# A 28-week, double-blind, placebo-controlled study with Cerebrolysin in patients with mild to moderate Alzheimer's disease

**E. Ruether[a], R. Husmann[b], E. Kinzler[c], E. Diabl[d], D. Klingler[d], J. Spatt[e], R. Ritter[f], R. Schmidt[g], Z. Taneri[h], W. Winterer[f], D. Koper[j], S. Kasper[j], M. Rainer[k] and H. Moessler[j]**

*[a]Goettingen University Clinic for Psychiatry, Goettingen, Germany; [b]St John's Protestant Hospital, Bielefeld, Germany; [c]Private Clinic, Duesseldorf, Germany; [d]Linz General Hospital, Neurology Department, Linz, Austria; [e]Rosenhuegel Neurological Hospital, Vienna, Austria; [f]Private Ambulance, Freiburg, Germany; [g]University Hospital for Neurology, Graz, Austria; [h]Private Ambulance, Duisburg, Germany; [i]EBEWE Pharmaceuticals Ltd, Unterach, Austria; [j]ViennaGeneral Hospital, University Clinic for Psychiatry, Vienna, Austria and [k]Hospital SMZ-Ost, Psychiatry Department, Vienna, Austria*

Address correspondence to Prof Dr. E. Rüther: Psychiatrische Klinik und Poliklinik der Georg-August-Universität V. Siebold-Straße 5, 0-37075 Göttingen, Germany;
Tel: +49 551 396 600; fax: +49 551 392 798

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## Introduction

Cerebrolysin (Cere) is a compound with neurotrophic activity which has been shown to be effective in the treatment of Alzheimer's disease AD in earlier trials. The efficacy and safety of repeated treatments with Cere were investigated in this randomized, double-blind, placebo-controlled, parallel-group study.

## Methods

This was a 7 month, randomized, double-blind, placebo-controlled, parallel-group study conducted at nine investigational sites, hospitals and ambulances in Germany and Austria, with 149 patients being enrolled in two groups: Cere 30 ml (n=76) and placebo (n=73). Patients were screened for study entry within 14 days of the baseline visit, at which time eligible patients were randomized into the study. The selected demographic data are presented in Table 1. (No significant group differences were observed at baseline). Thereafter, patients received i.v. infusions of either Cere or placebo 5 days per week for 4 weeks. This regimen was repeated after 2 months treatment-free interval. The week 4 visit was scheduled 4 weeks after the baseline examination, within 8 days of the end of the first treatment. The week 12 visit was scheduled 12 weeks after baseline; the week 16 visit was scheduled 16 weeks after baseline, within 8 days from the end of the second treatment. A follow-up examination week 28 was scheduled 28 weeks after baseline, 3 months after the end of active treatment. The study was conducted under double-blind conditions until after the week 28 follow-up visit, and thus, followed current guideline recommendations requiring a 6-month double-blind study period.

**Table 1. Selected demographic data and baseline disease characteristics**

| | Treatment | |
|---|---|---|
| | **Cerebrolysin (n = 74)** | **Placebo (n = 70)** |
| Age (years)[a] | 72.5 ± 0.92 | 73.5 ± 0.91 |
| Gender (%) | | |
| Male | 26 (35.1) | 34 (48.6) |
| Female | 48 (64.9) | 36 (51.4) |
| GDS (%) | | |
| Stage 2 | 2 (2.7) | 5 (7.1) |
| Stage 3 | 14 (18.9) | 12 (17.1) |
| Stage 4 | 29 (39.2) | 26 (37.1) |
| Stage 5 | 25 (33.8) | 22 (31.4) |
| Stage 6 | 4 (5.4) | 4 (5.7) |
| CGI Severity of disease[a] | 5.24 ± 0.07 | 5.16 ± 0.07 |
| HIS[a] | 3.0 ± 0.17 | 3.2 ± 0.16 |
| MMSE[a] | 17.0 ± 0.45 | 17.5 ± 0.53 |
| ADAS-cog[a] | 32.0 ± 1.44 | 30.2 ± 1.57 |

[a]Values are means ± SEM. No significant group differences were observed at baseline.

