Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration

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# *Cerebrolysin in Patients With Acute Ischemic Stroke in Asia – The CASTA trial*

**Wolf-Dieter Heiss, Michael Brainin, Natan M. Bornstein, Jaakko Tuomilehto, Zhen Hong**

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*Patrick Altmann*

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# Overview

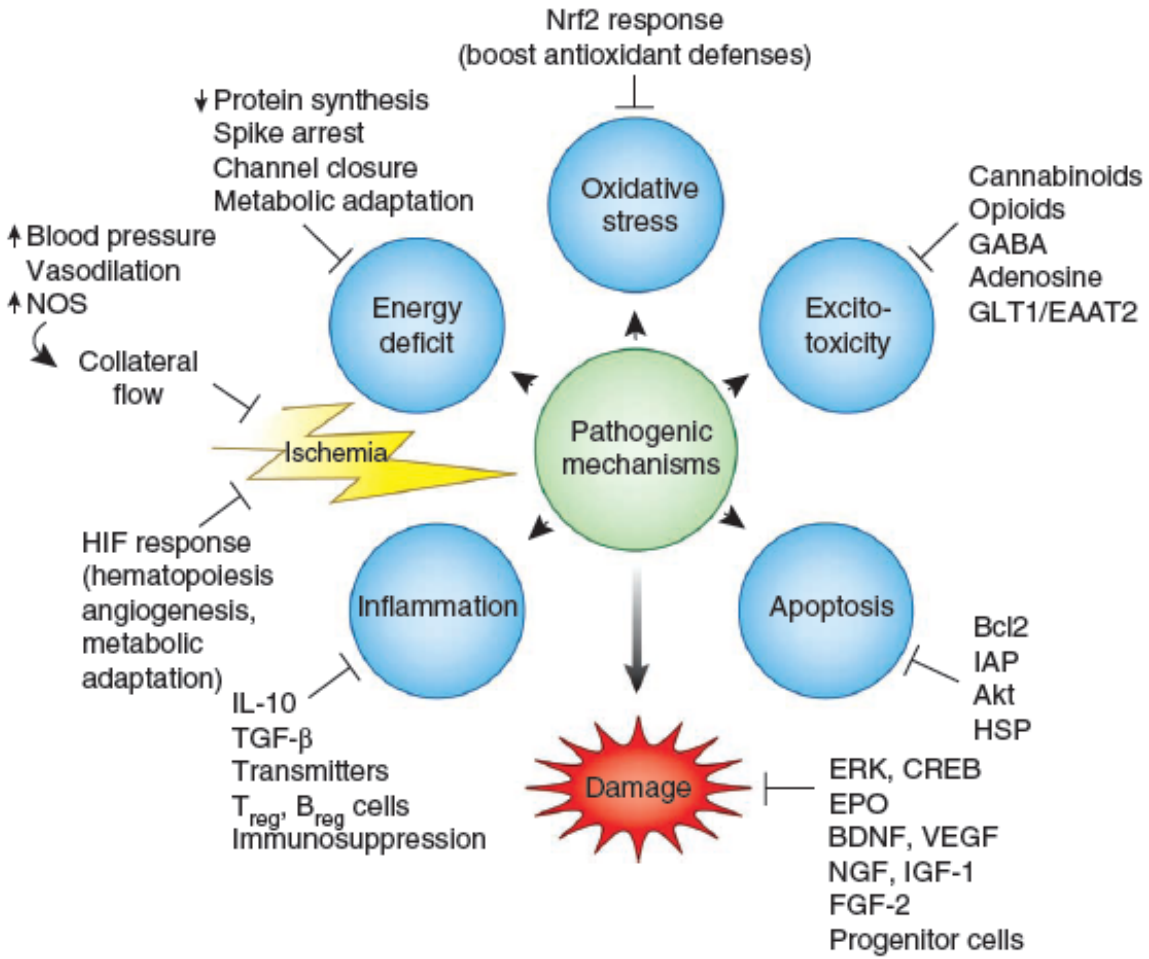
- Background
- Methods
- Stroke Scales
- Results
- Discussion

