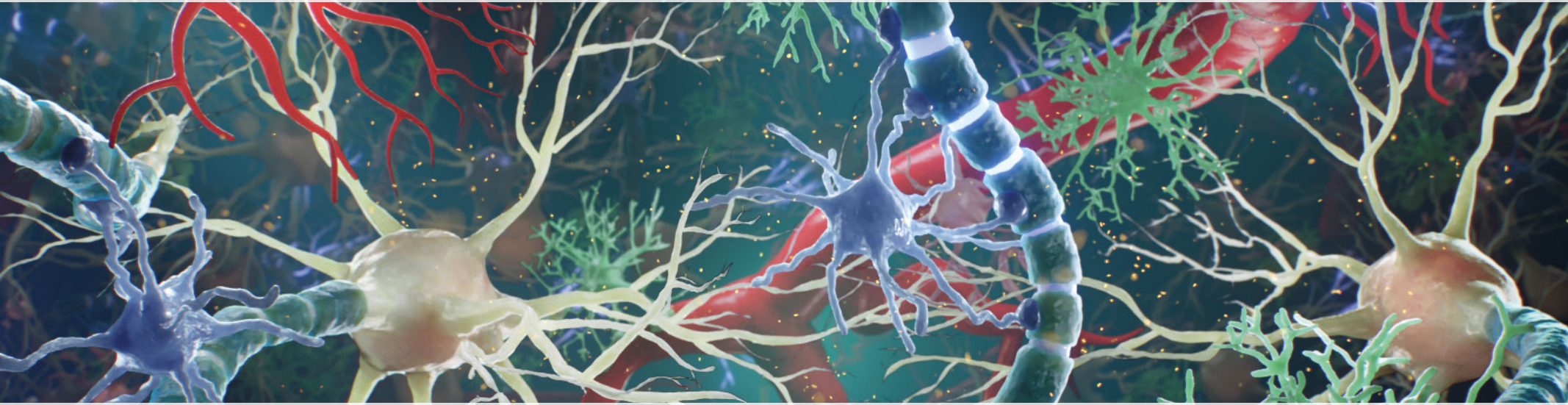
EVER PHARMA

Official symposium of the
"17th World Stroke Congress"
October 22 – 24 I Barcelona, ESP

WSC Symposium Report I 23 October 2025 I International Barcelona Convention Center



Breakthroughs in AIS Therapy:
Recent trial results in evidence-based cerebroprotection

Chair: **Jennifer Manzano (Philippines)**

Sławomir Michalak (Poland): Circulating Tight Junction Proteins in Acute Ischemic Stroke Patients after Reperfusion Therapy combined with Cerebrolysin

Daniel Šaňák (Czech Republic): CREGS – Results of a large High-Quality Comparative Effectiveness Research Study

Breakthroughs in AIS Therapy:
Recent trial results in evidence-based cerebroprotection

The World Stroke Congress (WSC), held in October 2025 in Barcelona, Spain, brought together over 2700 leading, clinicians and researchers from around the globe to discuss the latest developments in stroke treatment and neurorehabilitation.

This report provides an overview about the EVER Pharma symposium which included the moderation by Dr. Jennifer Manzano and the lectures of two experts. Prof. Slawomir Michalak presented new research on blood–brain barrier integrity and endothelial protection during the hyperacute phase of stroke, highlighting the role of Cerebrolysin in stabilizing tight junction proteins and reducing the risk of hemorrhagic transformation when used alongside reperfusion therapy. Dr. Daniel Sanak presented results from the recently published CREGS study, a large international, real-world investigation evaluating the effectiveness and safety of Cerebrolysin in patients with moderate acute ischemic stroke (AIS). His presentation emphasized the clinical value of adjunctive cerebroprotective therapy in improving functional recovery and extending benefits beyond reperfusion.

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Jennifer Manzano

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Introduction

Dr. Manzano welcomed the participants and opened the session by introducing recent advances in treatment in AIS, with a focus on cerebroprotective agents. While reperfusion and recanalization remain the gold standard in the treatment of AIS, thrombolysis alone results an excellent functional outcome (modified Rankin Scale ≤2) in only 46% of patients, and fewer than 27% achieve complete recovery (MRS <1). *(figure 1)* This highlights the need for adjunctive therapies to improve outcomes.

