EVER PHARMA

STROKE

TBI

DEMENTIA

Effective pharmacological treatment for **STROKE** patients

Cerebrolysin **A**nd **R**ecovery after **S**troke (CARS),
Muresanu D.F. et al., Stroke 2016; 47:151-159

Published in

Stroke

CARS results -
Cerebrolysin in patients after STROKE

- Improvement of motor functions
- Early recovery
- Regain full independence
- Increase quality of life

Cerebrolysin®

Reconnecting Neurons.
Empowering for Life.

Objective and design of the study

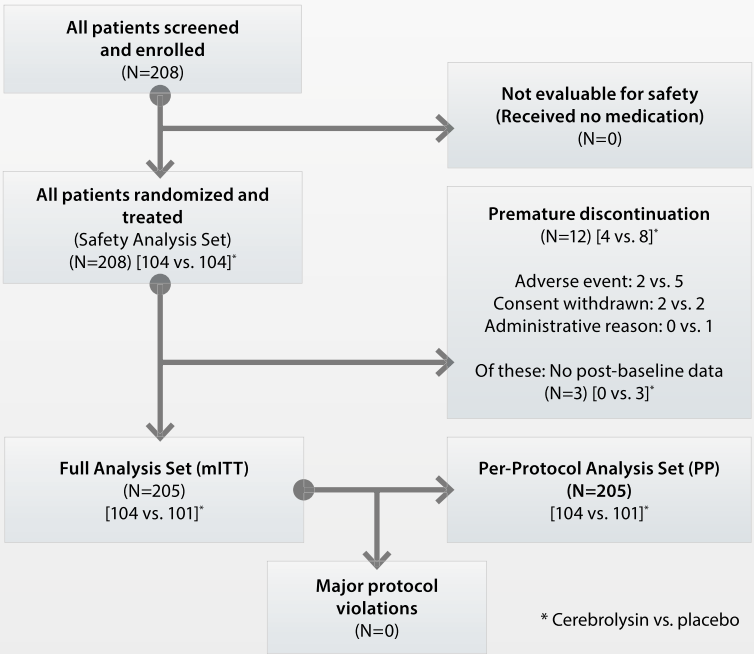
OBJECTIVE

The aim of this trial was to investigate whether stroke patients who receive Cerebrolysin (added to early rehabilitation) show improved motor function in the upper extremities at day 90 compared with patients who receive placebo (rehabilitation only).

DESIGN

- Prospective, **multicenter, randomized, double-blind, placebo-controlled,** parallel-group study
- 208 stroke patients (18-80 years of age) with confirmed ischemic supratentorial stroke with a volume >4cm^3 were included
- Patients included had no significant pre-stroke disability, no other stroke within the previous three months, an Action Research Arm Test (ARAT) score of <50 and a Goodglass and Kaplan Communication Scale score of >2
- Study compared the effects of **30ml Cerebrolysin** versus placebo during early rehabilitation after stroke
- **Cerebrolysin, n=104; Placebo, n=104**
- Treatment started **24-72 hours post stroke** and **continued for 21 days**
- All patients participated in an accompanying **standardized rehabilitation program** for 21 days (5 days/week, 2 hours/day)
- The rehabilitation program included massages and passive and active movements of the upper and lower limbs. After discharge patients continued 2x15 min of active movement three days per week.
- The **primary study endpoint** was ARAT score at day 90
- Study visits were conducted on day 7, 14 and 21 after baseline assessment and on day 42 and 90 post-stroke

Enrollment and disposition of all patients participating in the clinical study



Primary Efficacy Criterion

The primary efficacy criterion was the change from baseline in the Action Research Arm Test (ARAT) score on day 90, assessing the recovery of the upper limb motor function.

