Clinical trial results:
Cerebrolysin and Recovery after Stroke (CARS) - A Randomized, Placebo-Controlled, Double-Blind, Multicenter, Phase II Clinical Study.

Summary

EudraCT number	2007-000870-21
Trial protocol	PL
Global end of trial date	29 December 2010

Results information

Result version number	v1 (current)
This version publication date	28 April 2022
First version publication date	28 April 2022

Trial information

Trial identification

Sponsor protocol code	EBE-RO-061215

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	EVER Neuro Pharma GmbH
Sponsor organisation address	Oberburgau 3, Unterach, Austria, 4866
Public contact	Clinical Research & Development, EVER Neuro Pharma GmbH , +43 7665 20555 0, studies@everpharma.com
Scientific contact	Clinical Research & Development, EVER Neuro Pharma GmbH , +43 7665 20555 0, studies@everpharma.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	12 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 December 2010
Global end of trial reached?	Yes
Global end of trial date	29 December 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this trial was to investigate whether patients randomized to Cerebrolysin showed improved ARAT scores over the 90-day study observation period in comparison with patients randomized to placebo.

Protection of trial subjects:

Informed consent was obtained from all trial subjects.
Safety assessments included physical examination, lab tests (haematology, chemistry panel and urinalysis), vital signs (incl. blood pressure in supine position, heart rate, and respiration rate), and adverse events.
A negative urine pregnancy test was required for female patients in reproductive years.
Concomitant illnesses and medication were documented.

Background therapy:

At the investigator’s discretion: Basic stroke treatment for general management including thrombolysis on an as-needed basis without restriction, a compensation of fluid and electrolyte balance and acid-base balance, and substances needed for adequate management of secondary symptoms including but not limited to antihypertensive agents, cardiovascular treatment, anti-diabetic agents, antibiotics, and treatment for sleep disturbances and body temperature lowering.

Evidence for comparator:

The comparator is a placebo (sodium chloride solution 0.9%).

Actual start date of recruitment	17 April 2008
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	Romania: 182
Country: Number of subjects enrolled	Ukraine: 26
Worldwide total number of subjects	208
EEA total number of subjects	182

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)	97
From 65 to 84 years	111
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period: 17 April 2008 - 01 October 2010
Recruitment territories: Romania (N=182; 8 sites), Ukraine (N=26; 3 sites), Poland (N=0)

Pre-assignment

Screening details:

In-patients were screened for in-/exclusion criteria.
Screening failures and reasons were not documented as agreed pre-study.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Assessor

Blinding implementation details:

The packaging material for the infusion solution was designed to ensure the study medication of both treatment groups to be indistinguishable in appearance:
- the volume of the infusion solution was identical in both treatment groups
- a colored sleeve was put over the infusion bag to mask potential slight colour differences between the active treatment and placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cerebrolysin

Arm description:

Cerebrolysin was administered once daily as an intravenous infusion. Each infusion consisted of 30 ml Cerebrolysin + 70 ml sodium choloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Arm type	Experimental
Investigational medicinal product name	Cerebrolysin
Investigational medicinal product code	EV Substance code: SUB74627; CAS number:12656-61-0
Other name	Renacenz, Cognicer
Pharmaceutical forms	Solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 30 ml/day (3x10 ml ampoules)
Administration: intravenous infusion of 30 ml Cerebrolysin + 70 ml sodium chloride solution 0.9%, once daily for 21 consecutive days

Arm title	Placebo

Arm description:

Placebo was administered once daily as an intravenous infusion. Each infusion consisted of 100 ml sodium chloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Arm type	Placebo
Investigational medicinal product name	Sodium chloride solution 0.9%
Investigational medicinal product code	EV Substance code: SUB20079
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 100 ml/day
Administration: intravenous infusion, once daily for 21 consecutive days

Number of subjects in period 1	Cerebrolysin	Placebo
Started	104	104
Completed	104	104

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

The packaging material for the infusion solution was designed to ensure the study medication of both treatment groups to be indistinguishable in appearance:
- the volume of the infusion solution was identical in both treatment groups
- a colored sleeve was put over the infusion bag to mask potential slight colour differences between the active treatment and placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cerebrolysin

Arm description:

