PORCINE BRAIN: FACTS OR FICTION

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Cerebrolysin® ...

- Peptide preparation produced by the biotechnological standardized enzymatic breakdown of purified porcine brain proteins
- Consists of ~ 15% peptides with a MW not exceeding 10kD and 85% AA based on total nitrogen
- The solution, ready for injection or infusion, is free of proteins, lipid and antigenic properties
- 1 ml of Cerebrolysin® contains 215.2 mg of porcine brain-derived peptide preparation in aqueous solution

Pharmacological Profile

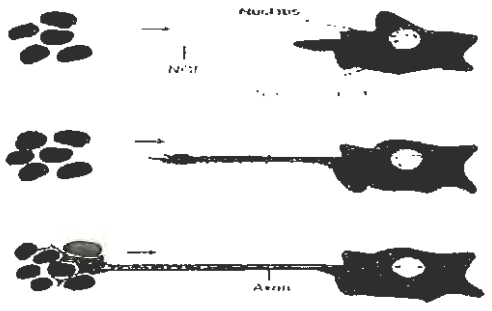
Effects of the Peptides

- *Neurotrophic Stimulation:* secures the survival and differentiation and protects nerve cells from insults
- *Neuromodulation:* improves behaviors, memory learning, changes of neuronal and synaptic plasticities
- Metabolic Regulation: protects nerve cells of the brain from lactate acidosis and improves oxygen utilization inside the nerve cells

Mechanisms of Action

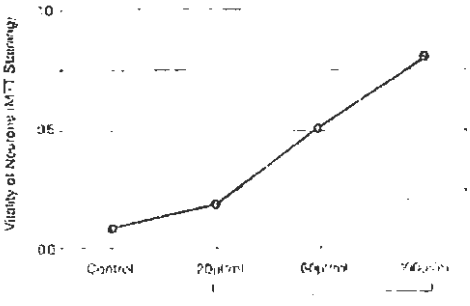
- Its action assumed to be similar to naturally occurring neurotrophic factors (NGF) which are a group of proteins with characteristic effects:
  - Neuronal differentiation (sprouting of axons and dendrites)
  - Maintenance of the functional integrity of the nerve cells
  - Protection the nerve cells from lesions
- R. Levi-Montalcini discovered neurotrophic factors or NGF in 1950s

Action of NGF



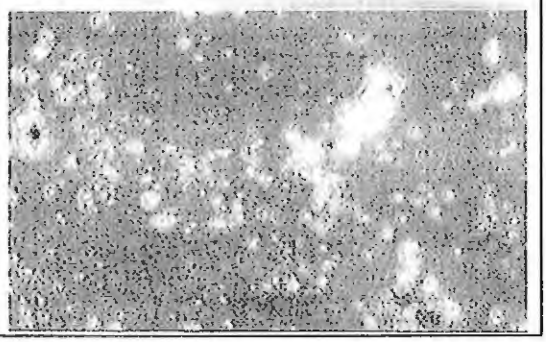
Neurotrophic Stimulation

Cerebrolysin improves the survival of brainstem of chick embryo (Albrecht et al., 1992)



