CLINICAL STUDY PROTOCOL

Efficacy and Safety of Cerebrolysin in the Treatment of Aphasia after Acute Ischemic Stroke (ESCAS)

Study Code	ESCAS
Protocol Number	FSNN20200207
Version	2.0
Date	May 28th, 2020
Coordinating Institution	Foundation for the Study of Nanoneurosciences and Neuroregeneration (FSNN)

Confidential Information

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

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PROTOCOL SUMMARY / SYNOPSIS

Coordinating Institution (Academic Study)	FSNN – Foundation for the Study of Nanoneurosciences and Neuroregeneration
Title	***Efficacy and Safety of Cerebrolysin in the Treatment of Aphasia after Acute Ischemic Stroke (ESCAS)***
Study Code	ESCAS
Study Locations	Spitalul Clinic Județean de Urgență Cluj-Napoca
	Institutul RoNeuro Cluj-Napoca
Investigational Medicinal Product	Cerebrolysin Solution for Injection (CRB)
Name of Active Substance	Cerebrolysin Concentrate
Phase	IV
Indication	Acute Ischemic Stroke
Study Design	Exploratory, prospective, randomized-controlled, double-blinded
Study Duration	Study start: 05/2020 Study end: 05/2022
Sample Size	N=120 • Group 1 – Cerebrolysin N = 60 • Group 2 – Placebo N = 60
Primary Objective	To assess the efficacy of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at **30, 60 and 90 days after baseline** using the Western Aphasia Battery (Romanian translated version).
Secondary Objectives	• To assess the efficacy of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at 30, 60 and 90 days after baseline using measures of motor, neurological and global functional outcome (NIHSS, BI, mRS). • To evaluate the safety of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at 30, 60 and 90 days after baseline.
Primary Variables	Western Aphasia Battery
Secondary Variables	Demographics (including education) Medical history NIHSS modified Rankin Scale Barthel Index
Safety Variables	Adverse Events (AE) Severe Adverse Events (SAE)

Inclusion Criteria	• Radiologically (CT or MRI) and clinically confirmed diagnosis of acute ischemic stroke in the left MCA territory; • Broca or mixed non-fluent aphasia, *including transcortical motor aphasia"* • Inclusion between 3-5 days post stroke; • Right-handedness; • Romanian as language of daily use; • Signed informed consent.
Exclusion Criteria	• Prior symptomatic ischemic or hemorrhagic stroke; • Severe comprehension deficit that may compromise informed consent or understanding of instructions: fluent aphasias (ex. Wernicke aphasia); global aphasias. • Preexisting neurodegenerative or psychiatric disease; • Epilepsy or EEG-documented epileptic discharges; • Severe chronic renal or liver failure; (AST, ALT > 4 times normal values, creatinine > 4); • Life-threatening diseases; • Auditory or visual deficits that cannot be corrected and might impair testing.
Visit Schedule	**Visit 1 - Day 0 - Baseline** *3-5 days post-stroke* • Demographics • Medical history • Western Aphasia Battery • NIHSS **Visit 2 - Day 30 ± 3** • Western Aphasia Battery • NIHSS • Barthel Index • modified Rankin Scale • Adverse Events (AE) • Severe Adverse Events (SAE) **Visit 3 - Day 60 ± 3** • Western Aphasia Battery • NIHSS • Barthel Index • modified Rankin Scale • Adverse Events (AE) • Severe Adverse Events (SAE) **Visit 4 - Day 90 ± 3** • Western Aphasia Battery • NIHSS