Secondary Efficacy Criteria

Secondary efficacy criteria were changes from baseline to day 21 (the last day on which the study medication was administered) and to day 90 in:

- Gait velocity (Gait Velocity Test)
- Fine motor function (9-Hole Peg Test)
- The global neurological state (National Institutes of Health Stroke Scale [NIHSS])
- The level of disability or dependence in activities of daily living (Barthel Index, modified Rankin Scale [mRS])
- The extent of aphasia (Goodglass and Kaplan Communication Scale)
- The extent of neglect (Line Cancellation Test, Gap Detection Test)
- Quality of life (SF-36 Health Survey, Physical Component Summary [PCS], Mental Component Summary [MCS])
- The extent of depression (Geriatric Depression Scale)

Safety Analyses

A complete medical history and physical examination including vital signs were performed at screening. All adverse events have been documented and evaluated in terms of severity and causality.

Baseline characteristics

Comparison of Baseline Characteristics (Safety Analysis Set)

Demographic Parameter	Total N=208	Cerebrolysin N=104	Placebo N=104
Male sex: N (%)	133 (63.9)	70 (67.3)	63 (60.6)
Right-handed: N (%)	199 (95.7)	99 (95.2)	100 (96.2)
Mean age: years (SD)	64.0 (10.2)	64.9 (9.8)	63.0 (10.6)
Mean BMI: kg/m^2 (SD)	27.4 (4.2)	27.2 (4.1)	27.6 (4.3)
Mean time until treatment initiation*: hours SD)	53.2 (12.3)	51.9 (12.7)	54.6 (11.7)
Thrombolytic treatment: N (%)	4 (1.9)	2 (1.9)	2 (1.9)
Prevalence of risk factors: N (%)			
Hypertension	173 (83.2)	86 (82.7)	87 (83.7)
Hyperlipidemia	105 (50.5)	55 (52.9)	50 (48.1)
Diabetes mellitus	39 (18.8)	19 (18.3)	20 (19.2)
Arrhythmia	54 (26.0)	26 (25.0)	28 (26.9)
Coronary artery disease	83 (39.9)	38 (36.5)	45 (43.3)
Past/current smoker	67 (32.2)	33 (31.8)	34 (32.7)
Baseline efficacy criteria (mITT): mean+SD		Cerebrolysin N=104	Placebo N=101
ARAT (paretic side)		10.1±15.9	10.7±16.5
NIHSS		9.1±3.2	9.2±3.2
Barthel index		35.5±24.9	35.4±24.6
Modified Rankin scale		3.9±0.8	3.9±0.8

ARAT, Action Research Arm Test; BMI, body mass index; mITT, intention-to-treat; mean, arithmetic mean; N, Number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation. * Calculated from stroke onset.

Cerebrolysin significantly **improves motor functions**

The median ARAT scores increased from 0.0 at baseline to 51.0 on day 90 in the Cerebrolysin group (30ml/day) and from 2.0 to 27.0 in the placebo group (Figure 1).

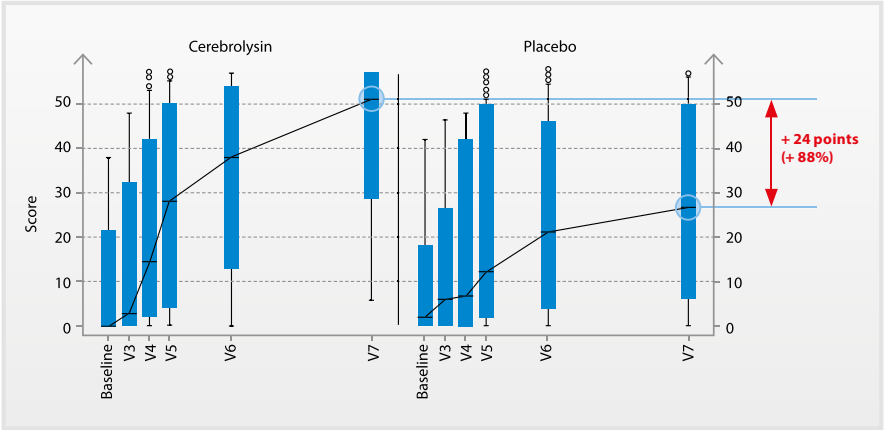


Figure 1: Time course of the Action Research Arm Test (ARAT) with Cerebrolysin (30ml/d) and the placebo, shown as boxplot diagrams (P10 and P90) for days 7 (V3), 14 (V4) and 21 (V5) post baseline and days 42 (V6) and 90 (V7) post stroke, mITT-LOCF

Nonparametric LOCF analysis demonstrated a large superiority of Cerebrolysin on day 90, with an MW=0.71. Already on day 14 Cerebrolysin showed a superiority relative to the placebo (Figure 2).