# Cerebrolysin

- Porcine brain-derived preparation of low molecular-weight neuropeptides (10kDa) and free amino acids
- Pharmacodynamic properties similar to those of naturally occurring neurotrophic factors
- … reduces Apoptotic Processes in the ischemic boundary zone
- … amplifies neuroblast migration into the injured brain region
- … stimulates neurogenesis in the subventricular zone of the ischemic brain

***Zhang Ch**, et al. Journal of Neuroscience Research (2010)*
***Chopp M**, et al. European Neurological Review (2011)*

# Protective pathways activated by cerebral ischemia




*Iadecola C. et al. Nature Neuroscience (2011)*

# Study Design

- Phase IV clinical trial
- Multicenter, randomized, double blind
- Placebo-controlled, parallel-group
- 51 centers from China (1024 patients); Hong Kong (4 patients); South Korea (16 patients); Myanmar (26 patiens)
- 09/2005 - 09/2009
- 30mL Cerebrolysin iv VS. Placebo

  both plus 100mg Aspirin orally
- Primary + Secondary efficacy criteria

# [Clinical trial phases]

| Summary of clinical trial phases | | | | |
|---|---|---|---|---|
| **phase** | **goal** | **dose** | **typical number of participants** | **notes** |
| preclinical | nonhuman efficacy, toxicity and pharmacokinetic information | unrestricted | in vitro and in vivo animal | |
| phase 0 | pharmacodynamics and pharmacokinetics | very small, subtherapeutic | 10 people | often skipped for phase I |
| phase I | pharmacovigilance and dose-ranging | often subtherapeutic, but with ascending doses | 20-100 | determines whether drug is safe to check for efficacy |
| phase II | testing of drug on healthy volunteers | therapeutic dose | 100-300 | determines whether drug can have any efficacy |
| phase III | testing of drug for intended use as therapy | therapeutic dose | 2000-3000 | determines a drug's therapeutic effect |
| phase IV | Postmarketing surveillance - watching drug use in public | therapeutic dose | anyone seeking treatment from their physician | watch drug's long term effects |
| phase V | translational research | no dosing | all reported use | research on data collected |

*Wikipedia: "Phases of Clinical Research": http://en.wikipedia.org/wiki/Phases_of_clinical_research*

# Inclusion criteria

- *Inclusion criteria:*

  *) both male and female; 18-85 yrs

  *) focal neurological deficit and a clinical diagnosis of acute hemispheric ischemic stroke (CT or MRI)

  *) Scores:

  - NIHSS 6-22

  - functionally independent before stroke with a prestroke Rankin Scale score of 0 or 1

# Exclusion criteria

- *Exclusion criteria:*

  *) Evidence of ICH on CT/MRI

  *) Decreased consciousness (≥2 on NIHSS Question 1a)

