Prevention of epilepsy in stroke patients at high risk of developing unprovoked seizures: anti-epileptogenic effects of eslicarbazepine acetate

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STATISTICAL ANALYSIS PLAN

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DOCUMENT REVISION HISTORY

Version Draft 0.1 (30-SEP-2022): Document was created.

Version Draft 0.2 (21-MAR-2023): Document was updated after sponsor's review:

- 2.2.1 / 2.2.2 Definition of 'failure rate' was specified
- 3.1 Definition of 'Per-protocol set' was adapted
- 3.2 Subgroups were defined
- 4.5 Definition for 'visit slots' was added if a visit was not scheduled (e.g. vital signs)
- 4.8 Baseline definition for NIHSS was changed to 'post-stroke until V1b'
- 5.5.1 p-value for Fisher's test was added
- 5.5.2.3 Tables 15.2.5.2.1 and 15.2.5.2.2 and figures 15.2.1.2.3 and 15.2.1.2.4 were deleted
- 5.4.1.1 Definition of treatment duration was changed: treatment interruptions are incorporated

Version Draft 0.3 (11-AUG-2023): Document was updated after sponsor's review:

- Secondary objective and endpoint "Time to first US after stroke occurrence" was deleted as it is closely related to the forth secondary endpoint "Time to first US after randomisation"
- Subgroup analysis "NIHSS 4-10 versus NIHSS ≥11" was deleted
- Definition of study periods was updated
- Definition of the EEG analysis set was changed

Version Draft 0.4 (17-OCT-2023): Document was updated after sponsor's review:

- Secondary objective and endpoint "4-week rate of USs" was deleted as this information will not be meaningful for this trial
- Table 15.3.2.2.4 was deleted as this parameter was only collected at V1a

Version Draft 0.5 (14-NOV-2023): Document was updated after sponsor's review and Blind Data Review Meeting:

- Subgroup Analysis was changed (subgroup analysis now only for unprovoked seizures after 18 months)
- General Definition: it was included that all p-values are two-sided and no multiplicity adjustments are performed.
- Visit Slotting: new definition included if V1b was not scheduled
- Table 15.2.1.5.3 – Table 15.2.1.5.8 were included
- 5.5.1 Included: In case of a re-stroke, the date of re-stroke will be used as 'Date of withdrawal'
- FAS definition updated
- Study period definitions were added for 1, 3, 9 and 15 months
- 15.1.2 Explanation regarding COVID-19 pandemic deviation added
- Per-protocol set: new rule was added

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Description of Abbreviation
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
ATC	Anatomical therapeutic chemical
BI	Barthel Index original
BDR	Blind data review
β-hCG	β-human chorionic gonadotropin
CAVE	**C**ortical involvement, **A**ge < 65 years, **V**olume of intracerebral haemorrhage > 10 mL and **E**arly seizure within 7 days after intracerebral haemorrhage
CI	Confidence interval
CPK	Creatine phosphokinase
CT	Computed tomography
CTP	Clinical trial protocol
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	Early discontinuation visit
EEG	Electroencephalogram
eGFR	Estimated glomerular filtration rate
EoT	End of Trial
ES	Enrolled set
ESL	Eslicarbazepine acetate
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HLGT	High level group term
HLT	High level term
ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
INR	International normalised ratio
LDH	Lactate dehydrogenase
LLT	Lowest level term
MCA	Middle cerebral artery
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PDF	Planned first treatment date
PHQ	Patient Health Questionnaire
PLD	Planned last treatment date
PPS	Per protocol set
PT	Preferred term

PTD	Planned total dose
RBC	Red blood cell
RD	Risk Difference
RS	Randomised set
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System
S_{Cr}	Standardised serum creatinine
SeLECT	**Se**verity of stroke, **L**arge-artery atherosclerotic aetiology, **E**arly seizures, **C**ortical involvement, **T**erritory of MCA
SOC	System organ class
SS	Safety set
TEAE	Treatment emergent adverse event
TDTT	Total Down Titration Time
UNS	Unscheduled visit
US	Unprovoked seizure
V	Visit
WBC	White blood cell
WHO	World Health Organization

INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical trial protocol (CTP) and its modifications:

Final Protocol Version and Date:	Final Version 2.0, 24-OCT-2018
	Version 1.0_AT, 12-Jul-2019
	Version 1.0_DE, 21-Jan-2019
	Version 1.0_SE, 27-May-2019
	Version 1.0_UK, 15-Jul-2019
Protocol Amendment Version and Date:	
Implementation of Global Amendment #1, 20-JAN-2020 for all countries: .	Final Version 3.0, 20-JAN-2020
	Final Version 2.0_AT, 30-JAN-2020
	Final Version 2.0_DE, 30-JAN-2020
	Final Version 2.0_DE_2001, 30-JAN-2020
	Final Version 2.0_PT, 31-MAR-2020
	Final Version 2.0_SE, 30-JAN-2020
	Final Version 2.0_UK, 30-JAN-2020

The SAP includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data, and it is structured according to different data types. The SAP is finalised and signed-off prior to unblinding the trial. The statistical considerations described in the SAP amend the considerations in the CTP.

All analysis datasets and statistical output will be produced by the statistics department of Scope International AG using SAS® for Windows (SAS Institute Inc., Cary, NC, USA) [1] version 9.4 or higher. The actual version used will be documented in the Validation Plan for Statistical Programming.

1. SCHEDULE OF TRIAL PROCEDURES

Visits	**V1a[2]**	**V1b[2]**	**V2[15]**	**V3[15]**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[12]**	**EDV[3]**	**UNS[1]**
Days / Weeks after V1b			**+7 days**	**+37 days**	**+12 weeks**	**+26 weeks**	**+38 weeks**	**+52 weeks**	**+ 64 weeks**	**+ 78 weeks**		
On-site visit ⊗/telephone contact ☎	⊗	⊗	⊗	⊗	☎	⊗	☎	⊗	☎	⊗	⊗	⊗/☎
Day (CTP Final Version 3.0)	**(within 120 h after stroke)**	**1 (within 120 h after stroke)**	**8±2**	**38+4**	**85±10**	**183±10**	**267±10**	**365±10**	**449±10**	**547±10**		
Day (CTP Final Version 2.0)	**-3 to -1**	**1 (within 96 h after stroke)**										
Initiation procedures												
Informed consent	●[9]		●[10]									(●)[14]
Demographics	●											
Medical history	●		●[10]									(●)[14]
Prior medication	●		●[10]									(●)[14]
Concomitant medication	●	●	●	●	●	●	●	●	●	●	●	●
SeLECT score/CAVE score[11] (CTP Final Version 3.0)			●[17]	(●[17])								
SeLECT score/CAVE score[11] (CTP Final Version 2.0)	●[4]											
Modified Rankin Scale (mRS)	●[4]											
Inclusion/exclusion criteria	●	●	●[10]									
Randomisation (1:1)		●										
Medication												
First investigational medicinal product (IMP) administration		●										
Dispense IMP		●										(●)
IMP accountability				●							●[13]	(●)
Efficacy												
Issue diary (seizures)	●		●	●		●		●				(●)
Review and collect diary		●[8]	●	●		●		●		●	●	(●)
Seizure screening questionnaire	●	●	●	●	●	●	●	●	●	●	●	●

Visits	**V1a[2]**	**V1b[2]**	**V2[15]**	**V3[15]**	**V4**	**V5**	**V6**	**V7**	**V8**	**EoT[12]**	**EDV[3]**	**UNS[1]**
Days / Weeks after V1b			**+7 days**	**+37 days**	**+12 weeks**	**+26 weeks**	**+38 weeks**	**+52 weeks**	**+ 64 weeks**	**+ 78 weeks**		
On-site visit ⊗/telephone contact ☎	⊗	⊗	⊗	⊗	☎	⊗	☎	⊗	☎	⊗	⊗	⊗/☎
Day (CTP Final Version 3.0)	**(within 120 h after stroke)**	**1 (within 120 h after stroke)**	**8±2**	**38+4**	**85±10**	**183±10**	**267±10**	**365±10**	**449±10**	**547±10**		
Day (CTP Final Version 2.0)	**-3 to -1**	**1 (within 96 h after stroke)**										
Record seizures (diary/questionnaire)[16]	●	●	●	●	●	●	●	●	●	●	●	●
Barthel Index (BI)	●			●		●		●		●	●	(●)
National Institutes of Health Stroke Scale (NIHSS)	●[4]		●	●		●		●		●	●	(●)
Patient Health Questionnaire (PHQ-9)	●			●		●		●		●	●	(●)
Electroencephalogram (EEG, optional)[5]	(●[4])									(●)		(●)
Safety												
Adverse events (AEs)	●	●	●	●	●	●	●	●	●	●	●	●
Vital signs (blood pressure, heart rate, tympanic body temperature)	●		●	●		●		●		●	●	(●)
Blood withdrawal (haematology and biochemistry)[6]	●		●	●							●[13]	(●)
Urinalysis	●		●	●							●[13]	(●)
12-lead electrocardiogram (ECG)	●[4]		●	●							●[13]	(●)
Physical and neurological examination	●		●	●		●		●		●	●	(●)
Serum pregnancy test[7]	●											
Urine pregnancy test[7]	●		●	●							●[13]	(●)

1. Unscheduled visits (UNSs) will be performed at the discretion of the investigator. Assessments in brackets are optional and can be performed at the discretion of the investigator.
2. If all conditions for V1a and V1b are fulfilled, V1a and V1b can be performed on the same day.
3. An early discontinuation visit (EDV) should be performed within 10 days, if possible, on withdrawal.
4. If examination was done after primary stroke, the results should be used and the examination does not need to be repeated at V1a.
5. EEGs are optional assessments and will be performed at the discretion of the investigator.

6. Including eGFR and coagulation. At V1a also thyroid function.
7. Only in women of childbearing potential. Frequency may be adapted to meet specific country-specific/local requirements.
8. The diary will only be reviewed but not be collected at V1b.
9. If a patient is unable to give written or verbal consent at V1a, patient consent can be deferred or the patient's legal representative must provide written informed consent (according to country specific requirements). Written or verbal witnessed informed consent from the patient must be obtained until V2.
10. Only applicable for patients who were unable to give informed consent at V1a.
11. The scores for "**Se**verity of stroke, **L**arge-artery atherosclerotic aetiology, **E**arly seizures, **C**ortical involvement, **T**erritory of middle cerebral artery" (SeLECT score) in patients with an acute ischaemic stroke and for "**C**ortical involvement, **A**ge < 65 years, **V**olume of intracerebral haemorrhage > 10 mL and **E**arly seizure within 7 days after intracerebral haemorrhage" (CAVE score) in patients with acute intracerebral haemorrhagic stroke.
12. EoT: End of Trial visit
13. Only applicable, if EDV is performed before V3.
14. Only applicable if performed prior to V2 and only for patients who were unable to give informed consent at V1a.
15. The patients will be reminded via phone call on the working day before Day 30 to either take the last tablet on Day 30 (those with ESL 400 mg) or to take half a tablet from Day 31 to Day 37 (those with ESL 800 mg) and (if applicable) to start the down-titration of AED/benzodiazepines according to the respective SmPC on Day 31, if not already discontinued before.
16. Seizure records based on diary entries may be applicable in case of on-site visits, only.
17. In case V2 is scheduled earlier than 7 days post stroke, the assessment of early seizures after stroke will be done at V3.

2. OBJECTIVES AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this trial is to assess if eslicarbazepine acetate (ESL) treatment (started within 120 hours after stroke occurrence and continued for 30 days) changes the incidence of unprovoked seizures (Uss) within the first 6 months after randomisation as compared to placebo.

2.1.2 Secondary Objectives

The secondary objectives of this trial are:

1. To assess if ESL treatment (started within 120 hours after stroke occurrence and continued for 30 days) changes the incidence of USs – within the first 12 months after randomisation as compared to placebo
2. To assess if ESL treatment (started within 120 hours after stroke occurrence and continued for 30 days) changes the incidence of USs during the course of the trial – until 18 months after randomisation as compared to placebo
3. To assess the number of acute symptomatic seizures (Ass)

To assess the effect of ESL treatment over 18 months follow-up period on:

4. Time to first US after randomisation
5. Number of Uss
6. Functional outcome, assessed by Barthel Index original 10-item version (BI)
7. Functional outcome, assessed by National Institutes of Health Stroke Scale (NIHSS)
8. Post-stroke depression, assessed by Patient Health Questionnaire (PHQ-9)
9. Overall survival

2.1.3 Safety Objectives

The safety objectives of this trial are to assess the effect of ESL treatment on:

10. Treatment emergent adverse events (TEAEs) incl. findings from physical and neurological examinations
11. Laboratory parameters
12. Vital signs
13. Electrocardiogram (ECG)
14. Suicidal ideation and behaviour, assessed by PHQ-9 (question 9)

2.1.4 Exploratory Objectives

The exploratory objective of the trial is the evaluation of electroencephalogram (EEG) (optional).

2.2 Study Endpoints

2.2.1 Primary Efficacy Endpoints

The primary endpoint of this trial is the proportion of patients who experience the first US within the first 6 months after randomisation. Deaths before the first US or patients without evaluable assessment of the primary endpoint (i.e. drop-outs independently of the reason) will be counted as treatment failures (failure rate).

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this trial are:

1. Proportion of patients (same criteria for failure rate as in 2.2.1) who experience the first US during the first 12 months after randomisation (12 months failure rate)
2. Proportion of patients (same criteria for failure rate as in 2.2.1) who experience the first US during the course of the trial – until 18 months after randomisation (18 months failure rate)
3. Number of Ass
4. Time to first US after randomisation
5. Number of Uss
6. BI
7. NIHSS
8. PHQ-9
9. Overall survival

2.2.3 Safety Endpoints

The safety endpoints of this trial are:

10. TEAEs incl. findings from physical and neurological examinations
11. Laboratory parameters (haematology and biochemistry, including eGFR and coagulation, urinalysis)
12. Vital signs
13. ECG
14. Suicidal ideation and behaviour (as per PHQ-9, question 9)

2.2.4 Exploratory Endpoint

The exploratory endpoint of this trial is EEG (optional assessment).

