autonomy (better outcome).

End point type	Primary

End point timeframe:

Baseline and 14 Months

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	57	61	64
Units: Units on a scale				
least squares mean (standard error)	-3.5 (± 1.80)	-2.0 (± 1.03)	-3.9 (± 1.24)	-6.7 (± 1.50)

End point values	All Treated Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	169			
Units: Units on a scale				
least squares mean (standard error)	-3.2 (± 0.78)			

Statistical analyses

Statistical analysis title	All Treated Sujects versus Control (Sham) Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.03
Method	Mixed model for repeated measures

Notes:

[2] - Statistical comparison of the combined active treatment groups to the Control (Sham) Group

Other pre-specified: ADAS-Cog Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:22-26

End point title	ADAS-Cog Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:22-26

End point description:

ADAS-Cog total score as a change from baseline to 14 months in patients with Mini-Mental State Examination (MMSE):22-26
The ADAS-Cog Scale is a questionnaire that assesses cognitive performance in 12 different domains. The domains are: word recall, commands, constructional praxis, delayed word-recall task, naming objects/figures, ideational praxis, orientation, word recognition, remembering test instructions, comprehension, word finding difficulty, and spoken language ability. The total score ranges from 0 to 80, where a higher score indicates more cognitive impairment.

End point type	Other pre-specified

End point timeframe:

Baseline and 14 Months

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	37	25	38
Units: Units on a scale				
least squares mean (standard error)	-0.9 (± 1.51)	-0.3 (± 1.04)	-0.6 (± 1.12)	0.6 (± 1.12)

End point values	All Treated Subjects			

Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: Units on a scale				
least squares mean (standard error)	-0.6 (± 0.68)			

Statistical analyses

Statistical analysis title	All Treated Subjects versus Control Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.379
Method	Mixed model for repeated measures

Notes:

[3] - Statistical comparison of the combined active treatment groups to the control group

Other pre-specified: ADCS-ADL Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:22-26

End point title	ADCS-ADL Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:22-26

End point description:

ADCS-ADL total score as a change from baseline to 14 months in patients with baseline Mini-Mental State Examination (MMSE):22-26
The ADCS-ADL comprises 23 questions covering a wide array of activities of daily living. Many of the activities begin with an assessment of whether that activity is relevant and then, if yes, follow with an assessment of the difficulty. The total score over all activities ranges from 0 to 78, where a higher score indicates more autonomy (better outcome).

End point type	Other pre-specified

End point timeframe:

Baseline and 14 Months

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	23	37	25	38
Units: Units on a scale				
least squares mean (standard error)	-2.4 (± 1.68)	0.8 (± 0.98)	-0.9 (± 1.43)	-1.3 (± 1.29)

End point values	All Treated Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: Units on a scale				

least squares mean (standard error)	-0.6 (± 0.75)			

Statistical analyses

Statistical analysis title	All Treated Subjects versus Control (Sham) Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.664
Method	Mixed model for repeated measures

Notes:

[4] - Statistical comparison of the combined active treatment groups to the control group

Other pre-specified: ADAS-Cog Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:18-21

End point title	ADAS-Cog Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:18-21

End point description:

ADAS-Cog score as a change from baseline to 14 months in patients with baseline Mini-Mental State Examination (MMSE):18-21
The ADAS-Cog Scale is a questionnaire that assesses cognitive performance in 12 different domains. The domains are: word recall, commands, constructional praxis, delayed word-recall task, naming objects/figures, ideational praxis, orientation, word recognition, remembering test instructions, comprehension, word finding difficulty, and spoken language ability. The total score ranges from 0 to 80, where a higher score indicates more cognitive impairment.

End point type	Other pre-specified

End point timeframe:

Baseline and 14 months

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	20	36	26
Units: Units on a scale				
least squares mean (standard error)	2.4 (± 1.95)	1.9 (± 2.44)	3.3 (± 1.49)	6.4 (± 1.34)

End point values	All Treated Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	83			
Units: Units on a scale				
least squares mean (standard error)	2.6 (± 1.07)			

Statistical analyses

Statistical analysis title	All Treated Subjects versus Control (Sham) Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.054
Method	Mixed model for repeated measures

Notes:

[5] - Statistical comparison of the combined active treatment groups to the Control (Sham) Group

Other pre-specified: ADCS-ADL Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:18-21

End point title	ADCS-ADL Total Score (Changes From Baseline to 14 Months) in Patients With Baseline MMSE:18-21

End point description:

ADCS-ADL total score as a change from baseline to 14 months in patients with baseline Mini-Mental State Examination (MMSE):18-21
The ADCS-ADL comprises 23 questions covering a wide array of activities of daily living. Many of the activities begin with an assessment of whether that activity is relevant and then, if yes, follow with an assessment of the difficulty. The total score over all activities ranges from 0 to 78, where a higher score indicates more autonomy (better outcome).