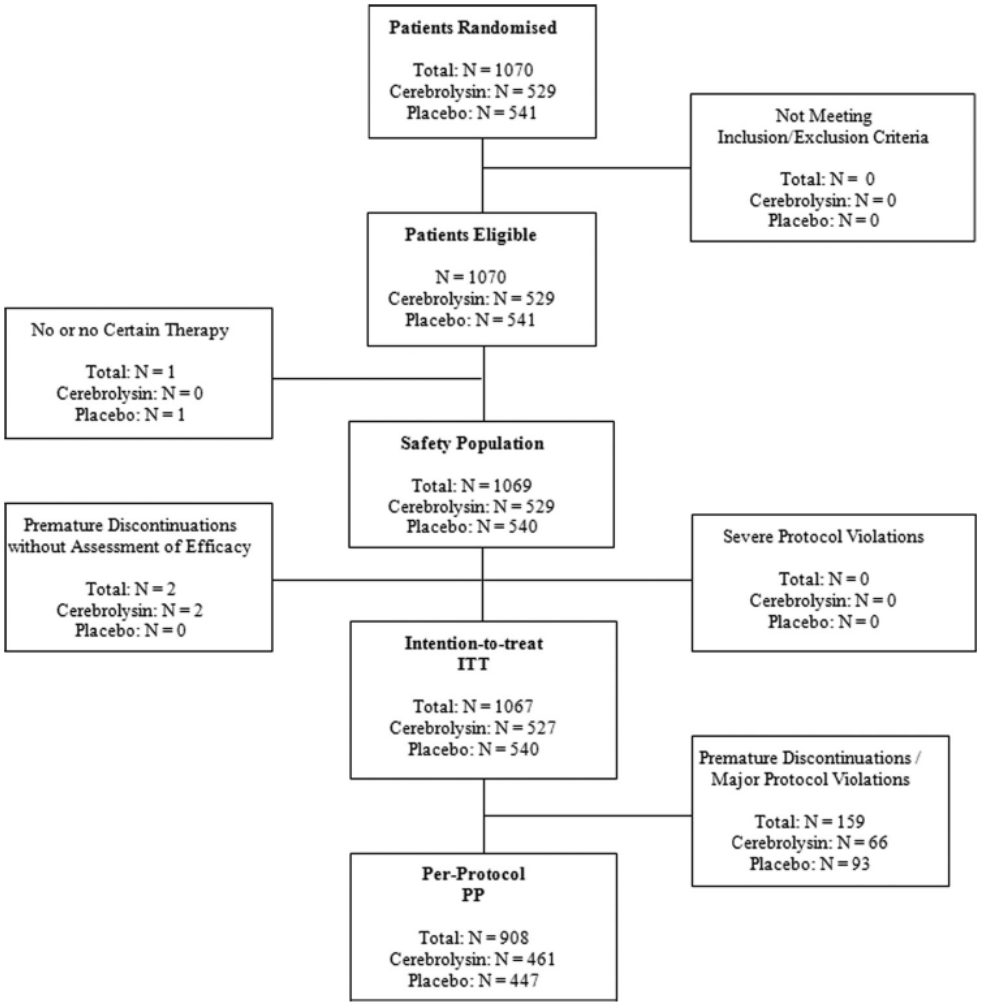
  *) Neurological signs and symptoms that were likely to resolve completely within 24 hours

  *) BPsys >220 mmHg or BPdia >120 mmHg

  *) severe congestive heart failure/AMI

  *) pre-existing systemic disease significantly limiting life expectancy

# Study design



# NIHSS

http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale_Booklet.pdf

- 0= no stroke
- 1-4= minor stroke
- 5-15= moderate stroke
- 15-20= moderate/severe stroke
- 21-42= severe stroke


# NIH Stroke Scale

# NIHSS

- Level of Consciousness
- Best Gaze
- Visual
- Facial Palsy
- Motor Arm
- Motor Leg
- Limb Ataxia
- Sensory
- Best Language
- Dysarthria
- Extinction and Inattention

# 7

## Limb Ataxia

### Instructions

**Limb Ataxia:**
This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN) and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.

### Scale Definition

| | |
|---|---|
| 0 | **Absent.** |
| 1 | **Present in one limb.** |
| 2 | **Present in two limbs.** |
| UN | **Amputation** or joint fusion, explain: |

Score

# mRS (1)

| | | |
|---|---|---|
| 1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?) | YES ○ | NO ○ |
| 2. Are you able to do the same work as before? | YES ○ | NO ○ |
| 3. Are you able to keep up with your hobbies? | YES ○ | NO ○ |
| 4. Have you maintained your ties to friends and family? | YES ○ | NO ○ |
| 5. Do you need help making a simple meal, doing household chores, or balancing a checkbook? | YES ○ | NO ○ |
| 6. Do you need help with shopping or traveling close to home? | YES ○ | NO ○ |
| 7. Do you need another person to help you walk? | YES ○ | NO ○ |
| 8. Do you need help with eating, going to the toilet, or bathing? | YES ○ | NO ○ |
| 9. Do you stay in bed most of the day and need constant nursing care? | YES ○ | NO ○ |

# mRS (2)

- 0 - No symptoms.
- 1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requires some help, but able to walk unassisted.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

# Barthel Index

- Activities of Daily Living:

  bowels; bladder; grooming; toilet use; feeding; transfer; mobility; dressing; stairs; bathing