Cerebrolysin was administered once daily as an intravenous infusion. Each infusion consisted of 30 ml Cerebrolysin + 70 ml sodium choloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Arm type	Experimental
Investigational medicinal product name	Cerebrolysin
Investigational medicinal product code	EV Substance code: SUB74627; CAS number:12656-61-0
Other name	Renacenz, Cognicer
Pharmaceutical forms	Solution for injection, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 30 ml/day (3x10 ml ampoules)
Administration: intravenous infusion of 30 ml Cerebrolysin + 70 ml sodium chloride solution 0.9%, once daily for 21 consecutive days

Arm title	Placebo

Arm description:

Placebo was administered once daily as an intravenous infusion. Each infusion consisted of 100 ml sodium chloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Arm type	Placebo
Investigational medicinal product name	Sodium chloride solution 0.9%
Investigational medicinal product code	EV Substance code: SUB20079
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage: 100 ml/day
Administration: intravenous infusion, once daily for 21 consecutive days

Number of subjects in period 2	Cerebrolysin	Placebo
Started	104	104
Completed	100	96
Not completed	4	8
Adverse event, serious fatal	-	3
Administrative cause	-	1
Consent withdrawn by subject	2	2
Adverse event, non-fatal	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Cerebrolysin

Reporting group description:

Cerebrolysin was administered once daily as an intravenous infusion. Each infusion consisted of 30 ml Cerebrolysin + 70 ml sodium choloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Reporting group title	Placebo

Reporting group description:

Placebo was administered once daily as an intravenous infusion. Each infusion consisted of 100 ml sodium chloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Reporting group values	Cerebrolysin	Placebo	Total
Number of subjects	104	104	208
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	46	51	97
From 65-84 years	58	53	111
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.9	63.0	
standard deviation	± 9.8	± 10.6	-
Gender categorical Units: Subjects			
Female	34	41	75
Male	70	63	133

End points reporting groups

Reporting group title	Cerebrolysin

Reporting group description:

Cerebrolysin was administered once daily as an intravenous infusion. Each infusion consisted of 30 ml Cerebrolysin + 70 ml sodium choloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Reporting group title	Placebo

Reporting group description:

Placebo was administered once daily as an intravenous infusion. Each infusion consisted of 100 ml sodium chloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Reporting group title	Cerebrolysin

Reporting group description:

Cerebrolysin was administered once daily as an intravenous infusion. Each infusion consisted of 30 ml Cerebrolysin + 70 ml sodium choloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Reporting group title	Placebo

Reporting group description:

Placebo was administered once daily as an intravenous infusion. Each infusion consisted of 100 ml sodium chloride solution 0.9%. The infusion was administered over 20 minutes, once daily over 21 consecutive days. The first infusion was administered after baseline assessment and within 24-72 h after onset of stroke.

Subject analysis set title	mITT-LOCF (nonparametric re-analysis)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT analysis set was defined as all randomized patients who have had at least 1 dose of study medication and have assessments for the primary end point (ARAT) at baseline and at least 1 time point after the first dose of study medication.

Subject analysis set title	Full analysis LOCF (parametric analysis)
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized patients who have had at least one dose of study medication and have assessments for the primary endpoint (ARAT score) at baseline and at least one time point after first dose of study medication.

Primary: ARAT score change from baseline to day 90 in the paretic arm

End point title	ARAT score change from baseline to day 90 in the paretic arm

End point description:

The Action Reasearch arm test (ARAT) assesses upper limb functioning and is a 19 item measure divided into 4 sub-tests (grasp, grip, pinch, and gross arm movement). Performance on each item is rated on a 4-point ordinal scale (performs test normally: 3, completes test but takes abnormally long or has great difficulty: 2, performs test partially: 1, can perform no part of test: 0). The first item of each sub-test represents the most difficult item, thus, if a patient scores 3 points on the first item, he will be automatically credited with 3 points on the following items of that sub-test. Similarly, the second item of each sub-test represents the easiest item, thus, if a patient scores 0 points in the second item, he will be automatically credited with 0 points on the following items of that sub-test. The score ranges from 0 – 57.