End point type	Other pre-specified

End point timeframe:

Baseline and 14 Months

End point values	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin	Control (Sham) Group
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	28	20	36	26
Units: Units on a scale				
least squares mean (standard error)	-4.5 (± 2.97)	-5.7 (± 2.11)	-6.0 (± 1.75)	-14.1 (± 2.67)

End point values	All Treated Subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	84			
Units: Units on a scale				
least squares mean (standard error)	5.5 (± 1.33)			

Statistical analyses

Statistical analysis title	All Treated Subjects verus Control (Sham) Group
Comparison groups	Control (Sham) Group v All Treated Subjects
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.002
Method	Mixed model for repeated measures

Notes:

[6] - Statistical comparison of the combined active treatment groups to the Control (Sham) Group

Adverse events

Adverse events information

Timeframe for reporting adverse events:

14 Months

Adverse event reporting additional description:

1 randomized subject in the control group was implanted by error with a real central catheter and was then transferred and treated as a high albumin + immunoglobulin subject.
Therefore, this subject was considered for the evaluable population as control but moved to high albumin + immunoglobulin group for safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	High Albumin + Immunoglobulin

Reporting group description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with high dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)

Reporting group title	Low Albumin + Immunoglobulin

Reporting group description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% or immunoglobulin 5% (maintenance treatment period)

Reporting group title	Low Albumin

Reporting group description:

Therapeutic plasma exchange with albumin 5% (intensive treatment period) + Low volume plasma exchange with low dose of albumin 20% (maintenance treatment period)

Reporting group title	Control (Sham) Group

Reporting group description:

Simulated plasma exchange procedure

Serious adverse events	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 79 (20.25%)	19 / 86 (22.09%)	8 / 78 (10.26%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events	0	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Jugular vein thrombosis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Bladder neoplasm surgery			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 79 (2.53%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional medical device removal by patient			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis in device			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinitis allergic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Self-injurious ideation	Additional description: Self-injurious behaviour		
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaesthetic complication cardiac			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			

subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 79 (1.27%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amyloid related imaging abnormalities			
subjects affected / exposed	2 / 79 (2.53%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrovascular accident			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 79 (2.53%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 79 (1.27%)	1 / 86 (1.16%)	3 / 78 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis staphylococcal			
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia	Additional description: Lobar pneumonia		
subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	1 / 78 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control (Sham) Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 79 (10.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectal adenocarcinoma			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Bladder neoplasm surgery			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Knee operation			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intentional medical device removal by patient			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis in device				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Apnoea				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rhinitis allergic				
subjects affected / exposed	1 / 79 (1.27%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Completed suicide				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Self-injurious ideation	Additional description: Self-injurious behaviour			
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Anaesthetic complication cardiac			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Amyloid related imaging abnormalities			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lacunar infarction			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 79 (1.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			

subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocarditis staphylococcal				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia	Additional description: Lobar pneumonia			
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypovolaemia				
subjects affected / exposed	0 / 79 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	High Albumin + Immunoglobulin	Low Albumin + Immunoglobulin	Low Albumin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 79 (84.81%)	77 / 86 (89.53%)	72 / 78 (92.31%)
Investigations			
Blood fibrinogen decreased			
subjects affected / exposed	3 / 79 (3.80%)	5 / 86 (5.81%)	1 / 78 (1.28%)
occurrences (all)	4	8	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 79 (3.80%)	9 / 86 (10.47%)	4 / 78 (5.13%)
occurrences (all)	4	10	4
Vascular access complication			
subjects affected / exposed	6 / 79 (7.59%)	4 / 86 (4.65%)	4 / 78 (5.13%)
occurrences (all)	11	5	7
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 79 (3.80%)	5 / 86 (5.81%)	3 / 78 (3.85%)
occurrences (all)	3	6	4
Hypertension			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	3 / 78 (3.85%)
occurrences (all)	0	0	4
Hypotension			
subjects affected / exposed	16 / 79 (20.25%)	16 / 86 (18.60%)	21 / 78 (26.92%)
occurrences (all)	34	39	43
Poor venous access			
subjects affected / exposed	7 / 79 (8.86%)	6 / 86 (6.98%)	4 / 78 (5.13%)
occurrences (all)	10	7	6
Cardiac disorders			
Bradycardia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 86 (3.49%)	1 / 78 (1.28%)
occurrences (all)	6	3	1
Nervous system disorders			
Dizziness			

