EVER PHARMA

Product Monograph

Cerebrolysin®

Reconnecting Neurons.
Empowering for Life.

TABLE OF CONTENTS

1 INTRODUCTION

Cerebrolysin is a multi-modal neuropeptide drug with a fast onset of action that helps to regain and maintain the independence of patients suffering from stroke, TBI, dementia and cognitive impairment.

Cerebrolysin improves the brain's ability for self-repair by stimulating neurorecovery.

Cerebrolysin is effective, safe and well-tolerated as shown in clinical studies including randomized, double-blind, controlled trails.

Cerebrolysin is of European/Austrian quality.

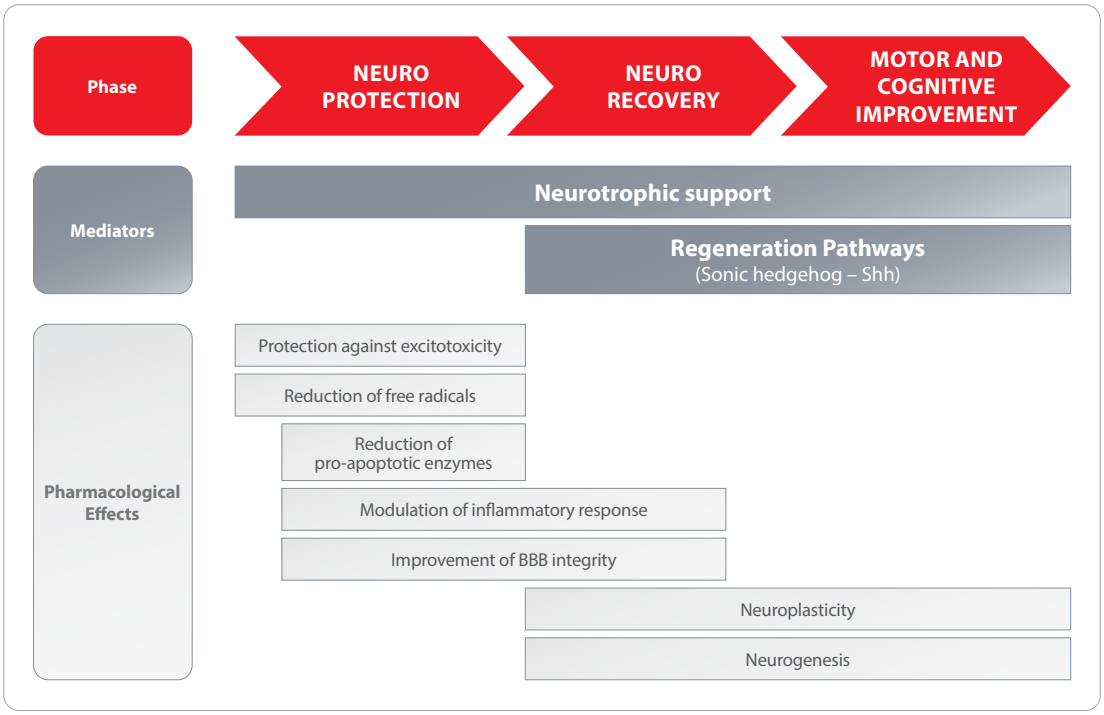
Clinical benefits of Cerebrolysin:

Stroke	• Early recovery • Improvement of motor functions • Regained independence • Increased quality of life • Improvement of cognitive functions • Higher survival rate
Traumatic Brain Injury	• Effective treatment after TBI • Saves lives • Early recovery • Better quality of life • Improvement of memory and concentration
Dementia	• Improvement of cognitive performance • Higher quality of life • Prolong active and independent life • Prevention of behavioral disorders

2 MODE OF ACTION

Cerebrolysin is a neurotrophic peptidergic drug with multimodal pharmacological properties and is indicated for the treatment of acute and chronic central nervous system (CNS) disorders. Cerebrolysin counteracts the pathophysiological mechanisms by:

1. Support of endogenous repair and recovery processes as a consequence of injury or degenerative diseases
2. Protection against pathological events and cascades caused by an injury or a degenerative disease



The natural repair and recovery processes in the CNS start immediately upon injury and play an important role in the continuous defense against neurodegeneration in chronic CNS disorders (e.g. Alzheimer's disease). Cerebrolysin has shown to modify two major signalling pathways: the neurotrophic factor (NTF) and sonic hedgehog (Shh) signalling pathway. These pathways regulate on a molecular level the cellular processes of neurogenesis, angiogenesis, dendrite arborisation, axonal sprouting, myelination, and integrity of the neurovascular unit, thereby supporting the maintenance and repair of the neuronal network.

The pathological events and cascades after stroke or trauma lead to secondary injuries, which further compromise motor and cognitive functions of a patient. Among the most relevant molecular processes targeted by Cerebrolysin in the **acute phase** of an injury are events of the ischemic cascade, like

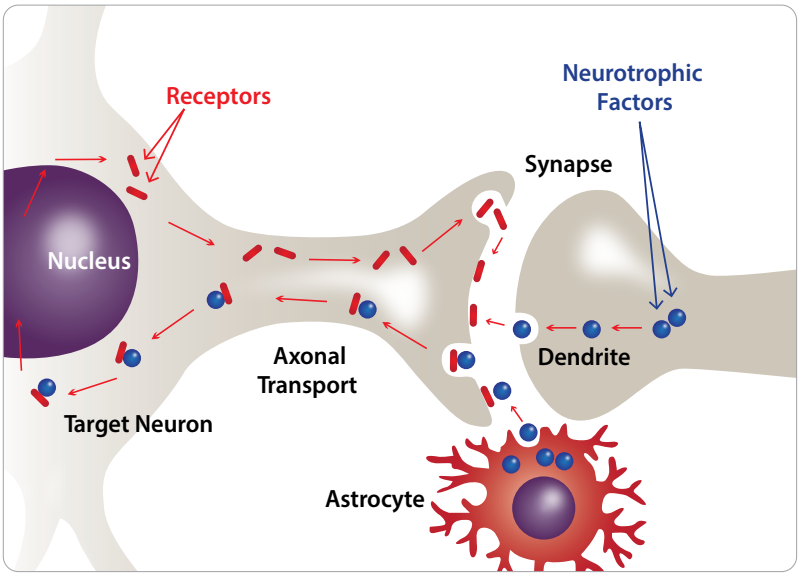
- Excitotoxicity
- Uncontrolled apoptosis
- Overactivation of proteolytic enzymes
- Overproduction of reactive oxygen species (ROS).

In the early **post-acute phase**, Cerebrolysin prevents formation of toxic protein aggregates and lowers the level of inflammatory processes, both linked to neurodegeneration if not prohibited.

2.1 MEDIATORS

2.1.1 NEUROTROPHIC SUPPORT

Neurotrophic factors (NTFs) are signalling molecules that maintain, protect, and restore the neuronal network and ensure proper functioning of the brain.



NTFs play an important role in the survival and regeneration of the neuronal network upon stroke, TBI or in chronic diseases. NTFs act on multiple targets, for example prevent nervous cells from initiation of apoptosis in damaged nervous tissue. Numerous NTFs have been described in the literature, such as:

- **BDNF:** Brain Derived Neurotrophic Factor
- **GDNF**: Glial Derived Neurotrophic Factor
- **NGF**: Nerve Growth Factor
- **IGF**: Insulin like growth Factor
- **CNTF**: Ciliary Neurotrophic Factor
- …

Cerebrolysin **mimics** and **modulates** the level of such endogenous NTFs.

Chen et al. 2007[1] have identified structurally similar or identical fragments of these NTFs in Cerebrolysin.

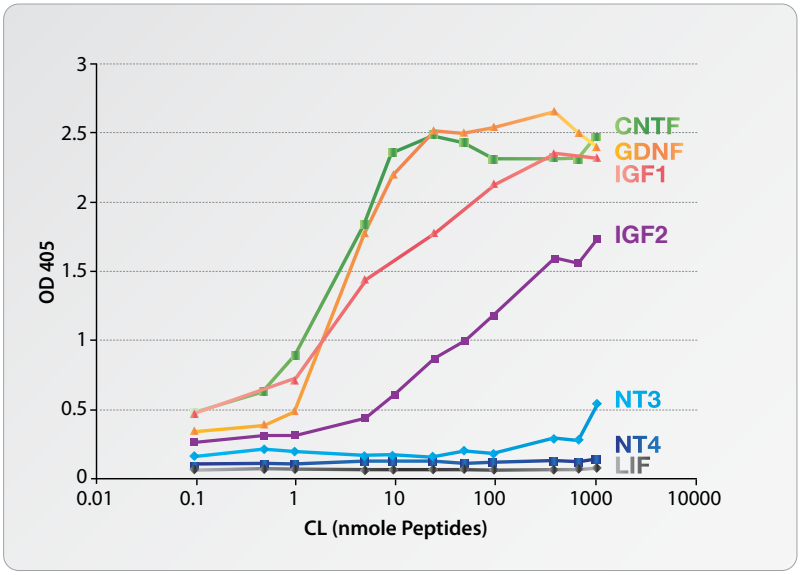


Figure 1 – *Detection of NTF-like neuropeptides in Cerebrolysin by immunoassay (ELISA).*[1]

Moreover, these fragments of NTFs were biologically active and promoted **neurogenesis** in cultured neuronal progenitor cells obtained from murine hippocampus (**Chen et al. 2007**[1]).

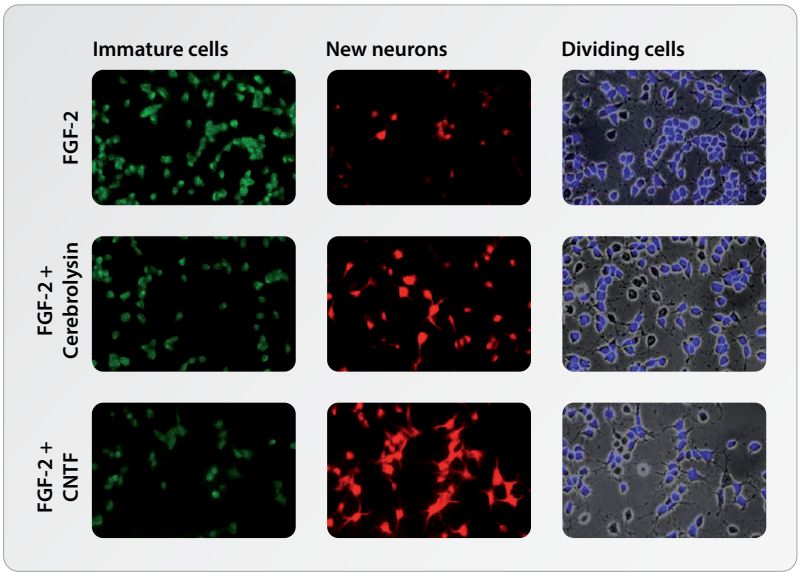


Figure 2 – *Cerebrolysin increases the number of new neurons in a cell culture model so a similar extent as CNTF.*[1]

A study by **Hartbauer et al. 2001**[2] compared the effects of the peptide fraction of Cerebrolysin with an artificial amino acid mixture (similar to the free amino acid component of Cerebrolysin) in a cell culture model. After 8 days, BDNF-like effects were shown only with the peptide fraction, while the effects of amino acids disappeared after 4 days and provided nutritional support only. This observation supports the neurotrophic effect of Cerebrolysin.

Besides the mimicry of neurotrophic factor like activity, several studies have demonstrated that Cerebrolysin also **modulates** endogenous NTFs. For example, **Ubhi et al. 2013**[3] demonstrated an increase in levels of mature NGF and GDNF upon Cerebrolysin treatment.

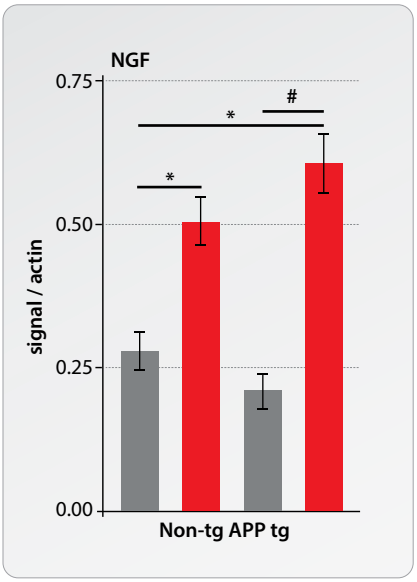


Figure 3 – *Analysis of an NGF-immunoreactive band in vehicle and Cerebrolysin-treated non-tg or hAPP tg mice.* [3]

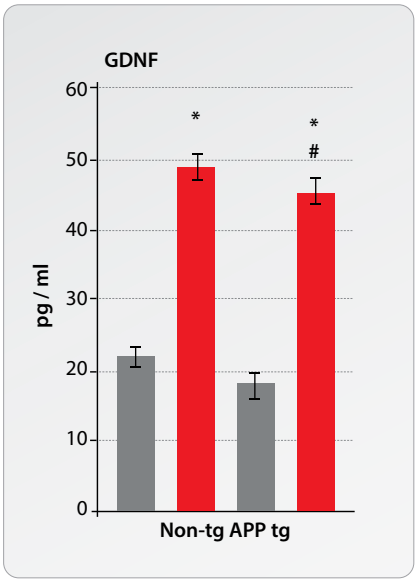


Figure 4 – *Analysis of GDNF protein levels in vehicle- and Cerebrolysin-treated non-tg or hAPP tg mice.*[3]

Zhang et al. 2010[4] showed BDNF-like activity of Cerebrolysin by activation of the PI3K/Akt pathway, which plays an important role in cell growth, proliferation, differentiation and migration *(see Figure 5 on page 10)*.

Studies showed also modifying effects of Cerebrolysin on the levels of **NTFs in patients**. Blood sera of Cerebrolysin treated patients showed a reduction in TNF-α and an increase of IGF-I in a dose-related way with respect to placebo (**Alvarez et al. 2009**[5]). These levels were detected as early as week 12 and were maintained until the end of follow-up at week 24 and correlated with clinical observations. Furthermore, Cerebrolysin increased serum BDNF and the combined therapy with donepezil augmented and prolonged this effect (**Alvarez et al. 2016**[6]).

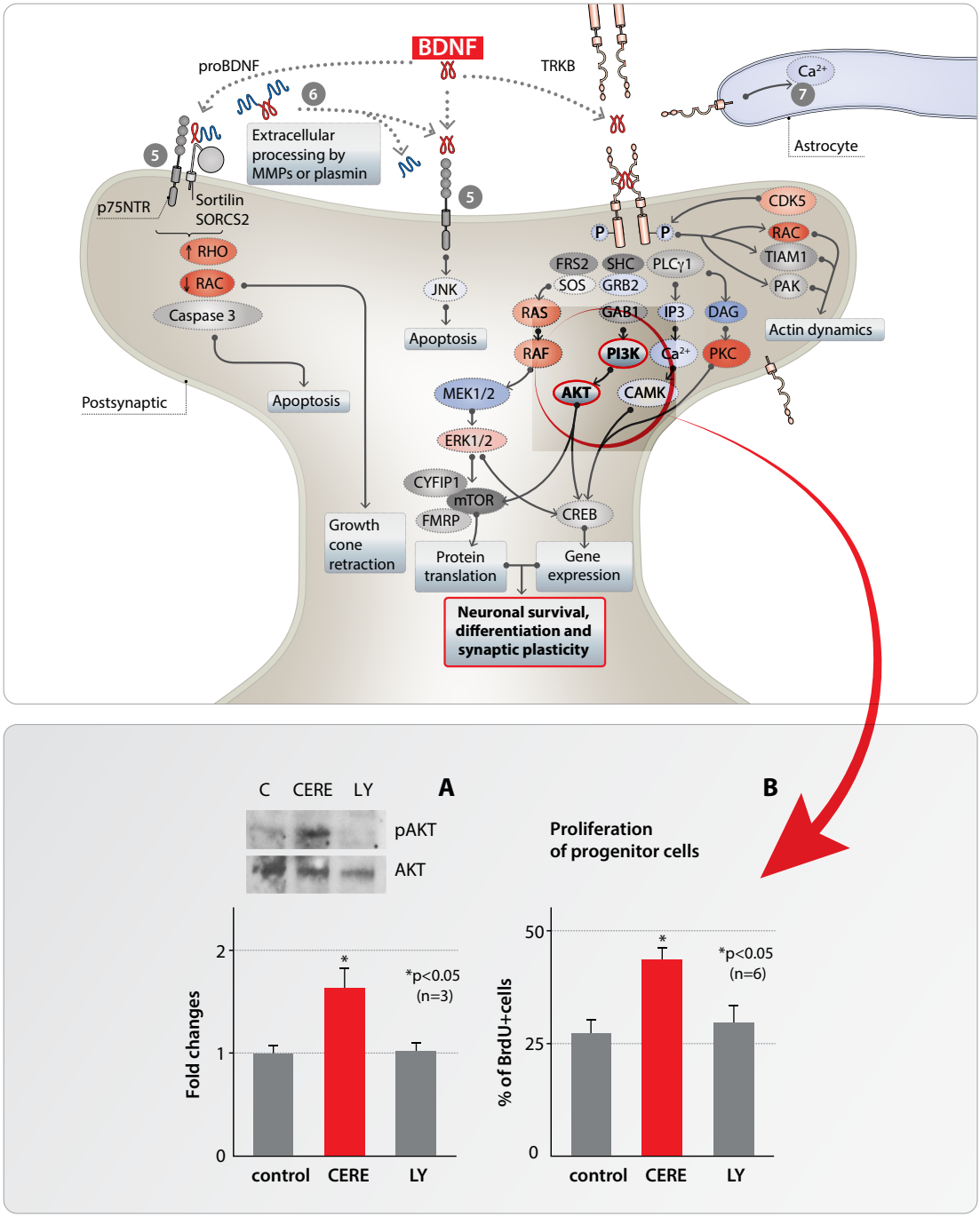


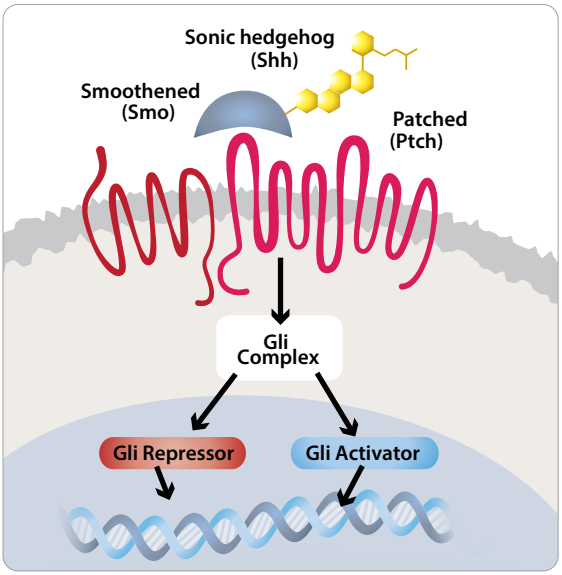
Figure 5 – *Cerebrolysin, stimulates the PI3K/AKT complex, a key component of the neurotrophic regulatory pathway.*[4]

A: *Western blots and quantitative analysis investigating Cerebrolysin-dependent activation of AKT kinase in the absence and in the presence of LY (specific inhibitor of PI3K/AKT pathway).*

B: *Quantitative analysis of Cerebrolysin-induced neurogenesis in the absence and in the presence of LY (specific inhibitor of PI3K/AKT pathway).*

2.1.2 REGENERATION PATHWAYS (SONIC HEDGEHOG)

The Sonic Hedgehog (Shh) protein is part of a signalling pathway that regulates the development of organs including the organization of the brain. For example, the Shh signalling pathway activates the **Gli complex**, which is responsible for the expression of developmental genes underpinning natural recovery processes.



Studies confirm the important role of the sonic hedgehog pathway in **post-stroke brain repair** and functional recovery, and suggest the Shh pathway to be a possible target for prolongation of the therapeutic window after stroke[7].

Already back in **2013 Zhang et al.**[8] showed a promoting effect of Cerebrolysin on neurogenesis and oligodendrogenesis via the Shh signalling pathway.

Cerebrolysin increases mRNA modulation of Shh and its receptors 'Patched' (Ptch) and 'Smoothened' (Smo).

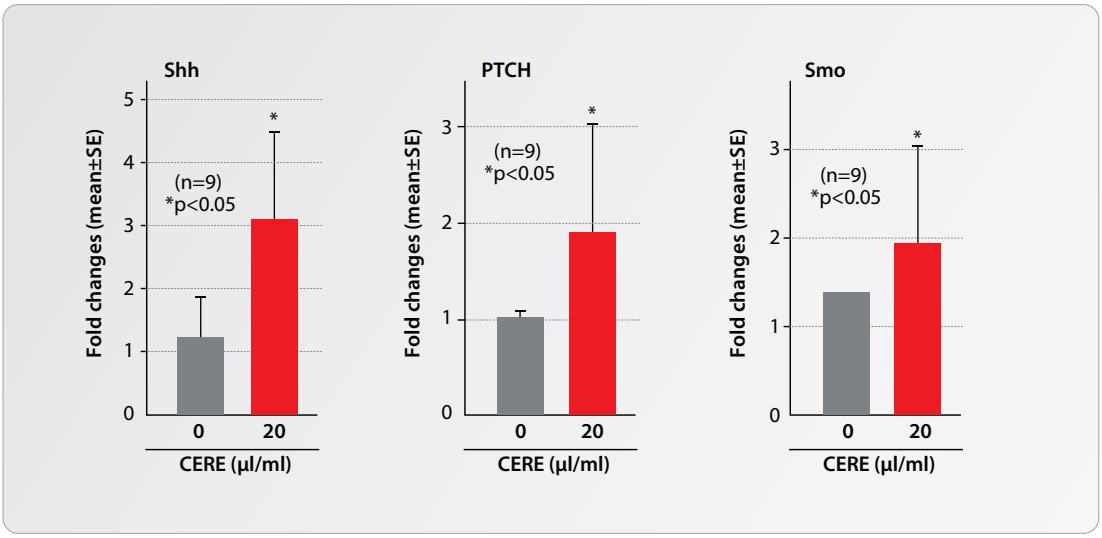


Figure 6 – *Cerebrolysin stimulates the expression of the sonic hedgehog signalling pathway components in neural progenitor cells. Graphs show mRNA levels in an in vitro experiment.*[8]

These effects together with the observed axonal remodelling in the peri-infarct area were linked to a profound improvement of the neurological functions.

Furthermore, **Zhang et al. 2013**[8] showed a neurogenesis effect of Cerebrolysin by increasing proliferation levels of neural progenitors cells (promoting BrdU) and their differentiation into neurons (TuJ1).

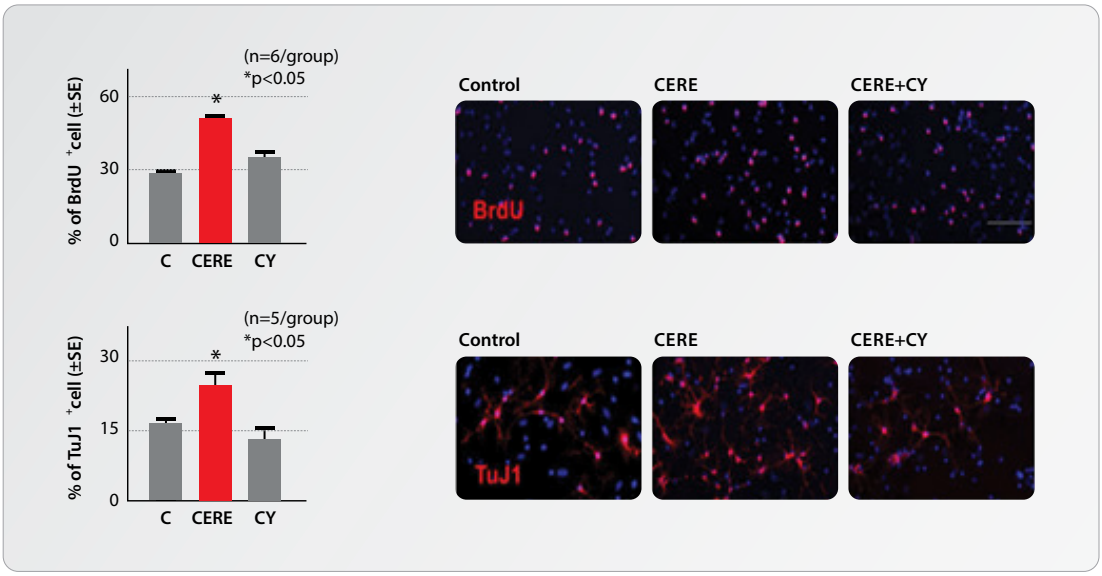


Figure 7 – *Cyclopamine (CY) – a Shh inhibitor – reduces Cerebrolysin-induces neurogenesis. Immunostaining with BrdU anti-body (a specific marker of proliferating cells), and TuJ1 antibody (a specific marker of mature neurons) and quantitative analysis. Cerebrolysin increases both the proliferation of neural progenitors and their differentiation into neurons. These stimulatory effects are eliminated by cyclopamine. Control – neural progenitor cells staining, CERE – increased neurogenesis in presence of Cerebrolysin, CERE+CY – total elimination of Cerebrolysin-induced neurogenesis by cyclopamine.*[8]

Addition of the Shh inhibitor cyclopamine (CY) reduced the stimulation of restorative processes initiated by Cerebrolysin, the proliferation of neural progenitor cells, the differentiation into neurons and the functional recovery.

2.2 PHARMACOLOGICAL EFFECTS

2.2.1 PROTECTION AGAINST EXCITOTOXICITY

Excitotoxicity is a pathological process caused by overstimulation of neuronal cells by excitatory neurotransmitters (e.g. Glutamate). Excitotoxicity occurs after stroke, traumatic brain injury and in neuro-degenerative diseases like Alzheimer's disease.

