CLINICAL STUDY PROTOCOL

Combined Neuropsychological, Neurophysiological and Psychophysiological Assessment of the Effects of N-Pep-12 On Neurorecovery in Patients after Ischemic Stroke

(N-PEP-12 – EXTENSION)

Academic, Investigator-Initiated Study

STUDY IDENTIFICATION: N-Pep-12 / EXTENSION

Version	Date
3.0	2020-03-13

This protocol has been written in accordance with the ICH-GCP guidelines and the *Declaration of Helsinki* in current versions.

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1. ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
AR	Adverse Reaction
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
GCP	Good Clinical Practice
h	Hour
HADS	Hospital Anxiety and Depression Scale
ICH	International Committee for Harmonization
IEC	Independent Ethics Committee
incl.	including
mL	Milliliter
NA	Not Applicable
NIHSS	National Institute of Health Stroke Scale
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
VCI	Vascular Cognitive Impairment
WAIS	Wechsler Adult Intelligence Scale

2. PROTOCOL SUMMARY / SYNOPSIS

Title	Combined Neuropsychological, Neurophysiological and Psychophysiological Assessment of the Effects of N-Pep-12 on Neurorecovery in Patients After Ischemic Stroke – N-PEP-12 EXTENSION
Name of product	MemoProve / Cebrium
Name of active substance	N-PEP-12
Phase	Phase IV
Indication	Ischemic Stroke
Study Design	Exploratory, prospective, randomized, open label, controlled study
Number of sites & countries	1 center Romania
Sample Size	**Stroke Group – minimum 90 patients** Intervention Group: N = 60 Reference Group: N = 30
Primary Objectives	• To assess the efficacy of 360 days of once-daily diet supplementation with 90 mg N-Pep-12 on the neurocognitive function and neurorecovery outcome in patients with post-stroke cognitive impairment.
Secondary Objectives	• To assess the safety of 360 days of once-daily diet supplementation with 90 mg N-Pep-12 on the neurocognitive function and neurorecovery outcome in patients with post-stroke cognitive impairment. • To assess study group baseline differences between N-PEP-12 treated patients and controls using quantitative electroencephalography (QEEG) and eye tracking (ET) at day 360, in patients with available recordings (subgroup

	analysis).
Primary Variable	**Stroke Group** • Montreal Cognitive Assessment (MoCA) • Hospital Anxiety and Depression Scale (HADS) • Digit Span (DS) • Color Trial Test (CTT) • Processing Speed Index (PSI)
Secondary Variables	• AE, SAE o Date/time o Relationship/Seriousness/Outcome • Mortality: o Date/time o Cause • Subgroup analysis o QEEG parameters o Eye tracking parameters
Inclusion Criteria	• Stroke onset – 30-120 days prior to screening • Stroke is ischemic in origin, supratentorial, and radiologically confirmed (CT or MRI) • No significant pre-stroke disability (pre-stroke Modified Rankin Score of 0 or 1) • Goodglass and Kaplan Communication Scale Score of > 2 at screening • No other radiologically confirmed stroke in the 3 months preceding index stroke • Age between 18 and 80 years, inclusive • Signed informed consent form

Exclusion Criteria	• Pre-existing and active major neurological disease • Pre-existing and active (e.g., on chronic medication) major psychiatric disease, such as major depression, schizophrenia, bipolar disease, or dementia (the short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score >3) • Advanced liver, kidney, cardiac, or pulmonary disease • A terminal medical diagnosis consistent with survival < 1 year • Major drug dependency, including alcohol (in the investigator's judgment). • Injury of writing hand influencing cognitive or other outcome measures, in the investigator's judgment. • Females who are pregnant or lactating.
Visit Schedule	Visit 1 – Screening / Baseline **Day – Baseline - 30-120 days from stroke onset** Visit 2 – Efficacy / Safety **Day – 90 days from baseline** Visit 3 – Efficacy / Safety **Day – 360 days from baseline**
Documented parameters	**Visit 1 – 30-120 days from stroke onset** ○ Patient logistics ○ Patient demographic data (age, gender, ethnicity) ○ Patient medical history and risk factors ○ Inclusion/exclusion criteria ○ All primary efficacy assessment scales