Efficacy was evaluated based on the cognitive performance and the clinical global assessment of the patients. Primary efficacy measures were the Alzheimer's Disease Assessment Scale cognitive subpart (ADAS-cog) and the Clinical Global Impression (CGI). The CGI is a seven-point ordinal scale and our version provided for ratings from 1 to 8, where 5 reflected no change from baseline, ratings of 4, 3, 2, reflected increasing degrees of improvement of global impression and 6, 7 and 8 reflected increasing worsening from baseline. A rating of 1 was used if the patient could not be assessed. Secondary outcome measures included the Syndrome-Short-Test (SKT), the Montgomery-Asberg Depression Rating Scale (MADR-S), the activities of daily living subpart of the Nuremberg Age Inventory (NAI) and the behavioral subpart of the ADAS, the ADAS-noncog.

## Results

One hundred and forty-nine patients were randomized into two treatment groups: 76 patients to Cere and 73 patients to placebo. Of these patients, 76 of Cere and 71 of the placebo group received study medication and 70 and 66 completed the study, respectively. Table 2 and Fig. 3 summarize the descriptive statistics for the primary and for selected secondary efficacy outcome measures for the ITT population. Mean change from baseline, standard error of mean, 95% confidence interval CI and exact probability are shown.

**Table 2. Changes from baseline of primary and selected secondary efficacy parameters (ITT-analysis)**

| | CGI | | ADAS-cog | |
|---|---|---|---|---|
| | **Cere (n = 74)** | **Placebo (n = 70)** | **Cere (n = 74)** | **Placebo (n = 70)** |
| Endpoint: Week 16 | | | | |
| Mean change from baseline | 4.18 ± 0.11 | 4.60 ± 0.11 | –2.1 ± 0.69 | 1.1 ± 0.59 |
| Drugplacebo difference | –0.42 | | –3.2 | |
| 95% Confidence interval | –0.12/–0.72 | | –1.42/–4.98 | |
| P (Cere versus placebo) | 0.004 | | 0.001 | |
| Mean change at week 4 | 4.47 ± 0.08[†] | 4.70 ± 0.10 | –2.4 ± 0.49[**] | –0.4 ± 0.56 |
| Mean change at week 28 | 4.81 ± 0.12 | 4.86 ± 0.12 | 0.0 ± 0.65[*] | 1.6 ± 0.59 |
| | **NAI** | | **ADAS-noncog** | |
| | **Cere (n = 74)** | **Placebo (n = 70)** | **Cere (n = 74)** | **Placebo (n = 70)** |
| Endpoint: Week 16 | | | | |
| Mean change from baseline | –0.5 ± 0.29 | 0.0 ± 0.21 | –1.2 ± 0.45 | –0.2 ± 0.29 |
| Drugplacebo difference | –0.5 | | –1.0 | |
| 95% Confidence interval | –1.2/0.2 | | –2.05/0.05 | |
| P (Cere versus placebo) | 0.071[†] | | 0.003 | |
| Mean change at week 4 | –0.3 ± 0.25 | –0.3 ± 0.19 | –1.3 ± 0.24[**] | –0.3 ± 0.25 |
| Mean change at week 28 | 0.0 ± 0.32[†] | 0.4 ± 0.30 | –0.1 ± 0.38[*] | 0.9 ± 0.37 |

Values are means ± SEM; For the CGI, lower scores indicate improvement. For the ADAS-cog, the NAI and the ADAS-noncog, negative score changes indicate improvement. [†]p<0.1; [*]p<0.025; [**]p<0.01.

Cere-treated patients exhibited significantly superior clinical global impression when compared to placebo-treated patients at the week 16 primary endpoint of the study, after the end of the active therapy. At week 28, according to the responder analysis, patients treated with Cere still had superior CGI scores compared to placebo patients (Fig. 2). Comparable results were observed in the cognitive domain, the second primary parameter of this study. Changes in the ADAS-cog over time are depicted in Fig. 1. Improvement of cognitive function correlated well with improvement of the clinical global score. At week 16, 27 of the 47 Cere-treated patients 57.4% who responded in the CGI also showed an improvement of ≥4 points in the ADAS-cog. The percentage of combined responders was significantly higher in the Cere group, at week 16 as well as at week 28.