Cerebrolysin has shown to reduce glutamate-induced injury of cultured neurons.[9]

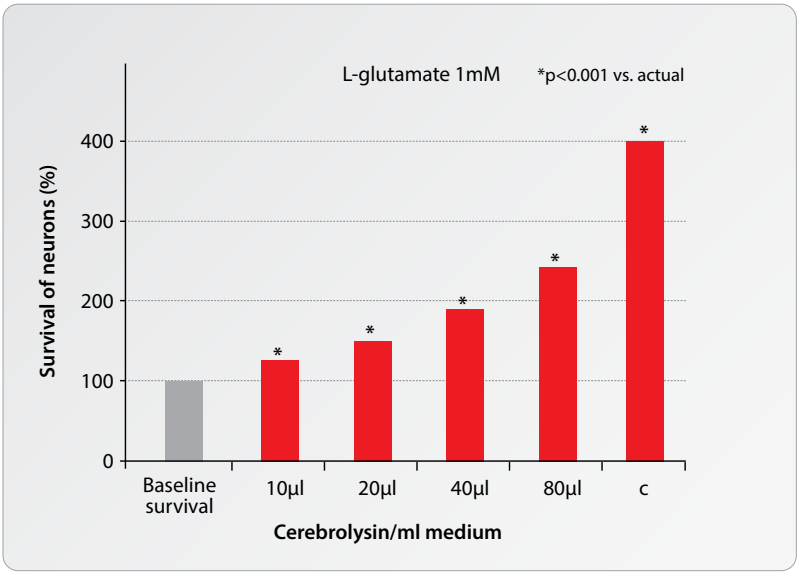


Figure 8 – *Dose-dependent increase of neurons. Toxic effects of glutamateric exposure were prevented by Cerebrolysin. 80µl Cerebrolysin/ml medium doubled the survival rate of Cerebrolysin-treated cells compared to untreated control cells.*[9]

2.2.2 REDUCTION OF FREE RADICALS

Free radicals accumulate during many pathological processes such as the ischemic cascade and are thought to be a basic pathway leading to neurodegeneration in Alzheimer's disease.

Therefore, reduction of free radicals in endangered nervous tissue is considered to be one of the potential neuroprotective strategies.

Cerebrolysin reduces the production of free radicals in an experimental ischemia model. The level of free radicals (2.3-DHBA and 2.5-DHBA) was significantly reduced in the hippocampus and in the cortex, indicating the neuroprotective function of Cerebrolysin during ischemic processes.[10]

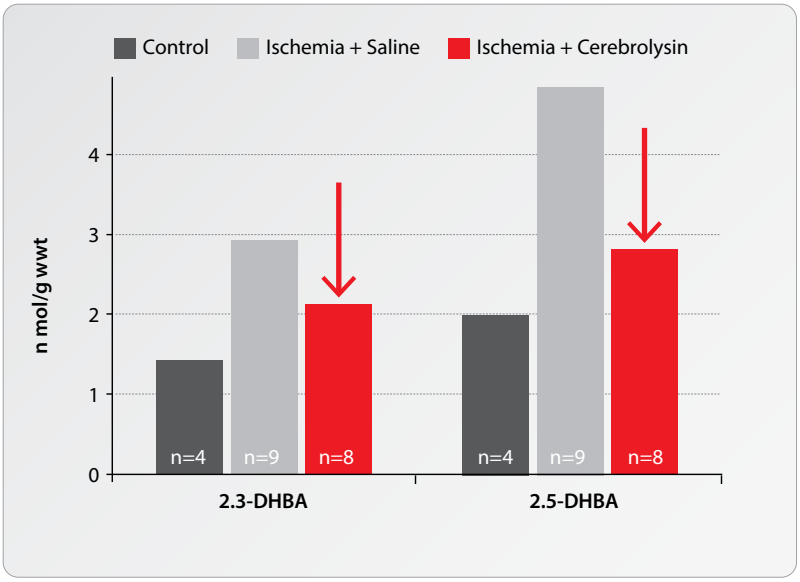


Figure 9 – *Products of the reaction of OH radicals with the salicylate molecule, concentrations of 2.3-DHBA and 2.5-DHBA in the hippocampus; the level of free radicals was reduced indicating the neuroprotective function of Cerebrolysin.*[10]

2.2.3 REDUCTION OF PRO-APOPTOTIC ENZYMES

Apoptosis occurs as the result of acute or chronic cellular damage.

Overactivation of calpains, a group of key enzymes involved in cellular apoptosis, results in degradation of microtubules and thus of the cytoskeleton.

Cerebrolysin has been shown to inhibit calpain in vitro by about 60%, which results in less tissue damage.[11]

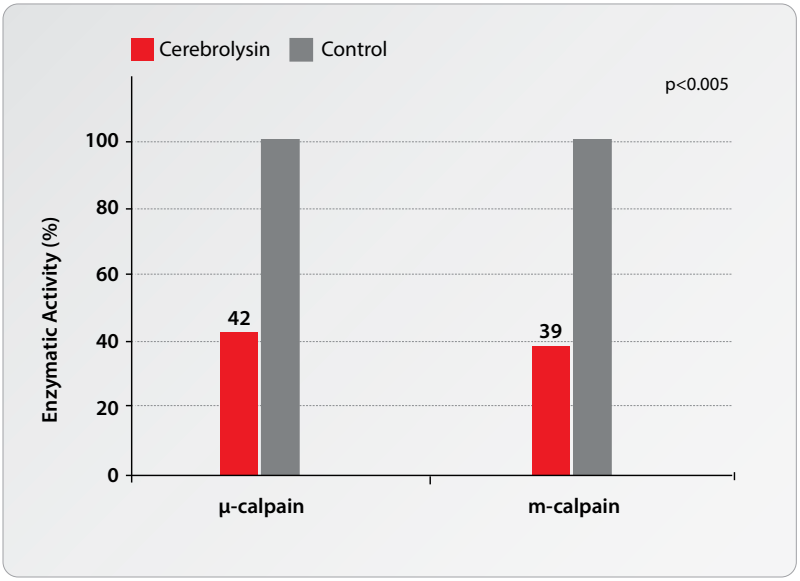


Figure 10 – *Cerebrolysin inhibits calpain activity by approximately 60%.*[11]

Another protein involed in apoptosis is caspase-3, the main caspase in APP-cleavage. In an experimental graft of neural stem cells (NSCs) into the hippocampus Cerebrolysin enhanced the survival of the grafted NSCs by reducing active caspase-3. These results are in line with previous findings of anti-apoptotic effects of Cerebrolysin – a major predictor of clinical efficacy in both the early stages of disease and during the rehabilitation period.[12]

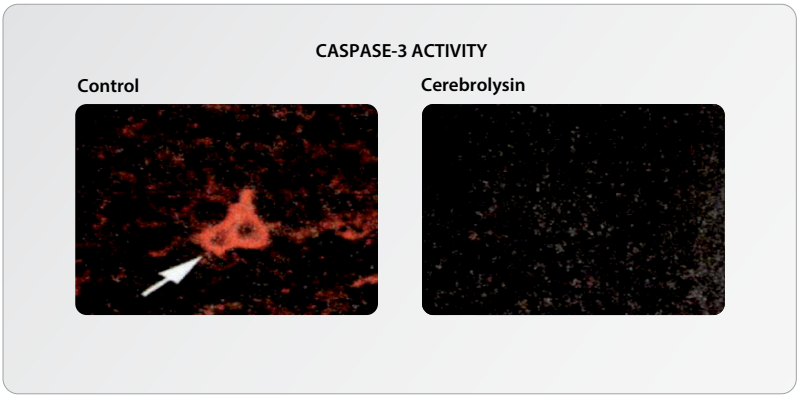
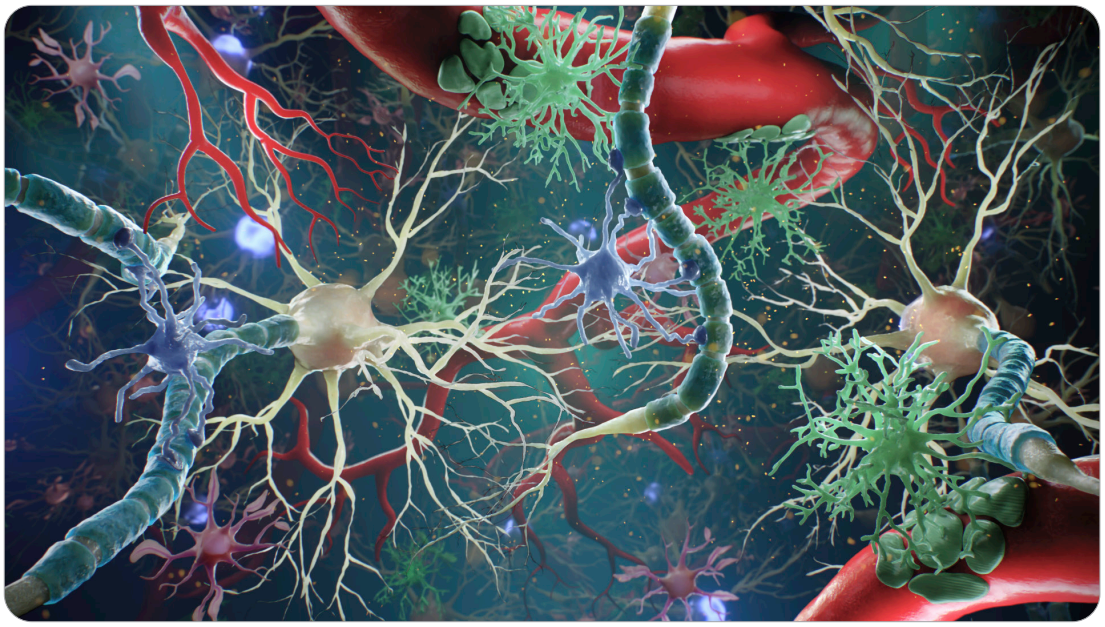


Figure 11 – *Immunohistochemical analysis of activated caspase-3 in neuronal progenitor cells from the hippocampal subgranual zone of the dentate gyrus, in APP tg mice treated with Cerebrolysin.*[12]

2.2.4 MODULATION OF INFLAMMATORY RESPONSE

Neurons and glial cells represent two major cell types in the nervous system. Among different types of glial cells having different functions, microglia acts as the brain's immune defence system, destroying pathogens and removing dead tissue.

Whereas short-term activation is essential and supports the protective mechanisms, long-term activation has detrimental effects. In stroke, TBI or chronic pathologies like dementia microglia remain activated and causes the release of pro-inflammatory substances such as interleukin (IL-1ß), TNF α, ICAM1. These cause severe damage to neurons leading to neuronal cell death.



In primary cell cultures Cerebrolysin reduced lipopolysaccharide (LPS)-induced activation of microglia and downregulated IL-1β expression (**Lombardi et al. 1999**[13]).

Similar effects were reported in a rat model of neurodegeneration induced by intrahippocampal injection of the β-amyloid 1 – 40 fragment (Aβ4) followed by administration of LPS (**Alvarez et al. 2000**[14]). Cerebrolysin reduced microglial activation by decreasing brain IL-1β levels and the expression of ectodermal dysplasia 1 (ED1), a marker protein showing the presence of immunological response.

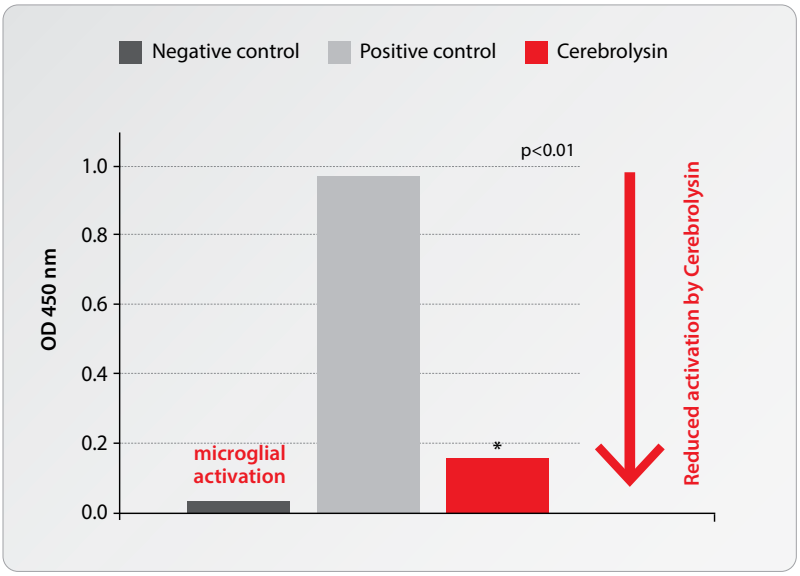
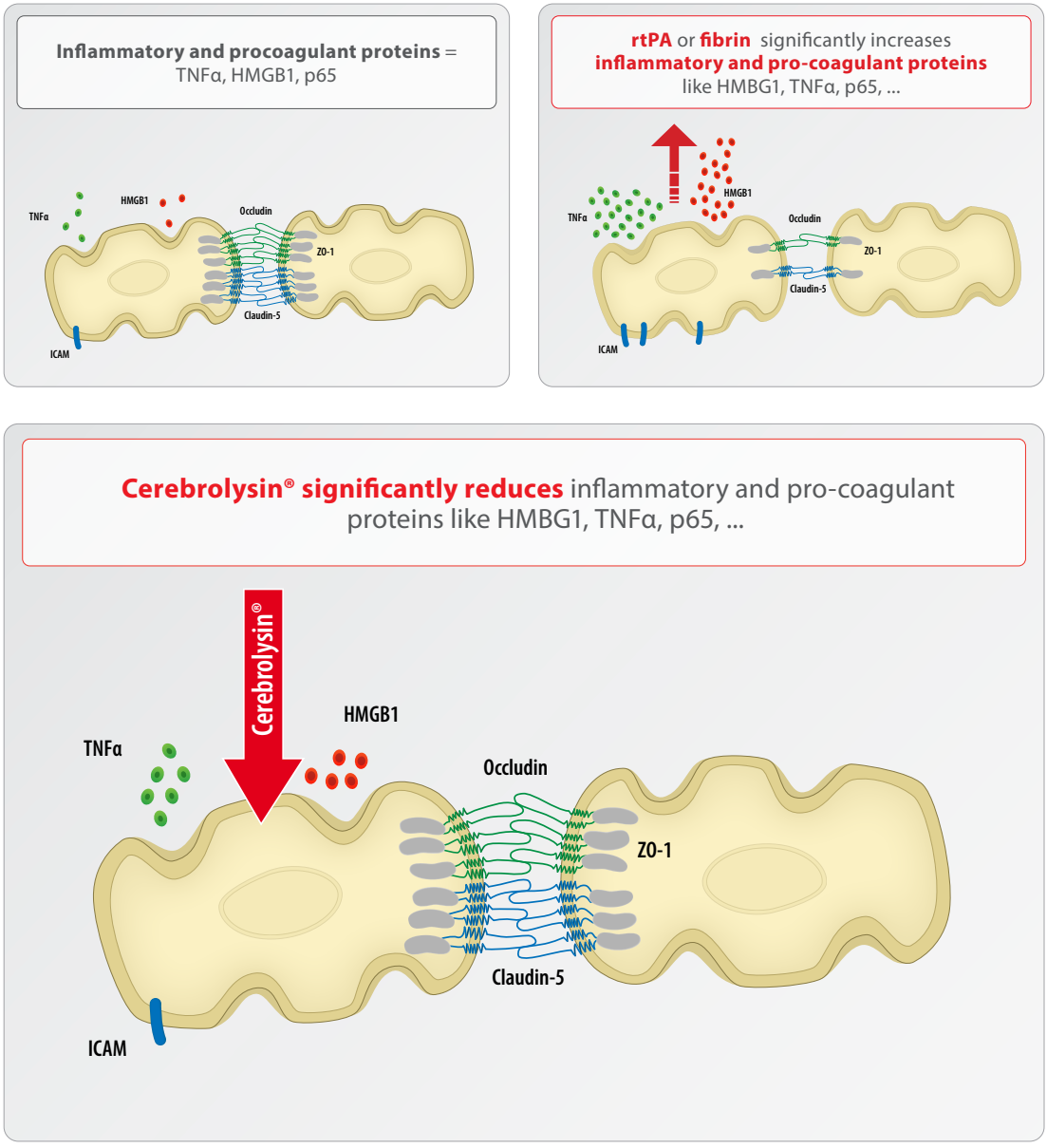


Figure 12 – *Reduced inflammatory response by Cerebrolysin in a microglial cell culture model.*[14]

The Henry Ford University in Detroit, USA investigated Cerebrolysin in combination with rtPA after stroke. It was shown that rtPA or fibrin significantly elevate inflammatory and pro-coagulant proteins like HMBG1, TNFα, p65. This means that rtPA and fibrin directly induce proinflammatory responses, which promote disruption of the blood brain barrier (BBB) and parenchymal cell damage. The risk of intracranial bleeding increases.[15]

Teng et al. 2021[15] demonstrated a significant decrease of rtPA or fibrin-induced proinflammatory and procoagulant proteins in human cells treated with Cerebrolysin and diminish the cytokines to their basal level in endothelial cells.



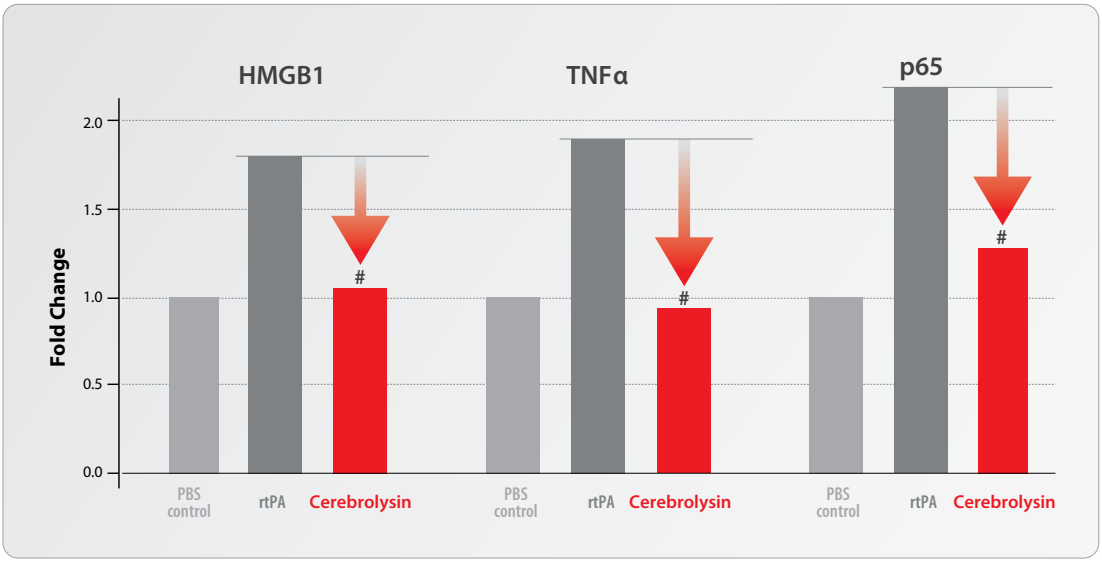
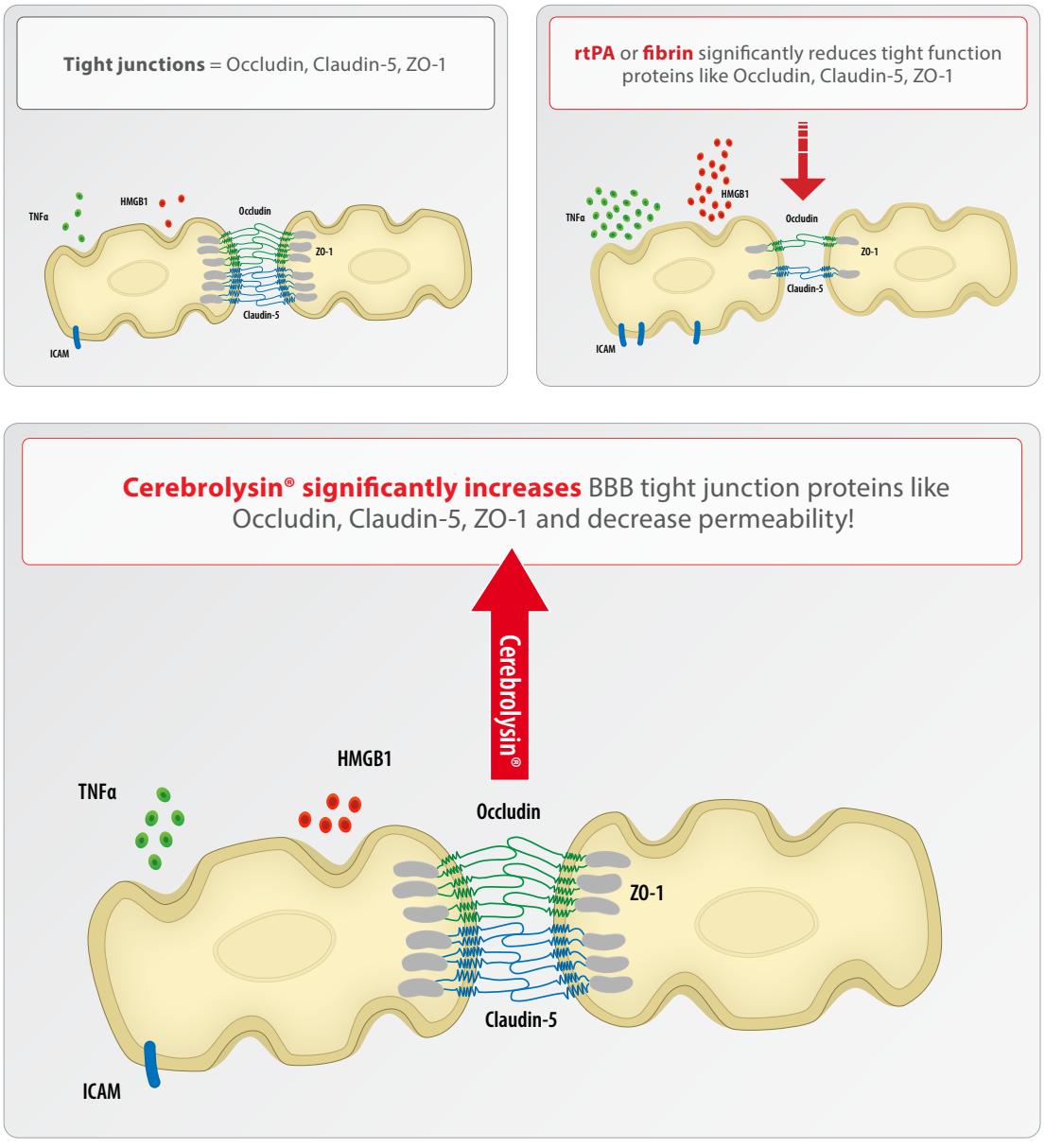


Figure 13 – *Western blot showed protein levels in the individual experimental groups treated with Cerebrolysin in combination with rtPA, #P<0.001 vs. rtPA or fibrin. HMG1, high mobility group box 1; TNFα, tumor necrosis factor α; p65, phosphorylated nuclear factor kappa B (NFkB)-p65N.* [15]

2.2.5 IMPROVEMENT OF BBB INTEGRITY

Cerebral endothelial cells play an important role in maintaining the blood brain barrier (BBB) – an adjustable barrier between the blood vessel and the extravascular space. They form a continuous endothelium in the CNS, which is connected by tight junctions. So, tight junction proteins, including ZO-1, occludin and claudin-5, are critical for the formation and maintenance of BBB integrity.

Teng et al. 2021[15] demonstrated that rtPA and fibrin reduce tight junction proteins in the endothelial cells. Thus, rtPA or fibrin increases BBB permeability, and the risk of hemorrhagic transformation.



While the benefits of rtPA treatment greatly outweigh the risks of bleeding the question remains if this risk can be further reduced. It was demonstrated that Cerebrolysin improves the cerebral endothelial cell integrity by significantly increasing levels of tight junction proteins reduced by rtPA or fibrin.[15]

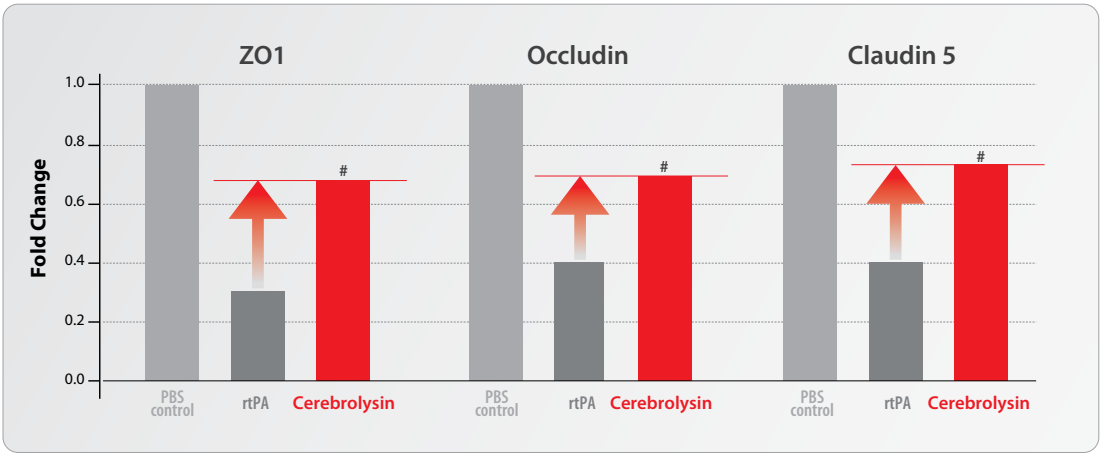


Figure 14 – *Western blot showed protein levels in the individual experimental groups treated with Cerebrolysin in combination with rtPA, #P<0.001 vs. rtPA or fibrin. Zo1 = zonular 1.* [15]

Cerebrolysin significantly reduces rtPA or fibrin augmented permeability by more than 50% and makes the BBB tighter again!

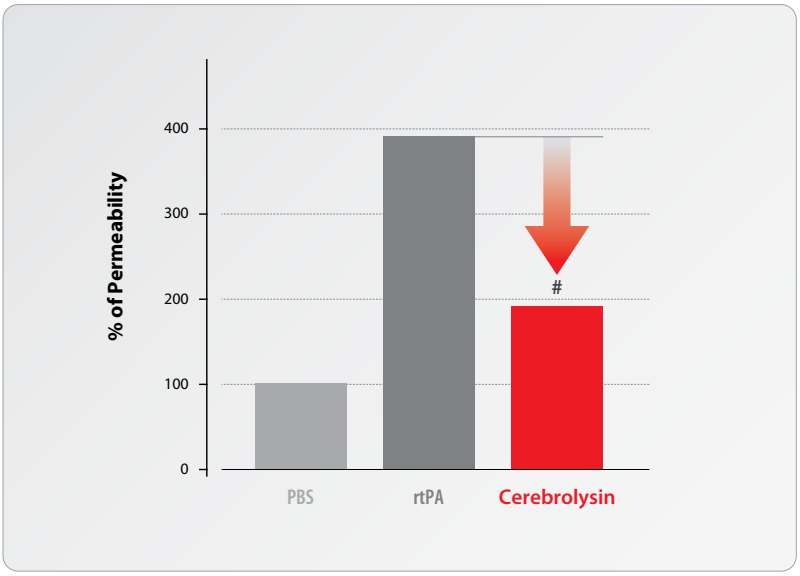


Figure 15 – *Reduced inflammatory response by Cerebrolysin in a microglial cell culture model.*[14]

Cerebrolysin increases the number of tight junctions and thereby increases the integrity of the blood brain barrier and the tightness of the vessels.

