Cerebrolysin in Vascular Dementia: Improvement of Clinical Outcome in a Randomized, Double-Blind, Placebo-Controlled Multicenter Trial

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on behalf of the Cerebrolysin Investigators

No drug to treat vascular dementia (VaD) has yet been approved by the American or European authorities, leaving a large population of patients without effective therapy. Cerebrolysin has a long record of safety and might be efficacious in this condition. We conducted a large, multicenter, double-blind, placebo-controlled study in 242 patients meeting the criteria for VaD. The primary endpoint was the combined outcome of cognition (based on Alzheimer’s Disease Assessment Scale Cognitive Subpart, Extended Version [ADAS-cog+] score) and overall clinical functioning (based on Clinician’s Interview-Based Impression of Change plus Caregiver Input [CIBIC+] score) assessed after 24 weeks of treatment. Intravenous Cerebrolysin 20 mL was administered once daily over the course of 2 treatment cycles as add-on therapy to basic treatment with acetylsalicylic acid. The addition of Cerebrolysin was associated with significant improvement in both primary parameters. At week 24, ADAS-cog+ score improved by 10.6 points in the Cerebrolysin group, compared with 4.4 points in the placebo group (least squares mean difference, 6.17; P < .0001 vs placebo). CIBIC+ showed a mean improvement of 2.84 in the treatment arm and 3.68 in the placebo arm, a treatment difference of 0.84 (P < .0001 vs placebo).

These findings were confirmed by responder analyses demonstrating higher rates in the Cerebrolysin group (ADAS-cog+ improvement of ≥4 points from baseline, 82.1% vs 52.2%; CIBIC+ score of <4 at week 24, 75.3% vs 37.4%; combined response in ADAS-cog+ and CIBIC+, 67.5% vs 27.0%). For Cerebrolysin, the odds ratio for achieving a favorable CIBIC+ response was 5.08 (P < .05), and that for achieving a favorable combined response was 5.63 (P < .05). Our data indicate that the addition of Cerebrolysin significantly improved clinical outcome, and that the benefits persisted for at least 24 weeks. Cerebrolysin was safe and well tolerated. Key Words: Vascular dementia—neurotrophic factors—Cerebrolysin—RCT.

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The prevalence of VaD increases steeply with age and varies greatly from country to country, ranging between 1.2% and 4.2% of individuals over age 65 years. The annual incidence of VaD is more homogeneous and is estimated at 6-12 cases per 1,000 persons over age 70 years. This figure is expected to rise given the increasing life expectancy and progressive aging of the world’s population.\(^3,4\) Most importantly, VaD is stepping out from under the shadow of AD and is generating legitimate interest that has been long overdue.

In this respect, identification and implementation of novel therapeutic strategies focusing on stabilization and improvement of cognitive impairment associated with cerebrovascular diseases is of paramount importance. Over the years, substantial attention has focused on potential treatments for VaD, including calcium-channel blockers, acetyllycic acid, platelet aggregation inhibitors, citicoline, the γ-aminobutyric acid derivatives piracetam and oxiracetam, the serotonin 5-HT2 receptor antagonist naftidrofuryl, the xanthine derivatives pentoxifylline and propentofylline, and cholinesterase inhibitors.\(^5\)

The efficacy of purely symptomatic treatment of VaD remains a matter of a debate. According to a recently published meta-analysis on the efficacy and adverse effects of cholinesterase inhibitors (eg, donepezil, rivastigmine, galantamine) and the N-methyl d-aspartate receptor antagonist memantine, these symptomatic medications provide only small benefits in cognition of uncertain clinical significance in patients with mild to moderate VaD. Consequently, substantial effort has been expended in developing therapies for various stages of VaD.\(^6,7\)

One exceptional component for treating VaD seems to be Cerebrolysin, which is commonly used to treat AD. Cerebrolysin is a neuropeptide preparation that mimics the action of neurotrophic factors. Because of its composition, it requires parenteral administration for full bioavailability. Because of its mode of action, it must be administered over a short time period.

Data from earlier clinical studies have shown positive clinical effects of Cerebrolysin in patients with VaD and AD. Significant improvement has been demonstrated in cognitive performance, as demonstrated by clinical global impression tests (eg, Clinician’s Interview-Based Impression of Change [CIBIC+], Clinical Global Impression [CGI]), neuropsychological tests (eg, Alzheimer’s Disease Assessment Scale Cognitive Subpart, Extended Version [ADAS-cog+], Mini Mental State Examination, Syndrom-Kurz-Test [SKT]), executive function tests (eg, Trail-Making Test), and activities of daily living tests (eg, disability assessment in dementia [DAD], physical self maintenance scale [PSMS], instrumental activities of daily living [IADL]).\(^8-17\) These findings have been supported by the results of electrophysiologic testing, including electroencephalography.\(^18\) These findings suggest a potential for Cerebrolysin as an effective treatment in VaD.

