STATISTICAL ANALYSIS PLAN

Cerebrolysin and repetitive Transcranial Magnetic Stimulation (rTMS) in patients with Traumatic Brain Injury

Sponsor:	FSNN
Investigational Product:	*Cerebrolysin*
Study Title:	*Cerebrolysin and repetitive Transcranial Magnetic Stimulation (rTMS) in patients with Traumatic Brain Injury*
Study ID:	*Captain rTMS*
Protocol No/ Version:	FSNN040418, v1.1
Therapeutic Area:	Rehabilitation
Indication:	*Traumatic Brain Injury*
Phase:	*II*
Version No:	*1*

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1. BACKGROUND

After an acute brain lesion, there is always an endogenous continuous brain defense response consisting of two main sequences: an immediate one that aims to reduce brain damage, known as neuroprotection, and a later one that aims to repair the brain damage, known as neurorecovery, which is based on neurotrophicity, neuroplasticity and neuro-genesis.

Neurotrophic factors are the most important endogenous molecules involved in brain protection and recovery. Cerebrolysin has a neurotrophic factor-like activity based on the four important endogenous neurobiological processes: neurotrophicity, neuroprotection, neuroplasticity and neurogenesis. Additionally, this activity may have similar effects as the real sequence of endogenous post-lesional regulation.

Transcranial magnetic stimulation (TMS) operates on Faraday's principle of electromagnetic induction. There are several studies regarding a beneficial role of repetitive TMS (rTMS) in neurorehabilitation, including in TBI patients such as: motor recovery including spasticity, depression treatment, and speech rehabilitation. Regarding rTMS as an add-on to pharmacological treatment in cognitive rehabilitation, there are too few data to establish its efficacy. There are several studies on rTMS as add-on treatment in depression, with good results when the magnetic stimulation was performed with high frequencies. In TBI, this study is the first one in order to test the efficacy of the combining treatment rTMS + pharmacological intervention (CRB) in cognitive rehabilitation.

2. DEFINITIONS AND ABBREVIATIONS

AE	Adverse Event
A(D)R	Adverse (Drug) Reaction
CANTAB	Cambridge Neuropsychological Test Automated Battery
CRB	Cerebrolysin
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed tomography
DLPFC	Dorso-lateral pre-frontal cortex
ET	Eye tracking
FSNN	Foundation for the Study of Neuroprotection and Neuroplasticity
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GOS-E	Extended Gasgow Outcome Scale

H	Hour
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Rating Scale for Depression
Hz	Hertz
ICH	International Conference for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
incl.	including
IUD	Intrauterine device
IV	Intra-venous
mL	Milli Liter
MoCA	Montreal Cognitive Assessment Scale
MRI	Magnetic resonance imaging
MTT	Multi-tasking test
NA	Not Applicable
OTS	One Touch Stocking of Cambridge
PLC	Placebo
PSI	Processing Speed Index
qEEG	Qantitative electroencephalography
rTMS	Repetitive transcranial magnetic stimulation
RT	Reaction Time
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
SAR	Serious Adverse Reaction
SESAR	Suspected Expected Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
WAIS	Wechsler Adult Intelligence Scale
WHO-UMC	World Health Organization-Uppsala Monitoring Center

3. SOFTWARE UTILIZED

Statistical procedures were performed using the R programming language and SAS® OnDemand for Academics.

4. CODING SYSTEMS UTILIZED

All variables were coded to create the primary efficacy analysis.