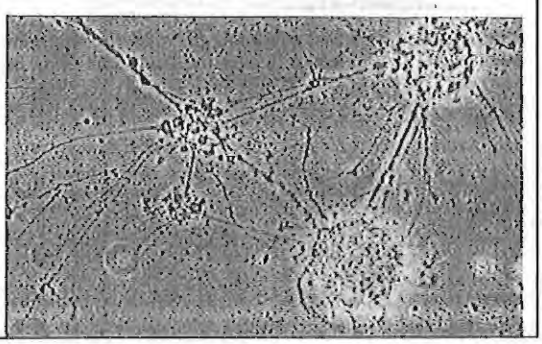
Neurotrophic Stimulation

Nerve cell culture without Cerebrolysin



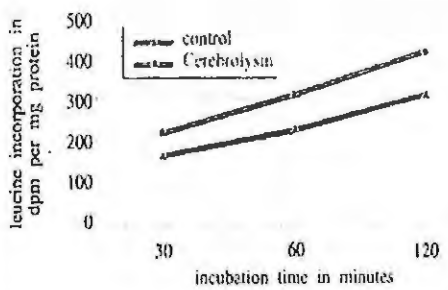
Neurotrophic Stimulation

Nerve cell culture with Cerebrolysin



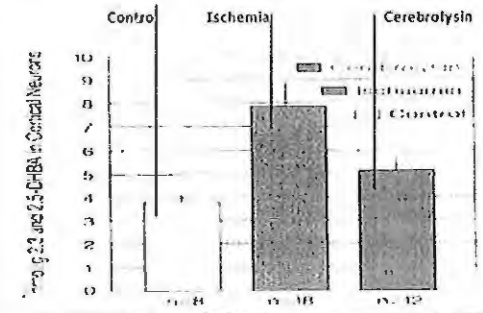
Neurotrophic Stimulation

Cerebrolysin on brain protein synthesis of old rats



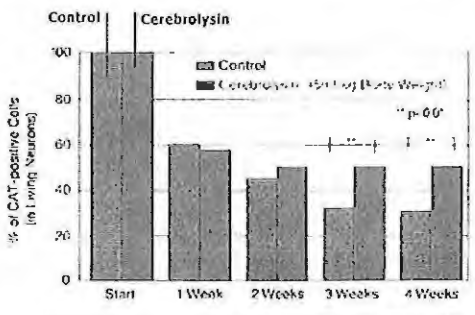
Neurotrophic Stimulation

Cerebrolysin decreases free radicals in ischemia



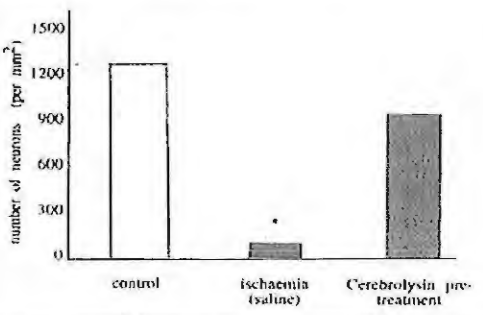
Neurotrophic Stimulation

Cerebrolysin facilitates regeneration of cholinergic neurons after septohippocampal transection



Neurotrophic Stimulation

Cerebrolysin delays cell death in an ischemia/reperfusion model



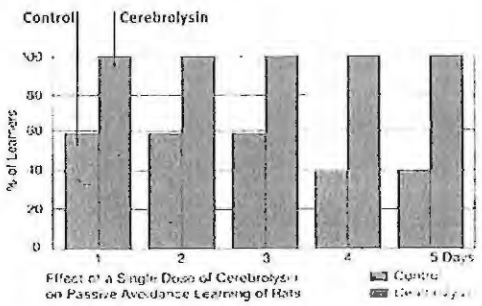
Neuromodulation
Cerebrolysin increases synaptic density, plasticity and performance

- Cerebrolysin increases the synaptic density in the hippocampus, dentate gyrus and the entorrhinal cortex of 24-month-old rats. (Reinprecht I, et al., Histochem J 1999; 31:395-401)
- Cerebrolysin ameliorates the neurodegenerative and performance deficits in aged apolipoprotein E-deficient mice. (Masliah E, et al., Pharmacol Biochem Behav 1999; 62:239-45)

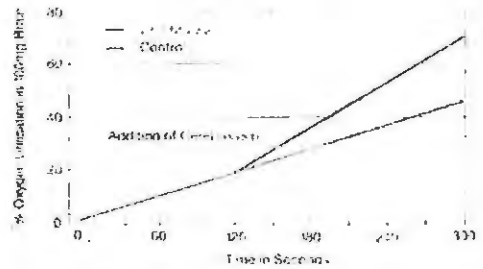
Neuromodulation
Cerebrolysin decreases beta-amyloid deposition

- Cerebrolysin might have neuroprotective effects by decreasing the production of beta-amyloid- protein (1-42) antibody and reducing amyloid deposition in transgenic mice expressing mutant human amyloid precursor protein 751 (APP751) cDNA (Rockenstein E, et al. Effects of Cerebrolysin on amyloid-beta deposition in a transgenic model of Alzheimer's disease. J Neural Transm Suppl 2002;(62):327-36)