Cerebroprotective agents, particularly Cerebrolysin and related neuropeptides, have emerged as promising adjuncts. These agents are designed to act during the hyperacute and subacute phases of stroke, and even during neurorehabilitation, with evidence-based benefits in improving motor function, aphasia, activities of daily living, and overall quality of life. Landmark clinical trials – including the CARS, ECOMPASS and ESCAS studies – have demonstrated their efficacy in acute stroke care and post-stroke rehabilitation. *(figure 2)*

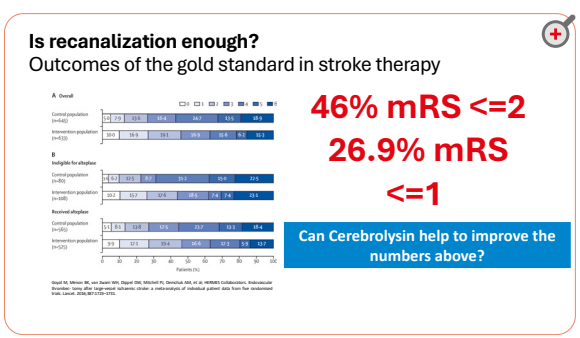
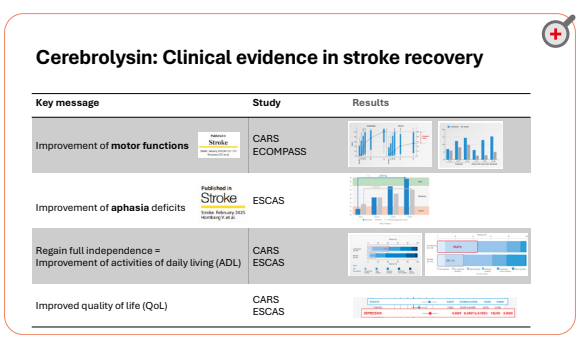


Figure 1



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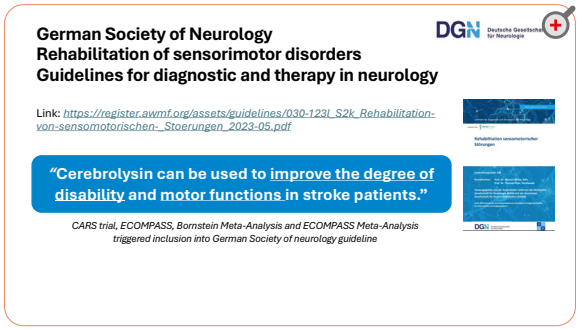

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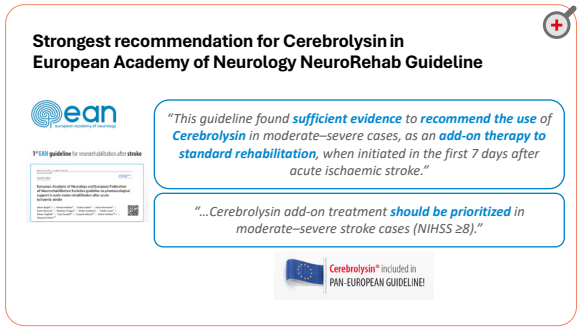

Figure 4

International guidelines now recognize the clinical relevance of cerebroprotective agents. The German Society of Neurology recommends their use to improve sensorimotor disorders and to reduce disability in stroke patients, while the European Academy of Neurology specifically endorses cerebroprotective agents as adjunct therapy for moderate to severe stroke (NIHSS ≥8) when initiated within the first seven days. Mechanistically, these compounds act by reducing free radicals, exerting anti-inflammatory effects, stabilizing the blood-brain barrier and enhancing neuroplasticity and neurorestoration throughout the acute- and recovery phases. *(figure 3, 4)*

Sławomir Michalak

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Circulating Tight Junction Proteins in Acute Ischemic Stroke Patients after Reperfusion Therapy combined with Cerebrolysin

ABSTRACT

Background and Aims: The CERBERUS study investigated whether Cerebrolysin stabilizes blood–brain barrier (BBB) integrity in a manner that can be monitored through serum levels of key tight junction proteins and other biomarkers involved in BBB degradation, and whether it protects against hemorrhagic transformation in ischemic stroke patients following reperfusion therapy. This aim was supported by Teng et al., who demonstrated that Cerebrolysin promotes neurovascular protection by stabilizing BBB integrity and modulating levels of relevant tight junction proteins in vitro.