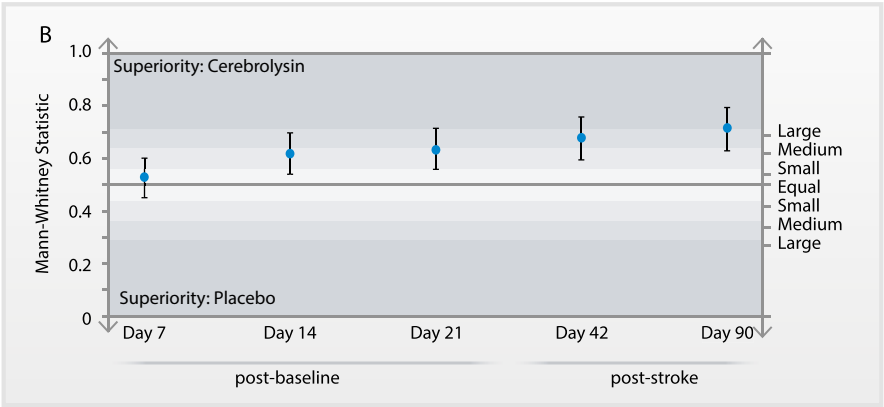


Figure 2: Effect sizes (Mann-Whitney) of the ARAT score changes from baseline in the mITT-LOCF population (Cerebrolysin, N=104; placebo N=101)

CONCLUSIONS

- A **beneficial effect** of Cerebrolysin was shown in the primary efficacy criterion, the ARAT score
- Treatment with Cerebrolysin leads to **a significant improvement of upper limb motor functions by +88%**
- **Early therapeutic success** on day 14 in the Cerebrolysin group
- The large superiority of Cerebrolysin on day 90 may be interpreted to have occurred as a result of **neurorecovery**, the neurorestorative action of Cerebrolysin, which intensifies initial improvement and beneficial effects of rehabilitation

Cerebrolysin significantly **improves quality of life**

Similar to the results of the primary outcome - ARAT score - substantial differences were also found in the secondary efficacy criteria between the Cerebrolysin and placebo group.