Neuromodulation
Cerebrolysin facilitates and maintains learning performance



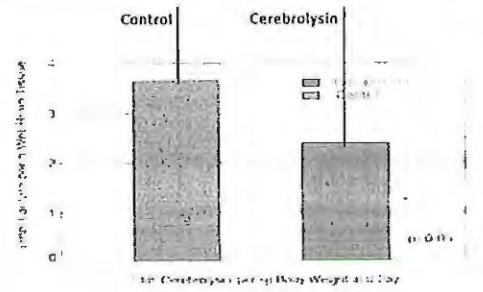
Metabolic regulation
Cerebrolysin facilitates oxygen utilization in rat brain homogenates



Metabolic regulation

- Cerebrolysin inncreases the expression of GLU1 transporter gene of the blood-brain-barrier (Boado RJ. Molecular regulation of the blood-brain barrier GLUT1 glucose transporter by brain-derived factors. J Neural Transm Suppl 1998;53:323-31)

Metabolic regulation
Cerebrolysin prevents lactate acidosis in rat brain



MAD-8

Cerebrolysin® ...

- Is in clinical use since many years and currently available in 25 countries
  - Germany
  - Austria
  - Portugal
  - ...
- Has IND status in USA and Canada
  - US FDA approval March 1998
  - Canadian HPB approval August 1995
  - Is available for clinical use in Canada through HPB's Emergency Drug Release program

MAD-8

Clinical Trial Data

- More than 70 clinical studies published to date, with over 4,200 patients enrolled
  - Dementia
  - Stroke
  - Brain Injuries
- Recent studies in Alzheimer's disease
  - German GCP Study (Ruether, 1994)
  - Austrian Phase IV Study (Rainer, 1997)
  - Canadian GCP Study (Panisset & Gauthier, 1999)
  - German/Austrian GCP Study (Ruether, 1999)

MAD-8

Objective

- Assessment of safety and efficacy of Cerebrolysin®
- Investigation of repeated treatment courses
- Investigation of long-term effects after drug withdrawal

MAD-8

Efficacy Measures

- Primary
  - Global function — CGI-C
  - Cognitive Performance — ADAS-COG
- Secondary
  - Behaviour — ADAS-NONCOG
  - Activities of Daily Living — NAB
  - Depressive Symptoms — MADR-S

Safety Measures

- Adverse Events
- Lab Parameters
- Vital Signs

MAD-8

Patient Population

Inclusion Criteria

- Men or Women
- Age 50–85 Years
- NINCDS-ADRDA
- ICD-10
- MMSE 14–24
- CGI – Severity of Disease > 2

Exclusion Criteria

- CT or MRI Incompatible with Diagnosis of AD
- Vascular Dementia
- Other Neurological Diseases
- Severe Concomittant Illnesses
- ....

MAD-8

Dosage & Treatment

- Dosage
  - Group A: 30 ml Cerebrolysin® + 70 ml Saline Solution
  - Group B: 100 ml Saline Solution
- Total of 40 IV Infusions, Once Daily
- Treatment Schedule
  - Treatment 1: 5 Days/Week for 4 Consecutive Weeks
  - 2-Month Treatment-Free Interval
  - Treatment 2: 5 Days/Week for 4 Consecutive Weeks

Efficacy Analysis

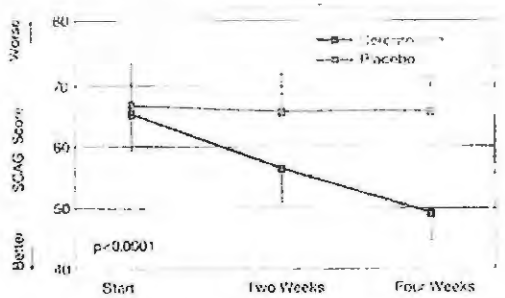
- Primary Endpoint: Month 4 Visit
- Primary Parameters: CGI-C, ADAS-COG
- Primary Population: ITT
- Scoring Option: LOCF

... Cerebrolysin® produces a statistically significant improvement over Placebo in *both* primary efficacy parameters ...