	• Barthel Index • modified Rankin Scale • Adverse Events (AE) • Severe Adverse Events (SAE)
Investigational Product	Cerebrolysin Solution for Injection (CRB): • 30 ml diluted with 0.9% saline solution to a total solution of 250 ml, administered by IV infusion
Reference Product	250 ml 0.9% saline solution administered by IV infusion *Procedural i.v. administration blinding will be enforced for both therapeutic products.*
Treatment Schedule	Eligible patients with aphasia will be divided into two groups: • Control group - patients receiving NaCl procedural placebo and speech therapy for 1h per day during the study period (30 treatment days). • Treatment group – patients receiving: o 30ml Cerebrolysin/Day + Speech Therapy (1h/day), 30 days during the study period; **Treatment Cycle 1 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)** Study days 1 – 14 30ml Cerebrolysin/saline i.v. 1h Speech Therapy **Treatment Cycle 2 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)** Study days 29-42 30ml Cerebrolysin/saline i.v. 1h Speech Therapy **Treatment Cycle 3 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)** Study days 57-70 30ml Cerebrolysin/saline i.v. 1h Speech Therapy

1. EVALUATION METHODS

Western Aphasia Battery

Western Aphasia Battery (WAB) is an instrument for assessing the language function of adults with suspected neurological disorders as a result of a stroke, head injury, or dementia. There is an updated version, the Western Aphasia Battery-Revised (WAB-R). It helps discern the presence, degree, and type of aphasia. It also measures how the patient performed on the test to provide a baseline so they can detect changes throughout their time in therapy. This also allows to see the patient's language strengths and weaknesses so that they can figure out what to treat, and lastly, it can infer the location of the lesion that caused aphasia. The WAB targets English speaking adults and teens with a neurological disorder between the ages of 18 and 89 years old. The WAB tests both linguistic and non-linguistic skills. The linguistic skills assessed include, speech, fluency, auditory comprehension, reading and writing. The nonlinguistic skills tested include drawing, calculation, block design and apraxia. This study will use a Romanian linguistically validated version of WAB.

NIH Stroke Scale

The NIH Stroke Scale assesses neurologic deficit and is a 15 items scale that covers the level of consciousness, gaze, visual fields, facial palsy, motor functions, limb ataxia, aphasia, dysarthria and extinction and inattention. The NIHSS is observer-rated and takes 5-8 min to complete. Items have 3- to 5-point response scales, scored from 0 to 4 with higher score indicative of more severe disability. In case of patient death, the worst score possible will assigned. The NIHSS will be used to assess the severity of the stroke at baseline as well as in the follow-up examinations as a measure of neurological function deficit.

Modified Rankin Score

The Modified Rankin Score is a functional outcome scale measuring global outcome. It is used for grading the outcome and the level of disability after a stroke. The Modified Rankin Score is a 7-point ordinal scale with a score of 0 indicative of no residual symptoms at all and the worst possible score of 6 which is assigned in case of death. The Modified Rankin Scale is observer rated and takes about 5 min to complete.

Barthel Index

The Barthel Scale/Index (BI) is an ordinal scale used to measure performance in activities of daily living (ADL). Ten variables describing ADL and mobility are scored, a higher number being a reflection of greater ability to function independently following hospital discharge. Time taken and physical assistance required to perform each item are used in determining the assigned value of each item. The Barthel Index measures the degree of assistance required by an individual on 10 items of mobility and self care ADL.

2. STUDY OBJECTIVES

This study shall assess the efficacy and safety of Cerebrolysin in the treatment of aphasia after acute ischemic stroke.

2.1. Primary Objective

It is the primary objective of this clinical study to assess the efficacy of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at 30, 60 and 90 days after baseline using the Western Aphasia Battery (Romanian translated version).

2.1.1. Primary Variable

Western Aphasia Battery

2.2. Secondary Objectives

- To assess the efficacy of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at 30, 60 and 90 days after baseline using measures of motor, neurological and global functional outcome (NIHSS, BI, mRS).
- To evaluate the safety of Cerebrolysin and Speech Therapy versus Placebo and Speech Terapy at 30, 60 and 90 days after baseline.