	○ QEEG/ET parameters **Visit 2 – 90 days from baseline** ○ Patient logistics ○ All primary efficacy assessment scales ○ QEEG/ET parameters **Visit 3 – 360 days from baseline** ○ Patient logistics ○ All primary efficacy assessment scales ○ QEEG/ET parameters
Statistical methods	The statistical analyses in this study will be exploratory in nature because the study is not powered to address any pre-defined statements but to generate valid hypotheses on efficacy and safety issues for future studies. A formal sample size calculation for confirmatory trials was not performed.

3. INTRODUCTION

3.1. Background information

Cognitive impairment is a common finding in patients with stroke, regardless of severity, and it has an important impact on quality of life. Vascular cognitive impairment (VCI) describes a spectrum of cognitive disorders ranging from mild cognitive impairment (MCI) to dementia, with consequences for all cognitive domains and behavior (Jellinger K. A., 2013). However, there is increasing evidence to suggest the disproportionate impairment of executive function, including working memory, abstraction, reasoning, verbal fluency, and cognitive flexibility (Sachdev P.S. et al, 2004; Sörös P. et al., 2015). In epidemiological studies of stroke, cognitive impairment ranges from 20% to 80%; this variation depends on several factors, especially the diagnostic criteria (Sun J.H. et al., 2014). For example, the prevalence of the cognitive impairment 3 months after stroke can present a variation up to 72% depending on the complexity of the neuropsychological assessment (Gutiérrez P.C. et al., 2011; Douiri A., et al, 2013).

This is a pilot study to investigate the effects of N-Pep-12 diet supplementation on the neurorecovery of patients with post-stroke cognitive impairment. N-Pep-12 is a proprietary, peptide-based nutritional supplement that has been shown to exert neuroprotective and pro-cognitive effects in experimental studies (Hutter-Paier B. et al., 2015) as well as in earlier

clinical studies in patients suffering from age-related cognitive deficits (Alvarez X.A. et al., 2005; Crook T.H. et al., 2005). Remarkably, N-Pep-12 has been shown to significantly improve memory impairment in older adults with subjective memory complaints after only 30 days of a once-daily intervention with 90 mg of the compound (Crook T. H. et al., 2005). The compound is available in the form of film-coated tablets or capsules under the brand names Memoprove and Cebrium. Furthermore, qEEG power analysis showed that N-Pep-12 is able to improve vigilance after only a single dose (Alvarez X.A. et al., 2005).

This study will use a multidimensional approach that will combine neuropsychological outcome scales, neurophysiological investigations (qEEG), psychophysiological investigations (eye-tracking), and clinical parameters.

Eye tracking involves looking at targets on a computer screen while a special system records eye movements and changes in pupil diameter in response to the movements of the targets. Patterns of eye movements offer information about what a person is processing at a particular moment and the time course of processing visual information. Smooth pursuit and saccades are the two components of tracking eye movements. Smooth pursuit, or just pursuit, is a class of slow eye movements that minimizes retinal target motion. Saccades are rapid eye movements that align the fovea with the target. Their coordination is usually studied by investigating the latencies of pursuit onset in response to a moving target appearing simultaneously with the disappearance of the stationary fixation target. Because the saccades and fixations recruit the same neuroanatomical circuitries as attention, involving the dorsolateral prefrontal cortex, and also because eye movements can be influenced by emotions, it has been suggested that eye tracking can be used as a biomarker for cognitive dysfunction (Munoz D.P., 2002; Seligman S. C. and Giovannetti T., 2015).