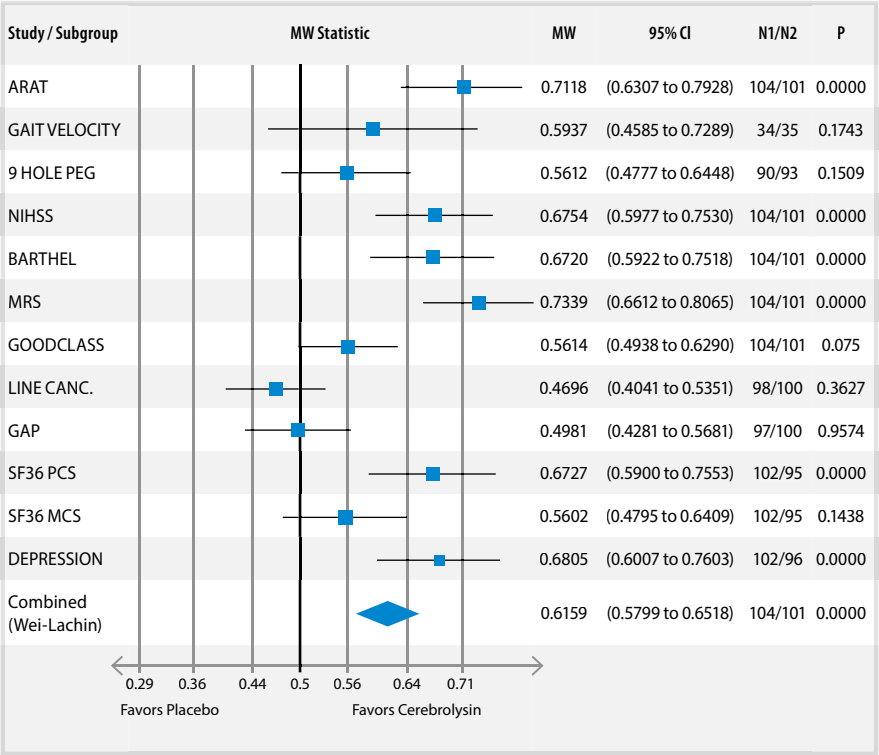


Figure 3: Global status on day 90. The effect sizes (Mann-Whitney MW) for the single and combined (Wei-Lachin procedure) efficacy parameters reflect changes from baseline in the mITT-LOCF (n=205).

CONCLUSIONS

- The results in stroke patients undergoing early rehabilitation demonstrate a **beneficial effect of Cerebrolysin** compared to placebo for the global outcome after 90 days
- **NIHSS**: The improvement of this scale by 3 points demonstrates an excellent outcome of Cerebrolysin after 90 days considering that the overall median initial score was 8.
- **Barthel index**: Very strong improvement in activities of daily living – this correlates perfectly with the SF36-PCS.
- The self-assessment of **SF36-PCS** shows that patients treated with Cerebrolysin feel a significant better improvement in their daily life vs. group treated with early rehabilitation only.
- Early onset of therapy success correlates strongly with improved patient motivation. As a consequence post-stroke depression is far less prevalent in the combination therapy group.
- A superiority (MW > 0.56) of Cerebrolysin was also demonstrated using the Gait Velocity Test, 9-Hole Peg Test, Goodglass and Kaplan Communication Scale and the SF-36-MCS
- Cerebrolysin did not affect neglect (Line Cancellation Test, Gap Detection Test); the proportion of patients with neglect at baseline was very low in both groups

Regain full independence
with Cerebrolysin

A favorable mRS score of 0 and 1 was found in 42.3% of the patients in the Cerebrolysin group compared to 14.9% of those in the placebo group. Similar results were found for mRS scores of 0 to 2.

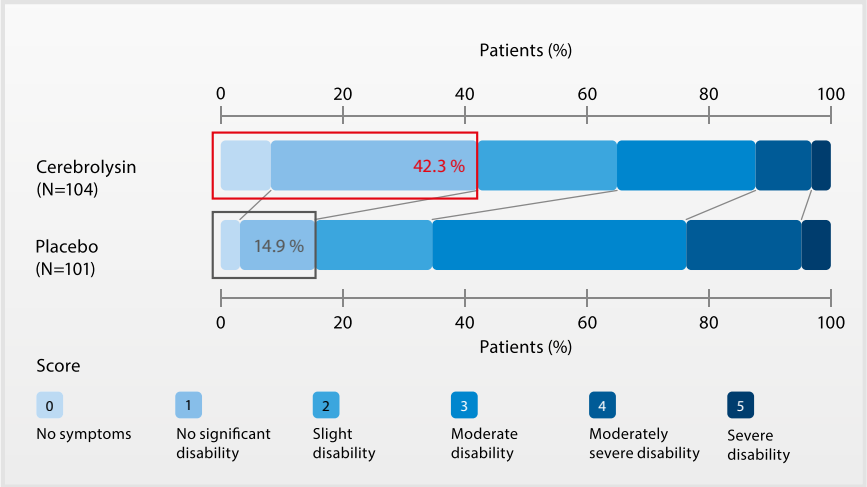


Figure 4: Distribution of Modified Rankin Scale scores at day 90

Cerebrolysin is **safe and well tolerated**

The safety of Cerebrolysin was compareable with that of the placebo, suggesting that Cerebrolysin possesses a favorable benefit/risk ratio.