AGE	Age of patients
COMP1	Composite score at Day 100

COMP2	Composite score at Day 180
CWTTM1_1	Stroop Color Word Test – Word Task - Number of seconds at Visit 1 - Baseline
CWTTM1_2	Stroop Color Word Test – Word Task - Number of seconds at Visit 2 – Day 100
CWTTM1_3	Stroop Color Word Test – Word Task - Number of seconds at Visit 3 – Day 180
CWTTM2_1	Stroop Color Word Test – ColorTask - Number of seconds at Visit 1 - Baseline
CWTTM2_2	Stroop Color Word Test – Color Task - Number of seconds at Visit 2 – Day 100
CWTTM2_3	Stroop Color Word Test – Color Task - Number of seconds at Visit 3 – Day 180
CWTTM3_1	Stroop Color Word Test – Color-Word Task - Number of seconds at Visit 1 - Baseline
CWTTM3_2	Stroop Color Word Test – Color-Word Task - Number of seconds at Visit 2 – Day 100
CWTTM3_3	Stroop Color Word Test – Color-Word Task - Number of seconds at Visit 3 – Day 180
DGBRES_1	Digit Span – Digit Backward Total Score at Visit 1 - Baseline
DGBRES_2	Digit Span – Digit Backward Total Score at Visit 2 – Day 100
DGBRES_3	Digit Span – Digit Backward Total Score at Visit 3 – Day 180
DGFRES_1	Digit Span – Digit Forward Total Score at Visit 1 - Baseline
DGFRES_2	Digit Span – Digit Forward Total Score at Visit 2 – Day 100
DGFRES_3	Digit Span – Digit Forward Total Score at Visit 3 – Day 180
DS_B_v1-baseline	Digit Span Backward Baseline Difference Day 100
DS_B_v2-baseline	Digit Span Backward Baseline Difference Day 180
DS_F_v1-baseline	Digit Span Forward Baseline Difference Day 100
DS_F_v2-baseline	Digit Span Forward Baseline Difference Day 180
D_PRESDT_VISDTC_2	D_PRESDT_VISDTC_2
D_PRESDT_VISDTC_3	D_PRESDT_VISDTC_3
GROUP	GROUP
HADS_v1-baseline	Hamilton Anxiety Rating Scale Baseline Difference Day 100
HADS_v2-baseline	Hamilton Anxiety Rating Scale Baseline Difference Day 180
HARTS_1	Hamilton Anxiety Rating Scale - Total score at Visit 1 - Baseline
HARTS_2	Hamilton Anxiety Rating Scale - Total score at Visit 2 – Day 100
HARTS_3	Hamilton Anxiety Rating Scale - Total score at Visit 3 – Day 180
HDRS_v1-baseline	Hamilton Depression Rating Scale Baseline Difference Day 100
HDRS_v2-baseline	Hamilton Depression Rating Scale Baseline Difference Day 180
HDTS_1	Hamilton Depression Rating Scale - Total score at Visit 1 - Baseline
HDTS_2	Hamilton Depression Rating Scale - Total score at Visit 2 – Day 100
HDTS_3	Hamilton Depression Rating Scale - Total score at Visit 3 – Day 180
MOCA_v1-baseline	Montreal Cognitive Assessment Baseline Difference Day 100
MOCA_v2-baseline	Montreal Cognitive Assessment Baseline Difference Day 180
MOTS_1	Montreal Cognitive Assessment – Total Score at Visit 1 - Baseline
MOTS_2	Montreal Cognitive Assessment – Total Score at Visit 2 – Day 100
MOTS_3	Montreal Cognitive Assessment – Total Score at Visit 3 – Day 180
MTT1_v1-baseline	CANTAB Multitasking Test – Total Correct Baseline Difference Day 100
MTT1_v2-baseline	CANTAB Multitasking Test – Total Correct Baseline Difference Day 180
MTT2_v1-baseline	CANTAB Multitasking Test – Total Incorrect Baseline Difference Day 100
MTT2_v2-baseline	CANTAB Multitasking Test – Total Incorrect Baseline Difference Day 180
MTTTC01_1	CANTAB Multitasking Test – Total Correct at Visit 1 - Baseline
MTTTC01_2	CANTAB Multitasking Test – Total Correct at Visit 2 – Day 100
MTTTC01_3	CANTAB Multitasking Test – Total Correct at Visit 3 – Day 180