End point type	Primary

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	Full analysis LOCF (parametric analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	103	207	
Units: Score				
least squares mean (confidence interval 95%)	30.5 (27.0 to 34.0)	15.3 (11.8 to 18.8)	30.5 (27.0 to 34.0)	

Attachments (see zip file)	ARAT score change from baseline/ARAT.png

Statistical analyses

Statistical analysis title	ARAT change from baseline - parametric analysis

Statistical analysis description:

The primary evaluation on ARAT was an analysis of covariance (ANCOVA) on the change scores from baseline to day 90 comparing the differences among study groups. The ANCOVA model included the day 90 change score as dependent variable and the baseline score as a covariate. Estimates of least square means and associated 95% confidence intervals were provided. The LOCF approach was used for missing data, baseline data were not carried forward.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Least square means
Point estimate	15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.3
upper limit	20.1

Post-hoc: ARAT score change from baseline to day 90 in the paretic arm - nonparametric re-analysis

End point title	ARAT score change from baseline to day 90 in the paretic arm - nonparametric re-analysis

End point description:

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.7118 (0.6307 to 0.7928)	0.7118 (0.6307 to 0.7928)	0.7118 (0.6307 to 0.7928)	

Attachments (see zip file)	ARAT score change from baseline (MW estimate)/Global status.

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of ARAT

Statistical analysis description:

Nonparametric analyses were performed using the Wilcoxon–Mann–Whitney test because of the skewness and non-normality of the distributions (Shapiro–Wilk; P=0.0137) and the presence of outliers. The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[1]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.7118
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6307
upper limit	0.7928

Notes:

[1] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

The traditional benchmark values for the MW are 0.29 (large inferiority), 0.36 (medium inferiority), 0.44 (small inferiority), 0.50 (equality), 0.56 (small superiority), 0.64 (medium superiority), and 0.71 (large superiority).

Post-hoc: Gait velocity change from baseline to day 90 - nonparametric re-analysis

End point title	Gait velocity change from baseline to day 90 - nonparametric re-analysis

End point description:

Gait velocity is measured as the time taken to walk the middle 8 meters of 10 meters and is timed by a

chronometer. The first and last meters, considered respectively warm-up and the deceleration phases, are not included in the calculation. Participants begin the GV test on the word "go" and are instructed to "walk at a comfortable and secure pace." Each participant performs the task twice, with the final score being the time in seconds of the quicker of the two timed trials.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	34	35	69	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.5937 (0.4585 to 0.7289)	0.5937 (0.4585 to 0.7289)	0.5937 (0.4585 to 0.7289)	

Attachments (see zip file)	Gait velocity change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of gait velocity

Statistical analysis description:

The Mann-Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon-Mann-Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	69
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5937
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4585
upper limit	0.7289

Notes:

[2] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: 9-Hole Peg Test change from baseline to day 90 - nonparametric re-analysis

End point title	9-Hole Peg Test change from baseline to day 90 - nonparametric re-analysis

End point description:

The 9-HPT is a brief, standardized, quantitative test of upper extremity function. Both the dominant and non-dominant hands are tested twice. The patient is seated at a
table with a small, shallow container holding nine pegs and a wood or plastic block containing nine empty holes. On a start command when a stopwatch is started, the
patient picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as
possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are
immediately followed by two consecutive trials with the non-dominant hand.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	90	93	183	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.5612 (0.4777 to 0.6448)	0.5612 (0.4777 to 0.6448)	0.5612 (0.4777 to 0.6448)	

Attachments (see zip file)	9 Hole Peg Test change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of 9 Hole Peg Test

Statistical analysis description:

The Mann-Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon-Mann-Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	183
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5612
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4777
upper limit	0.6448

Notes:

[3] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: NIHSS change from baseline to day 90 - nonparametric re-analysis

End point title	NIHSS change from baseline to day 90 - nonparametric re-analysis

End point description:

The NIHSS assesses neurologic deficit and is a 15 item scale that covers the level of consciousness, gaze, visual fields, facial palsy, motor functions, limb ataxia, aphasia, dysarthria and extinction and inattention.
Items have 3- to 5-point response scales, scored from 0 to 4 with higher score indicative of more severe disability. In case of patient death, the worst score possible is assigned.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.6754 (0.5977 to 0.7530)	0.6754 (0.5977 to 0.7530)	0.6754 (0.5977 to 0.7530)	

Attachments (see zip file)	NIHSS change from baseline (MW estimate)/Global status.png