Due to its highly accurate temporal resolution, the qEEG technique (with 19 channels) provides a unique window to assess the brain dynamics underlying cognitive functions. qEEG has been used for the evaluation of Alzheimer's disease (Chen C.C. et al., 2013), vascular dementia (Neto E. et al, 2015), and Parkinson's disease-associated dementia (Caviness J.N. et al., 2015). It also can reveal abnormalities in the preclinical stages of cognitive impairment (When D. et al., 2015). Typical EEG findings in patients with Alzheimer's disease (AD) include increased slow wave and decreased fast wave activities. (Alvarez X. A. et al., 2000; Alvarez X.A. et al, 2003; Alvarez X. A. et al, 2008).

4. STUDY OBJECTIVES

The study shall assess the therapeutic effect and the safety of a single daily dose of 90 mg of N-Pep-12 in supporting neurorecovery in comparison to a control group of patients after stroke. This is an exploratory study, and the dosage, route of administration and intervention duration were chosen according the current instructions for use provided by the manufacturer of N-Pep-12. The study aims to show the superiority of N-Pep-12 over the control group in the neurorecovery outcome after 360 days.

4.1. Primary Objective

To assess the efficacy of 360 days of once-daily intervention duration with 90 mg N-Pep-12 on neurocognitive function and neurorecovery outcome in patients with post-stroke cognitive impairment.

4.1.1. Primary End-Points

- MoCA
- HADS
- CTT
- DS
- PSI

4.2. Secondary Objective

To assess the safety of 360 days of once-daily intervention duration with 90 mg N-Pep-12 on neurocognitive function and neurorecovery outcome in patients with post-stroke cognitive impairment.

4.2.1. Secondary End-Points

- Safety variables.
- Subgroup analysis
  - QEEG parameters
  - Eye tracking parameters

5. STUDY DESIGN

Exploratory, prospective, randomized, open label, controlled study.

6. STUDY CENTER

‘‘RoNeuro’’ Institute for Neurological Research and Diagnostic, Cluj-Napoca, Romania.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

- Stroke onset – 30-120 days prior to screening
- Stroke is ischemic in origin, supratentorial, and radiologically confirmed (CT or MRI)
- No significant pre-stroke disability (pre-stroke Modified Rankin Score of 0 or 1)
- Goodglass and Kaplan Communication Scale Score of > 2 at screening
- No other radiologically confirmed stroke in the 3 months preceding index stroke
- Age between 18 and 80 years, inclusive.
- Signed informed consent form

7.2. Patient Exclusion Criteria

- Pre-existing and active major neurological disease
- Pre-existing and active (e.g., on chronic medication) major psychiatric disease, such as major depression, schizophrenia, bipolar disease, or dementia (the short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score >3)
- Advanced liver, kidney, cardiac, or pulmonary disease
- A terminal medical diagnosis consistent with survival < 1 year
- Major drug dependency, including alcohol (in the investigator's judgment).
- Injury of writing hand influencing cognitive or other outcome measures, in the investigator's judgment.
- Females who are pregnant or lactating.

7.3. Stopping and Discontinuation Criteria

7.3.1. Discontinuation Criteria related to the Study

- Insufficient recruitment of less than 30% of the total patient sample in one year
- If reasonable suspicion exists that any serious and life-threatening side effects occur significantly more frequently than usual in patients with the inclusion diagnosis, the study will be discontinued.

7.3.2. Discontinuation Criteria Related to the Patient

Patients will be advised in the informed consent forms that they have the right to withdraw from the study at any time without prejudice, and they may be withdrawn at the investigator's discretion at any time. In the event that a patient drops out of the study or is withdrawn, the withdrawal/study termination page in the CRF should be completed. On the withdrawal page, the investigator should record the date of the withdrawal, the person who initiated withdrawal

and the reason for withdrawal. Reasonable effort should be made to contact any patient lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data and study supplies.

Withdrawn by the Investigator due to:

- Lack of efficacy
- Adverse event
- Consent withdrawn
- Lost to follow-up
- Administrative reasons

The patient or his/her representative requested withdrawal due to:

- Adverse event (for which the investigator did not consider removal from the study)
- Perceived insufficient therapeutic effect
- Withdrawal of consent for any other reason (data recorded until withdrawal will be kept in the database if not explicitly denied by the patient).