- 0-100 points

- Subgroup analyses…

# Population

| Characteristic | Cerebrolysin (N=527) | Placebo (N=540) |
|---|---|---|
| Male sex, no., percent | 314 (59.6%) | 326 (60.4%) |
| Mean age, y, SD | 65.0 (12.22) | 65.5 (11.71) |
| Mean body mass index, $kg/m^2$, SD | 23.7 (3.04) | 24.0 (3.20) |
| Mean time until Hospital Admission (hrs/SD) | 5.6 (3.00) | 5.6 (3.75) |
| Mean time until start of treatment, h, SD* | 7.7 (5.97) | 7.6 (3.69) |
| Thrombolysis treatment, no., percent | 50 (9.49%) | 44 (8.15%) |
| Prevalence of risk factors, no., percent | | |
| Hypertension | 331 (62.8%) | 332 (61.6%) |
| Diabetes | 108 (20.5%) | 117 (21.7%) |
| Arrhythmia | 71 (13.5%) | 90 (16.7%) |
| Coronary heart disease | 72 (13.7%) | 86 (16.0%) |
| Baseline efficacy criteria, median (range) | | |
| NIHSS maximum (range, 0–42 points) | 9 (6–33) | 9 (6–26) |
| Barthel Index maximum (range, 0–100 points) | 30 (0–100) | 30 (0–100) |
| Modified Rankin Scale maximum (range, 0–6 points) | 4 (0–5) | 4 (0–5) |

ITT indicates intention-to-treat; NIHSS, National Institutes of Health Stroke Scale.

*Calculated from stroke onset.

# Results: Primary efficacy criteria



- Day 90:

| | | |
|---|---|---|
| NIHSS: | Cerebrolysin: | +6 points |
| | Placebo: | +5 points |
| BI: | Cerebrolysin: | +30 points |
| | Placebo: | +30 points |
| mRS: | Cerebrolysin: | 2 points |
| | Placebo: | 2 points |

→ No group difference found in the study patients

→ CI-LB is 0,47 (P=0,5)

# Stratification…

## Stratified (Subgroup) Analyses

There were 4 stratified analyses of the BI preplanned in the blind review with subgroups as follows: (1) stratification for thrombolysis therapy; (2) for age (≤65 years/age >65 years); (3) for severity of disease at baseline (NIHSS ≤7, NIHSS 8–12, NIHSS >12);and (4) side of infarction.

## Post Hoc Analyses

Additionally, post hoc stratified analyses were performed, for example, for NIHSS and mRS (with strata as defined previously for BI). Furthermore, there were post hoc subgroup analyses for baseline NIHSS >17 points, study centers in Hong Kong and South Korea only, primary efficacy criterion in subgroup NIHSS >12, mortality in subgroup NIHSS >12, and responder in subgroup NIHSS >12.

The secondary study end points included responder analysis based on responder definitions for mRS, BI, and NIHSS. Again, the criteria were evaluated combined into 1 global test.

Before unblinding the study, a blind review of the data was performed. The review was within the framework of the requirements of the ICH Guideline E9.[17] The cutoff was reanalyzed during blind review and a cutoff at 9 points on the NIHSS was considered to be appropriate for all responder analyses due to the median baseline NIHSS. For the purpose of the treatment responder analysis, the definition of excellent outcome on the BI and mRS was stratified by baseline stroke severity. The final responder definitions were established during the blind review process (Table 1).

Additional secondary study end points included the global test as described for the confirmatory analysis, but this time evaluated for Day 30 instead of Day 90, quality-of-life assessment using the SF-12 at Day 90, overall death rate, and time to death.

# Secondary efficacy criteria



**Table 1. Responder Definitions for BI, mRS, and NIHSS Established During the Blind Review**

| Scale | Baseline NIHSS ≤9 | Baseline NIHSS >9 |
|---|---|---|
| BI | Score of 95–100 | Score >60 |
| mRS | mRS of 0–1 | mRS of 0–2 |
| NIHSS | Excellent outcome on the NIHSS was defined as an NIHSS score of 0 or 1 or an improvement from the baseline NIHSS score of >6 points | |

BI indicates Barthel Index; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

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# Results: Secondary efficacy criteria

- Responder Rate according to NIHSS:

