EVER PHARMA

STROKE

TBI

DEMENTIA

Cerebrolysin treatment of subacute STROKE

Promotes recovery by enhancing motor network plasticity

Effects of **C**erebrolysin **o**n **m**otor recovery in **pa**tients with **s**ubacute **s**troke (ECOMPASS)

Cerebrolysin combined with rehabilitation promotes motor recovery in patients with severe motor impairment after stroke. Chang et al. BMC Neurology (2016) 16:31

ECOMPASS results - Cerebrolysin in patients after STROKE

- Improvement of motor functions
- Recovery of motor-neuron network
- Significant recovery with Cerebrolysin treatment start 8 days post stroke

Cerebrolysin®

Reconnecting Neurons.
Empowering for Life.

Objective and design of the study

OBJECTIVE

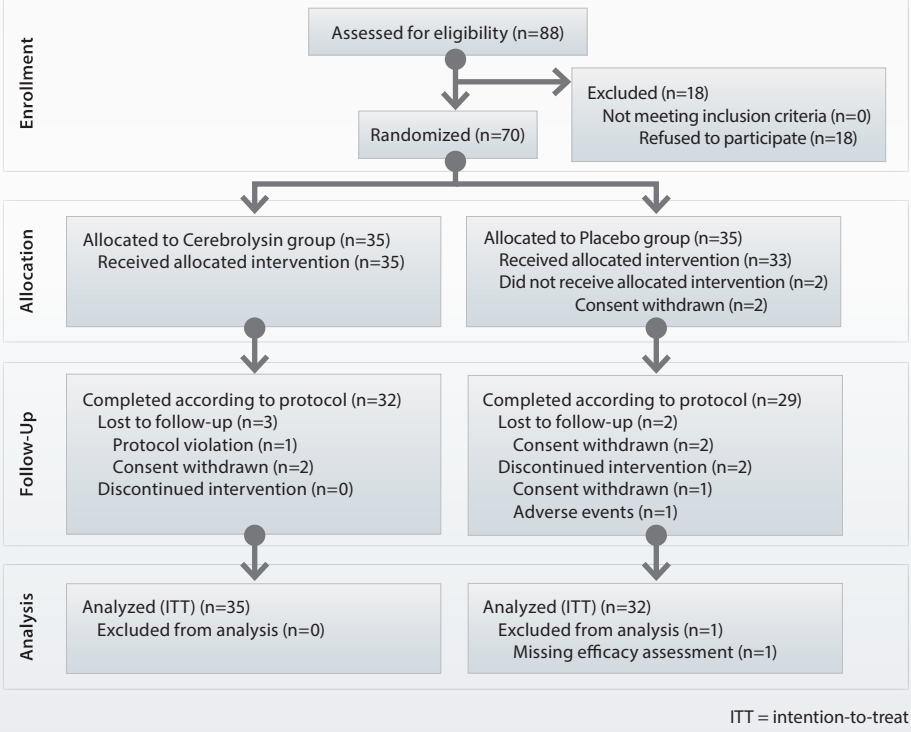
The study was designed according to the clinical reality of rehab physicians in most countries.

It's purpose was to investigate the additional benefit of Cerebrolysin on motor recovery (Fugl-Meyer Assessment) at day 29 post-stroke when given in addition to a standardized rehabilitation therapy in the subacute phase of stroke. Treatment starts at day 8 after onset of Stroke.

DESIGN

- Phase IV trial designed as a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study
- Stroke patients with moderate to severe motor function impairment (Fugl-Meyer Assessment [FMA] score 0-84) were included within 7 days after stroke onset and were randomized to receive a 21-day treatment course (days 8-28) of either Cerebrolysin or placebo, given in addition to standardized rehabilitation therapy
- All patients received a standardized rehabilitation program consisting of two hours of physical therapy and one hour of occupational therapy daily on workdays (Monday to Friday) over three weeks
- Assessments were performed at baseline (day 8, T0), immediately after the treatment course (day 29, T1), as well as two (day 60, T2) and three (day 90, T3) months after stroke onset
- The plasticity of the motor network was assessed by diffusion tensor imaging (DTI) and resting state functional magnetic resonance imaging (rsfMRI)

Enrolment and disposition of all patients participating in the clinical study



ITT = intention-to-treat

Primary Efficacy Criterion

The primary efficacy criterion was defined as the change from baseline (T0) to Day 29 (T1) in the FMA score. Follow-up assessments were performed two (T2) and three (T3) months after stroke. A pre-planned subgroup analysis was performed for severe motor impairment at baseline (FMA<50).