7.4. Randomization, Blinding and Unblinding

8. PATIENTS WHO MEET THE INCLUSION AND EXCLUSION CRITERIA WILL BE RANDOMLY ASSIGNED TO THE TREATMENT GROUP OR CONTROL GROUP, IN A 2:1 RATIO. PATIENTS IN THE TREATMENT GROUP WILL RECEIVE ACTIVE DIET SUPPLEMENTATION MEANWHILE, THE PATIENTS IN THE CONTROL GROUP WILL NOT RECEIVE ANY KIND OF MEDICATION OR PLACEBO. INVESTIGATIONAL PRODUCTS

The regular marketable merchandise of N-Pep-12 (Cebrium) capsules will be obtained from pharmaceutical wholesalers in Romania.

8.1. Name and Description of the Investigational Product(s)

N-Pep-12 (Cebrium)

For detailed information (Instructions for Use) on these products, please refer to **Appendix 1**.

8.1.1. Dosage, Formulations and administration

Active Diet Supplementation: N-Pep-12 (90 mg) capsules will be administered once per day.

8.2. Packaging and Labeling

Regular marketable merchandise will be used.

8.3. Storage

The study medication will be stored at room temperature in a dry place.

8.4. Investigational Product Accountability and Destruction

Not applicable.

9. CONCOMITANT THERAPY

There will be no restrictions on concomitant treatments or therapies for the study participants. However, any concomitant treatment or therapy will be recorded in the patient's CRF.

10. DEFINITION OF THE PRIMARY AND SECONDARY VARIABLES

Five neuro-psychological scales will be used in stroke patients: MoCA, HADS, CTT, DS and PSI. These scales have been established as reliable and valid and have been used extensively in other clinical trials on stroke and cognitive impairment (Quinn T.J., 2011; Aben I., 2002; Pendlebury S. T., 2013; Poon W., 2015).

10.1. Primary Variables

- **MoCA**

  Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. The time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

- **Processing Speed Index, Wechsler Adult Intelligence Scale, Fourth Edition**

  The Processing Speed Index (PSI) assesses skills such as focusing attention and quick scanning as well as discriminating between and sequentially ordering visual information. It requires persistence and planning ability, but it is sensitive to motivation, difficulty working under time pressure, and motor coordination as well. It is also related to reading, mathematical, and memory skills. Cultural factors seem to have little impact on processing speed. Processing Speed (PS) refers to the speed at which cognitive processes can be performed.

- **Digit Span, Wechsler Adult Intelligence Scale, Fourth Edition**

  The Digit Span task exercises a patient's verbal working memory. Attention and comprehension also contribute to performance. The digit span task is a common component of many IQ tests, including the widely used WAIS (Wechsler Adult Intelligence Scales).

Performance on the digit span task is also closely linked to language learning abilities. The procedures for this assessment of working memory are considered standard. A list of numbers is read out loud at a rate of one number per second, and the participant is then asked to recall the numbers in order. The first list consists of three numbers and increases until the person begins to make errors. Lists with recognizable patterns (e.g., 1, 3, 5, 7, and 9) should be avoided, as people may remember these numbers more easily. At the end of each sequence, the participant is asked to the recall items in order. The average adult can remember a sequence of seven numbers, plus or minus two. This test can be distributed both backwards and forwards. Scores are thought to correlate with age and not intelligence.

- **Hospital Anxiety and Depression Scale**

The Hospital Anxiety and Depression Scale (HADS) is commonly used to determine a patient's levels of anxiety and depression. The HADS is a fourteen item scale that generates: seven of the items relate to anxiety and seven relate to depression. Each item had been answered by the patient on a four-point (0–3) response category so the possible scores ranged from 0 to 21 for anxiety and 0 to 21 for depression. A score of 0 to 7 could be regarded as being in the normal range, a score of 8 to 10 as borderline abnormal, and a score over 11 as abnormal. The patient is asked to provide answers regarding his/her feelings during the past week. While answering the questions, the patient should answer with immediate reactions, thus giving a more accurate representation of his/her feelings.