The main objective of the present study was to investigate whether treatment with Cerebrolysin improved both cognition and overall clinical functioning in a larger VaD patient cohort, using the 2 primary outcome variables of ADAS cog+ score and CIBIC+ score. The secondary objectives were to evaluate the efficacy of Cerebrolysin on activities of daily living and executive function, and to assess Cerebrolysin’s clinical safety and tolerability. We report the results of a multicenter, double-blind, placebo-controlled clinical trial that demonstrate the efficacy and safety of Cerebrolysin in VaD.

**Methods**

This was a 24-week, randomized, double-blind, placebo-controlled clinical trial conducted to evaluate the safety and efficacy of Cerebrolysin in patients with VaD. The trial was conducted in accordance with the Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects in the 1989 Declaration of Helsinki, and the protocol and consent forms were approved by independent ethics committees.

**Patient Population**

Male or postmenopausal female patients age 50-85 years with a diagnosis of VaD were considered for inclusion, based on the National Institute of Neurologic Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) criteria\(^19\) and confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan. Only patients with mild to moderately severe dementia (MMSE score of 10-24) and with a modified Hachinski Ischemic Score\(^20\) of >4 and a Hamilton Depression Rating Scale\(^21\) score of ≤15 were included. Patients with severe concomitant neurologic or psychiatric illnesses were excluded, as were patients with any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol, and patients with a history of systemic cancer within the preceding 2 years.

Care was taken to include only patients suffering from dementia of vascular origin, as clearly reflected in the inclusion and exclusion criteria. However, due to the complex etiology of VaD, the possibility that patients with other forms of dementia were included cannot be ruled out.

**Protocol**

Patients were assigned to either the Cerebrolysin arm or the placebo arm according to a random allocation. **PROC PLAN** in SAS version 8.2 (SAS Institute, Cary NC) was used for randomization. Block randomization (blocks of 4 patients each) was used to ensure that the 2 treatment arms were of nearly equal size.

The random allocation sequence was concealed throughout the trial through the use of sealed, sequentially
CEREBROLYSIN IN VASCULAR DEMENTIA

numbered, identical cardboard boxes containing blinded study medication according to the allocation sequence. Each site’s investigator enrolled eligible patients and assigned them in ascending order to either treatment group. All patients and study personnel, including those who administered the study medications and those who assessed outcomes, were blinded to treatment assignment during the entire study period. Success of patient blinding was not evaluated.

Both treatment arms received 100 mg acetylsalicylic acid orally daily during the entire 24-week study period. Patients in the Cerebrolysin-treated arm received 20 mL Cerebrolysin once daily, diluted with physiological saline solution to a total volume of 100 mL and administered as an intravenous infusion over a period of up to 30 minutes. In the placebo-treated arm, patients received 100 mL of physiological saline solution on the same schedule.

Patients in both the Cerebrolysin and placebo arms received therapy on 5 days per week for 4 consecutive weeks (weeks 1-4), followed by a 2-month treatment-free interval (weeks 5-12) and then resumption of the 5-day-per-week schedule (weeks 13-16), for a total of 40 infusions. Clinical evaluation visits were scheduled for day 0 (screening/baseline), day 28 (end of the first treatment course), day 84 (beginning of the second treatment course), day 112 (end of the second treatment course), and day 168 (study endpoint). These visits involved psychometric evaluations, physical and neurologic examinations, and adverse event (AE) monitoring. CT or MRI scans had to be compatible with a clinical diagnosis of VaD.

Outcome Measures

Primary Efficacy Assessments

The primary efficacy measures were the ADAS-cog+ score and CIBIC+ score. The changes in both scores from baseline to week 24 were defined as the primary study endpoints. ADAS-cog+ is an extended version of the original ADAS-cog test designed to increase the sensitivity to detect changes in patients with milder impairment. Three brief subtests extend the cognitive domains covered and assess visual attention (digit cancellation), executive function (a maze), and delayed recall.

Words used in subtests were adapted to national linguistic usage. The ADAS-cog+ test has a maximum score of 85, with an increasing score indicating cognitive deterioration. The test was administered by qualified investigators.