A total of 70 patients (Cerebrolysin n=35, placebo n=35) have been enrolled and 61 patients completed the study (Cerebrolysin n=32, placebo n=29).

Sample size	Treatment window	Dosage (ml)	Duration of treatment	Study endpoint	Follow-up assessment	Severity
70	Day 8	30	21 days	FMA on day 29 (T1); change from BL (T0)	FMA on days 60 (T2) and 90 (T3) in all patients and FMA<50 sub-group	Moderate to severe motor impairment (FMA 0-84) at baseline (T0)

Schedule	Screening	Baseline	On-Treatment	Follow-up	
Study visit	-	T0	**T1**	T2	T3
Day post-stroke	<7	8	**29**	60	90

Primary study endpoint

Significant recovery of motor functions
caused by Cerebrolysin treatment

Patients were included 7 days after stroke onset and baseline data were collected at day 8 (T0) with Fugl-Meyer Assessment (FMA). Changes from baseline were measured at day 29 (T1), day 60 (T2) and day 90 (T3) for Cerebrolysin and placebo. **Significant group differences** were observed in the subgroup with **severe motor impairment** at days 60 and 90.

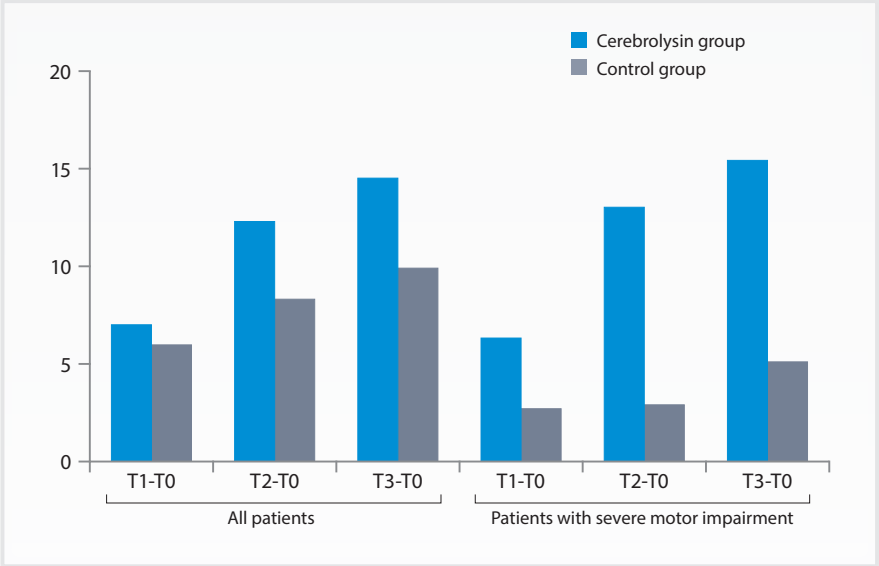


Figure 1: ***Changes in FMA for Cerebrolysin and placebo*** *– Impovement from base line are given for the upper limb subscore*

CONCLUSIONS

- Cerebrolysin stimulates recovery of motor function in post-acute stroke patients with moderate to severe impairment (FMA 0-84)
- Significant recovery despite delayed treatment start (8 days post stroke)
- Significant improvement of motor function by 200%
- Regain upper limp functionality – increased independence

Significant improvement in motor network plasticity
caused by Cerebrolysin treatment

Diffusion tensor imaging (DTI) shows alterations in brain connectivity resulting from neuroplasticity after stroke. This is the DTI analysis of the Corticospinal track based on the subgroup analysis of patients with severe motor impairment.