subjects affected / exposed	11 / 79 (13.92%)	12 / 86 (13.95%)	8 / 78 (10.26%)
occurrences (all)	12	16	10
Headache			
subjects affected / exposed	12 / 79 (15.19%)	4 / 86 (4.65%)	7 / 78 (8.97%)
occurrences (all)	13	4	9
Paraesthesia			
subjects affected / exposed	5 / 79 (6.33%)	1 / 86 (1.16%)	9 / 78 (11.54%)
occurrences (all)	12	1	16
Presyncope			
subjects affected / exposed	10 / 79 (12.66%)	14 / 86 (16.28%)	8 / 78 (10.26%)
occurrences (all)	14	18	9
Syncope			
subjects affected / exposed	4 / 79 (5.06%)	4 / 86 (4.65%)	4 / 78 (5.13%)
occurrences (all)	4	5	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 79 (21.52%)	17 / 86 (19.77%)	16 / 78 (20.51%)
occurrences (all)	17	19	20
Iron deficiency anaemia			
subjects affected / exposed	5 / 79 (6.33%)	1 / 86 (1.16%)	3 / 78 (3.85%)
occurrences (all)	5	1	3
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	3 / 79 (3.80%)	3 / 86 (3.49%)	4 / 78 (5.13%)
occurrences (all)	4	3	6
Device connection issue			
subjects affected / exposed	0 / 79 (0.00%)	0 / 86 (0.00%)	0 / 78 (0.00%)
occurrences (all)	0	0	0
Extravasation			
subjects affected / exposed	10 / 79 (12.66%)	7 / 86 (8.14%)	7 / 78 (8.97%)
occurrences (all)	15	13	12
Infusion site extravasation			
subjects affected / exposed	7 / 79 (8.86%)	4 / 86 (4.65%)	2 / 78 (2.56%)
occurrences (all)	10	6	3
Oedema peripheral			

subjects affected / exposed	1 / 79 (1.27%)	0 / 86 (0.00%)	3 / 78 (3.85%)
occurrences (all)	2	0	3
Catheter site pain			
subjects affected / exposed	2 / 79 (2.53%)	0 / 86 (0.00%)	9 / 78 (11.54%)
occurrences (all)	2	0	11
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 79 (5.06%)	6 / 86 (6.98%)	3 / 78 (3.85%)
occurrences (all)	6	7	3
Nausea			
subjects affected / exposed	5 / 79 (6.33%)	5 / 86 (5.81%)	8 / 78 (10.26%)
occurrences (all)	6	8	11
Vomiting			
subjects affected / exposed	3 / 79 (3.80%)	6 / 86 (6.98%)	5 / 78 (6.41%)
occurrences (all)	4	6	5
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 79 (0.00%)	1 / 86 (1.16%)	4 / 78 (5.13%)
occurrences (all)	0	1	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	6 / 79 (7.59%)	2 / 86 (2.33%)	6 / 78 (7.69%)
occurrences (all)	11	4	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 79 (3.80%)	3 / 86 (3.49%)	4 / 78 (5.13%)
occurrences (all)	3	3	4
Muscle spasms			
subjects affected / exposed	18 / 79 (22.78%)	5 / 86 (5.81%)	9 / 78 (11.54%)
occurrences (all)	34	6	18
Pain in extremity			
subjects affected / exposed	4 / 79 (5.06%)	4 / 86 (4.65%)	2 / 78 (2.56%)
occurrences (all)	5	4	2
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	6 / 79 (7.59%)	3 / 86 (3.49%)	7 / 78 (8.97%)
occurrences (all)	6	3	7
Respiratory tract infection			
subjects affected / exposed	1 / 79 (1.27%)	4 / 86 (4.65%)	3 / 78 (3.85%)
occurrences (all)	1	4	3
Upper respiratory tract infection			
subjects affected / exposed	6 / 79 (7.59%)	1 / 86 (1.16%)	6 / 78 (7.69%)
occurrences (all)	6	1	6
Urinary tract infection			
subjects affected / exposed	5 / 79 (6.33%)	6 / 86 (6.98%)	1 / 78 (1.28%)
occurrences (all)	6	7	1
Catheter site infection			
subjects affected / exposed	1 / 79 (1.27%)	4 / 86 (4.65%)	4 / 78 (5.13%)
occurrences (all)	1	5	4