2.3 Overall Study Design

This is a multicentre, double-blind, randomised, placebo-controlled, parallel-group trial in patients at high risk of developing unprovoked seizures after acute intracerebral haemorrhage or an acute ischaemic stroke.

At the first visit (screening/baseline, V1a), patients will undergo several examinations to check eligibility. The next visit (V1b) has to be performed within 120 hours after primary stroke occurrence or since last time seen well. After eligibility has been confirmed, patients will be randomised to treatment with ESL 800 mg or placebo.

Patients will start treatment with the investigational medicinal product (IMP) i.e. ESL or placebo within 120 hours after primary stroke occurrence, or since last time seen well at V1b. They will continue treatment until Day 30 after randomisation and then be tapered off. Thereafter, patients will be followed up until 18 months after randomisation.

If one or more AS(s) occur(s) within 7 days after primary stroke, this will not result in change of IMP dose. Patients having a first US will discontinue IMP treatment and will be treated at the discretion of the investigator until 18 months after randomisation, except with commercially available ESL.

2.4 Randomisation

After confirmed eligibility at V1b, patients will be randomised (randomisation ratio 1:1) to treatment with ESL 800 mg or placebo.

2.5 Treatments

Treatment name	Dosage Form	Active ingredient	Strength/concentration
ESL	Tablet	Eslicarbazepine acetate (ESL)	800 mg
Placebo	Tablet	None	Not applicable

Treatment with IMP will start at V1b (i.e. within 120 hours after primary stroke, or since last time seen well) and will be continued for 30 days. Thereafter, the IMP will be tapered off, as applicable. The dosing will be as follows:

Patients with an eGFR > 60 mL/min/1.73 m^2 will take one tablet once daily (800 mg ESL or placebo). Patients with moderate renal impairment at V1a, defined as eGFR 30 – 60 mL/min/1.73 m^2, will take half a tablet once daily (400 mg ESL or placebo). As soon as eGFR has improved to > 60 mL/min/1.73 m^2, the dose will be increased to one tablet once daily (800 mg ESL or placebo). Patients developing moderate renal impairment during IMP intake should be adjusted to 400 mg, if applicable. Worsening of renal function with an eGFR < 30 mL/min/1.73 m^2 must lead to discontinuation of IMP intake (dose independent) without down-titration.

Patients taking one tablet once daily (800 mg ESL or placebo) must be down-titrated for 7 days before stopping intake of IMP i.e. those patients will take half a tablet (400 mg ESL or placebo) from Day 31 to Day 37. Patients taking half a tablet once daily (400 mg ESL or placebo) on Day 30 do not require down-titration i.e. they will take the last IMP on Day 30.

2.6 Sample Size

Based on retrospective historical data, 26% of patients are expected to experience the first US (i.e. failure rate) within the first 6 months after stroke with standard of care. As this is a pilot trial, no empirical estimate of the treatment effect in patients randomised to ESL is available. For the purpose of sample size estimation, the trial is planned to have at least 80% power to demonstrate a significantly lower failure rate under ESL compared to placebo under the following assumptions:

- An expected failure rate (including death and other reasons of missing data before the first US) of 26% under placebo within the first 6 months after stroke
- An expected failure rate (including death and other reasons of missing data before the first US) of 8% under ESL within the first 6 months after stroke

Under these assumptions 100 randomised patients per treatment arm will ensure a power of the trial of at least 80% to demonstrate a significantly lower failure rate under ESL compared to placebo by means of a two-sided chi-square test on a 5%-level of significance.

Recruitment was terminated before reaching the estimated sample size.

2.7 Blinding

ESL and placebo tablets will be identical in size, colour, taste and appearance. The packaging and labelling will not allow for any distinction between test drug and placebo.

No person involved in conducting the trial may have access to the randomisation code before the blind is officially broken.

3. ANALYSIS SETS AND SUBGROUPS

3.1 Analysis Sets

The **Enrolled Set** (ES) will be defined as all patients who have been enrolled in the trial (i.e. informed consent form (ICF) signed by patient, by witness in case of verbal consent or by patient´s legal representative or deferral of informed consent adequately documented and signed by the investigator).

The **Randomised Set** (RS) will be defined as all patients who were randomised.

The **Safety Set** (SS) will be defined as all patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients will be assigned to treatment groups as treated.

The **Full Analysis Set** (FAS) will be defined as all patients who were randomised and were treated with at least one dose of IMP (ESL or placebo). Patients will be assigned to treatment groups as randomised.

The **Per-Protocol Set** (PPS) will be defined as all patients of the FAS without any major protocol deviations and with verbal witnessed or signed written consent. Patients will be assigned to treatment groups as randomised.

The **EEG analysis subset** will be defined and described in the separate EEG report.

3.2 Subgroups

For analysis of efficacy endpoints the following subgroups will be defined based on:

1. Acute intracerebral haemorrhagic stroke versus acute ischemic stroke

2. Time of treatment start (treatment start within the first 72 hours after primary stroke vs. treatment start after 72 hours after primary stroke). In case of unknown start time of IMP, it will assumed that first IMP intake was at 23:59.

Exploratory subgroup analysis of unprovoked seizures only at 18 months will performed in the FAS.

Final decision concerning subgroup analyses and definitions were made during Blind Data Review (BDR).

4. GENERAL DEFINITIONS AND NAMING CONVENTIONS

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of patients with data at the visit (n),
- number of patients with missing data (nmiss),
- mean,
- standard deviation (SD),
- median,
- first quartile (Q1) and third quartile (Q3)
- minimum (min) and maximum (max)

for patients with data.

Mean, median, and the quartiles will be presented to one more decimal place than the raw value. The minimum and maximum values will be presented with the same decimal precision as the raw value. SD will be reported to two decimal places greater than the original value.

For qualitative (categorical) variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default frequency tabulations. Where appropriate and present, the number of missing values will be displayed as "Missing" category.

Percentage values are to be presented to one decimal place, for example, 52.3%.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

All reported p-values will be two-sided. No adjustment for multiplicity will be performed.

4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalised; articles, prepositions, and conjunctions, and "to" in infinitives will not be capitalised, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline and endpoint value will be described in a footnote in every TLF where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: yyyy-mm-dd (e.g. 2003-11-20). Times will be listed in the format: hh:mm (e.g. 13:15) or in the format hh:mm:ss if seconds are collected. When date and time are collected, these are listed in the format: yyyy-mm-ddThh:mm (e.g. 2003-11-20T09:15), yyyy-mm-ddThh, or yyyy-mm-ddThh:mm:ss.

Partial missing dates will be listed in the format yyyy-mm (e.g. 2013-11) if only day is missing or in the format yyyy (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by treatment group, patient number and visit number where applicable, unless specified otherwise.

4.3 Treatment Group Names and Labels

Statistical output will be presented by treatment group and the treatment labels to be used in the tables, listings and figures are defined in Table 1 below.

Table 1: Treatment Group Labels

Number	Description	Label in TLFs
1	One or half of 800 mg ESL tablet once daily	ESL
2	One or half of placebo tablet once daily	Placebo

4.4 Visit Names and Labels

The names to be used in the analysis datasets and the labels to be used in the tables, listings and figures for the different study visits are defined in Table 2 below.

Table 2: Visit Labels

Name	Description	Label in TLFs
Visit 1a	Screening/baseline, within 120 hours after stroke, or since last time seen well	V1a
Visit 1b	Day 1, within 120 hours after stroke, or since last time seen well	V1b
Visit 2	Day 8 ± 2	V2
Visit 3	Day 38 + 4	V3
Visit 4	Day 85 ± 10	V4
Visit 5	Day 183 ± 10	V5
Visit 6	Day 267 ± 10	V6
Visit 7	Day 365 ± 10	V7
Visit 8	Day 449 ± 10	V8
EoT	Day 547 ± 10	EOT
EDV	Early discontinuation visit	EDV
UNS	Unscheduled visits	USV X.X

4.5 Visit Slotting

Due to COVID-19 pandemic visits might be delayed. Therefore, visit slots will be used for the analysis of efficacy (where applicable) and safety variables (where applicable). For a visit slot the closest non-missing assessment in time (scheduled or unscheduled) to the target day will be used (see Table 3).

Table 3: Visit Slotting

Visit Slot/ Label	Target Day	Description
V1a	-	Screening/baseline, within 120 hours after stroke, or since last time seen well
V1b	1	Day 1, within 120 hours after stroke, or since last time seen well
V2	8	Closest non missing assessment to target day between study day 2 and 31
V3	38	Closest non missing assessment to target day between study day 32 and 71
V4	85	Closest non missing assessment to target day between study day 72 and 171
V5	183	Closest non missing assessment to target day between study day 172 and 242
V6	267	Closest non missing assessment to target day between study day 243 and 353
V7	365	Closest non missing assessment to target day between study day 354 and 437
V8	449	Closest non missing assessment to target day between study day 438 and 533
EOT	547	Closest non missing assessment to target day between study day 534 and >547

EDV	EDV	Early discontinuation visit

If, for any variable, a visit was not scheduled (e.g. V4 for vital signs), the respective measurement will be assigned to the visit slot with the closest target day where a visit was scheduled. If two measurements fall into that slot, the closest one to target day will be used.

If, for any safety variable, V1b is not scheduled and a measurement is taken on Study Day 1, this measurement will be slotted to V2 if the assessment was done after first IMP intake.

4.6 Study Day Numbering

All assessment dates will be related to the date of first IMP intake. The date of first IMP intake is referred to as Day 1. Day –1 is the day preceding Day 1 and Day 0 will not be defined. The numbering is such that Day –2 is the day before Day -1, Day 2 is the day after the first IMP intake, etc.

4.7 Study Periods for primary and secondary efficacy analysis

Treatment Period

The period from Day 1 to Day of last IMP intake will be defined as the treatment period.

1-month-period!

The period from Day 1 to Day 30 (Day 30 included) is defined as the 1-month-period.

3-month-period

The period from Day 1 to Day 91 (Day 91 included) is defined as the 3-month-period.

6-month-period

The period from Day 1 to Day 182 (Day 182 included) is defined as the 6-month-period.

9-month-period

The period from Day 1 to Day 273 (Day 273 included) is defined as the 9-month-period.

12-month-period

The period from Day 1 to Day 365 (Day 365 included) is defined as the 12-month-period.

15-month-period

The period from Day 1 to Day 456 (Day 456 included) is defined as the 15-month-period.

18-month-period

The period from Day 1 to Day 547 (Day 547 included) or EOT (scheduled visit) is defined as the 18-month-period.

4.8 Baseline and Endpoint Value

Baseline value

The baseline value for efficacy variables (BI, PHQ-9) is defined as value collected at visit V1a (within 120h after stroke). For the NIHSS score the worst value post-stroke until V1b will be defined as baseline.

The baseline value for all other variables is defined as the last non-missing value collected before the first IMP intake.

For EEG subgroup, the baseline values and the exploratory analysis will be defined in a separate report.

Endpoint value

The endpoint value for an efficacy variable is defined as the last non-missing value collected after first intake of IMP before or at the respective endpoint (within the time window of interest i.e. 6 month-period, 12 month-period and 18 month-period).

The endpoint for a safety variable is defined as the last non-missing value collected after first intake of IMP that is no baseline value.

Absolute change from baseline will be calculated as

$$Absolute\ Change\ from\ Baseline\ at\ Visit\ X = Value\ at\ Visit\ X - Baseline\ Value$$

Relative change from baseline (%) will be calculated as

$$Relative\ Change\ from\ Baseline\ at\ Visit\ X = \frac{Value\ at\ Visit\ X - Baseline\ Value}{Baseline\ Value} \times 100$$

Note: Patients with a baseline value of '0' will be excluded from the calculation of relative change.

See section 5.4.1 for the definition of first and last IMP intakes.

4.9 Coding Systems and Conventions

4.9.1 Coding of adverse events and medical history

Adverse event and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), in the version as specified in the Data Management Plan (DMP) [2].

4.9.2 Coding of medications

Medications are classified according to active drug substance using the World Health Organization-(WHO) drug dictionary WHODrug Global, version as specified in the DMP [3]. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this study, ATC codes are defined to the 4th level.

4.9.3 Coding of therapies

Therapies investigator terms are assigned to preferred term (PT) and System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA), in the version as specified in the Data Management Plan (DMP) [2].

4.10 Handling of Missing Data

The analysis of missing data impact on the primary efficacy endpoint is described in the Section 5.5.1.1.

All other data will be analysed as reported and missing data will not be imputed.

5. STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

5.1 Patient Disposition

5.1.1 Disposition and Withdrawals

The following disposition data will be collected:

- Did the patient give his/her informed consent?
  - if Yes, date of written informed consent or date of verbal witnessed informed consent
  - if No, reasons for IC absence:
    a) the patient refused to give his/her consent or
    b) the patient died or
    c) the patient did not regain the ability to give consent.
    d) Only applicable for Portugal: a legal representative gave his/her informed consent at V1a
- deferred consent date or date of legal representative's consent (if patient was unable to give written or verbal consent at V1a)
- date and time of first IMP intake
- time (h) of first IMP intake after primary stroke
- date of last IMP intake
- date of trial termination
- did the patient complete the 6/ 12/ 18 month period (yes,no)
- did the patient complete the trial as scheduled (yes, no)
- primary reason for premature trial termination, including specification

Screening failures will be all patients who have been enrolled in the trial (i.e. ICF signed by patient, by witness in case of verbal consent or by patient´s legal representative or deferral of informed consent adequately documented and signed by the investigator), but discontinue the trial prior to randomisation at V1b due to whatever reason (withdrawal of consent by patient or legal representative, do not fulfil criteria, by decision of investigator, etc.).

Withdrawals will be all patients who have been enrolled and, for whatever reason, discontinue the trial after randomisation at V1b. Patients may be withdrawn from the trial at any time, either on their own or upon legal representative request or at the discretion of the investigator.

The following statistical outputs will be provided:

Table 15.1.1.1 Analysis Sets – Enrolled Set
The number and percentage of patients included in the enrolled, randomised, safety, full analysis, per-protocol and EEG analysis sets will be provided by treatment group and in total. Percentages will be based on the number of patients in the enrolled set. Date of first patient first visit and date of last patient last visit will be displayed.