2.2.1. Secondary Variables

- Demographics (including education)
- Medical history
- NIHSS
- modified Rankin Scale
- Barthel Index

3. STUDY DESIGN

Exploratory, prospective, randomized-controlled, double-blinded, phase IV study

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Patient Inclusion Criteria

- Radiologically (CT or MRI) and clinically confirmed diagnosis of acute ischemic stroke in the left MCA territory;
- *Broca or mixed non-fluent aphasia , including transcortical motor aphasia";*
- Inclusion between 3 and 5 days post stroke;
- Right-handedness;
- Romanian as language of daily use;
- Signed Informed Consent

4.2. Patient Exclusion Criteria

- Prior symptomatic ischemic or hemorrhagic stroke;
- Severe comprehension deficit that may compromise informed consent or understanding of instructions: fluent aphasias (ex. Wernicke aphasia); global aphasias;
- Preexisting neurodegenerative or psychiatric disease;
- Epilepsy or EEG-documented epileptic discharges;
- Severe chronic renal or liver failure; (AST, ALT > 4 times normal values, creatinine > 4);
- Life-threatening diseases;
- Auditory or visual deficits that cannot be corrected and might impair testing.

4.3. Stopping and Discontinuation Criteria

4.3.1. Discontinuation Criteria related to the Study

- *Insufficient recruitment*
- *Continuous serious protocol violation and deviation*

4.3.2. 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 may be withdrawn at the Investigator's / Coordinator'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

- Serious Adverse Drug Reaction
- Lack of efficacy
- Consent withdrawn
- Administrative reasons

The patient or his/her representative requested withdrawal due to

- An 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).

4.4. Randomisation, Blinding and Unblinding

This study will be performed under double-blind conditions to keep investigators, other study personnel and patients blinded to treatment allocation. Cerebrolysin is an amber-colored solution; therefore, colored infusion lines will be used for drug administration.

A set of envelopes for each patient enrolled should be distributed to the study nurse preparing the ready-to-use-infusion solution. These nurses are only responsible for the preparation and administration of infusion solutions, and they should not be involved in any further study-related procedures. This person should not be allowed to disclose any information about treatment allocation. A treatment envelope should not be opened until the patient's first ready-to-use-infusion has been prepared.

Patients meeting in- and exclusion criteria will obtain a random number corresponding to the random list generated in advance by a biometrician selected by the Coordinator. Based on the random list sealed, opaque randomization/emergency envelops will be provided as follows:

- To the study center to break blinding if reasonable suspicion of harm to the patient exists
- To the person assigned to prepare the ready-to-use-infusion
- To the study coordinator

On opening, the randomization/emergency envelopes are dated (date, hour) and signed by the person who has opened the envelope. The Investigator should promptly document and explain to the Coordinator any premature unblinding of the Investigational Product(s). The whole study will be unblinded after closure of the database and determination of the analysis populations.

5. INVESTIGATIONAL PRODUCTS

The Investigational Products will be made available by the Coordinator (FSNN)

5.1. Name and Description of the Investigational Products

Cerebrolysin Solution for Injection

5.1.1. Dosage, Formulation and Administration

- 30 ml diluted with 0.9% saline solution to a total solution of 250 ml, administered by IV infusion

5.2. Packaging and Labelling

The investigational product and the reference product will be packaged and labelled for use in clinical trial according to GMP Annex 13 and local legislation.

5.3. Storage

CRB should be kept and stored under 25 degrees Celsius, in its original package.

All supplies must be kept in a locked place, inaccessible to unauthorised persons until they are delivered to the individual patient.

5.4. Investigational Product Accountability and Destruction

The amount of used medication will be recorded in the CRF. All unused medication will be counted and documented and unused investigational products will be destroyed upon completion of accountability.

6. CONCOMITANT MEDICATION

Not allowed concomitant medication: monoamine oxidase inhibitors, antipsychotic drugs or nootropic molecules.
All concomittant medications and therapies will be recorded in the CRF.