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of NIHSS

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Cerebrolysin v Placebo
Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.6754
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5977
upper limit	0.753

Notes:

[4] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Barthel Index change from baseline to day 90 - nonparametric re-analysis	
End point title	Barthel Index change from baseline to day 90 - nonparametric re-analysis

End point description:

The Barthel Index is a functional outcome scale measuring activities of daily living and is based on observed functions. The scale covers feeding, mobility from bed to chair, personal toilet (washing etc.), getting on/off the toilet, bathing, walking on level surface, going up/down stairs, dressing and incontinence (bladder and bowel).
Items have 2- to 3-point response scales, scored 0, 5 or 0, 5, and 10 with higher scores indicative of better function. Individuals are scored on ten activities which give a total score of 0 (totally dependent) to 100 (fully independent) with 5-point increments. In case of patient death, the worst score possible is assigned.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.6720 (0.5922 to 0.7518)	0.6720 (0.5922 to 0.7518)	0.6720 (0.5922 to 0.7518)	

Attachments (see zip file)	Barthel Index change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of Barthel Index

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[5]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.672

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5922
upper limit	0.7518

Notes:

[5] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: mRS change from baseline to day 90 - nonparametric re-analysis

End point title	mRS change from baseline to day 90 - nonparametric re-analysis

End point description:

The modified Rankin Scale (mRS) is a functional outcome scale measuring global outcome. It is used for grading the outcome and the level of disability after a stroke. The mRS is a 7-point ordinal scale with a score of 0 indicative of no residual symptoms at all and the worst possible score of 6 which is assigned in case of death.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.7339 (0.6612 to 0.8065)	0.7339 (0.6612 to 0.8065)	0.7339 (0.6612 to 0.8065)	

Attachments (see zip file)	mRS change from baseline (MW estimate)/Global status.png

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of mRS

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Cerebrolysin v Placebo

Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[6]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.7339
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6612
upper limit	0.8065

Notes:

[6] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Goodglass and Kaplan Communication Scale change from baseline to day 90 - nonparametric re-analysis

End point title	Goodglass and Kaplan Communication Scale change from baseline to day 90 - nonparametric re-analysis

End point description:

This 6-point ordinal scale requires simple categorical assignment to determine the severity of an aphasia, which is based entirely on communicative ability.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.5614 (0.4938 to 0.6290)	0.5614 (0.4938 to 0.6290)	0.5614 (0.4938 to 0.6290)	

Attachments (see zip file)	G&K Comm Scale change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of Goodglass and Kaplan

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Cerebrolysin v Placebo

Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[7]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5614
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4938
upper limit	0.629

Notes:

[7] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: SF-36 physical component summary change from baseline to day 90 - nonparametric re-analysis

End point title	SF-36 physical component summary change from baseline to day 90 - nonparametric re-analysis

End point description:

The SF-36 Health Survey is a 36-item short-form (SF-36) and consists of eight scales yielding two summary measures: physical and mental health. The physical health measure includes four scales of physical functioning (10 items), role-physical (4 items), bodily pain (2 items), and general health (5 items). The mental health measure is composed of vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items).

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	95	197	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.6727 (0.5900 to 0.7553)	0.6727 (0.5900 to 0.7553)	0.6727 (0.5900 to 0.7553)	

Attachments (see zip file)	SF-36 PCS change from baseline (MW estimate)/Global status.

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of SF-36 PCS

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	197
Analysis specification	Post-hoc
Analysis type	superiority[8]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.6727
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.7553

Notes:

[8] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Line cancellation test change from baseline to day 90 - nonparametric re-analysis

End point title	Line cancellation test change from baseline to day 90 - nonparametric re-analysis

End point description:

At the line cancellation test (score range from 0 to 36 points), subjects are presented with a single sheet of paper on which 6 lines in varying orientations are drawn, 18 on each side. They are instructed to make a mark through all of the lines. Left- sided neglect was indicated by a failure to mark more lines on the left side than on the right. Degree of neglect is assessed by the proportion of lines omitted relative to the total number of lines. The line cancellation test sheet is divided into right and left portions and a right and then a left correct answer rates are analyzed.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	98	100	198	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.4696 (0.4041 to 0.5351)	0.4696 (0.4041 to 0.5351)	0.4696 (0.4041 to 0.5351)	

Attachments (see zip file)	Line Canc Test change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of Line Canc Test

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the Wilcoxon–Mann–Whitney test.