Table 15.1.1.2 Reasons for Exclusions from Analysis Sets – Randomised Set
The number and percentage of patients excluded from the safety, full analysis and per-protocol sets will be provided by treatment group and in total. Percentages will be based on the number of patients in the randomised set. The reasons of exclusion from the analysis sets will be incorporated into the table.

Table 15.1.2 Screening Failures – Enrolled Set
Counts and percentages of patients who discontinued the study during the screening phase prior to randomisation to treatment will be summarised by reasons associated with the discontinuation. Percentages will be based on the number of patients in the enrolled set.

Table 15.1.3 Patient Disposition – Safety Set
Counts and percentages of patients who completed the 6-month-period, the 12-month-period, the 18-month-period (= patients who completed the trial as scheduled) and patients who prematurely

terminated the trial will be summarised by treatment group and in total. Reasons for discontinuation will be included. Percentages will be based on the number of patients in the safety set.

Table 15.1.4.1.1 Number of Patients by Country and Site – Enrolled Set
Counts and percentages of patients in each country and site in total. Percentages will be based on the number of patients in the enrolled set.

Table 15.1.4.1.2 Number of Patients by Country and Site – Safety Set
Counts and percentages of patients in each country and site by treatment group and in total. Percentages will be based on the number of patients in the safety set.

Table 15.1.4.2.1 Number of Patients by Visit – Safety Set
Counts and percentages of patients attending each scheduled visit will be presented by treatment and in total. Percentages will be based on the number of patients in the respective set.

Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Set
The number of patients with the occurrence of each protocol milestone (Enrolment, Randomisation, Completion) will be displayed. The number of screening failures and discontinuations as well as their reasons will also be summarised.

Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set
The number of patients in each analysis set will be displayed.

Listing 16.2.1.1 Patient Disposition – Randomised Set
The disposition data including the informed consent date and type, first and last IMP intake date, trial termination date, if the patient completed the trial as scheduled (yes/no) and reasons for premature termination (if applicable) will be listed by treatment group.

Listing 16.2.1.2 Screening Failures – Enrolled Set
Patients who discontinued the study prior to the randomisation to treatment will be listed. Informed consent data and type, reason in case of informed consent absence and reasons for premature trial termination will be displayed.

Listing 16.2.1.3 Patient Visits – Enrolled Set
All patient visits and visit dates and the respective study day will be listed by patient.

Listing 16.2.1.4 Exclusions from Analysis Sets – Randomised Set
Patients excluded from the safety, full analysis and per-protocol set and corresponding reasons for exclusion will be listed.

Listing 16.2.1.5 Patient Randomisation to Treatments – Randomised Set
Randomisation numbers and treatment assignments will be listed for all randomised patients.

5.1.2 Protocol Deviations

Protocol deviations are deviations from the procedures outlined in the clinical study protocol or from subsequent protocol-related instructions like missed evaluations, incorrect timing of evaluations, non-compliance with IMP and intake of prohibited medications or any non-adherence to the clinical study protocol that impacts patient's rights, safety or welfare.

Major protocol deviations will be summarised. Protocol deviations (including COVID-19 pandemic related protocol deviations) will be evaluated as major or minor during BDR (See Section 6).

Patients will be excluded from the PPS for the following reasons:

- No acute intracerebral haemorrhage or acute ischaemic stroke confirmed by Magnetic resonance imaging (MRI)/ Computed tomography (CT).
- First administration of IMP was more than 96/120 hours after stroke occurrence respective to the protocol version, or since last time seen well.
- Brain scanning has not excluded structural brain lesions that can mimic stroke, e.g. cerebral tumor or brain abscess, etc.

- Use of prohibited medication or treatments
- Other events occur that may have a relevant impact on the efficacy evaluations. Such trial conditions, which may or may not represent a protocol deviation or violation, will be identified during the data review meeting.

COVID-19 pandemic related protocol deviations will be taken from Global-PD-Log (PD category 13: COVID-19 pandemic).

The following statistical outputs will be provided:

Table 15.1.5.1 Major Protocol Deviations – Safety Set
The number and percentage of patients with major protocol deviations will be summarised by treatment group and in total. The categories of major protocol deviations will be included. Percentages will be based on the number of patients in the respective analysis set.

Listing 16.2.1.6.1 Major Protocol Deviations – Safety Set
Patients with major protocol deviations will be listed by treatment group.

Listing 16.2.1.6.2 Protocol Deviations related to COVID-19 – Enrolled Set
Minor and major deviations related to COVID-19 will be listed by patient by treatment group (ESL, placebo and Screening Failures).

5.1.3 Inclusion/Exclusion

For each inclusion/exclusion criterion, as appropriate, a response of "Yes/No" is to be obtained at V1a and V1b. Inclusion criteria at V2 are checked only for patients who were unable to give informed consent at V1a except for Portugal.

The following statistical output will be provided:

Listing 16.2.1.7 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set
Inclusion criteria which were not met and exclusion criteria which were met will be listed by treatment group.

5.2 Demographic and Other Baseline Characteristics

5.2.1 Demographics

The following demographic characteristics will be presented:

- Age
- Year of birth
- Gender
- Childbearing potential (yes/no), if patient is female
- Race

The following statistical outputs will be presented:

Table 15.1.6.1 Demographics – Safety Set
Table 15.1.6.2 Demographics – Per-Protocol Set
Demographic data will be summarised for each treatment group and in total in the respective set. Overall summary will also be included. Percentage of females of childbearing potential will be based on the number of females while all other percentages will be based on the number of patients in the respective analysis set.

Listing 16.2.1.8 Demographics– Enrolled Set
Demographic data will be listed for patients in the enrolled set.

5.2.2 Primary Stroke Characteristics

Information concerning the primary stroke will be collected:

- mRS

- total NIHSS (worst score post-stroke until V1b)
- (Total) SeLECT/CAVE score
- Primary stroke and brain imaging details
- For acute ischemic stroke only: Development of a secondary haemorrhage details

The **Modified Rankin Scale (mRS)** is a single item, global outcomes rating scale which was designed to measure post-stroke recovery. However, in the present trial the scale is used to measure pre-stroke disability and confirm patient eligibility.

Modified Rankin Scale Description	Grade
No symptoms at all	0
No significant disability despite symptoms; able to carry out all usual duties and activities	1
Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	2
Moderate disability; requiring some help, but able to walk without assistance	3
Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance	4
Severe disability; bedridden, incontinent, and requiring constant nursing care and attention	5

The **National Institutes of Health Stroke Scale** (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficits (see also section 5.5.2.6 below). The worst total NIHSS score post-stroke until V1b will collected.

To calculate the **CAVE score or SeLECT score,** brain scanning results (MRI/CT) will be used. The assessment will be performed at V2 (V1a in the CTP Final Version 2.0). In case V2 is scheduled earlier than 7 days post stroke the assessment of early seizures after stroke will be done at V3.

For patients included according to the CTP Final Version 2.0 or respective country-specific protocol versions, the **initial** CAVE score and **initial** SeLECT score were assessed by the investigators at V1a (less than 7 days after the primary stroke). Due to the fact that acute seizures can occur within 7 days after the primary stroke, the **total** CAVE score or **total** SeLECT score after 7 days could theoretically be higher than respective scores documented at V1a. It was confirmed (for patients included according to the CTP Final Version 2.0 or respective country-specific protocol versions) that no acute seizures have occurred after V1a. For patients with ischaemic stroke also the total worst NIHSS score was compared to NIHSS documented within the SeLECT score and total scoring was confirmed to be correct for all patients. The **total** CAVE and **total** SeLECT score are therefore identical to the initial scores for all patients and comparable to the scores collected for patients included according to the CTP Final Version 3.0 or respective country-specific protocol versions. A manual correction of the total CAVE or total SeLECT scores was therefore not applicable.

The **SeLECT score** was developed to calculate the patient's individual risks of having a seizure after an acute ischemic stroke. The patient's individual total SeLECT score will be calculated by adding the points associated with each predictor [4]:

Predictors of SeLECT Score:	Category	Points
(Se) Severity of stroke	NIHSS ≤ 3	0
	NIHSS 4 to 10	1
	NIHSS ≥ 11	2
(L) Large-artery atherosclerosis	No	0
	Yes	1
(E) Early seizure (≤ 7 days)	No	0
	Yes	3
(C) Cortical involvement	No	0
	Yes	2
(T) Territory of MCA	No	0
	Yes	1

The **CAVE score** was developed to calculate the patient's individual risks of having a seizure after intracerebral haemorrhage. To calculate an individual's CAVE score, the points associated with each predictor will be added to obtain the total risk score: [5].

Predictors of CAVE Score	Points
Cortical involvement of intracerebral haemorrhage	1
Age < 65 years	1
Volume of intracerebral haemorrhage > 10 mL	1
Early seizure within 7 days of intracerebral haemorrhage	1

The following **details for the primary stroke** will be collected:

- Date/time of primary stroke
- Type of primary stroke (acute intracerebral haemorrhagic stroke or acute ischaemic stroke)
- If type is acute intracerebral haemorrhagic stroke:
    - Cortical involvement of intracerebral haemorrhage (yes/no)
    - Age <65 years (yes/no)
    - Volume of intracerebral haemorrhage >10 m (yes/no)
    - Early seizure within 7 days of intracerebral haemorrhage (yes/no)
    - CAVE Score
- If type is acute ischaemic stroke:
    - Severity of stroke (NIHSS ≤ 3, NIHSS 4 to 10, NIHSS ≥ 11)
    - Large-artery atherosclerosis (yes/no)
    - Early seizure (≤ 7 days) (yes/no)
    - Cortical involvement (yes/no)
    - Territory of middle cerebral artery (MCA) (yes/no)
    - SeLECT Score
- mRS

The **brain imaging (MRI/CT) details** include:

- Type of procedure (MRI or CT)
- Date of procedure
- Scan conclusion

If the type of primary stroke is "acute ischaemic stroke", the details about the **development of a secondary haemorrhage** will be collected:

- Development of a secondary haemorrhage (yes / no / unknown)
- If yes, then:
    - Date/time identified after primary acute ischaemic stroke
    - Volume of the haemorrhage > 10mL (yes/no)
    - Involvement of the cerebral cortex, even if the origin of the bleeding was in deep structures (yes/no)

The following statistical outputs will be provided:

Table 15.1.7.1 Summary of Primary Stroke Characteristics – Safety Set
Table 15.1.7.2 Summary of Primary Stroke Characteristics – Per-Protocol SetPrimary Stoke characteristics will be summarised for the SS, FAS and PPS by treatment group and in total. Counts and percentages of patients by the type of stroke (acute ischaemic stroke or acute intracerebral haemorrhagic stroke) will be presented. Total SeLECT and total CAVE scores as well as mRS will be summarised by means of descriptive statistics. The number of patients that developed a secondary haemorrhage will be summarised.

Listing 16.2.1.9 (Primary) Stroke and Brain Imaging Details – Enrolled Set
Date, time and type of primary stroke, brain imaging details, worst total NIHSS and mRS will be listed for the ES by treatment group. Data about the development of a secondary haemorrhage will be included, if applicable.

Listing 16.2.1.10 SeLECT and CAVE Scores – Enrolled Set
Total SeLECT and CAVE scores will be listed by treatment group including points for each predictor and if a correction was necessary, type of stroke will be indicated for each patient.

5.2.3 Medical History

Medical history encompasses relevant (former 6 month) previous or ongoing relevant diseases, conditions, hospitalisation and surgical procedures except the primary stroke. Medical history records are collected at V1a. If the patient was unable to give informed consent at V1a, medical history is collected at V2.

A stroke occurring within 7 days after the primary stroke will be considered as re-stroke and documented in the medical history if occurred before patient enrolment.

Medical history of the patients includes:

- Diagnosis
- Start date
- Ongoing (yes/no)
- Stop date, if applicable
- Medication taken (at the time of patient's enrolment)? (yes/no)

Medical history is classified as:

- **Previous medical conditions** are the conditions which started and ended prior to V1a.
- **Ongoing medical conditions** are the conditions which are marked as ongoing at V1a or with a stop date at or after V1a.

If the stop date of a medical history condition is incomplete or missing, it will be assumed to be ongoing except if the incomplete stop date indicates that the condition stopped prior to the V1a.

The following statistical output will be provided:

Table 15.1.8.1.1 Previous Medical Conditions – Safety Set
Table 15.1.8.2.1 Ongoing Medical Conditions – Safety Set
Medical history except for the primary stroke will be summarised by treatment group and in total displaying counts and percentages of patients having at least one medical condition and will be presented by Primary System Organ Class (SOC) and by Preferred Term (PT) within SOC. SOCs and PT within SOC are to be sorted by descending order of overall incidence. Patients with two or more occurrences of the same condition (as qualified by its PTs) will be counted only once for the respective PT. Percentages will be based on the number of patients in the respective analysis set.

Listing 16.2.1.11 Medical History – Enrolled Set
Medical history conditions will be listed for patients in the enrolled set by treatment group.

5.3 Previous and Concomitant Medications and Therapies

The following information is documented about previous and concomitant medications and concomitant therapies in the eCRF:

- Medication / therapy name
- Indication
- Total Daily Dose
- Units
- Route
- Frequency
- Start date of medication/ therapy
- Ongoing (yes, no)
- Stop date of medication, if applicable

Total daily dose, units and route will be collected as NA for concomitant therapies.

Medications will be classified as 'previous', 'concomitant' or 'post' based on start/stop dates:

- **Previous medications** are defined as those medications starting and ending prior to the first IMP intake.
- **Concomitant medications** are defined as medications started at or after first IMP intake and at or before the last IMP intake. It also includes medications that started prior to the first IMP intake but continued after the first IMP intake.
- **Post-treatment [subsequent] medications** are defined as medications which started after the last IMP intake.
- **Therapies related to primary stroke** are defined as therapies (preferred terms) that are related to the primary stroke according to the indication provided by the investigator (primary stroke or related post-stroke rehabilitations). The indications of therapies were manually reviewed and evaluated by the Medical Monitor to select "Therapies related to primary stroke".