**Fig. 1. Time course of the ADAS-cog: mean change from baseline (± SEM) of Cere-treated and placebo-treated patients. ITT analysis, n=74 for Cere and n=70 for placebo. Negative score differences indicate improvement. [*]p<0.025, [**]p<0.01, [***]p<0.001. Dashed lines indicate the timing of the infusion treatment**

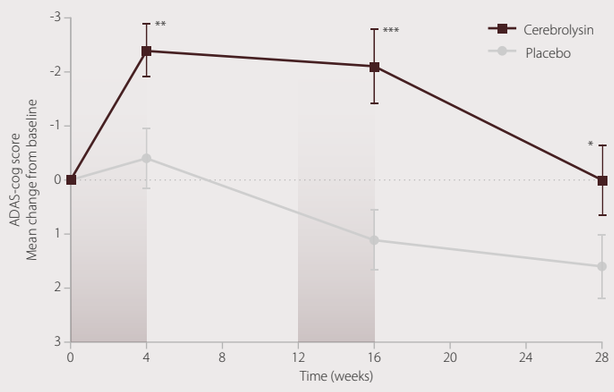
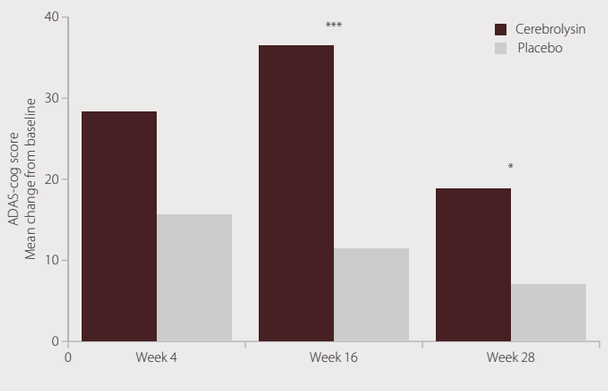
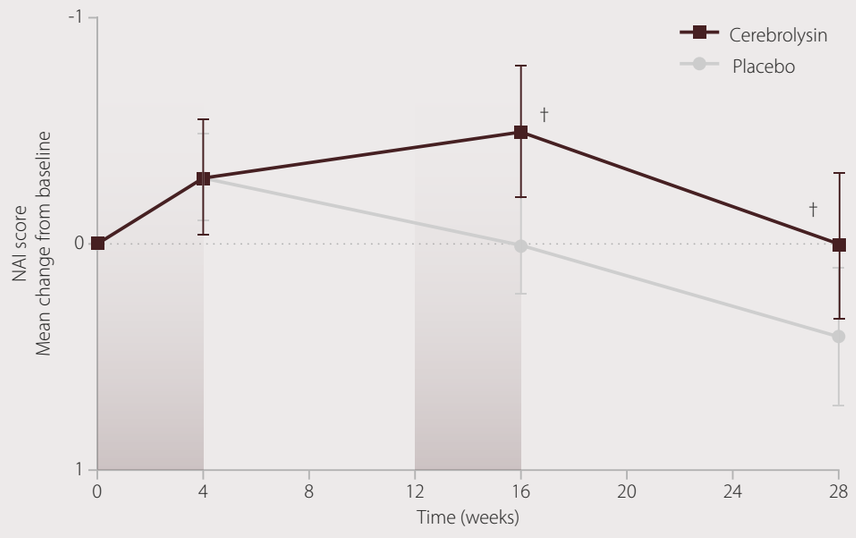



**Fig. 2. Responder analysis. Percentage of patients with treatment response in both primary outcome measures, in the CGI (score <5) and in the ADAS-cog (improvement from baseline ≥4 points). ITT analysis, n=74 for Cere and n=70 for placebo. [*]p<0.025, [***]p<0.001**




