

CEREBROLYSIN IMPROVES SYMPTOMS AND DELAYS PROGRESSION IN PATIENTS WITH ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA

R.F. Allegri¹ and A. Guekht²

¹Service of Cognitive Neurology, Instituto de Neurologia Raul Carrea (FLENI), Buenos Aires, Argentina;

²Department of Neurology and Neurosurgery, Russian National Research Medical University, Moscow City Hospital No 8 for Neuropsychiatry, Moscow, Russia

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SUMMARY

Dementia is the result of various cerebral disorders, leading to an acquired loss of memory and impaired cognitive ability. The most common forms are Alzheimer's disease (AD) and vascular dementia (VaD). Neurotrophic factors are essential for the survival and differentiation of developing neurons and protecting them against damage under pathologic conditions. Cerebrolysin is a peptide preparation that mimics the pleiotropic effects of neurotrophic fac-

tors. Several clinical trials investigating the therapeutic efficacy of Cerebrolysin in AD and VaD have confirmed the proof of concept. The results of these trials have shown statistically significant and clinically relevant treatment effects of Cerebrolysin on cognitive, global and functional domains in mild to moderately severe stages of dementia. Doses of 10 and 30 mL were the most effective, but higher doses of up to 60 mL turned out to be most effective in improving neuropsychiatric symptoms, which become relevant at later stages of the disease. Combining treatment with cholinesterase inhibitors and Cerebrolysin indicated long-term synergistic treatment effects in mild to moderate AD. The efficacy of Cerebrolysin persisted for up to several months after treatment suggesting Cerebrolysin has

Correspondence: Ricardo F. Allegri, MD, PhD, FAAN, Service of Cognitive Neurology, Instituto de Neurologia Raul Carrea (FLENI), Montaneses 2325, (C1428AQK) Buenos Aires, Argentina. E-mail: rallegri@fleni.org.ar.

not merely symptomatic benefits, but a disease-delaying potential. This paper reviews the clinical efficacy of Cerebrolysin in the treatment of dementia. Data were obtained from international, multicenter, randomized clinical trials performed in compliance with Good Clinical Practice and the principles of the Declaration of Helsinki (1964) and subsequent revisions.

INTRODUCTION

Dementia is one of the most important neurological disorders in the elderly. As life expectancy increases, the worldwide number of patients with dementia is projected to grow up to 80 million in 2040 (1). Pathological changes in dementia result in an acquired loss of memory and impaired cognitive ability. In its fourth edition, the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* defines dementia as a syndrome characterized by the development of multiple cognitive deficits, including memory impairment and at least one of the following: cognitive disturbances, aphasia, apraxia, agnosia or disturbance in executive functions (2). The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning that cannot be accounted for by other psychiatric or neurological conditions (3). As a consequence, patients may require constant supervision, which often results in institutionalization. The risk of dementia increases with aging accounting for an estimated prevalence rate of 20% in individuals older than 85 years (4). The decline affects cognition and memory function, but also manifests as behavioral and mood changes, as well as the inability to perform activities of daily living. With the aging population, the number of patients with dementia will rise and place an increasing burden on families and the healthcare system.

Dementia is a frequent complication of various cerebral disorders. In Western countries, the most common forms of dementia include chronic diseases like Alzheimer's disease (AD) and vascular dementia (VaD) (5). AD is the most common primary neurodegenerative disorder in the elderly. The prevalence of AD in the U.S. alone has been estimated at 5.3 million patients, with a new case developing every 70 seconds (6).

Neuropathological hallmarks of AD are intracellular protein clusters of hyperphosphorylated microtubule-associated protein tau forming neurofibrillary tangles and extracellular β -amyloid ($A\beta$) protein aggregates. These aggregates are the result of an abnormal amyloid pre-

cursor protein (APP, amyloid β A4 protein) cleavage by β - and γ -secretases that initiates a pathogenic, self-perpetuating cascade ultimately leading to neuronal loss and consequently to dementia (7). Autopsy series from dementia clinics report that coexisting vascular pathology occurs in 24-28% of AD cases. Community-based autopsy studies consistently find higher proportions of both VaD and mixed dementia (8, 9).

It is believed that VaD is a clinical and pathological entity distinct from AD, although elements of vascular disease may be present in both conditions. Epidemiologically, VaD is considered the second most prevalent type of dementia after AD, which has a frequency of 70% among all dementias (10). The estimated prevalence ranges from 1-4% in individuals aged 65 years (11), increasing to 14-16% in individuals over 80 years old (12). VaD represents a clinical syndrome that includes a wide spectrum of cognitive dysfunctions arising from insufficient blood supply to brain tissue as a consequence of vascular disease (12-14). This triggers neurodegeneration by depriving nerve cells of oxygen and glucose (15, 16).

Facing an increasing prevalence of AD and VaD due to the general population aging, the search for drugs capable of reducing manifestations of cognitive function deficits has become a challenging priority. Recently, substances with neurotrophic properties have drawn considerable attention (17). Neurotrophic factors are essential for the survival and differentiation of normally developing neurons and also play important roles in the protection and recovery of mature neurons under pathologic conditions (18). Certain neurotrophic factors have been shown to protect neurons against damage—even ischemic—and promote axon and dendrite branching thus restoring functional connections between cerebral neurons (19-21). Patients suffering from degenerative brain disorders may therefore benefit from substances with neurotrophic properties.

Cerebrolysin is a parenterally administered neuropeptide preparation that has pharmacodynamic neurotrophic and neuroprotective activity mimicking endogenous neurotrophic factors. In clinical trials, Cerebrolysin was safe and well tolerated and has shown to enhance cognitive and functional performance and to improve behavioral symptoms and the clinical global impression. Furthermore, the beneficial effects of Cerebrolysin were maintained for up to several months after treatment indicating a disease-delaying effect.

CEREBROLYSIN IN THE TREATMENT OF ALZHEIMER'S DISEASE

The main therapeutic approach to AD includes cholinesterase inhibitors and NMDA receptor antagonists, depending on the stage of severity. However, these drugs provide symptomatic benefit only without influencing disease progression and have considerable side effects. An alternative treatment approach to these single-target drugs is the use of drugs mimicking the action of endogenous neurotrophic factors like Cerebrolysin, a peptide preparation interacting with different pathways of the pathological cascade in AD.

Several clinical trials have been performed to investigate safety and efficacy of Cerebrolysin in patients suffering from mild to moderately severe AD (Table I). Diagnosis of

dementia was performed according to criteria as defined in the current version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R, DSM-IV) and was further specified by the NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association). Inclusion and exclusion criteria were generally consistent across trials and were defined to exclude other causes of dementia by a careful history based on neurological examination, analytical methods and imaging, including MRI or CT. Therapeutic efficacy was assessed in the cognitive, functional and global domains; furthermore, the proportion of patients who achieve a clinically meaningful benefit (response) was assessed. Most of the randomized, double-blind, placebo-controlled trials (22-25) used as efficacy variables the

Table I. Summary of main clinical trials of Cerebrolysin in Alzheimer's disease.

Trials	N (Cerebrolysin/placebo)	Arms	Treatments	Doses	Main outcomes	Ref.
Alvarez et al., 2006 and 2011 (dose-finding)	279 (10 mL: 69; 30 mL: 70; 60 mL: 71/69)	Cerebrolysin 0.9% NaCl	12 weeks	10/30/ 60 mL	ADAS-cog+ CIBIC+	(25, 30)
Alvarez et al., 2009 (combination trial)	217 (Cerebrolysin: 70; donepezil: 75; combination: 72)	Cerebrolysin Donepezil Combination	2 x 4 weeks 28 weeks	10 mL	ADAS-cog+ CIBIC+	(27)
Muresanu et al., 2002	60 (30/30)	Cerebrolysin 0.9% NaCl	6 weeks	30 mL	ADAS-cog CIBIC+	(26)
Panisset et al., 2002	192 (97/95)	Cerebrolysin 0.9% NaCl	4 weeks	30 mL	ADAS-cog CIBIC+	(23)
Bae et al., 2000	53 (34/19)	Cerebrolysin 0.9% NaCl	4 weeks	30 mL	ADAS-cog CGI	(22)
Ruether et al., 2001 and 2002	120 (60/60)	Cerebrolysin 0.9% NaCl	4 weeks	30 mL	CGI SCAG Trail-Making Test	(24, 29)
Xiao et al., 2000	157 (74/83)	Cerebrolysin 0.9% NaCl	4 weeks	30 mL	MMSE CGI	(33)
Ruether et al., 1994 and 2000 (MAD-B)	149 (76/73)	Cerebrolysin 0.9% NaCl	2 x 4 weeks	30 mL	ADAS-cog CGI	(31, 32)
Gavrilova et al., 2005	60 (30/30)	Cerebrolysin 0.9% NaCl Rivastigmine	2 x 4 weeks	30 mL	ADAS-cog IADL MMSE CGI	(28)

ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CIBIC+, Clinicians Interview-Based Impression of Change plus caregiver input; or CGI, Clinical Global Impression; IADL, Instrumental Activities of Daily Living; MMSE, Mini-Mental State Examination; SCAG, Sandoz Clinical Assessment-Geriatric.