2.2.6 NEUROPLASTICITY

Neuroplasticity allows the brain to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment. Brain re-organization takes place by mechanisms such as axonal sprouting in which undamaged axons reconnect to neurons and thus contribute to the restoration of neuronal pathways.

Cerebrolysin stimulates neuroplasticity in cell cultures and in animal models. Neuronal sprouting and networking induced by Cerebrolysin was shown in a primary neuronal cell culture.[2]

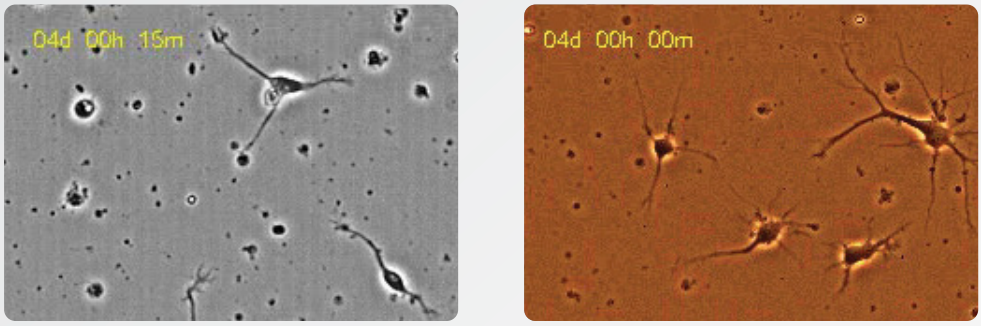


Figure 16 – *Stimulation of neuronal sprouting and viability promoting effect of Cerebrolysin in primary neuronal cell cultures.*[2]

In a transgenic (tg) animal model of Alzheimer's disease Cerebrolysin significantly increased the number of new synapses in various hippocampal regions. This effect was reflected in improved behavioral performance of animals treated with Cerebrolysin.[16]

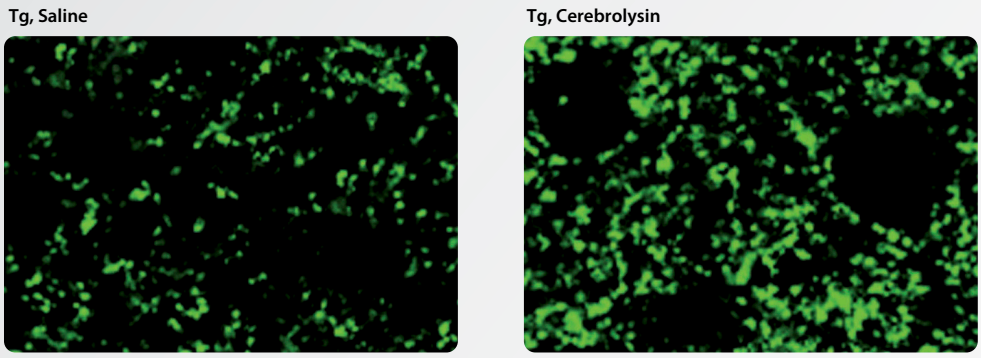


Figure 17 – *In a transgenic animal model of Alzheimer's disease characterized by impaired synaptic plasticity, amyloid ß plaque deposition and neurodegeneration, Cerebrolysin significantly increased the number of new synapses in hippocampus (green dots).*[16]

Oligodendrogenesis and subsequent remyelination of axonal fibers is a necessary step for restoration of damaged structures and a prerequisite for functional recovery.

The studies by **Zhang et al. 2013**[8] have shown that Cerebrolysin enhances oligodendrogenesis in the ischemic brain as corresponding marker proteins (NFH and CNPase) were significantly increased in the peri-infarct area.

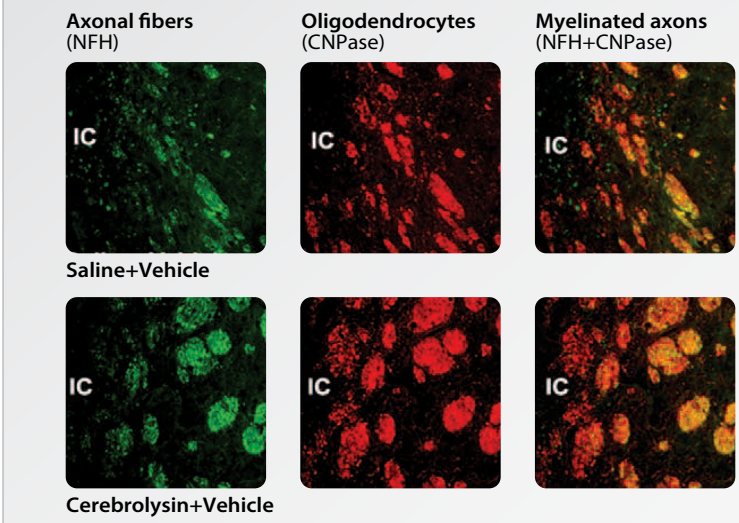


Figure 18 – *Immunofluorescent images of neurofilament heavy chain (NFH; green; indicating axon fibers) and CNPase (red; indicating oligodendrocytes) in the ischemic boundary of animals treated with saline (upper) or Cerebrolysin (lower).*[8]

Blocking these effects by co-administration of cyclopamine, an inhibitor of 'smo', suggests the involvement of the Shh pathway in this myelination process enhanced by Cerebrolysin.

2.2.7 NEUROGENESIS

Recovery from brain tissue damage depends on effective stimulation of neuroregeneration processes such as stimulation of neurogenesis.

The newborn cells originating from this process become fully integrated into the surrounding brain tissue where they e.g. have important functions for learning and memory in the hippocampus. Exercise and enriched environment promote the survival of new neurons and their successful integration into the neuronal network of the hippocampus. Pharmacological stimulation of neurogenesis is regarded as a potential tool to promote recovery from brain lesions.

Cerebrolysin significantly increased the number of neuroblasts and promoted neurogenesis in the dentate gyrus, both, in an AD model[12] *(see Figure 19)* and in an TBI model[17] *(see Figure 20)*.

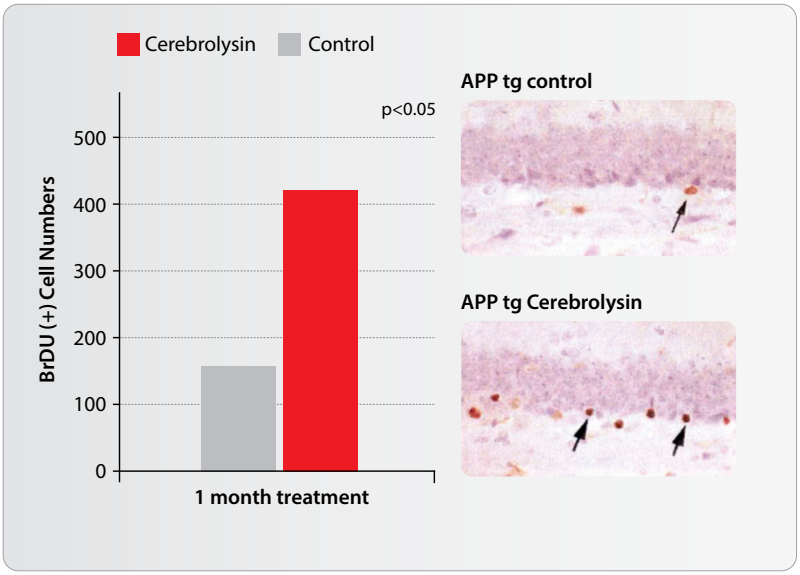


Figure 19 – *Cerebrolysin stimulates neurogenesis in the sub-granular zone of the dentate gyrus in a transgenic model of Alzheimer's disease (APP tg mice).*[12]

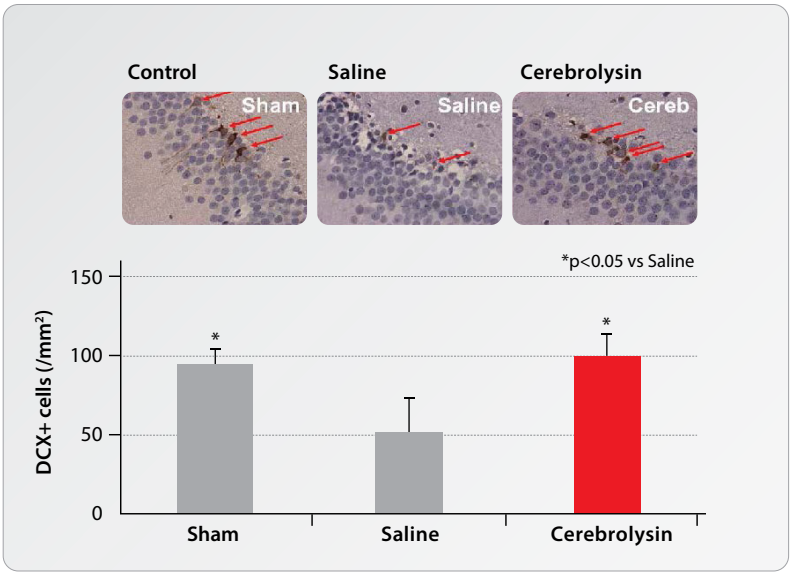


Figure 20 – *The effects of Cerebrolysin on the number of DCX-expressing neuroblasts in the dentate gyrus. Compared with the saline-treated group Cerebrolysin treatment significantly increased DCX-positive neuroblasts in the dentate gyrus 90 days after mTBI, which is comparable to the level observed in animals without TBI lesion (sham).*[17]

3 STROKE

Stroke has become the second leading cause of long-term disability and the second cause of death worldwide[18]. Annually, 15 million people suffer a stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on their family and community.[19]

A stroke happens when the blood supply to a part of the brain is suddenly interrupted (ischemic stroke) or when a blood vessel in the brain bursts, spilling blood into the spaces surrounding brain cells (haemorrhagic stroke).[20]

In Western societies, about 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion, and the remaining 20% are caused by haemorrhages.[21]

Shortages of oxygen and nutrients lead to brain cells death. Although stroke is a disorder of the brain, it can affect the entire body and may cause the following problems:

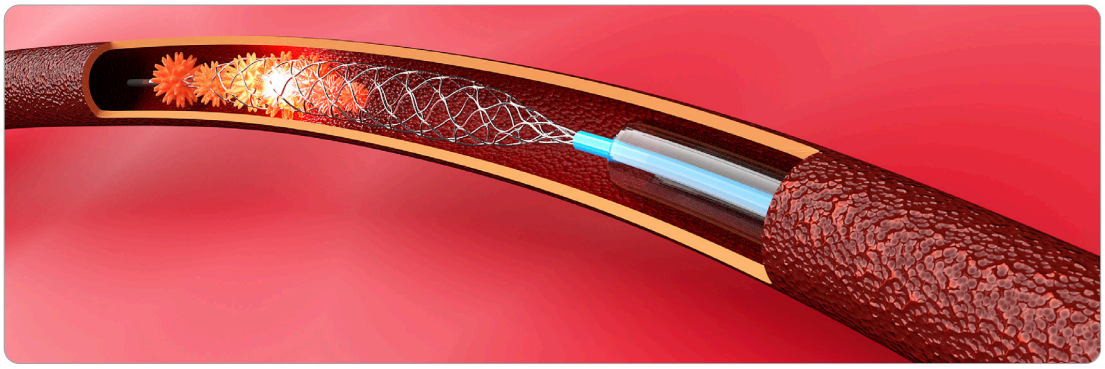
- Trouble with walking, loss of balance or coordination
- Problems with thinking, awareness, attention, learning, judgment, and memory
- Post-stroke depression
- Vascular dementia (more details in chapter 5.2)
- …

3.1 TREATMENT

Acute stroke therapies include several treatment options depending on the cause of stroke.

If a patient suffers from an **ischemic stroke** caused by a blood clot the healthcare professional may recommend the following options.[22]

- **Drug Treatment:** There is only one approved drug treatment for acute ischemic stroke: tissue plasminogen activator (**rtPA**) is given via intravenous therapy (IV) and works by dissolving the clot and restoring blood flow to the part of the brain being deprived of blood flow. For safety reasons rtPA is given within 4.5 hours post-stroke.
- **Mechanical Devices (thrombectomy):** A surgeon inserts the mechanical device via a catheter into the blocked artery. Once inside, the tool traps and removes the clot out of the brain and reopens the blocked blood vessel.



In case of **haemorrhagic stroke,** the first steps are to find the cause of bleeding in the brain and then to control it. Some of the options for treatments include:

- Surgical clips
- Coils inserted in aneurysms
- Surgery to remove the bleeding vessel and blood that has spilled into the brain
- Hemicraniectomy to reduce Intercranial Pressure (ICP)

Post-stroke rehabilitation is essential for individuals to overcome impairments and disabilities. The goals of rehabilitation are to help survivors become as independent as possible and to attain the best possible quality of life.

More than 25% of patients[23] are functionally severely impaired after a stroke and benefit from early rehabilitation and Cerebrolysin.

Cerebrolysin is an additional evidence-based therapy in acute stroke and in rehabilitation phase. Clinical data confirm benefits in earlier and better motor recovery, increased quality of life and regained independence.

3.2 CEREBROLYSIN IN STROKE

The complex stroke pathology requires multimodal treatments.

Cerebrolysin is an agent that safely contributes to recovery and is an important enrichment to the current pharmacologic armamentarium.

It is already used in the acute phase as well as in the post–stroke rehabilitation phase to enhance neuroprotection and neurorecovery functions. It is recommended that Cerebrolysin should be used as an add-on treatment to standard intervention and should be initiated as early as possible, usually within a few hours post-stroke.

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Stroke	20 – 50 ml	as soon as possible	10 – 21 days

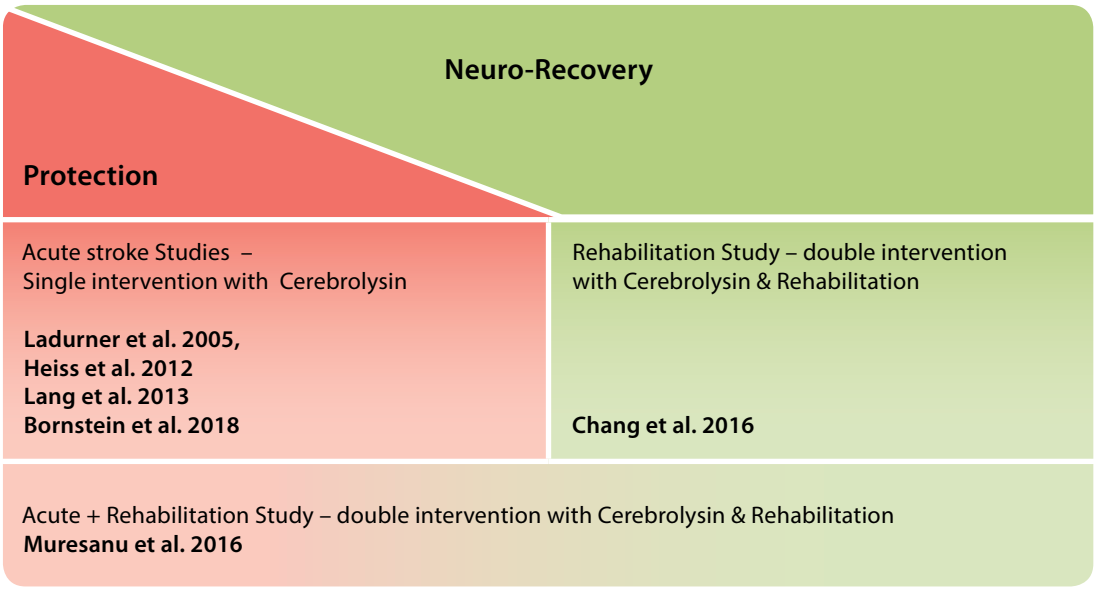
3.3 CLINICAL EFFICACY OF CEREBROLYSIN

The efficacy and safety of Cerebrolysin in stroke has been assessed in randomized, double-blind studies with more than 3.000 patients. In this monograph, the most relevant for the current standard of care and the most recent RCTs are discussed.

Cerebrolysin is safe and well tolerated in both, in ischemic and hemorrhagic stroke.

Publication	Daily dosage Cerebrolysin	Treatment Duration	Efficacy parameters	Benefits
Meta-analysis				
Bornstein et al. 2018	30 – 50 ml	10 – 21 days	NIHSS, mRS	Early recovery Regained independence
Prospective, randomized, double-blind, placebo controlled trials				
Ladurner et al. 2005 Maksimova at al. 2009	50 ml	21 days	CNS, BI, MMSE, SST	Early recovery Regained independence Improvement of cognitive functions
Heiss et al. 2012	30 ml	10 days	mortality	Higher survival rate
Lang et al. 2013	30 ml	10 days	NIHSS, BI, mRS	Early recovery
Muresanu et al. 2016	30 ml	21 days	ARAT, mRS, GDS, Mann-Whitney	Early recovery Improvement of motor functions Regained independence Increased quality of life
Chang et al. 2016	30 ml	21 days	FMA, rsfMRI	Improvement of motor functions

Studies focus on ischemic stroke in acute-treatment and in the rehabilitation-phase (neurorecovery) or are combining both phases in one study. Below please find an overview.



Single intervention = pharmacological treatment (standard care & Cerebrolysin)
Double intervention = pharmacological treatment (standard care & Cerebrolysin) & rehabilitation therapy

Investigators showed the following key benefits of Cerebrolysin:

- Early recovery
- Improvement of motor functions
- Regained independence
- Increased quality of life
- Improvement of cognitive functions
- Higher survival rate

In hemorrhagic stroke, **Maksimova et al. 2009**[24] showed that Cerebrolysin treated patients significantly improved in the NIHSS (p=0.004), Barthel Index (p=0.001), and modified Rankin Scale (p=0.002), which means less neurological impairment and disability for the patient.

3.3.1 EARLY RECOVERY

The early phase of recovery after stroke seems to offer treatment opportunities that were largely overlooked until the concept of early mobilization became a part of the international stroke guidelines.

The early therapeutic progress of the treatment in the acute phase of stroke is well represented by frequent measurement techniques of the neurological impairment (e.g. NIHSS). Fast improvement of neurological functions is linked with improved stroke prognosis, lower mortality rates and improved motor rehabilitation of the affected extremities. Moreover, it is linked to readiness of stroke patients for neurorehabilitation.

The basis for an effective therapy design is that the patient has a certain attention period. That means they should be able to understand therapeutic instructions, implement therapeutic instructions, and ideally remember these instructions, enabling them to repeat the exercises independently as required.

Accelerated recovery during Cerebrolysin treatment was shown in a double-blind, placebo-controlled, multicentre trial by **Ladurner et al. 2005**[25]. The most pronounced effects were observed within the first three days in the CNS (Canadian Neurological Scale), BI (Barthel Index), MMSE (Mini-Mental State Examination) and SST (Syndrome Short Test).

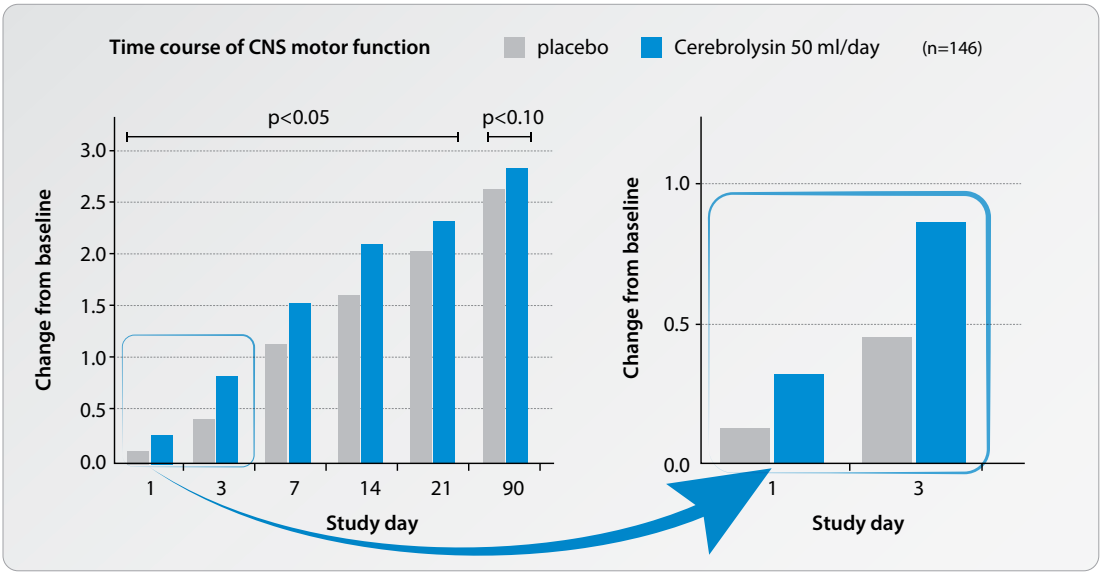


Figure 21 – *Improvement of motor functions after stroke. Mean chance from baseline in the Canadian Neurological Scale (CNS) for the Cerebrolysin group and placebo group.* [25]

Lang et al. 2013[26] investigated the combination therapy Cerebrolysin with alteplase (rt-PA). Patients with acute ischemic hemispheric stroke, randomly assigned to a treatment starting with rt-PA within three-hours after onset of symptoms plus Cerebrolysin or placebo treatment administered 1 hour after thrombolytic treatment.

Cerebrolysin consistently showed an **earlier improvement** in all efficacy scales.

Already on day 2, the NIHSS responder rate was significantly higher with Cerebrolysin as compared to placebo. The Cerebrolysin group showed significantly more patients with an improvement of 6 or more points (or a total score of 0 or 1) than in the placebo group. Differences reached its maximum at day 5 with a responder rate of 66.1% in the Cerebrolysin group vs. 37.3% in the placebo group treated with rtPA alone.

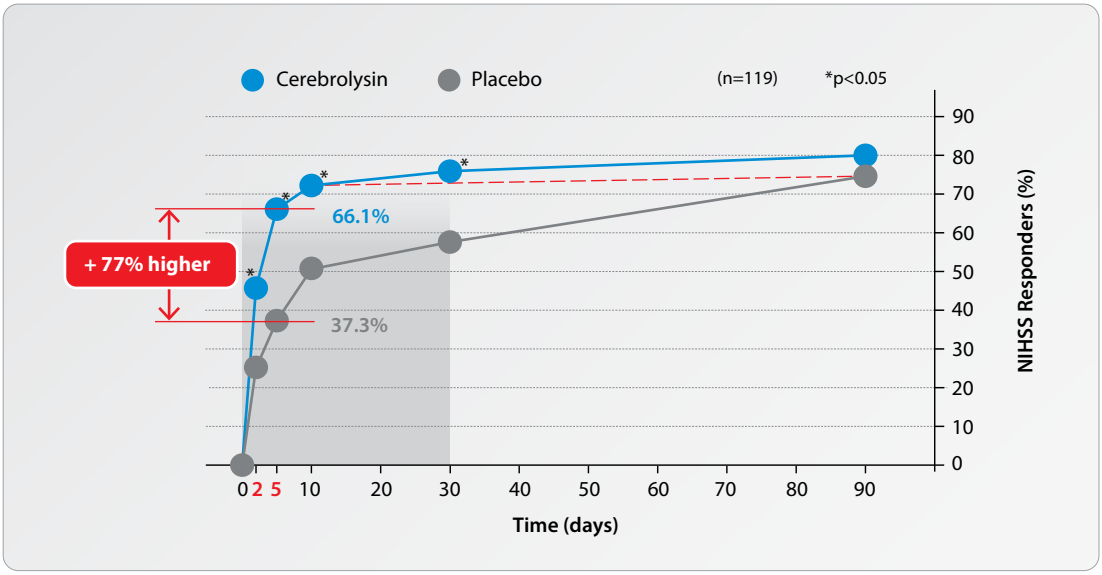


Figure 22 – *Responder analysis (ITT population) of NIHSS.* [26]

Similar results were observed in the responder analysis of the Barthel index (BI) and the modified Rankin Scale (mRS). Cerebrolysin produced a consistently faster improvement in all efficacy scales compared to rt-PA as a stand-alone treatment.

Muresanu et al. 2016[27] showed also an early recovery effect. Patients treated with Cerebrolysin showed superior motor recovery already at day 14.

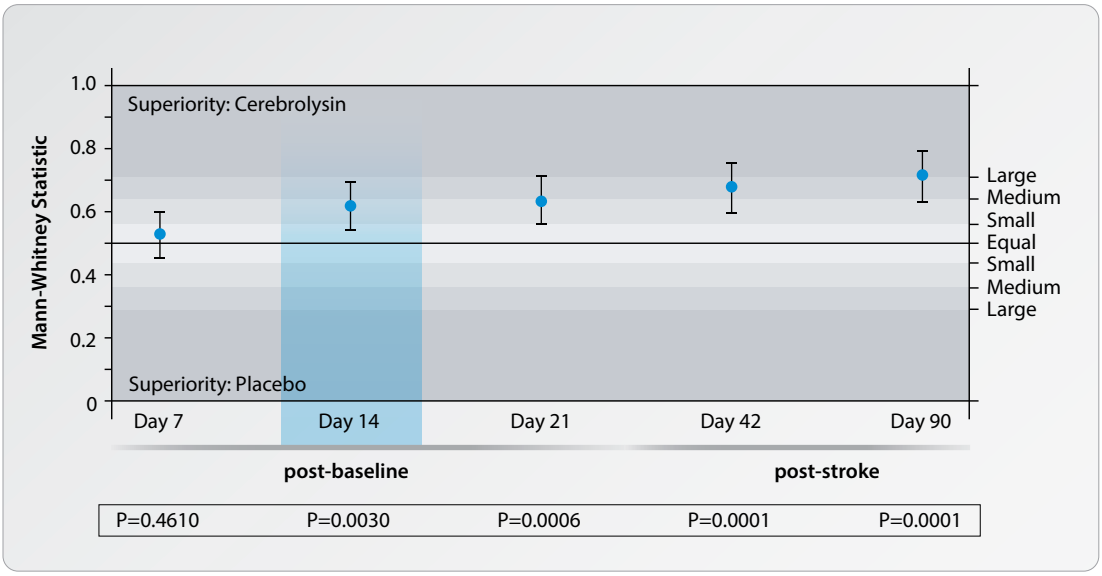


Figure 23 – *Effect sizes (Mann-Whitney) of the ARAT score changes from baseline in the mITT-LOCF population.*[27]

A **meta-analysis** (**Bornstein et al. 2018**[28]) comprised of 1.879 stroke patients showed **early beneficial clinical** effects of Cerebrolysin compared to placebo by measuring NIHSS (National Institutes of Health Stroke Scale) on day 30. The number needed to treat (**NNT**) for clinically relevant changes in early NIHSS was **7.7** (95% CI 5.2 – 15.0), which means: Treat eight patients with Cerebrolysin and one patient more will show clinically significant changes in NIHSS at day 30.