Methods: CERBERUS is a prospective, longitudinal study conducted in ischemic stroke patients divided into three groups:

A) reperfusion therapy only (intravenous thrombolysis and/or mechanical thrombectomy),
B) reperfusion therapy plus Cerebrolysin, and
C) no reperfusion therapy and no Cerebrolysin.

Patients in Group B with NIHSS > 8 received 30 mL of Cerebrolysin in 500 mL of buffered crystalloid solution intravenously within 12 hours of symptom onset. Blood samples were collected at admission, between days 1–3, and on day 7 or upon reaching a predefined clinical endpoint. Serum levels of occludin, claudin-5, and ZO-1 were measured using in-house ELISA assays to assess BBB integrity.

Results: In the Cerebrolysin group, preliminary results show improved neurological outcomes by day 7, reflected by decreased NIHSS scores. Additionally, reduced serum levels of tight junction proteins suggest a stabilizing effect on BBB integrity.

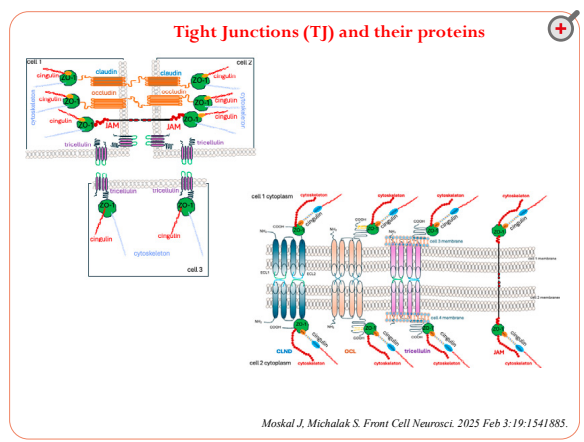
Conclusion: The CERBERUS study underscores the importance of biomarker analysis in stroke management and highlights the potential of Cererboylsin as adjunct therapy.

SUMMARY OF THE PRESENTATION

Prof. Michalak presented findings from the CERBERUS (NCT06078215) study on circulating tight junction (TJ) proteins and blood-brain barrier (BBB) integrity during the hyperacute phase of ischemic stroke. Tight junctions, composed of proteins like claudin, occludin and junctional adhesion molecules, regulate molecular transport and cell migration between blood and the central nervous system. *(figure 5)* BBB disruption, influenced by inflammation, oxidative stress and the overexpression of metalloproteinases, increases the risk of hemorrhagic transformation and futile reperfusion during stroke, particularly in patients with diabetes, hypertension, advanced age or severe strokes. *(figure 6)*

Prof. Michalak emphasized that current methods of reperfusion – thrombolysis and thrombectomy – do not always produce the expected results. This phenomenon is known as "futile reperfusion," meaning that there is no clinical improvement despite radiologically effective recanalization. Several mechanisms contribute to this lack of effect. One is the "no-reflow" phenomenon, in which microcirculation remains insufficient even when flow in the large artery has been restored. Collateral circulation is also crucial as assessing their density. density is important for predicting the outcomes of reperfusion therapy. Collateral flow can be influenced by maintaining adequate blood pressure and managing hypotension, hypocapnia, fever, or brain edema.

Prof. Michalak highlighted that while the focus is often on arteries, the venous system is equally important. Insufficient venous drainage can lead to poor treatment outcomes. Comprehensive, integrated and continuous stroke care is essential. In systems using the "drip-and-ship" model for thrombolysis and mechanical thrombectomy, a pre-recanalization phase can be identified. Together with the pre-hospital and recanalization phases, this



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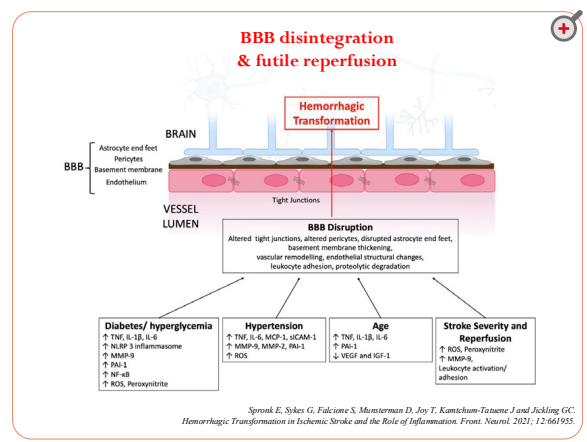