ADAS-cog (Alzheimer's Disease Assessment Scale-cognitive subscale) or its extended version ADAS-cog+ for assessing cognition and the CIBIC+ (Clinicians Interview-Based Impression of Change plus caregiver input) or CGI (Clinical Global Impression) for assessing the overall clinical response (global assessment) as primary efficacy variables. One of the trials was designed as a dose-finding study (25); another randomized, placebo-controlled trial (26) had an open design. Two active-comparator trials were performed: a double-blind trial comparing Cerebrolysin with donepezil and the combination of both (27) and an open trial comparing Cerebrolysin with rivastigmine (28). Statistical analyses were performed on the intention-to-treat (ITT) and the per-protocol (PP) patient populations. Results of the ITT population are summarized in this review; results of the PP analyses were basically similar to those of the ITT analyses. Subgroup analyses of patients at a more advanced stage (Mini-Mental State Examination [MMSE] ≤ 20) were performed in three of the trials (24, 25, 27).

In a double-blind, placebo-controlled, multicenter, short-term trial performed by Bae et al. (22), 53 patients with mild to moderate AD (MMSE 10-24) were randomized in a ratio of 2:1 to Cerebrolysin ($n = 34$) or placebo ($n = 19$). Patients received intravenous infusions of 30 mL of Cerebrolysin or placebo once daily on 5 days per week over 4 weeks, 20 infusions in total. The main study endpoints were week 4 assessments of cognitive (ADAS-cog) and global (CGI) responses. Baseline characteristics were similar between treatment groups. After 4 weeks of treatment, patients on Cerebrolysin had a mean change from baseline of -3.23 points (± 4.75 SD) in the ADAS-cog compared to -0.36 points (± 3.59 SD) in the placebo group, yielding a drug-placebo difference of -2.87 (95% confidence interval [CI] 0.35/5.39; $P = 0.02$). Also in the global domain as measured by the CGI, Cerebrolysin was superior to placebo showing a mean drug-placebo difference of -0.74 points ($P = 0.01$) and an improvement rate of 61.8% compared to 21.1% in the placebo group. Secondary efficacy parameters included a significant cognitive improvement in the MMSE, with a drug-placebo difference of 1.57 points (95% CI 0.04/2.96; $P = 0.04$). A trend for improvement after treatment with Cerebrolysin was shown in scales measuring neuropsychiatric symptoms and activities of daily living. It is especially noteworthy that significant and clinically relevant improvements of the cognitive deficits and global function in patients with mild to moderate AD were observed as early as 1 month after active treatment, indicating a fast onset of action.

Longer-term effects of Cerebrolysin were investigated by Parisset et al. in a randomized, double-blind, placebo-controlled, multicenter trial over 24 weeks (23). Of 192 patients enrolled (MMSE 14-26), 97 were randomized to Cerebrolysin and 95 to placebo. Patients received intravenous infusions of 30 mL Cerebrolysin or placebo once daily on 5 days per week over 4 weeks. Study endpoint was on week 12, but a follow-up examination was performed 24 weeks after baseline, 5 months after end of therapy. Primary outcome measures were ADAS-cog and CIBIC+. Baseline differences were observed for age and age of onset of dementia, which were significantly higher in the placebo group (age 75.19 years and onset 72.33 years in the placebo group vs. age 73.20 years and onset 69.76 years in the Cerebrolysin group), and in the number of patients with hallucinations, which was significantly higher in the Cerebrolysin group ($n = 7$; placebo $n = 1$). At week 12, CIBIC+ scores showed a significant drug-placebo difference of -0.21 (95% CI $-0.50/-0.08$; $P = 0.033$) favoring Cerebrolysin with a mean score change from baseline of 4.08 (± 0.10 SE). This result is in line with the responder analysis at week 12 showing that 75% of patients treated with Cerebrolysin improved or at least did not deteriorate compared to 57% of patients treated with placebo ($P = 0.007$). In the Cerebrolysin group, global improvement was maintained for 2 months after end of therapy, whereas patients on placebo started to deteriorate immediately thereafter. A similar course was observed in the ADAS-cog for Cerebrolysin patients; of note is the fact that patients on placebo did not deteriorate until week 12, thus failing to reach a significant treatment difference. Non-deterioration of placebo-treated patients was also observed in the MMSE, which might be explained by the mild cognitive impairment at baseline (MMSE: Cerebrolysin 20.22, placebo 20.93). Consequently, factors other than cognitive improvements must have driven the positive CIBIC+ rating. Improved performance with a time course similar to CIBIC+ was observed in the activities of daily living as measured by the Disability Assessment in Dementia (DAD) scale. Furthermore, a trend towards improvement was also seen in the Cornell Depression Scale. Since hallucination symptoms are associated with diffuse Lewy body disease, a post-hoc analysis was performed on the PP population of patients without hallucinations. Results showed an even greater effect on the CIBIC+ with a drug-placebo difference of -0.54 points (95% CI $-0.97/-0.11$; $P = 0.007$) favoring Cerebrolysin, and a responder rate of 84% for Cerebrolysin versus 50% for placebo-treated patients ($P = 0.007$). Furthermore, a

drug–placebo difference of 6.02 points (95% CI 0.74/11.30; $P = 0.0371$) in favor of Cerebrolysin was reported in the DAD scale. This trial showed that even after a relatively short treatment period, the beneficial effects of Cerebrolysin lasted for up to 2 months after the end of active treatment.

Ruether et al. reported the results of a 28-week, double-blind, multicenter trial with 149 enrolled patients (MMSE 14–24) randomized to Cerebrolysin ($n = 76$) or placebo ($n = 73$) (24). Patients received intravenous infusions of 30 mL Cerebrolysin or placebo once daily on 5 days per week over 4 weeks. This regimen was repeated after a 2-month treatment-free interval, accounting for a total of 40 infusions. Study endpoint was week 16, but a follow-up examination was performed 28 weeks after baseline, 3 months after last active treatment in order to investigate potential stabilizing effects of Cerebrolysin. Main efficacy outcomes were CGI and ADAS-cog. Baseline characteristics were similar between treatment groups. At study endpoint, patients on Cerebrolysin were significantly superior over patients on placebo in both the CGI, with a drug–placebo difference of 0.42 points (95% CI

$-0.12/-0.72$; $P = 0.004$), and the ADAS-cog, with a drug–placebo difference of -3.2 points (95% CI $-1.42/-4.98$; $P < 0.001$). Mean changes from baseline were 4.18 points (± 0.11 SE) in the CGI and -2.1 (± 0.69 SE) in the ADAS-cog (Fig. 1).

Results were confirmed by responder analyses, defined as a CGI score of < 5 and ADAS-cog improvement of ≥ 4 points. Overall clinical response (CGI) was reported in 63.5% of patients in the Cerebrolysin group compared to 41.4% of patients in the placebo group ($P = 0.006$). Response in cognitive function (ADAS-cog) was reported in 47.3% of Cerebrolysin-treated patients compared to 15.7% of placebo-treated patients ($P < 0.001$). At the follow-up visit on week 28, patients on Cerebrolysin maintained baseline cognitive performance with a significant drug–placebo difference of -1.6 points ($P = 0.016$). The percentage of combined responders (responders on CGI and the ADAS-cog) decreased until week 28 but the group difference was still significant. On secondary outcome measures, Cerebrolysin was also superior to placebo with a treatment difference of -1.0 points (95% CI $-2.05/0.05$; $P = 0.003$) at week 16