Cerebrolysin treated patients are ahead.
Patients benefit from an earlier and better starting point for rehabilitation!

3.3.2 IMPROVEMENT OF MOTOR FUNCTIONS

Stroke often causes serious long-term disabilities. Symptoms are heterogeneous and patients may have widely differing handicaps. One of the ultimate goals in stroke treatment is to improve the patient's motor functions.

Recently published studies demonstrated that Cerebrolysin significantly improves the motor function in patients after stroke.

Muresanu et al. 2016[27] combined early and prolonged administration of Cerebrolysin (within 24 – 72 h post-stroke, lasting for 21 days) with structured rehabilitation, in order to better understand the role of Cerebrolysin as a component of multimodal rehabilitation. This Cerebrolysin and Recovery After Stroke (**CARS**) trial had a prospective, randomized, double-blind, placebo-controlled, multi-center, parallel-group design comparing the effects of 30 ml Cerebrolysin versus placebo. Each patient included in the study participated in an accompanying standardized rehabilitation program for 21 days, beginning within 48 to 72 hours after stroke onset.

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

The effect size analysis demonstrated a large superiority of Cerebrolysin relative to the placebo on day 90.The ARAT scores increased by median values from 0 at baseline to 51.0 on day 90 in the Cerebrolysin group and from 2.0 to 27.0 in the placebo group. The median absolute changes in the ARAT scores at 90 days post stroke compared with those at baseline were 32.0 for Cerebrolysin and 11.0 for the placebo.

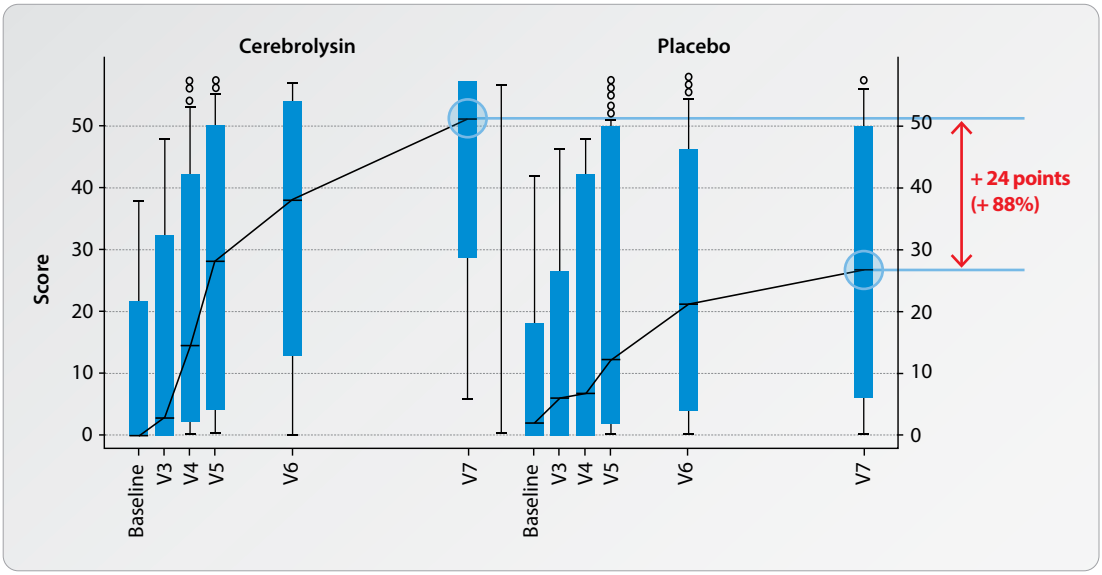


Figure 24 – *Improvement of ARAT with Cerebrolysin and placebo, shown as boxplot diagrams.* [27]

An increase in the ARAT score was observed in 96 of 104 (92.3%) of the Cerebrolysin-treated patients and in 85 of 101 (84.2%) of the placebo-treated patients.

The effect of Cerebrolysin in the subacute phase of stroke was assessed in the ECOMPASS study (**Chang et al. 2016**[29]). ECOMPASS (= **E**ffects of **C**erebrolysin **O**n **M**otor recovery in **PA**tients with **S**ubacute **S**troke) investigated effects of Cerebrolysin in combination with rehabilitation during the subacute phase of stroke, initiated administration from day 8 after stroke. This approach reflected the clinical reality and practice of early rehabilitation of stroke patients in South Korea and other countries.

The trial was designed as a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. The well established Fugl-Meyer Assessment (FMA) was used as primary outcome measure of motor function assessment.

The results of this study showed a trend towards improvement in the Cerebrolysin treatment arm at three months after stroke onset compared to the placebo treatment arm. However in patients suffering from severe motor impairment at inclusion, Cerebrolysin together with standardized rehabilitation significantly improved motor functions at day 90.

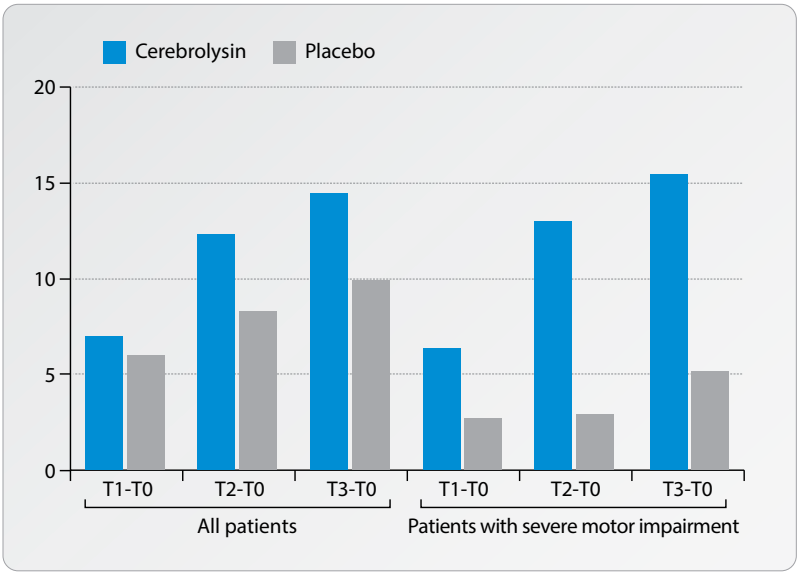


Figure 25 – *Improvement of the Fugl-Meyer-assessment (FMA) for Cerebrolysin and placebo at baseline (Day 8, T0), immediately after treatment (Day 29, T1) as well as two months (Day 60, T2) and three months (Day 90, T3) after stroke onset.* [29]

Additional evidence for the effects of Cerebrolysin on neuroplasticity has been investigated by using functional neuroimaging. The changes in neuroplasticity of the motor network were assessed by resting state functional magnetic resonance imaging (rsfMRI).

Cerebrolysin treatment induced changes in the sensorimotor network by stimulating symmetric functional connectivity between the bilateral primary sensori-motor cortices. The observed therapeutic effect shows a positive impact of the treatment. The symmetric functional connectivity was more pronounced in patients treated with Cerebrolysin suggesting better recovery of motor cortical function.

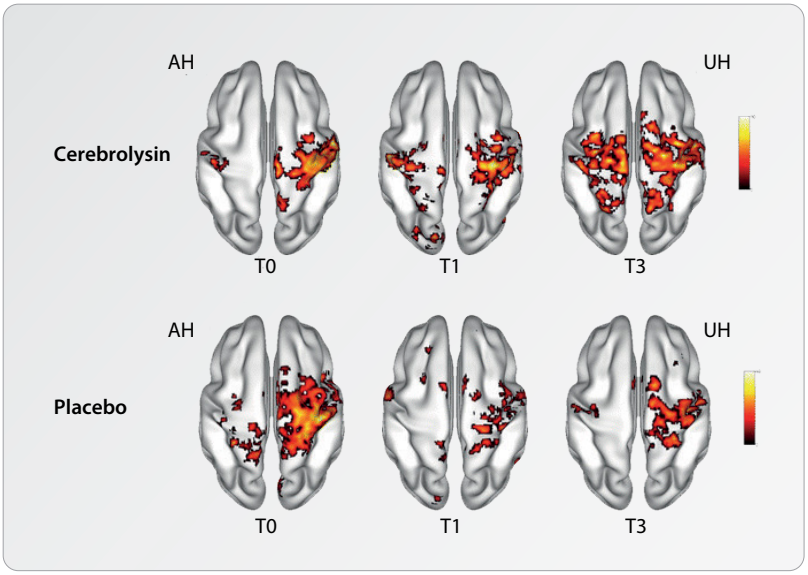


Figure 26 – *Resting state of sensory motor network by functional MRI (rsfMRI). Affected (AH) and unaffected (UH) hemispheres at baseline (Day 8, T0), immediately after treatment (Day 29, T1) and three (Day 90, T3) months after stroke onset.* [29]

ECOMPASS confirmed findings of the CARS trial that the combination of standard rehabilitation therapy with Cerebrolysin treatment is highly relevant for enhanced recovery of motor functions after stroke.

Beneficial effects of Cerebrolysin in the acute and subacute phase after stroke!

3.3.3 REGAINED INDEPENDENCE

Stroke survivors often suffer from varying degrees of permanent disability and sustain impairments that significantly affect their family and social well-being. Therefore the primary goal after stroke is to regain everyday functions, which include activities of daily living like dressing, feeding, bathing, so that patient can live an independent life.

Common scales measure the improvements of activities of daily living (ADL) and the dependence on caregivers:

- The **Barthel Index (BI)** measures the extent to which somebody can function independently and has mobility in ADL
- The **modified Rankin Scale (mRS)** is a commonly used scale for measuring the degree of disability or dependence in the daily activities

In the trial of **Ladurner et al. 2005**[25], the activities of daily living were assessed with the Barthel index. Cerebrolysin treatment vs. placebo reached the level of statistical significance. The study showed that patients treated with Cerebrolysin are at least one week ahead in their recovery compared to placebo patients.

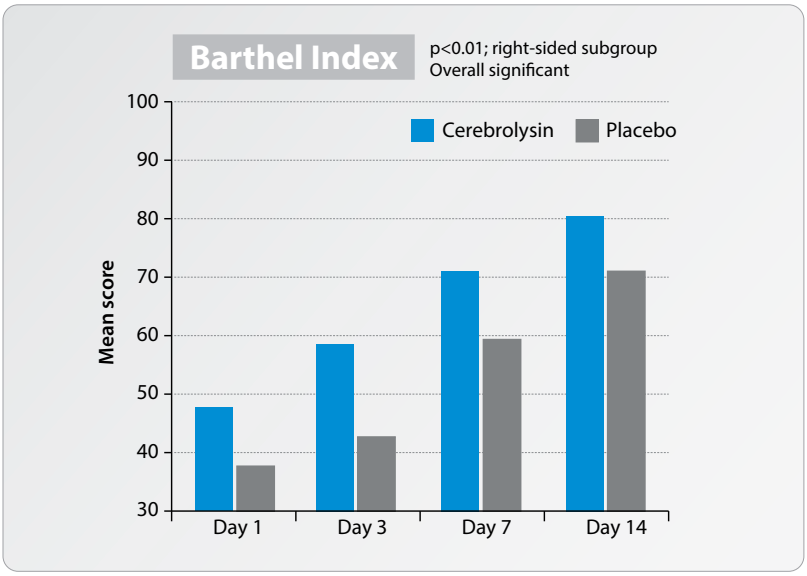


Figure 27 – *Improvement of Barthel Index. Mean change from baseline in the BI score of the Cerebrolysin and placebo groups.*[25]

In the **CARS study** (Cerebrolysin and Recovery after Stroke, Muresanu et al. 2016[27]) in which patients participated in an early rehabilitation programme incl. Cerebrolysin treatment a favourable mRS score of 0 (no symptoms) and 1 (no significant disability) was found in 42.3% of patients. In the placebo group only 14.9% reached this level of recovery. Similar picture shows mRS scores of 0 to 2 (no symptoms to slight disability). In the Cerebrolysin group 65.4% reached at least the level of slight disability, in the placebo group only 33.7%.

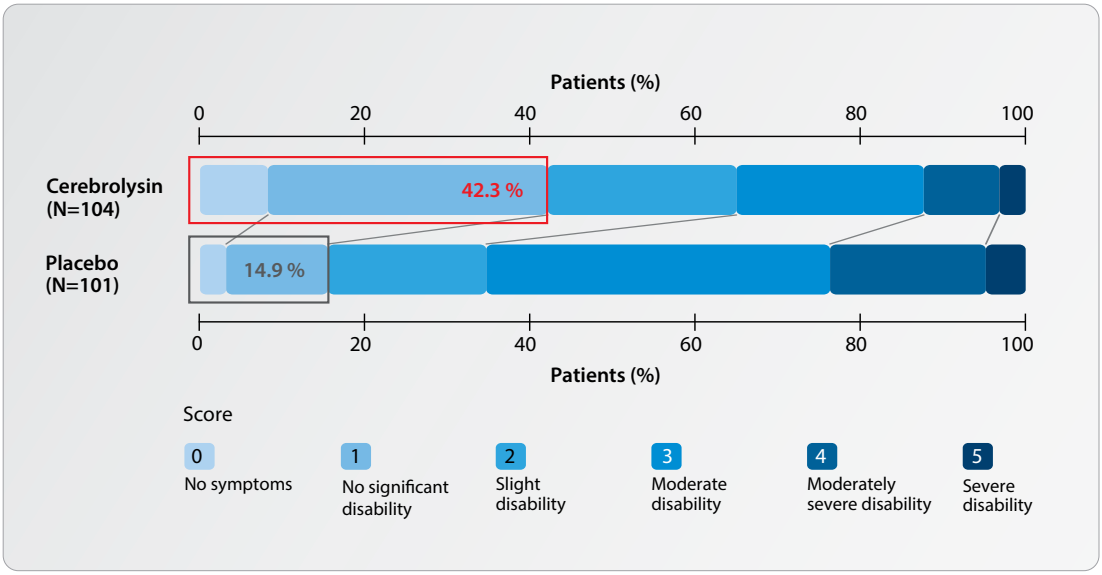


Figure 28 – *Distribution of modified Rankin Scale scores at day 90.*[27]

The meta-analysis of Bornstein et al. 2018[28] investigated mRS at day 90 in moderate-severe patients (NIHSS>12) showing a statistically significant result in favour of the Cerebrolysin group (MW 0.61, 95% CI 0.52 to 0.69, P=0.01, N=314; Wei-Lachin pooling procedure). This means that 61% of patients have a chance for a better outcome when treated with Cerebrolysin.

Cerebrolysin supports patients to live an independent life!

3.3.4 INCREASED QUALITY OF LIFE

Post-stroke depression is one of the most serious obstacles for effective recovery and long-term independence. According to epidemiological studies, nearly 30% of stroke patients develop depression, either in the early or in the late stages after stroke. Although depression may affect functional recovery and quality of life after stroke, this condition is often ignored.

In **Muresanu et al. 2016**[27] major improvements for depression were observed in the Cerebrolysin group. As shown by results of the Geriatric Depression Scale, Cerebrolysin reduces depression and increases the patient's quality of life.

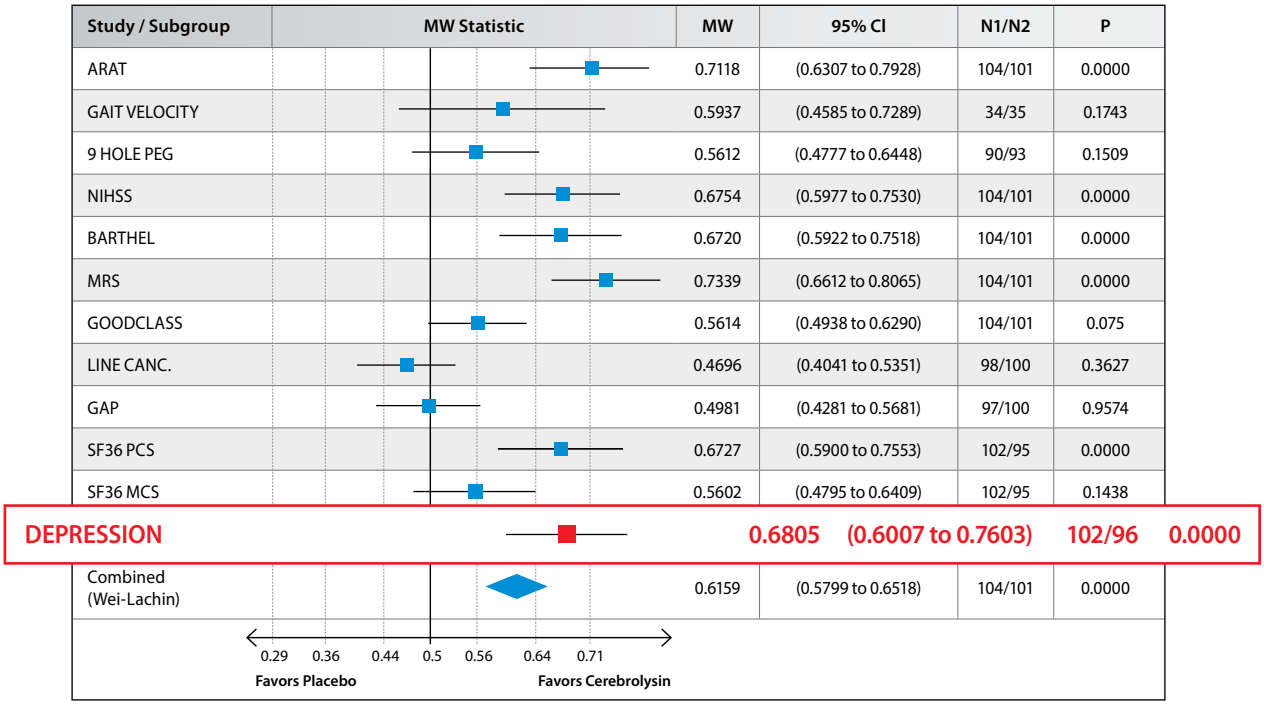


Figure 29 – *Global status on day 90. The effect sizes (Mann-Whitney MW) for the single and combined (Wei-Lachin procedure) efficacy parameters reflect chances from baseline in the mITT-LOCF (n=205).* [27]

With Cerebrolysin patients are satisfied with their quality of life at a high level!

3.3.5 IMPROVEMENT OF COGNITIVE FUNCTIONS

Cognitive deficits are changes in thinking, like difficulty solving problems and concentrating. This category also includes memory and orientation problems, as well as many kinds of emotional challenges. All these changes can be measured by the MMSE (Mini-Mental State Examination) which consists of 22 simple questions or tasks grouped into five cognitive domains: orientation, registration, attention and calculation, recall and language.

The effect of Cerebrolysin on cognitive functions was assessed by **Ladurner et al. 2005**[25]. Patients treated with Cerebrolysin significantly improved in cognitive performance. The MMSE increased significantly in the Cerebrolysin group as compared to the placebo group. In consideration of rehabilitation, patients can follow therapeutic rehabilitation instructions more easily and will perform better.

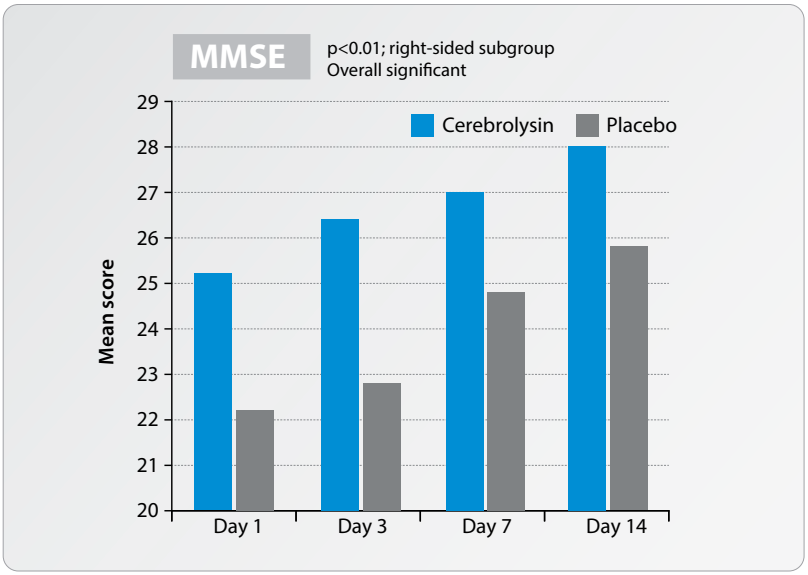


Figure 30 – *Improvement of MMSE. Mean change from baseline in the MMSE score of the Cerebrolysin and placebo groups.* [25]

Furthermore 25% of stroke patients develop **vascular dementia** within 1 year of stroke. Vascular dementia is caused when stroke or small vessel disease affects the blood supply to the brain. It is the second most common form of dementia. Further information provides the chapter Dementia – 5.2.[30]

Cerebrolysin facilitates ability to follow rehabilitation instructions!

3.3.6 HIGHER SURVIVAL RATE

Stroke has become second cause of death worldwide.[31] Annually, 5.5 million people die.[32]

In a multicenter, randomized, double-blind, placebo-controlled trial (CASTA – **C**erebrolysin in patients with **A**cute ischemic **St**roke in **A**sia –) reported by Heiss et al. 2012[33], 1.067 patients with a clinical diagnosis of acute hemispheric ischemic stroke were included. When the mortality of the more severely affected subgroup with NIHSS>12 was analyzed, after 90 days, the cumulative percentage of patients who died was 20.2% in the placebo group but only 10.5% in the Cerebrolysin group. In the survival time analysis, an even more pronounced superiority of Cerebrolysin could be seen (p=0.02485).

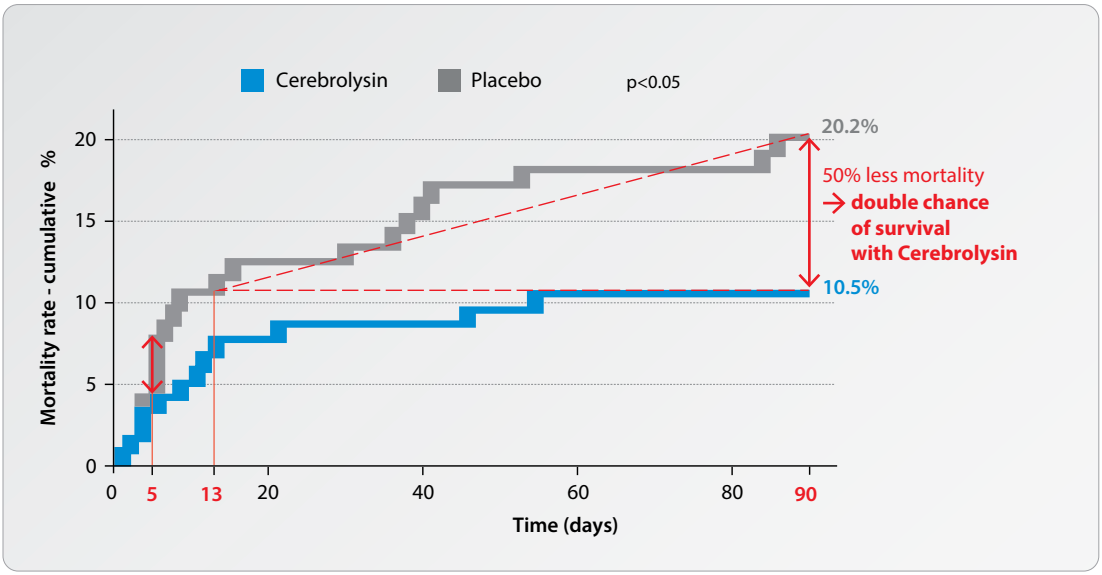


Figure 31 – *Kaplan-Meier survival curve (comulative percentage) for subgroup baseline NIHSS >12 points (N=252, 126 patients per group).* [33]

Although the relationship between Cerebrolysin treatment and the initiation of a patient's mobilization was not directly assessed in CASTA, the significantly increased survival rate of patients treated with Cerebrolysin can be interpreted on the basis of known correlations between early recovery and the decreased prevalence of serious post-stroke complications which often lead to death.

Cerebrolysin improves chances for survival after stroke!

4 TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) affects approx. 15 million[34] individuals annually worldwide and is one of the leading causes of death. It is associated with high rates of hospitalization, mortality and disability.

TBI occurs when a sudden trauma causes damage to the brain. TBI can result from sudden and violent hits to the head, or when an object penetrates the skull, injuring brain tissue. In Europe, the main causes of TBI are road traffic accidents, falls and assaults. In Asian countries traffic accidents causing TBI mainly involve two-wheeled vehicles.[35]

Depending on the extent of the damage to the brain, symptoms of a TBI can be mild, moderate, or severe.

A person with a **mild TBI** may remain conscious or may experience a loss of consciousness for a few seconds or minutes in addition to headache, confusion, light-headedness, dizziness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, a change in sleep patterns, behavioral or mood changes, and trouble with memory, concentration, attention or thinking.

A person with a **moderate or severe TBI** may show these same symptoms, but may also have a headache that gets worse or does not disappear, repeated vomiting or nausea, convulsions or seizures, an inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness or agitation.

4.1 TREATMENT

Optimisation of primary care and reduction of post-traumatic impairment are primary goals to improve the patient's chances in rehabilitation and to reduce suffering.

