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Cerebrolysin
A Review of its Use in Dementia

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Data Selection

Sources: Medical literature published in any language since 1980 on 'cerebrolysin', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search term was 'cerebrolysin'. Searches were last updated 1 October 2009.

Selection: Studies in patients with dementia who received cerebrolysin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Cerebrolysin, neurotrophic, Alzheimer's disease, vascular dementia, dementia, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Cerebrolysin is a parenterally administered, porcine brain-derived peptide preparation that has pharmacodynamic properties similar to those of endogenous neurotrophic factors. In several randomized, double-blind trials of up to 28 weeks' duration in patients with Alzheimer's disease, Cerebrolysin was superior to placebo in improving global outcome measures and cognitive ability. A large, randomized comparison of Cerebrolysin, donepezil or combination therapy showed beneficial effects on global measures and cognition for all three treatment groups compared with baseline. Although not as extensively studied in patients with vascular dementia, Cerebrolysin has also shown beneficial effects on global measures and cognition in this patient population. Cerebrolysin was generally well tolerated in clinical trials, with dizziness (or vertigo) being the most frequently reported adverse event. Although further studies with Cerebrolysin, including longer term trials and further exploration of its use in combination with cholinesterase inhibitors, are needed to more clearly determine its place in the management of Alzheimer's disease and vascular dementia, available data suggest that Cerebrolysin is a useful addition to the treatment options available for dementia.

Pharmacological Properties

Several *in vitro* and *in vivo* studies have shown that Cerebrolysin has neurotrophic effects similar to those of endogenous neurotrophic factors. Cerebrolysin improved the viability of cultured neurons *in vitro* and rescued medial septal cholinergic neurons following intraperitoneal administration in rats after transections of fimbria-fornix in the brain. Peripheral administration of Cerebrolysin also produced neuroprotective effects, limiting neuronal dysfunction and maintaining the structural integrity of neurons under detrimental conditions in preclinical studies in animal models. In addition, Cerebrolysin showed effects as a synaptic modulator, potentially improving the integrity of neuronal circuits in a transgenic mouse model of Alzheimer's disease (mThy1-hAPP751), and various *in vitro* and *in vivo* studies showed that Cerebrolysin promotes neurogenesis. Behavioural effects, including amelioration of performance deficits in transgenic mice (mThy1-hAPP751), have also been demonstrated with Cerebrolysin. Although its mechanism of action at a molecular level has not been fully elucidated, a potentially significant effect of Cerebrolysin is that of reduced phosphorylation of the amyloid precursor protein and amyloid-β peptide production via modulation of kinases GSK3β and CDK5. Taken together, preclinical and radiolabelling studies indicate that, following peripheral administration, Cerebrolysin crosses the blood-brain barrier in sufficient concentrations to produce pharmacodynamic effects in the CNS.

Therapeutic Efficacy

Several randomized, double-blind, placebo-controlled studies of up to 28 weeks' duration in patients with Alzheimer's disease have demonstrated that, compared with placebo, intravenously administered Cerebrolysin produced a consistent, statistically significant improvement on global measures, as assessed by Clinician Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) or Clinical Global Impression (CGI) of severity or change (CGIS/C). Several of these studies also showed statistically significant improvements on cognition, as assessed by the Alzheimer's Disease Assessment Scale (ADAS-cog) or its extended version (ADAS-cog-plus). Beneficial effects of Cerebrolysin on these co-primary outcomes were observed in patients with mild to moderate disease as well as in subgroups of patients with greater cognitive impairment at baseline, and when outcomes were measured at the end of the treatment period or several weeks after the final dose. A large, randomized, 28-week comparison of Cerebrolysin, donepezil or combination therapy showed beneficial effects on global measures (CIBIC-plus scores) and cognition (ADAS-cog-plus scores) for all three treatment groups compared with baseline. Although effects on cognitive improvement were most pronounced with combination therapy (–2.339), followed by Cerebrolysin (–1.708) then donepezil (–1.258), there were no statistically significant differences between groups. The proportions of CIBIC responders in the respective treatment groups were 62.7%, 64.1% and 37.8%. Beneficial effects of Cerebrolysin on other outcomes, including behaviour (as assessed by the Neuropsychiatric Inventory), were shown in some trials.

In patients with vascular dementia, Cerebrolysin was superior to placebo, as assessed by CIBIC-plus and ADAS-cog (co-primary endpoints) in a large, well designed, 24-week trial. Other studies with Cerebrolysin in patients with vascular dementia have also demonstrated beneficial effects on global outcomes and cognition.

Tolerability

Tolerability data from studies in patients with dementia indicate that Cerebrolysin was generally well tolerated in all clinical trials. The incidence of any treatment-emergent adverse event was 43.4–64% with Cerebrolysin compared with 38.0–73% with placebo in three larger, placebo-controlled trials in patients with Alzheimer's disease. Commonly reported adverse events with both Cerebrolysin and placebo included dizziness (or vertigo), headache, increased sweating, nausea, urinary tract infection, depression and fever, although there was marked variability between studies in terms of the type and incidence of adverse events. The incidence of adverse events in the large, active-comparator trial was generally similar between Cerebrolysin, donepezil and combination therapy arms. The most frequently reported adverse events with Cerebrolysin-containing regimens included aggression, agitation, anorexia, arthralgia, delusion, dizziness, headache, hypokinesia, insomnia and urinary tract infection. Donepezil was most frequently associated with diarrhoea, dysthymic disorder, muscle spasms and nausea. In general, adverse events reported with Cerebrolysin in patients with Alzheimer's disease were broadly similar to those reported in patients with vascular dementia.

1. Introduction

Dementia is a decline in mental ability that usually develops and progresses slowly, affecting memory, thinking, judgement and personality,[1] although the nature, onset and progression of symptoms also depends on the type of dementia.[1,2] It primarily affects individuals aged >60 years and is a leading cause of disability in the elderly.[3]

Alzheimer's disease is an age-related neurodegenerative disorder and the most common form of dementia,[1,4] representing ≈50–70% of cases.[1] It is usually associated with a gradual decline in cognitive function, with symptoms such as memory impairment, lapses of judgement and subtle changes in personality in early stages of the disease.[2] As the disease progresses, memory and language problems worsen, changes in behaviour and emotional responsiveness develop, and difficulties arise in performing activities of daily living. Ultimately, Alzheimer's disease affects almost all brain functions, including motor function control.[2]

Vascular dementia, which can develop after successive strokes (multi-infarct dementia), small vessel disease or other mechanisms,[1,2] is the second most common form of dementia, representing ≈30% of cases.[1] Vascular dementia often has a rapid onset and is generally not associated with personality changes or abnormal levels of emotional responsiveness until the later stages of the disease.[2]

The worldwide prevalence of dementia in 2001 was estimated at >24 million, including 5 million in the EU and 3.4 million in North America (2.9 million in the US alone).[3] Estimates for 2009 suggest that 5.3 million individuals in the US have Alzheimer's disease.[5] Each year, an estimated 4.6 million new cases of dementia develop worldwide, and global projections suggest that >42 million individuals will be living with dementia in 2020.[3] The health burden of dementia in older individuals and their family caregivers is substantial, as is the associated economic burden.[3,5]

In general, most treatments for dementia do not reverse or halt disease progression.[2] For example, cholinesterase inhibitors, which are widely used in the treatment of patients with Alzheimer's disease, can improve symptoms and slow disease progression, but are unable to reverse existing brain damage or stop the progression to more advanced disease stages.[2,6-11]

Among areas of interest in the search for disease-modifying therapies in dementia is the use of neurotrophic factors. Different neurotrophic factors act on specific receptors to mediate brain development, neuronal maintenance and neuroprotective effects; therefore, in neurodegenerative disorders, the use of neurotrophic factors may rescue degenerating neurons and stimulate terminal outgrowth.[12]

Cerebrolysin is a porcine brain-derived peptide preparation that acts like endogenous neurotrophic factors.[13] It is produced by a standardized enzymatic breakdown of lipid-free brain protein powder and consists of low molecular weight peptides and free amino acids. It is available in over 45 countries in Europe, Asia and the Americas as a solution ready for injection or infusion. The solution is free of proteins, lipids and antigenic properties and each millilitre contains 215.2 mg of the active pharmaceutical ingredient Cerebrolysin concentrate in aqueous solution.[13] This article reviews the pharmacology and therapeutic use of Cerebrolysin in Alzheimer's disease and vascular dementia.

2. Pharmacodynamic Properties

The pharmacodynamic properties of Cerebrolysin have been evaluated in a number of *in vitro* and *in vivo* studies, including cell culture models, models of cognitive impairment or dementia, and biochemical assays. Several of these pharmacodynamic studies have focused on the neurotrophic (growth factor-like) effects of Cerebrolysin (section 2.1). Other studies evaluated behaviour changes associated with Cerebrolysin in animal models (section 2.2) or putative mechanisms of action of Cerebrolysin at a molecular level (section 2.3).

2.1 Neurotrophic Effects

Various pharmacodynamic studies have shown that Cerebrolysin has neurotrophic effects similar to those of endogenous neurotrophic factors, which play an important role in the maintenance of

neuronal function. These pharmacodynamic effects of Cerebrolysin can be categorized in terms of neuronal survival (e.g. trophic and survival-promoting actions), neuroprotection (e.g. limiting neuronal dysfunction, especially in adverse conditions), neuroplasticity (e.g. adaptive responses to changing conditions) and neurogenesis (e.g. promoting differentiation of progenitor cells).