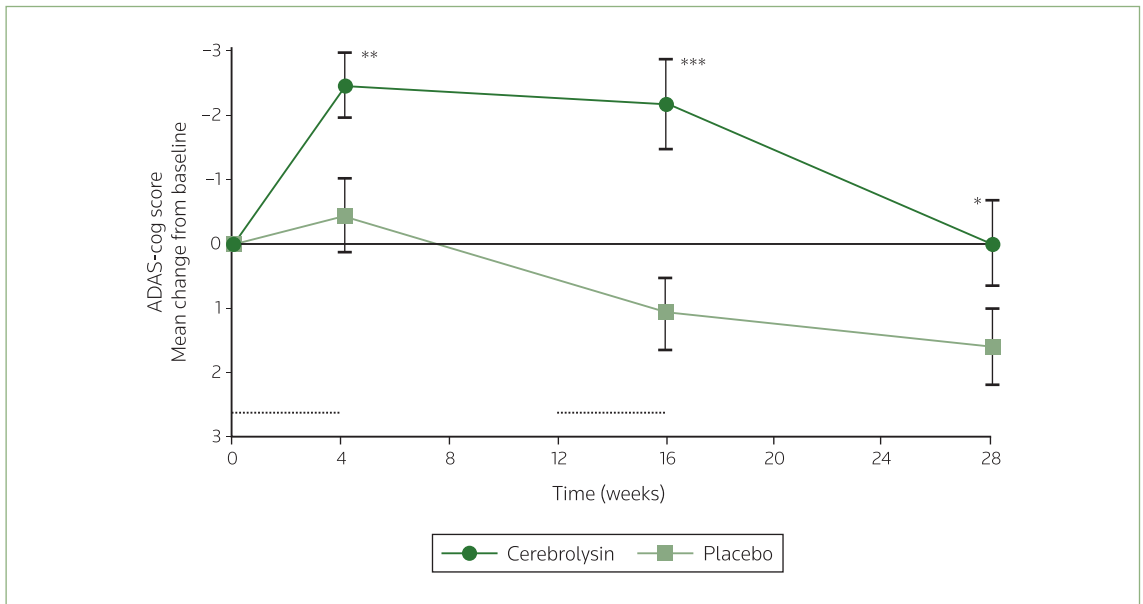


Figure 1. Time-course of the Alzheimer's Disease Assessment Scale-cognitive subpart (ADAS-cog) score mean change from baseline in mild to moderate patients with Alzheimer's disease treated with Cerebrolysin ($n = 76$) or placebo ($n = 73$) during weeks 1–4 and 12–16 (dotted lines indicate treatment periods), with an observation for residual effects at week 28, 3 months after treatment discontinuation. (Intent-to-treat analysis; negative score differences indicate improvement.) * $P < 0.025$; ** $P < 0.01$; *** $P < 0.001$ versus placebo. (Reproduced with permission from Ruether, E. et al. *A 28-week, double-blind, placebo-controlled study with Cerebrolysin in patients with mild to moderate Alzheimer's disease.* *Int Clin Psychopharmacol* 2001, 16(5): 253–63 [24].)

in the ADAS-noncog measuring behavior; a trend was also observed in the activities of daily living (Nuremberg Age Inventory; NAI). Similar results were shown in a subgroup analysis of 109 moderate patients (MMSE < 20) (29). In both the CGI and the ADAS-cog, patients on Cerebrolysin were significantly superior to patients on placebo and improved even more until week 16 and 28 compared to the total patient population. Due to the more pronounced deterioration of patients in the placebo group, the drug–placebo difference was slightly greater at week 16 and 28 compared to the total population. These results are in line with the responder analyses showing slightly higher responder rates in the Cerebrolysin group and slightly lower responder rates in the placebo group when compared to the total population. Supportive evidence for the efficacy of Cerebrolysin was also observed in the activities of daily living (NAI) and the behavioral domain (ADAS-noncog) in patients with AD of moderate severity (Fig. 2). Since observed drug–placebo differences were maintained until week 28, these data indicate beneficial effects of Cerebrolysin

for up to 3 months after drug withdrawal in patients suffering from mild to moderate AD.

In order to explore the optimal dose of Cerebrolysin in the treatment of mild to moderate AD, Alvarez et al. investigated three different doses in a randomized, double-blind, placebo-controlled trial over 24 weeks (25). A total of 279 patients were enrolled and randomized to 10 (n = 69), 30 (n = 70) or 60 mL (n = 71) of Cerebrolysin or placebo (n = 69). Study medication was administered by intravenous infusion on 5 days per week for the first 4 weeks (week 1-4) and thereafter on 2 days per week for 8 weeks (week 5-12), giving a total of 36 infusions. Study endpoint was on week 24, 3 months after end of therapy. Primary outcome measures were ADAS-cog+ and CIBIC+. There were no differences at baseline except for the annual rate of disease progression, which was significantly slower in the placebo group (2.6 points/year in MMSE vs. 3.5 [$P = 0.037$; 10 mL], 3.7 [$P = 0.011$; 30 mL] and 3.9 [$P = 0.011$; 60 mL] points/year). In the ADAS-cog+ at week 24, patients on Cerebrolysin 10 mL had a

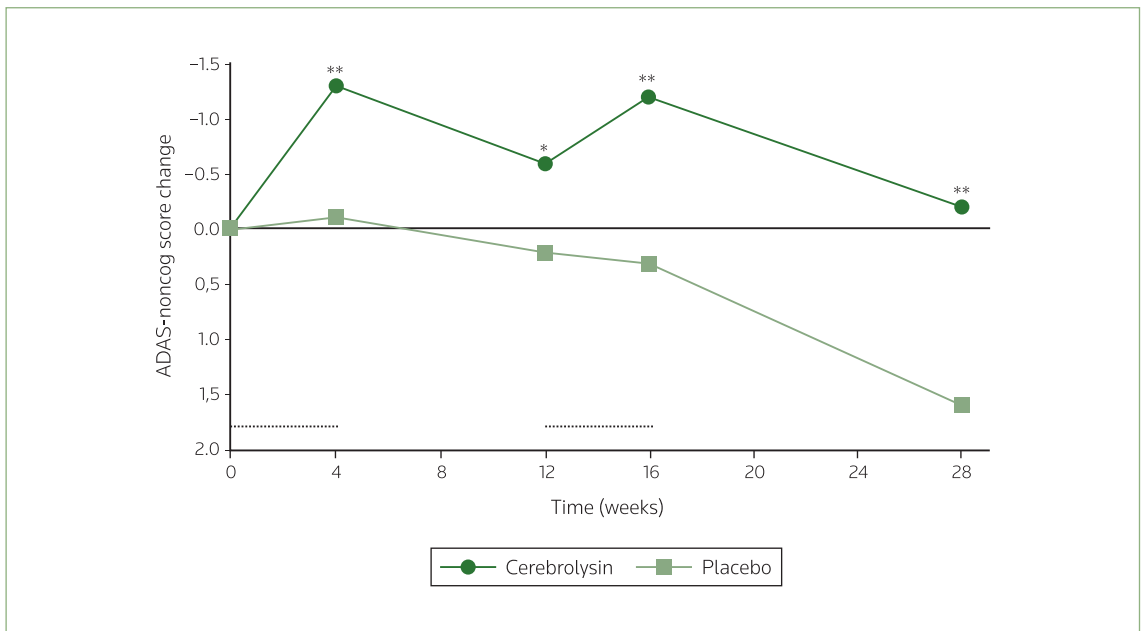


Figure 2. Time course of the Alzheimer's Disease Assessment Scale-noncognitive subpart (ADAS-noncog) in moderately severe Alzheimer's disease patients (Mini-Mental State Examination < 20): mean change from baseline (\pm SEM) of Cerebrolysin- and placebo-treated patients (n = 60 and 49, respectively). Negative score differences indicate improvement. * $P < 0.05$, ** $P < 0.01$. (Adapted with permission from Ruether, E. et al. *Sustained improvement of cognition and global function in patients with moderately severe Alzheimer's disease: a double-blind, placebo-controlled study with the neurotrophic agent Cerebrolysin*. J Neural Transm Suppl 2002(62): 265-75 [29]; Springer-Verlag Wien.)

mean change from baseline of -1.83 points (± 1.16 SE) compared to 2.27 points (± 1.18 SE) in the placebo group, yielding a drug-placebo difference of -4.10 (95% CI $-8.02/-0.18$; $P = 0.038$) (Fig. 3). A trend in the treatment difference was observed for the 30-mL dosage (-3.62 ; 95% CI $-7.45/0.21$; $P = 0.069$) but no significant effect was observed for the 60-mL dose. These findings were confirmed in a responder (improvement from baseline > 4) analysis with responder rates of 41.7% (10 mL), 36.9% (30 mL), 29.4% (60 mL) and 24.1% (placebo). The odds ratio for a clinical response with 10 mL Cerebrolysin was 2.24 (95% CI 1.02/4.95; $P < 0.05$) indicating that patients on 10 mL Cerebrolysin had a 2.24 times higher probability of achieving a response in the ADAS-cog+ than patients on placebo.