If the start or stop date of a medication is incomplete or missing, it will be assumed to be concomitant except if the incomplete start or stop date indicates that the medication stopped prior to the first IMP intake or started after the last IMP intake.

The following statistical output will be provided:

Table 15.1.9.1 Previous Medications – Safety Set
Table 15.1.9.2 Concomitant Medications – Safety Set
The number and percentage of patients with at least one previous or concomitant medication within each ATC 2nd level subgroup and substance name (or combination of substances) will be presented by treatment and in total for the respective analysis set. The ATC 2nd level subgroups and substance names within ATC 2nd level subgroup will be ordered by descending overall incidence.

Table 15.1.9.3.1 Therapies Related to Primary Stroke – Safety Set
Table 15.1.9.3.2 Therapies Related to Primary Stroke – Per-Protocol Set
The number and percentage of patients with at least one therapy related to indication "primary stroke or related post-stroke rehabilitation" will be presented by therapy name (PT) and in total for the respective analysis set. The PT will be ordered by descending overall incidence.

Table 15.1.9.4.1 Concomitant Anti-Epileptic Drugs – Safety Set
Table 15.1.9.4.2 Concomitant Anti-Epileptic Drugs – Per-Protocol Set
Number and percentages of patients receiving Anti-epileptic drugs (AEDs) as concomitant therapy will be presented by treatment group and in total, including substance name, for the respective set.

Listing 16.2.1.12 Medications – Enrolled Set
All medications, previous, concomitant and post [subsequent], will be listed for patients in the enrolled set by treatment group. Anti-epileptic drugs will be marked.

Listing 16.2.1.13 Therapies – Enrolled Set
All therapies (all indications) will be listed for patients in the enrolled set by treatment group.

5.4 Exposure to IMP and Compliance

5.4.1 Exposure to IMP

IMP will be taken from V1b (Day 1) to Day 30 by all patients. Patients taking once daily one tablet will take in addition half a tablet from Day 31 to Day 37.

At V3, patients will bring back their IMP bottle including all unused tablets and drug accountability will be performed.

Exposure data from eCRF include:

- Date and time of first IMP intake
- Prescribed dose of IMP (mg)
- Prescribed from (date)
- Prescribed until (date)
- This is tampering-off dose (tick)
- Reason for change
- Number of IMP tablets
- Date of last IMP intake
- Total number of IMP tablets patient should have taken according to prescription
- Bottle number of dispensed IMP
- Bottle number of returned IMP
- Number of tablets returned
- Reason of IMP accountability discrepancy.

The **treatment duration** (while on treatment) in days will be calculated as follows:

- treatment duration (days) = (date of last IMP intake – date of first IMP intake + 1) – (end date of interruption – start date of interruption +1)

The **total dose of IMP** taken will be calculated in tablets as follows:

$$\text{Total dose (tablets)} = 40 \times \text{Number of bottles dispensed} - \text{Total number of IMP tablets returned}$$

Note: Each IMP bottle is a monthly pack containing 40 tablets.

The **mean daily dose of IMP** in mg will be calculated as follows:

$$\text{Mean daily dose (mg)} = \frac{\text{Total dose (tablets)} \times \text{Tablet strength}}{\text{Treatment duration (while on treatment) (days)}}$$

Note: Tablet strength for patients who received ESL will be 800 mg. For patients who received placebo the mean daily dose will not be available (n.a.).

The following statistical output will be provided:

Table 15.1.10.1.1 Exposure to IMP – Safety Set
Table 15.1.10.1.2 Exposure to IMP – Per-Protocol Set
The default summary statistics of treatment duration, total dose of IMP (tablets) and the mean daily dose (mg) will be presented by treatment group and overall. The prescribed number and percentages of tablets will be summarised. The number of patient with a treatment duration ≤ 4 days will be displayed.

Listing 16.2.2.1 Exposure to IMP– Safety Set
Exposure to treatment data will be displayed for each patient in the safety set.

5.4.2 Compliance

Overall treatment compliance will be calculated as:

$$Overall\ compliance\ (\%) = \frac{Number\ of\ IMP\ tablets\ taken}{Number\ of\ IMP\ tablets\ the\ patient\ should\ have\ taken} \times 100$$

The number of IMP tablets taken and the number of IMP tablets the patient should have taken will be collected in eCRF. The "Number of IMP tablets taken" will be calculated by "Dispensed Amount of Tablets" – "Returned Amount of Tablets".

In case an IMP bottle is not returned, the overall compliance will be considered as missing.

All patients with a compliance <80% and >120% will be discussed at BDRM. It was decided during BDRM that all patients with a treatment duration > 4 days are compliant, as this is the very minimum amount of intakes to reach steady state serum level of ESL. Patients with missing compliance were discussed at BDRM and compliance was assessed on a case-by-case basis.

The following statistical output will be provided:

Table 15.1.10.2.1 Treatment Compliance (%) – Safety Set
Table 15.1.10.2.2 Treatment Compliance (%) – Per-Protocol Set
The default summary statistics of compliance will be presented by treatment group and overall. The number and percentage of patients within each compliance category (< 80%, ≥ 80% and ≤ 120%, >120%) will also be summarised. Percentages will be based on the number of patients in the corresponding analysis set.

Listing 16.2.2.2 Treatment Duration and Compliance– Safety Set
Treatment duration as well as the total dose of IMP, mean daily dose of IMP, planned total dose of IMP and overall compliance will be displayed for each patient in the safety set.

Listing 16.2.2.3 IMP Accountability– Safety Set
IMP accountability data will be displayed for each patient in the safety set.

5.5 Efficacy Analysis

5.5.1 Primary Efficacy Analysis

The FAS and the PPS will be used for the analysis of the primary efficacy analysis.

The primary endpoint is the proportion of patients who experience the first US within the first 6 months (until Day 182) after randomisation (failure rate). First US within the first 6 month, deaths before the first US and patients without evaluable assessment of the primary endpoint will be counted as treatment failures. The first occurring event will be used for this analysis e.g. if a patient experiences an US and dies later, this patient will be included as a patient with an US. If a patient experienced a re-stroke, the patient will be counted as a withdrawal with the date of re-stroke as 'Date of withdrawal'.

To show that ESL is different to placebo, the primary null hypothesis

$$H_0: p_{ESL} \geq p_{placebo}$$

will be tested against the alternative hypothesis

$$H_1: p_{ESL} < p_{placebo}$$

where p_{ESL} and $p_{placebo}$ denote the proportions of patients with the first US within 6 months after randomisation in ESL and placebo patients, respectively.

The primary hypotheses will be assessed in the FAS by means of a chi-square test with continuity correction on the significance level of 5% (two-sided, which corresponds to the significance level of

2.5% one-sided). The Odds Ratio for Placebo vs. ESL and the corresponding 95% score CI will be provided. The Risk Difference (RD) of failing between Placebo and ESL with corresponding 95% continuity-corrected Newcombe Confidence Interval (CI) for the risk difference Placebo – ESL will be calculated. Additionally, the p-value of Fisher's exact test will be provided.

For this purpose, the following SAS code will be used:

Note: Data should be sorted by descending treatment group (first "ESL" then "Placebo") and by treatment failures (first "Failure" then "Non-failure").

```
PROC FREQ DATA = <dataset> order=data;
      TABLE <Treatment group> * < Treatment Failure>
      /CHISQ RISKDIFF (CL =Newcombe (Corrected)) OR(CL =SCORE) ALPHA=0.05;
RUN;


PROC FREQ DATA = <dataset> order=data;
      tables <Treatment group> * < Treatment Failure>/ fisher;
run;
```

The following statistical outputs will be created:

Table 15.2.1.1.1 Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set
Table 15.2.1.1.2 Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per-Protocol Set
Number and percentage of failures (overall, US, death, early withdrawal, missing) and non-failures 6 months after randomisation will be tabulated, including degrees of freedom (DF), value and p-value for chi-square test, p-value for Fisher's exact test, RD of failing between ESL and Placebo with corresponding 95% continuity-corrected Newcombe CI as well as ESL vs. PlaceboOR with 95% score confidence interval.

Listing 16.2.3.1 Seizure Screening Questionnaire – Enrolled Set
Seizure screening questionnaire data will be listed.

Listing 16.2.3.2 Seizure Information after the Primary Stroke Occurrence – Enrolled Set
Seizure information after the primary stroke occurrence will be listed.

5.5.1.1 Sensitivity Analyses

For the primary analysis, patients withdrawing early during the trial will be considered as non-seizure free (treatment failure). This replacement strategy is defined under the assumption that it cannot be excluded that "missingness" is related to treatment failure and thus not at random. In order to assess the effect of missing data, the following sensitivity analyses will be performed:

The primary analysis will be repeated by imputing the missing values (patient withdrew from study before primary endpoint was reached) in both groups (ESL and Placebo) multiple times assuming the rate of treatment failures among the missing data follows the observed rate of treatment failures in the placebo group.

The following SAS code will be used:

Note: Treatment Failure will be 1 if a patient had an US or died, 0 if not and '.' if the data is missing (patient withdrew). A dummy baseline variable that consists only 0 will be created. Treatment group will be 1, if the patient received ESL and 2 if the patient received placebo. n will be the number of patients that experienced at least one US until 6 months.

```
proc mi data=<data> seed=14823 nimpute=&n. out=<out> noprint;
      class <Treatment group> <Treatment Failure>;
      var <Baseline Dummy> <Treatment Failure>;
      monotone logistic(<Treatment Failure> /detail);
      mnar model(<Treatment Failure> / modelobs=(trt='2'));
      run;
```

The chi-square test as described in 5.5.1 will be applied to each of the imputed datasets. The results will be pooled by Rubin's rule. For the Odds Ratio, the logarithm will be applied before pooling and afterwards the exponential function will be applied:

```
DATA lgsodds_t;
      SET < DATA ODDS>;
      log_or_lr_value=LOG(ODDSRATIO);
      log_or_lr_se=(LOG(UPPERCL)-LOG(LOWERCL))/(2*1.96);
RUN;
*** Combine transformed estimates;
PROC MIANALYZE DATA=lgsodds_t;
      ODS OUTPUT PARAMETERESTIMATES=mian_lgsodds_t;
      MODELEFFECTS log_or_lr_value;
      STDERR log_or_lr_se;
RUN;
*** Back-transform combined values;
DATA mian_lgsodds_bt; SET mian_lgsodds_t;
      Estimate_back = EXP(ESTIMATE); *Pooled odds ratio;
      LCL_back=Estimate_back*EXP(-1.96*STDERR); *Pooled lower limit;
      UCL_back=Estimate_back*EXP(+1.96*STDERR); *Pooled upper limit;
RUN;
```

A tipping point analysis based on multiple imputation relating the outcome of the primary efficacy analysis to the assumed rate of treatment failure among missing data under ESL and placebo, respectively, will be performed. In the primary analysis, patients with missing data will be classified as 'treatment failure'. By contrast, the tipping point analysis proceeds as follows: Assuming there will be $N = 1, \dots, n$ missing values for patients in the treatment group and $M = 1, \dots, m$ missing values for the patients in the placebo group. $N * M$ datasets will be created, one for each possible combination of imputation for the missing values ('treatment failure' or 'treatment success').

The chi-square test presented in the primary analysis 5.5.1 will be conducted for each of the datasets.

Results will be tabulated and p-values will be presented via a heatmap where significant and non-significant p-values will be differently colored. .

Another sensitivity analysis will be conducted based on observed Unprovoked Seizures only as Failure Rate. Death, Withdrawals or patients with missing data will not be counted as a Failure but as a Non-Failure. The primary efficacy analysis will be repeated for this scenario.

The following statistical outputs will be presented:

Table 15.2.1.3.1 Sensitivity Analysis of Treatment Failure Rate within 6 Months after Randomisation Using Multiple Imputation for Missing Data – Full Analysis Set
Table 15.2.1.3.2 Sensitivity Analysis of Treatment Failure Rate within 6 Months after Randomisation Using Multiple Imputation for Missing Data – Per-Protocol Set
Degrees of freedom (DF), value and p-value for chi-square test, RD of failing between ESL and Placebo with corresponding 95% continuity-corrected Newcombe CI as well as ESL vs Placebo OR with 95% score confidence interval for the multiple imputed datasets that are combined by Rubin's Rule will be presented.

Table 15.2.1.4.1 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set
Table 15.2.1.4.2 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per-Protocol Set
Degrees of freedom (DF), value and p-value for chi-square test, RD of failing between ESL and Placebo with corresponding 95% continuity-corrected Newcombe CI as well as ESL vs Placebo OR with 95% score confidence interval will be presented for all possible combinations of imputed non-failures in ESL and Placebo arm.

Table 15.2.1.5.1 Sensitivity Analysis of Unprovoked Seizures within 6 Months after Randomisation– Full Analysis Set
Table 15.2.1.5.2 Sensitivity Analysis of Unprovoked Seizures within 6 Months after Randomisation– Per-Protocol Set
Table 15.2.1.5.3 Sensitivity Analysis of Unprovoked Seizures within 12 Months after Randomisation – Full Analysis Set
Table 15.2.1.5.4 Sensitivity Analysis of Unprovoked Seizures within 12 Months after Randomisation – Per-Protocol Set
Table 15.2.1.5.5 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation – Full Analysis Set
Table 15.2.1.5.6 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation – Per-Protocol Set
Table 15.2.1.5.7 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation (Subgroup 1) – Full Analysis Set
Table 15.2.1.5.8 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation (Subgroup 2) – Full Analysis Set
Number and percentage of unprovoked seizures and non-failures 6, 12 or 18 months after randomisation will be tabulated, including degrees of freedom (DF), value and p-value for chi-square test, p-value for Fisher's exact test, RD of failing between ESL and Placebo with corresponding 95% continuity-corrected Newcombe CI as well as ESL vs Placebo OR with 95% score confidence interval.

Figure 15.2.1.1.1 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set
Figure 15.2.1.1.2 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per-Protocol Set
Results (p-values) of the tipping point analysis will be presented via heatmap.

5.5.2 Analysis of Secondary Efficacy Variables

The FAS and the PPS will be used for the analysis of secondary efficacy variables.

All data will be analysed as reported and missing data will not be imputed.