The results of the secondary outcome parameters provided supportive evidence for the efficacy of Cere, most prominently in the activities of daily living and behavioral disturbances. In the activities of daily living NAI score treatment differences at the study endpoint favored the Cere group. Although not reaching statistical significance, there was a clear trend P=0.071 in favour of Cere with a drug-placebo difference of 0.5 points (CI -1.2/0.2). Cere patients then started to deteriorate slowly in the washout phase, from week 16 to the week 28 visit, at which time they got back to their baseline levels, but still performed 0.4 points better than the control group P=0.071 (Table 2 and Fig. 3). A significant superiority of Cere over placebo was evident in the ADAS-noncog (Table 2). The analysis of the remaining secondary efficacy measures MADR-S, SKT revealed no important effects.

**Fig. 3. Activities of Daily Living (NAI score): mean change from baseline (± SEM) of Cere-treated and placebo-treated patients. ITT analysis, n=74 for Cere and n=70 for placebo. Negative score differences indicate improvement. [†]p=0.071. Dashed lines indicate the timing of the infusion treatment**




To explore the effects in patients with moderate AD a subgroup analysis of patients with MMSE scores 20 at baseline was performed. One-hundred subjects, 56 Cere and 44 placebo, were included in this analysis. The findings of the ITT analysis were confirmed in this subgroup but drug-placebo differences were even more pronounced. This was largely due to a markedly reduced response of placebo patients in this sample, whereas the response of patients to Cere either remained unchanged or was slightly higher when compared to the ITT sample. In this subgroup, again, a significant superiority of Cere over placebo was evident for both primary parameters at the study endpoint (Table 3).

**Table 3. Results of subgroup analysis of patients with MMSE score <20 at baseline**

| | Week 16 Visit | | Week 28 Visit | |
|---|---|---|---|---|
| | **Cere (n = 56)** | **Placebo (n = 44)** | **Cere (n = 56)** | **Placebo (n = 44)** |
| CGI | | | | |
| Score[a] | 4.18 ± 0.13 | 4.91 ± 0.13 | 4.80 ± 0.14 | 5.11 ± 0.13 |
| Drug/Placebo diff. | –0.73[***] | | –0.31[†] | |
| ADAS-cog | | | | |
| Score change[a] | –2.8 ± 0.82 | 1.5 ± 0.78 | –0.7 ± 0.72 | 2.2 ± 0.84 |
| Drug/placebo diff. | –4.3[***] | | –2.9[**] | |
| NAI | | | | |
| Score change[a] | –0.4 ± 0.33 | 0.2 ± 0.29 | 0.0 ± 0.37 | 0.6 ± 0.41 |
| Drug/Placebo diff. | –0.6[†] | | –0.6 | |
| ADAS-noncog | | | | |
| Score change[a] | –1.0 ± 0.54 | 0.3 ± 0.39 | 0.0 ± 0.39 | 1.7 ± 0.51 |
| Drug/Placebo diff. | –1.3[***] | | –1.7[***] | |

[a]Values are means ± SEM. Negative differences represent improvement. [†]p<0.05; [**]p<0.01; [***]p<0.001.

## Conclusion

**The neurotrophic compound Cerebrolyisn is safe and effective for the treatment of patients with AD and leads to a statistically significant and clinically relevant improvement of cognitive performance and clinical global impressions. Most importantly, the therapeutic benefit is maintained in part for at least 3 months after drug withdrawal, suggesting a stabilizing effect of Cere in patients with AD. Long-term studies are warranted to further explore the possibility for Cere to slow the progression of AD. Issues such as the optimal therapy-free interval between successive treatments will need to be addressed.**

## Related references

1. Original article: International Clinical PSYCHOPHARMACOLOGY.2001,16:253-263
2. POSTER: Gauthier S et al., 2014. Cerebrolysin in mild to moderate Alzheimer's disease: A meta-analysis of randomized controlled clinical trials