- **Color Trails Test**

The Color Trails Test (CTT) was developed to meet the need for a test with the sensitivity and specificity of the standard Trail Making Test (TMT) but that was as free as possible from the influences of language and cultural bias. The CTT retains the psychometric properties of the standard TMT, but the CTT substitutes the use of color for the use of English alphabet letters, making it more suitable in cross-cultural and other special needs contexts.

10.2. Secondary variables

- AE, SAE
  - Date/time
  - Relationship/Seriousness/Outcome
- Mortality:
  - Date/time
  - Cause

- Subgroup analysis
  - QEEG parameters
  - Eye tracking parameters

10.3. Source Documents

Variable	Source document
Informed consent	Informed consent form
Patient's data (e.g., demographics: sex, age, weight, indication, concomitant diseases, medical history, concomitant medication)	CRF
Vital signs	CRF
Outcome variables (evaluation scales)	CRF
Patient safety data	CRF

11. ASSESSING AND REPORTING OF ADVERSE EVENTS

Throughout the course of the clinical study, particular attention will be paid to the adverse events and adverse drug reactions mentioned below.

11.1. Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or subject of clinical investigation administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not it is related.

11.2. Adverse Drug Reaction (ADR)

All untoward and unintended responses to an investigational product related to any application/dose administered, i.e., having a reasonable causal relationship as judged by the Investigator. This means that there is evidence or argument to suggest a causal relationship.

11.3. Serious Adverse Event or Serious Adverse Reaction (SAE/SAR)

An adverse drug reaction is considered SERIOUS if it:

- Results in death
- Is life threatening

- Requires additional inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability / incapacity
- Results in a congenital anomaly or birth defect
- Other medically significant event that requires immediate medical or surgical intervention

An adverse drug reaction is considered UNEXPECTED if it:

- Is not consistent with the Investigators' Brochure or SPC

CAUSAL RELATIONSHIP means:

- There are facts/evidence to suggest a causal relationship
- As judged by the reporting health care professional to have a reasonably suspected causal relationship

Expedited Reporting is required if all of the following criteria apply (ICH E2A):

- Serious
- Unexpected
- Causal relationship to study treatment

NOTE

Death: is the outcome of an adverse event. The event to be reported comprehensively is the medical condition leading to death, e.g., underlying disease or accident.

Life-threatening: in the definition of a serious adverse event or adverse reaction, "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

11.4. Suspected Expected Serious Adverse Reaction (SESAR)

Any adverse reaction that is classified as serious in nature and that is consistent with the available information on the product in question according to:

a. In the case of a licensed product, the summary of product characteristics (SPC) for that product

b. In the case of any other investigational medicinal product, the Investigator's Brochure (IB) relating to the study in question

11.5. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classified as serious in nature and that is **not** consistent with the available information on the medicinal product in question according to:

a. In the case of a licensed product, the SPC for that product
b. In the case of any other investigational medicinal product, the IB relating to the study in question.

11.6. Recording of Adverse Events

All adverse events, whether they are considered serious or not, will be documented and applicably reported according to previously provided definitions.

The investigator must report in detail all adverse signs and symptoms that are either volunteered by patients or observed during or following the course of Investigational Product administration on the appropriate CRF page.

Included in the description should be the nature of the sign or symptom; the date of onset; date of resolution (duration); the severity/intensity; the relationship to the study treatment or other therapy; the action taken (if any); and the outcome.