5.5.2.1 Twelve- and Eighteen-Month Failure Rates

The same approach employed for the primary analysis will be used for the analyses of the twelve-month failure rate (until Day 365) and the eighteen-month failure rate (until Day 547 or scheduled EoT).

The following statistical outputs will be presented:

Table 15.2.2.1 Analysis of Treatment Failure Rate within 12 Months after Randomisation – Full Analysis Set
Table 15.2.2.2 Analysis of Treatment Failure Rate within 12 Months after Randomisation – Per-Protocol Set
Table 15.2.3.1 Analysis of Treatment Failure Rate within 18 Months after Randomisation – Full Analysis Set
Table 15.2.3.2 Analysis of Treatment Failure Rate within 18 Months after Randomisation – Per-Protocol Set
Number and percentage of failures (overall, US, death, early withdrawal, missing) and non-failures 12 or 18 months after randomisation will be tabulated, including degrees of freedom (DF), value and p-value for chi-square test, p-value for fisher's exact test, RD of failing between ESL and Placebo with corresponding 95% continuity-corrected Newcombe CI as well as ESL vs Placebo OR with 95% score confidence interval.

5.5.2.2 Number of Acute Symptomatic Seizures

The number of patients that experience at least one AS will be analysed.

The following statistical outputs will be created:

Table 15.2.4.1 Summary of Acute Symptomatic Seizures – Full Analysis Set
Table 15.2.4.2 Summary of Acute Symptomatic Seizures – Per-Protocol Set
The number of ASs will be summarised by means of descriptive statistics for patients with at least one AS (FAS and PPS) by treatment group and in total. The number and percentage of patients without and with AS(s) will be incorporated into the table.

5.5.2.3 Time to First Unprovoked Seizure after Randomisation

For the following analyses, patients will be censored at their last day in the trial.

The time to first US after randomisation will be analysed and presented by means of the Kaplan-Meier estimate (including censored data e.g. withdrawals) after 6, 12 and 18 months for the failure time and corresponding simultaneous CI, a log-rank test (p-value) as well as estimates for 25% percentile, median, and 75% percentile failure time and corresponding CI. The time to first US will be analysed from the day of randomisation.

For this purpose, the following SAS code will be used:

```
ODS OUTPUT  Quartiles=quartiles;
ODS OUTPUT  ProductLimitEstimates=limit;
ODS OUTPUT  HomTests= tests;
PROC LIFETEST DATA=<dataset> METHOD=KM CONFBAND=EP TIMELIST= 182 365 547;
      TIME <Time to first US>*<Status> (0);
      STRATA <Treatment group> /TEST=LOGRANK;
RUN;
```

The Kaplan-Meier product limit estimate and simultaneous equal precision 95% confidence bands will be graphed.

In case of deaths before the first US, the competing risk of deaths and US will be evaluated exploratively using cause-specific cumulative incidence function and Gray's test for homogeneity in addition.

The following SAS code will be used:

Note: the status will be 0 for censored observations, 1 if US occurred and 2 if the patient died before experiencing an US.

```
ODS OUTPUT  GrayTest= graytest;
```

```
PROC LIFETEST DATA=<dataset>;
      TIME <Time to first US or death>*<Status> (0) /eventcode=1;
      STRATA <Treatment group> / order=internal;
RUN;
```

The following statistical outputs will be presented:

Table 15.2.5.1.1 Time to First Unprovoked Seizure after Randomisation– Full Analysis Set
Table 15.2.5.1.2 Time to First Unprovoked Seizure after Randomisation – Per-Protocol Set
The time to first US after randomisation will be presented by estimates for 25% percentile, median, and 75% percentile failure time and corresponding CI; means of the Kaplan-Meier estimate after 6, 12 and 18 months for the failure time and corresponding simultaneous CI (equal precision bands) and the p-value of a log-rank test

Figure 15.2.1.2.1 Time to First Unprovoked Seizure after Randomisation – Full Analysis Set
Figure 15.2.1.2.2 Time to First Unprovoked Seizure after Randomisation – Per-Protocol Set
The Kaplan Meier Product Limit Estimate and simultaneous equal precision 95% confidence bands will be presented for the treatment groups.

5.5.2.4 Number of Unprovoked Seizure

The total number in all patients and in patients with US(s) only will be summarised by means of descriptive statistics.

The following statistical output will be presented:

Table 15.2.5.4.1 Summary of Unprovoked Seizures– Full Analysis Set
Table 15.2.5.4.2 Summary of Unprovoked Seizures – Per-Protocol Set
Number and percentage of patients with and without US(s) will be presented. The total number of USs will be summarised by means of descriptive statistics for all patients and for patients that experienced US(s).

5.5.2.5 Barthel Index

BI data is collected at V1a, V3, V5, V7 and EOT or EDV and, if applicable, UNS.

The BI is a widely used score to measure the performance in activities of daily living of patients with stroke and other neuromuscular or musculoskeletal disorders in the following 10 categories:

1. Feeding (scored as 0, 5, 10)
2. Moving from a wheelchair to a bed and back again (scored as 0, 5, 10, 15)
3. Personal hygiene (scored as 0, 5)
4. Getting on and off the toilet (scored as 0, 5, 10)
5. Self-bathing (scored as 0, 5)
6. Walking on a level surface (scored as 0, 5, 10, 15)
7. Ascending and descending stairs (scored as 0, 5, 10)
8. Dressing (scored as 0, 5, 10)
9. Controlling bowels (scored as 0, 5, 10)
10. Controlling bladder (scored as 0, 5, 10)

Items are weighted according to the level of nursing care required and are rated in terms of whether individuals can perform activities independently, with some assistance, or are dependent (scored as 0, 5, 10 or 15). The total BI score (possible range 0 – 100) will be calculated as the sum of the individual scores from each item.

General ranges of BI describe patients' disability as follows:

80-100 – patient should be able to live independently
60-79 – minimally dependent

40-59 – partially dependent
20-39 – very dependent
<20 – total dependence.

The BI can be used to determine a baseline level of function and to monitor improvements in activities of daily living over time [4].

The BI total score at baseline and post-baseline visits of each patient will be calculated adding the individual scores from each item.

The BI total score and its change from baseline at each time of examination will be summarised by means of descriptive statistics. Differences between the treatment groups (ESL-Placebo) will be evaluated exploratively using multiple exact Wilcoxon-Mann-Whitney Test and exact Hodge-Lehmann CIs at each time of examination.

The following SAS Code will be used:

Note: Data should be sorted by treatment group (first "ESL" then "Placebo")

```
proc npar1way hl correct=no alpha=.05 data=<dataset>;
   class <treatment_group>;
   var <change from baseline of BI_total_score at specific timepoint>;
   exact wilcoxon;
   exact hl;
   ods select WilcoxonScores WilcoxonTest HodgesLehmann;
run;
```

If this SAS code runs for more than 10 minutes, maxtime=50 will be used and the normal approximate result will be tabulated. A higher maxtime does not lead to a change of the result.

Cumulative incidence of USs will be illustrated using Kaplan-Meier curves by the BI Baseline categories (<=79, 80-100) and treatment group. Patients without an event or lost to follow-up will be censored at their last visit or termination date. Time to event will be calculated from time of randomisation to first US.

The following statistical outputs will be presented:

Table 15.2.6.1.1 Summary of Barthel Index Total Score – Full Analysis Set
Table 15.2.6.1.2 Summary of Barthel Index Total Score – Per-Protocol Set
The default summary statistics for the BI total score will be presented by visit slots by treatment group at Baseline, V3, V5, V7, EOT, EDV (if applicable) and Endpoint.

Table 15.2.6.2.1 Analysis of Barthel Index Total Score Differences – Full Analysis Set
Table 15.2.6.2.2 Analysis of Barthel Index Total Score Differences – Per-Protocol Set
The Hodges-Lehmann estimate of location shift and the corresponding 95% CIs including the Wilcoxon Mann Whitney test p-value will be presented by visit slots for V3, V5, V7 and Endpoint for ESL-Placebo.

Figure 15.2.2.1 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by Barthel Index Total Score – Full Analysis Set
Figure 15.2.2.2 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by Barthel Index Total Score – Per-Protocol Set
Cumulative incidence curves of USs using Kaplan-Meier curves displayed by time of randomisation and treatment group for each category of the BI total score.

Listing 16.2.3.3 Barthel Index – Enrolled Set
The BI items and total score data will be listed by treatment group.

5.5.2.6 National Institutes of Health Stroke Scale

NIHSS data is collected at V1a (the worst total NIHSS score post-stroke until V1b is collected), V2, V3, V5, V7 and EOT or EDV and, if applicable, UNS.

The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficits. The stroke scale is valid for predicting lesion size and can serve as a measure of stroke severity. A trained investigator or a qualified delegate will record the patient's ability to answer questions and perform activities on the level of consciousness, extraocular movement, visual fields, facial muscle function, extremity strength, sensory function, coordination (ataxia), language (aphasia), speech (dysarthria), and hemi-inattention (neglect). The sum of all 15 individual scores will provide the patient's total NIHSS score where 0 is "no stroke symptoms" and 42 is "severe stroke" [5].

Stroke severity will be stratified based on NIHSS total score as follows:

<11 – mild and moderately severe
≥11 – severe.

The following questions will be asked:

1a. Level of Consciousness (LOC) (scored as 0, 1, 2, 3)
1b. LOC Questions (scored as 0, 1, 2)
1c. LOC Commands (scored as 0, 1, 2)
2. Best Gaze (scored as 0, 1, 2)
3. Visual (scored as 0, 1, 2, 3)
4. Facial Palsy (scored as 0, 1, 2, 3)
5a. Motor Arm (Left Arm) (scored as 0, 1, 2, 3, 4)
5b. Motor Arm (Right Arm) (scored as 0, 1, 2, 3, 4)
6a. Motor Leg (Left Leg) (scored as 0, 1, 2, 3, 4)
6b. Motor Right (Right Leg) (scored as 0, 1, 2, 3, 4)
7. Limb Ataxia (scored as 0, 1, 2)
8. Sensory (scored as 0, 1, 2)
9. Best Language (scored as 0, 1, 2, 3)
10. Dysarthria (scored as 0, 1, 2)
11. Extinction and Inattention (formerly Neglect) (scored as 0, 1, 2)

For each patient, the total NIHSS score at baseline and each post-baseline visit will be calculated adding the individual scores from each item.

The NIHSS score and its change from baseline at each time of examination will be summarised by means of descriptive statistics. Differences between the treatment groups (ESL-Placebo) will be evaluated exploratively using the Wilcoxon-Mann-Whitney Test and exact Hodge-Lehmann CIs at each time of examination (if the SAS code runs for more than 10 minutes, maxtime=50 will be used and the approximate result will be tabulated. A higher maxtime does not lead to a change of the result).

Cumulative incidence of USs will be illustrated using Kaplan-Meier curves by the NIHSS baseline categories (<11, ≥11) and treatment group. Patients without an event or lost to follow-up will be censored at their last visit or termination date. Time to event will be calculated from time of examination since randomisation to first US.

The following statistical outputs will be presented:

Table 15.2.7.1.1 Summary of NIHSS Total Score – Full Analysis Set
Table 15.2.7.1.2 Summary of NIHSS Total Score – Per-Protocol Set
The default summary statistics for the NIHSS total score will be presented by treatment group by visit slots at Baseline, V2, V3, V5, V7, EOT, EDV (if applicable) and Endpoint.

Table 15.2.7.2.1 Analysis of NIHSS Total Score Differences – Full Analysis Set
Table 15.2.7.2.2 Analysis of NIHSS Total Score Differences – Per-Protocol Set
The Hodges-Lehmann estimate of location shift and the corresponding 95% CIs including the p-value will be presented by visit slots for V3, V5, V7 and Endpoint for ESL-Placebo.

Figure 15.2.3.1 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by NIHSS Total Score – Full Analysis Set
Figure 15.2.3.2 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by NIHSS Total Score – Per-Protocol Set
Cumulative incidence curves of USs using Kaplan-Meier curves displayed by time after randomisation and treatment group for each category of the NIHSS total score.

Listing 16.2.3.4 National Institutes of Health Stroke Scale (NIHSS) – Enrolled Set
The NIHSS items and total score data will be listed by treatment group.

5.5.2.7 Patient Health Questionnaire

The PHQ-9 will be collected at V1a, V3, V5, V7 and EOT or EDV and, if applicable, UNS.

The PHQ-9 can be used for screening, diagnosing and measuring the severity of depression in stroke patients. The patient will rate on a scale from 0 (not at all) to 3 (nearly every day) how often each of the 9 symptoms occurred during the past 2 weeks. With question 9, the presence and duration of suicide ideation will be screened [6].

The PHQ-9 consists of the following questions:

Over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Poor appetite or overeating
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down
7. Trouble concentrating on things, such as reading the newspaper or watching television
8. Moving or speaking so slowly that other could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or of hurting yourself in some way

The individual scores from each item of the PHQ-9 will be added to calculate the total PHQ-9 score for each time of examination.

The PHQ-9 total score will be categorised as follows:

≤4 – minimal depression
>4 – mild to severe depression

The individual scores from each item of the PHQ-9 will be added to calculate the total PHQ-9 score for each time of examination. The PHQ-9 score and its change from baseline will be summarised by means of descriptive statistics and differences between the treatment groups (ESL-Placebo) will be evaluated exploratively using the Wilcoxon-Mann-Whitney Test and exact Hodge-Lehmann Cis (if the SAS code runs for more than 10 minutes, maxtime=50 will be used and the approximate result will be tabulated. A higher maxtime does not lead to a change of the result).

Cumulative incidence curves of USs vs. the PHQ-9 score (≤4, >4) will be displayed graphically by time after randomisation and treatment group.

PHQ-9 question 9 (related to suicidal ideation) will also be evaluated for the safety set.

The following statistical outputs will be presented:

Table 15.2.8.1.1 Summary of PHQ-9 Total Score – Full Analysis Set
Table 15.2.8.1.2 Summary of PHQ-9 Total Score – Per Protocol Set
The default summary statistics for the PHQ-9 total score will be presented by visit slots by treatment group at Baseline, V3, V5, V7, EOT, EDV (if applicable) and Endpoint.