2.1.1 Neuronal Survival

Cerebrolysin was associated with survival-promoting effects on neurons in a low serum (2%) cell stress *in vitro* model in which apoptosis was the primary type of cell death.[14,15] Compared with control, significant ($p < 0.01$) improvements in neuronal viability were demonstrated with Cerebrolysin (0.4 mg/mL medium) after 4 and 8 days.[14] A transient effect was noted with an amino acid mixture, which showed a similar, significant increase in viability after 4 days but not after 8 days. The effect at day 4 was thought to result from improved nutritional supply to the cultured neurons. Cerebrolysin also showed an anti-apoptotic effect, whereas the amino acid culture did not.[14] The mechanism of the anti-apoptotic effect of Cerebrolysin was not determined, but may have resulted from inhibition of calpain,[14] an effect previously demonstrated with Cerebrolysin *in vitro*.[16] Cerebrolysin also prevented the degeneration and atrophy of impaired septal cholinergic neurons when administered intraperitoneally (5 mL/kg/day) for up to 4 weeks in rats after transections of fimbria-fornix in the brain.[17]

2.1.2 Neuroprotection

Various studies suggest that Cerebrolysin has a neuroprotective effect, limiting neuronal dysfunction and maintaining the structural integrity of neurons under detrimental conditions.[18-21] In a murine model of neurodegenerative disease, mice treated with Cerebrolysin (5 mL/kg/day intraperitoneally for 4 weeks) prior to kainic acid-induced lesioning had improved dendritic morphology compared with control animals.[19] However, there was evidence of gliosis in the brains of the Cerebrolysin-treated mice, indicating that Cerebrolysin did not block the damaging effects of kainic acid, but rather promoted regeneration after the lesion.[19] Neuroprotective effects (e.g. changes in rat microglial cell morphology and inhibition of microglial activation) of Cerebrolysin were also shown *in vitro*[18] and in murine models of neurodegeneration.[18,20,21]

2.1.3 Neuroplasticity

Cerebrolysin appears to have beneficial effects on neuronal connectivity in the brain, facilitating adaptive responses to detrimental changes, such as those resulting from neurodegenerative disorders. Neurotrophic effects of Cerebrolysin that promote neuroplasticity have been shown *in vitro* and include the preservation of a well differentiated neuronal network in a chronic low serum (2%) cell stress model of embryonic chick cortical neurons.[22] In an amyloid precursor protein (APP) transgenic mouse model of Alzheimer's disease (mThy1-hAPP751), which overexpresses mutated human APP751 under the control of murine Thy-1 promoter, Cerebrolysin (5 mL/kg/day intraperitoneally for 4 weeks) showed effects as a synaptic modulator, potentially improving the integrity of neuronal circuits.[23,24] In this model, Cerebrolysin-induced increases in synaptophysin levels in the brain were also positively correlated with improved behavioural performance.[23] In addition, Cerebrolysin increased synaptic density (the number of synaptophysin-immunoreactive presynaptic terminals) in specific areas of the brain in murine models.[25-27]

Cerebrolysin 5–20 μL/mL promoted the outgrowth of nerve fibres in explant cultures of dorsal root ganglia and sympathetic trunks from chick embryos, although its effects were less than that observed with nerve growth factor, and higher Cerebrolysin concentrations (e.g. 80 μL/mL) did not increase nerve fibre outgrowth.[28-30] In a human neuronal cell line (NT2N), Cerebrolysin increased synaptic protein expression, which appeared to be mediated by regulation of APP expression.[31] Moreover, neuronal dendrite sprouting was observed in the plasma of healthy volunteers for up to 24 hours after both 1 and 7 days' administration of Cerebrolysin 5–20 mL/day intravenously.[32]

2.1.4 Neurogenesis

Cerebrolysin (5 mL/kg/day intraperitoneally for 1 or 3 months) was associated with neurogenic

effects in the hippocampus of transgenic mice (mThy1-hAPP751), as demonstrated by a significant increase in neuronal progenitor cells in the subgranular zone of the dentate gyrus compared with non-transgenic controls.[33] In contrast, saline-treated transgenic mice showed a significant reduction in neuronal progenitor cells. Cerebrolysin was also associated with a reduction in the rate of apoptosis of neuronal progenitors.[33] *In vitro*, Cerebrolysin increased neuron-like differentiated adult rat hippocampal progenitors by inhibiting spontaneous apoptosis,[34] and attenuated the negative effect of elevated fibroblast growth factor-2 on neurogenesis and neuronal differentiation.[35] In addition, Wistar rats treated with Cerebrolysin had a marked increase in the number of newborn neurons in the dentate gyrus, and neurogenesis was correlated with improved water maze performance.[34]

2.2 Behavioural Effects

Cerebrolysin ameliorated spatial learning and memory deficits and improved passive avoidance behaviour in a number of animal models. Behavioural effects were typically evaluated using the Morris water maze, a circular swimming pool with a transparent platform hidden just below the water surface. Cerebrolysin (2.5–5 mL/kg/day intraperitoneally for up to 4 weeks) was associated with amelioration of performance deficits in the Morris water maze in transgenic mice (mThy1-hAPP751),[23] apolipoprotein E-deficient mice,[25] aged rats,[36] rats with fimbria-fornix lesion[37,38] and rats with sensorimotor cortical lesion.[39] In the latter study, the lesion-induced spacial learning and memory acquisition deficit was attenuated by Cerebrolysin when evaluated immediately after the 2-week treatment, but not when measured at 7 or 8 months.[39] As mentioned in section 2.1.4, neurogenic effects observed with Cerebrolysin have also been correlated with improved water maze performance.[34] Cerebrolysin (2.5 mL/kg/day subcutaneously for 7 days) also improved passive avoidance behaviour (a step-through avoidance task using footshock) in aged female (but not aged male) rats.[40]

2.3 Molecular Pharmacodynamics

The biochemical mechanisms by which Cerebrolysin exerts its neurotrophic effects have not been fully elucidated. The peptides of Cerebrolysin may interact with receptors of inhibitory modulators in the brain, such as adenosine A_1 and $GABA_B$.[41-43] Cerebrolysin 2–10 μL/mL suppressed electrically induced synaptic transmission in a concentration-dependent manner in the rat hippocampus *in vitro*, with the most pronounced effect in the CA1 area.[43,44] Although the effect of Cerebrolysin was not blocked by application of a specific $GABA_A$ antagonist,[44] it was partially blocked by a $GABA_B$ antagonist and, to a smaller extent, by the opioid receptor antagonist naloxone in a similar study.[42] These effects appeared to be mediated presynaptically by reducing the release of neurotransmitter, as assessed by membrane input resistance and quantal analysis experiments.[42] Results of a further study showed that Cerebrolysin also appears to act indirectly on presynaptic adenosine A_1 receptors in the rat hippocampus, possibly via release of adenosine.[41]

Cerebrolysin appears to have immunomodulatory effects that may attenuate inflammatory mechanisms associated with neurodegenerative disease, as supported by *in vitro*[18,45] and *in vivo*[18] studies showing that Cerebrolysin reduces microglial expression and lipopolysaccharide (LPS)-induced interleukin-1β release. Potential immunomodulatory mechanisms of the neuroprotective effects of Cerebrolysin were shown *in vitro* in microglial cells from rat brain and *in vivo* in a rat model of neurodegeneration (Aβ4LPS).[18] Cerebrolysin inhibited microglial activation in a concentration-dependent manner *in vitro*, as assessed by changes in rat brain microglial cell morphology and LPS-induced interleukin-1β release. *In vivo*, Cerebrolysin (0.5 and 2 mL/kg/day intraperitoneally for 7 days) was associated with reduced cortical interleukin-1β overexpression and reductions in brain ED1 expression.[18]

Findings from a transgenic mouse model of Alzheimer's disease (mThy1-hAPP751), in which Cerebrolysin 5 mL/kg/day administered

intraperitoneally for 6 months was associated with a reduction in the neurodegenerative pathology (e.g. amyloid burden in the brain, reduced synaptic pathology), suggest that these beneficial effects may be mediated by regulating APP maturation and transport to sites where amyloid-β peptide (Aβ), the proteolytic product of APP, is generated.[21] Shorter term administration of Cerebrolysin in this model has also been associated with a reduction in Aβ burden in the brain[23] and amelioration of age-associated amyloid deposition in the cerebral vasculature.[46]

Cerebrolysin-induced attenuation of synaptic and behavioural deficits in APP transgenic mice appeared to be mediated by a reduction in APP phosphorylation resulting from changes in the activity of specific kinases (glycogen synthase kinase-3β [GSK3β]) and cyclin-dependent kinase-5 [CDK5]), which also regulate the microtubule-associated protein TAU.[21] Amelioration of neurodegenerative alterations in the hippocampus of a new combined AAV2-mutTAU/APP transgenic mouse model was accompanied by significant reductions in TAU phosphorylation at GSK3β- and CDK5-dependent sites after 3 months' treatment with Cerebrolysin 2.5 mL/kg intraperitoneally.[20]