Unlike in the other tests, for the Clinical Interview-Based Impression of Severity (CIBIC+) test, the patient and caregiver interviews were conducted together, and the rater had access to the results of other testing instruments used in the study. At all subsequent visits, the investigator conducting the CIBIC+ and CIBIS+ test did not have access to any patient information collected before or during the study or any other assessment measures. The CIBIC+ test was administered by a qualified independent rater assigned by the investigator. The test rates patients on a 7-point ordinal scale (4 points, no change; 5, 6, and 7 points, increasing degree of deterioration; 3, 2, and 1 points, increasing degree of improvement).

Secondary Efficacy Assessments

The secondary efficacy measures used in this study included the MMSE, the ADCS-ADL (Alzheimer’s Disease Cooperative Study–Activities of Daily Living), the Trail-Making Test A, and the Clock-Drawing Test, all of which were administered by qualified investigators.

Safety Assessments

Safety was assessed at every visit by recording AEs, physical and neurologic examinations, vital signs, and laboratory results (chemistry, hematology, and urinalysis). AEs were recorded at each visit throughout the study period. All events were coded using Medical Dictionary for Regulatory Activities terminology. A Data Safety Monitoring Board was not used. AEs were followed up until the event had subsided, the condition was considered medically stable, or the patient was no longer available for follow-up. Any AEs occurring after a patient provided informed consent were documented in the case report form (CRF) and were rated by the investigator in terms of severity (mild, moderate, or severe) and relationship to Cerebrolysin therapy (not related, unlikely, possible, probable, or definite).

Statistical Analysis

Sample size calculation for this study was based on the ADAS-cog+ results of earlier clinical studies in AD, in which the Cerebrolysin arm showed an improvement from baseline to week 24 of 1.8 ± 9.0 points, whereas the placebo arm worsened by 2.3 ± 9.0 points over the same period, accounting for a treatment difference of 4.1 points. On the basis of this mean change in the ADAS-cog+ score, the required sample size was calculated, assuming a one-sided α-level of 0.025 and desired power of 90%. A total of 103 patients per group was needed to reject the null hypothesis. Taking into account potential ambiguities associated with this sample size calculation, the final sample size for this study was set at 120 patients per group.

The primary and confirmatory analyses were based on the intention-to-treat (ITT) analysis data set. The last observation carried forward (LOCF) method was applied to account for missing data.

The primary analysis for ADAS-cog+ was an analysis of covariance (ANCOVA) on the change in score from baseline to week 24, comparing the differences among
study groups. The ANCOVA model included the week 24 ADAS-cog+ change score as a dependent variable and the ADAS-cog+ baseline score as a covariate. The primary analysis for CIBIC+ compared the distribution of the week 24 (visit 5) scores between the 2 treatment arms, using the $\chi^2$ test of no overall association between treatment and CIBIC+ score.

In addition, a supportive analysis was performed after the scales were dichotomized for defining responders. For the ADAS-cog+, responders were defined as those with at least a 4-point improvement in ADAS-cog+ score from baseline to visit 5. For the CIBIC+, responders were defined as those with a CIBIC+ score of <4 at visit 5. This allowed for another interpretation of treatment group differences, as well as external validation of study results with reference to other trials.

Center and age were explored as covariates in the analysis of both primary endpoints. In addition, the MMSE score at screening was evaluated as a possible confounder in the analysis of the CIBIC+. The ANCOVA of each efficacy endpoint also included the baseline value of that endpoint as another covariate.

For the secondary efficacy analyses, the ADAS-cog+ and CIBIC+ scores and the combined response of both were analyzed at weeks 4, 12, 16, and 24 using logistic regression. The ANCOVA model was used to assess the change from baseline at weeks 4, 12, 16, and 24 for the MMSE score, ADCS-ADL score, Trail-Making Test time, and Clock-Drawing Test score. All safety evaluations were analyzed in a descriptive sense.

### Results

#### Subject Disposition

A total of 260 patients were screened, and 242 entered the study and were randomized to receive either placebo ($n = 121$) or Cerebrolysin ($n = 121$). A total of 217 patients (89.7%) completed the study. The number of patients who discontinued the study early was similar in the 2 groups, 14 (5.8%) in the Cerebrolysin arm and 11 (4.5%) in the placebo arm. Withdrawal of consent was the main reason cited for patient discontinuation in both groups (Fig 1). Whenever possible, patients who discontinued were followed for the entire study period.