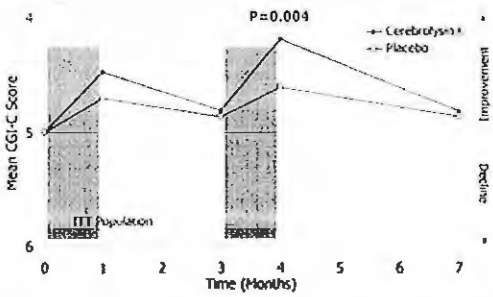
Results

- Primary Outcome Measures
- Secondary Outcome Measures
- Safety Data

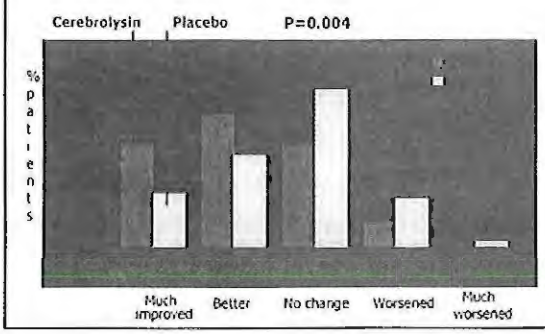
Sandoz Clinical Assessment-Geriatrics (SCAG)



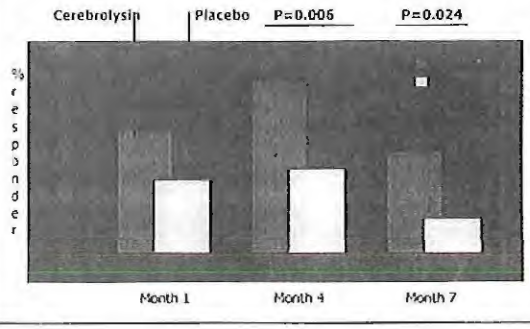
Clinical Global Impression (GCI)