Comparison groups	Cerebrolysin v Placebo
Number of subjects included in analysis	198
Analysis specification	Post-hoc
Analysis type	superiority[9]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.4696
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4041
upper limit	0.5351

Notes:

[9] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Gap detection test change from baseline to day 90 - nonparametric re-analysis

End point title	Gap detection test change from baseline to day 90 - nonparametric re-analysis

End point description:

In the gap-detection test, twenty circles and forty pseudo-circles, each with a diameter of 15 mm, are drawn in a random manner on a sheet of white paper (29.7 x 42 cm) and are arranged evenly on either side of the vertical midline of the paper. Half of the pseudo-circles have a missing portion on the right side, and the rest have a missing portion on the left side. The patient is instructed to circle every complete circle and to cross out every incomplete circle with a pen held in the hand. To investigate neglect, the total number of figures correctly circled or crossed out is calculated for the left and right side of the stimulus sheet (body-centered neglect) and with respect to the three types of circles (stimulus-centered neglect).

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	100	197	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.4981 (0.4281 to 0.5681)	0.4981 (0.4281 to 0.5681)	0.4981 (0.4281 to 0.5681)	

Attachments (see zip file)	Gap Detect Test change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of Gap Detection Test

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the well-known Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	197
Analysis specification	Post-hoc
Analysis type	superiority[10]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.4981
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4281
upper limit	0.5681

Notes:

[10] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: SF-36 mental component summary change from baseline to day 90 - nonparametric re-analysis

End point title	SF-36 mental component summary change from baseline to day 90 - nonparametric re-analysis

End point description:

The SF-36 Health Survey is a 36-item short-form (SF-36) and consists of eight scales yielding two summary measures: physical and mental health. The physical health measure includes four scales of physical functioning (10 items), role-physical (4 items), bodily pain (2 items), and general health (5 items). The mental health measure is composed of vitality (4 items), social functioning (2 items), role-emotional (3 items), and mental health (5 items).

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	95	197	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.5602 (0.4795 to 0.6409)	0.5602 (0.4795 to 0.6409)	0.5602 (0.4795 to 0.6409)	

Attachments (see zip file)	SF-36 MCS change from baseline (MW estimate)/Global status.

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of SF-36 MCS

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the well-known Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	197
Analysis specification	Post-hoc
Analysis type	superiority[11]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.5602
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4795
upper limit	0.6409

Notes:

[11] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Geriatric Depression Scale change from baseline to day 90 - nonparametric re-analysis

End point title	Geriatric Depression Scale change from baseline to day 90 - nonparametric re-analysis

End point description:

The Geriatric Depression Scale (GDS) is a 30-item self-report assessment designed specifically to identify depression in the elderly. The items may be answered yes or no, which is thought to be simpler than scales that use a five-category response set. It is generally recommended as a routine part of a comprehensive geriatric assessment. One point is assigned to each answer and corresponds to a scoring grid. A score of 10 or 11 or lower is the usual threshold to separate depressed from nondepressed patients.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	102	96	198	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.6805 (0.6007 to 0.7603)	0.6805 (0.6007 to 0.7603)	0.6805 (0.6007 to 0.7603)	

Attachments (see zip file)	GDS change from baseline (MW estimate)/Global status.png

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of GDS

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the well-known Wilcoxon–Mann–Whitney test.

Comparison groups	Cerebrolysin v Placebo
Number of subjects included in analysis	198
Analysis specification	Post-hoc
Analysis type	superiority[12]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.6805
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6007
upper limit	0.7603

Notes:

[12] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Post-hoc: Global status change from basline to day 90 - nonparametric re-analysis

End point title	Global status change from basline to day 90 - nonparametric re-analysis

End point description:

The global outcome is the summary of all 12 efficacy parameter.