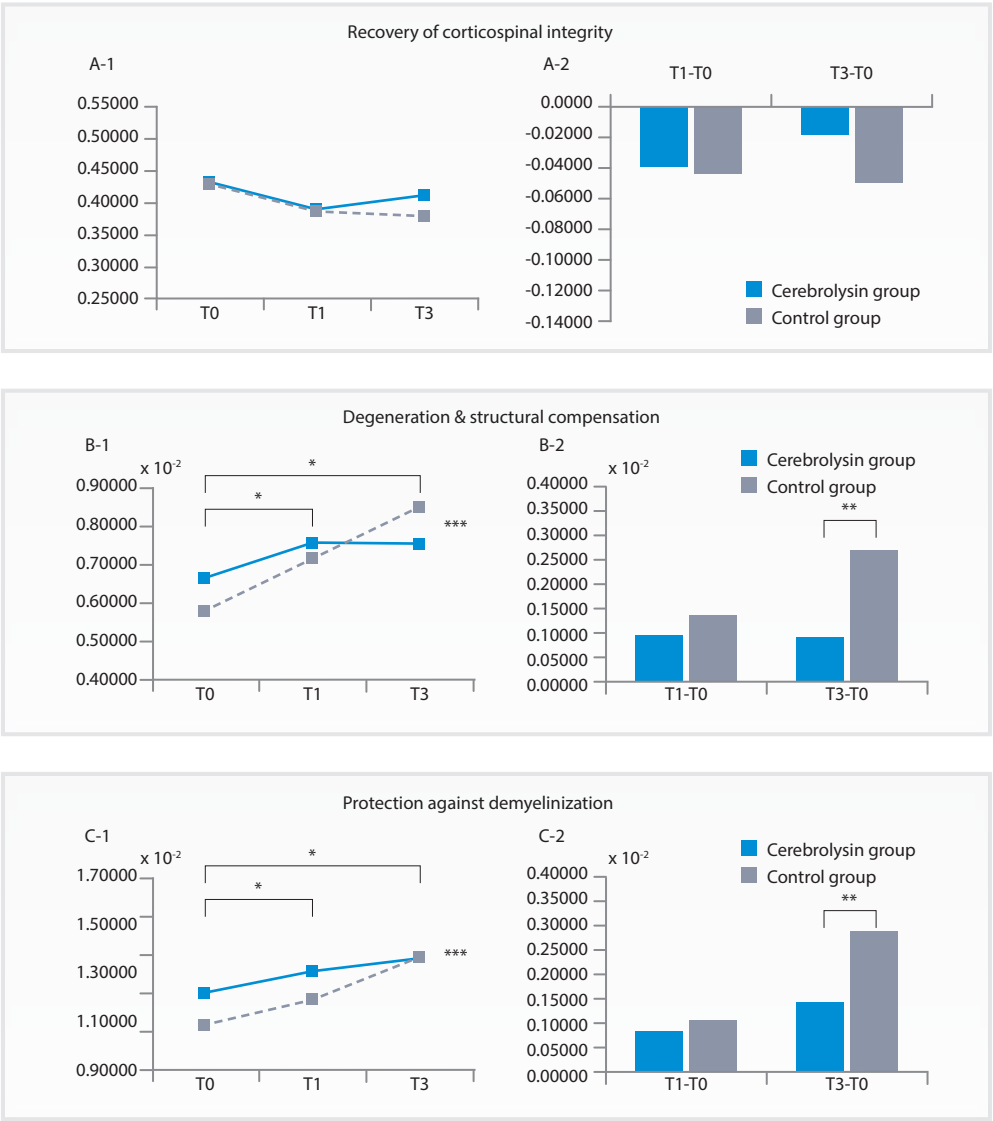


Figure 2: ***Changes in the diffusion tensor imaging (DTI)*** *from baseline (day 8, T0) to days 29 (T1) and 90 (T3) for Cerebrolysin and placebo. Time courses (1) and changes from baseline (2) are given for the fractional anisotropy (A), the axial diffusivity (B), and the radial diffusivity (C).*

CONCLUSIONS

- In the Cerebrolysin group significant group differences were demonstrated in axial and radial diffusivity at day 90
- Cerebrolysin treatment indicates:
  - recovery of corticospinal integrity
  - protection against degeneration and structural compensation
  - protection against demyelinization

Motor network recovery
after Cerebolysin combination therapy

Changes in the sensorimotor network across time showed increased symmetric functional connectivity between the bilateral primary sensorimotor cortices (SM1s) specifically in the Cerebrolysin group.