11.6.1. Definition of Adverse Event Intensity

Intensity	Definition
Mild	Patient is aware of signs and symptoms, but they are easily tolerated
Moderate	Signs/symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities

11.6.2. Definition of Adverse Event causality

Based on the WHO-UMC system for standardized case causality assessment (www.who-umc.org), the following categories will be used to describe the degree of causality (all points should reasonably comply):

Definite

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)

- Event is definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Re-challenge satisfactory, if necessary

Probable

- Event or laboratory test abnormality, with reasonable time relationship to product intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable (for details refer to WHO-UMC)
- Re-challenge not required

Possible

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

Not related

The event does not follow a reasonable temporal sequence from administration of the IMP and is clearly related to other factors, such as clinical state, therapeutic intervention or concomitant therapy.

Not assessable

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

All cases judged as having a “reasonable causal relationship” to the IMP qualify as ADR. This corresponds to the categories “definite,” “probable” and “possible”.

11.7. Reporting of Serious Adverse Events

All serious adverse reactions and all unexpected serious adverse reactions with at least a suspicion of a causal relationship to the investigational product must be reported to the manufacturer within 24 hours (one working day) of the Investigator first becoming aware.

Fatal or life-threatening SUSARs must be reported to the Ethics Committee and relevant regulatory bodies within 7 days; all other SUSARs must be reported within 15 days of knowledge if no other timelines are set out in the local drug law.

11.8. Adverse Event/Reaction follow-up procedures

Adverse events/reactions will be followed-up throughout the course of the clinical study.

12. STUDY SCHEDULE

12.1. Procedures at Each Visit

Visit 1: Screening/Baseline – 30-120 days from stroke onset

Patients will be informed about the study and an Informed consent will be obtained before any study-specific procedures will be carried out. Inclusion/exclusion criteria will be assessed and documented in the CRF. Patients who provide an informed consent and who meet all inclusion/exclusion criteria will be included in the study, and a randomization code will be assigned. After randomization, the medical history, vital signs, and patient demographic data as well as any concomitant medication will be measured or retrieved and recorded in the CRF. The baseline tests for all efficacy parameters (primary and secondary) will then be administered, and the results will be recorded in the CRF. Treatment with the study drug will be initiated with the first dose, and patients will receive the study drug for first 90 days of treatment.

Visit 2: 90 days from baseline

Vital signs will be taken, and changes in any of the concomitant medications will be recorded in the CRF. Any adverse events reported by the patient or noted by the investigator will be assessed and recorded in the CRF. Compliance with the study medication will be checked and recorded in the CRF. Tests for primary and secondary efficacy parameters will be administered and recorded. Patients will receive the study drug for the next 270 days of treatment.

VISIT 3: 360 days from baseline

Vital signs will be taken, and changes in any of the concomitant medications will be recorded in the CRF. Any adverse events reported by the patient or noted by the investigator will be assessed and recorded in the CRF. Compliance with the study medication will be checked and recorded in the CRF. Tests for primary and secondary efficacy parameters will be administered and recorded.

12.2. Tabular Overview of Assessments

Visit 1 – Screening & Baseline	***Visit 2 – Efficacy Evaluation***	***Visit 3 – Efficacy Evaluation primary endpoint***
Informed Consent		
Inclusion Criteria		
Exclusion Criteria		
Patient Demographics		
Medical History	*Changes in Medical History*	*Changes in Medical History*
Concomitant Medication	*Changes in Concomitant Medication*	*Changes in Concomitant Medication*
Vital Signs	*Vital Signs*	*Vital Signs*
Primary Efficacy Parameters	*Primary Efficacy Parameters*	*Primary Efficacy Parameters*
Adverse Events	*Adverse Events*	*Adverse Events*
	Compliance with Study Drug	*Compliance with Study Drug*
Subgroup analysis (QEEG, ET)	*Subgroup analysis (QEEG, ET)*	*Subgroup analysis (QEEG, ET)*

13. STATISTICS

13.1. Statistical methods

The study data will be analyzed, and the statistical report written as soon as all study data are entered into the study database and the entered data are validated.

14. ACCESS TO SOURCE DATA / DOCUMENTS

The investigators will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections, providing direct access to primary patient data (i.e., source data), which support the data on the CRFs for the study.