In the CIBIC+, all Cerebrolysin doses were superior ($P < 0.001$) to placebo showing drug-placebo differences of -1.56 (10 mL), -1.44 (30 mL) and -1.38 (60 mL) points at week 24. Response rates were 65% (10 mL), 60% (30 mL), 58.8% (60 mL) and 20.7% (placebo). Odds ratios

for achieving response in the CIBIC+ were 7.12 (95% CI 3.11/16.29), 5.75 (95% CI 2.57/12.88) and 5.48 (95% CI 2.47/12.16) for the 10, 30 and 60 mL Cerebrolysin groups, respectively, all being highly significant versus placebo ($P < 0.001$). Secondary outcome measures provided supportive evidence for the efficacy of the 10- and 30-mL Cerebrolysin doses. At week 24, both dose groups were superior to placebo in all secondary measures, although the differences did not reach statistical significance, probably due to the low number of patients per group. The best secondary effects of the 10- and 30-mL doses were seen in the DAD, which indicates that these two doses of Cerebrolysin exert beneficial effects on the capability of patients with AD to perform activities of daily living. Interestingly, the 60-mL dose resulted in the largest and most significant improvement of behavioral disturbances, as evidenced by the Neuropsychiatric Inventory (NPI) score with a drug-placebo difference of -5.4 points (95% CI $-9.1/-1.7$; $P < 0.05$) in favor of Cerebrolysin (Fig. 4).

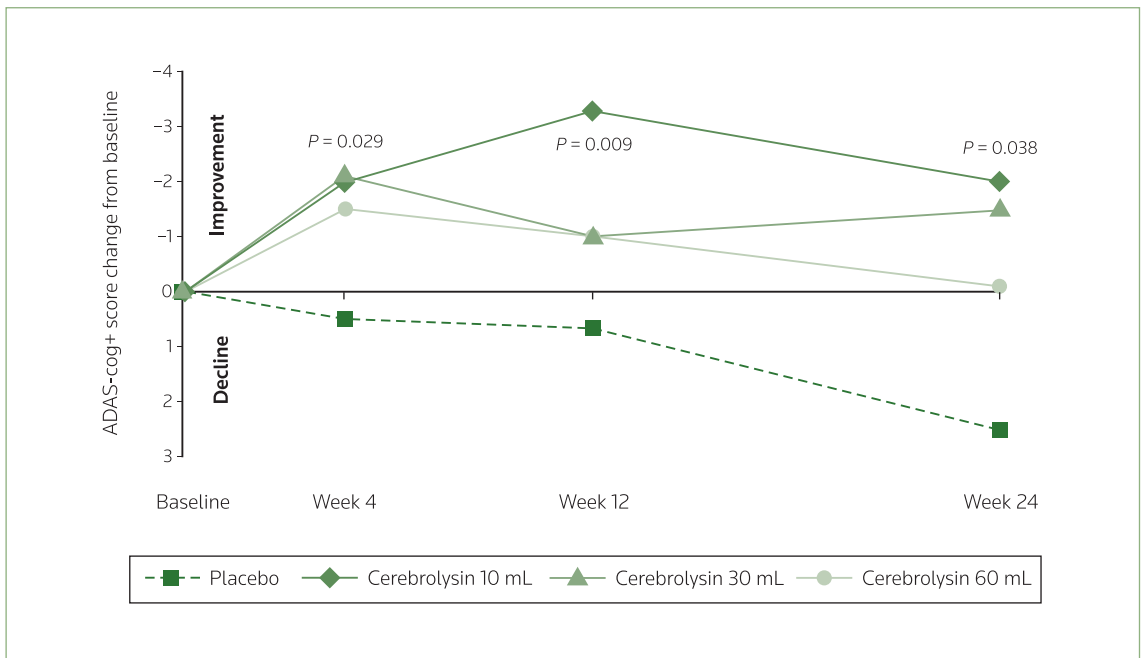


Figure 3. Time-course of the Alzheimer's Disease Assessment Scale-cognitive subpart, extended version (ADAS-cog+) score change from baseline in patients treated with Cerebrolysin 10 mL ($n = 60$), Cerebrolysin 30 mL ($n = 65$), Cerebrolysin 60 mL ($n = 68$) or placebo ($n = 58$) (ITT analysis; $n = 251$). Negative score differences indicate improvement. Exact P values for comparison to placebo are given for Cerebrolysin 10 mL. (Adapted with permission from Alvarez, X.A. et al. A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease. *Eur J Neurol* 2006, 13(1): 43-54 [25].)

A subgroup analysis of 133 patients at a more advanced stage (MMSE ≤ 20) largely confirmed the findings of the total patient population (30). The ADAS-cog+ showed a drug–placebo difference of -6.38 (95% CI $-12.67/-0.09$; $P = 0.046$) for the 10-mL dosage and of -4.53 (95% CI $-10.66/1.60$; $P = 0.195$) for the 30-mL dosage, which was considerably higher as compared to the total patient population. This outcome was largely due to the more pronounced deterioration over time of placebo patients.

In summary, these results indicate an inverted dose-dependent treatment effect of Cerebrolysin in mild to moderate AD with doses of 10 and 30 mL being most effective. Inverted dose-dependent treatment effects are typical for growth factors and due to the variety of peptides contained in Cerebrolysin, different dose-response curves are expected. According to the results of this study, a dose range of 10–30 mL is most appropriate to treat AD patients at the early stage of the disease when changes of cognitive performance are the focus of therapeutic approach. Later on, when behavioral problems become predominant, higher doses up to 60 mL might

be useful for improving neuropsychiatric and behavioral symptoms.

The results of these randomized, double-blind, placebo-controlled trials are supported by further trials using other primary parameters (31–33) or having an open-label design (26). Ruether et al. investigated the effects of Cerebrolysin on patients with mild to moderate AD in a randomized, double-blind, placebo-controlled, multicenter trial over 28 days (31). Primary outcome measures were CGI, the geriatric clinical assessment scale SCAG (Sandoz Clinical Assessment-Geriatric) and the Trail-Making Test of the NAI for assessment of cognitive performance. Of 120 patients enrolled (MMSE 15–25), 60 were randomized to Cerebrolysin and 60 to placebo. Patients received intravenous infusions of Cerebrolysin 30 mL or placebo once daily on 5 days per week over 4 weeks, yielding a total of 20 infusions. Study endpoint was on week 4; a follow-up examination was performed 28 weeks after baseline. Baseline characteristics were similar between treatment groups. At study endpoint in the CGI, 61.7% of patients were classified as being much improved

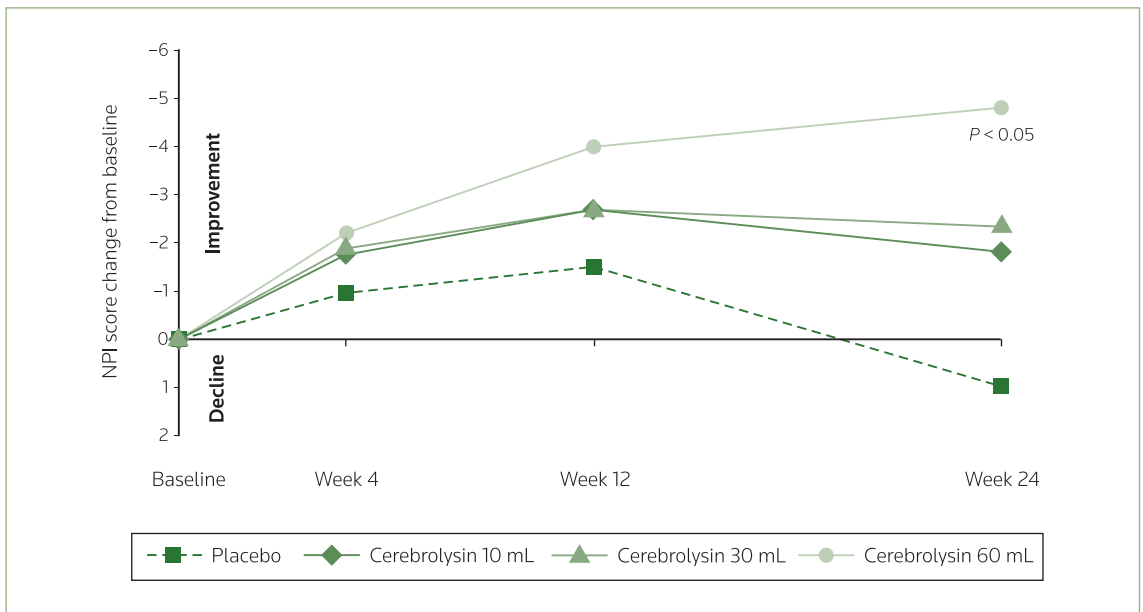


Figure 4. Time-course of the Neuropsychiatric Inventory (NPI) score changes from baseline in patients treated with Cerebrolysin 10 mL ($n = 60$), 30 mL ($n = 65$) or 60 mL ($n = 68$), or placebo ($n = 58$) (ITT analysis; $n = 251$). Negative score differences indicate improvement. $P < 0.05$ for comparison to placebo published only for the Cerebrolysin 60-mL group at week 28. (Adapted with permission from Alvarez, X.A. et al. A 24-week, double-blind, placebo-controlled study of three dosages of Cerebrolysin in patients with mild to moderate Alzheimer's disease. *Eur J Neurol* 2006, 13(1): 43–54 [25].)