Cerebrolysin-induced biochemical changes were correlated with behavioural and functional improvements in a subgroup of patients with Alzheimer's disease in a clinical trial[47] (discussed further in section 4[48]). At week 24 (12 weeks after study treatment), serum levels of tumour necrosis factor-α (TNFα) were significantly reduced ($p < 0.01$) and serum levels of dissociable insulin-like growth factor-I (IGF-I) were significantly increased ($p < 0.05$) in a dose-dependent manner with Cerebrolysin compared with placebo.[47] Although there was no significant correlation between biochemical and clinical results in the overall cohort of 207 patients, increased total IGF-I levels were positively correlated with improvement in activities of daily living (Disability Assessment in Dementia [DAD] score) [$r = 0.191$; $p = 0.034$] and negatively correlated with neuropsychiatric symptoms (Neuropsychiatric Inventory [NPI] score) [$r = -0.194$; $p = 0.031$] in the subgroup of patients with late-onset Alzheimer's disease.[47]

Cerebrolysin increased the expression of the blood-brain barrier GLUT1 glucose transporter in the brains of young and old rats[49] and *in vitro* via messenger RNA stabilization.[50] Increased abundance of GLUT1 associated with Cerebrolysin may contribute the effects of Cerebrolysin on cognitive function, as the transport of glucose (a critical nutrient for the brain) from blood to brain is mediated by the blood-brain barrier GLUT1 glucose transporter.[49,50]

3. Pharmacokinetic Properties

Pharmacokinetic data on Cerebrolysin are limited, as might be expected for a product that consists of amino acids and low molecular weight peptides with similarity to endogenous peptides. Data are derived primarily from animal tissue distribution studies that directly or indirectly assessed whether Cerebrolysin components cross the blood-brain barrier;[51,52] one of these studies has not yet been published.[51]

Tissue concentrations of ^{125}I-Cerebrolysin were measured by quantitative gamma counting ≈35 minutes after intravenous administration of a mixture of labelled and unlabelled Cerebrolysin (mean 0.79 mg [111 μL] and 35.24 μCi) in Sprague-Dawley rats.[51] Across various regions of the brain (e.g. frontal cortex, hippocampus, septal nucleus, pons, medulla, cerebellum), the mean tissue concentrations of ^{125}I-Cerebrolysin were 170–237 ng per gram of tissue; mean concentrations ranged from 188–329 ng/g in spinal cord tissue. Much higher concentrations were found in peripheral organs or tissues (e.g. kidney 32 159, liver 1707, lung 774 and muscle 774 ng/g). At ≈30 minutes after intravenous administration, the mean concentration of ^{125}I-Cerebrolysin in blood was 4501 ng/g.[51]

Additional evidence that Cerebrolysin crosses the blood-brain barrier comes from a study using a rat model of cerebral ischaemia.[52] Bilateral carotid artery occlusion was associated with deterioration in motor ability, which was counteracted by administration of Cerebrolysin by intraperitoneal

Table I. Commonly used instruments to assess the clinical efficacy of Cerebrolysin in dementia (adapted from Scott and Goa[7] with permission)

Instrument	Scale	Efficacy measure assessed and properties
ADAS-cog	0–70 points; higher scores reflect greater cognitive impairment	An 11-item questionnaire that examines various aspects of cognitive function, including memory, comprehension, orientation, attention and reasoning. A change of ≥4 points generally reflects a clinically significant change[53]
ADCS-ADL	0–78 points; higher scores indicate better functioning	Assesses ability to undertake activities of daily living, including personal care, communicating and interaction with others, maintaining a household, conducting hobbies and interests, and making judgements and decisions
CIBIC-plus	7-point scale; 1 indicates a marked improvement, 4 no change and 7 a marked worsening	Encompasses the patient's global state, cognition, behaviour and activities of daily living and involves observation of the patient plus interviews with both the patient and caregiver
CGI (CGIS/C)	7-point scale; disease severity: 1 indicates not ill and 7 indicates extremely ill; global change: 1–3 varying degrees of improvement; 4 no change; 5–7 varying degrees of deterioration	Based on investigator's experience with patients and assesses disease severity and/or global change on the basis of a comprehensive interview
DAD	0–46 points; higher scores indicate better functioning	Assesses patient's ability to undertake activities of daily living, including basic self care, social interaction, participation in housework and hobbies, and handling of financial matters
MMSE	30-point scale; higher scores indicate better functioning	A 30-item questionnaire that uses simple questions and problems to screen for cognitive impairment. A change of ≥3 points generally reflects a clinically significant change[53]
NPI	0–120 points; higher scores reflect greater disturbances	Scores ten behavioural disturbances and neuropsychiatric symptoms that occur in patients with dementia (including anxiety, disinhibition, delusions, hallucinations and agitation/aggression)

ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale; **ADCS-ADL** = Alzheimer's Disease Cooperative Study that includes Activities of Daily Living inventory; **CGI** = Clinical Global Impression; **CGIS/C** = Clinical Global Impression of Severity/Change; **CIBIC-plus** = Clinician Interview-Based Impression of Change plus Caregiver Input; **DAD** = Disability Assessment in Dementia; **MMSE** = Mini Mental State Examination; **NPI** = Neuropsychiatric Inventory.

administration (100 mg/kg/day) or continuous intraventricular infusion (0.0057 mg/day) for 3 or 4 days. Also of note is that a much higher dose of Cerebrolysin (0.57 mg/day) by intraventricular infusion adversely affected motor activity and spatial memory of intact rats.[52] This appears to be in agreement with results of a placebo-controlled, dose-finding study, which showed an inverted dose-dependent treatment effect of Cerebrolysin on cognition (section 4.1.1).[48]

4. Therapeutic Efficacy

The clinical efficacy of Cerebrolysin in dementia has been evaluated in a number of studies in patients with Alzheimer's disease (section 4.1) or vascular dementia (section 4.2). Although most of the clinical trials with Cerebrolysin have been of short duration (typically involving 4–12 weeks of treatment), some longer term follow-up data (up to 28 weeks) are available. A wide range of instruments was used in the assessment of clinical efficacy across the trials; some of the more commonly used instruments in clinical trials with Cerebrolysin are briefly described in table I. In all trials, Cerebrolysin was administered intravenously.

4.1 Alzheimer's Disease

Clinical trial data on the efficacy of Cerebrolysin in Alzheimer's disease are available from several randomized, double-blind, placebo-controlled studies,[48,54-61] a randomized, open-label, placebo-controlled trial,[62] a recently completed, randomized, double-blind comparison with donepezil (including a combination treatment arm),[63,64] and an open-label comparison with oral rivastigmine.[65] One of the placebo-controlled trials is a dose-finding study,[48] and a subgroup analysis in patients with greater cognitive impairment has also been conducted.[54] A similar subgroup analysis[58] of

another placebo-controlled trial[57] is also available, as is a longer term extension[59] of a different placebo-controlled trial.[60] To date, the subgroup analysis of the dose-finding study[54] and the comparative trial with donepezil[63,64] have not yet been fully published. Results of placebo-controlled trials are discussed in section 4.1.1 and those from active-comparator trials are discussed in section 4.1.2.

Inclusion and exclusion criteria were generally consistent across the trials. Patients were eligible for inclusion if they had a probable diagnosis of Alzheimer's disease according to National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[48,54-58,61,62,64,65] a Modified Hachinski Ischemia score ≤4[48,54,55,60,61,64,65] or <5,[56-58] a Mini-Mental State Examination (MMSE) score of 15–25,[60] 14–24,[57,61] 14–25,[48,62] 12–25,[64] 12–24,[65] 10–24,[55] or 10–26,[56] and age ≥50,[48,54,55,57,62,64,65] ≥55[60,61] or >60[56] years. The two subgroup analyses in patients with more severe cognitive impairment included those with MMSE scores ≤19[58] or ≤20.[54] Some studies also used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or earlier versions) for a probable diagnosis of Alzheimer's disease,[48,54,61,62,64,65] and one trial required patients to be hospitalized as part of its inclusion criteria.[55] Essentially all of the studies used the same exclusion criteria to ensure Alzheimer's disease as the cause of dementia. As such, patients with psychiatric disorders such as schizophrenia or major depression were excluded, and an MRI or CT scan was required within the previous year to exclude cerebrovascular disease.

4.1.1 Placebo-Controlled Trials

Although a wide range of instruments was used to evaluate the efficacy of Cerebrolysin in placebo-controlled trials (particularly for assessment of secondary endpoints), several randomized, double-blind studies used similar co-primary endpoints of (i) change from baseline in ADAS-cog or the extended version of ADAS-cog (ADAS-cog-plus) score; and (ii) scores for CIBIC-plus (or CGIS/C) [see table I for full names of instruments].[48,54-58] In some cases, these co-primary endpoints were assessed at the end of the treatment period,[55,57,58] whereas in other trials they were assessed several weeks after the treatment period.[48,54,56] All of these trials used an intent-to-treat (ITT) analysis, with the last observation carried forward (LOCF) method applied in the case of missing data[48,54-58] (see section 7 for a commentary on the use of LOCF in dementia studies).