Current knowledge indicates of today indicates that modern therapy of brain injuries should optimally target various pathological mechanisms simultaneously rather than focus on a single therapeutic target. [36, 37]

The general management of TBI includes:

- Initial emergency treatment for patient stabilization, including surgery
- Acute treatment aimed at minimizing secondary injury, including mechanical ventilation, control of intracranial pressure, cerebral perfusion pressure and edema, as well as sedative-, seizure- and antiepileptic treatment
- Rehabilitation therapy
- Pharmacological therapy

Such a **multimodal approach** is most effective for assuring optimal recovery after brain injuries.

4.2 CEREBROLYSIN IN TBI

By stimulating natural neuroprotective and neurorecovery processes, Cerebrolysin can alleviate short-and long-term consequences of TBI while providing an excellent safety profile.

Cerebrolysin is an add-on therapy to standard care and should be initiated as soon as possible and continued throughout the rehabilitation phase.

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Traumatic Brain Injury	20 – 50 ml	as soon as possible	7 – 30 days

4.3 CLINICAL EFFICACY OF CEREBROLYSIN

The effects of Cerebrolysin were evaluated with various clinical outcome scales during acute and post-acute TBI phases.

Publication	Daily dosage Cerebrolysin	Treatment Duration	Efficacy parameters	Benefits
Meta-analysis				
Vester et al. 2021	50 ml (+ 2 additional cycles with 10ml)	10 days (Start day 1, 30, 60)	Multi-dimensional approach	Effective treatment after TBI Save lives Early recovery Better quality of life
Prospective, randomized, double-blind, placebo controlled trials				
König et al. 2006	50 ml	21 days	GCS, CGI, SST	Effective treatment after TBI Early recovery Improvement of memory and concentration
Chen et al. 2013	30 ml	5 days	MMSE, CASI	Improvement of memory and concentration
Muresanu et al. 2020	50 ml (+ 2 additional cycles with 10ml)	10 days (Start day 1, 30, 60)	Multi-dimensional approach	Effective treatment after TBI Early recovery Better quality of life Improvement of memory and concentration
Prospective, open-label trials				
He et al. 2002	10 – 30 ml	4 weeks	GCS	Effective treatment after TBI Early recovery
Alvarez et al. 2003	30 ml	4 weeks	Power ratio, SST, GOS	Improvement of memory and concentration
Alvarez et al. 2008	30 ml	4 weeks	Power ratio, SST	Improvement of memory and concentration
Asghari et al. 2014	10 ml	10 days	mortality	Save lives
Retrospective trials				
Chaisoonthon et al. 2011	30 ml	10 days	mortality	Save lives
Muresanu et al. 2015	20 – 30 ml	10 days	GOS, RDS	Effective treatment after TBI Early recovery

The following clinical benefits of Cerebrolysin in TBI treatment have been shown:

- Effective treatment after TBI
- Save lives
- Early recovery
- Better quality of life
- Improvement of memory and concentration

4.3.1 EFFECTIVE TREATMENT AFTER TBI

The severity of traumatic brain injury is commonly measured by using the Glasgow Coma Scale (GCS). This grades a person's level of responsiveness on a scale of 3 – 15 based on verbal, motor, and eye responses. The Glasgow Outcome Scale (GOS) assesses recovery and predicts the long-term prognosis of the patient but is not sensitive enough to show even small improvements. An innovative multidimensional approach was used in the CAPTAIN trials that takes into account the overall impression of the TBI patient and thus reflects the reality after a TBI much better.

In the trial of **He et al. 2002**[38] patients with acute traumatic brain injury treated with Cerebrolysin showed a significant improvement in the Glasgow Coma Scale (GCS) compared to the placebo group.

After 4 weeks of treatment, **He et al. 2002**[38] showed that significantly more patients improved in the Cerebrolysin group (93.7%) compared to the control group (80.0%)

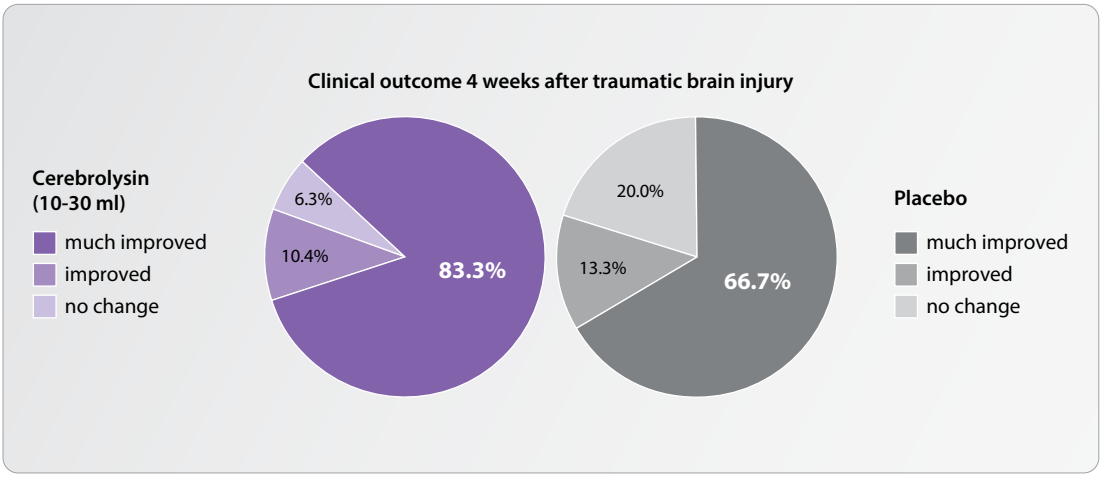


Figure 32 – *Clinical improvement observed in patients as measured with the Glasgow Coma Scale. Much improved: clinical symptoms disappear (GCS increased by more than 2 scores); improved: clinical symptoms eased up (GCS increased by 1 score); no change: unmodified clinical symptoms.*[38]

König et al. 2006[39] found significant outcome differences in Glasgow Coma Scale items like 'Eye opening', 'Best verbal response' and 'Best motor response'.

Muresanu et al. 2015 [40] is one of the largest, ever conducted, observational studies in TBI. This multicentre retrospective study with 7.769 patients proved the severity-related efficacy and safety of Cerebrolysin in TBI patients.

The study showed similar outcome as the trials above but was also able to specify the results regarding severity and dosage:

- Significant better recovery in **mild, moderate and severe** TBI patients treated with Cerebrolysin already on day 10 → Treatment of Cerebrolysin leads to an **earlier recovery**
- **Significant higher effectiveness** in moderate to severe TBI patients on day 30 in Cerebrolysin group
- Independent of severity a daily dose of 30 ml Cerebrolysin was more effective than a dose of 20 ml

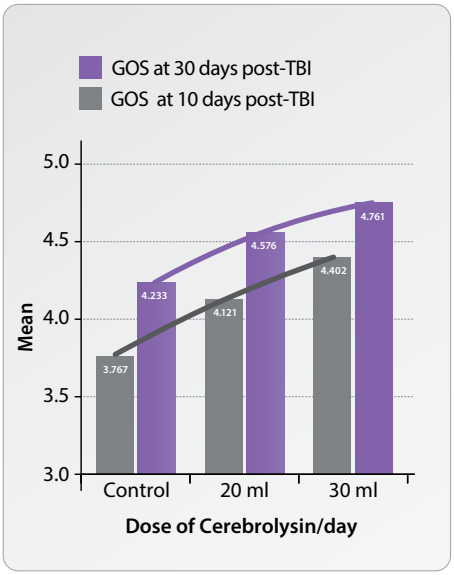


Figure 33 – *GOS scores at 10 and 30 days post TBI in the treatment group of moderate TBI patients.* [40]

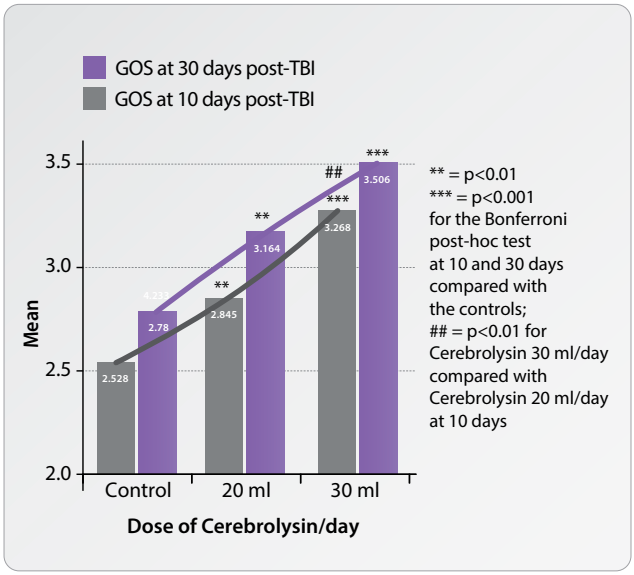


Figure 34 – *GOS scores at 10 and 30 days post TBI in the treatment group of severe TBI patients.* [40]

Poon et al. 2019 (CAPTAIN 1) [41] and **Muresanu et al. 2020 (CAPTAIN 2)** [42] reported the results of a randomized, double-blind, placebo-controlled trial, which assessed efficacy and safety of Cerebrolysin in patients with moderate to severe traumatic brain injury (GCS 7-12) in the acute (day 10) and chronic phases (day 30 and 90). Since no single outcome measure captures the heterogenous nature of TBI, the primary endpoint was a **multidimensional ensemble of 13 outcome scales** assessing different domains like depression, activities of daily living, and cognition.

CAPTAIN 1 showed statistical significant superiority of Cerebrolysin in the per-protocol analysis with effect sizes of six single outcomes lying above the benchmark for large superiority. Safety aspects were comparable to placebo.

In CAPTAIN 2 at day 90, a significant effect size of Cerebrolysin (MW = 0.60, 95% CI 0.53 to 0.68) was shown in the multidimensional outcome ensemble. In all 13 single outcome scales Cerebrolysin® was superior to placebo and 6 outcome scales demonstrated stand-alone statistical significance. Safety and tolerability observations were comparable between treatment groups.

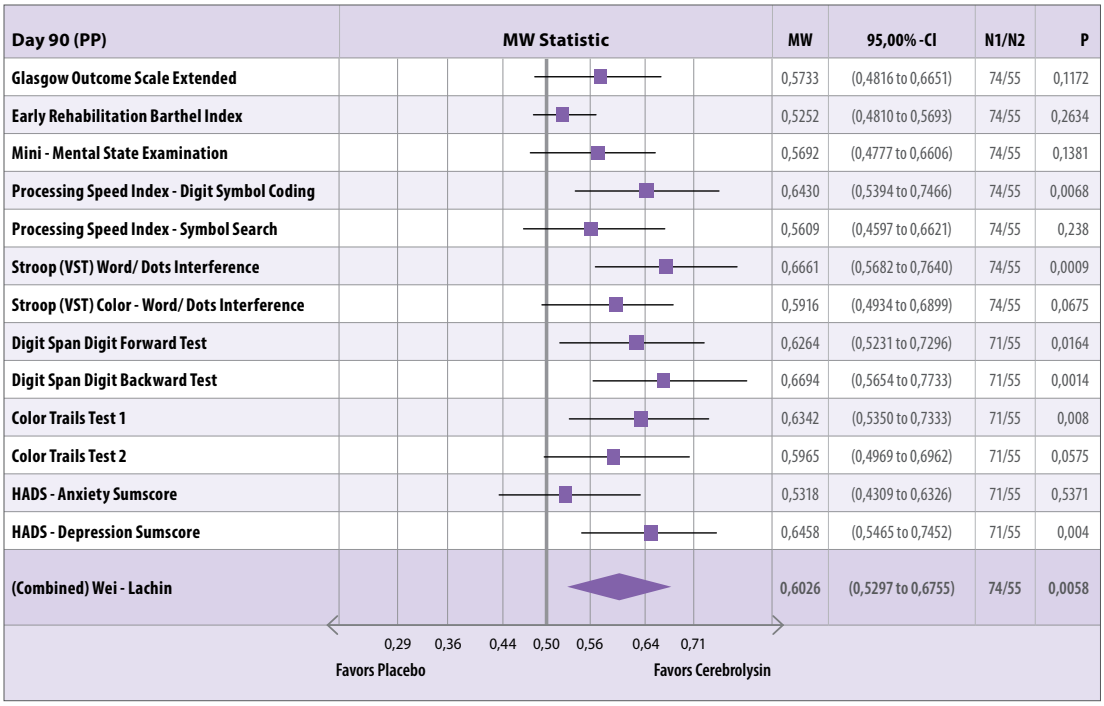


Figure 35 – *Multidimensional Ensemble, Day 90, PP.* [42]

The meta-analysis of the CAPTAIN trials (**Vester et al. 2021**[43]) confirmed beneficial effects of Cerebrolysin in the overall outcome, which opens a new horizon in acute neuroprotection and for long-term neurorecovery in this field. At day 90, Cerebrolysin showed a significant superiority (MW = 0.63, P Wei-Lachin = 0.0039, two-sided; 95% CI 0.54 to 0.71) after moderate-to-severe TBI

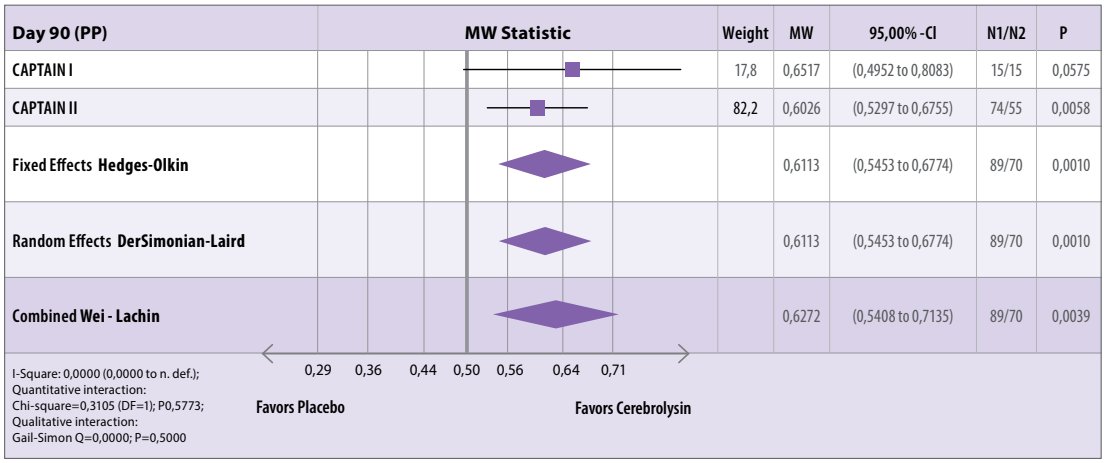


Figure 36 – *Confirmatory Multivariate Outcome Ensemble at Day 90, PP (Neurorecovery Phase).* [43]

Cerebrolysin add-on to standard care improves clinical and functional recovery after TBI

4.3.2 SAVE LIVES

Traumatic brain injury is one of the leading causes of mortality worldwide.

The study of **Chaisoonthon et al. 2011**[44], showed a significant decrease of the average mortality rate of TBI patients treated with Cerebrolysin. The mortality rate decreased from 83.33% to only 28.57% in the Cerebrolysin group.

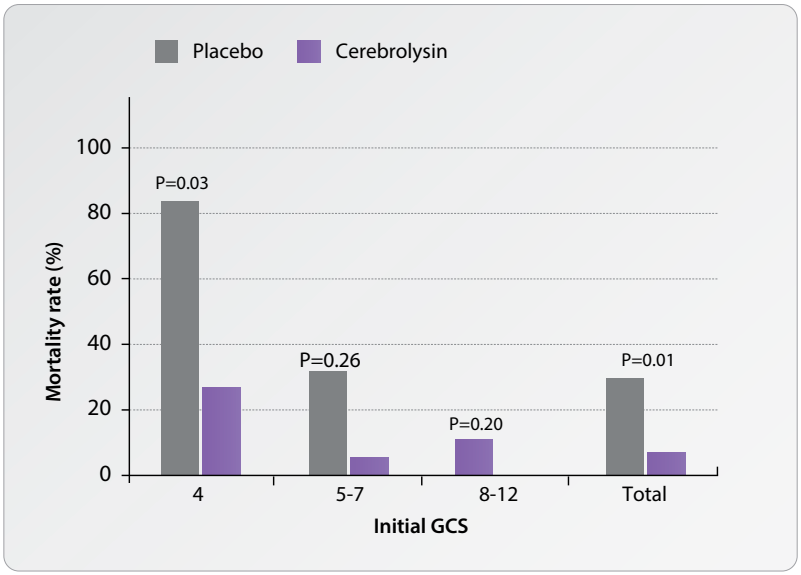


Figure 37 – *Mortality rate of all patients with various initial GCS.*[44]

A reduction of the mortality rate was also shown in a trial of **Asghari et al. 2014**[45]. In this trial, the mortality rate in the placebo group was 4 times higher than in the Cerebrolysin group.

The same trend was also reported in the meta-analysis of **Vester et al. 2021**[43], as 3.9% of patients died in the Cerebrolysin group versus 8.4% in the placebo group. Also, adverse events were less in the Cerebrolysin group.

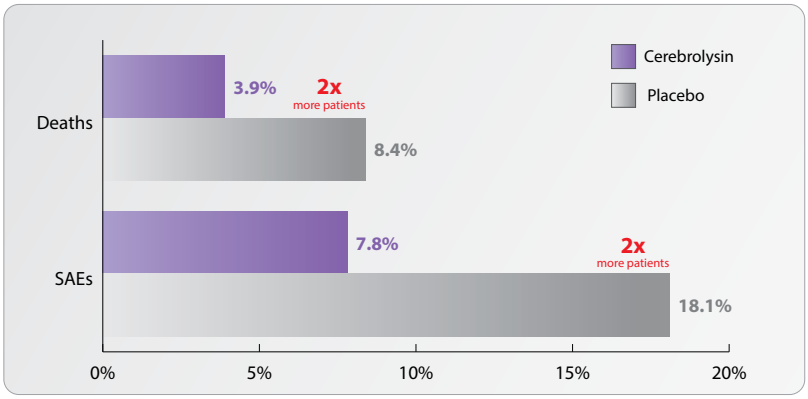


Figure 38 – *Safety Meta-Analyses.*[43]

Cerebrolyin decreases mortality of TBI patients!

4.3.3 EARLY RECOVERY

TBI has a very high economic impact on individuals, their families, and on society as a whole.[46] In order to reduce costs, it is essential that TBI patients recover quickly with the aim of early discharge from the hospital and early transfer to rehabilitation.

König et al. 2006[39] demonstrated significantly faster clinical recovery of Cerebrolysin treated patients.

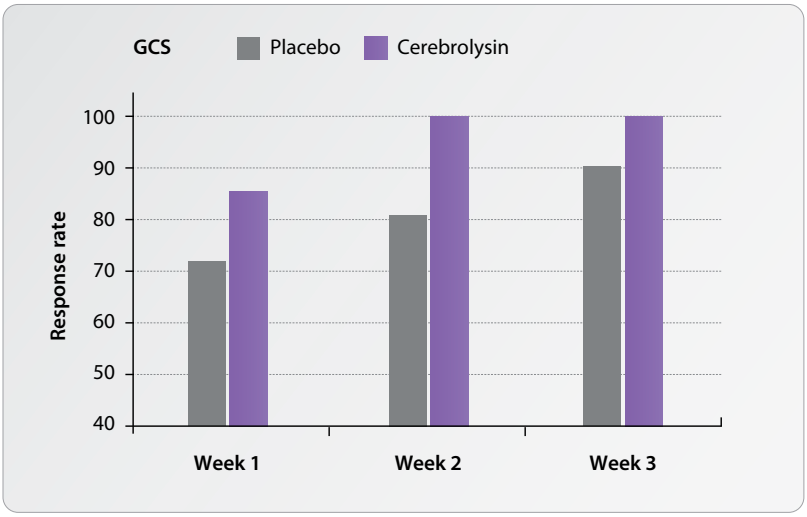


Figure 39 – *Augmentation of number of cases (%) with unimpaired consciousness in GCS overtime of treatment.*[39]

Both, **CAPTAIN 2** (Muresanu et al. 2020[42]) and the **CAPTAIN meta-analysis** (Vester et al. 2021[43]) reported early recovery with Cerebrolysin.

As early as on day 10, **CAPTAIN 2** (Muresanu et al. 2020[42]) showed superiority of Cerebrolysin versus placebo overall (MW = 0.54) and in 6 out of 7 single outcome scales. On day 30, the effect size increased to MW = 0.576. So already one early treatment cycle brings medium superiority on day 30.

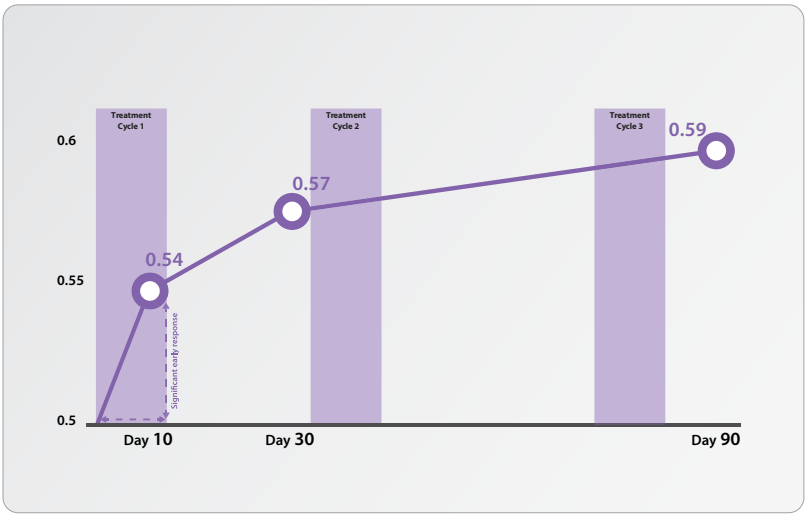


Figure 40 – *Multidimensional Ensemble, Combined Wei-Lachin, Day 10, 30 and 90, ITT.*[42]

The **CAPTAIN meta-analysis** (Vester et al. 2021[43]) showed superiority of Cerebrolysin (MW = 0.6023, 95% CI 0.52 to 0.68) already on day 10.

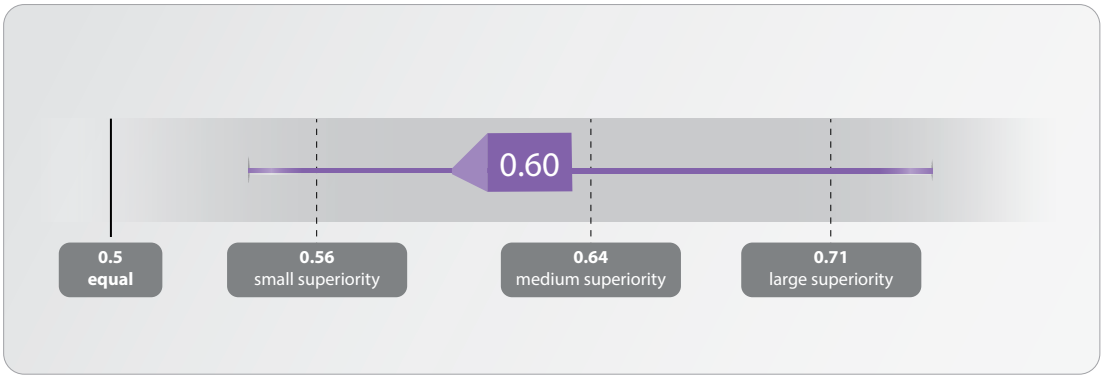


Figure 41 – *Confirmatory Multivariate Outcome Ensemble at Day 10, PP (Neuroprotection Phase).*[43]

Cerebrolysin results in early recovery:
Treat your TBI patient with Cerebrolysin as soon as possible!

4.3.4 BETTER QUALITY OF LIFE

One of the most common comorbidities after TBI is depression. About half of TBI patients are affected by depression within the first year after injury and two-thirds within seven years.[47] Depression is a feeling of sadness, loss, despair, and hopelessness that does not get better over time and is overwhelming enough to interfere with daily life. There is cause for concern if the feeling of depression or loss of interest in usual activities occurs at least several days per week and lasts more than two weeks.[48]

Symptoms of depression include:

- Feeling down, sad, blue or hopeless.
- Loss of interest or pleasure in usual activities.
- Feeling worthless, guilty, or that you are a failure.
- Changes in sleep or appetite.
- Difficulty concentrating.
- Withdrawing from others.
- Tiredness or lack of energy.
- Moving or speaking more slowly or feeling restless or fidgety.
- Thoughts of death or suicide.

Treatment of post-TBI consequences is essential and indicated for Cerebrolysin!

The CAPTAIN trials looked deeper into this topic and came to the result that Cerebrolysin significantly reduced depression!

In **CAPTAIN 2** (Muresanu et al. 2020[42]) Cerebrolysin showed large-sized superiority (MW = 0.65, 95% CI 0.55 to 0.74) in the HADS (Hospital Anxiety and Depression Scale) on day 90. HADS showed stand-alone significance as early as on day 30.

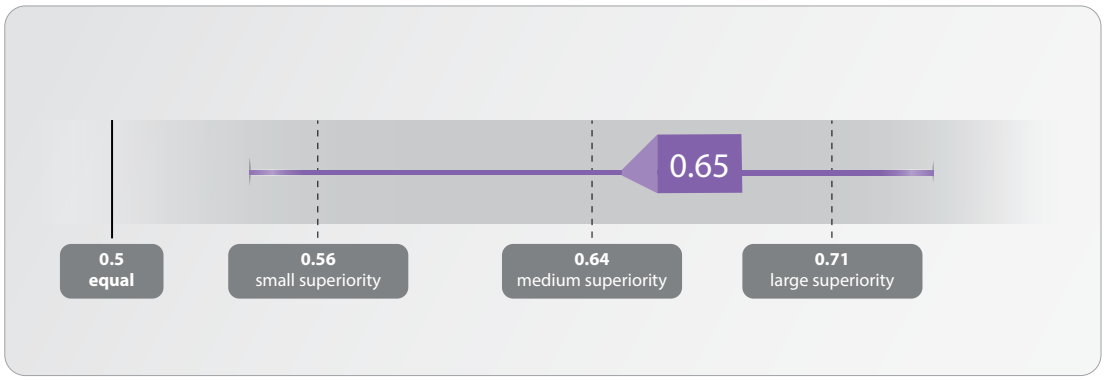


Figure 42 – *Figure: HADS depression sumscore, MW, Day 90, PP.*
Large inferiority = 0.29; Medium inferiority = 0.36, Small inferiority = 0.44; Equality = 0.50; Small superiority = 0.56; Medium superiority = 0.64; Large superiority = 0.71.[42]

The **CAPTAIN meta-analysis** (Vester et al. 2021)[43] found normalization of the HADS score (Score 0-7 at Day 90) in 70.5% of patients treated with Cerebrolysin as compared to 39.5% of patients in the placebo group. The rate difference of 31% is a substantial reduction of depression.