Table 15.2.8.2 Summary of PHQ-9 Question 9 Score – Safety Set
The default summary statistics for the PHQ-9 Question 9 score will be presented by visit slots by treatment group at Baseline, V3, V5, V7, EOT, EDV (if applicable) and Endpoint.

Table 15.2.8.3.1 Analysis of PHQ-9 Total Score Differences – Full Analysis Set
Table 15.2.8.3.2 Analysis of PHQ-9 Total Score Differences – Per-Protocol Set
The Hodges-Lehmann estimate of location shift and the corresponding 95% CIs including the p-value will be presented by visit slots for V3, V5, V7 and Endpoint for ESL-Placebo.

Figure 15.2.4.1 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by PHQ-9 Total Score – Full Analysis Set
Figure 15.2.4.2 Cumulative Incidence Curves of Unprovoked Seizures using Kaplan-Meier Curves by PHQ-9 Total Score – Per-Protocol Set
Cumulative incidence curves of USs using Kaplan-Meier curves displayed by time after randomisation and treatment group for each category of the PHQ-9 total score.

Listing 16.2.3.5 Patient Health Questionnaire (PHQ-9)– Enrolled Set
The PHQ-9 items and total score data will be listed by treatment group.

5.5.2.8 Overall Survival

Overall survival (time to death relative to the date of randomisation) will be analysed and presented by means of the Kaplan-Meier estimates (including censored data e.g. withdrawals) after 6 months (Day 182), 12 months (Day 365) and 18 months (Day 547) for the survival rates including pointwise CI, log-rank test as well as estimates for 25% percentile, median, and 75% percentile survival time and corresponding CI.

For this purpose, the following SAS code will be used:

```
ODS OUTPUT  Quartiles=quartiles;
ODS OUTPUT  ProductLimitEstimates=limit;
ODS OUTPUT  HomTests= tests;
PROC LIFETEST DATA=<dataset> METHOD=KM TIMELIST= 182 365 547;
      TIME <Time to death>*<Status> (0);
      STRATA <Treatment group> /TEST=LOGRANK;
RUN;
```

Kaplan-Meier plot for overall survival will be presented.

The following statistical outputs will be presented:

Table 15.2.9.1 Overall Survival – Full Analysis Set
Table 15.2.9.2 Overall Survival – Per Protocol Set
Number and percentage of patients who died and patients censored will be tabulated. The time to death in days will be presented by estimates for 25% percentile, median, and 75% percentile and corresponding CI; means of the Kaplan-Meier estimate after 6, 12 and 18 months for the time to death and corresponding pointwise CI and the p-value of a log-rank test will be presented.

Figure 15.2.5.1 Overall Survival – Full Analysis Set
Figure 15.2.5.2 Overall Survival – Per Protocol Set
The Kaplan-Meier Product Limit Estimate and simultaneous equal precision 95%-Confidence bounds will be presented.

5.6 Safety Analysis

Safety will be assessed by evaluation of the following variables:

- TEAEs incl. findings from physical and neurological examinations

- Laboratory parameters (haematology and biochemistry, including eGFR and coagulation, urinalysis)
- Vital signs
- ECG
- Suicidal ideation and behaviour (as per PHQ-9, question 9)

The safety set will be used for the analysis of safety data.

5.6.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version as defined in the Data Management Plan.

Adverse event data includes:

- adverse event name
- start date and time
- ongoing? (yes/no)
- stop date and time, if applicable
- severity (mild, moderate, severe)
- frequency (single event, intermittent, continuous)
- causal relationship to IMP (not related, unlikely, possible, probable, definite)
- action taken with IMP (dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, unknown, not applicable)
- other action taken (none, medication required, tests required, hospitalisation required or prolonged, withdrawn from the trial, other, including specification)
- outcome (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
- seriousness (yes/no)

All AEs will be presented in listings.

Summaries of adverse events will include AEs defined as **treatment-emergent adverse events (TEAEs)**, defined as AEs with the first onset or worsening after the first IMP intake until 14 days after the last IMP intake. AEs not considered treatment-emergent according to this definition or with missing data will be medically reviewed during the blind data review meeting and will be considered treatment-emergent if appropriate.

If the relationship to IMP is missing, the event will be classified as unrelated, if it started before first IMP intake. In all other cases it will be assumed to be possibly related.

If the start date of an AE is incomplete or missing, it will be assumed to be treatment-emergent except if the incomplete start date or the stop date indicates that the event started prior to the first IMP intake or later than 14 days after last IMP intake.

Adverse events will be further assigned to the following categories:

- **Serious Adverse Events (SAEs):** defined as AEs considered by the investigator as serious, including AEs with an unknown or missing seriousness assessment.
- **Related TEAEs**: TEAEs with a causal relationship to IMP assessed as “possible” or “probable” and “definite”, including events with missing IMP relationship assessment.
- **Unrelated TEAEs**: TEAEs with a causal relationship to IMP assessed as “not related” or “unlikely”.
- **Severe TEAEs**: TEAEs assessed as “severe” in severity, including events with missing severity assessments.
- **TEAEs leading to discontinuation of IMP:** TEAEs for which “action taken with study medication” is indicated as “drug withdrawn”.

- **TEAEs leading to dose reduction:** TEAEs for which "action taken with IMP" is indicated as "dose reduced"
- **TEAEs requiring medication:** TEAEs for which "action taken with study medication" is indicated as "medication required".
- **TEAEs leading to death:** TEAEs documented as having a "fatal" outcome.
- **Ongoing TEAEs at the end of the trial:** TEAEs documented without an end date of the TEAE.

The **duration of the AE** will be calculated from the start date (or onset) to the AE stop date. If the start or stop dates of the AE are incomplete or AE is still ongoing at the end of the study, duration of AE will not be calculated.

The following statistical output will be provided:

Table 15.3.1.1 Overall Summary of TEAEs – Safety Set
An overview of TEAEs:

- TEAEs
- Non-serious TEAEs
- Serious TEAEs
- Related TEAEs
- Related Serious TEAEs
- Severe TEAEs
- TEAEs leading to discontinuation of IMP
- TEAEs leading to dose reduction
- TEAEs requiring medication
- TEAEs leading to death
- Ongoing TEAEs at the end of the trial

will be displayed by treatment group and in total for the patients in the safety set.

Table 15.3.1.2.1 Incidence of TEAEs – Safety Set
Table 15.3.1.2.2 Incidence of Non-Serious TEAEs – Safety Set
Table 15.3.1.2.3 Incidence of Serious TEAEs – Safety Set
Table 15.3.1.2.4 Incidence of Related TEAEs – Safety Set
Table 15.3.1.2.5 Incidence of Related Serious TEAEs – Safety Set
Table 15.3.1.2.6 Incidence of TEAEs Leading to Discontinuation of IMP – Safety Set
Table 15.3.1.2.7 Incidence of TEAEs Leading to Dose Reduction – Safety Set
Table 15.3.1.2.8 Incidence of TEAEs Requiring Medication– Safety Set
Table 15.3.1.2.9 Incidence of TEAEs Leading to Death – Safety Set
TEAEs will be summarised by treatment group and in total by displaying the numbers of adverse events, as well as counts and percentages of patients having experienced adverse events. Percentages will be based on the number of patients in the safety set. SOCs and PTs within each SOC will be ordered by descending number of adverse events in the total column.

Table 15.3.1.3.1 Incidence of TEAEs by Maximum Severity – Safety Set
Table 15.3.1.3.2 Incidence of Related TEAEs by Maximum Severity – Safety Set
Table 15.3.1.3.3 Incidence of Serious TEAEs by Maximum Severity – Safety Set
TEAEs will be summarised as above within each severity category (mild, moderate, severe).

Table 15.3.1.4.1 Incidence of Preferred Term: TEAEs– Safety Set
Table 15.3.1.4.2 Incidence of Preferred Term: Serious TEAEs – Safety Set
Table 15.3.1.4.3 Incidence of Preferred Term: Related TEAEs – Safety Set
Table 15.3.1.4.4 Incidence of Preferred Term: Serious Related TEAEs – Safety Set
Table 15.3.1.4.5 Incidence of Preferred Term: TEAEs Leading to Discontinuation of IMP – Safety Set
Table 15.3.1.4.6 Incidence of Preferred Term: Most Frequent (≥ 2% of patients in any treatment group) TEAEs – Safety Set
Frequency counts and percentages of PTs will be summarised for each treatment group and in total. Percentages will be based on the overall number of PTs in the safety set. PTs will be ordered by descending percentages in the total column.

Listing 16.2.4.1.1 Adverse Events: MedDRA Coding
MedDRA system organ class and preferred terms assigned to each reported AE name will be displayed.

Listing 16.2.4.2.1 Serious Adverse Events – Enrolled Set
Listing 16.2.4.2.2 AEs Leading to Discontinuation of IMP – Safety Set
Listing 16.2.4.2.3 AEs Leading to Death – Enrolled Set
All AEs will be displayed by patient including the PT of an AE, start and stop dates, date of last IMP intake and other characteristics of AEs.

5.6.2 Clinical Laboratory Evaluation

Clinical laboratory values (haematology, biochemistry, including eGRF and coagulation, urinalysis) are collected at V1a, V2. V3, EDV (if EDV performed before V3) and, if applicable, UNS for each laboratory parameter. Thyroid function will be assessed at V1a.

A serum pregnancy test at V1a and urine pregnancy tests at V1a, V2, V3, EDV (if EDV performed before V3) and, if applicable, UNS will be performed for all females of childbearing potential.

The following parameters are collected:

Haematology: Haemoglobin, haematocrit, red blood cell (RBC) count, white blood cell (WBC) count, differential - neutrophils, eosinophils, lymphocytes, monocytes and basophils, and platelet count.

Biochemistry: Sodium, potassium, chloride, calcium, phosphate, blood urea nitrogen, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase, creatine phosphokinase (CPK), creatinine, glucose, C-reactive protein, albumin, total protein, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, and total bilirubin (bilirubin will be fractionated direct/indirect if elevated).

Sodium levels will be monitored for signs of **hyponatraemia**. Patients will be classified by their minimum post-baseline sodium level according to the following categories:

≥ 135 mEq/L

130 - < 135 mEq/L

125 - < 130 mEq/L

< 125 mEq/L

and for any decrease from baseline > 10 mEq/L.

eGFR will be estimated based on serum creatinine value (see CTP 11.4.3).

Coagulation: INR and activated partial thromboplastin time (aPTT).

Thyroid function (at V1a only): total triiodothyronin, free triiodothyronine, total thyroxine, free thyroxine, thyroid stimulating hormone.

Serum pregnancy test (at V1a only): β-hCG in females of childbearing potential.

Urinalysis:

- local: pH, specific gravity, protein, blood, glucose, ketones, bilirubin, urobilinogen, leukocytes, nitrite (local dipstick). Microscopy and other appropriate tests (as needed) will be performed if dipstick indicates any significant abnormality.
- central: U-Casts, U-Crystals, U-Epithelials, U-Erythrocytes quan., U-Leucocytes quan., U-Others.

Urine pregnancy tests: in females of childbearing potential.

All laboratory values will be classified as normal or abnormal according to the laboratories' normal ranges and as clinically significant (yes/no) according to the assessment of the investigator.

The following statistical outputs will be provided:

Table 15.3.2.1.1 Summary of Clinical Laboratory Tests: Haematology – Safety Set
Table 15.3.2.1.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set
Table 15.3.2.1.3 Summary of Clinical Laboratory Tests: Coagulation – Safety Set
The default summary statistics of clinical laboratory test results for haematology, biochemistry (including eGRF) and coagulation will be presented by treatment group and in total by visit slots (if applicable) at V1, baseline, V3, EDV (if applicable) and Endpoint. The absolute change from baseline will be presented as well.

Table 15.3.2.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set
Table 15.3.2.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set
Table 15.3.2.2.3 Clinical Laboratory Tests: Incidence of Coagulation Abnormalities – Safety Set
The number and percentage of patients with Low, CS Low, Normal, High, and CS High categories of each laboratory parameter will be displayed by treatment group and in total. Percentages will be based on the number of patients at the specified visit slot.

Table 15.3.2.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results from Baseline to Endpoint – Safety Set
Table 15.3.2.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results to Endpoint– Safety Set
Table 15.3.2.3.3 Clinical Laboratory Tests: Shift Table of Coagulation Results to Endpoint – Safety Set
Shift tables showing changes in the number and frequency of patients with respect to the normal range and clinical significance between baseline and endpoint by treatment will be provided. Patients with missing data will be presented as part of a "missing" category.

Table 15.3.2.4.1 Clinical Laboratory Tests: Shift Table of Haematology Results from Baseline to Worst Post Baseline Value – Safety Set
Table 15.3.2.4.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results from Baseline to Worst Post Baseline Value – Safety Set
Table 15.3.2.4.3 Clinical Laboratory Tests: Shift Table of Coagulation Results from Baseline to Worst Post Baseline Value – Safety Set
Shift tables showing changes in the number and frequency of patients with respect to the normal range and clinical significance between baseline and the worst-post-baseline-value by treatment will be provided. Patients with missing data will be presented as part of a "missing" category.

Table 15.3.2.5.1 Clinical Laboratory Tests: Incidence Clinically Significant Urinalysis Results (Local Dipstick) – Safety Set
Clinically significant values of urinalysis parameters (collected using local dipstick) will be summarised by visit using default frequency tabulation by treatment group and in total. The number of patients with any CS abnormalities will be summarised. Visit Slots will be used.

Table 15.3.2.5.2 Clinical Laboratory Tests: Incidence of Urinalysis Results (Central Laboratory) – Safety Set
Clinically significant values of urinalysis parameters (provided by central laboratory) will be summarised by visit using default frequency tabulation by treatment group and in total. The number of patients with any CS abnormalities will be summarised. Visit Slots will be used.

Table 15.3.2.6 Signs of Hyponatraemia – Safety Set
Number and frequency of patients will be presented by sodium level categories and by visit. This table will be provided by treatment group and in total. Visit Slots will be used.