7. DEFINITION OF THE PRIMARY AND SECONDARY VARIABLES

7.1. Primary Variable

Western Aphasia Battery

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7.2. Secondary Variables

NIHSS

The NIH Stroke Scale assesses neurologic deficit and is a 15 items scale that covers the level of consciousness, gaze, visual fields, facial palsy, motor functions, limb ataxia, aphasia, dysarthria and extinction and inattention. The NIHSS is observer-rated and takes 5-8 min to complete. Items have 3- to 5-point response scales, scored from 0 to 4 with higher score indicative of more severe disability. In case of patient death, the worst score possible will assigned. The NIHSS will be used to assess the severity of the stroke at baseline as well as in the follow-up examinations as a measure of neurological function deficit.

modified Rankin Scale

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Barthel Index

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7.3. Further Variables

Neurological and physical examinations will be performed according to hospital standard procedures and will be recorded in the CRF.

Anamnestic data will be collected according to standard hospital procedures and the medical history will be documented in the CRF.

Vital signs including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature will be measured and documented in the CRF.

Standard laboratory parameters will be analysed according to standard procedures.

Information on all concomitant treatments and medications will be collected and documented.

Information on adverse events and patient safety will be collected in the CRF.

7.4. Source Documents

The following definitions of source documents shall apply:

Variable	Source document
Informed consent form	Patient File
Patient's demographic data such as sex, age, weight, indication, concomitant diseases, medical history, medication (history and concomitant), physical examination etc.	Patient File
Outcomes Variables	Patient File
Adverse Events	Patient File

8. ASSESSING AND REPORTING OF ADVERSE EVENTS

Throughout the course of the clinical study particular attention is paid to the Adverse Events and Adverse Drug Reactions mentioned below.

8.1. Adverse Events (AE)

A Serious/Adverse Event (S/AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an Investigational Product, whether or not related.

8.2. Adverse Drug Reaction (ADR)

All untoward and unintended responses to an Investigational Product related to any application / dose administered. The phrase “responses to an Investigational Product” means having a reasonable causal relationship as judged by either the Investigator or the Coordinator. The expression reasonable means to convey in general that there is evidence or argument to suggest a causal relationship.

Regarding marketed Investigational Products: a response to a product which is noxious and unintended and which occurs at applications normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

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

Serious Adverse Events will due to the underlying constitution of the patient be considered for AE documentation. Serious Adverse Drug Reactions will be dealt with as described below.

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

1. Serious
2. Unexpected
3. Reasonable causal relationship to study treatment.

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

Unexpected means:

- Not consistent with Investigators Brochure or SmPC

Causal Relationship means:

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

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, accident.

Life-threatening: in the definition of a Serious Adverse Event or Adverse Reaction 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 which hypothetically might have caused death if it was more severe.

Medical judgement 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 hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

8.3. Suspected Expected Serious Adverse Reaction (SESAR)

Any adverse reaction that is classed in nature as serious and which is consistent with the available information on the medicinal product in question set out in the SmPC

8.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse reaction that is classed in nature as serious and which is **not** consistent with the available information on the medicinal product in question set out in the SmPC

8.5. Recording of Adverse Events

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

The Investigator must report in detail all adverse signs and symptoms which 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 study treatment or other therapy; the action taken (if any), and the outcome.

8.5.1. 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

8.5.2. Definition of Adverse Event causality

On the basis of the WHO-UMC system for standardised case causality assessment (www.who-umc.org), the following categories are used to describe the degree of causality (all points should be reasonably complied with):

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

Probable

- Event or laboratory test abnormality, with reasonable time relationship to drug 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 by any or both assessors as having a “reasonable causal relationship” to the IMP qualify as ADR. This corresponds to the categories “definite”, “probable” and “possible”.

8.6. Reporting Serious Adverse Events

All Serious Adverse Reactions and all Unexpected Serious/Adverse Reactions with at least a suspicion of causal relationship to the investigational product must be reported to the Coordinator within 24 hours (one working day) of the Investigator becoming first knowledge. Preference in the reporting is the SAE report by e-mail at research@ssnn.ro.