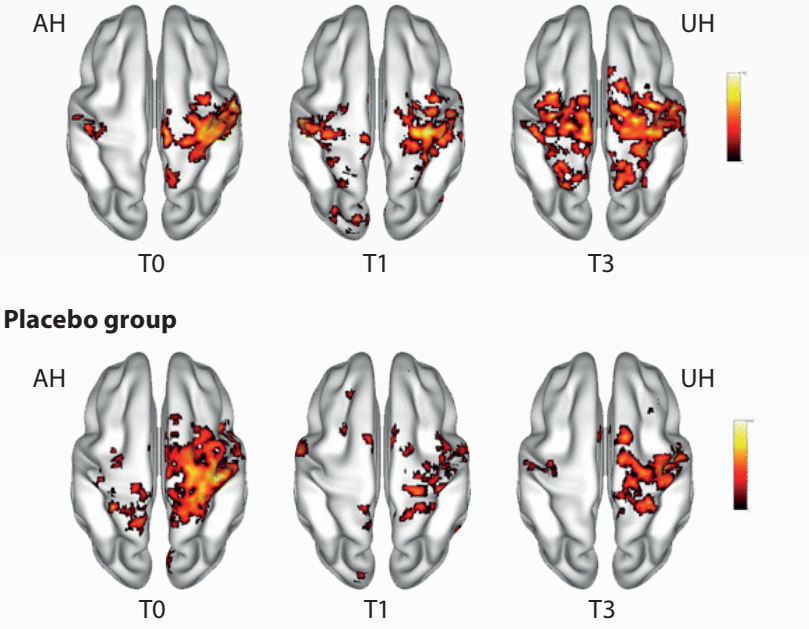


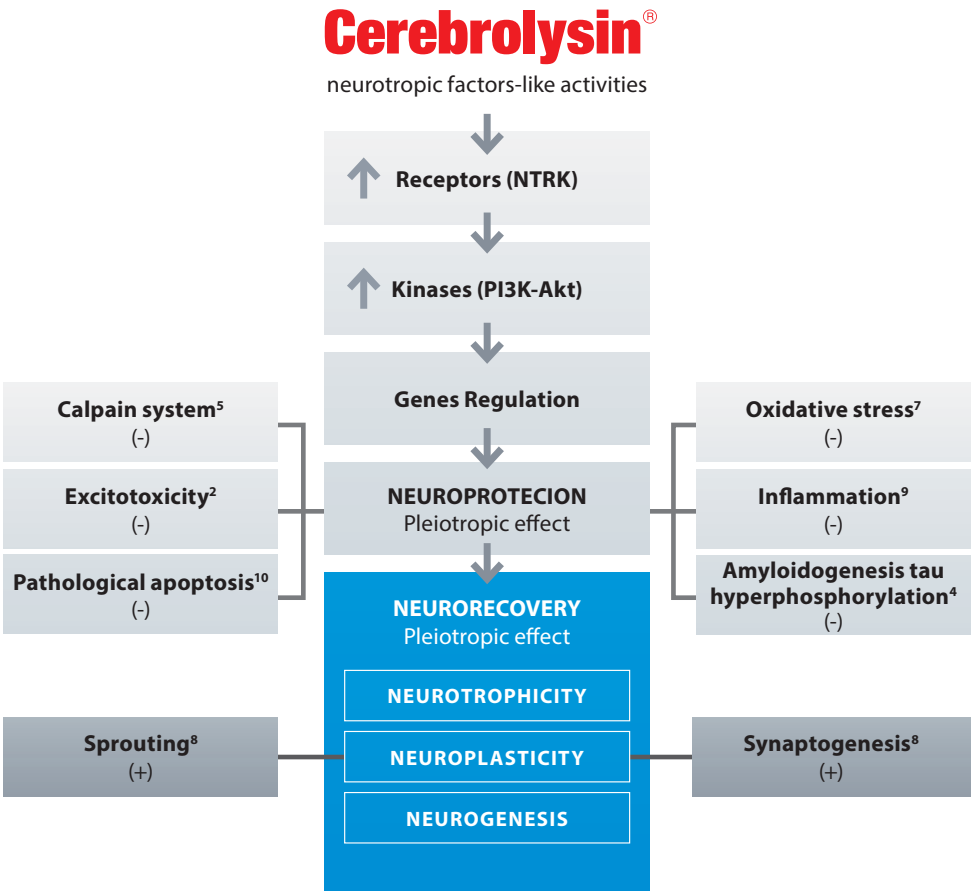
Figure 3: ***Resting state of sensory motor network by functional MRI (rsfMRI).*** *Affected (AH) and unaffected (UH) hemispheres at baseline (Day 8, T0), immediately after treatment (Day 29, T1) and three (Day 90, T3) months after stroke onset.*

CONCLUSIONS

- Symmetric functional connectivity was more pronounced with Cerebrolysin -> better recovery of motor cortical function
- Reactivation of affected brain regions caused by combination therapy with Cerebrolysin
- Visualization of Motor-Neuron Network Recovery induced by Cerebrolysin for the 1st time

Cerebrolysin's mode of action
Cerebrolysin combination therapy

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



Summary

This study shows that Cerebrolysin treatment over 3 weeks in combination with rehabilitation therapy in the subacute phase of stroke is safe and demonstrates positive effects on recovery in patients with severe motor impairment.

- Cerebrolysin **significantly improved functional recovery** in stroke patients with severe motor impairment; group differences were **significant already at day 60**
- **Imaging** of the underlying **network plasticity** indicated that **Cerebrolysin facilitates neurorecovery** by enhancing neuronal plasticity
- **Reconnected neuronal networks** lead to **improved mobility** and **independence**
- **Cerebrolysin treatment** – Improved physiological **basis for successful rehabilitation**

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 Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). 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

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