  Cerebrolysin / Placebo: 47,9% / 46,5%
- Responder Rate according to BI:

  Cerebrolysin / Placebo: 44,0% / 45,9%
- Responder Rate according to mRS:

  Cerebrolysin / Placebo: 37,6% / 38,5%

→ No group difference found

→ CI-LB is 0,47 (P=0,57)

# Results: Mortality

- A total of 60 patiens died
- 28 deaths in the Cerebrolysin group
- 32 deaths in the Placebo group

- Cumulative percentage of patients who died (day 90):

  6,6% in the Placebo group

  5,3% in the Cerebrolysin group

The hazard ratio is 1.26 (CI-LB, 0.75; $P$=0.19), which indicates a small superiority for the Cerebrolysin group.

# Preplanned Subgroup Analyses



***Preplanned Subgroup Analyses***

For the criterion BI, a preplanned stratification by severity of disease according to baseline NIHSS result was performed. In the strata NIHSS ≤7 (OR, 0.99; CI-LB, 0.79; $P$=0,45) and NIHSS 8 to 12 (OR, 0.97; CI-LB, 0.79; $P$=0.41), there were no group differences to be found. The same goes true for the subgroup with baseline NIHSS >12 (OR, 0.97; CI-LB, 0.73; $P$=0.41). The combined (ie, adjusted) result is OR=0.98 (CI-LB, 0.85; $P$=0.37) and does not indicate a superiority of Cerebrolysin. Also, other predefined subgroup analyses (side of infarction, stratification for age, and stratification for thrombolysis) did not indicate a statistical significant difference between the treatment groups.

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# Post Hoc Analysis for Subgroup w/ Baseline NIHSS>12

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**Table 3. NIHSS (Change From Baseline, LOCF), Descriptive Statistics for Subgroup Baseline NIHSS >12, ITT Population**

| NIHSS | Baseline | Visit 2 | Visit 3* | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|---|
| Cerebrolysin | 16.6 | −0.6 | −1.4 | −2.6 | −4.1 | −4.8 |
| Mean/SD | 3.40 | 2.97 | 6.52 | 8.02 | 9.36 | 10.76 |
| Placebo | 16.2 | −0.5 | −0.8 | −1.1 | −1.4 | −1.8 |
| Mean/SD | 3.02 | 4.74 | 7.77 | 9.73 | 11.92 | 13.87 |

NIHSS indicates National Institutes of Health Stroke Scale; LOCF, last observation carried forward; ITT, intention-to-treat.

*Start of LOCF substitution.