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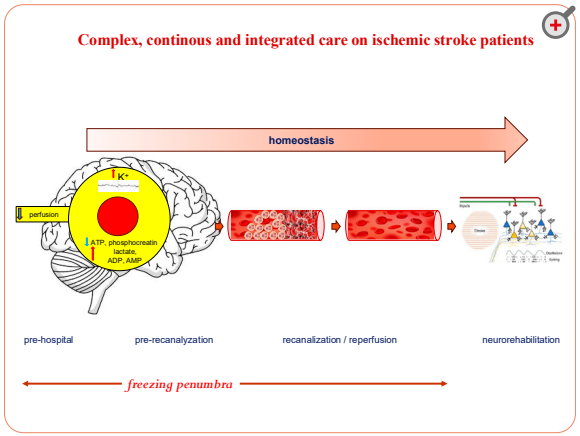

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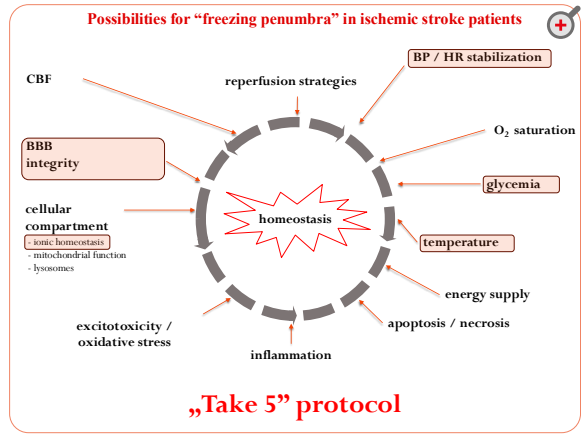

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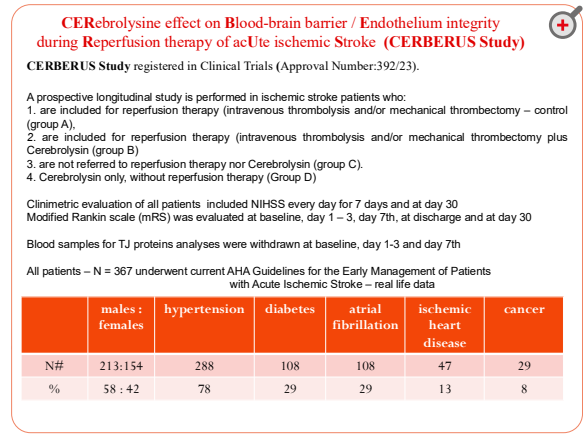


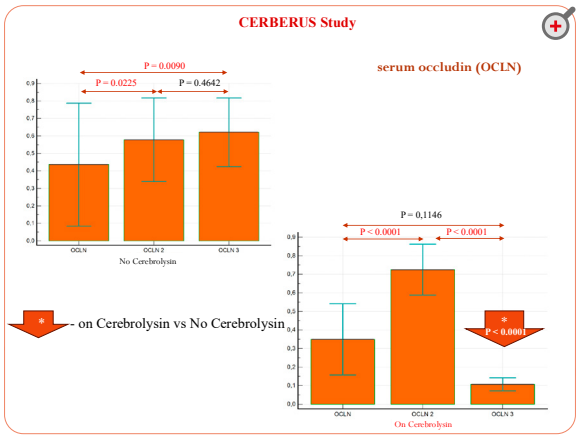
Figure 9

is the critical period in which efforts should focus on freezing the penumbra – maintaining the hypoperfused area and preventing infarct growth progression. *(figure 7)*

To achieve this, several homeostatic factors must be controlled: temperature, blood pressure, ionic balance, glycemia, and the integrity of the blood–brain barrier (BBB). On this basis, the "Take Five" protocol was developed, highlighting these five elements of homeostasis needed to freeze the penumbra. One key component is cerebroprotection. Introducing the term "cerebroprotection" instead of "neuroprotection" – a concept that failed to translate successfully from experimental to clinical settings – reflects a broader approach targeting not only neurons but the entire neurovascular unit, including the BBB. *(figure 8)*

Prof. Michalak highlighted Cerebrolysin, which contains neurotrophic factors, as an adjunct to reperfusion. It stabilizes TJ proteins (claudin, occludin), reduces inflammation and promotes neurogenesis, thereby preserving BBB integrity. Evidence from in vitro studies and previous clinical trials (CARS, ESCAS and others) supports its use in improving functional outcomes, reducing mortality and lowering hemorrhagic transformation risk.