#### Baseline Characteristics

The 2 study groups had similar demographic and other baseline characteristics. A similar pattern was found for other analysis data sets, inclusive the safety analysis set. Notably, approximately 70% of patients in both groups were diagnosed with probable VaD according to the NINDS-AIREN criteria. In terms of risk factors, signs of peripheral arterial disturbance (1.7% overall) and depression (3.0% overall) were rare, whereas hypertension (97.0%) was very common.

Key baseline characteristics for the individual treatment groups (ITT data set) are presented in Table 1. No individual center results are presented, because the centers did not have sufficient numbers of patients to make such analyses potentially valuable.

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**Figure 1.** Patient disposition; ITT = intention to treat analysis.
**Primary Efficacy Outcome**

**Change in ADAS-cog+ Score From Baseline to Week 24**

One of the 2 primary study endpoints was the change in ADAS-cog+ score from baseline to week 24 for the ITT analysis data set, using LOCF for missing data. The mean baseline ADAS-cog+ scores were 29.5 for Cerebrolysin and 30.2 for placebo. The least squares (LS) mean change from baseline to week 24 was −10.6 points in the Cerebrolysin arm and −4.4 points in the placebo arm (Fig 2). These results indicate improved cognitive function from baseline to week 24 in both groups. Comparison of the LS mean change from baseline showed a significant \( P < .0001 \) superiority of Cerebrolysin over placebo, with a difference of −6.2 points at week 24. Results from the ANCOVA model, which included treatment as a factor and baseline ADAS-cog+ score as a covariate, demonstrated \( P < .0001 \) for treatment and \( P = .0525 \) for baseline score. ANCOVA analyses adjusted for age or center as an exploratory prognostic factor resulted in \( P \) values of <.0001 for both treatment groups.

**CIBIC+ Score at Week 24**

The second primary endpoint of this study was ordinal response in the change from baseline to week 24 for the ITT analysis data set using LOCF for missing data. \( P \) values obtained from the row mean score differs (or \( \chi^2 \)) test of Cerebrolysin versus placebo indicated a significant association between treatment group and response \( (P < .0001) \).

Statistical results of the shift in CIBIC+ score at week 24 for the ITT analysis data set using LOCF indicated that the majority of patients in the Cerebrolysin group (75.3%, vs 37.4% in the placebo group) demonstrated improvement. In the placebo group, the majority of patients remained unchanged (45.2%, vs 17.1% in the Cerebrolysin group) (Fig 3).
Secondary Efficacy Outcome

In the MMSE, measuring cognitive impairment, Cerebrolysin was significantly superior over placebo (LS mean difference, 1.486 points; 95% confidence interval [CI], 0.039-2.931 points; \( P = .0442 \)) at week 24. Similar results were found in the realms of activities of daily living, as measured by the ADGS-ADL (LS mean difference, 6.325 points; 95% CI, 4.185-8.463 points; \( P < .0001 \)), and executive function, as measured by the Trail-Making Test (LS mean difference, -15.312 seconds; 95% CI, -30.284 to -0.340 seconds; \( P = .0451 \)) and the Clock-Drawing Test (LS mean difference, 0.917 points; 95% CI 0.448-1.387 points; \( P = .0002 \)) (Table 2).

Similar results for the primary and secondary efficacy parameters were obtained in the per-protocol data set.

Safety Assessment

The safety data set comprised all patients randomized into the study who received at least one dose of the study drug. The incidence of treatment-emergent AEs was low, with 32 events in 11 patients (9.1%) in the Cerebrolysin arm and 9 events in 7 patients (5.9%) in the placebo arm. There was no difference in the incidence of individual AEs between the 2 groups. In both groups, the majority of AEs were of mild intensity. The most common AEs were headache, asthenia, and dizziness. No serious AEs were reported in the placebo arm. Three serious AEs (ie, acute pyelonephritis, malignant lung neoplasm, and rectosigmoid cancer) occurred in the Cerebrolysin arm but were considered unrelated to Cerebrolysin treatment.

The number of patients who discontinued the study because of AEs was similar in the 2 groups, 3 patients (2.5%) in the Cerebrolysin arm and 2 patients (1.7%) in the placebo arm. Analyses of laboratory parameters (hematology, clinical chemistry, and urinalysis) revealed no group-specific differences or relevant changes from baseline to week 24. No deaths were reported in the study group. In summary, treatment with Cerebrolysin was safe and well tolerated in this study.