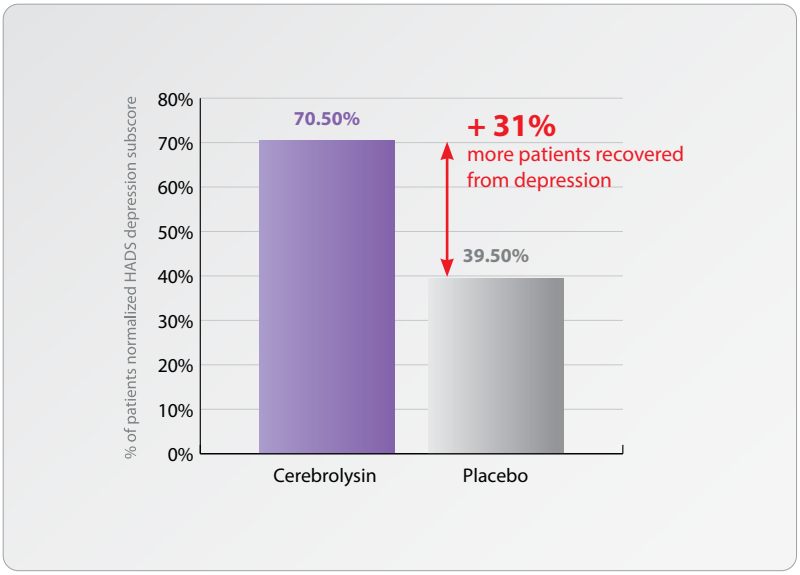


Figure 43 – *Normalization of the HADS score (Score 0-7) at Day 90.*[43]

Better quality of life with Cerebrolysin!

4.3.5 IMPROVEMENT OF MEMORY AND CONCENTRATION

Memory loss, the most common cognitive impairment among people with head injuries, occurs in 20–79% of people with head trauma, depending on the trauma severity. Patients who have suffered a TBI may also have difficulty with speaking or processing language or with more subtle aspects of communication such as body language.

Different studies show that Cerebrolysin enhances cognitive functions of mild, moderate and severe TBI patients in the acute and post-acute phase.

König et al. 2006[39] assessed cognitive function of patients in the **acute phase** treated with Cerebrolysin at a daily dosage of 50 ml for 21 days.

Patients treated with Cerebrolysin achieved significant cognitive improvements in the Syndrome-Short Test (SST) at endpoint (3 weeks) ($p<0.05$), and at follow-up at weeks 6 ($p=0.045$) and 9 ($p=0.024$), compared to those treated with placebo. The largest difference between study groups appeared within 2 weeks after injury, and the positive treatment trend continued in the follow-up period up to 42 days post-injury.

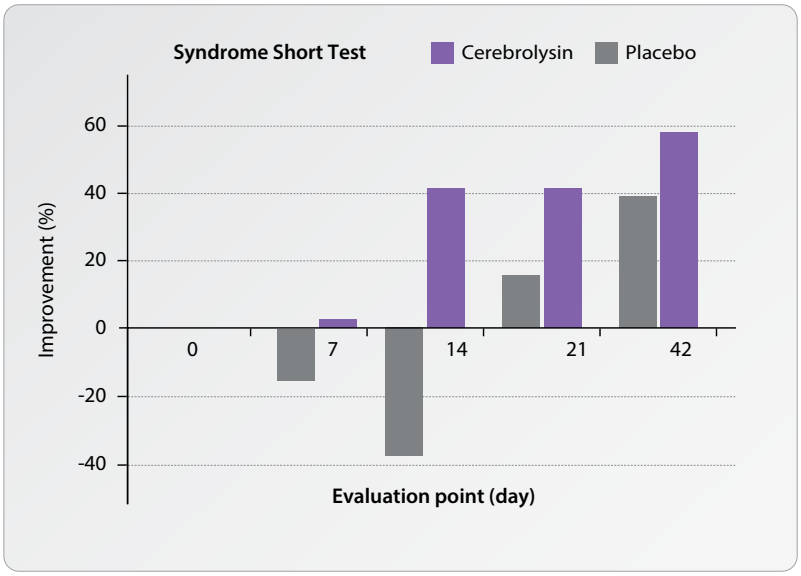


Figure 44 – *Improvement (%) in the SST.*[39]

Alvarez et al. 2003[49] showed improved cognitive performance also in **post-acute** TBI patients. Cerebrolysin enhances brain activity irrespective of the severity and time course of the injury. This effect is reflected in topographic brain maps and in significant reductions in power ratio values calculated from quantitative EEG.

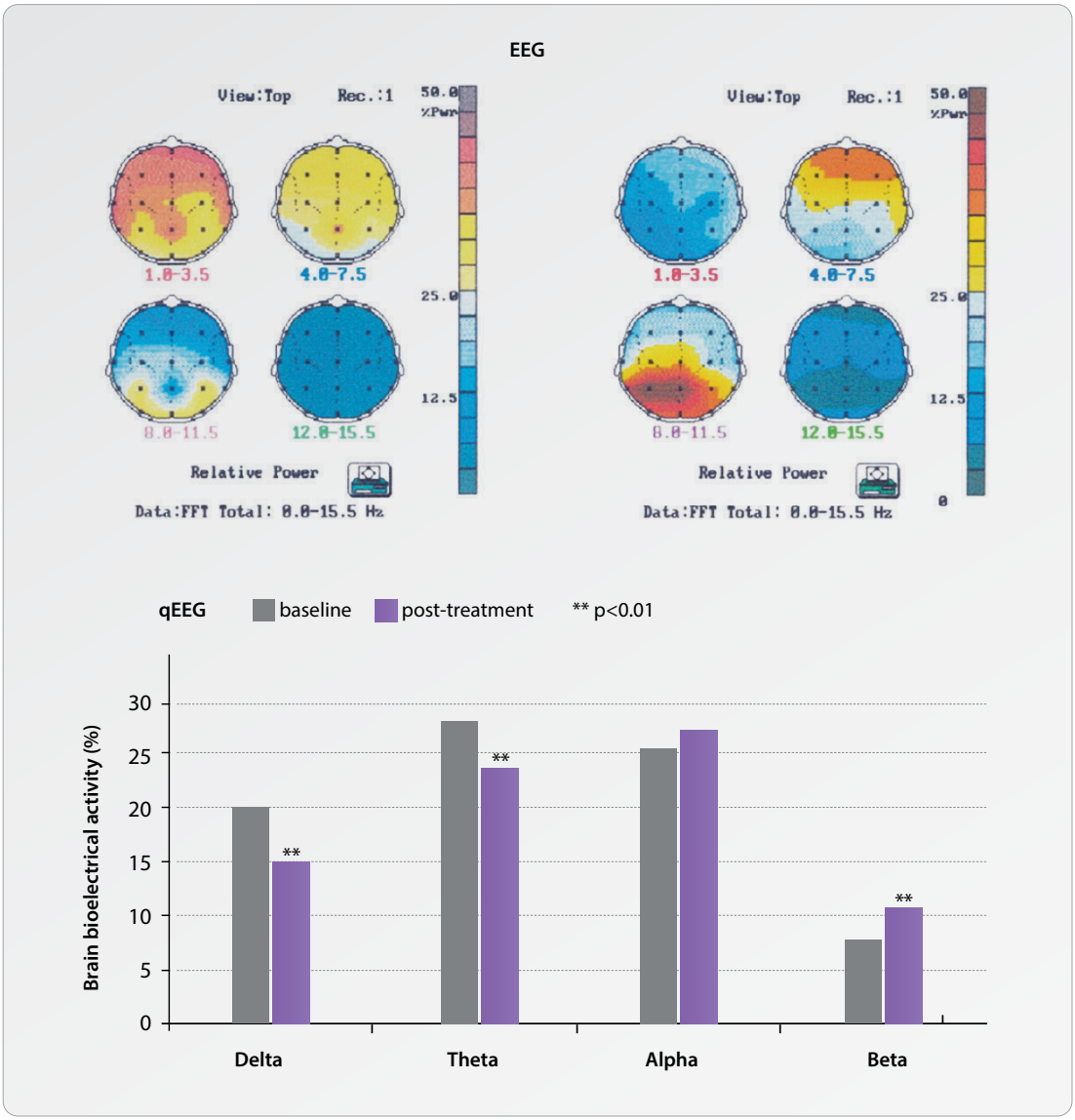


Figure 45 – *Topographic brain maps obtained from a traumatic brain injury patient at baseline (left) and after treatment with Cerebrolysin (right). A decrease in slow (delta and theta) activity and an increase in fast (alpha and beta) frequencies can be observed.*[49]

These positive qEEG data correlate well with the results of the Syndrome Short Test demonstrating significant improvements in several subtests in the Cerebrolysin group compared to the placebo group.[49]

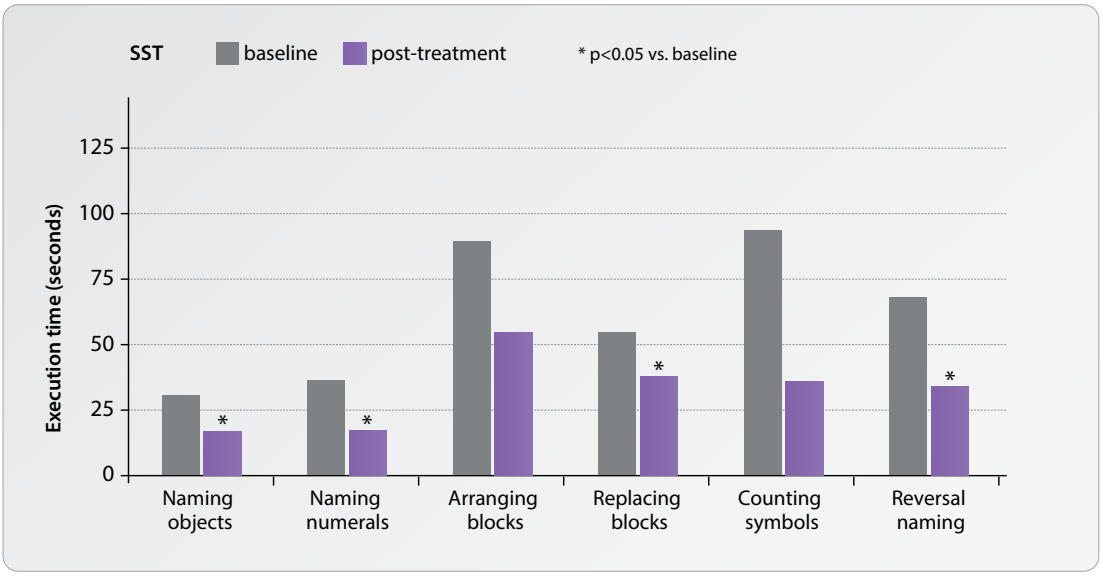


Figure 46 – *Improvement of execution time (in seconds).*[49]

80% of all TBI cases are categorized as mild.[50] However, up to 50% of mild TBI patients suffer from cognitive deterioration.[51] The purpose of the study by **Chen et al. 2013**[52] was to investigate how Cerebrolysin therapy affects cognitive performance of patients suffering from mild TBI.

The primary outcome measures were differences in cognitive function assessed with the Cognitive Abilities Screening Instrument (CASI) and Mini-Mental State Examination (MMSE). In the Cerebrolysin group the **CASI** score difference between baseline and week 12 was significantly higher than that of the placebo group (p=0.046).

The **MMSE** scores reflected those of the CASI.

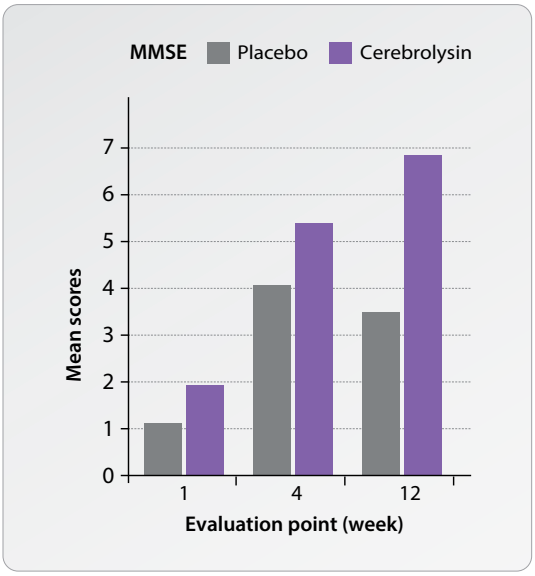


Figure 47 – *Improvement in MMSE.*[52]

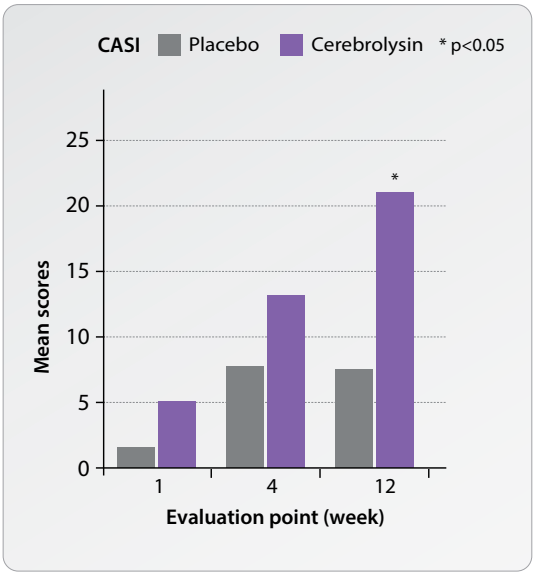


Figure 48 – *Improvement in CASI.*[52]

In **moderate to severe head injury Alvarez et al. 2008**[53] found beneficial effects on cognition after Cerebrolysin therapy.

TBI patients improved their cognitive performance in attention- and memory-related tasks like replacing blocks and reversal naming. These findings indicate a progressive recovery of attention and working memory, which might contribute to enhanced execution and processing speed, the most affected functions in TBI patients.[54]

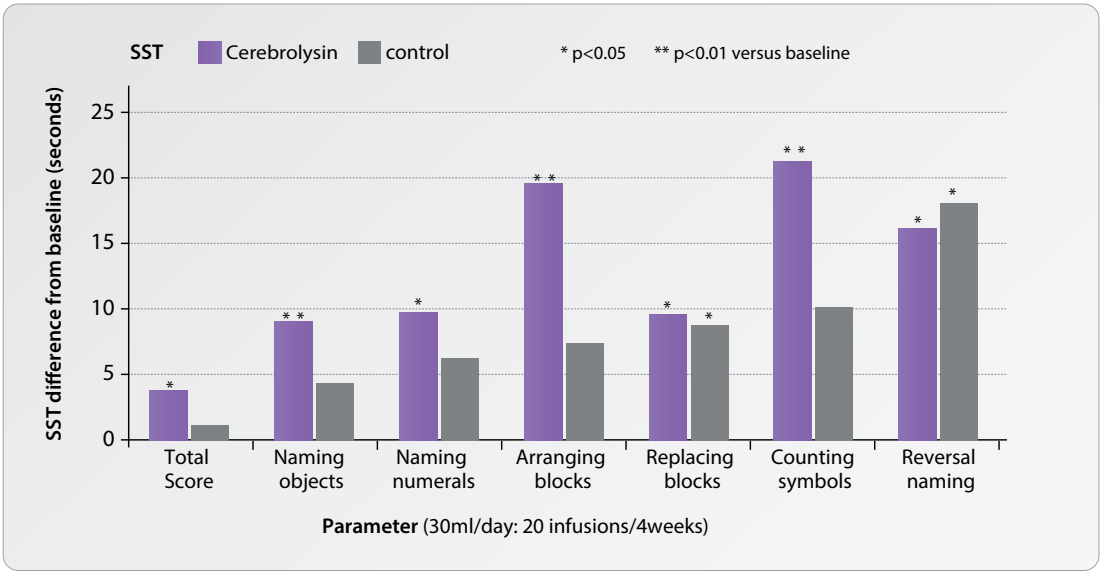


Figure 49 – *Improvement of rehabilitation potential measured by the SST.*[53]

The most common neurocognitive consequences of TBI at all levels of severity are disturbances of memory, attention, and executive functioning.[55] The **CAPTAIN 2 study** (Muresanu et al., 2020)[42] investigated exactly these important domains with the following assessment tools:

- Digit span backward test
- Processing speed index and
- Stroop word/dots test.

The study showed large-sized, significant improvements in these three assessments. The digit span backward test showed large treatment effects already on day 30.

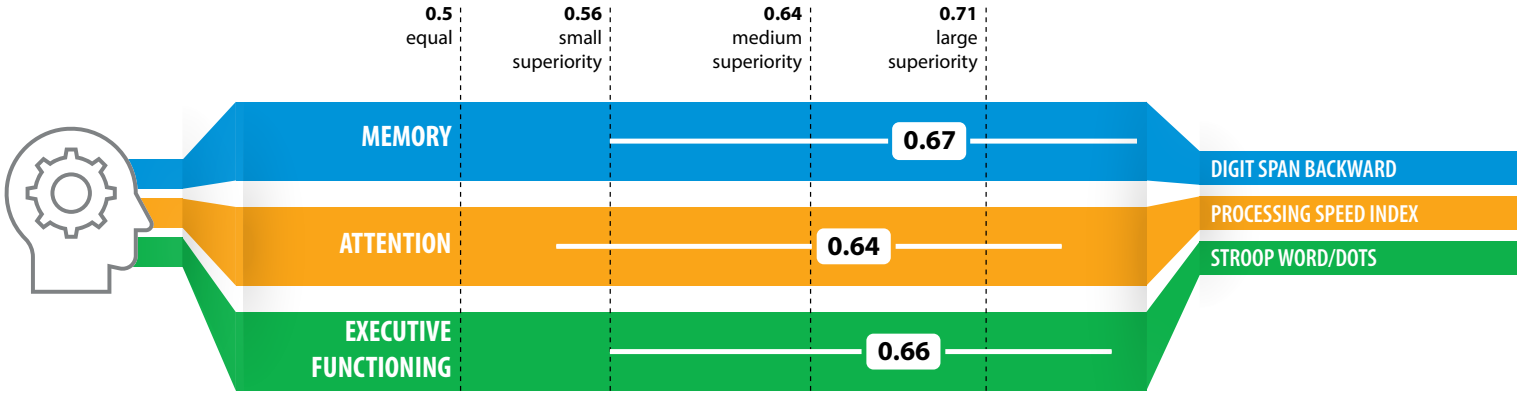


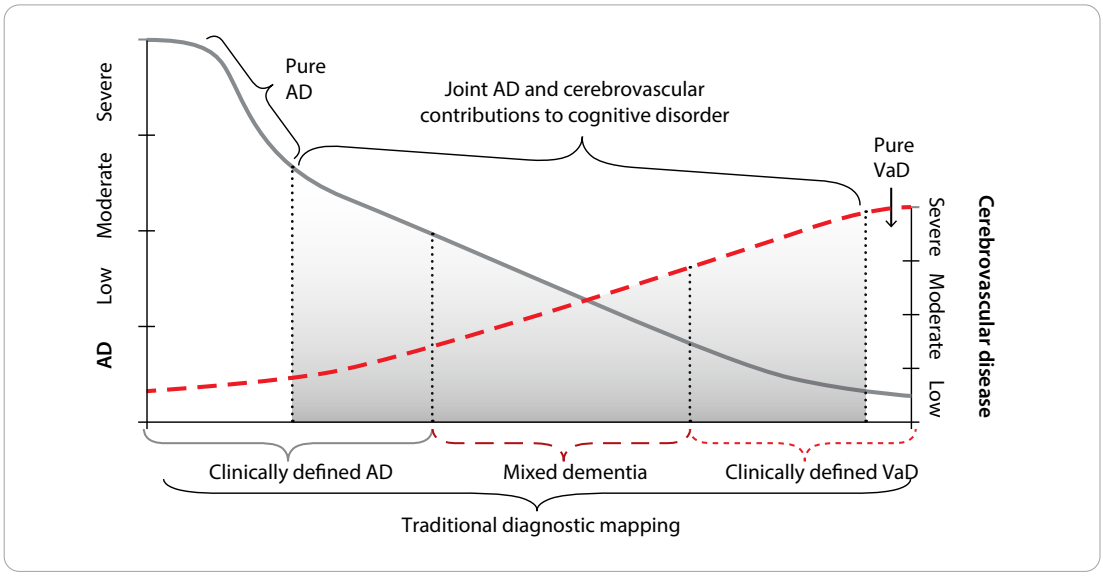
Figure 50 – *Single cognitive outcomes, MW, Day 90, PP.*[42]
Large inferiority = 0.29; Medium inferiority = 0.36, Small inferiority = 0.44;
Equality = 0.50; Small superiority = 0.56; Medium superiority = 0.64; Large superiority = 0.71

Cerebrolysin supports cognitive improvement in patients with mild, moderate or severe TBI in the acute, subacute and post-acute phase!

5 COGNITIVE IMPAIRMENT INCLUDING DEMENTIA

Dementia is the loss of cognitive performance to such an extent that it interferes with a person's daily life and activities. Dementia ranges from the mildest stage, when it is just beginning to affect a person's orientation, to the most severe stage, when a person completely depends on others for basic activities of daily living.

Among various types of dementia, the most common forms are **Alzheimer's disease (AD)** and **vascular dementia (VaD)**, while both types often coexist (form of **mixed dementia**). Consequently, a treatment found effective in AD might also be useful in vascular dementia (and vice versa).



In the treatment of dementia, early and accurate diagnosis is one of the key issues. Often, the early signs of dementia only become apparent when looking back in time. The tendency of physicians to dismiss memory complaints as normal aging should be replaced by an enhanced awareness of mild cognitive impairment.

Mild cognitive impairment (MCI) is the earliest stage of dementia. The difficulty of diagnosis is that this group scores between 27 and 30 on the Mini-Mental State Examination (MMSE), which is a normal score. They may have some difficulties with memory and trouble finding words, but they solve everyday problems and handle their own life affairs well.

However, 70%[56] of those diagnosed with MCI progress to develop dementia at some point. Experts recommend that a person diagnosed with MCI to be re-evaluated every six months to determine if symptoms are staying the same, improving or growing worse.

Cerebrolysin should be already part of the therapy in the beginning of MCI. The impact of Cerebrolysin on the transition rate from mild cognitive impairment (MCI) to Alzheimer's dementia was assessed in studies with a duration of up to three years (**Gavrilova et al. 2008**[57]**; 2010**[58]). At study endpoint, clinical manifestation of Alzheimer's disease was reported in 3 – 4% of patients treated with Cerebrolysin every six months; the transition rate in control patients was 13 – 14%. Both trials indicated beneficial effects of Cerebrolysin on slowing cognitive decline and thus delaying the time point for the clinical diagnosis of dementia of Alzheimer's type.

5.1 ALZHEIMER'S DISEASE

Alzheimers's disease (AD) is the most common cause of dementia among people aged 65 and older.[59]

AD is characterised by extracellular plaques containing misfolded amyloid beta peptides (Aß), formed in the brain many years before clinical signs are observed. Intracellular neurofibrillary tangles together with these plaques form the pathological hallmarks of the disease. However, why and how the disease develops is under intense investigation and no satisfying answers have been found until now.

Disease progression is characterised by deterioration in cognition (thinking, reasoning) and functional abilities (activities of daily living) and a disturbance in behavior and mood at a later stage. Changes in one or more of these domains and their effects on the person provide the basis for diagnosis and they are used to assess the severity and progression of the condition.[60]

MMSE scores, for example, categorize the severity of cognitive impairment as follows:[60]

no Alzheimer's disease	MMSE 27 – 30
mild Alzheimer's disease	MMSE 21 – 26
moderate Alzheimer's disease	MMSE 15 – 20
moderately severe Alzheimer's disease	MMSE 10 – 14
severe Alzheimer's disease	MMSE less than 10

5.1.1 TREATMENT

In spite of enormous efforts in academic and industrial research, there has still been no major breakthrough in therapies for neurodegenerative diseases, in particular Alzheimer's disease.

All pharmacological attempts to treat dementia aim to preserve and improve cognitive function and to delay progression to the later stages of the disease. Appropriate management of the disease by currently available drugs aim to stabilize the condition for a certain period, to improve cognition, to reduce behavioral disturbances and thus to delay the need for institutionalization.

The following agents are associated with similar degrees of short-term improvement (six to 12 months) in cognition and global functioning. The benefit to AD is a symptomatic improvement rather than a disease delaying or preventing effect.

- **Cholinesterase inhibitors** are indicated for the treatment of mild to moderate Alzheimer's disease. However, these drugs often induce considerable side effects including typical peripheral cholinergic and gastrointestinal side effects, such as nausea, vomiting, diarrhoea, loss of weight, headache, vertigo and muscle seizures.
- **Memantine** is indicated for mild, moderate and severe dementia inhibiting the excessive stimulation of NMDA receptors. Controlled clinical trials in dementia have shown improvements of cognitive disturbances, drive, motivation and enhancement of motor functions in mild to severe dementia.
- **Nootropic drugs**, such as piracetam, antioxidants in general, anti-inflammatory drugs and oestrogens are all widely used in the treatment of dementia but the evidence to support their use is unclear.

5.1.2 CEREBROLYSIN IN ALZHEIMER'S DISEASE

An alternative treatment approach in Alzheimer's disease is the use of multimodal drugs that mimic the action of endogenous neurotrophic factors, like Cerebrolysin. A sustained neurotrophic regulation is essential for counteracting neurodegenerative processes and endogenous repair processes.

The effects of Cerebrolysin in AD seem to go beyond a pure symptomatic effect and suggest a disease-modifying effect by slowing down the progression of the disease.

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Alzheimer's disease	10 – 30 ml	as soon as possible	1 cycle = 5 days weekly / 4 weeks 2 – 4 cycles / year

5.1.3 CLINICAL EFFICACY OF CEREBROLYSIN

To date, more than 3000 patients have been included in clinical trials evaluating the efficacy of Cerebrolysin® in dementia. RCTs in Alzheimer's disease are listed below.