End point type	Post-hoc

End point timeframe:

Baseline to day 90

End point values	Cerebrolysin	Placebo	mITT-LOCF (nonparametric re-analysis)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	104	101	205	
Units: Mann-Whitney (MW)				
number (confidence interval 95%)	0.6159 (0.5799 to 0.6518)	0.6159 (0.5799 to 0.6518)	0.6159 (0.5799 to 0.6518)	

Attachments (see zip file)	Global status change from baseline (MW estimate)/Global

Statistical analyses

Statistical analysis title	Nonparametric re-analysis of global status

Statistical analysis description:

The Mann–Whitney estimator (MW) was calculated as the effect size measure associated with the well-known Wilcoxon–Mann–Whitney test.

Comparison groups	Placebo v Cerebrolysin
Number of subjects included in analysis	205
Analysis specification	Post-hoc
Analysis type	superiority[13]
P-value	≤ 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mann-Whitney
Point estimate	0.6159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5799
upper limit	0.6518

Notes:

[13] - The null and alternative hypotheses for the comparison of the effects of Cerebrolysin versus placebo can be formulated as follows (superiority test; T: test treatment; C: control treatment):
Null hypothesis H0: MWTC≤0.50
Alternative hypothesis HA: MWTC>0.50

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to day 90.

Adverse event reporting additional description:

At each visit, AEs were documented and evaluated in terms of nature, date and time of onset, duration, severity, causality, action taken, outcome, and seriousness.
Patients with AEs were followed up until the event has subsided, the condition was considered medically stable, or the patient was no longer available to follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups

Reporting group title	Cerebrolysin

Reporting group description:

Subjects entering the treatment phase (randomization V2) and randomized to active treatment group, received intravenous infusion of 100 ml solution (3 x 10 ml ampoules of Cerebrolysin in 70 ml NaCl 0.9 %) once daily for 21 successive days at the same time every day.

Reporting group title	Placebo

Reporting group description:

Subjects entering the treatment phase (randomization V2) and randomized to placebo group, received intravenous infusion of 100 ml 0.9 % NaCl once daily for 21 successive days at the same time every day.

Serious adverse events	Cerebrolysin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 104 (2.88%)	7 / 104 (6.73%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events	0	4	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Peripheral ischemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carotid artery occlusion			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multi-organ disorder			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 104 (0.96%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 104 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 104 (0.00%)	2 / 104 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	

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

Non-serious adverse events	Cerebrolysin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 104 (64.42%)	60 / 104 (57.69%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	9 / 104 (8.65%)	12 / 104 (11.54%)	
occurrences (all)	15	18	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 104 (5.77%)	3 / 104 (2.88%)	
occurrences (all)	8	3	
Carotid artery stenosis			
subjects affected / exposed	6 / 104 (5.77%)	2 / 104 (1.92%)	
occurrences (all)	6	3	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	6 / 104 (5.77%)	4 / 104 (3.85%)	
occurrences (all)	6	5	
Hepatobiliary disorders			
Cytolytic hepatitis			
subjects affected / exposed	10 / 104 (9.62%)	8 / 104 (7.69%)	
occurrences (all)	10	8	
Psychiatric disorders			
Depression			
subjects affected / exposed	11 / 104 (10.58%)	10 / 104 (9.62%)	
occurrences (all)	11	10	
Insomnia			
subjects affected / exposed	6 / 104 (5.77%)	4 / 104 (3.85%)	
occurrences (all)	6	4	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 104 (12.50%)	17 / 104 (16.35%)	
occurrences (all)	15	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2008	Amendment 1 / Study protocol V2.0: - inclusion of further study sites - increase of sample size
02 September 2008	Amendment 2 / Study protocol V2.1: - change of study biometrician - revision of the statistics section - change of inclusion criterion 2
21 November 2008	Amendment 3 / Study protocol V2.2: - re-change of inclusion criterion 2 - correction of time windows for visits 3, 4, 5; - adjustment of discontinuation criteria and action taken/outcome - inclusion of further study sites - change of sponsor's company name
15 April 2009	Amendment 4 / Study Protocol V2.3: - inclusion of further study sites - update of sample size calculation - increase of sample size - update of study timelines - changes in packaging and preparation of study drug
12 November 2009	Amendment 5 / Study protocol V2.4 - change of sponsor’s company name - update of study timelines - amended information on the Gap Detection Test
10 June 2010	Amendment 6 / Study protocol V2.5 - change of sponsor's company address and phone number - change of study safety officer - update of study medication label - correction of information on NIHSS

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26564102