8.7. Exemption from expedited reporting

Not applicable

8.8. Adverse Event/Reaction follow-up procedures

Adverse Events/ Reactions will be followed up throughout the course of the clinical study and any changes will be recorded in the CRF.

9. STUDY SCHEDULE

9.1. Procedures at Each Visit

Visit 1 – Baseline – 3-5 days post-stroke (Study Day 1)

- Demographics
- Medical history
- Western Aphasia Battery
- NIHSS

Visit 2 – Study Day 30 ± 3

- Western Aphasia Battery
- NIHSS
- Barthel Index
- modified Rankin Scale
- Adverse Events (AE)
- Severe Adverse Events (SAE)

Visit 3 – Study Day 60 ± 3

- Western Aphasia Battery
- NIHSS
- Barthel Index
- modified Rankin Scale
- Adverse Events (AE)
- Severe Adverse Events (SAE)

Visit 4 - Study Day 90 ± 3

- Western Aphasia Battery
- NIHSS
- Barthel Index
- modified Rankin Scale
- Adverse Events (AE)

- Severe Adverse Events (SAE)

Treatment cycles

Treatment Cycle 1 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)

Study days 1 – 14

30ml Cerebrolysin/saline i.v.

1h Speech Therapy

Treatment Cycle 2 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)

Study days 29-42

30ml Cerebrolysin/saline i.v.

1h Speech Therapy

Treatment Cycle 3 – 30 ml Cerebrolysin/saline and ST for 2 x 5 days (2 weeks)

Study days 57-70

30ml Cerebrolysin/saline i.v.

1h Speech Therapy

9.2. Assessment of Compliance

Compliance will be documented by recording the date and time of the administration in the CRF. The number of IV infusions actually administered to each patient will be calculated as the percentage of the total number of IV infusions planned per protocol and will provide a measure of treatment compliance.

9.3. Risk assessment and Precautionary Measures

The investigational medicinal product is in clinical use for many years and has demonstrated a very benign safety profile.
The safety information for the IMP is provided in the SmPC in Appendix 1.

10. STUDY AND TREATMENT DURATION

Study/Treatment start: 06 / 2020

Study/Treatment end: 06 / 2022

11. STATISTICS

The this is an exploratory study and the statistical analysis will be defined in a statistical analysis plan which will be finalized before unblinding of the study data.

12. ACCESS TO SOURCE DATA / DOCUMENTS

The Investigator will permit study-related monitoring, audits, IRB / IEC review and regulatory inspections, providing direct access to primary patient data (i.e. source data) which supports the data on the CRFs for the study, i.e. general practice charts, appointment books, original laboratory records etc.

12.1. Source Data

Source data are defined as all information in 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).

12.2. 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 check lists, 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 pharmacy, at the laboratories and at medico technical departments involved in clinical study).

12.3. Direct Access

Direct access is defined as the permission to examine, analyse, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g. domestic and foreign regulatory authorities, the Coordinator and / or authorised representatives of the Coordinator such as monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory

requirements to maintain the confidentiality of patient identities and Coordinator proprietary information.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. 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 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.

13.2. Study Monitoring

Authorized, qualified Clinical Trial Monitor will visit the investigational site in regular intervals established based on the needs of the project, to verify adherence to protocol and local legal requirements, to perform source data verification and to assist the Investigator in his study related activities.

13.3. 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.

13.4. Inspection

An Inspection is defined as the act by an authority (IRB/IEC) of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Coordinators and / or clinical research organisation facilities or at any other establishments deemed appropriate by the authorities.

13.5. Audit

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, designated Standard OperatingProcedure (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study.

14. ETHICAL AND LEGAL CONSIDERATIONS

14.1. Ethical Considerations

Before initiating a study, the Investigator will have written and dated approval / favourable opinion from the relevant IRB / IEC for the study protocol as well as for any amendments. Approval will be indicated in writing with reference to the final protocol number and date. Details of the IRB / IEC's constitution including names of its members and their function in the committee (e.g. chairman, specialist, lay-member) should be made available for inclusion in the Trial Master File.During the study all documents that are subject to review should be provided to the IRB / IEC by the Investigator.