and qualified as "good responders," while the remaining 38.3% of patients were minimally improved resulting in a 100% response to Cerebrolysin. In the placebo group, 20% of patients showed minor improvement and 80% remained unchanged. The differences for change from baseline were highly significant ($P < 0.0001$) in favor of Cerebrolysin. Continuous improvement was reported for Cerebrolysin in the SCAG (30% from baseline at week 4) and in the Trail-Making Test, whereas no changes were observed in the placebo group ($P < 0.0001$ for treatment differences). Substantial improvements with similar time courses were also observed in the secondary outcome measures, the NAI assessing activities of daily living (40% improvement from baseline at week 4) and the Zerssen self-assessment of the subjective clinical state of the patient (40% improvement from baseline at week 4). These significant and clinically relevant improvements until week 4 were largely maintained during the follow-up period indicating that a relatively short treatment course may have a long-term influence on disease progression in patients with mild to moderate AD (32).

In the randomized, double-blind, placebo-controlled, multicenter trial conducted by Xiao et al., MMSE and CGI were the primary measures to assess the efficacy of Cerebrolysin in patients with mild to moderate AD (MMSE 15-25) (33). In all, 157 patients were enrolled and randomized to Cerebrolysin ($n = 74$) or placebo ($n = 83$). Patients received intravenous infusions of 30 mL of Cerebrolysin or placebo once daily on 5 days per week over 4 weeks. Study endpoint was on week 4. No group differences were observed at baseline. At study endpoint, patients treated with Cerebrolysin improved by 2.5 points on the MMSE compared to 1.4 points of improvement in placebo-treated patients ($P = 0.043$). In the CGI, 72% of patients on Cerebrolysin responded to therapy and 24% did not deteriorate compared to 60% of improved patients in the placebo group and 35% who remained unchanged. A significant treatment difference favoring Cerebrolysin was observed ($P = 0.02$). Supportive evidence for the beneficial effect of Cerebrolysin in mild to moderate AD derived also from secondary outcome measures, with significant drug-placebo differences in the NAI ($P = 0.003$),

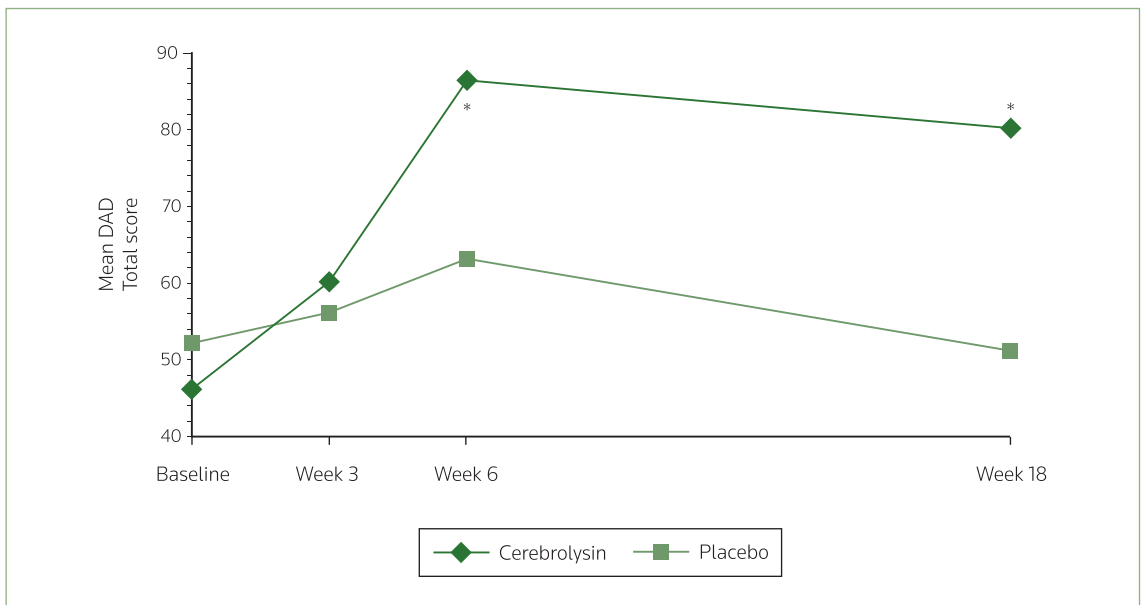


Figure 5. Time-course of the Disability Assessment in Dementia (DAD) score of patients with mild to moderate Alzheimer's disease (Mini-Mental State Examination range 14-25). For DAD, higher scores indicate higher levels of function. Intention-to-treat analysis. * $P < 0.05$; $n = 60$. (Adapted with permission from Muresanu, D.F. et al. *Improved global function and activities of daily living in patients with AD: a placebo-controlled clinical study with the neurotrophic agent Cerebrolysin*. *J Neural Transm Suppl* 2002(62): 277-85 [26]; Springer-Verlag Wien.)

SCAG ($P = 0.014$) and the Trail-Making Test ($P = 0.023$).

A randomized, open-labeled, placebo-controlled trial over 18 weeks was performed by Muresanu et al. in patients with mild to moderate AD patients (MMSE 14-25) (26). This trial enrolled 60 patients, who were randomized to Cerebrolysin ($n = 30$) or placebo ($n = 30$). Study medication was administered as 30-mL intravenous infusions once daily on 5 days per week over 6 weeks. Study endpoint was week 18; primary parameters were ADAS-cog and CIBIC+. Baseline characteristics were similar between both treatment groups. At study endpoint, patients on Cerebrolysin had a CIBIC+ score of 2.40 (± 2.33 SD) yielding a significant drug-placebo difference of -2.20 points ($P < 0.05$). In the ADAS-cog, Cerebrolysin-treated patients improved by 2.89 points (± 2.40 SD) from baseline resulting in a drug-placebo difference of -1.01 points ($P < 0.01$). A significant treatment difference in favor of Cerebrolysin was also reported in the DAD score (28 points vs. placebo; $P < 0.05$), which was largely due to the fast functional decline of placebo patients after week 6 (Fig. 5). The results of this trial confirmed the prolonged beneficial effects of Cerebrolysin of up to 3 months after end of therapy in patients suffering from mild to moderate AD.

In order to investigate potential synergistic treatment effects by combining neurotrophic treatment (Cerebrolysin) with cholinesterase inhibitors (donepezil), Alvarez et al. performed a randomized, double-blind, multicenter comparison trial over 28 weeks (27). A total of 217 enrolled patients (MMSE 12-25) were randomized to Cerebrolysin (10 mL; $n = 70$), donepezil (10 mg; $n = 75$) or both treatments ($n = 72$). Cerebrolysin and the corresponding placebo were administered as intravenous infusions once daily on 5 days per week over 4 weeks. This regimen was repeated after a 2-month treatment-free interval, accounting for a total of 40 infusions. Donepezil and the corresponding placebo were administered orally once daily over 28 weeks. Study endpoint was on week 28, 3 months after the last infusion of Cerebrolysin. Primary outcome measures were CIBIC+ and ADAS-cog+. Baseline characteristics were similar between treatment groups. At study endpoint, patients in all treatment groups had improved to a similar extent in the cognitive (ADAS-cog+) and global (CIBIC+) domains (Fig. 6).

Pairwise comparison showed significant superiority ($P < 0.05$) of Cerebrolysin over donepezil in the CIBIC+ (Fig. 6B) with responder rates of 64.1% in the Cerebrolysin

group, 62.7% in the combination group and 37.8% in the donepezil group. Odds ratios for improvement were significantly higher for Cerebrolysin versus donepezil (2.92; 95% CI 1.43/5.96; $P < 0.05$). Improvement in the cognitive domain was most pronounced in the combination group (-2.3 points ± 0.8 SE), followed by Cerebrolysin (-1.7 points ± 0.8 SE) and donepezil (-1.3 points ± 0.8 SE) (Fig. 6A). Remarkably, patients in the combination group performed better at all study visits compared to patients receiving monotherapy.