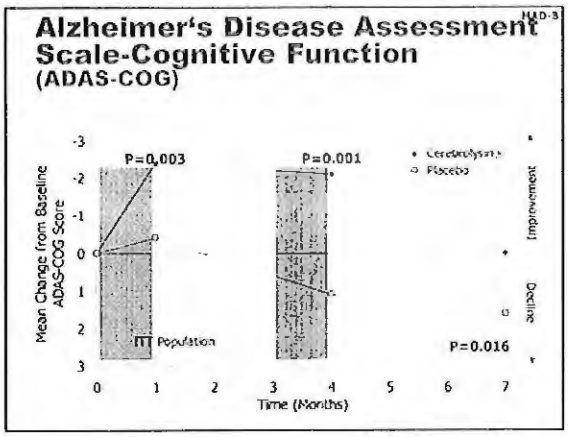


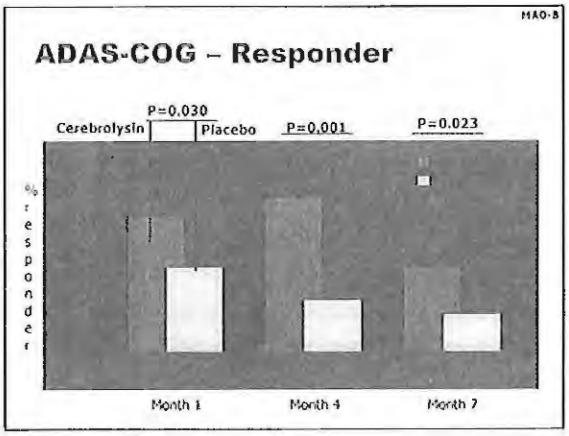
CGI-C – Score Distribution

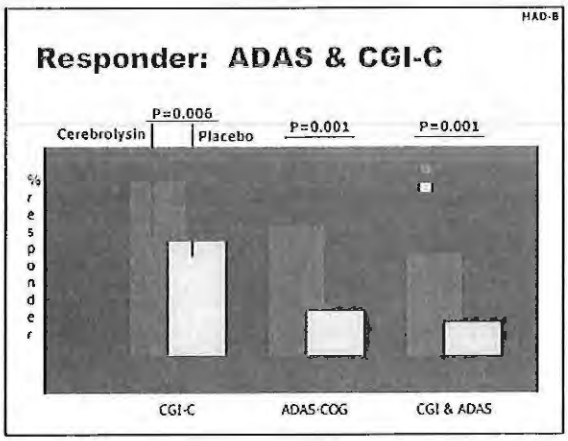


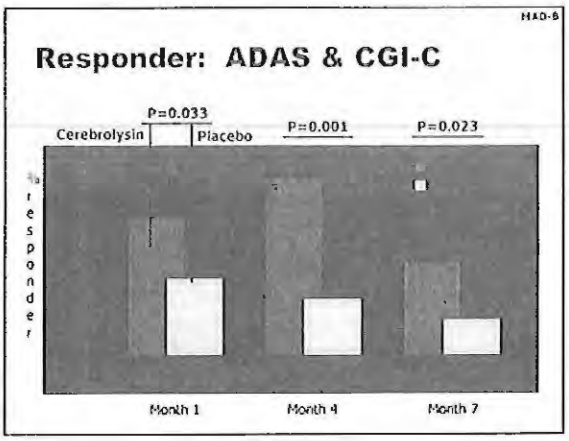
CGI-C – Responder

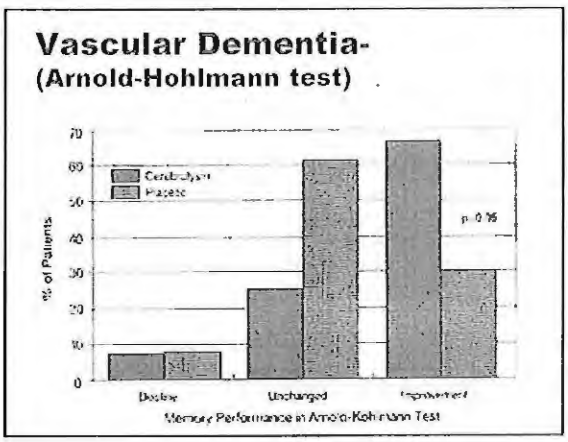


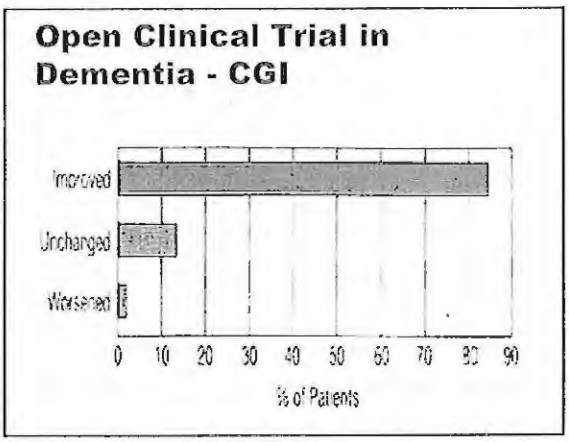

Alzheimer's Disease Assessment Scale-Cognitive Function
(ADAS-COG)
HAD-8
Mean Change from Baseline ADAS-COG Score
P=0.003
P=0.001
P=0.016
Population
Improvement
Decline
Time (Months)


ADAS-COG – Responder
HAD-8
P=0.030
Cerebrolysin
Placebo
P=0.001
P=0.023
% responder
Month 1
Month 4
Month 7


Responder: ADAS & CGI-C
HAD-8
P=0.006
Cerebrolysin
Placebo
P=0.001
P=0.001
% responder
CGI-C
ADAS-COG
CGI & ADAS


Responder: ADAS & CGI-C
HAD-8
P=0.033
Cerebrolysin
Placebo
P=0.001
P=0.023
% responder
Month 1
Month 4
Month 7


Vascular Dementia-
(Arnold-Hohlmann test)
% of Patients
Cerebrolysin
Placebo
p=0.16
Decline
Uncharged
Improvement
Memory Performance in Arnold-Kohlmann Test


Open Clinical Trial in Dementia - CGI
Improved
Uncharged
Worsened
0 10 20 30 40 50 60 70 80 90
% of Patients