Non-serious adverse events	Control (Sham) Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 79 (70.89%)		
Investigations			
Blood fibrinogen decreased			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 79 (5.06%)		
occurrences (all)	4		
Vascular access complication			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 79 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	5 / 79 (6.33%)		
occurrences (all)	7		

Hypotension subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Poor venous access subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 7		
Headache subjects affected / exposed occurrences (all)	14 / 79 (17.72%) 20		
Paraesthesia subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Presyncope subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Syncope subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 5		
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
General disorders and administration site conditions Catheter site erythema			

subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Device connection issue subjects affected / exposed occurrences (all)	4 / 79 (5.06%) 8		
Extravasation subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Infusion site extravasation subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Oedema peripheral subjects affected / exposed occurrences (all)	5 / 79 (6.33%) 5		
Catheter site pain subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 79 (2.53%) 2		
Nausea subjects affected / exposed occurrences (all)	0 / 79 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	3 / 79 (3.80%) 3		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 79 (1.27%) 1		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 79 (1.27%) 1 3 / 79 (3.80%) 3 1 / 79 (1.27%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Catheter site infection subjects affected / exposed occurrences (all)	 3 / 79 (3.80%) 5 4 / 79 (5.06%) 4 5 / 79 (6.33%) 6 3 / 79 (3.80%) 3 0 / 79 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2011	Protocol Version 1.5 was issued in November 2011 (12 subjects were enrolled in Spain only under this amendment) and implemented the following changes in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • Revision of the control group and blinding technique following The Cochrane Library about the invasive "placebo" controls* to avoid the use of sham procedures * Cyna AM, Costi D, Middleton P. Randomised controlled trials using invasive 'placebo' controls are unethical and should be excluded from Cochrane Reviews [editorial]. The Cochrane Library 2011 (15 June). • Inclusion of Columbia-Suicide Severity Rating Scale (C-SSRS), Quality of Life AD Measure (QoL-AD) and Resource Utilization in Dementia (RUD-Lite©) Questionnaire • Update to timing for assessment of efficacy measurements from baseline (week -2 to -1), week 6, month 5, 8, 11 and 14 to baseline (week -2 to -1), intermediate visit (week 7-8), months 6, 9, 12 and 14. • Inclusion of Appendix 11 – STUDY SUMMARY TABLE AND STUDY FLOW CHART and modification of Appendix 3 - AUTO-C CLINICAL PROTOCOL
30 April 2012	Protocol Version 1.6 was issued in April 2012 (after 12 subjects had been enrolled under the previous version, 6 new subjects were enrolled in Spain only under this amendment) and implemented the following changes in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • Substitution of secondary efficacy variable Boston Naming Test (BNT) to Neuropsychological Assessment Battery Naming Test (NAB) • Update to Appendix 4 - REPORTING OF SERIOUS AND/OR UNEXPECTED AES, elimination of Appendix 5 - STUDY CONTACT INFORMATION • Update to inclusion criteria#3 related to include current stable treatment of memantine and for inclusion criteria #6 related to neuroimaging was clarified. • Extend timing for screening phase to 3 weeks; and provide time-window for FPE visits (window of ± 1 day), Intermediate visit (window of ± 2 days) and LVPE visits window of ± 5 days) • The number of scheduled MRI and FDG-PET assessments for brain structural changes was increased from 3 to 6. • Elimination of AD genetic markers (ApoE and presenilin), update laboratory parameters and AD biomarkers.