Rates of combined responders, defined as having improved by at least 4 points on the ADAS-cog+ and having a CIBIC+ score of less than 4, were 37.3% in the combination group, 31.3% in the Cerebrolysin group and 21.2% in the donepezil group. Beneficial effects of Cerebrolysin and its combination with donepezil were also reported in the activities of daily living (ADCS-ADL). Patients in both treatment groups improved slightly until week 16 followed by a slight deterioration to baseline level until week 28. In contrast, patients on donepezil deteriorated continuously over 28 weeks. Regarding neuropsychiatric symptoms as measured by the NPI, monotherapy was superior to the combination and Cerebrolysin to donepezil. All patients improved until week 16, thereafter neuropsychiatric symptoms stabilized in patients receiving Cerebrolysin as monotherapy or in combination with donepezil, whereas patients on donepezil reverted to baseline level. In conclusion, these results indicate that Cerebrolysin is as effective as or even superior to donepezil, and that the combination of a neurotrophic treatment (Cerebrolysin) with a cholinesterase inhibitor (donepezil) provides synergistic effects in patients suffering from mild to moderate AD.

Throughout the literature, there are indications that support a role of the *APOE*E4* genotype as a risk factor in AD pathogenesis, correlating with a more progressive clinical outcome of the disease and with a more severe cholinergic deficit (34, 35). Gavrilova et al. (28) compared clinical efficacy of Cerebrolysin with the cholinergic drug rivastigmine in dependence of the *APOE*E4* genotype in patients with mild to moderate AD (MMSE 12-24). This trial had an open-labeled design and included 60 patients (30 in each group) receiving either 2 treatment courses of 30 mL of Cerebrolysin (5 infusions per week over 4 weeks) with a treatment-free period of 8 weeks between treatment courses or the maximum tolerable daily dose of rivastigmine (3-12 mg/day) over 16 weeks. Apolipoprotein E-dependent responses were assessed by combined response in CGI (moderate or

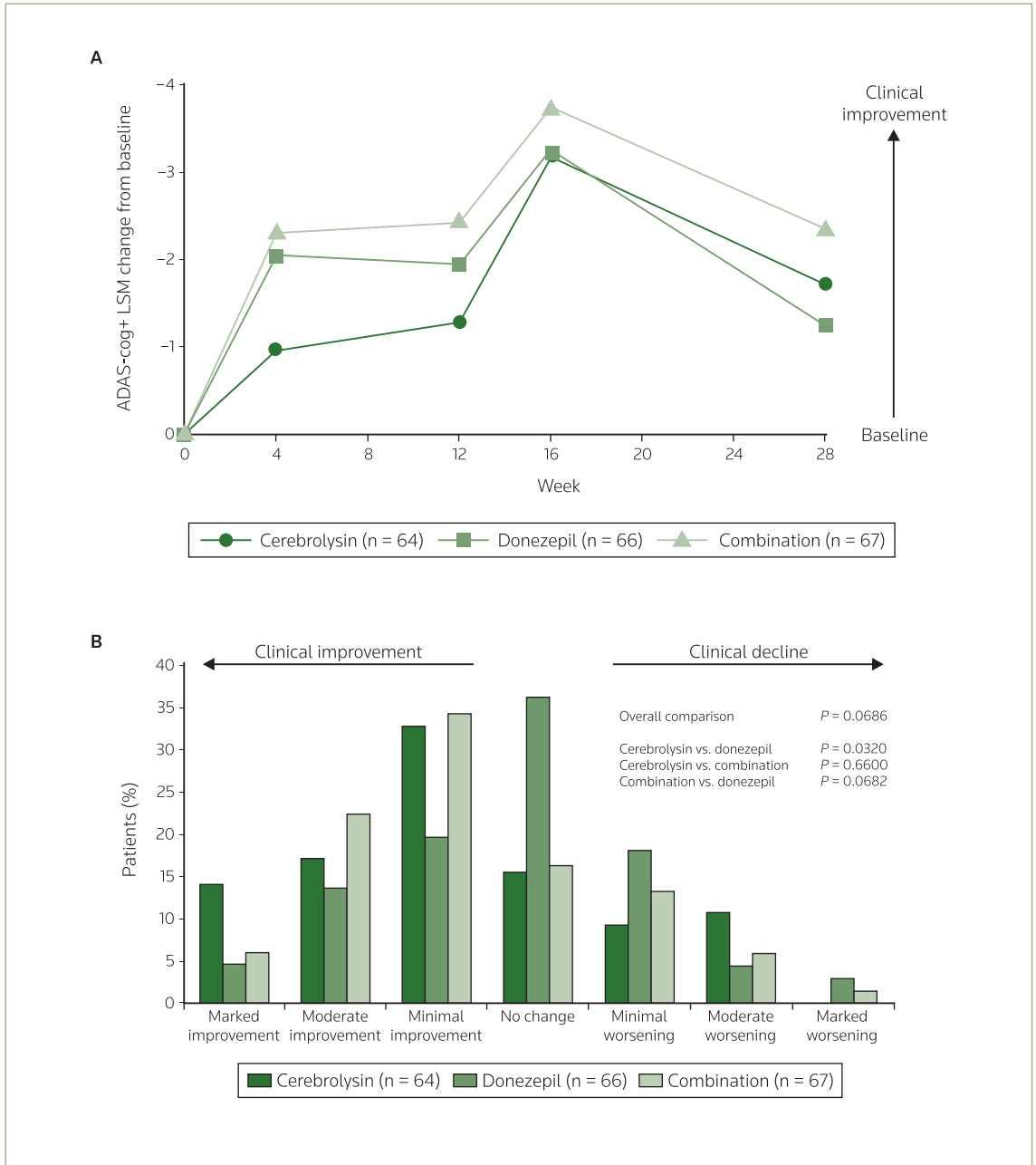


Figure 6. Changes in the Alzheimer's Disease Assessment Scale-cognitive subpart (ADAS-cog) (A) and Clinicians Interview-Based Impression of Change plus caregiver input (CIBIC+) scores (B) after 28 weeks of treatment with Cerebrolysin, donepezil or the combination. A) Least squares mean (LSM) changes from baseline in ADAS-cog+. Negative score changes represent cognitive improvement from baseline. B) CIBIC+ rating at week 28 (study endpoint). N = 197. Intention-to-treat data set. (Reproduced with permission from Alvarez, A. et al. *Combined treatment with Cerebrolysin and donepezil in mild to moderate Alzheimer's disease: Results of a double-blind, randomized clinical trial.* Int Conf Alzheimer's Dis Relat Disord (ICAD) (July 11-16, Vienna) 2009 [27].)

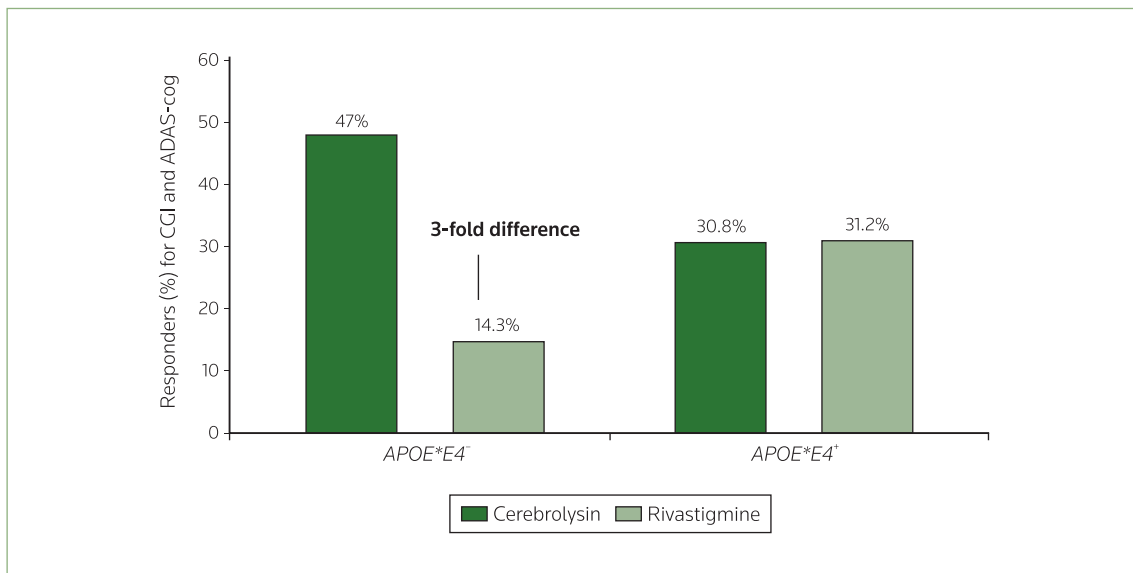


Figure 7. *APOE*E4* genotype-related percentage of responders for Clinical Global Impression (CGI) and Alzheimer's Disease Assessment Scale-cognitive subpart (ADAS-cog), at week 16 after treatment with Cerebrolysin or rivastigmine. The rate of responders among patients with *APOE*E4*⁻ in the first group was more than three times higher than that in the rivastigmine group. No differences were noted in *APOE*E4*⁺ carriers. N = 60. Data from Gavrilova et al. (28).

considerable improvement) and ADAS-cog (improvement of ≥ 4 points). *APOE*E4*⁺ carriers comprised 43.4% in the Cerebrolysin group and 53.5% in the rivastigmine group. At study endpoint, responder rates were about 30% among *APOE*E4*⁺ carriers in both treatment groups. Most interestingly, the responder rate in patients not carrying the *APOE*E4* genotype was 47.0% in the Cerebrolysin group and 14.3% in the rivastigmine group (Fig. 7).