14.1. Source Data

Source data are defined as all information in the original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

14.2. Source Documents

Source documents are defined as original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation

checklists, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, patient files, records kept at the pharmacy laboratories and at medical/technical departments involved in the clinical study).

14.3. Direct Access

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of a clinical study. Any party (e.g., domestic and foreign regulatory authorities, study monitors, auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of the patients' identities and the sponsor's proprietary information.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Quality Control

Quality control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for the quality of the study-related activities have been fulfilled. Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

15.2. Study Monitoring

The study coordinator will visit the investigational site at regular intervals to verify adherence to the protocol and local legal requirements and to assist the investigator in his study-related activities.

15.3. Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded) and reported in compliance with good clinical practice (GCP) and the applicable regulatory requirements.

15.4. Audit

An independent audit at the study site may take place at any time during or after the study if considered necessary by mutual agreement of the principal investigator and the study coordinator.

16. ETHICAL AND LEGAL CONSIDERATIONS

16.1. Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

IEC/ IRB approval will be obtained before the start of the study.

16.2. Informed Consent

Patients will be informed about the study procedures and potential risks and benefits of the study. Their consent to participate in this study will be obtained before any study-specific procedures are carried out. A sample informed consent form is provided in Appendix 2.

16.3. Modification of Protocol

Modifications of the protocol will require the mutual agreement of the principal investigator and the study coordinator. Necessary protocol amendments will be documented and submitted to the appropriate IEC for approval. The only exceptions are when changes are necessary to eliminate an immediate hazard to study patients, or when the changes involve only logistical or administrative aspects of the study.

16.4. Conduct of Study

This clinical study will be conducted in accordance with the current version of the Declaration of Helsinki. It will be conducted in compliance with this protocol, good clinical practice (2001/20/ EEC, CPMP/ICH/135/95), and with local laws and regulations relevant to the use of investigational medicinal products in the country of conduct.

16.5. Personal Data and Data Protection

All data obtained in the context of the clinical study are subject to data protection. The patient's name in addition to other data related to persons (excluding date of birth/age and sex) are not to be disclosed by the investigator or the investigating physicians. The latter will ensure that the case report forms or other documents contain no names, but other identifiers (patient's number and date of birth). The storage of data for statistical assessment shall be performed under the patient's identifier. Only the Investigator and the investigating physicians can assign the identifier to the personal data.

16.6. Data Handling and Record Keeping

16.6.1. Completion of Case Report Forms

Any data to be recorded directly into the CRFs will be identified at the start of the study.

The investigator will ensure the accuracy, completeness, legibility and timeliness of data reported in the CRF and all required reports. Any change or correction to a paper CRF must be dated, initialed and explained and must not obscure the original entry. Data reported on the CRF that are derived from source documents should be consistent with the source documents, or the discrepancies should be explained. Within two weeks after the completion of each patient, the investigator should agree to have completed and signed CRFs available for full inspection by the clinical monitor.

16.6.2. Archiving

On termination of the study, the study documents are to be filed and stored at the RoNeuro Institute. The informed consent forms and all the original (raw) data are to be retained by the principal investigator of the clinical study or the investigating physicians for at least 15 years.

16.7. Confidentiality

The aim and contents of the study, in addition to its results, are to be treated as confidential by all persons involved in the clinical study.

16.8. Responsibilities

The responsibilities of the clinical study personnel regarding the handling of data, storage of data, planning, assessment and quality assurance are regulated by the recommendations of good clinical practice of the International Conference on Harmonization (ICH) and apply to this clinical study.

17. FINAL REPORT AND PUBLICATION POLICY

The principal investigator and the study coordinator must agree on the final study report. The latter will be signed by the investigator, the investigating physicians involved and the study coordinator. It is intended that the results of the study will be published as scientific literature.

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19. SIGNATURES

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date: **Signature:**

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Fior-Dafin Muresanu
Study Coordinator

APPENDICES

Appendix 1 *Investigational Products - Instructions for Use*

Appendix 2 *Informed Consent Form*