The **CERBERUS** (**CER**ebrolysine effect on **B**lood-brain barrier / **E**ndothelium integrity during **R**eperfusion therapy of ac**U**te ischemic **S**troke) **study** included over 360 stroke patients divided into four groups. *(figure 9)*



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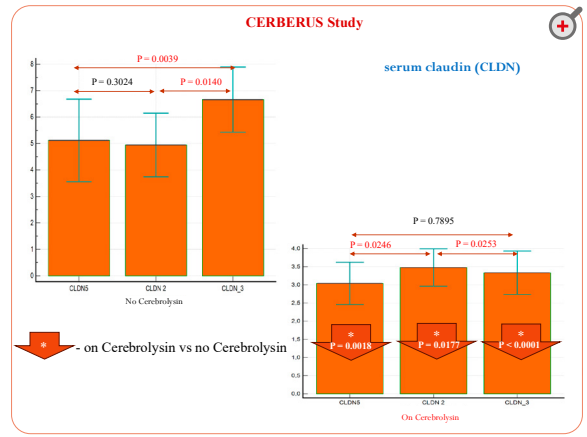

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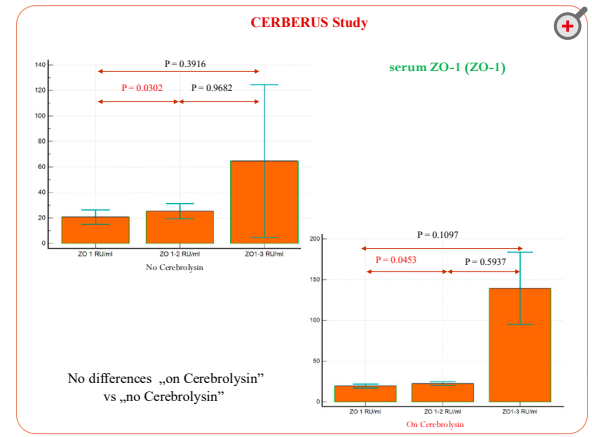

Figure 12

Preliminary results:

- Cerebrolysin therapy reduces NIHSS scores by day 3–7, indicating early clinical improvement.
- Circulating tight junction (TJ) proteins are decreased with Cerebrolysin therapy, suggesting BBB stabilization. *(figure 10, 11,12)*
- A recent neuropathology study confirmed higher TJ protein levels in ischemic vessels of Cerebroylsin treated patients.
- An advanced cluster analysis showed that patients treated with Cerebrolysin had lower TJ proteins in blood and fewer hemorrhagic complications.

Conclusions:

- BBB disruption during acute ischemic stroke worsens outcomes.
- Adjunctive Cerebrolysin with reperfusion is safe, stabilizes endothelial and TJ integrity, reduces hemorrhagic risk and improves clinical outcomes.

Cerebrolysin therapy has a pleiotropic effect on inflammation, apoptosis and neurogenesis, supporting its use in the hyperacute phase to preserve BBB function.

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CREGS – Results of a large High-Quality Comparative Effectiveness Research Study

ABSTRACT

Background and Aims: The multinational CREGS study evaluated the hypothesis that the addition of Cerebrolysin to standard stroke treatment improves functional and cognitive recovery after acute ischemic stroke in patients with moderate neurological deficits in a real-world setting.

Methods: CREGS was conducted across 16 countries as a prospective, open-label comparative effectiveness study following High-Quality Comparative Effectiveness Research (HQCER) and GRACE principles. The study's design incorporated several methodological mechanisms to ensure the validity of the results, including pre-specified analyses, centralized risk-based statistical monitoring and a restricted cohort design. The primary endpoint was the modified Rankin Scale (mRS) at day 90; secondary endpoints included the National Institutes of Health Stroke Scale (NIHSS), mRS at day 21, and the Montreal Cognitive Assessment (MoCA) at day 90 after stroke onset.

Results: Among the 1865 enrolled patients, 1021 received Cerebrolysin in addition to standard care. The treatment group showed superiority in global functional outcome (mRS day 90: MW 0.6157; $p<0.0001$), in NIHSS at both timepoints, and in MoCA scores at day 90 with marked benefits in cognitively vulnerable patients. No differences in safety endpoints were found between groups. Study data integrity was high with 90.9 % of participants demonstrating valid mRS score and with 5.7 % dropouts.