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

The study protocol including all amendments and the study CRF will be submitted to the IRB/EC of the study centre before initiation of the study. IRB/EC approval for the study protocol and all amendments will be obtained prior to the start of any study specific procedures.

14.3. 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.

14.4. Modification of Protocol

The Investigator or the Coordinator should not implement any deviation from, or changes of, the protocol without mutual agreement, prior review and documented approval from the IEC of a respective amendment. The only exceptions are where necessary to eliminate an immediate hazard to study patients, or when the changes involve only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). The party initiating an amendment must confirm it clearly in writing and it must

be signed and dated by the Coordinator and the Principal Investigator. Necessary protocol amendments will be submitted to the appropriate IECs.

14.5. Conduct of Study

This clinical study will be conducted in accordance with the Declaration of Helsinki. It will be conducted in compliance with this protocol, Good Clinical Practice (2001/20/ EEC, CPMP/ICH/135/95), designated Standard Operating Procedures, and with local laws and regulations relevant to the use of investigational new drugs in the country of conduct.

14.6. 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 shall take care that the case report forms or other documents (e.g. copies of reports on special findings) transmitted to the FSNN contain no names, but another identifier. The storage of data for statistical assessment shall be performed under the patient's identifier. Only the Investigator and the investigating physicians can perform assignment of the identifier to the personal data.

If it becomes necessary in the course of the study to identify a patient's name for medical reasons, all the individuals involved are subject to an obligation to maintain secrecy.

If personal data are stored and processed, the requirements of data protection legislation are to be observed.

14.7. Data Handling and Record Keeping

14.7.1. 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 must 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, initialled and explained (in case of an eCRF data entries are already monitored by an audit trail) and must not obscure the original entry, this applies to both written and electronic changes.

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 completion of each patient, the Investigator should agree to have completed and signed CRFs available for full inspection by the clinical monitor.

14.7.2. Archiving

On termination of the study, the study documents, including the emergency envelopes are to be returned to the Coordinator. These records are to be retained for the periods required by ICH-GCP, i. e. until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product (CPMP/ICH/135/95), or by national legal requirements, whichever is longer, but not less than 15 years after routine/premature termination of a clinical study.

The final report shall be retained for at least 2 years after the Investigational Products are removed from the last market. The informed consent forms and all the original (raw) data are to be retained by the head of the clinical study or the investigating physicians for at least 15 years.

14.8. 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.

14.9. Responsabilities

The responsibilities of the Investigator, Monitor and Coordinator of the clinical study as regards handling of data, storage of data, planning, assessment and quality assurance are regulated by the recommendations on ”Good Clinical Practice” of the ”International Conference on Harmonisation” (ICH) and apply to this clinical study.

15. FINAL REPORT AND PUBLICATION POLICY

The Coordinator and Investigator shall agree on the final study report. The latter is to be signed by the Investigator and the investigating physicians involved.

It is intended that the results of the study may be published as scientific literature. Results may also be used in submissions to regulatory authorities. The following conditions are to protect commercial confidential materials (patents, etc.), not to restrict publication.

All information concerning the Investigational Product (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the Investigator by the Coordinator and not previously published) is considered confidential and shall remain the sole property of the Coordinator. The Investigator agrees not to use it for other purposes without the Coordinator's written consent.

It is understood by the Investigator that the Coordinator will use the information developed in this clinical study in connection with the development of the Investigational Product and therefore may be disclosed as required to other Investigators or any appropriate international Regulatory Authorities. In order to allow for the use of information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Coordinator with complete test results and all data developed during this study.

16. 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:**

_____ **Prof. Dr. Dafin F Muresanu**
(Coordinating Investigator)

_____ **Dr. Adina Dora Stan**
(Principal Investigator)

_____ **Dr. Olivia Verisezan-Rosu**
(Study Coordinator)