Results of the randomized, double-blind, placebo-controlled studies with Cerebrolysin in which these co-primary endpoints were evaluated (table II) showed a consistent, statistically significant improvement on global measures (CIBIC-plus or CGIS/C) in all four trials in patients with mild to moderate Alzheimer's disease[48,55-57] and in the two subgroup analyses of patients with greater cognitive impairment at baseline.[54,58] In addition, statistically significant improvements on cognition (ADAS-cog or ADAS-cog-plus) were shown in several of the placebo-controlled trials[48,55,57] and subgroup analyses.[54,58] Moreover, these effects occurred whether primary efficacy outcomes were assessed at the end of the treatment period[55,57,58] or several weeks after the final dose of study treatment.[48,54,56] The only trial that did not show a statistically significant between-group difference in ADAS-cog or ADAS-cog-plus scores was one in which a 4-week course of Cerebrolysin was administered and the primary analysis was conducted several weeks later (at week 12).[55] Although improvements in ADAS-cog or ADAS-cog-plus scores from baseline to endpoint with Cerebrolysin generally did not exceed 3 points in these trials, between-group differences at endpoint were often ≥4 points (table II). As indicated in table I, a change in ADAS-cog score of ≥4 points generally reflects a clinically meaningful change.

As not all studies showed specific details for between-group comparisons of the ordinal CIBIC-plus (or CGIS/C) responses (1–3 improvement, 4 no change, 5–7 worsening), global function outcomes reported in table II are for the responder analyses (i.e. the proportion of individuals with minimal, moderate or marked improvement), which

Table II. Efficacy of Cerebrolysin (CER) in randomized, double-blind, placebo (PL)-controlled trials in patients (pts) with Alzheimer's disease. Studies that used ADAS-cog (or ADAS-cog-plus) and CIBIC-plus (or CGI [CGIS/C]) as co-primary endpoints are included. Co-primary endpoints were assessed at the end of,[55,57,58] or several weeks after,[48,54,56] treatment. Except where indicated by footnotes, studies were multicentre trials in pts with mild to moderate disease, and results shown are for the intent-to-treat population

Reference	Regimen (mL/day)[a] [no. of pts]	Time of primary analysis (wk)	ADAS-cog or ADAS-cog-plus score (mean change from baseline)[b]	CIBIC-plus or CGI (% of pts with improvement from baseline)[c]
Alvarez et al.[48]	CER 10 (5/7×4 wk then 2/7×8 wk) [60]	24	–1.833*	65.0***
	CER 30 (5/7×4 wk then 2/7×8 wk) [65]	24	–1.356	60.0***
	CER 60 (5/7×4 wk then 2/7×8 wk) [68]	24	–0.063	58.8***
	PL [58]	24	2.266	20.7
Alvarez et al.[54] [subgroup analysis][d]	CER 10 (5/7×4 wk then 2/7×8 wk) [32]	24	–1.838*	59***
	CER 30 (5/7×4 wk then 2/7×8 wk) [34]	24	0.007	56***
	CER 60 (5/7×4 wk then 2/7×8 wk) [35]	24	1.672	46***
	PL [32]	24	4.538	9
Bae et al.[55]	CER 30 (5/7×4 wk) [34]	4	–3.23*	61.8**
	PL [19]	4	–0.36	21.1
Panisset et al.[56]	CER 30 (5/7×4 wk) [93]	12	0.04	76**[e]
	PL [94]	12	–0.88	57
Ruether et al.[57]	CER 30 (5/7×4 wk then no treatment×8 wk then 5/7×4 wk) [74]	16	–2.1***	63.5**[f]
	PL [70]	16	1.1	41.4
Ruether et al.[58] [subgroup analysis][g]	CER 30 (5/7×4 wk then no treatment×8 wk then 5/7×4 wk) [60]	16	–3.0***	65**[h]
	PL [49]	16	1.1	24.5

a CER was administered intravenously in all trials. Notation such as 5/7 or 2/7 indicates the number of days per wk on which the study drug was administered.

b Negative values indicate improvement. Mean baseline values were 34.6–38.2,[48] 43.5–49.7,[54] 32.5–33.5,[55] 23.6–24.2,[56] 30.2–32.0,[57] 35.7–35.8.[58] ADAS-cog-plus used by Alvarez et al.;[48,54] all other studies used ADAS-cog.

c Statistical analysis (p-values) reflect results of the overall CIBIC-plus (or CGIS/C) analysis for ordinal responses (1–3 improvement, 4 no change, 5–7 worsening); specific values shown are the percentage of pts with marked, moderate or minimal improvement from baseline (i.e. scores of 1–3). CIBIC-plus was used by Alvarez et al.[48,54] and Panisset et al.;[56] all other trials used CGI.

d Subgroup analysis of Alvarez et al.[48] in pts with moderate to moderately severe disease (MMSE score ≤20) [results from a single centre in Spain and not fully published].

e Results shown are based on a responder analysis that included pts with no change (as well as those with improvement). Mean treatment difference (–0.21; $p = 0.033$) also favoured CER.

f Although a slightly modified scoring system was used, the responder analysis included only those pts showing improvement. Mean treatment difference (–0.42; $p = 0.004$) also favoured CER.

g Subgroup analysis of Ruether et al.[57] in pts with moderate to moderately severe disease (MMSE score ≤19).

h Although a slightly modified scoring system was used, the responder analysis included only those pts showing improvement. Different p-values were reported in the text (*** $p \leq 0.001$) and abstract (** $p \leq 0.01$) of this study[58] for the comparison of 65% vs 24.5%. Mean treatment difference (–0.75; $p < 0.001$) also favoured CER.

ADAS-cog = cognitive subscale of the Alzheimer's Disease Assessment Scale; **ADAS-cog-plus** = extended version of ADAS-cog; **CGI** = Clinical Global Impression; **CGIS/C** = Clinical Global Impression of Severity/Change; **CIBIC-plus** = Clinician Interview-Based Impression of Change plus Caregiver Input; **MMSE** = Mini Mental State Examination; * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL.

confirmed the results of the CIBIC-plus (or CGIS/C) score analysis in all of the trials.

In the dose-finding study by Alvarez et al.[48] in patients with mild to moderate disease, Cerebrolysin 10, 30 and 60 mL/day (5 days/week for 4 weeks then 2 days/week for a further 8 weeks) was associated with improvement according to CIBIC-plus in 58.8–65.0% of patients compared with 20.7% for placebo ($p < 0.001$ for all comparisons vs placebo). However, there was an inverted dose-dependent treatment effect of Cerebrolysin on cognition, with only the 10 mL/day dosage achieving a statistically significant advantage over placebo for improvement from baseline in ADAS-cog-plus scores at week 24 (treatment difference –4.099 points; 95% CI –8.016, –0.182; $p = 0.038$) [table II]. This was confirmed in the responder analysis of cognitive function outcome, which showed that at week 24 the percentages of patients with a >4-point improvement from baseline in ADAS-cog-plus scores were 41.7%, 36.9% and 29.4% in the Cerebrolysin 10, 30 and 60 mL/day groups, respectively, compared with 24.1% in the placebo group. With respect to secondary outcomes, all Cerebrolysin groups combined improved behavioural disturbances (as assessed by NPI scores) compared with placebo at all timepoints ($p = 0.041$ for the factor treatment effect at week 24). In contrast to the primary efficacy outcomes, the greatest effect on NPI scores was with the highest dose of Cerebrolysin. There were no statistically significant differences between any Cerebrolysin group and placebo for effects on DAD, MMSE and Trails-A scores.

In the subgroup analysis of the dose-finding study in patients with greater cognitive impairment at baseline,[54] placebo recipients had a greater worsening (i.e. increase) in ADAS-cog-plus scores relative to the entire cohort of placebo recipients, whereas the effects of Cerebrolysin in the subgroup with more severe disease were generally similar to those of the entire cohort (table II). As was shown in the overall cohort, there was a statistically significant difference ($p < 0.05$) favouring Cerebrolysin 10 mL/day over placebo for ADAS-cog-plus scores at week 24 in the subgroup analysis. Across all groups, the proportion of patients with minimal, moderate or marked improvement in CIBIC-plus was lower than in the entire cohort, but all doses of Cerebrolysin remained superior to placebo ($p < 0.001$). Results for secondary outcomes were also broadly similar to those for the entire cohort.

Favourable results were demonstrated with Cerebrolysin 30 mL/day (5 days/week) for 4 weeks in a smaller trial in 53 patients with mild to moderate Alzheimer's disease.[55] The study showed significant improvement with Cerebrolysin compared with placebo for both of the co-primary efficacy variables (table II), as well as for the secondary outcome of change in MMSE score from baseline (1.57-point difference favouring Cerebrolysin; 95% CI 0.04, 2.96; $p = 0.04$). Although there was a trend towards more favourable results with Cerebrolysin compared with placebo for other secondary endpoints (Geriatric Depression Scale, Activities of Daily Living, Instrumental Activities of Daily Living [IADL]), none of the between-group differences reached statistical significance.