Discussion

The results of this double-blind, placebo-controlled trial of patients with mild to moderate VaD demonstrate that patients given Cerebrolysin as an add-on to acetysalicylic acid therapy had significant improvements in all primary and secondary outcome measures compared with baseline and compared with those given placebo. These outcome measures included assessment of cognition (ie, ADAS-cog, MMSE), global function (ie, CIBIC+), activities of daily living (ie, ADGS-ADL), and executive functions (ie, Trail-Making Test, Clock-Drawing Test).

The drug-placebo differences seen in the present study were not driven by worsening status in the placebo group. The relative lack of deterioration observed in the placebo arm is supported by the results of previous studies that used NINDS-AIREN criteria to enroll patients and found minimal cognitive decline well beyond 24 weeks. The lack of deterioration in the placebo-treated patients might be explained by treatment of vascular disease risk factors and concomitant conditions.28

What cannot be fully explained is the response in the placebo arm over time. Some evidence suggests an additive nature of specific treatment effects and placebo

![Figure 3](image-url)
effects. The placebo effect also depends strongly on the route of drug administration. The improvement effect might be even more pronounced in patients receiving intravenous infusions, as was done in the present study.

Improved cognitive function was observed in both treatment groups but was significantly more pronounced in the Cerebrolysin arm. Of note, improvement continued after cessation of active treatment. The second treatment cycle reinforced the improvement; however, the extent was less pronounced.

A recent study in patients with mild to moderate AD demonstrated a statistically significant treatment effect of Cerebrolysin, with a drug-placebo difference of 4.1 points on the ADAS-cog+ test. This value is lower than that found in the present study possibly because of the greater memory impairment in AD compared with the multifocal cognitive deficits in VaD.

Comparable improvement was seen in the MMSE score at week 24. Cerebrolysin was superior over placebo (LS mean difference, 1.486 points; 95% CI, 0.039-2.932 points; \( P = .0442 \)) at week 24. The stabilization of cognitive decline observed over the 24-week period is certainly relevant to clinical practice. The long-term effect is in excellent agreement with Cerebrolysin's known neurotrophic activity.

A previous meta-analysis of the efficacy of cholinesterase inhibitors and memantine in treating VaD found significant effects on the ADAS-cog score for all drugs studied, ranging from a 1.10-point mean difference for rivastigmine to a 2.17-point mean difference for 10 mg donepezil. These differences would be of uncertain clinical significance for VaD patients, providing only symptomatic benefits for a limited time. Cerebrolysin has quite different pharmacologic and clinical properties, however.

In the CIBIC+ test, a global measurement of improvement showed a statistically significant treatment difference between Cerebrolysin and placebo at week 24. These findings were confirmed by responder analyses. In the CIBIC+, the rate of responders was higher in the Cerebrolysin group, with 75.3% reflecting significant clinical improvements, as opposed to only 37.4% in the placebo group.

Cerebrolysin had favorable effects on activities of daily living, as demonstrated by significant improvements compared with placebo. This is in agreement with earlier findings in AD, affecting a major component of VaD. Patients with VaD have early executive dysfunction. Loss of executive control function is characterized by poor planning and disorganized thoughts, behaviors, and emotions. The Trail-Making Test and the Clock-Drawing Test both showed significant improvement over time with Cerebrolysin treatment, far exceeding that seen in the placebo arm (Table 2).

Patients with VaD represent a frail population given their comorbid conditions and concomitant medication use. Thus, the safety profile of medical interventions is of paramount importance in these patients. The AEs reported in this trial were mild to moderate in intensity and transient in effect. The incidence of treatment-emergent AEs was quite low, with only 32 events occurring in 11 patients (9.1%) in the Cerebrolysin arm and 9 events in 7 patients (5.9%) in the placebo arm. No deaths occurred during the study period.

In summary, the results of the present study demonstrate that Cerebrolysin at a daily dose of 20 mL is safe and effective for treating patients with mild to moderately severe VaD. These benefits extend for at least 24 weeks. With improvements continuing for up to 8 weeks after active treatment, Cerebrolysin demonstrated an effect that apparently extends beyond symptomatic treatment, similar to that reported in previous studies of patients with AD. A multinational study is needed to confirm these results and to further evaluate the effects of Cerebrolysin in patients with VaD.

We thank Professor Amos Korczyn for reviewing the manuscript.

Table 2. Estimated treatment differences for change from baseline to week 24 in MMSE score, ADCS-ADL score, Clock-Drawing Test score, and Trail-Making Test time (seconds), ITT data set

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References

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