Listing 16.2.4.3.1 Laboratory Data – Haematology – Enrolled Set
Listing 16.2.4.3.2 Laboratory Data – Biochemistry – Enrolled Set
Listing 16.2.4.3.3 Laboratory Data – Coagulation – Enrolled Set
Listing 16.2.4.3.4 Laboratory Data – Thyroid Function – Enrolled Set
Safety laboratory test results will be listed.

Listing 16.2.4.3.5 Laboratory Data – Clinically Significant Urinalysis Results (Local Dipstick) – Enrolled Set
All clinically significant urinalysis (local dipstick) data will be listed by treatment group.

Listing 16.2.4.3.6 Laboratory Data –Signs of Hypontraemia – Enrolled Set
All patients with signs of hyponatraemia will be listed by treatment group.

Listing 16.2.4.3.7 Laboratory Data –Urinalysis Results (Central Laboratory) – Enrolled Set
All urinalysis (provided by central laboratory) data will be listed by treatment group.

Listing 16.2.4.3.8 Pregnancy Tests– Enrolled Set
Urine and serum pregnancy test results will be listed by treatment group for female patients, including cases when test was not done.

5.6.3 Vital Signs

Vital signs (tympanic body temperature, systolic and diastolic blood pressure and pulse rate) after five minutes at rest are collected at V1a, V2, V3, V5, V7, EOT, EDV and, if applicable, UNS.

Results for tympanic body temperature, systolic and diastolic blood pressure and pulse rate will be classified according to whether the value was lower than (L), within (N) or higher than (H) the reference range for that parameter. The normal ranges are provided in Table 4.

Table 4: Normal Ranges for Vital Signs

Parameter	Lower Reference Range	Upper Reference Range
Tympanic body temperature	36.0	38.5
Systolic blood pressure [mmHg]	80	160
Diastolic blood pressure [mmHg]	50	110
Pulse rate [bpm]	50	100

Clinical significance (not significant/significant) of vital sign abnormalities will be assessed by the investigator.

The following statistical output will be provided:

Table 15.3.3.1.1 Summary of Vital Signs – Safety Set
Vital sign parameters will be summarised including change from baseline at each visit slot where assessments were made by treatment group and in total.

Table 15.3.3.1.2 Incidence of Vital Signs Abnormalities – Safety Set
The number and percentage of patients with Low, Normal and High categories of each vital sign parameter will be displayed by treatment group and in total. Percentages will be based on the number of patients at the specified visit slot.

Listing 16.2.4.4 Vital Signs – Enrolled Set
Vital signs data will be listed.

5.6.4 12-Lead Electrocardiogram Data

A standard 12-lead electrocardiogram (ECG) is performed at V1a, V2, V3, EDV (if EDV performed before V3) and, if applicable, UNS.

If an ECG was done after primary stroke, the results will be used and the examination does not need to be repeated at V1a. ECG assessment after primary stroke, if available, otherwise the last collected value before IMP intake will be defined as baseline value.

ECG results will be assessed by an investigator if normal, abnormal or CS abnormal and assessments will be documented in the eCRF.

The following statistical outputs will be presented:

Table 15.3.3.2 Summary of ECG Assessments – Safety Set
The number and percentage of patients with normal, abnormal, and CS abnormal ECG assessments will be displayed by treatment group and in total. Percentages will be based on the number of patients at the specified visit slot.

Listing 16.2.4.5 Lead ECG Assessments – Enrolled Set
12-lead electrocardiogram findings will be listed.

5.6.5 Physical and Neurological Examination Findings

Physical examinations are performed at V1a, V2, V3, V5, V7, EOT, EDV and, if applicable, UNS on relevant body systems (appearance, skin, eyes, ears-nose-throat, lungs-chest, heart, abdomen, extremities, other).

Neurological examinations are performed at V1a, V2, V3, V5, V7, EOT, EDV and, if applicable, UNS. Complete neurological examination will include mental status, cranial nerves, motor system, sensory system, reflexes, co-ordination, gait and station.

Physical and neurological examination findings will be assessed by an investigator if normal or abnormal and if abnormal, clinical significance (significant/not significant) will be assessed.

The following statistical outputs will be presented:

Table 15.3.3.3 Summary of Physical Examination Findings – Safety Set
The number and percentage of patients with normal, abnormal, and CS abnormal physical examinations findings will be displayed at all visits by treatment group and in total. Percentages will be based on the number of patients at the specified visit slot.

Table 15.3.3.4 Summary of Neurological Examination Findings – Safety Set
The number and percentage of patients with normal, abnormal, and CS abnormal neurological examinations findings will be displayed at all visits by treatment group and in total. Percentages will be based on the number of patients at the specified visit slot.

Listing 16.2.4.6 Physical Examination Findings – Enrolled Set
Physical examination findings will be listed.

Listing 16.2.4.7 Neurological Examination Findings – Enrolled Set
Physical examination findings will be listed.

5.6.6 Analysis of Exploratory Endpoint

Recording of the Electroencephalogram (EEG) is optional. All EEG analyses will be presented for the EEG analysis subset.

EEG will be performed at V1a, EOT and, if applicable, UNS. If an examination was done after primary stroke, the results will be used, and the examination does not need to be repeated at V1a.

EEG parameters will be evaluated exploratively using descriptive statistics and provided in a separate report.

6. BLIND DATA REVIEW

A BDR will be performed after data entry and following a database lock. The following goals are defined for the BDR:

- to identify major/minor protocol deviations
- to identify patients that are not eligible for the per protocol population
- to identify protocol deviations that may affect the primary endpoint, i.e. patients with insufficient IMP compliance, patients with intake of prohibited medications during the observation period
- to discuss any open data issues

All decisions made during the BDR will be documented in the BDR report before the closure of the database and the randomisation code release.

An appropriate clinical study team, including a physician, will review potential protocol deviations and relevant information regarding those deviations to determine a possible impact on efficacy endpoints. An assessment will be made as to the effect of each of the possible deviations to determine if it is considered major or minor. The status, major or minor, of each protocol deviation will be documented in the BDR report. A patient may have one or more major protocol deviations resulting in the exclusion of that patient from the per-protocol analysis set.

Protocol deviations will, if possible, be validated against data recorded in the eCRF. Where an answer for an inclusion/exclusion tick box differs from the algorithmic check of the criteria, the algorithmic check will overrule the tick box.

Protocol deviations of the following categories will be reviewed during the BDR.

Inclusion Criteria

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#01.	1. Male or female patient not aged 18 years and above.	

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#02.	**2a. CTP V3.0:** To not have one of the following confirmed by magnetic resonance imaging (MRI)/computed tomography (CT): • Acute ischaemic **or** intracerebral haemorrhagic stroke **with** - an acute symptomatic seizure until 120 hours post-stroke **and** - cerebral cortex involvement OR • Acute ischaemic stroke **with** - National Institutes of Stroke Scale (NIHSS) ≥ 11 **and** - cerebral cortex involvement **and** - large-artery atherosclerosis **and/or** territory of middle cerebral artery (MCA) OR • Acute ischaemic stroke **with** - NIHSS 4-10 **and** - cerebral cortex involvement **and** - large-artery atherosclerosis **and** - territory of MCA OR • Acute intracerebral haemorrhagic stroke **with** - cerebral cortex involvement **and** - volume of intracerebral haemorrhage > 10 mL. **2b CTP V2.0:** Acute intracerebral haemorrhage with a CAVE score ≥ 3or acute ischaemic stroke with a SeLECT score ≥6, in each case confirmed by magnetic resonance imaging computed tomography	
PD#03.	**CTP 2.0:** Time of stroke occurrence is known and V1b is not planned within 96 hours. **CTP 3.0.** Time of stroke occurrence is known and V1b is not planned within 120 hours since the known time of stroke occurrence, or since last time seen well.	
PD#04.	Brain scan analysis has reliably excluded structural e.g. cerebral tumour or brain abscess, etc. brain lesions that can mimic stroke,	
PD#05.	a. Patient is not able to give informed consent and to write and has not signed written informed consent OR b. Patient is not able to give informed consent, and unable to write and has provided verbal witnessed consent OR c. Patient is unable to give informed consent, and not likely to regain this ability until V2, and the informed consent is not deferred OR d. Patient is unable to give informed consent, but likely to regain this ability until V2, but patient's legal representative (according to the respective national/local requirements) has noz provided written informed consent.	

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#06.	Female patients without childbearing potential (2 years postmenopausal, bilateral oophorectomy or tubal ligation, or complete hysterectomy) are eligible. Female patients with childbearing potential must not be pregnant as confirmed by a negative pregnancy test and sexually active females must use a medically acceptable effective nonhormonal method of contraception up to the end of the current menstrual cycle after stopping treatment. Acceptable methods for women are surgical intervention (e.g. bilateral tubal occlusion), intrauterine device, double-barrier methods, true sexual abstinence (i.e. when this is in line with the preferred and usual lifestyle of the patient) and vasectomised male partner, provided that he is the sole partner of that patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.	
PD#07.	V1b is within 96 hours (CTP 2.0) / 120 hours (CTP 3.0) after stroke occurrence.	
PD#08.	Inclusion criteria at V2 (only applicable for patients who were unable to give informed consent at V1a.) 8. a. Patient is able to give informed consent and to write and has signed a written informed consent OR b. Patient is able to give informed consent, but unable to write and has provided verbal witnessed consent.	

Exclusion Criteria

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#09.	1. Contraindication to ESL, i.e. known hypersensitivity to ingredients of ESL formulation or other carboxamide derivatives (e.g., oxcarbazepine, carbamazepine), or second or third degree atrioventricular (AV) block.	
PD#10.	2. Known Han Chinese or Thai ancestry.	
PD#11.	3a. CTP 3.0: History of previous clinical cerebral cortical stroke (other than the one described in inclusion criteria no. 2 - 3) within the last two years prior to Visit 1a. 3b. CTP 2.0: History of previous stroke (other than the one described in inclusion criteria no. 2 - 3).	
PD#12.	4. Sinus venous thrombosis.	
PD#13.	5. Spontaneous sub-arachnoid haemorrhage due to e.g. aneurysmatic or arteriovenous malformation.	
PD#14.	6. History of USs prior to primary (index) stroke.	
PD#15.	7. Impaired pre-stroke level of function, i.e. modified Rankin Scale (mRS) score > 3 prior to first stroke occurrence.	

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#16.	8. History of AED use within the last 2 years (CTP V3.0) or last 5 years (CTP V2.0) as defined in the list of not allowed AEDs (see CTP).	
PD#17.	9. Use of ESL unless provided as IMP of this trial and oxcarbazepine.	
PD#18.	10. Severe hepatic impairment	
PD#19.	11. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (measured at V1a).	
PD#20.	12. Known or suspected acute or chronic alcoholism, delirium tremens, or toxic psychosis.	
PD#21.	13. History of suicidal ideation or suicide attempt within the past 3 years.	
PD#22.	14. Presence of any other significant or progressive/unstable medical condition that, in the opinion of the investigator, would compromise evaluation of the trial treatment or may jeopardise the patient's safety, compliance or adherence to protocol requirements, such as significant psychiatric, cardiovascular, respiratory, metabolic, endocrine, haematologic, infectious or neurological disease.	
PD#23.	15. For women: Pregnancy or breast-feeding	
PD#24.	16. Previous enrolment in this trial or participation in any other investigational drug trial within the past 30 days (or 5 half-lives of IMP whichever is longer) prior to V1a.	
PD#25.	17. Persons committed to an institution by virtue of an order issued either by the judicial or other authorities.	
PD#26.	18. Employees of the investigator or trial centre, with direct involvement in the proposed trial or other studies under the direction of that investigator or trial centre, as well as family members of the employees or the investigator.	

Additional study conduct deviations

No.	Deviation	Major/ Minor/ Case by case review
PD#27.	IMP treatment compliance according to eCRF or diary <80% or >120%, compliance <80% or <120% will not be considered as major PD but patients must have at least 4 consecutive treatment days (first IMP intake until last IMP intake to reach steady state serum level of ESL	Case by case
PD#28.	IMP repeatedly taken not according to schedule	Case by case
PD#29.	Intake of prohibited medications or treatments as per CTP	Case by case
PD#30.	Visits performed not according to the study protocol schedule	Case by case
PD#31.	No acute intracerebral haemorrhage or acute ischaemic stroke confirmed by MRI/CT.	Case by case
PD#32.	First administration of IMP was more than 120 hours after stroke occurrence, or since last time seen well.	Case by case
PD#33.	Brain scanning has not excluded structural brain lesions that can mimic stroke, e.g. cerebral tumour or brain abscess, etc.	Case by case

No.	Deviation	Major/ Minor/ Case by case review
PD#34.	Treated not according to the randomisation plan	Case by case
PD#35.	Missing efficacy assessments (seizure information and seizure questionnaire)	Case by case
PD#36.	PDs from the global Protocol deviations log that may significantly affect the primary study objective and are not covered by other listings	Case by case

Reference listings will be made available to facilitate the review of the protocol deviations. The specific content and format of listings to be reviewed during the BDR meeting (including any additional requirements that may be necessary to aid in review) will be determined outside the scope of this SAP.

7. INTERIM ANALYSIS

No Interim Analysis will be performed.

8. CHANGES TO THE ANALYSIS AS LAID DOWN IN THE PROTOCOL AND MODIFICATIONS

The study was considered to be terminated earlier due to sponsor's decision. Recruitment was terminated before reaching the estimated sample size.

The secondary objective and endpoint "Time to first US after stroke occurrence" was decided to be deleted as it is closely related to the forth secondary endpoint "Time to first US after randomisation" and therefore would not really have any additional value.
The secondary objective and endpoint "4-week rate of USs" was decided to be deleted as this information will not be meaningful for this trial.

9. REFERENCES

1. SAS® Institute Inc., Cary, North Carolina, United States of America, Version 9.4.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, version as specified in the DMP.
3. WHO – Drug Dictionary. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden, version as specified in the DMP.
4. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel index. Md State Med J 1965 Feb:1461-65
5. Brott T et. al. Measurements of acute cerebral infarction: a clinical examination scale, Stroke. 1989 Jul;20(7):864-70
6. Kroenke K, Spitzer RL and Williams JBW. The PHQ-9 Validity of a Brief Depression Severity Measure. J Gen Intern Med. 2001 Sep; 16(9): 606–613.