A larger trial in 187 patients with mild to moderate disease also found that Cerebrolysin 30 mL/day (5 days/week) for 4 weeks was associated with a favourable, statistically significant treatment difference compared with placebo for CIBIC-plus scores (treatment difference –0.21 points; 95% CI –0.50, –0.08; $p = 0.033$) and for the percentage of individuals with stable disease or improvement at week 12 (76% vs 57%; $p = 0.007$).[56] Cerebrolysin did not appear to have an effect on ADAS-cog scores (table II), although it is noteworthy that the co-primary endpoints were evaluated 8 weeks after the last dose of study treatment. Interestingly, placebo recipients did not have a deterioration in ADAS-cog scores at any timepoint during the study, which included a 6-month follow-up. As with ADAS-cog scores, there were no significant differences between Cerebrolysin and placebo at any timepoint in the trial for MMSE scores (a secondary endpoint for cognition). The study also included a pharmacogenetic analysis, which found no significant relationship between ApoE4 genotype and response to treatment.[56]

Another trial showed that two successive 4-week courses of Cerebrolysin 30 mL/day (5 days/week), with an 8-week nontreatment period between courses, was associated with statistically significant improvements in both co-primary endpoints compared with placebo at week 16 in 144 patients with mild to moderate Alzheimer's disease (table II).[57] For ADAS-cog scores, the treatment difference was −3.2 points (95% CI −4.98, −1.42; p = 0.001), and for CGI scores, the treatment difference was −0.42 (95% CI −0.72, −0.12; p = 0.004). The proportion of individuals with improved CGI scores from baseline was also significantly higher in the Cerebrolysin group than in the placebo group (63.5% vs 41.4%; p = 0.006). The study also included a 28-week follow-up visit (i.e. 12 weeks after the last dose of study treatment), and the beneficial effects of Cerebrolysin were maintained at this timepoint; the treatment difference for ADAS-cog scores (−1.6; p = 0.016) and for CGI responder analysis (45.9% vs 28.6%; p = 0.024) significantly favoured Cerebrolysin. Cerebrolysin was also superior to placebo at weeks 16 and 28 with respect to beneficial effects on behaviour, as assessed by the noncognitive subscale of ADAS (a secondary outcome).[57]

For the primary efficacy outcomes (ADAS-cog and CGI) at week 16, results also significantly favoured Cerebrolysin over placebo in a subgroup analysis in 109 patients with greater cognitive impairment at baseline (MMSE scores <20) [table II].[58] Cerebrolysin was also superior to placebo with respect to behavioural changes at weeks 16 and 28 in this subgroup.[58]

In general, results from the randomized, double-blind, placebo-controlled studies included in table II are supported by those from other placebo-controlled trials in patients with mild to moderate Alzheimer's disease (n = 60–157) that were conducted using an open-label design[62] or used other primary endpoints.[59-61] In the open-label trial, 6 weeks of treatment with Cerebrolysin 30 mL/day (5 days/week) was superior to placebo for all three of the co-primary efficacy outcomes (ADAS-cog, CIBIC-plus, DAD) assessed at week 18.[62] A 4-week trial also showed superiority of Cerebrolysin 30 mL/day (5 days/week) to placebo for all three co-primary endpoints (Sandoz Clinical Assessment-Geriatric [SCAG], CGI and a trail-making test [ZVT-G] to assess cognitive performance).[60] Results for SCAG, which assesses clinical symptomatology, remained significantly in favour of Cerebrolysin at week 28 (i.e. 6 months after the end of treatment) in a follow-up analysis[59] that included 101 of 120 patients enrolled in the initial trial, and there was a general trend favouring Cerebrolysin at week 28 for other primary and secondary variables. Another 4-week study showed that Cerebrolysin 30 mL/day (5 days/week) achieved significantly better results than placebo for the co-primary endpoints (MMSE and CGI), as well as for some secondary endpoints including SCAG, one of two trail-making tests assessed, and the Nuremberg Activities Inventory (NAI).[61]

Data are also available from a meta-analysis that included data from five randomized, double-blind, placebo-controlled trials in 772 patients with Alzheimer's disease who received Cerebrolysin (typically 30 mL/day [5 days/week]) for ≥4 weeks.[66] The meta-analysis used a random-effect model to estimate the pooled effect size of Cerebrolysin on CGI/C and ADAS-cog scores.[66] The pooled log-odds ratio of Cerebrolysin versus placebo was 1.1799 (95% CI 0.7463, 1.6135; p < 0.05) for CGI/C, indicating a beneficial effect, and −2.01 (95% CI −4.03, 0.01) for ADAS-cog (not statistically significant). A small but statistically significant effect size (−0.78; 95% CI −1.39, −0.17) was noted for the MMSE scale, but Cerebrolysin had little effect on activities of daily living. However, the meta-analysis may have been limited by the relatively small number of studies and patients included in the various analyses.

4.1.2 Active-Comparator Trials

Two active-comparator trials have been undertaken with Cerebrolysin in patients with mild to moderate Alzheimer's disease: a recently completed, large, randomized, double-blind comparison between Cerebrolysin, donepezil and combination therapy,[63,64] and a smaller, open-label study

comparing the efficacy of Cerebrolysin and rivastigmine.[65]

Comparison with Donepezil and Combination Therapy

Patients were randomized to one of three treatment groups as follows: (i) Cerebrolysin (10 mL/day [5 days/week] intravenously for 4 weeks, followed by an 8-week treatment-free interval, then a second course of 10 mL/day [5 days/week] for 4 weeks); (ii) donepezil (5 mg/day orally for 4 weeks then 10 mg/day for a further 24 weeks); or (iii) combination therapy (Cerebrolysin plus donepezil, as described).[63,64] The co-primary endpoints of the study were change from baseline in ADAS-cog-plus score at week 28 and CIBIC-plus score at week 28; a number of secondary endpoints were also evaluated. A total of 217 patients were randomized, and the primary efficacy analysis was conducted for the ITT population of 197 patients (with the LOCF method applied in the case of missing data). A subgroup analysis was also conducted for patients with greater cognitive impairment at baseline (MMSE ≤20; n = 143). As mentioned earlier in section 4, inclusion and exclusion criteria were similar to those of the placebo-controlled trials, and results of this active-comparator trial have not yet been fully published.

Patient characteristics were well matched between treatment groups. Overall for the ITT data set, the mean age was 75.2 years and 77.2% were female.[63,64] Mean age at the time of first symptoms was 71.3 years, mean duration of illness was 3.9 years and mean MMSE score at baseline was 17.5 (range 12–25). Baseline ADAS-cog scores ranged from 41.2 to 41.8 across the three treatment groups.

All three groups showed improvement from baseline to week 28 in cognitive function (figure 1). Although the effect was most pronounced with combination therapy (ADAS-cog-plus –2.339), followed by Cerebrolysin (–1.708) then donepezil (–1.258), there were no statistically significant differences between groups for comparisons of the least squares mean change from baseline to week 28.[63,64] The effect of treatment on cognitive function appeared to be most rapid in the donepezil-containing arms, as seen by numerically greater ADAS-cog-plus score changes from baseline to week 4 (figure 1).

The other co-primary endpoint was the change from baseline to week 28 for ordinal CIBIC-plus responses. Between-group differences achieved statistical significance only for the comparison between Cerebrolysin and donepezil, which favoured Cerebrolysin ($p < 0.05$).[63,64] The responder analysis for CIBIC-plus at week 28 showed that minimal, moderate or marked improvement was seen in 62.7% of those who received combination therapy, 64.1% of Cerebrolysin recipients and 37.8% of donepezil recipients.

Of note among secondary outcomes was that neuropsychiatric symptoms (as assessed by NPI) improved in all three groups to week 16 (least squares mean change in NPI scores ranged from –1.886 to –2.369) then stabilized in the monotherapy groups but reverted towards baseline levels in the combination therapy arm.[63,64]

Subgroup analysis in 143 patients with MMSE ≤20 at baseline showed that the least squares mean changes from baseline to week 28 for ADAS-cog-plus scores were –0.675 with Cerebrolysin, –1.139 with donepezil and –1.852 with combination therapy.[64] There were no statistically significant treatment differences. There were also no statistically significant differences between groups for CIBIC-plus scores at week 28. When compared with the overall cohort, the effects of treatment on cognitive function and global measures were generally lower in the subgroup of patients with greater cognitive impairment at baseline.