Publication	Daily dosage Cerebrolysin	Treatment Duration	Efficacy parameters	Benefits
Meta-analysis				
Gauthier et al. 2015	20-40 ml	various	cognitive function, global clinical change, global benefit	Improvement of cognitive performance Higher quality of life
Prospective, randomized, double-blind, placebo controlled trials				
Bae et al. 2000	30 ml	cycle = 5 days/4 weeks 1 cycle	ADAS-cog	Improvement of cognitive performance
Xiao et al. 2000	30 ml	cycle = 5 days/4 weeks 1 cycle	MMSE, Trail making test	Improvement of cognitive performance
Ruether et al. 2001	30 ml	cycle = 5 days/4 weeks 2 cycles	ADAS-cog, NAI, ADAS-noncog	Improvement of cognitive performance Prolong active and independent life Prevention of behavioral disorders
Ruether et al. 2002	30 ml	cycle = 5 days/4 weeks 2 cycles	ADAS-cog	Improvement of cognitive performance
Panisset et al. 2002	30 ml	cycle = 5 days/4 weeks 1 cycle	CIBIC+, DAD	Higher quality of life Prolong active and independent life
Alvarez et al. 2006	10/30/60 ml	1. cycle = 5 days/4 weeks 2. cycle = 2days/8 weeks	ADAS-cog+, DAD, NPI	Improvement of cognitive performance Prolong active and independent life Prevention of behavioral disorders
Alvarez et al. 2011	10/30/60 ml	1. cycle = 5 days/4 weeks 2. cycle = 2days/8 weeks	ADAS-cog+	Improvement of cognitive performance
Prospective, open-label trials				
Alvarez et al. 2011	10 ml	cycle = 5 days/4 weeks 2 cycles	ADAS-cog+, CIBIC+	Improvement of cognitive performance

Key clinical benefits of Cerebrolysin in Alzheimer's disease are:

- Improvement of cognitive performance
- Higher quality of life
- Prolong active and independent life
- Prevention of behavioral disorders

5.1.3.1 IMPROVEMENT OF COGNITIVE PERFORMANCE

The cognitive domain is of key importance in patients suffering from AD. The most noticeable deficit is memory loss, which manifests itself in the form of difficulty in remembering recently acquired facts and the inability to acquire new information. Problems with executive functions such as attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory (memory of meanings and concept relationships) are gradually aggravated as the disease progresses. Apathy remains the most persistent neuropsychiatric symptom throughout the course of the disease.

ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) is the standard cognitive testing instrument used in clinical trials. It consists of 11 tasks measuring the disturbances of memory, language, attention and other cognitive abilities. Also the MMSE (Mini-Mental State Examination) is used for assessment of cognitive performance in AD patients.

Both double-blind, placebo-controlled multicenter AD trials performed by **Bae et al. 2000**[61] and **Xiao et al. 2000**[62] reported significant cognitive improvements in patients treated with Cerebrolysin over 4 weeks.

Bae et al. 2000[61] showed in ADAS-cog that patients receiving Cerebrolysin had a mean change from baseline of –3.23 points (±4.75 SD) compared to –0.36 points (±3.59 SD) in the placebo group. A significant cognitive improvement was also seen in the MMSE, with a drug–placebo difference of 1.57 points (p=0.04).

In the trial of **Xiao et al. 2000**[62] patients treated with Cerebrolysin improved by 2.5 points on the MMSE compared to 1.4 points of improvement in the placebo group (p=0.043). The secondary outcome parameter, the Trail-Making Test, confirmed the beneficial effects of Cerebrolysin treatment (p=0.023).

The studies performed by **Ruether** analysed long-term cognitive effects of Cerebrolysin.

Ruether et al. 2001[63] showed cognitive improvements in mild to moderate AD patients in the ADAS-cog. Treatment effects were significant at week 16 and 28, three months after completion of therapy indicating disease modifying and stabilizing effects of Cerebrolysin.

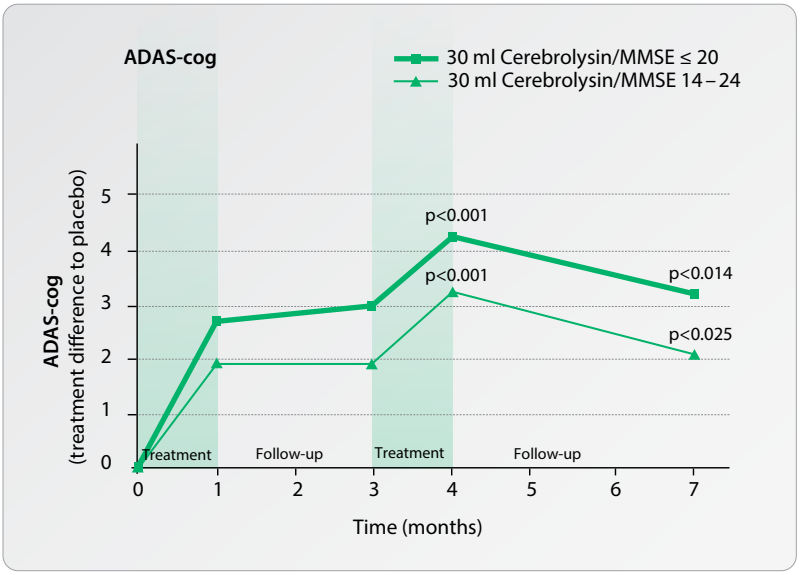


Figure 51 – *Long term positive outcome indicating disease modifying and stabilizing effects of the treatment.* [56]

Results were even more pronounced in the moderate to severe subgroup MMSE<20 (**Ruether et al. 2002**)[64]. After completion of therapy, patients treated with Cerebrolysin had improved from baseline by 3.0 points, while placebo patients worsened by 1.1 points, resulting in a treatment difference of 4.1 points (p=0.001).

Responder rates at week 16 were 55% in the Cerebrolysin group compared to 16.3% in the placebo group (p=0.001). These results were largely maintained until the follow-up examination at week 28.

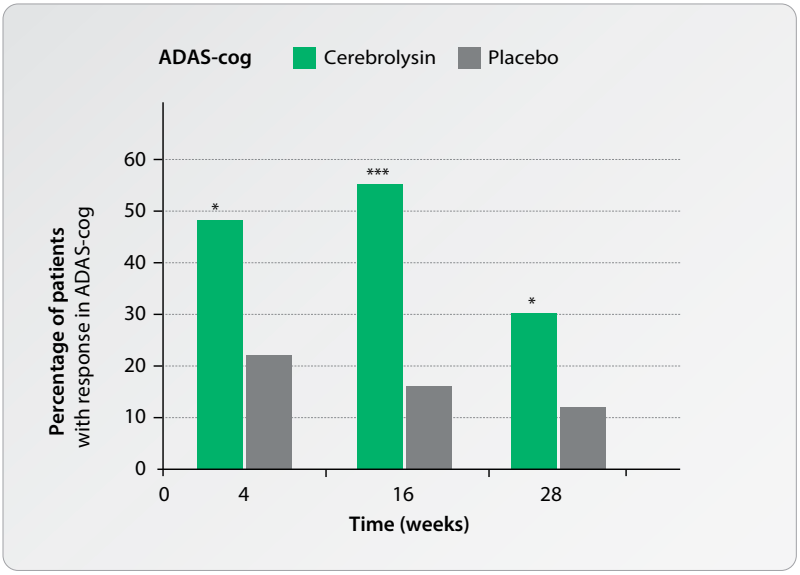


Figure 52 – *Responder analysis, percentage of patients with treatment response in ADAS-cog.* [57]

Alvarez reported similar benefical ADAS-cog-results of Cerebrolysin in **mild-moderate** AD patients (**Alvarez et al. 2006**[66]) and in moderate-moderately severe AD patients (**Alvarez et al. 2011**[68]).

Furthermore, daily dosages of 10 ml to 30 ml Cerebrolysin turned out to be most effective in the cognitive and global domain.

Another very interesting aspect was shown by **Alvarez** in a trial published in **2011**[68] which was designed to compare the safety and efficacy of Cerebrolysin versus donepezil versus a combination therapy of both agents in probable AD patients. Donepezil is a cholinesterase inhibitor (ChEI) and considered as gold standard treatment in AD.

The trial showed similar efficacy for Cerebrolysin-10 ml and donepezil-10 mg but potential longterm benefits of the **combination treatment** with both drugs in patients with mild to moderate AD.

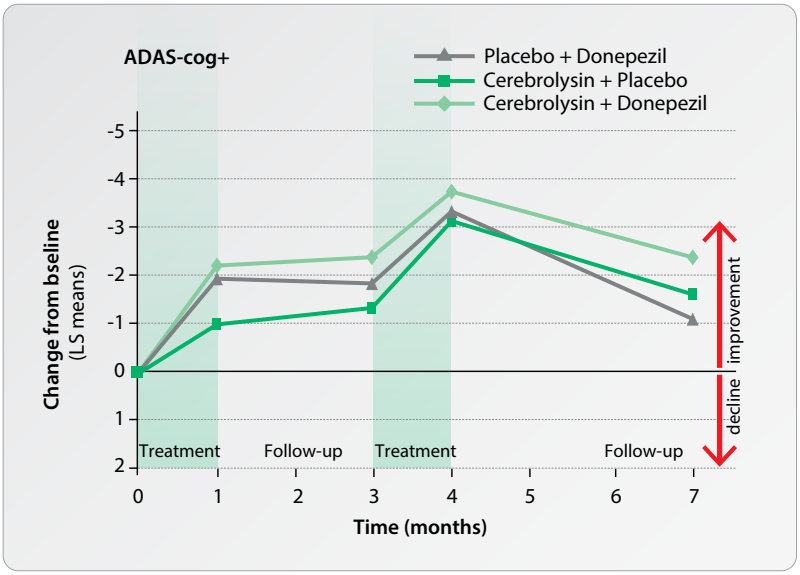


Figure 53 – *Improvement of ADAS-cog+.*[68]

A **meta-analysis**, considered as the highest level of evidence, by **Gauthier et al. 2015**[65] provides a systematic and quantitative summary of benefit and risk of Cerebrolysin in patients with mild-to-moderate Alzheimer's disease.

This meta-analysis was based on six RCTs with a follow-up period of six months showing superiority of Cerebrolysin over placebo with a statistically significant difference as early as four weeks after treatment initiation.

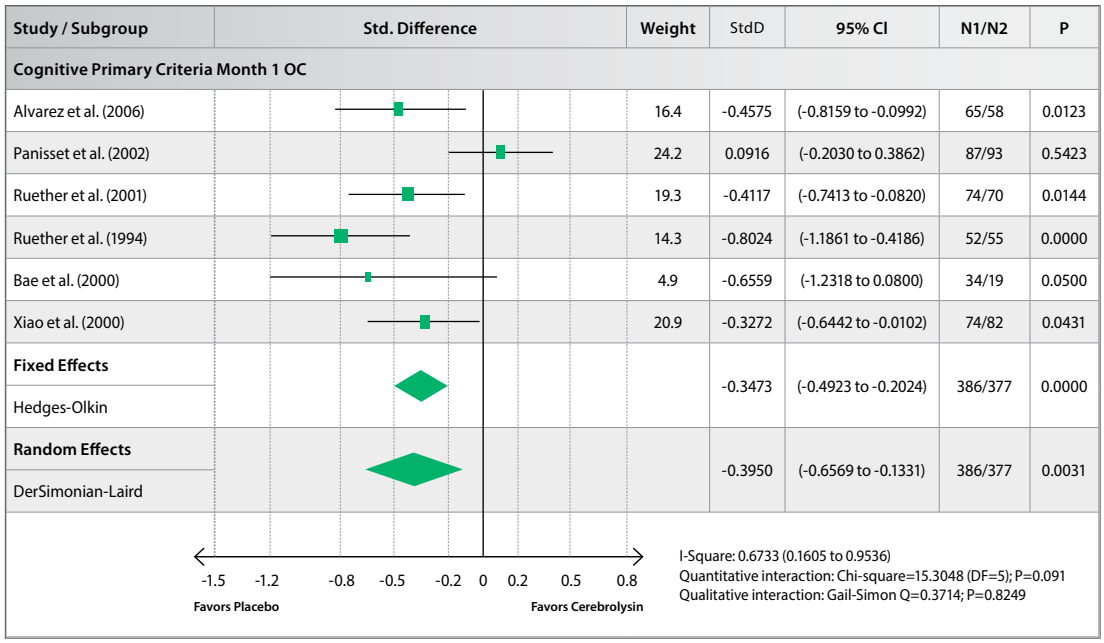


Figure 54 – *Comparison of Cerebrolysin (30 ml/day) vs. placebo at month 1; changes from baseline; effect size: standardized mean difference (SMD); OC .*[65]

Cerebrolysin significantly improves cognitive performance of patients with Alzheimer's disease and is a safe option for a combined therapy with ChEI!

5.1.3.2 HIGHER QUALITY OF LIFE

Evaluation of global functions helps to determine the general performance of AD patients.

CIBIC+ (Clinicians Interview-based Impression of Change with Caregiver Input scale) assess the global function of AD patients and their clinical changes during treatment.

In a study performed by **Panisset et al. 2002**[70] the global clinical data were analyzed by using the CIBIC+. At week 12, CIBIC+ scores showed a significant drug–placebo difference (p=0.033) favoring Cerebrolysin. The responder analysis at week 12 showed that 76% of patients treated with Cerebrolysin improved (CIBIC+ score <5) or did not deteriorate, versus 57% of patients treated with placebo (p=0.007). In the Cerebrolysin group, global improvement was maintained for 2 months after the end of therapy, whereas patients treated with placebo started to deteriorate immediately thereafter.

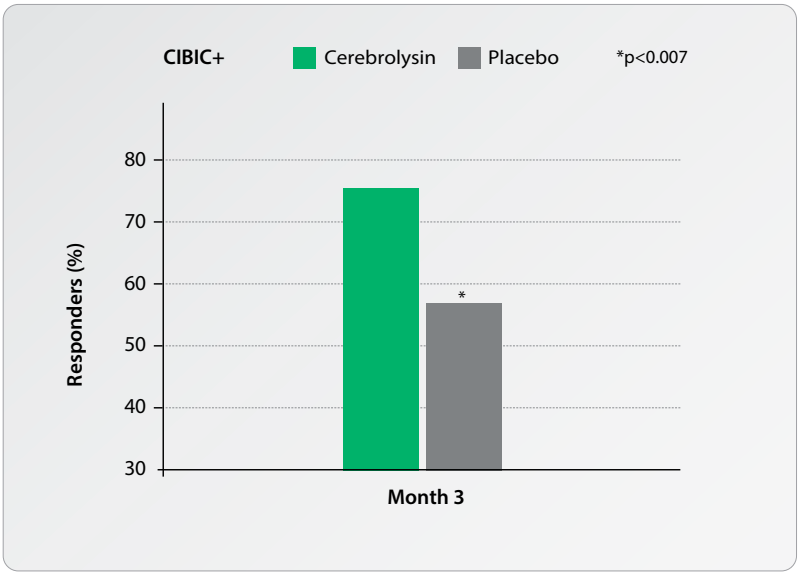


Figure 55 – *Responder analysis of patient treated with Cerebrolysin or placebo at month 3.*[70]

The effects of Cerebrolysin shown in these trials prompted **Alvarez et al. 2011**[68] to test the combination therapy with standard AD treatment (ChEI – donepezil) looking for potential synergistic therapeutic effects.

Pairwise comparison showed significant superiority (p<0.05) of Cerebrolysin over donepezil in the CIBIC+ analysis with responder rates of 64.1% in the Cerebrolysin group, 62.7% in the combination group and 37.8% in the donepezil group. Patients treated with Cerebrolysin (mono- or combined-therapy) performed better at all study visits compared to donepezil.

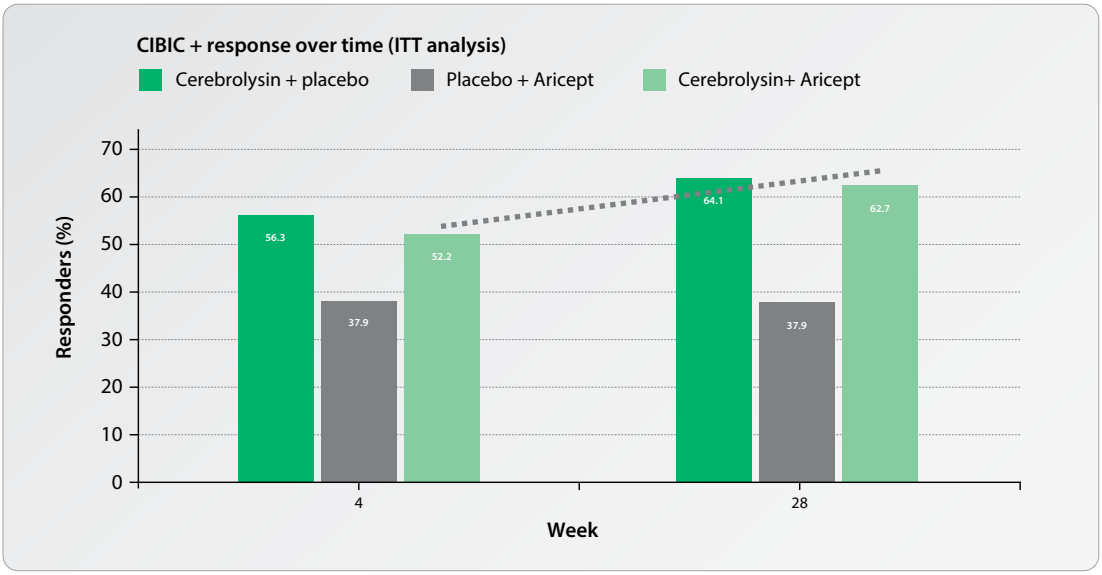


Figure 56 – *Responder analysis of CIBIC+ of patient (<4 CIBIC+) treated with Cerebrolysin, Donepezil, Cerebrolysin+Donepezil.*[68]

Moreover, patients in the combination group, who responded in both the ADAScog+ and CIBIC+ test showed a sustained response rate three months after completion of Cerebrolysin therapy. This is a highly desirable outcome, as postponing the patients' deterioration is one of the major goals in the treatment of dementia.

In the meta-analysis in mild-to-moderate AD patients **Gauthier et al. 2015**[65] confirmed the beneficial effects of Cerebrolysin on a Global-clinical-change.

After four weeks the chance of global clinical improvement was three times higher in the Cerebrolysin group than in the placebo group, at six-months follow-up the probability was **five times higher**.

Study / Subgroup	Std. Difference	Weight	OR	95% CI	N1/N2	P
CIBIC+ CGI Improvements Month 6 OC						
Alvarez et al. (2006)		27.5	5.7830	(2.5290 to 13.3820)	61/54	0.0000
Panisset et al. (2002)		29.7	1.1170	(0.5040 to 2.5020)	88/85	0.7868
Ruether et al. (2001)		36.1	2.3780	(1.1590 to 4.9550)	70/66	0.0194
Ruether et al. (1994)		6.7	84.3330	(21.3300 to 616.8670)	49/52	0.0000
Fixed Effects Hedges-Olkin			3.0840	(1.9931 to 4.7720)	268/257	0.0000
Random Effects DerSimonian-Laird			4.9771	(1.3664 to 18.1287)	268/257	0.0150

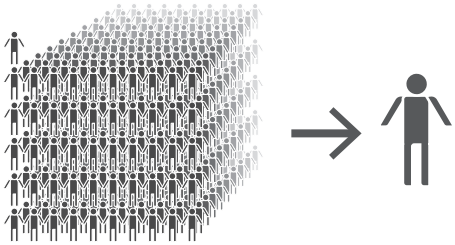
Figure 57 – *Comparison of Cerebrolysin (30 ml/day) vs. placebo at month 6; effect size: odds ratio (OR); OC.*[65]

Furthermore, there was a positive benefit-risk ratio in favour of Cerebrolysin with respect to the 6 months data:

- NNT (number needed to treat) for benefit = 2.9
- NNT (number needed to treat) for harm = 501

BENEFIT (number needed to treat for benefit): **2.9**

RISK (number needed to treat for harm): **501**



These results give a comparable or better picture to oral standard therapy and provide better safety results!

5.1.3.3 PROLONG ACTIVE AND INDEPENDENT LIFE

Activities of daily living (ADL) such as any self-care duties (e.g. feeding, bathing, dressing, grooming), are an important measure for patients independence effected by dementia.

Already mentioned German investigators (Ruether) that primarily assessed efficacy of Cerebrolysin in the cognitive domain, analysed in the secondary outcome measures the NAI (Nuremberg Age Inventory) assessing activities of daily living of the patient.

Results in **Ruether et al. 2001**[63] showed a positive trend in the activities of daily living (NAI). The number of patients experiencing benefits from Cerebrolysin remained constant throughout the active treatment period and during the three-month follow-up phase.

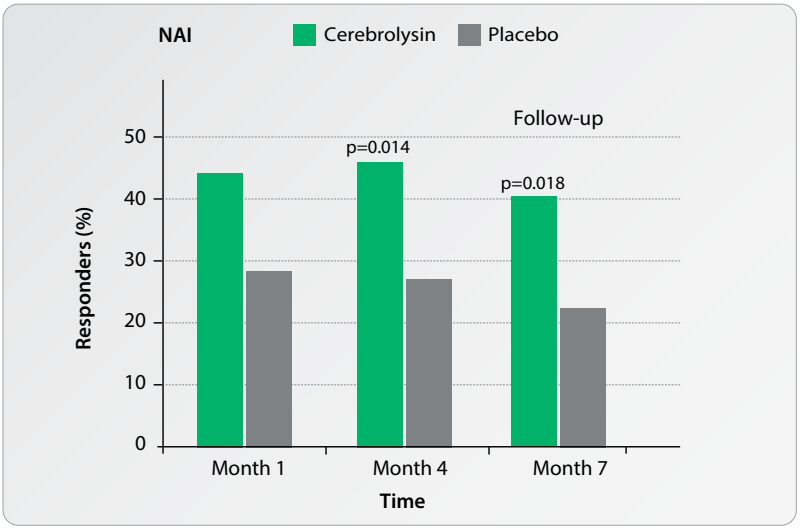


Figure 58 – *Responder analysis of NAI treated with Cerebrolysin or placebo.*[63]

In the Canadian study conducted by **Panisset et al. 2002**[70] improved performance in the section ADL was observed, as measured with the Disability Assessment in Dementia (DAD) scale.

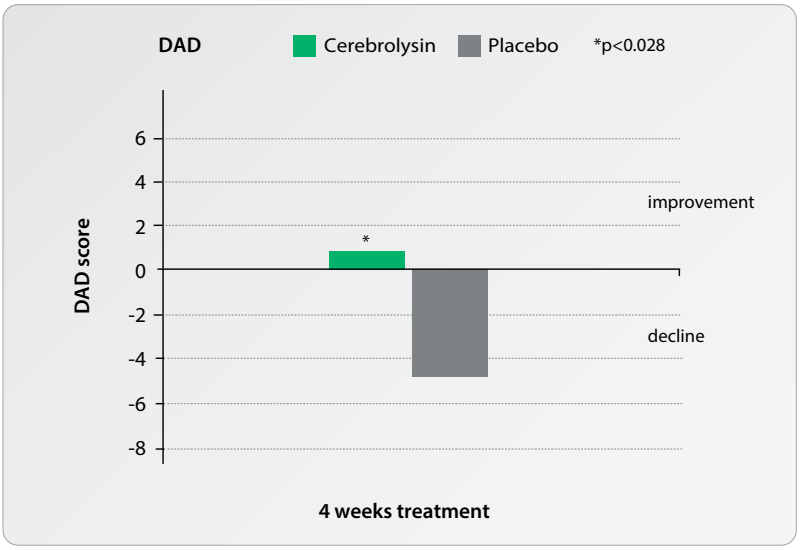


Figure 59 – *Improvement/Decline of DAD score in Cerebrolysin and placebo group at month 3.*[70]

Furthermore, a trend towards improvement was also seen in the Cornell Depression Scale.

When **Alvarez et al. 2006**[66] assessed different doses of Cerebrolysin best results were seen in the DAD with a daily dose of **30 ml** Cerebrolysin. This demonstrates that a dose of 30 ml Cerebrolysin exerts a beneficial effect on patients capabilities to cope with ADL and confirms findings in cognitive and global clinical domains.

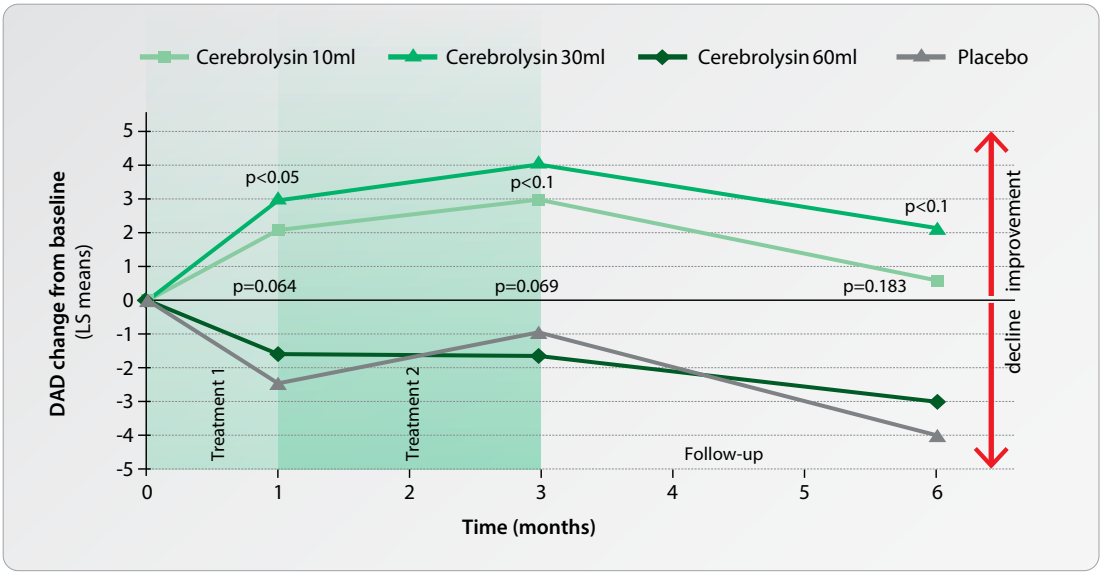


Figure 60 – *Improvement/Decline of DAD in patients treated with different doses of Cerebrolysin or placebo.*[58]

Cerebrolysin offers a long-term stabilizing effect, lasting up to four months after active treatment!