16 November 2012	Protocol Version 1.7 was issued in November 2012 (after 18 subjects had been enrolled under the previous version, no new subjects were enrolled under this amendment) and implemented the following changes in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • Update to Appendix 3 – AUTO-C CLINICAL PROTOCOL and Appendix 4 - REPORTING OF SERIOUS AND/OR UNEXPECTED AES, elimination of Appendix 8 – SAMPLE INFORMED CONSENT TEMPLATE and Appendix 9 - SAMPLE CAREGIVER CONSENT TEMPLATE • Modification of Investigational Plan since the third group of treatment was changed from 1/3 of albumin dose (13 g) and IVIG (7 g) to albumin dose only group (20 g) • Clarification of exclusion criteria #1 (plasma exchange contraindications), #10 (uncontrolled high blood pressure), #12 (heart diseases), #16 (years of education) and #17 (stable treatment for behavioral disorders) • Update of safety assessments to include a chest X-ray to confirm the correct placement of the catheter; vital signs were assessed at 15-30 min before PE, during and 15-30 min after PE; addition of monitoring of subjects for number and type of bacterial infections requiring antibiotic, and addition of troponin assessment at screening and at each post-PE during intensive FPE period. • Update timing for primary criterion of safety (percentage of PE associated with at least one procedure-related AE) to be assessed within 72 hours after infusion completion (or after the infusion stops). • Incorporation of Data Monitoring Committee (DMC)
29 January 2013	Amended Protocol Version 2.0 was issued in January 2013 (after 18 subjects had been enrolled under the previous version, 107 new subjects in Spain and US were enrolled under this amendment) and implemented the following changes in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • The planned enrollment was increased from 350 to 364 subjects to obtain an estimated sample size of 312 subjects (78 per treatment group) for evaluation. This sample size would provide joint power for the 2 co-primary endpoints (implemented in this protocol version; see below) of at least 90%. • Sham procedures mimicking plasmaphereses but with neither fluid exchange nor albumin or IVIG administration were implemented for the control group, following the same visit and assessment schedule used for the treated groups. The control group previously did not undergo these procedures and did not have visits or assessments during the intensive PE period (Weeks 1 to 6). • Exclusion criteria for uncontrolled high blood pressure (despite regular treatment during the previous 3 months) were increased from >140 to ≥160 mmHg (systolic) and from >90 to ≥100 mmHg (diastolic). • Change from baseline in ADCS-ADL inventory was added as a co-primary efficacy variable. • The number of scheduled MRI assessments for brain structural changes was decreased from 6 to 5. • The number of scheduled assessments for variation in FDG-PET patterns was decreased from 6 to 4. • aPTT was added to the scheduled laboratory assessments.

31 December 2015	Amended Protocol Version 3.0 was issued in December 2015 (after 125 subjects had been enrolled under the previous versions, 222 new subjects in Spain and US were enrolled under this amendment) and implemented the following changes in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • Guidelines for sham procedures and management of hypovolemia, fever, and thromboembolic events were added. • The exclusion criterion for bradycardia was decreased from <60 to <55/min. • An exclusion criterion was added for subjects being treated with anticoagulants or antiplatelet therapy. • A provision was added that a person accompanying the subject for study procedures should not be in the same room in order to maintain the blind except in cases of agitated subjects. • Premedication with corticosteroids for IVIG administration was added as a permitted concomitant treatment. • ACEIs were added as prohibited concomitant treatments. • Sampling of plasma bags corresponding to each PE (FPE and LVPE) at selected sites was added. • Central interpretation of FDG-PET and MRI assessments was added. • The requirement for immediate notification of unexpected AEs was removed.
28 November 2017	Amended Protocol Version 4.0 was issued in November 2017 (after 347 subjects had been enrolled under the previous versions, no new subjects were enrolled under this amendment) and implemented the following change in study conduct (excluding administrative and typographical changes or clarifications to the protocol): • Sites performing LVPE were allowed to use devices based on the Aurora™ device (Fresenius Kabi, Bad Homburg, Germany) for the procedure. This device is an upgrade of the Auto-C device.
21 February 2018	Amended Protocol Version 5.0 was issued in February 2018 in the US only, and administrative and typographical changes were implemented to the protocol. No changes to study conduct were specified, and no new subjects were enrolled under this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported