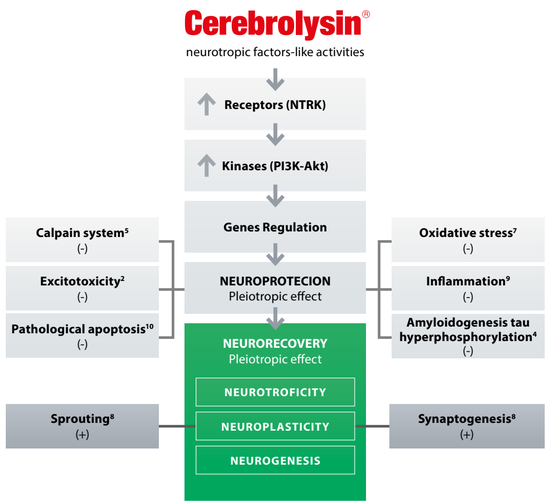
Cerebrolysin's mode of action

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



Product information

Dosage regime:

Disorder	Daily dosage	Initiation of treatment	Duration of treatment
Stroke	20-50 ml	as soon as possible	10-21 days
Traumatic brain injury	20-50 ml	as soon as possible	7-30 days
Vascular dementia	10-30 ml	as soon as possible	1 cycle: 5 days weekly/4 weeks 2-4 cycles per year
Alzheimer's disease	10-30 ml	as soon as possible	1 cycle: 5 days weekly/4 weeks 2-4 cycles per year

EVER PHARMA

LITERATURE

1. Gauthier S., Proano J. V., Jia J., Froelich L., Vester J. C., Doppler E., Cerebrolysin in mild to moderate Alzheimer's disease: a meta-analysis of randomized controlled clinical trials. Journal of Dementia and Geriatric Cognitive Disorders, 2015;39(5-6):332-47
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12. Chen H., Tung Y. C., Li B., Iqbal K., Grundke-Iqbal I., Trophic factors counteract elevated FGF-2-induced inhibition of adult neurogenesis, Neurobiology of Aging 2007;28(8):1148-11623

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.

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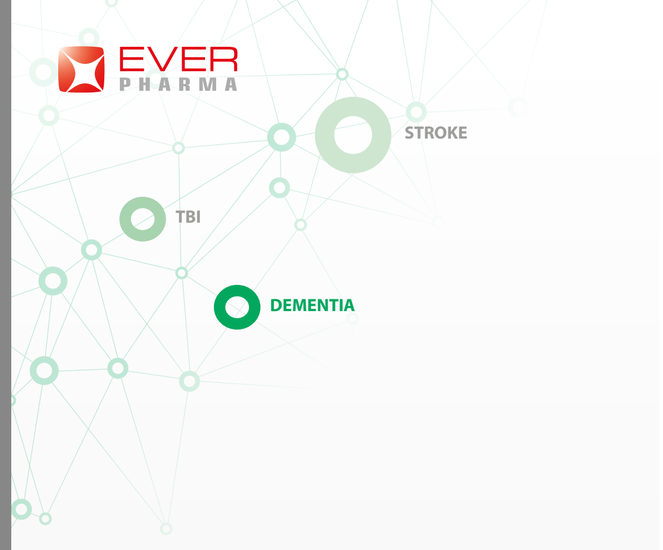


Beneficial results of Cerebrolysin in patients with **ALZHEIMER'S** disease

A meta-analysis of randomized clinical trials, Gauthier S. et. al., Dement Geriatr Cogn Disord 2015;39(5-6):332-47

Cerebrolysin®
Reconnecting Neurons.
Empowering for Life.

Objective and design of the study

OBJECTIVE

The aim of this study was to provide a systematic and quantitative summary of benefit and risk of Cerebrolysin in patients with mild-to-moderate Alzheimer's disease (AD).

DESIGN

- This is a meta-analysis of randomized double-blind placebo-controlled clinical trial comparing Cerebrolysin with placebo
- Patients with mild to moderate AD
- Patients received 30ml/day of Cerebrolysin or placebo
- Study duration: 1 month or 6 months

STUDY SELECTION

- Mixed meta-analysis approach
- 6 eligible placebo-controlled trials
  - 3 Individual Patient Data (IPD)
  - 3 Aggregate Data (AD) from publications
- Month 1 data are available for 6 studies on 763 (97,3%) of a total of 784 ITT patients
- Month 6 data are available for 4 studies on 519 (90,4%) of a total of 574 ITT patients

Trials	Data set	Trial duration	Total No. of ITT Patients (treated)		Age (mean)	Female (%)	MMSE (mean)
Alvarez et al., 2006	IPD	6 m	123	88.5%	73.6	70.7	19.7
Panisset et al., 2002	IPD	6 m	187	97.4%	74.2	58.3	20.6
Ruether et al., 2001	IPD	6 m	144	96.6%	73.0	58.3	17.3
Ruether et al., 1994	AD	6 m	120	100.0%	71.5	65.8	21.6
Bae et al., 2000	AD	4 w	53	100.0%	71.4	66.2	15.7
Xiao et al., 2000	AD	4 w	157	100.0%	70.4	50.3	19.0
Combined Studies		**var.**	**784**	**96.8%[a]**	**72.5**	**60.3**	**19.3**

Efficacy Criteria

OVERVIEW

Study	CIBIC+	CGI	ADAS-cog+	ADAS-cog	MMSE	ZVT
Alvarez (2006)	X		X			
Panisset (2002)	X			X		
Ruether (2001)		X		X		
Bae (2000)		X		X		
Xiao (2000)		X			X	
Ruether (1994)		X				X

Global benefit

Global clinical change

Cognitive function

EFFICACY CRITERIA OF INDIVIDUAL STUDIES

The following outcome measures were employed as primary endpoints in the eligible studies:

- **CIBIC+** Clinical Interview-Based Impression of Change plus caregiver input
- **CGI** Clinician's Global Impression of Change (Item 2 of CGI)
- **ADAS-cog+** Alzheimer's Disease Assessment Scale – cognitive subpart – modified (14 items)
- **ADAS-cog** Alzheimer's Disease Assessment Scale – cognitive subpart (11 items)
- **MMSE** Mini-Mental State Examination
- **ZVT** Trail-Making Test

MEASURE CRITERIA IN META-ANALYSIS

Cognitive function = red box

The cognitive function is assessed by ADAS-cog+, ADAS-cog, MMSE and ZVT

Global clinical change = blue box

The global clinical change is assessed by CIBIC+ and CGI

Global benefit = green box

The global benefit is a composite of the global clinical change and the cognitive functions

Significant beneficial treatment effects of Cerebrolysin after 1 month

Cognitive function: Beneficial and statistically significant treatment effects of Cerebrolysin compared to placebo.

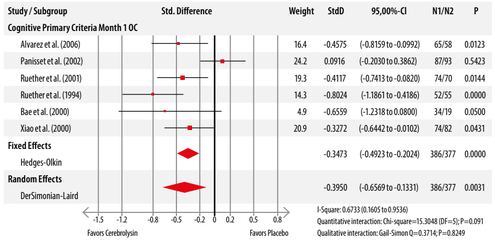


Figure 1: Comparison of Cerebrolysin (30 ml/day) vs. placebo at month 1; changes from baseline; effect size: standardized mean difference (SMD); OC

Global clinical change: After a 4-week treatment with Cerebrolysin the chance for global clinical improvement was 3 times higher as compared to placebo. The effect was statistically significant.

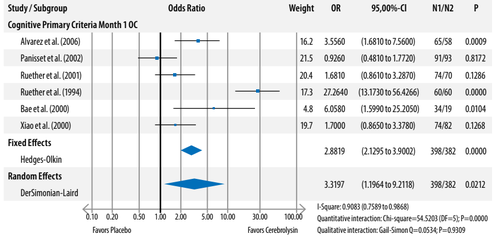


Figure 2: Comparison of Cerebrolysin (30ml/day) vs. placebo at month 1; effect size: odds ratio (OR); OC

Global benefit: A statistically significant advantage of Cerebrolysin over placebo was observed in the global benefit after 4 weeks of treatment.

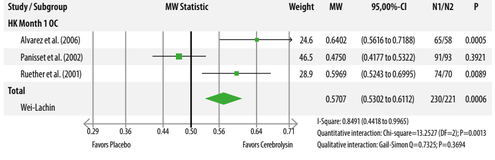


Figure 3: Comparison of Cerebrolysin (30ml/day) vs. placebo at month 1; combined global clinical change of cognitive function (multivariate); effect size: Mann-Whitney (MW); OC

Improved treatment effects of Cerebrolysin after 6 months

Cognitive function: At 6 months treatment effects on cognitive functions were clearly in favor of Cerebrolysin.

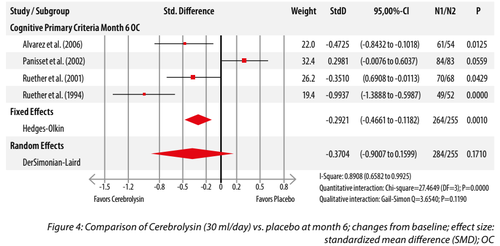


Figure 4: Comparison of Cerebrolysin (30 ml/day) vs. placebo at month 6; changes from baseline; effect size: standardized mean difference (SMD); OC

Global clinical change: At 6-month follow-up the chance for global clinical improvement is 5 times higher as compared to placebo. The effect was statistically significant.

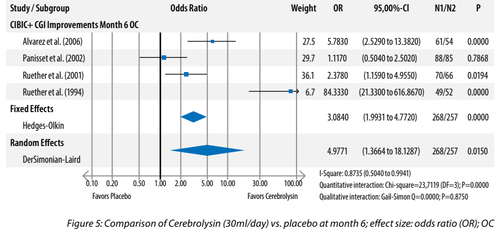


Figure 5: Comparison of Cerebrolysin (30ml/day) vs. placebo at month 6; effect size: odds ratio (OR); OC

Global benefit: The statistically significant advantage of Cerebrolysin over placebo was maintained for at least 6 months.

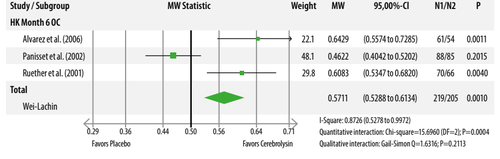
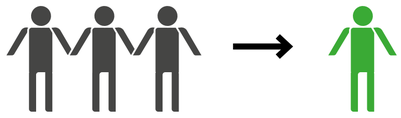


Figure 6: Comparison of Cerebrolysin (30ml/day) vs. placebo at month 6; combined global clinical change of cognitive function (multivariate); effect size: Mann-Whitney (MW); OC

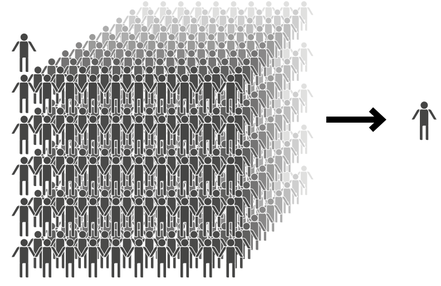
Positive benefit-risk ratio in favor of Cerebrolysin

There is a positive benefit-risk ratio in favor of Cerebrolysin with the NNT for benefit of 2.9 with respect to the 6-months global clinical change and the calculated NNT for harm of 501 with respect to risk ("patients with premature discontinuation due to AE"). The FDA (Food and Drug Administration) considers cognitive and global endpoints as the most important domains when assessing anti-dementia treatments.

BENEFIT (number needed to treat for benefit): 2.9



RISK (number needed to treat for harm): 501



Summary

- Statistically significant advantage of Cerebrolysin over placebo was observed in all 3 criteria
- 3 times higher (after 4 weeks) and 5 times higher (after 6 months) improvements of GCC (Global Clinical Change) were shown compared to placebo
- The safety aspects of Cerebrolysin were comparable to placebo, thus suggesting a favorable benefit-risk ratio in patients with mild-to-moderate Alzheimer's disease
- Results are comparable to oral standard therapy but provide better safety results