Conclusion: Improvement in mRS translates into greater autonomy and reduced long-term care needs. Enhanced MoCA performance reflects recovery in domains such as attention, executive functions and memory. The results of the CREGS thus support the clinical utility of Cerebrolysin as an adjunctive therapy targeting both physical and cognitive recovery after stroke.

SUMMARY OF THE PRESENTATION

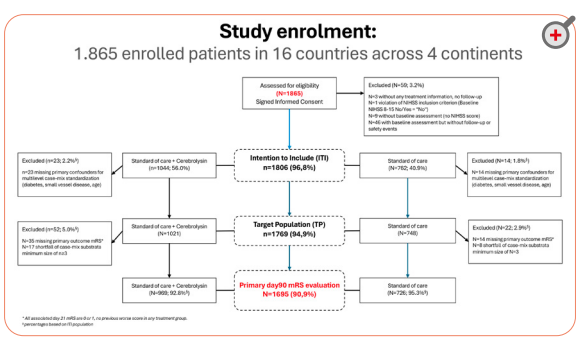
Despite the success of IV thrombolysis and mechanical thrombectomy, more than half of patients still do not achieve a satisfactory recovery, even when recanalization is successful. Therefore, there is a clear need for additional treatments that can support cerebroprotection and neurorecovery, especially for patients who cannot receive reperfusion therapy due to late hospital arrival.

Dr. Sanak presented the results of the prospective, international, multi-center CREGS study assessing the effectiveness of Cerebrolysin. The primary outcome measure was the mRS at 90 days.

The CREGS study was designed as a prospective, multinational, multi-center comparative effectiveness study. It involved 1,865 patients from 16 countries across four continents. The target population included patients with moderate ischemic stroke (NIHSS between 8 and 15), no previous stroke and no pre-stroke disability (mRS 0–1). A restricted cohort design with multi-level stratification was applied to ensure that the treated and control groups were comparable in terms of stroke severity, age, comorbidities like diabetes or small vessel disease. *(figure 13)*

- The primary outcome measure was the mRS at 90 days.
- Secondary outcome measures: NIHSS and mRS at 21 and 90 days, cognitive outcomes assessed by MoCA scale and safety evaluation

In addition to standard therapy, the treatment consisted of the administration of Cerebrolysin according to local clinical practice. The Cerebrolysin dosage was not predefined by the study protocol, it followed local standards. According to these, the median treatment dosage resulted in an average dose of 30 ml/day for 10 days. The most important finding of the study is the significant improvement in functional outcomes at 90 days in patients treated with Cerebrolysin. Patients receiving Cerebrolysin achieved more than a twofold increase in excellent recovery (mRS 0-1) compared with controls. Among non-thrombolyzed patients, 45% of those treated with Cerebrolysin reached an mRS of 0-1 versus 20% in the control group. *(figure 14)* In thrombolyzed patients, the rates were 47% versus 30%. All findings were statistically significant. *(figure 15)*



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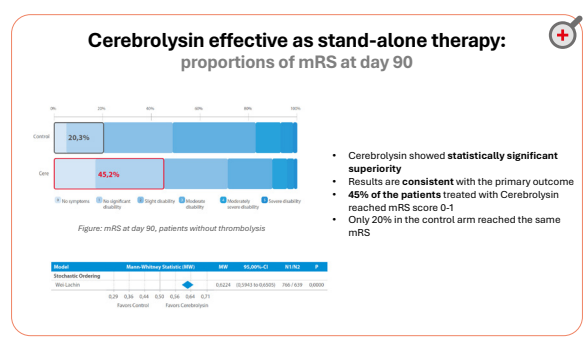

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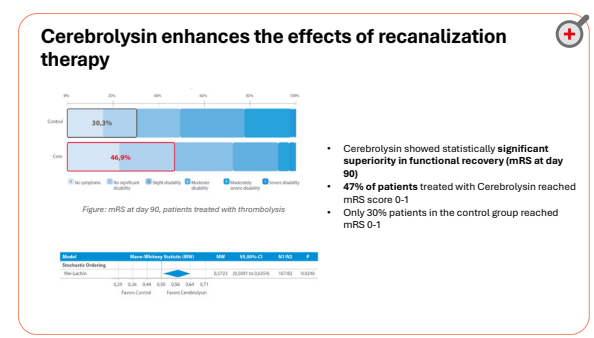