Comparison with Rivastigmine

An open-label study compared the efficacy of Cerebrolysin and rivastigmine in 60 patients with mild to moderate Alzheimer's disease, with the main objective being the identification of possible correlations between the presence of the ApoE4 genotype and the efficacy of Cerebrolysin and rivastigmine.[65] Patients assigned to the Cerebrolysin group (n = 30) received two 4-week courses of Cerebrolysin 30 mL/day (5 days/week) intravenously, separated by an 8-week treatment-free period. Patients assigned to rivastigmine (n = 30)

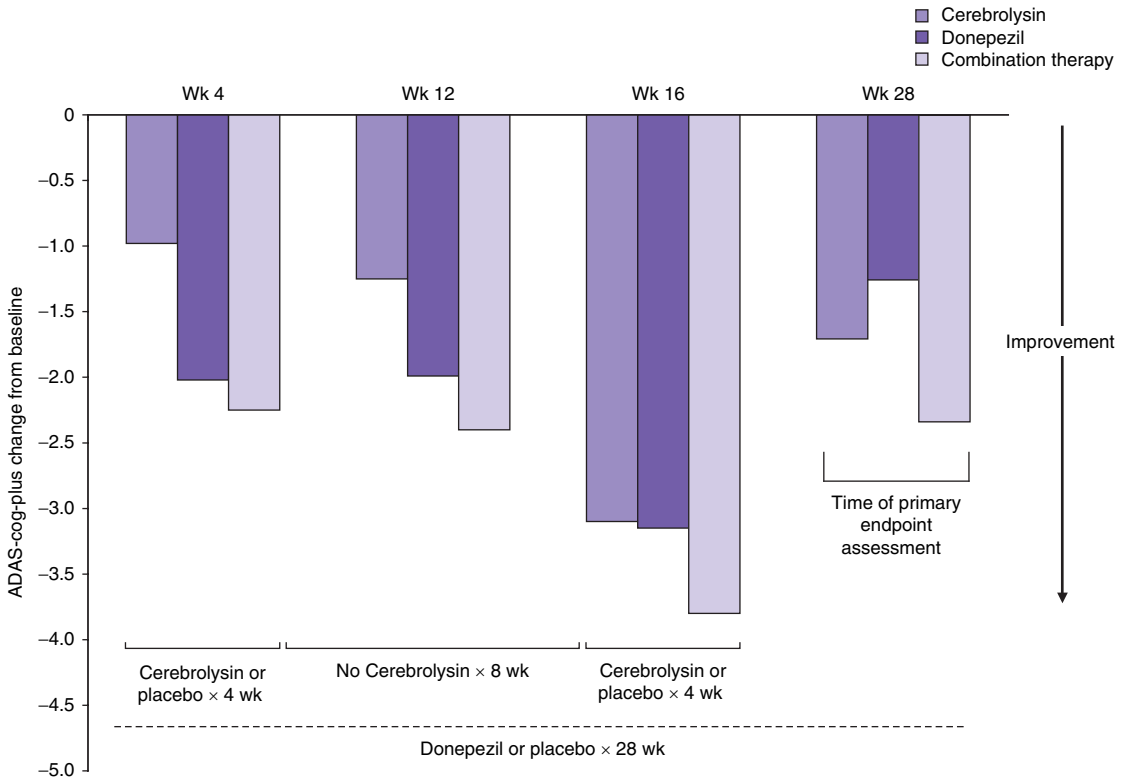

Fig. 1. Effect of Cerebrolysin, donepezil and combination therapy on cognitive function in Alzheimer's disease. Results for ADAS-cog-plus scores (least squares mean change from baseline) in a randomized, double-blind comparative trial.[63,64] Patients with mild to moderate Alzheimer's disease received one of three treatment regimens as follows: (i) Cerebrolysin 10 mL/day (5 days/wk) intravenously for 4 wk, followed by an 8 wk treatment-free interval, then a second course of Cerebrolysin for 4 wk (n = 64); (ii) donepezil 5 mg/day orally for 4 wk then 10 mg/day for a further 24 wk (n = 66); or (iii) combination therapy (Cerebrolysin plus donepezil, as described) [n = 67]. Matching placebos were also administered. Negative score changes represent cognitive improvement from baseline. **ADAS-cog-plus** = extended version of the cognitive subscale of the Alzheimer's Disease Assessment Scale.

received the drug orally at the individual maximum tolerated daily dose (3–12 mg/day) for 16 weeks. Most patients (76.7%) in the rivastigmine group received ≥6 mg/day; 53.3% received 12 mg/day. Follow-up assessment was carried out at week 24 using MMSE, ADAS-cog and IADL scales. In addition, results of ADAS-cog and CGI scores were used to compare response to therapy by ApoE4 genotype.

Approximately half of the patients enrolled in the trial had the ApoE4(+) genotype (43.3% in the Cerebrolysin group and 53.3% in the rivastigmine group).[65] Other patient characteristics, including severity of dementia (37% mild, 63% moderate in both groups), mean age (70.1 vs 70.5 years) and baseline MMSE (18.0 vs 17.6), ADAS-cog (34.8 vs 33.5) and IADL (21.9 vs 21.3) scores, were well matched between the Cerebrolysin and rivastigmine groups.

At week 24 (i.e. 8 weeks after the end of study treatment), there were no statistically significant changes from baseline scores for any of the psychometric scales in the rivastigmine group, whereas statistically significant improvements from baseline were observed in the Cerebrolysin group for ADAS-cog scores (–2.1; $p < 0.05$) and IADL (–0.8; $p < 0.01$), but not for MMSE (0.2).[65] However, at all timepoints assessed during active rivastigmine therapy (weeks 4, 12 and 16), there were statistically significant improvements compared with baseline for all scales. Similarly, at the end of each treatment

course of Cerebrolysin (weeks 4 and 16), there were statistically significant improvements from baseline for all scales. For example, at week 16 in the Cerebrolysin group, mean changes from baseline scores were 1.5 for MMSE, −3.9 for ADAS-cog and −1.2 for IADL (all $p < 0.01$ vs baseline). Among patients with the ApoE4(+) genotype, response to Cerebrolysin or rivastigmine therapy (which was defined as a CGI scale score that corresponded to a moderate or considerable improvement and an improvement in ADAS-cog of ≥4 points) was similar (30.8% vs 31.2%), but the response rate was 47.0% for Cerebrolysin compared with 14.3% for rivastigmine among those with the ApoE4(−) genotype (statistical analysis not reported).

4.2 Vascular Dementia

A number of clinical trials have evaluated the efficacy of Cerebrolysin in vascular dementia, including several randomized, double-blind, placebo-controlled trials,[67-70] a randomized, open-label, placebo-controlled trial,[71] and various pilot studies that concurrently assessed clinical and electrophysiological effects,[72-74] such as cognitive performance and quantitative EEG (qEEG) activity. Also, a large noncomparative trial evaluated the efficacy of Cerebrolysin in patients with vascular dementia or other dementias.[75] Although most of the trials reviewed in this section have been fully published, some are available only in non-English journals,[68,74] and the largest study with Cerebrolysin in vascular dementia (a recently completed, randomized, double-blind, placebo-controlled trial[69,70]) has not yet been fully published.

In general, inclusion and exclusion criteria used in clinical trials with Cerebrolysin in vascular dementia were not as consistent across studies as those used in Alzheimer's disease trials (section 4.1). Nevertheless, some of the vascular dementia trials shared common inclusion criteria, such as a diagnosis of vascular dementia according to criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN)[69,70,73] or DSM-IV[67] or both NINDS-AIREN and DSM-IV,[74] a Modified Hachinski Ischemia Scale score of >4[69,70] or a Hachinski Ischemia Scale score of ≥7,[67,74] MMSE score of 9–26,[73] 10–24[69,70] or 15–25,[67] and age ≥50[68-70,73] or ≥55[67] years. In several studies, diagnosis of vascular dementia was confirmed by MRI or CT scan.[67,69,70,73,74] Various studies excluded patients with psychiatric illnesses, including major depression.[67,69,70,73]

4.2.1 Larger, Randomized, Double-Blind, Placebo-Controlled Trials

In the largest trial, 242 patients with vascular dementia were randomized to receive (as add-on therapy to acetylsalicylic acid 100 mg/day orally) two 4-week courses of Cerebrolysin 20 mL/day (5 days/week) separated by an 8-week treatment-free interval, or placebo, with co-primary endpoints of change from baseline in ADAS-cog-plus score at week 24 and CIBIC-plus score at week 24.[69,70] In the ITT analysis (with LOCF), which included 232 patients, Cerebrolysin was superior to placebo ($p < 0.0001$) in terms of change from baseline in ADAS-cog-plus score at all timepoints evaluated (figure 2). At week 24 (8 weeks after the end of treatment), the least squares mean difference between Cerebrolysin and placebo was −6.17 points (95% CI −8.22, −4.13; $p < 0.0001$). The other co-primary endpoint was the change from baseline to week 24 for ordinal CIBIC-plus responses (1–3 improvement, 4 no change, 5–7 worsening). Cerebrolysin was also associated with a statistically significant advantage over placebo for this parameter ($p < 0.0001$). The responder analysis for CIBIC-plus showed that 75.2% of Cerebrolysin recipients compared with 37.4% of placebo recipients showed clinical improvement (odds ratio 5.081; 95% CI 2.889, 8.936; $p < 0.05$). Cerebrolysin also had statistically significant advantages over placebo for various secondary endpoints, including changes from baseline in MMSE, ADCS-ADL (see table I for full names of instruments), and trail-making and clock-drawing test scores.