USE OF CEREBROLYSIN FOR THE TREATMENT OF VASCULAR DEMENTIA

Prevention of recurrent strokes and progression of the disease are the main goals in the treatment of VaD, thus antiplatelet drugs and controlling major vascular risk factors represent the major therapeutic approaches. Therapeutic options also include hemorheologic agents, which have shown some cognitive improvement by increasing cerebral blood flow. Cholinesterase inhibitors are used in the treatment of VaD due to the involvement of the cholinergic system in VaD, although they show only symptomatic and small cognitive benefits and have not been approved to date for the treatment of VaD (36). Neurotrophic drugs are also under investigation and are

expected to be useful for VaD since they target a broader spectrum of the pathologic cascade.

Several clinical trials have been performed with Cerebrolysin to evaluate safety and efficacy in VaD (Table II). Diagnosis of VaD was performed according to NINDS-AIREN (National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences) and/or the DSM-IV and was confirmed by MRI or CT in several trials. Patients with psychiatric illnesses were excluded. Therapeutic efficacy was assessed in the cognitive, functional and global domains.

The largest clinical trial in VaD was recently performed by Guekht et al. (37) to confirm and extend previous findings in clinical trials. This study was designed as a randomized, double-blind, placebo-controlled, multicenter trial over 24 weeks having enrolled 242 patients. All patients received 100 mg p.o. acetylsalicylic acid over 24 weeks as basic therapy and intravenous infusion of 20 mL of Cerebrolysin (n = 121) or placebo (n = 121) once daily on 5 days per week over 4 weeks as add-on therapy. The intravenous course was repeated after a treatment-free interval of 2 months, accounting for a total of

Table II. Summary of main clinical trials of Cerebrolysin in vascular dementia.

Trials	N (Cerebrolysin/ placebo)	Arms	Treatments	Doses	Main outcomes	Ref.
Xiao et al., 1999	147 (75/72)	Cerebrolysin 0.9% NaCl	4 weeks	30 mL	MMSE, CGI, HamD, SCAG, NAI, ADL, Trail-Making Test	(38)
Muresanu, 1999	64 (32/32)	Cerebrolysin	30 days	30 mL	MMSE, Short Test of Mental Status	(40)
Guekht et al., 2011	242 (121/121)	Cerebrolysin 0.9% NaCl	2 x 4 weeks	20 mL	ADAS-cog, CIBIC+	(37)
Muresanu et al., 2008	41 (10 mL: 16; 30 mL: 15/10)	Cerebrolysin 0.9% NaCl	4 weeks	10/30 mL	MMSE, ADAS-cog, qEEG	(44)
Yakhno et al., 1996	20	Cerebrolysin	20 days	30 mL	Tinneti's standard clinical performance scale, MMSE, Orientation Memory Concentration Test, various memory assessment tests, test for the dynamic changes of speech, Schulte's test, WAIS, WCST, Special behavioral test, qEEG	(45)
Rainer et al., 1997	645	Cerebrolysin	18 days on average	30 mL	Clinical symptoms, CGI	(41)

ADL, Activities of Daily Living; HamD; Hamilton Rating Scale for Depression; NAI, Nuremberg Age Inventory; qEEG, quantitative electroencephalogram; WAIS, Wechsler Adult Intelligence Test; WCST, Wisconsin Cards Sorting Test. See Table I for other abbreviations.

40 infusions. Study endpoint was on week 24, 2 months after the last infusion. Subjects included were aged 50 to 85 years with a confirmed diagnosis of VaD, baseline MMSE scores between 10-24, modified Hachinski Ischemic score over 4, and Hamilton Rating Scale for Depression scores of 15 or less. Primary outcome measures were score changes from baseline in the ADAS-cog+ and CIBIC+; analyses were based on the ITT data set. No differences in baseline characteristics were observed. At study endpoint, patients on Cerebrolysin improved by -10,628 points in the ADAS-cog+ yielding a least squares mean (LSM) difference between Cerebrolysin and placebo of -6.17 points (95% CI -8.22/-4.13; $P < 0.0001$) (Fig. 8).

These findings were confirmed by responder (improvement ≥ 4 points) analyses with 82.1% of patients in the Cerebrolysin group responding compared to 52.2% in the placebo group. The odds ratio for achieving a response in the cognitive domain was 4.190 (95% CI

2.306/7.615; $P < 0.05$) for Cerebrolysin versus placebo at week 24, indicating a 4.2-fold increased probability of clinically significant cognitive improvement during the study period. In the CIBIC+, Cerebrolysin resulted in a mean score difference to placebo of -0.84 ($P < 0.0001$). The rate of responders (score of < 4) at week 24 was also higher in the Cerebrolysin group with 75.2% compared to 37.4% in the placebo group (Fig. 9). The odds ratio for achieving a favorable CIBIC+ response was 5.081 (95% CI 2.889/8.936; $P < 0.05$) for Cerebrolysin versus placebo. Responder rates of the combined response in ADAS-cog+ and CIBIC+ were 67.5% in the Cerebrolysin group compared to 27.0% in the placebo group. The odds ratio was 5.633 (95% CI 3.201/9.913; $P < 0.05$) for Cerebrolysin versus placebo at week 24. Also in the MMSE, Cerebrolysin was significantly superior over placebo with an LSM difference of 1.486 points (95% CI 0.039/2.931; $P = 0.0442$) at week 24. The same was noted regarding activities of daily living as measured by the ADCS-ADL (LSM difference

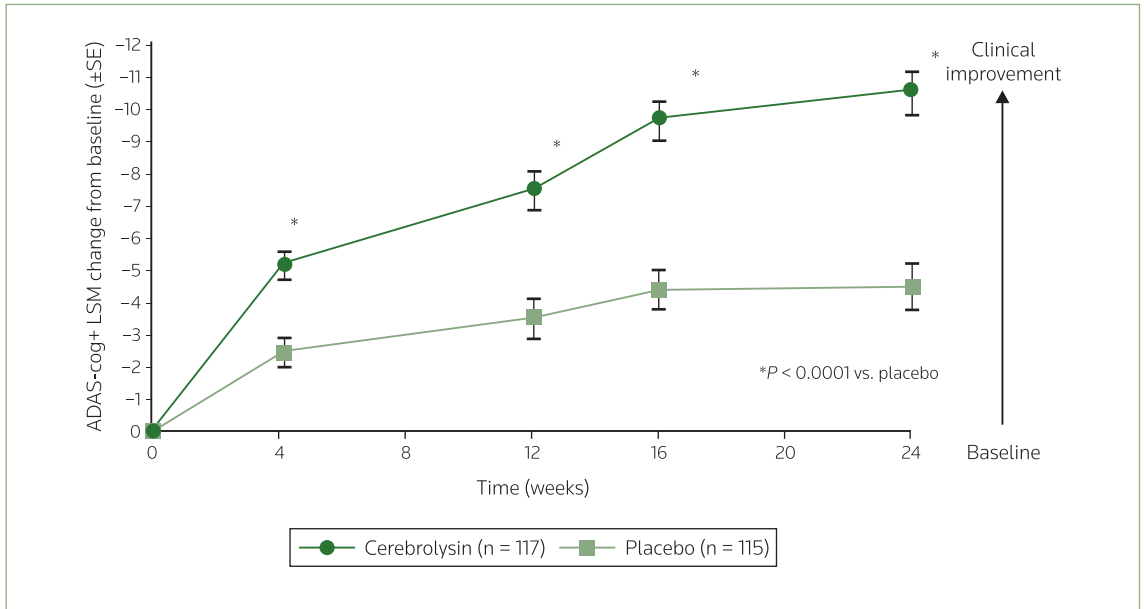


Figure 8. Least squares mean (LSM) changes from baseline in Alzheimer's Disease Assessment Scale-cognitive subpart, extended version (ADAS-cog+). Negative score changes represent cognitive improvement from baseline. N = 232. Intention-to-treat data set. *P < 0.0001. (Reproduced from Guekht, A.B. et al. *Cerebrolysin in vascular dementia: improvement of clinical outcome in a randomized, double-blind, placebo-controlled multicenter trial.* J Stroke Cerebrovasc Dis 2011, 20(4): 310-8 [37]. © 2011, with permission from Elsevier.)