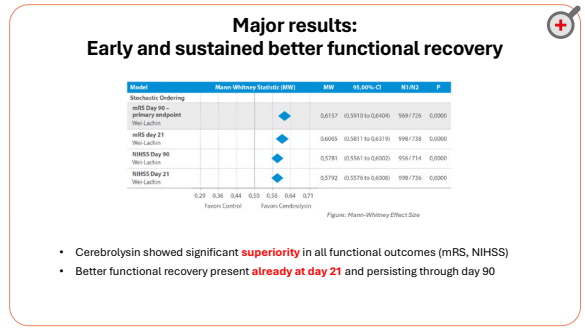
Figure 15

In terms of safety, only minor differences between groups in serious or non-fatal adverse events were recorded, confirming that Cerebrolysin is a safe treatment. *(figure 16)*

Dr. Sanak highlighted the clinical relevance of the CREGS study. It clearly demonstrated a significant positive effect of Cerebrolysin on functional recovery after ischemic stroke. CREGS evaluated the effectiveness of Cerebrolysin in everyday clinical practice, which is very important because patients were enrolled across four continents and 16 countries, each with different healthcare systems and local treatment standards. Despite these differences, the results were consistent, robust, and showed clear effictiveness of Cerebrolysin as a treatment option in acute stroke patients. This underscores the study's relevance in real-world stroke care settings across diverse health systems.

Dr. Sanak emphasized the importance of having an adjunct treatment option that can be used either alongside or independent of thrombolysis. Cerebrolysin represents an evidence-based therapeutic option for patients who miss or cannot receive reperfusion therapy. This is particularly relevant in countries where IV thrombolysis rates remain low. Thus, Cerebrolysin offers an important treatment option for patients who did not receive IV thrombolysis or mechanical thrombectomy. *(figure 17)*

Finally, Dr. Sanak highlighted his personal treatment recommendations and concluded that the CREGS study provides evidence for Cerebrolysin as the first and only pharmacological agent with demonstrated effectiveness in all acute ischemic stroke patients. The results show a robust and excellent effect on functional recovery after ischemic stroke – both when used alone as standard therapy and in patients who have undergone reperfusion therapy. *(figure 18)*



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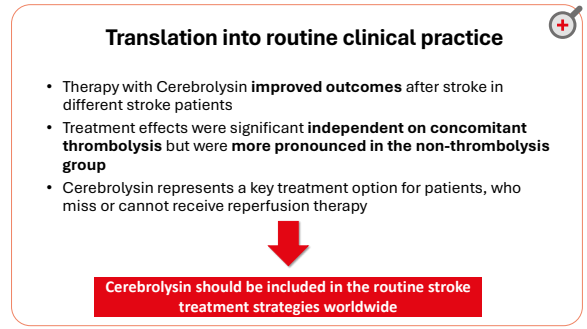

Figure 17

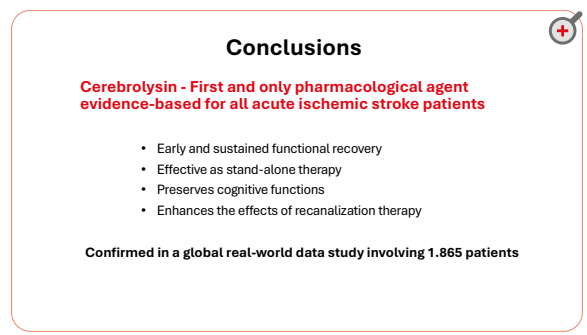

Figure 18

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Summary

The EVER Pharma symposium at WSC 2025 emphasized the growing role of cerebroprotection and neurorecovery in AIS management. Prof. Slawomir Michalak highlighted the importance of blood–brain barrier stabilization during the hyperacute phase and presented data showing that Cerebrolysin supports BBB integrity and reduces hemorrhagic transformation risk when used in combination of reperfusion therapy. Dr. Daniel Sanak presented results from the large CREGS study, demonstrating that Cerebrolysin significantly improves functional recovery and is safe in real-world stroke care.

The experts emphasized that although reperfusion remains the primary treatment for acute ischemic stroke, adjunctive therapies like Cerebrolysin can further improve outcomes and extend benefits to a wider patient population.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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