# Kaplan Meier

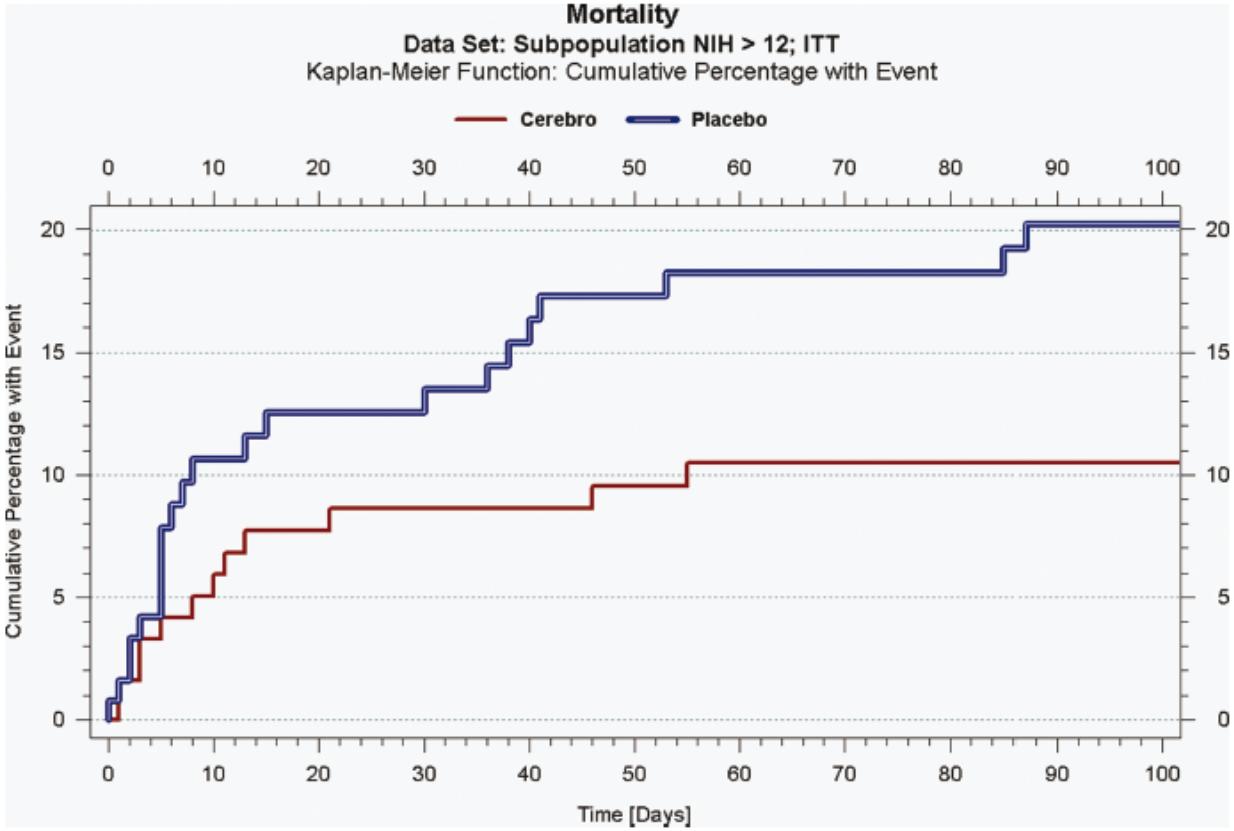


**Figure 2.** Kaplan-Meier survival curve (cumulative percentage) for subgroup baseline NIHSS >12 points (N=252, 126 patients per group); ITT population. HR, 1.9661 (CI-LB, 1.00; $P$=0.0497 in a 2-sided test with $\alpha$=0.05). NIHSS indicates National Institutes of Health Stroke Scale; ITT, intention-to-treat; HR, hazard ratio; LB, lower bound.

# Discussion

- No significant difference between the Cerebrolysin and Placebo groups
- Beneficial trend in favor of Cerebrolysin in the post hoc analysis

… due to large number of mild strokes included in the trial? (median BL NIHSS was 9 points – they show good outcome in most cases anyway)

[they expected a BL NIHSS of 12]

→ this is consistent with the low mortality rate of 5,6%

# Test yourself (1)

The CASTA trial enrolled patients from:

A Belgium

B USA

C Asia

D Austria

E Australia

# Test yourself (2)

The CASTA study compared…

A Aspirin VS Clopidogrel

B Cerebrolysin (+Aspirin) VS Placebo (+Aspirin)

C Cerebrolysin VS APOSEC

D Rosuvastatin VS Simvastatin

E Stenting VS CEA in Carotid Stenosis

# Test yourself (3)

The CASTA trial was conducted as a…

A Phase I clinical trial

B Phase II clinical trial

C Phase III clinical trial

D Phase IV clinical trial

E Phase V clinical trial

# Test yourself (4)

Which of the following statements is correct?

A The NIHSS-score is used to gauge the severity of a stroke

B The NIHSS ranges from 1-45

C The BI and mRS are the same tests but are used in different parts of the world

D The BI measures performances in *activities of daily living*

E The mRS is the most commonly used clinical outcome measurement tool in clinical stroke trials

F all of the above

# Test yourself (5)

The conclusion of the CASTA trial was:

A There is strong evidence that Cerebrolysin is beneficial in ischemic stroke, regardless of the severity

Ⓑ There was no significant difference between the Cerebrolysin and placebo groups in the primary end point

C Cerebrolysin is dangerous in severe stroke (NIHSS<12)

Ⓓ Post hoc analyses revealed a trend in favor of Cerebrolysin

Ⓔ One of the study‘s weakness regarding the population was the large number of mild strokes

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*Thank you for your attention!*