MTTTC02_1	CANTAB Multitasking Test – Total Incorrect at Visit 1 - Baseline
MTTTC02_2	CANTAB Multitasking Test – Total Incorrect at Visit 2 – Day 100
MTTTC02_3	CANTAB Multitasking Test – Total Inorrect at Visit 3 – Day 180
OTS01_1	CANTAB One Touch Stockings of Cambridge-Problems solved on first choice at Visit 1 - Baseline
OTS01_2	CANTAB One Touch Stockings of Cambridge-Problems solved on first choice at Visit 2 – Day 100
OTS01_3	CANTAB One Touch Stockings of Cambridge-Problems solved on first choice at Visit 3 – Day 180
OTS02_1	CANTAB One Touch Stokings of Cambridge-Mean choices to correct at Visit 1 - Baseline
OTS02_2	CANTAB One Touch Stokings of Cambridge-Mean choices to correct at Visit 2 – Day 100
OTS02_3	CANTAB One Touch Stokings of Cambridge-Mean choices to correct at Visit 3 – Day 180
OTS1_v1-baseline	CANTAB One Touch Stockings of Cambridge-Problems solved on first choice Baseline Difference Day 100
OTS1_v2-baseline	CANTAB One Touch Stockings of Cambridge-Problems solved on first choice Baseline Difference Day 180
OTS2_v1-baseline	CANTAB One Touch Stokings of Cambridge-Mean choices to correct Baseline Difference Day 100
OTS2_v2-baseline	CANTAB One Touch Stokings of Cambridge-Mean choices to correct Baseline Difference Day 180
PRESDT	Presentation Date
PSCNUM_1	Processing Speed Index – Digit Symbol Coding Number Correct at Visit 1- Baseline
PSCNUM_2	Processing Speed Index – Digit Symbol Coding Number Correct at Visit 2 – Day 100
PSCNUM_3	Processing Speed Index – Digit Symbol Coding Number Correct at Visit 3 – Day 180
PSI_DSC_v1-baseline	Processing Speed Index – Digit Symbol Coding Number Correct Baseline Difference Day 100
PSI_DSC_v2-baseline	Processing Speed Index – Digit Symbol Coding Number Correct Baseline Difference Day 180
PSI_SS_v1-baseline	Processing Speed Index – Symbol Search Number Correct Baseline Difference Day 100
PSI_SS_v2-baseline	Processing Speed Index – Symbol Search Number Correct Baseline Difference Day 180
PSSCNUM_1	Processing Speed Index – Symbol Search Number Correct at Visit 1 - Baseline
PSSCNUM_2	Processing Speed Index – Symbol Search Number Correct at Visit 2 – Day 100
PSSCNUM_3	Processing Speed Index – Symbol Search Number Correct at Visit 3 – Day 180
PSSINUM_1	Processing Speed Index – Symbol Search Number Incorrect at Visit 1 - Baseline
PSSINUM_2	Processing Speed Index – Symbol Search Number Incorrect at Visit 2 – Day 100
PSSINUM_3	Processing Speed Index – Symbol Search Number Incorrect at Visit 3 – Day 180
RTI1_v1-baseline	CANTAB RTI - Five choice movement time - Raw score Baseline Difference Day 100
RTI1_v2-baseline	CANTAB RTI - Five choice movement time - Raw score Baseline Difference Day 180
RTI2_v1-baseline	CANTAB RTI - Mean reaction time - Raw score Baseline Difference Day 100
RTI2_v2-baseline	CANTAB RTI - Mean reaction time - Raw score Baseline Difference Day 180
RTIFMRT_1	CANTAB RTI - Five choice movement time - Raw score at Visit 1 - Baseline
RTIFMRT_2	CANTAB RTI - Five choice movement time - Raw score at Visit 2 – Day 100
RTIFMRT_3	CANTAB RTI - Five choice movement time - Raw score at Visit 3 – Day 180
RTISMRT_1	CANTAB RTI - Mean reaction time - Raw score at Visit 1 - Baseline
RTISMRT_2	CANTAB RTI - Mean reaction time - Raw score at Visit 2 – Day 100