A shorter course of Cerebrolysin 30 mL/day (5 days/week) for 4 weeks was also associated with cognitive improvements, as assessed by change

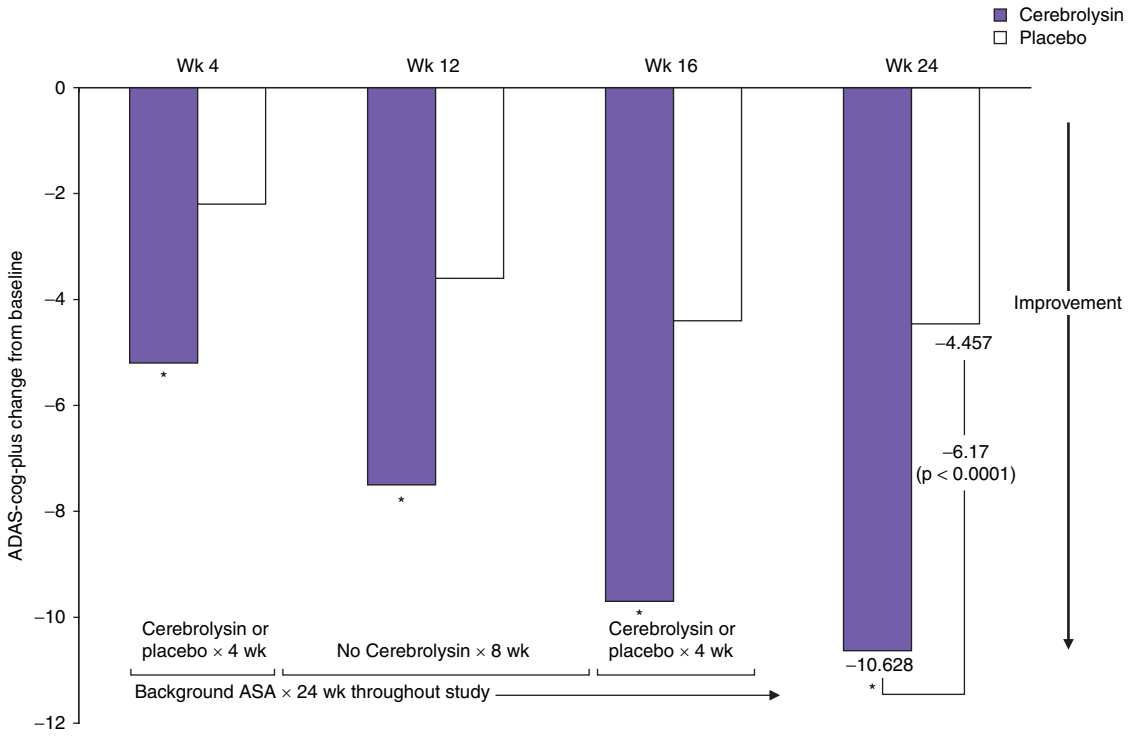

Fig. 2. Effect of Cerebrolysin on cognitive function in vascular dementia. Results for ADAS-cog-plus scores (least squares mean change from baseline) in a randomized, double-blind, placebo-controlled, multicentre trial.[69,70] Patients with vascular dementia received either Cerebrolysin 20 mL/day (5 days/wk) intravenously for 4 wk, followed by an 8 wk period without Cerebrolysin, then a second course of Cerebrolysin for 4 wk (n = 117) or placebo (n = 115). Negative score changes represent cognitive improvement from baseline. **ADAS-cog-plus** = extended version of the cognitive subscale of the Alzheimer's Disease Assessment Scale; **ASA** = acetylsalicylic acid; * $p < 0.0001$ vs placebo.

from baseline in MMSE score at the end of treatment (co-primary endpoint) in another randomized, double-blind, placebo-controlled, multicentre trial, which included 147 patients with mild to moderate vascular dementia.[67] The mean increase in MMSE score from baseline to week 4 was 2.7 points with Cerebrolysin compared with 1.7 points with placebo ($p = 0.028$). There was no statistically significant difference between groups for the other co-primary endpoint, which was the endpoint rating of the investigator's CGI. Several secondary endpoints were also evaluated; the only statistically significant difference was observed for mean changes in trail-making (ZVT) tests, which favoured the Cerebrolysin group ($p < 0.05$).

4.2.2 Other Studies

Beneficial effects of Cerebrolysin were also observed in a randomized, double-blind, placebo-controlled trial in 60 patients with vascular dementia, which found significant benefits with Cerebrolysin 15 mL/day compared with placebo for parameters such as abstract thinking and memory, when assessed after 4 weeks of treatment.[68] Cognitive improvement was also reported in a randomized, open-label trial in which Cerebrolysin 30 mL/day or placebo was administered for 1 month to 64 patients with vascular dementia.[71] Cerebrolysin was associated with a statistically significant advantage over placebo ($p < 0.05$) on five of six items/categories of the MMSE and on three of eight items/categories of the Short Test of Mental Status.

Data are also available from a large, non-comparative study in 645 patients with dementia who were treated with Cerebrolysin 10–50 mL/day for ≥7 days (mean duration 17.8 days);[75] 53% of patients had vascular dementia, 24% had Alzheimer's disease and 23% had mixed forms of dementia. Assessment of efficacy was made using a symptom scale (1 = mild to 5 = severe) for disturbances in memory, concentration, vertigo, fatigue and mood stability, as well as on the basis of CGI. Improvement in symptoms from baseline to the end of treatment was reported in 47–65% of patients, whereas 33–50% experienced no change in symptoms and a small proportion (3%) had signs of deterioration. Approximately 80% of patients were deemed to have improved according to CGI.

Various pilot studies (n = 20–41) assessed the cognitive effects of Cerebrolysin 10 or 30 mL/day (5 days/week) for 4 weeks in parallel with qEEG[73,74] or other electrophysiological changes[72] in patients with vascular dementia. In the only placebo-controlled analysis, Cerebrolysin (at the 10 mL/day dose) was superior to placebo in improving cognition, as assessed by changes from baseline in ADAS-cog scores, and was associated with reduced EEG slowing (at both 10 and 30 mL/day doses).[73] EEG slowing was associated with a decline in cognitive functioning in this patient population, and there was a significant, positive relationship between changes in cognition and qEEG activity induced by Cerebrolysin.[73]

5. Tolerability

Tolerability data on the use of Cerebrolysin in dementia are available from a number of clinical trials in patients with Alzheimer's disease (section 4.1) and vascular dementia (section 4.2). In addition, the summary of product characteristics for Cerebrolysin provides the following information across all (dementia and non-dementia) indications: rare adverse events (reported in >1 per 10 000 to <1 per 1000 patients) include metabolism and nutrition disorders (e.g. loss of appetite), psychiatric disorders (e.g. agitation), pruritus, and (if injected too quickly) dizziness, feelings of heat and/or sweating; very rare adverse events (reported in <1 per 10 000 patients) include immune system disorders (e.g. hypersensitivity, allergic or local inflammatory reactions), seizures, cardiac disorders (e.g. palpitations or arrhythmias if injected too quickly), gastrointestinal disorders (e.g. dyspepsia, diarrhoea, constipation), and injection-site reactions (e.g. redness or burning sensation).[13]

Cerebrolysin was generally well tolerated in clinical trials in patients with Alzheimer's disease (section 4.1), with most adverse events being mild in severity. In placebo-controlled studies (section 4.1.1), the incidence of adverse events reported with Cerebrolysin was broadly similar to that with placebo, although statistical analyses were not reported. There were also no clinically significant differences between Cerebrolysin and placebo for laboratory parameters (haematology, blood chemistry, urinalysis) or vital signs in studies that reported on these parameters.[48,56,57] Across these three larger studies, the incidence of any treatment-emergent adverse event was 43.4–64% in Cerebrolysin-treated groups and 38.0–73% in placebo-treated groups.[48,56,57] Dizziness (or vertigo) was generally the most frequently and consistently reported adverse event in these trials, but occurred with a similar frequency among Cerebrolysin (3.1–32.9%) and placebo (4.6–28.2%) recipients.[48,56,57] Other commonly reported adverse events with both Cerebrolysin and placebo included headache, increased sweating, nausea, urinary tract infection, depression and fever.[48,56,57] However, there was marked variability between studies in terms of the type and incidence of adverse events. For example, headache was not reported in the large, placebo-controlled, dose-finding trial,[48] but was among the most commonly reported adverse events in the other two placebo-controlled studies.[56,57] Tolerability data from the dose-finding study showed that all regimens of Cerebrolysin (10, 30 and 60 mL/day [5 days/week]) were generally well tolerated.[48]

In active-comparator trials in Alzheimer's disease (section 4.1.2), adverse events were reported by 1 of 30 patients in the Cerebrolysin arm (an episode of hyperexcitability) compared with 14 of 30 patients in

the rivastigmine arm (primarily gastrointestinal events) of one study,[65] while the much larger trial comparing Cerebrolysin, donepezil and combination therapy found that the incidence of treatment-emergent adverse events was generally similar across groups.[63,64] Adverse events most frequently reported with Cerebrolysin-containing regimens included aggression, agitation, anorexia, arthralgia, delusion, dizziness, headache, hypokinesia, insomnia and urinary tract infection. Patients who received donepezil-containing regimens most frequently reported diarrhoea, dysthymic disorder, muscle spasms and nausea.[63,64]

Broadly similar tolerability data were reported in clinical trials with Cerebrolysin in vascular dementia (section 4.2) to those reported in Alzheimer's disease. The largest trial included 240 patients in the safety analysis.[69,70] Adverse events were reported by 9.1% of Cerebrolysin recipients compared with 5.9% of those who received placebo, and the incidence of individual adverse events was generally similar between groups. Most adverse events were mild in intensity, and the most frequently reported events were headache (2.5% with Cerebrolysin, 1.7% with placebo), asthenia (3.3% vs 0%) and dizziness (2.5% vs 0%) [statistical analyses were not reported]. There were no clinically significant differences between groups with respect to changes in laboratory parameters.[69,70]

6. Dosage and Administration

The summary of product characteristics for Cerebrolysin suggests that patients with dementia receive a daily dosage of 5–30 mL intravenously over a total of 10–20 days (initial course).[13] After the initial course, repeated courses can be administered until no further benefit results; the frequency of administration may be reduced to two or three times per week after the initial course. A treatment-free period, equal in length to the therapy course, should be allowed between successive therapy courses.[13] A commonly used regimen in dementia, and one that is advocated by the manufacturer (personal communication, EBEWE Neuro Pharma GmbH), is two or three courses per year of Cerebrolysin 10 mL/day (up to 30 mL/day for severe cases) intravenously 5 days per week for 4 weeks.