Summary

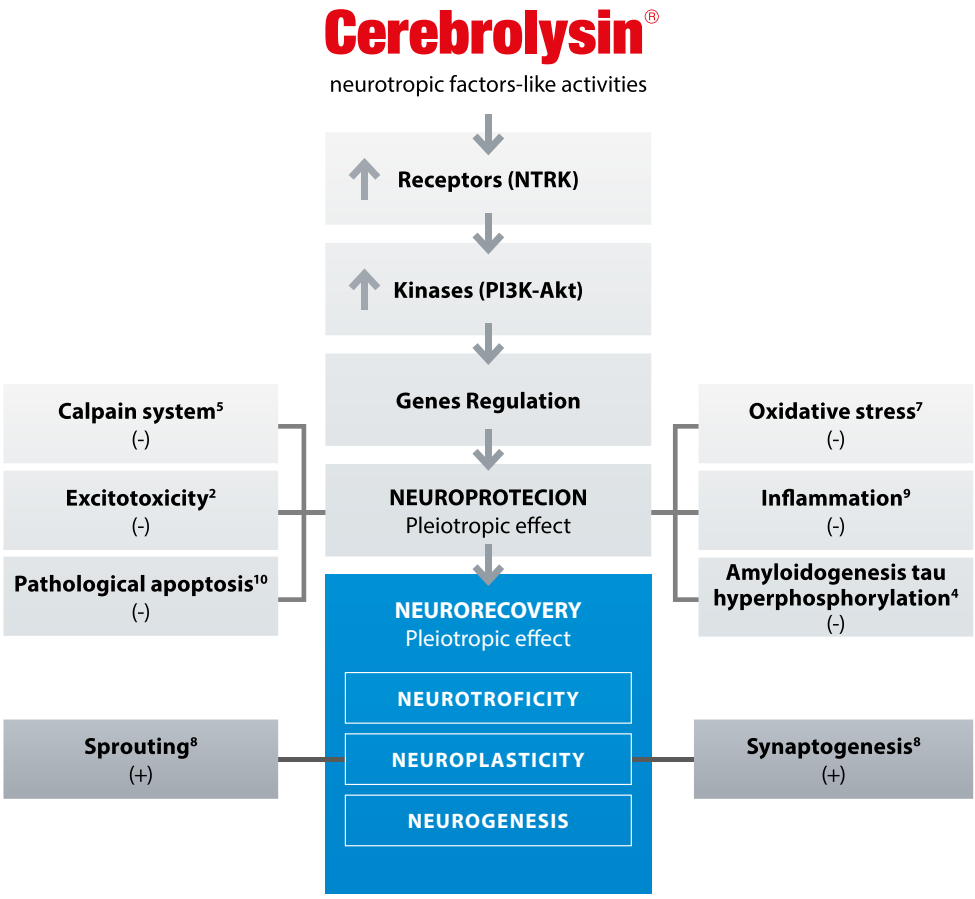
The results of this trial indicate that a comprehensive treatment strategy **combining pharmacological treatment with Cerebrolysin** and structured **rehabilitation** create synergisms and therefore improve the outcome of stroke patients.

Such a strategy should include the following:

- Interventions to re-establish, or at least improve, perfusion of the ischemic brain
- Early administration of drugs that interfere with the pathophysiological cascade and improves the neurorestorative capacity of the neuronal network such as Cerebrolysin (30ml/day)
- Rehabilitative activities to stimulate recovery of motor functions

Cerebrolysin's mode of action

Cerebrolysin is a multi-modal neuropeptide drug which improves the brain's ability for self-repair by stimulating neurorecovery.



Product information

Administration:

Disorder	Daily dosage	Initiation of treatment	Duration of treatment
Acute stroke	10-50 ml	Immediately after rt-PA or as soon as possible	Up to 20 days
Post acute stroke	10-50 ml	After acute treatment	Up to 20 days
Traumatic brain injury	10-50 ml	As soon as possible	Up to 30 days
Vascular dementia	5-30 ml	As soon as possible	2-4 cycles per year 1 cycle: 5 days weekly/4 weeks
Alzheimer's disease	5-30 ml	As soon as possible	2-4 cycles per year 1 cycle: 5 days weekly/4 weeks

LITERATURE

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ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type - Post-apoplectic complications - Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

EVER Neuro Pharma GmbH
Oberburgau 3
4866 Unterach
Austria
www.everpharma.com

CERE/A/02/2016/9