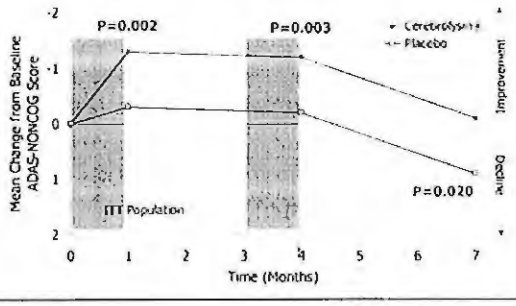
HAD-B

Secondary Measures

▮ Behaviour	ADAS-NONCOG
▮ Activities of Daily Living	NAB
▮ Depressive Symptoms	MADR-S
▮ Cognition/Concentration	SKT
▮ ITT-LOCF Analysis	Cerebrolysin® n=74 Placebo n=70

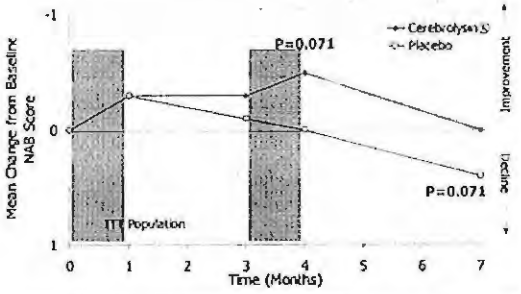
HAD-B

ADAS-NONCOG – Behavioural Disturbances



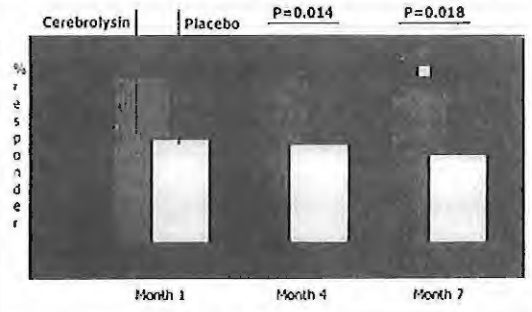
HAD-B

Activities of Daily Living (ADL)



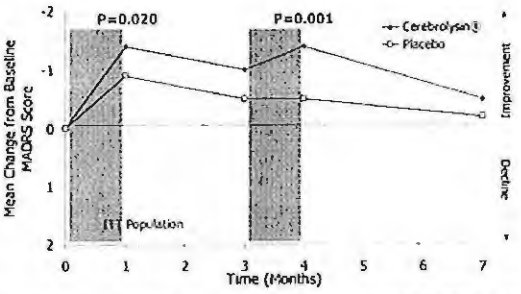
HAD-B

ADL – Responder

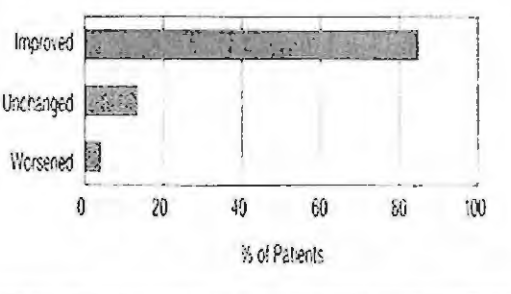


HAD-B

MADRS – Depressive Symptoms



Open Clinical Trial in Stroke - ADL



HAD-B

Safety Analysis

- Adverse Events
- Lab Parameters
- Vital Signs
- Safety Population Cerebrolysin® n=76
  Placebo n=71

HAD-B

Lab & Vital Signs

- No significant change in any of the lab parameters in both groups
- No change in vital signs
  - pre- and post infusion
  - as well as over time

HAD-B

Adverse Events

- *No differences in AEs* between Cerebrolysin® and Placebo groups

HAD-B

Summary

- Cerebrolysin® leads to statistically significant and clinically relevant improvement in both cognition and global function in patients with AD
- This is supported by findings in the secondary parameters, where significant improvement was evident in behaviour, depressive symptoms and activities of daily living
- Cerebrolysin® is safe and well tolerated

HAD-B

Conclusions

- Patients on Cerebrolysin® had significantly greater improvement than Placebo-treated patients after only one month of treatment

- Acute symptomatic improvement
- Fast onset of action

HAD-B

Conclusions

- Second Cerebrolysin® treatment after a treatment-free interval reinforces therapeutic improvement
- Patient's response to the second treatment is equal or greater than to the intial treatment

- Therapeutic concept:
  Long-term Cerebrolysin® treatment with therapy-free intervals