Cerebrolysin doses up to 10 mL may be administered undiluted by intravenous administration, whereas higher doses should be diluted in standard infusion solutions and administered by slow intravenous infusion.[13] Intramuscular administration is permitted for doses ≤5 mL. Local prescribing information should be consulted for information regarding preparation of the parenteral dose, precautions, contraindications, drug interactions and use in special patient populations.

7. Place of Cerebrolysin in the Management of Dementia

Pharmacotherapy for the management of dementia, particularly Alzheimer's disease, often involves the use of cholinesterase inhibitors (e.g. donepezil, rivastigmine, galantamine) for mild to moderate stages,[6-11] and memantine for moderate to severe stages.[76] Donepezil is also approved for use in severe Alzheimer's disease in the US.[77] Cholinesterase inhibitors prevent the degradation of the neurotransmitter acetylcholine, which is critical to neurons involved in cognition, and memantine is an antagonist of the *N*-methyl-D-aspartic acid (NMDA) receptor, an effect that influences memory and learning by preventing excess stimulation of the glutamate system.[2,6-11,76,78] While these drugs have demonstrated statistically significant effects on cognition and global measures in clinical trials in dementia, the beneficial effects have generally been modest in clinical terms,[78,79] and there is no evidence that cholinesterase inhibitors or memantine have disease-modifying effects.[2,6-11,76,78,79]

Among the more promising agents with potential disease-modifying effects in dementia are amyloid-β vaccines aimed at reducing accumulation of neurotoxic and aggregation-prone forms of Aβ, and agents with neurotrophic properties similar to those of endogenous neurotrophic factors, such as nerve growth factor, which affects survival and function of cholinergic and other types of neurons.[4,12,79-81] One of the challenges in developing amyloid-β immunisation for clinical use is finding the balance

between effectiveness and toxicity; for example, autoimmune reactions leading to encephalitis have occurred following active amyloid-β vaccination.[81]

Cerebrolysin has pharmacodynamic properties similar to those of endogenous neurotrophic factors, as demonstrated in a number of preclinical studies (section 2). Beneficial effects of Cerebrolysin included those affecting neuronal survival, neuroprotection, neuroplasticity and neurogenesis, as well as behaviour. Taken together, these results suggest that Cerebrolysin, via its neurotrophic effects, may have the potential for longer-lasting benefits in individuals with dementia.

Clinical trials with intravenously administered Cerebrolysin in patients with Alzheimer's disease and vascular dementia have shown statistically significant beneficial effects on clinical global outcomes and cognition (section 4). In particular, a number of randomized, double-blind trials in patients with Alzheimer's disease demonstrated that Cerebrolysin was consistently superior to placebo when assessed by CIBIC-plus or CGI scores, and several studies also showed a statistically significant advantage over placebo in the mean change from baseline ADAS-cog or ADAS-cog-plus scores (section 4.1). Moreover, the benefits of Cerebrolysin appeared to last for several months after stopping treatment in several studies. Behavioural and/or functional benefits, as assessed (usually as secondary endpoints) by NPI and activities of daily living, respectively, were also noted in some trials in patients with Alzheimer's disease or vascular dementia (section 4). In general, subgroup analyses in patients with more severe cognitive impairment at baseline showed similar overall benefits to the larger cohorts. Overall, Cerebrolysin was generally well tolerated in clinical trials (section 5).

The only large, randomized, head-to-head comparison with a cholinesterase inhibitor (section 4.1.2) showed a statistically significant advantage of Cerebrolysin over donepezil for CIBIC-plus in patients with mild to moderate Alzheimer's disease, and the use of Cerebrolysin in combination with donepezil was generally well tolerated and showed promising results.[63,64] Further study on the concurrent use of Cerebrolysin and cholinesterase inhibitors, which act via different mechanisms of action, may be warranted. Likewise, clinical trials comparing Cerebrolysin with memantine, and evaluating the combined use of Cerebrolysin and memantine, would also be of interest, particularly in the setting of advanced stages of Alzheimer's disease.

While several of the clinical studies conducted with Cerebrolysin in dementia have been well designed, randomized, controlled trials that used established instruments, such as ADAS-cog and CIBIC-plus, to evaluate outcomes, they also have limitations. To date, randomized clinical trials with Cerebrolysin have generally been of short duration, with the longest follow-up period being 28 weeks (section 4). Many of the studies had a small sample size, although three of the randomized, double-blind, placebo-controlled trials (and two of their substudies) included >100 patients (table II). In addition, the main focus of most of the trials was to evaluate changes in cognition and global measures over a relatively short time interval. However, it is also important to evaluate the effect of pharmacotherapy on more clinically meaningful outcomes, such as patient health-related quality of life and caregiver burden, and longer term trials could be designed to assess tangible milestones of disease progression, such as nursing-home placement.[79] The paucity of such trials is not unique to Cerebrolysin, as there is also a general lack of long-term trials with cholinesterase inhibitors that assess outcomes such as these in patients with dementia.[79]

As is often the case in studies with cholinesterase inhibitors,[53] improvements in ADAS-cog and CIBIC-plus scores in clinical trials with Cerebrolysin have generally been modest. For example, some guidelines suggest that a clinically significant change in ADAS-cog score is ≥4 points,[53] whereas average changes in ADAS-cog score from baseline were generally <4 points with Cerebrolysin. However, between-group differences were ≥4 in several placebo-controlled trials (section 4). Another potential limitation is that all of the placebo-controlled studies discussed in section 4.1.1 used LOCF as a strategy of imputing missing values. This method is

usually regarded as a conservative imputation technique when improvement with treatment is expected over time because the imputed values will tend to show less improvement than values in completers, as they were recorded at an earlier time. In the case of conditions where declines are expected with time, such as Alzheimer's disease, the opposite is true since patient values might be expected to be better early in treatment.[82] However, this issue is not unique to studies with Cerebrolysin, as LOCF is the technique most commonly used in ITT analyses in pharmacotherapy trials in dementia, and the issue may be of particular relevance to trials of cholinesterase inhibitors because dropout rates are often higher in the treatment than in the control group.[82]

Other areas of research with Cerebrolysin that would be of interest include determining whether there are patterns of behavioural effects on individual NPI items that may help to explain its efficacy as measured by global impression of change. For example, specific persistent benefits were observed with memantine on symptoms of agitation/aggression and delusion,[83] and cholinesterase inhibitors have shown specific effects on apathy.[84] The effect of Cerebrolysin on biomarkers for Alzheimer's disease, such as amyloid-β and total and phosphorylated tau protein analysis in CSF and plasma,[85,86] would also be of interest.

In addition, further studies may be needed to more clearly establish the optimal dosage regimen of Cerebrolysin in patients with Alzheimer's disease and in those with vascular dementia. Although dosage and administration guidelines are available for Cerebrolysin (section 6), a large dose-finding study in patients with Alzheimer's disease showed an inverted dose-dependent treatment effect on cognition, i.e. only the lowest dosage regimen evaluated achieved a statistically significant advantage over placebo (section 4.1.1).[48] In contrast, the greatest improvement on behavioural effects occurred with the highest dosage evaluated.[48] These results may not be unexpected, as other growth factors or neuropeptides have also demonstrated inverted U-shaped dose-response curves.[87,88] In addition, since Cerebrolysin is a mixture of different peptides, the potentially different dose-response curves and specific effects for each peptide may also have been a contributing factor.

For the pharmacological management of cognitive symptoms, most patients with mild to moderate Alzheimer's disease are offered cholinesterase inhibitors, which may also be helpful in those with more severe disease and in patients with vascular dementia.[77] These agents result in modest benefits in about 30–40% of patients[77] and have convenient oral (or in some cases transdermal) administration schedules,[6-11] but they also have a number of adverse events.[6-11,77] Therefore, a thorough discussion of their potential risks and benefits is necessary before a decision is made regarding initiating therapy.[77] Alternative therapy with parenterally administered Cerebrolysin may be an appropriate option for patients with Alzheimer's disease or vascular dementia. While there are potential limitations of parenteral administration of drug therapy in routine clinical settings, Cerebrolysin has shown benefits in these patient populations (section 4) and was generally well tolerated (section 5). However, further studies with Cerebrolysin, including longer term trials and further exploration of its use in combination with cholinesterase inhibitors, are needed to more clearly determine its place in the management of Alzheimer's disease and vascular dementia. Nevertheless, on the basis of available data, Cerebrolysin appears to be a well tolerated and useful addition to the treatment options available for dementia.

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