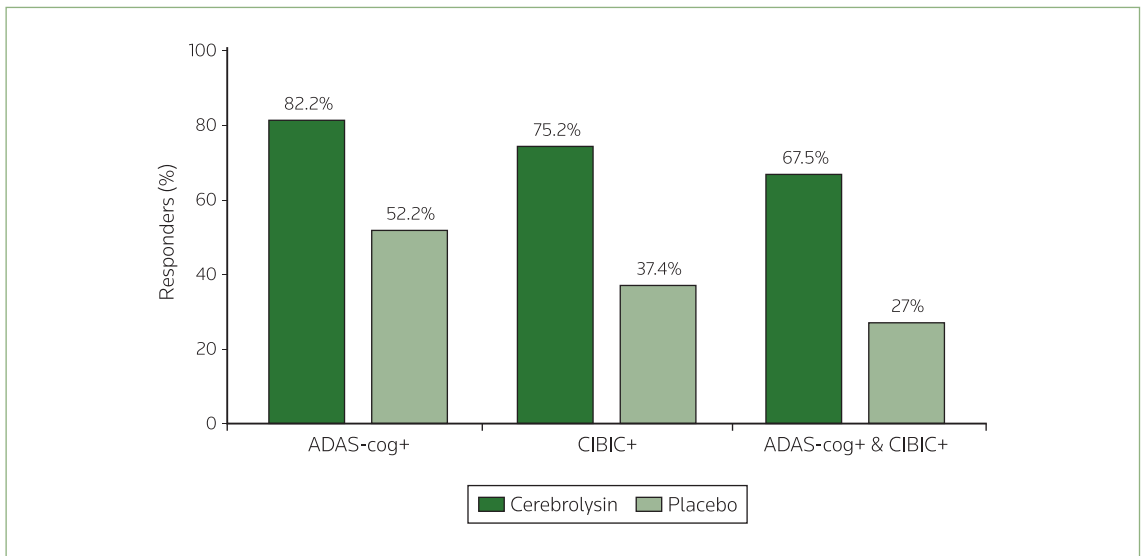


Figure 9. Responder rates to Cerebrolysin (20 mL) and placebo for Alzheimer's Disease Assessment Scale-cognitive subpart, extended version (ADAS-cog+) and Clinicians Interview-Based Impression of Change plus caregiver input (CIBIC+) at week 24 in patients with mild to moderately severe vascular dementia. Responders in ADAS-cog+ were defined as improvement ≥ 4 points from baseline; responders in the CIBIC+ had a score of > 4 , indicating improvement or no change from baseline. Intention-to-treat data set. Data from Guekht et al. (37).

6.325 points; 95% CI 4.185/8.463; $P < 0.0001$) and in the executive function as measured by the Trail-Making Test (LSM difference -15.312 s; 95% CI $-30.284/-0.340$; $P = 0.0451$) and the Clock-Drawing Test (LSM difference 0.917 points; 95% CI 0.448/1.387; $P = 0.0002$). Similar results for the primary and secondary efficacy measures were obtained in the PP data set. Results from the subgroup analysis of patients with more advanced cognitive impairment (MMSE ≤ 20) demonstrated that Cerebrolysin exerts even slightly larger treatment effects. In summary, the results of this study showed that Cerebrolysin improves clinical outcomes in patients suffering from mild to moderately severe VaD by improving cognition and overall clinical functioning; these benefits were maintained for at least 6 months.

Xiao et al. (38) reported the results of a randomized, double-blind, placebo-controlled, multicenter trial investigating the effects of Cerebrolysin on 147 patients suffering from mild to moderately severe VaD (Global Deterioration Scale 3-5; MMSE 15-25; Hamilton Rating Scale for Depression ≤ 15 ; Hachinski Ischemic Score ≥ 7). Diagnosis of VaD was supported by CT or MRI. The patients received intravenous infusions of 30 mL of Cerebrolysin ($n = 75$) or placebo ($n = 72$) once daily for 5 days per week over 4 weeks. Primary outcome measures were MMSE and CGI on week 4, the study endpoint. Baseline characteristics were similar between treatment groups. At week 4, patients on Cerebrolysin improved by 2.7 points in the MMSE compared to 1.7 points in the placebo group ($P = 0.028$). A statistical trend was observed for the drug effect in the CGI in favor of Cerebrolysin ($P = 0.08$). Beneficial effects of Cerebrolysin on functional abilities were observed in the Trail-Making Test ($P = 0.017$).

Supportive evidence for cognitive improvement in mild to moderate VaD derives from a randomized, double-blind, placebo-controlled trial performed by Vereschagin et al. (39). Patients received either 15 mL Cerebrolysin ($n = 30$) or placebo ($n = 30$) daily over 28 days. Evaluation on day 28 showed significant superiority ($P < 0.05$) of Cerebrolysin over placebo on abstract and practical thinking as well as on memory as measured by the Arnold-Kohlmann's psychological test. Beneficial influence of Cerebrolysin on cognitive performance in patients suffering from VaD was also reported by Muresanu (40) in a randomized, open-labeled, placebo-controlled trial. Of 64 patients included, 32 patients were treated with 30 mL Cerebrolysin or placebo once

daily over 30 days. A significant improvement was observed in five of six items in the MMSE and in orientation, instant memory (immediate recall), short memory (recall) and calculation items in the Short Test of Mental Status.

A postmarketing surveillance study in a patient cohort ($N = 645$) suffering from VaD (53%), AD (24%) or mixed forms of dementia (23%) was performed by Rainer et al. (41). After treatment with Cerebrolysin over approximately 18 days, patients improved in memory (62% of patients), concentration (65% of patients), mood and fatigue (50% of patients), and vertigo (47% of patients). Approximately 80% of patients improved in the CGI.

Smaller pilot studies compared the clinical effect of Cerebrolysin with its impact on attenuating electroencephalogram (EEG) slowing as observed in VaD (42, 43). A significant positive correlation between cognitive improvement (ADAS-cog) and attenuated EEG slowing was reported by Muresanu et al. (44) from a placebo-controlled trial with 41 patients. Similar results were observed in an open-labeled trial performed by Yakho et al. (45).

CONCLUSIONS

Clinical trials have consistently shown that Cerebrolysin is an effective treatment option for patients suffering from dementia of different origin. In VaD, Cerebrolysin improved cognitive deficits and global clinical impression and showed a correlating improvement of EEG activities. In patients with mild to moderate AD, Cerebrolysin significantly improved cognition and the overall clinical response for up to 3 months after active treatment. Beneficial effects were also reported in activities of daily living and in behavior. Due to the observed long-lasting treatment effects, Cerebrolysin improved symptoms but also seemed to delay disease progression, which is in line with its pleiotropic mode of action targeting different molecular pathways in the pathophysiologic cascade of AD. Treatment effects of Cerebrolysin were shown to be dose-related with doses of 10 to 30 mL being most effective in improving the cognitive deficits while higher doses of up to 60 mL were most effective in treating behavioral deficits, which become relevant at more advanced stages of the disease. Direct comparison of Cerebrolysin with cholinergic treatment resulted in comparable clinical efficacy in mild to moderate AD and synergistic treatment effects were observed by combining both treatment strategies.

In conclusion, clinical data have strongly shown that Cerebrolysin is an effective therapeutic option for patients diagnosed with AD or VaD. Patients treated with Cerebrolysin have evidenced statistically significant and clinically relevant improvements in cognitive abilities and overall clinical functioning. This effect was largely maintained over several months, indicating a long-term beneficial influence of Cerebrolysin on the disease. Due to the drug's pleiotropic mode of action, targeting distinct molecular pathways in the pathologic cascade, treatment with Cerebrolysin goes far beyond pure symptomatic improvement suggesting a potential delay in disease progression.

DISCLOSURES

The production of this manuscript was sponsored by EVER Neuro Pharma, the manufacturer of Cerebrolysin.

R.F. Allegri has been supported by grants from the "Consejo Nacional de Investigaciones Científicas y Tecnológicas" (CONICET) from Argentina, and the "Consejo de Investigación en Salud" (CIS) from the Government of Buenos Aires, Argentina. A. Guekht has received speaker fees from EVER Neuro Pharma and Nycomed-Takeda.

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