RTISMRT_3	CANTAB RTI - Mean reaction time - Raw score at Visit 3 – Day 180
SCWT_C-D_1	SCWT_C-D_1
SCWT_C-D_2	SCWT_C-D_2
SCWT_C-D_2_1	SCWT_C-D_2_1
SCWT_C-D_v1-baseline	SCWT_C-D_v1-baseline
SCWT_C-D_v2-baseline	SCWT_C-D_v2-baseline
SCWT_W-D_1	SCWT_W-D_1
SCWT_W-D_2	SCWT_W-D_2
SCWT_W-D_2_1	SCWT_W-D_2_1
SCWT_W-D_v1-baseline	SCWT_W-D_v1-baseline
SCWT_W-D_v2-baseline	SCWT_W-D_v2-baseline
SEX	Sex of patient
SUBJECT	Number of subject
TMRES01_1	Trial Making Test 1 - Time in seconds at Visit 1 - Baseline
TMRES01_2	Trial Making Test 1 - Time in seconds at Visit 2 – Day 100
TMRES01_3	Trial Making Test 1 - Time in seconds at Visit 3 – Day 180
TMRES05_1	Trial Making Test 2 - Time in seconds at Visit 1 - Baseline
TMRES05_2	Trial Making Test 2 - Time in seconds at Visit 2 – Day 100
TMRES05_3	Trial Making Test 2 - Time in seconds at Visit 3 – Day 180
TMT1_1_truncated	Trial Making Test 1 - Time in seconds at Visit 1 – Baseline - truncated
TMT1_2_truncated	Trial Making Test 1 - Time in seconds at Visit 2 – Day 100 - truncated
TMT1_3_truncated	Trial Making Test 1 - Time in seconds at Visit 3 – Day 180 - truncated
TMT1_v1-baseline	Trial Making Test 1 - Time in seconds Baseline Difference Day 100
TMT1_v2-baseline	Trial Making Test 1 - Time in seconds Baseline Difference Day 180
TMT2_1_truncated	Trial Making Test 2 - Time in seconds at Visit 1 – Baseline - truncated
TMT2_2_truncated	Trial Making Test 2 - Time in seconds at Visit 2 – Day 100- truncated
TMT2_3_truncated	Trial Making Test 2 - Time in seconds at Visit 3 – Day 180 - truncated
TMT2_v1-baseline	Trial Making Test 2 - Time in seconds Baseline Difference Day 100
TMT2_v2-baseline	Trial Making Test 2 - Time in seconds Baseline Difference Day 180
VISDTC_1	Visit 1 (Baseline Visit) - Date
VISDTC_2	Visit 2 Day 100 - Date
VISDTC_2_PROTOCOL_DIFF	VISDTC_2_PROTOCOL_DIFF
VISDTC_3	Visit 3 Day 180 - Date
VISDTC_3_PROTOCOL_DIFF	VISDTC_3_PROTOCOL_DIFF

5. STUDY OBJECTIVES

5.1. Primary Objective

To assess the efficacy of the combined rTMS and Cerebrolysin treatment versus CRB alone, upon a battery of neurocognitive outcomes at 3 and 6 months post TBI.

5.1.1. Primary Variable

- Processing Speed Index
- Stroop Color-Word Test
- Trail Making Test
- Digit Span
- Montreal Cognitive Assessment
- One Touch Stockings of Cambridge (CANTAB)
- Reaction Time (CANTAB)
- Multitasking Test (CANTAB)
- Hamilton Rating Scale for Depression
- Hamilton Anxiety Rating Scale

5.2. Secondary Objectives

- To assess the single efficacy criteria at three and six months post TBI.
- To test ET and qEEG parameters as biomarkers of cognitive dysfunction.
- To assess the safety of rTMS administrated starting with one month after TBI.
- To check assay sensitivity for the primary objective (rTMS + CRB versus CRB alone) by comparing CRB alone versus PLC.

5.2.1 Secondary Variables

- Eye tracking parameters
- Quantitative EEG parameters
- rTMS adverse events

6. STUDY DESIGN

6.1. Overview

Monocentric, randomized, double-blind, phase II study.

6.2. Sample Size

- Treatment Group CRB + rTMS: N=30
- Treatment Group CRB + sham rTMS: N=30
- Treatment Group placebo + sham rTMS: N=30

Sample size calculations were performed using nonparametric methods with the Nnpar 1.0 software from idv Data Analysis and Study Planning.

6.3. Randomisation

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.

Sham stimulation will be performed with a sham-coil (MCF-P-B 65, Magventure) which has a mechanical outline and sound level identical to MCF-B65, and also provides the same level of cutaneous discofort and muscle twiching as real stimulation. The rTMS (both sham and real) administration will be provided by two rTMS technicians who will not be involved in any further study-related procedures and will not be allowed to disclose any information about treatment procedure.

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 sponsor. Based on the random list sealed, opaque randomization/emergency envelops will be provided as follows:

- To the study centre to break blinding if reasonable suspicion of harm to the patients exists
- To the person assigned to prepare the read-to-use-infusion
- To the person assigned to administrate the rTMS protocol.
- 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 Sponsor 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.