5.1.3.4 PREVENTION OF BEHAVIORAL DISORDERS

Patients with Alzheimer's disease develop behavioral problems in the later stages of the disease, which place a very large burden on their families and caregivers. Often, these disturbances force caregivers to seek help in specialized permanent care institutions. Therefore, it is important to evaluate the therapy from the standpoint of ameliorating these symptoms for the benefit of patients, but also looking at a reduction of treatment costs.

The ADAS-noncog (Alzheimer's Disease Assessment Scale – Non-Cognitive Section) is measuring behavior in patients with AD.

Ruether et al. 2002[64] showed significant improvements of behavior in AD patients treated with Cerebrolysin.

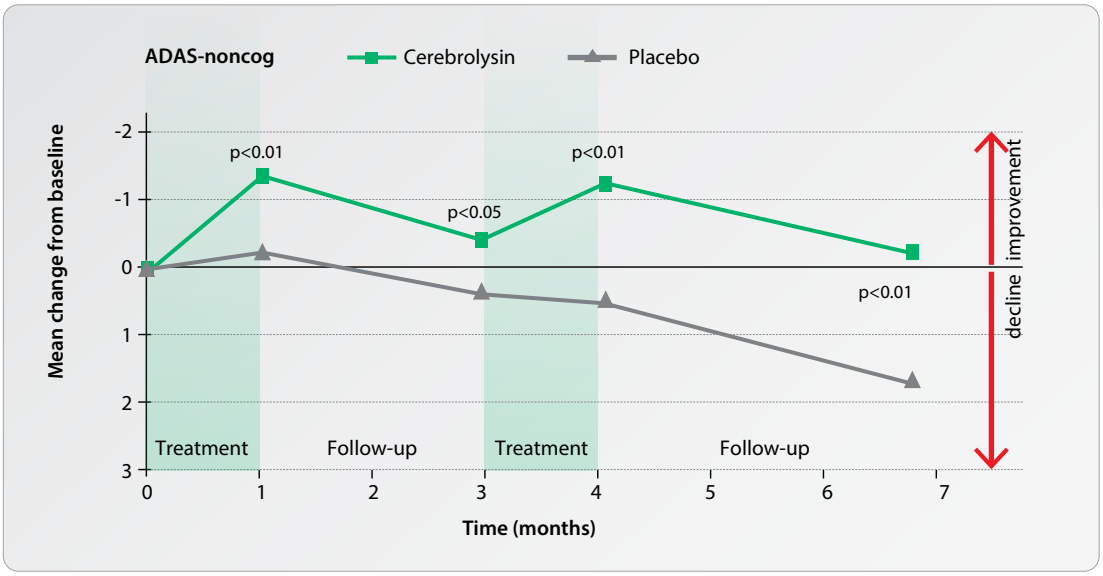


Figure 61 – *Improvement/Decline of ADAS-noncog in patients treated Cerebrolysin or placebo.*[64]

However, the optimal dosage for treatment of behavioral disturbances appears to be higher, especially when treating more severe cases. In a dose-finding study (**Alvarez et al. 2006**[66]), a daily 60 ml dosage was most effective in patients with more advanced behavioral symptoms. Higher drug dosages did not compromise the excellent safety profile of Cerebrolysin.

Cerebrolysin treatment improved behavioral problems, which may facilitate home care of AD patients!

5.2 VASCULAR DEMENTIA

Vascular dementia is a common disorder among the elderly patients, but can also occur in younger people. Incidence data vary considerably: it is the second most common form of dementia after Alzheimer's disease in the western world while it is deemed the most common cause of dementia in other countries. The differences may be due in part to different diagnostic criteria.[67]

Vascular dementia, also known as vascular cognitive impairment (VCI), is caused by problems in the supply of blood to the brain, typically a series of micro strokes, leading to cognitive decline that occurs stepwise.

The incidence of vascular dementia is nine times higher in patients who have had a stroke compared to healthy controls. 25% of stroke patients develop new-onset dementia within one year after stroke.[68]

5.2.1 TREATMENT OF VASCULAR DEMENTIA

Currently, there are no medications that have been approved specifically for prevention or treatment of vascular dementia. The use of medications for treatment of Alzheimer's disease, such as cholinesterase inhibitors and memantine, have shown small improvements of cognition in vascular dementia. This is most likely due to the drugs' actions on a co-existing AD-related pathology.[65]

5.2.2 CEREBROLYSIN IN VASCULAR DEMENTIA

Neurotrophic treatment targets the underlying pathology in a multimodal way. The neuroregenerative potential of Cerebrolysin creates a unique opportunity to stimulate processes of plasticity that can contribute to compensatory mechanisms responsible for maintaining cognitive functions. Attenuation of pathology-related apoptotic processes exerted by Cerebrolysin may also contribute to neuroprotection and preservation of endangered neurons in the affected brain region.

For the treatment of vascular dementia one therapy course corresponds to a therapy duration of 4 weeks (5 applications/week). The effectiveness of therapy can be increased by repeated courses after treatment-free periods of 2 – 3 months until no further benefit is observed. In the following therapy courses the frequency of application can be reduced from daily applications to 2 – 3 applications per week.

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Vascular dementia	10 – 30 ml	as soon as possible	1 cycle = 5 days weekly / 4 weeks 2 – 4 cycles / year

5.2.3 CLINICAL EFFICACY OF CEREBROLYSIN

Efficacy and safety of Cerebrolysin in vascular dementia has been assessed in randomized, double-blind, placebo-controlled trials and in one meta-analysis.

Publication	Daily dosage Cerebrolysin	Treatment Duration	Efficacy parameters	Benefits
Prospective, open-label trials				
Xiao et al. 1999	30 ml	cycle = 5 days/4 weeks 1 cycle	MMSE, Trail Making Test	Improvement of cognitive performance
Guekht et al. 2011 (Gusev)	20 ml	cycle = 5 days/4 weeks 2 cycles	ADAS-cog+, CIBIC+	Improvement of cognitive performance Higher quality of life
Muresanu et al. 2008	10/30 ml	cycle = 5 days/4 weeks 1 cycle	ADAS-cog+ and EEG	Improvement of cognitive performance
Prospective, open-label trials				
Chen et al. 2013 The Chochrane Collaboration	10-30 ml	various	cognitive function global function	Improvement of cognitive performance Higher quality of live

The data presented in the study list above confirm the efficacy of Cerebrolysin treatment in alleviating deficits typical of patients suffering from vascular dementia:

- Improvement of cognitive performance
- Higher quality of life

5.2.3.1 IMPROVEMENT OF COGNITIVE PERFORMANCE

Cognitive decline is the most prominent symptom of vascular dementia. Consistent with the clinical outcome observed in other indications, patients can benefit from significant improvement of their cognitive functions during and after active treatment periods with Cerebrolysin.

Xiao et al. 1999[71] reported the results of a randomized, double-blind, placebo-controlled, multi-center trial investigating the effects of Cerebrolysin on 147 patients suffering from mild to moderately severe VaD. Cognitive performance of patients treated with Cerebrolysin was significantly better compared to the placebo group. At week 4, patients treated with Cerebrolysin improved by 2.7 points in the MMSE compared to 1.7 points in the placebo group (p=0.028). The performance in the Trail Making Test was almost **4 times better** during the pre-treatment period.

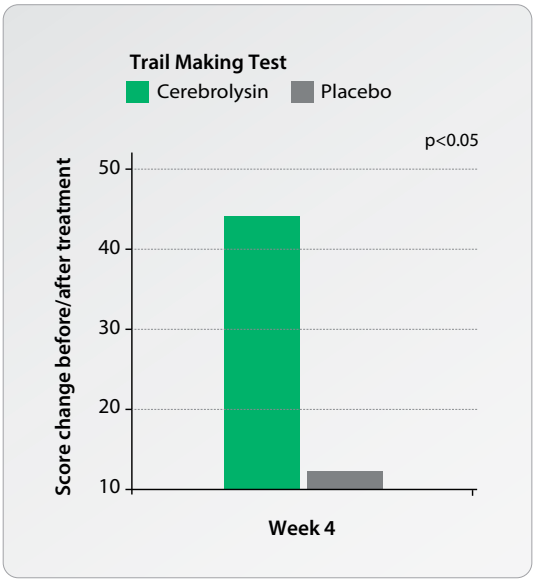


Figure 63 – *Improvement of MMSE in patients treated Cerebrolysin or placebo.*[71]

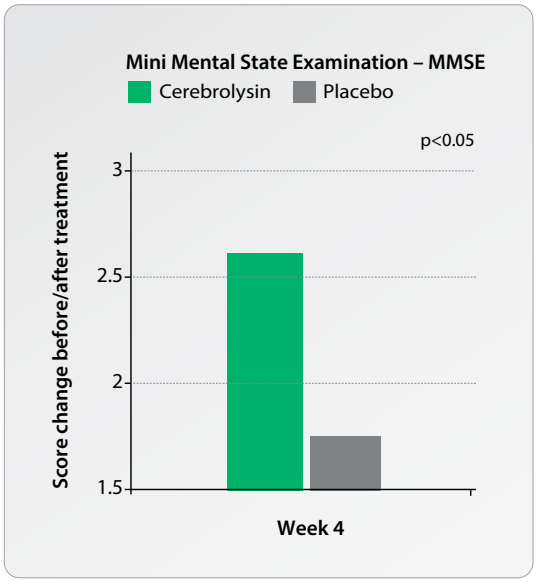


Figure 62 – *Improvement of Trail Making Test in patients treated Cerebrolysin or placebo.*[71]

The effect of Cerebrolysin on brain activity was investigated in the study of **Muresanu et al. 2010**[72], and showed a decreasing qEEG Power Ratio, indicating improved brain bioelectrical activity. A significant positive correlation between cognitive improvement (ADAS-cog) and increased brain activity was reported.

The largest clinical trial in VD to date was performed by **Guekht et al. 2011**[73]. One of the two primary study endpoints was ADAS-cog+ from baseline at week 24. Patients treated with Cerebrolysin improved by –10.62 points in the ADAS-cog+ and by -4.4 in the placebo group, resulting in a significant difference of -6.2 points at week 24 (p<0.0001) in favor of Cerebrolysin.

Results from the subgroup analysis of patients with more advanced dementia (MMSE≤20) indicated that Cerebrolysin exerts even larger treatment effects in this subgroup of patients.

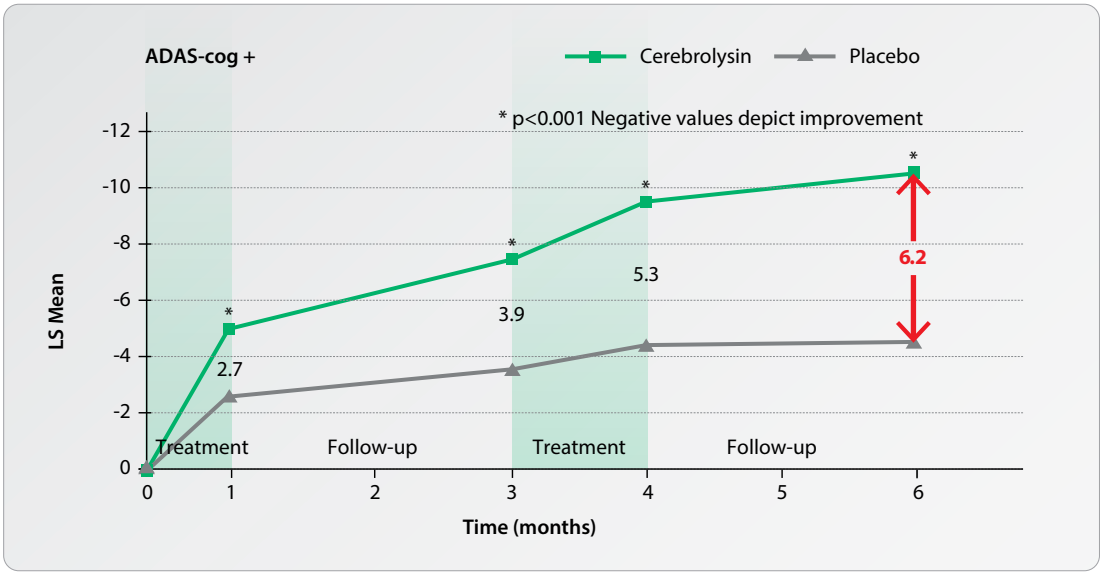


Figure 64 – *ADAS-cog+ change from baseline in patients treated Cerebrolysin or placebo.*[73]

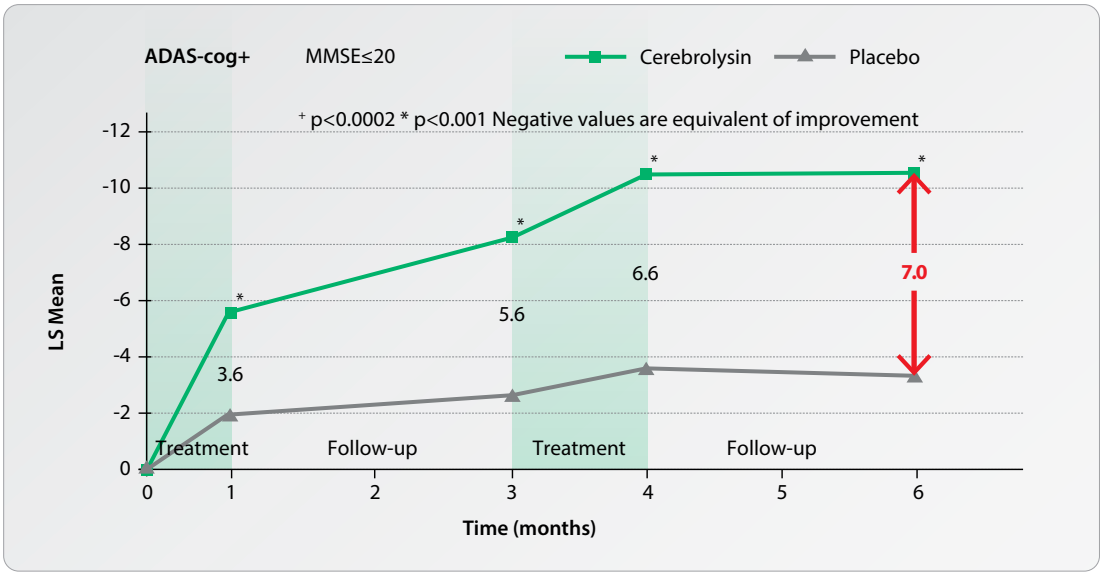


Figure 65 – *ADAS-cog+ change from baseline in patients with MMSE ≤ 20 treated Cerebrolysin or placebo.*[73]

Also in the MMSE Cerebrolysin was significantly superior over placebo at week 24.

Similar beneficial effects were shown in the Cochrane review of **Chen et al. 2013**[74]. The cognitive functions were evaluated using MMSE and ADAS-cog+. This meta-analysis showed a significant beneficial effect of Cerebrolysin in the MMSE (p=0.003) and in the ADAS-cog+ (p<0.00001).

	Cerebrolysin			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Guekht 2011	4.653	5.7	117	3.168	5.405	115	25.9%	1.48 [0.06, 2.91]	
Xiao 1999	2.68	2.61	75	1.72	2.61	72	74.1%	0.96 [0.12, 1.80]	
Total (95% CI)			192			187	100.0%	1.10 [0.37, 1.82]	

Heterogeneity: Chi2=0.38, df=1 (P=0.54); I2=0%
Test for overall effect: Z=2.96 (P=0.003)

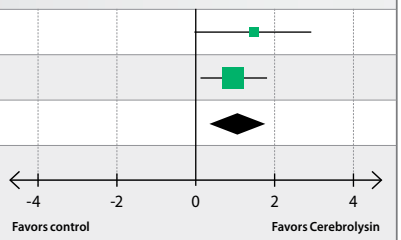


Figure 66 – *Forest plot of comparison: The change of general cognitive function measured by MMSE.*[74]

	Cerebrolysin			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Guekht 2011	-10.6	7.77	117	-4.49	8.13	115	43.7%	-6.11 [-8.16, -4.06]	
Muresanu 2008	-2.41	2.71	31	-0.03	2.47	10	56.3%	-2.38 [-4.18. -0.58]	
Total (95% CI)			148			125	100.0%	-4.01 [-5.36, -2.66]	

Heterogeneity: Chi2=7.18, df=1 (P=0.007); I2=86%
Test for overall effect: Z=5.81 (P=0.00001)

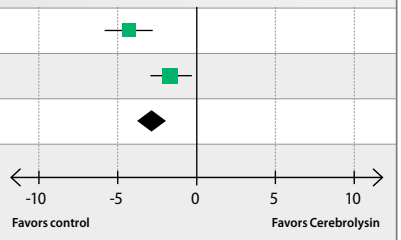


Figure 67 – *Forest plot of comparison: The change of general cognitive function measured by ADAS-cog+ score.*[74]

A responder analysis defined as a 4-point improvement from baseline in the ADAS-cog+ or at least 2-point improvement in the HDS (Hasegawa Dementia Scale) and MMSE confirmed the positive impact of Cerebrolysin treatment in the cognitive domain, yielding a significant therapeutic effect of Cerebrolysin in comparison with placebo (p<0.00001).

Cerebrolysin significantly improved cognitive functions in VaD patients!

5.2.3.2 HIGHER QUALITY OF LIFE

The impact of neurotrophic intervention on global functions is as pronounced and long-lasting as its impact on cognitive functions.

Guekht et al. 2011[73] evaluated CIBIC+ (Clinicians Interview-based Impression of Change with Caregiver Input scale), which is a comprehensive global measure of changes in cognition, function and behavior based on separate interviews with patients and caregivers. The test rates patients on a 7 point ordinal scale (4 points, no change; 5, 6, 7 points, increasing degree of deterioration; 3, 2 and 1 points, increasing degree of improvement).

The CIBIC+ assessment showed a significant shift towards improvement in the Cerebrolysin group when compared to placebo. The majority of patients in the Cerebrolysin group showed improvement (75.3%, vs 37.4% in the placebo group). In the placebo group, the majority of patients remained unchanged (45.2% vs 17.1% in the Cerebrolysin group).

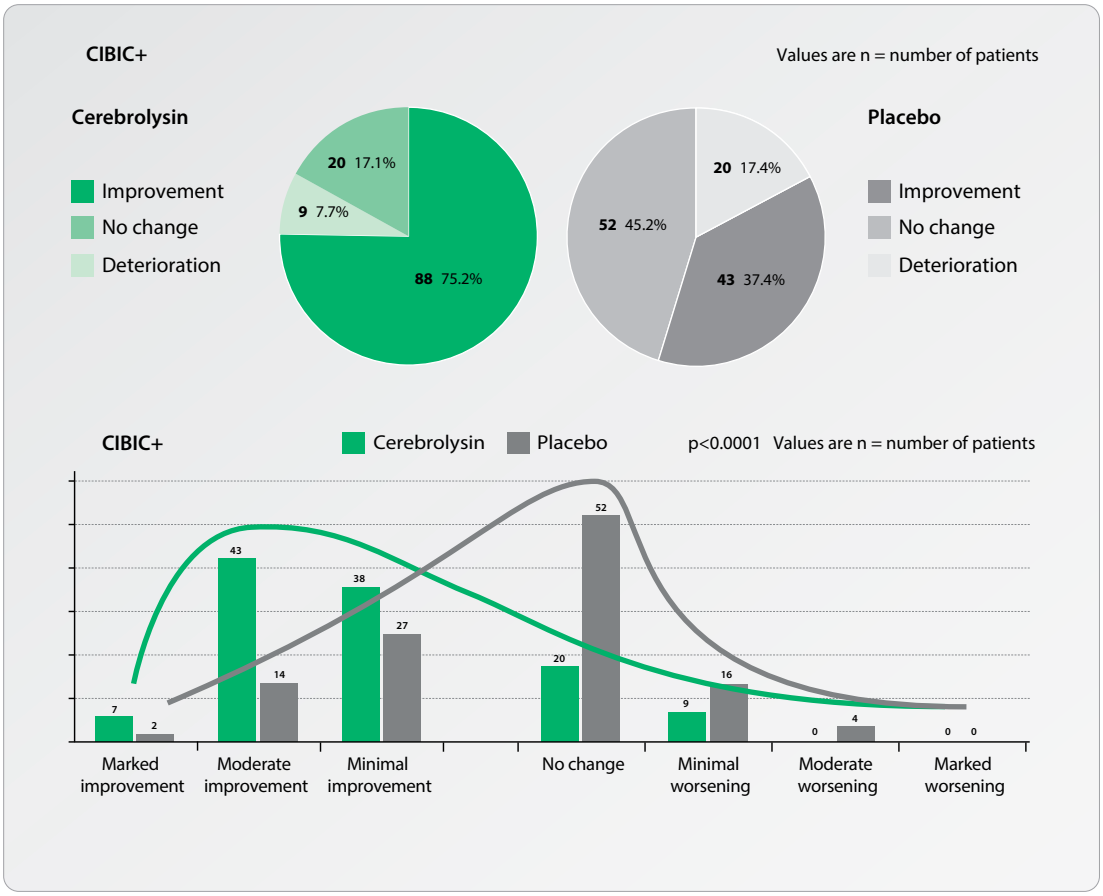


Figure 68 – *Impact of Cerebrolyin on global functions (CIBIC+) in VaD patients treated with Cerebrolysin or placebo.*[73]

In the meta-analysis of **Chen et al. 2013**[74] (N=379) similar beneficial effects on global clinical functions were observed.

	Cerebrolysin		Control			Mean Difference	Risk Ratio
Study or Subgroup	**Mean**	**Total**	**Mean**	**SD**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Guekht 2011	50	117	16	115	59.0%	3.07 [1.86, 5.07]	
Xiao 1999	25	75	11	72	41.0%	2.18 [1.16, 4.10]	
Total (95% CI)		**192**		**187**	**100.0%**	**2.71 [1.83, 4.00]**	
Total events	**75**		**27**				

Heterogeneity: Chi^2=0.38, df=1 (P=0.54); I2=0%
Test for overall effect: Z=2.96 (P=0.003)

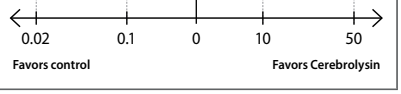


Figure 69 – *Forest plot of comparison: The change of general global functions reported as responder rate.*[74]

Cerebrolysin significantly improves global clinical outcomes up to at least 24 weeks!

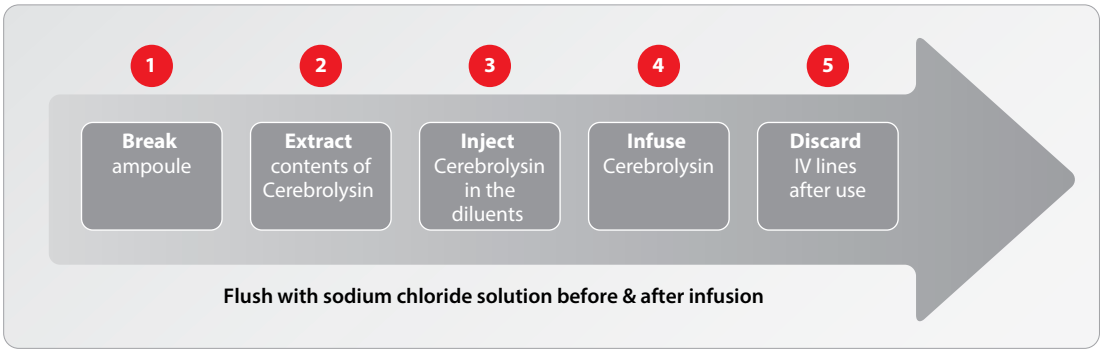
6 ADMINISTRATION

6.1 DOSAGE RECOMMENDATION

Disorder	Daily dosage	Initiation of treatment	Treatment Duration
Stroke	20 – 50 ml	as soon as possible	10 – 21 days
Traumatic Brain Injury	20 – 50 ml	as soon as possible	7 – 30 days
Alzheimer's disease	10 – 30 ml	as soon as possible	1 cycle = 5 days weekly / 4 weeks 2 – 4 cycles / year
Vascular dementia	10 – 30 ml	as soon as possible	1 cycle = 5 days weekly / 4 weeks 2 – 4 cycles / year

6.2 ROUTE OF ADMINISTRATION

Doses between **10 ml up to a maximum of 50 ml** are recommended only as a slow intravenous infusion. Dilution has to be prepared with the suggested standard infusion solutions (0.9% sodium chloride solution, Ringer solution or 5% glucose solution) in a total volume of 100 ml. Cerebrolysin should not be mixed with other drugs (vitamins, cardiovascular drugs,…). For the convenience and safety of the patient, the infusion should not be administered too fast. The duration of the infusion should be 15 minutes.



Doses of up to 5 ml can be injected **undiluted** intramuscularly (IM) and **up to 10 ml** Cerebrolysin can be injected through direct IV injection. In both cases, injection should be administered slowly over 3 minutes.

6.3 STERILITY ASPECTS

Special precautions to guarantee sterility must be taken during dilution and administration of Cerebrolysin:

- Remove solution from ampoules immediately before use
- Do not leave an open ampoule on the treatment table
- Always use only disposable one-way IV infusions sets and cannulas
- Start the infusion as quickly as possible after dilution
- Before and after infusion/injection flush with 0.9% NaCl solution
- When Cerebrolysin is administered via a long-term IV catheter, the catheter has to be rinsed before and after the application with physiological sodium chloride solution
- Pay special attention to recommended infusion/injection times on previous page

7 SAFETY

The experience with Cerebrolysin during many years of clinical application, the information from post-marketing surveillance studies, the safety data from double-blind, placebo-controlled clinical trials and EVER's pharmacovigilance database demonstrate the excellent clinical safety profile of Cerebrolysin.

According to EMA classification (European Medicines Agency), Cerebrolysin is in the SAFE category.

In general, reported adverse drug reactions are transient and mild in intensity.

Cerebrolysin is safe and well tolerated!

8 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.

This information is based on the Austrian Summary of Product Characteristics. The prescribing information in your country may vary; please consult your local prescribing information and/or contact your local EVER representative.

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ABBREVIATED PRESCRIBING INFORMATION - Cerebrolysin. 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.

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