7. STUDY SCHEDULE

Screening and Baseline Visit – within 30 days of onset of TBI (Study Day 30+/- 4 days)

- Neurological and physical exam
- Hematology and blood chemistry
- Demographic data
- Medical history
- Concomitant Medication
- Evaluation Scales

  - Processing Speed Index
  - Stroop Color-Word Test
  - Trail Making Test
  - Digit Span
  - Montreal Cognitive Assessment
  - Hamilton Anxiety Rating Scale
  - Hamilton Rating Scale for Depression
  - One Touch Stockings of Cambridge
  - Multitasking Test
  - Reaction Time
- ET
- qEEG

Visit 1 – Efficacy Evaluation (study day 101+/- 7days)

- Neurological and physical exam
- Evaluation Scales
  - Processing Speed Index
  - Stroop Color-Word Test
  - Trail Making Test
  - Digit Span
  - Montreal Cognitive Assessment
  - Hamilton Anxiety Rating Scale
  - Hamilton Rating Scale for Depression
  - One Touch Stockings of Cambridge
  - Multitasking Test
  - Reaction Time
- ET
- qEEG

Visit 2 – Efficacy Evaluation (study day 180+/- 4 days)

- Neurological and physical exam
- Evaluation Scales
  - Processing Speed Index
  - Stroop Color-Word Test
  - Trail Making Test
  - Digit Span
  - Montreal Cognitive Assessment
  - Hamilton Anxiety Rating Scale
  - Hamilton Rating Scale for Depression
  - One Touch Stockings of Cambridge
  - Multitasking Test
  - Reaction Time
- ET

- qEEG

Treatment cycles:

- Study days 31-40,
- Study days 61-70
- Study days 91-100

8. STUDY ENDPOINTS

8.1. Primary Endpoints

- Processing Speed Index
- Stroop Color-Word Test
- Trail Making Test
- Digit Span
- Montreal Cognitive Assessment
- One Touch Stockings of Cambridge (CANTAB)
- Reaction Time (CANTAB)
- Multitasking Test (CANTAB)
- Hamilton Rating Scale for Depression
- Hamilton Anxiety Rating Scale

8.2. Secondary Endpoints

- Eye tracking parameters
- Quantitative EEG parameters
- rTMS adverse events

8.2.1. Efficacy

An ensemble of appropriate single efficacy criteria shall be tested by a multivariate, directional test approach, reflecting the “global status of patients in TBI” (Bagiella, 2010), while simultaneously combining two points in time in the sense of a ‘repeated measures design’.

The following ensemble of appropriate single efficacy criteria shall be tested by a multivariate, directional test approach, reflecting the global status of patients in TBI after 3 and 6 months:

Multivariate Efficacy Ensemble

1. Processing Speed Index, Changes from Baseline, LPCF, ITT
2. Stroop Color-Word Test, Changes from Baseline, LPCF, ITT
3. Trail Making Test, Changes from Baseline, LPCF, ITT

4. Digit Span, Changes from Baseline, LPCF, ITT
5. Montreal Cognitive Assessment, Changes from Baseline, LPCF, ITT
6. Stockings of Cambridge (CANTAB) , Changes from Baseline, LPCF, ITT
7. Reaction Time (CANTAB) , Changes from Baseline, LPCF, ITT
8 Hamilton Rating Scale for Depression, Changes from Baseline, LPCF, ITT
9. Hamilton Anxiety Rating Scale, Changes from Baseline, LPCF, ITT

8.2.2. Safety

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.

Adverse Drug Reactions (ADR) are 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 Sponsor. 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.

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

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.

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 Sponsor within 24 hours (one working day) of the Investigator knowing. Preference in the reporting is the SAE report by e-mail.

9. SPECIFICATIONS OF EFFICACY CRITERIA

Multivariate Efficacy Ensemble

1. Processing Speed Index, Changes from Baseline, LPCF, ITT
2. Stroop Color-Word Test, Changes from Baseline, LPCF, ITT
3. Trail Making Test, Changes from Baseline, LPCF, ITT
4. Digit Span, Changes from Baseline, LPCF, ITT
5. Montreal Cognitive Assessment, Changes from Baseline, LPCF, ITT
6. Stockings of Cambridge (CANTAB) , Changes from Baseline, LPCF, ITT
7. Reaction Time (CANTAB) , Changes from Baseline, LPCF, ITT
8. Hamilton Rating Scale for Depression, Changes from Baseline, LPCF, ITT
9. Hamilton Anxiety Rating Scale, Changes from Baseline, LPCF, ITT

This ensemble of appropriate single efficacy criteria shall be tested by a multivariate, directional test approach, reflecting the global status of patients in TBI after 3 and 6 months.

All efficacy criteria will be analyze with descriptive group statistics.

10. ANALYSIS SETS

ITT population will be used for all efficacy analyses. ITT population is defined as all patients who have no “severe” violation of entry criteria, had at least one dose of medication and at least one post-baseline observation of at least one primary efficacy criterion (“modified” ITT). This way ITT is defined in the sense of the “full analysis set” according to ICH E9 § 5.2. (“Analysis Sets”) .

A sensitivity analysis will be performed for a per protocol (PP) data set as an exploratory approach. The PP population includes all patients who are eligible for ITT evaluation and who additionally do not show major protocol deviations. The supportive analysis by means of the per-protocol set will be regarded as of equal scientific importance as the ITT analysis, since it most closely reflects the scientific model underlying the protocol (see ICH E9, section 5.2.2).

Safety population includes all patients who have had at least one dose of study medication and one contact with the Investigator afterwards. It will be used for safety analysis.

11. DATA REVIEW

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, 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.

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.

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.

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. 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.

12. STATISTICAL METHODOLOGY

12.1. Data Handling

In order to identify each type of missing data, outcome scales will be coded for every patient and visit according to the following scheme (see also Bagiella, 2010):

1 = valid (complete task)
2 = unable to complete (TBI-related neurological reason) [describe reason]
3 = not completed (different reasons, not TBI related) [describe reason]

12.2. Descriptive Statistics

Descriptive account of all variables (raw and baseline difference)

- Range
- Minimum value
- Maximum value
- Mean (+ Std. error)

- Standard Deviation
- Variance
- Skewness (+ Std. error)
- Kurtosis (+ Std. error)

12.2 Confirmatory Statistics

Although this study is intended to be of exploratory nature, the analysis will be based on 'confirmatory' principles with pre-specification of the primary analyses and control of multiple level alpha.

Mean, median and distribution group difference hypotheses

- Kruskal-Wallis with Dunn's test.

Kruskal-Wallis Rank Sum Test will be used to assess the statistical significance of the differences across groups. The pairwise comparisons will be performed using Dunn's Kruskal-Wallis Multiple Comparisons, with the Bonferroni adjustment**.**

13. STATISTICAL ANALYSES

13.1. Study Patients

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 / Sponsor'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).

13.2. Demographic and Other Baseline Characteristics

Patients' demographics will be obtained at Screening (study day 30), alongside medical history, neurological and physical examinations and hematology and blood chemistry will be obtained.

Females who are pregnant or lactating will be excluded from the study. However, females of child bearing potential taking acceptable contraceptive precautions can be included. A highly effective method of birth control and one which is acceptable for this study, is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

Some concomitant medication will exclude the patient from the study: steroids, Ca2+-channel blockers or major anticoagulants (e.g., warfarin and other coumarin derivates), monoamine oxidase inhibitors, antipsychotic drugs or nootropic molecules. All other concomitant medications and therapies will be recorded in the CRF.

13.3. Treatment Compliance

Each patient will receive three cycles of treatment of 10 infusions on 10 consecutive days:

- Study days 31-40,
- Study days 61-70
- Study days 91-100

Patients with compliance for the entire study below 80% for the treatments will be considered protocol violators and will not be included in the per protocol analysis.

13.4. ANALYSIS OF EFFICACY

Descriptive statistics and graphs will be generated for the ITT population. In addition, nonparametric effect sizes and confidence intervals (Kruskal Wallis and Dunn's pot hoc test) will be provided for all primary and secondary efficacy criteria at all points in time.

13.5. ANALYSIS OF SAFETY

Safety analyses will be conducted on the ITT population and included the incidence of adverse events and serious adverse events.