10. APPENDICES

Shells for tables, listings, and figures are available in the following attachments:

1. BIA-2093-213_Table_Shells_Version_YYYYMMDD.docx

2. BIA-2093-213_Listing_Shells_Version_YYYYMMDD.docx

3. BIA-2093-213_Figure_Shells_Version_YYYYMMDD.docx

10.1 Tables

Appendix tables defined below will be provided in separate .rtf files for each output.

No	Table Identifier, Title	Output file
Baseline Characteristics etc.		
1	Table 15.1.1.1 Analysis Sets – Enrolled Set	BIA-2093-213-T-1501010100-sets-enr.rtf
2	Table 15.1.1.2 Reasons for Exclusion from Analysis Sets – Randomised Set	BIA-2093-213-T-1501010200-reas-excl-rs.rtf
3	Table 15.1.2 Screening Failures – Enrolled Set	BIA-2093-213-T-1501020000-scrf-enr.rtf
4	Table 15.1.3 Patient Disposition – Safety Set	BIA-2093-213-T-1501030000-disp-ss.rtf
5	Table 15.1.4.1.1 Number of Patients by Country and Site – Enrolled Set	BIA-2093-213-T-1501040101-no-pat-by-cntr-en.rtf
6	Table 15.1.4.1.2 Number of Patients by Country and Site – Safety Set	BIA-2093-213-T-1501040102-no-pat-by-cntr-ss.rtf
7	Table 15.1.4.2 Number of Patients by Visit – Safety Set	BIA-2093-213-T-1501040200-no-pat-by-vis-ss.rtf
8	Table 15.1.5 Major Protocol Deviations – Safety Set	BIA-2093-213-T-1501050000-mp-dev-enr.rtf
9	Table 15.1.6.1 Demographics – Safety Set	BIA-2093-213-T-1501060100-dm-ss.rtf
10	Table 15.1.6.2 Demographics – Per-protocol Set	BIA-2093-213-T-1501060200-dm-pps.rtf
11	Table 15.1.7.1 Summary of Primary Stroke Characteristics - Safety Set	BIA-2093-213-T-1501070100-pr-stoke-ss.rtf
12	Table 15.1.7.2 Summary of Primary Stroke Characteristics - Per-protocol Set	BIA-2093-213-T-1501070200-pr-stoke-pps.rtf
13	Table 15.1.8.1 Previous Medical Conditions – Safety Set	BIA-2093-213-T-1501080100-mh-prev-med-ss.rtf
14	Table 15.1.8.2 Ongoing Medical Conditions – Safety Set	BIA-2093-213-T-1501080200-mh-conc-med-ss.rtf
15	Table 15.1.9.1 Previous Medications – Safety Set	BIA-2093-213-T-1501090100-prev-med-ss.rtf
16	Table 15.1.9.2 Concomitant Medications – Safety Set	BIA-2093-213-T-1501090201-conmed-ss.rtf
17	Table 15.1.9.3.1 Therapies Related to Primary Stroke – Safety Set	BIA-2093-213-T-1501090301-th-rps-ss.rtf
18	Table 15.1.9.3.2 Therapies Related to Primary Stroke – Per-protocol Set	BIA-2093-213-T-1501090302-th-rps-pps.rtf
19	Table 15.1.9.4.1 Concomitant Anti-Epileptic Drugs – Safety Set	BIA-2093-213-T-1501090401-con-aed-ss.rtf
20	Table 15.1.9.4.2 Concomitant Anti-Epileptic Drugs – Per-protocol Set	BIA-2093-213-T-1501090402-con-aed-pps.rtf
21	Table 15.1.10.1.1 Exposure to IMP - Safety Set	BIA-2093-213-T-1501100101-exp-ss.rtf
22	Table 15.1.10.1.2 Exposure to IMP - Per-protocol Set	BIA-2093-213-T-1501100102-exp-pps.rtf
23	Table 15.1.10.2.1 Treatment Compliance (%) - Safety Set	BIA-2093-213-T-1501100201-compl-ss.rtf
24	Table 15.1.10.2.2 Treatment Compliance (%) - Per-protocol Set	BIA-2093-213-T-1501100202-compl-pps.rtf

No	Table Identifier, Title	Output file
Efficacy Data		
25	Table 15.2.1.1.1 Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502010101-treat-fail-6m-fas.rtf
26	Table 15.2.1.1.2 Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502010102-treat-fail-6m-pps.rtf
27	Table 15.2.1.3.1 Sensitivity Analysis of Treatment Failure within 6 Months after Randomisation Using Multiple Imputation for Missing Data–Full Analysis Set	BIA-2093-213-T-1502010301-sens-treat-fail-6m-fas.rtf
28	Table 15.2.1.3.2 Sensitivity Analysis of Treatment Failure within 6 Months after Randomisation Using Multiple Imputation for Missing Data– Per Protocol Set	BIA-2093-213-T-1502010302-sens-treat-fail-6m-pps.rtf
29	Table 15.2.1.4.1 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502010401-sens-tipp-fas.rtf
30	Table 15.2.1.4.1 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per-Protocol Set	BIA-2093-213-T-1502010402-sens-tipp-pps.rtf
30	Table 15.2.1.5.1 Sensitivity Analysis of Unprovoked Seizures within 6 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502010501-us-6m-fas.rtf
31	Table 15.2.1.5.2 Sensitivity Analysis of Unprovoked Seizures within 6 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502010502-us-6m-pps.rtf
32	Table 15.2.1.5.3 Sensitivity Analysis of Unprovoked Seizures within 12 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502010503-us-12m-fas.rtf
33	Table 15.2.1.5.4 Sensitivity Analysis of Unprovoked Seizures within 12 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502010504-us-12m-pps.rtf
34	Table 15.2.1.5.5 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502010505-us-18m-fas.rtf
35	Table 15.2.1.5.6 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502010506-us-18m-pps.rtf
36	Table 15.2.1.5.7 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation (Subgroup 1)– Full Analysis Set	BIA-2093-213-T-1502010507-us-18m-sgr1-fas.rtf
37	Table 15.2.1.5.8 Sensitivity Analysis of Unprovoked Seizures within 18 Months after Randomisation (Subgroup 2) – Full Analysis Set	BIA-2093-213-T-1502010508-us-18m-sgr2-fas.rtf
38	Table 15.2.2.1 Analysis of Treatment Failure Rate within 12 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502020100-treat-fail-12m-fas.rtf
39	Table 15.2.2.2 Analysis of Treatment Failure Rate within 12 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502020200-treat-fail-12m-pps.rtf
40	Table 15.2.3.1 Analysis of Treatment Failure Rate within 18 Months after Randomisation – Full Analysis Set	BIA-2093-213-T-1502030100-treat-fail-18m-fas.rtf
41	Table 15.2.3.2 Analysis of Treatment Failure Rate within 18 Months after Randomisation – Per Protocol Set	BIA-2093-213-T-1502030200-treat-fail-18m-pps.rtf
42	Table 15.2.4.1 Summary of Acute Symptomatic Seizures – Full Analysis Set	BIA-2093-213-T-1502020301-sum-stat-as-us-fas.rtf
43	Table 15.2.4.2 Summary of Acute Symptomatic Seizures – Per Protocol Set	BIA-2093-213-T-1502040200-ac-seiz-pps.rtf

No	Table Identifier, Title	Output file
44	Table 15.2.5.1.1 Time to First Unprovoked Seizure after Randomisation – Full Analysis Set	BIA-2093-213-T-1502050101-unpr-seiz-fas.rtf
45	Table 15.2.5.1.2 Time to First Unprovoked Seizure after Randomisation – Per Protocol Set	BIA-2093-213-T-1502050102-unpr-seiz-pps.rtf
46	Table 15.2.5.4.1 Summary of Unprovoked Seizures – Full Analysis Set	BIA-2093-213-T-1502050401-sum-us-fas.rtf
47	Table 15.2.5.4.2 Summary of Unprovoked Seizures – Per Protocol Set	BIA-2093-213-T-1502050402-sum-us-pps.rtf
48	Table 15.2.6.1.1 Summary of Barthel Index Total Score – Full Analysis Set	BIA-2093-213-T-1502060101-sum-stat-bi-fas.rtf
49	Table 15.2.6.1.2 Summary of Barthel Index Total Score – Per Protocol Set	BIA-2093-213-T-1502060102-sum-stat-bi-pps.rtf
50	Table 15.2.6.2.1 Analysis of Barthel Index Total Score Differences – Full Analysis Set	BIA-2093-213-T-1502060201-bi-diff-fas.rtf
51	Table 15.2.6.2.2 Analysis of Barthel Index Total Score Differences – Per Protocol Set	BIA-2093-213-T-1502060202-bi-diff-pps.rtf
52	Table 15.2.7.1.1 Summary of NIHSS Total Score – Full Analysis Set	BIA-2093-213-T-1502070101-sum-stat-nihss-fas.rtf
53	Table 15.2.7.1.2 Summary of NIHSS Total Score – Per Protocol Set	BIA-2093-213-T-1502070102-sum-stat-nihss-pps.rtf
54	Table 15.2.7.2.1 Analysis of NIHSS Total Score Differences – Full Analysis Set	BIA-2093-213-T-1502070201-nihss-diff-fas.rtf
55	Table 15.2.7.2.2 Analysis of NIHSS Total Score Differences – Per Protocol Set	BIA-2093-213-T-1502070202-nihss-diff-pps.rtf
56	Table 15.2.8.1.1 Summary of PHQ-9 Total Score – Full Analysis Set	BIA-2093-213-T-1502080101-sum-stat-phq9-fas.rtf
57	Table 15.2.8.1.2 Summary of PHQ-9 Total Score – Per Protocol Set	BIA-2093-213-T-1502080102-sum-stat-phq9-pps.rtf
58	Table 15.2.8.2 Summary of PHQ-9 Question 9 Score – Safety Set	BIA-2093-213-T-1502080200-sum-phq9-q9-score-ss.rtf
59	Table 15.2.8.3.1 Analysis of PHQ-9 Total Score Differences – Full Analysis Set	BIA-2093-213-T-1502080301-ph9q-diff-fas.rtf
60	Table 15.2.8.3.2 Analysis of PHQ-9 Total Score Differences – Per Protocol Set	BIA-2093-213-T-1502080302-ph9q-diff-pps.rtf
61	Table 15.2.9.1 Overall Survival – Full Analysis Set	BIA-2093-213-T-1502090100-ovr-surv-fas.rtf
62	Table 15.2.9.2 Overall Survival – Per Protocol Set	BIA-2093-213-T-1502090200-ovr-surv-pps.rtf

No	Table Identifier, Title	Output file
Safety Data		
63	Table 15.3.1.1 Overall Summary of TEAEs – Safety Set	BIA-2093-213-T-1503010100-sum-teae-ss.rtf
64	Table 15.3.1.2.1 Incidence of TEAEs – Safety Set	BIA-2093-213-T-1503010201-teae-ss.rtf
65	Table 15.3.1.2.2 Incidence of Non-Serious TEAEs– Safety Set	BIA-2093-213-T-1503010202-nser-teae-ss.rtf
66	Table 15.3.1.2.3 Incidence of Serious TEAEs – Safety Set	BIA-2093-213-T-1503010203-ser-teae-ss.rtf
67	Table 15.3.1.2.4 Incidence of Related TEAEs – Safety Set	BIA-2093-213-T-1503010204-rel-teae-ss.rtf
68	Table 15.3.1.2.5 Incidence of Serious Related TEAEs – Safety Set	BIA-2093-213-T-1503010205-rel-ser-teae-ss.rtf
69	Table 15.3.1.2.6 Incidence of TEAEs Leading to Discontinuation of IMP – Safety Set	BIA-2093-213-T-1503010206-teae-disc-ss.rtf
70	Table 15.3.1.2.7 Incidence of TEAEs Leading to Dose Reduction– Safety Set	BIA-2093-213-T-1503010207-teae-dose-ss.rtf
71	Table 15.3.1.2.8 Incidence of TEAEs Requiring Medication – Safety Set	BIA-2093-213-T-1503010208-teae-med-ss.rtf
72	Table 15.3.1.2.9 Incidence of TEAEs Leading to Death – Safety Set	BIA-2093-213-T-1503010209-teae-death-ss.rtf
73	Table 15.3.1.3.1 Incidence of TEAEs by Maximum Severity – Safety Set	BIA-2093-213-T-1503010301-teae-max-sev-ss.rtf
74	Table 15.3.1.3.2 Incidence of Related TEAEs by Maximum Severity – Safety Set	BIA-2093-213-T-1503010302-teae-rel-max-sev-ss.rtf
75	Table 15.3.1.3.3 Incidence of Serious TEAEs by Maximum Severity – Safety Set	BIA-2093-213-T-1503010303-teae-ser-max-sev-ss.rtf
76	Table 15.3.1.4.1 Incidence of Preferred Terms: TEAEs – Safety Set	BIA-2093-213-T-1503010401-teae-pt-ss.rtf
77	Table 15.3.1.4.2 Incidence of Preferred Terms: Serious TEAEs – Safety Set	BIA-2093-213-T-1503010402-ser-teae-pt-ss.rtf
78	Table 15.3.1.4.3 Incidence of Preferred Terms: Related TEAEs – Safety Set	BIA-2093-213-T-1503010403-rel-teae-pt-ss.rtf
79	Table 15.3.1.4.4 Incidence of Preferred Terms: Serious Related TEAEs– Safety Set	BIA-2093-213-T-1503010404-rel-ser-teae-pt-ss.rtf
80	Table 15.3.1.4.5 Incidence of Preferred Terms: TEAEs Leading to Discontinuation of IMP – Safety Set	BIA-2093-213-T-1503010405-teae-disc-pt-ss.rtf
81	Table 15.3.1.4.6 Incidence of Preferred Terms: (≥ 2% of patients in any treatment group) TEAEs – Safety Set	BIA-2093-213-T-1503010406-teae-2perc-pt-ss.rtf
82	Table 15.3.2.1.1 Summary of Clinical Laboratory Tests: Haematology – Safety Set	BIA-2093-213-T-1503020101-lbh-sum-ss.rtf
83	Table 15.3.2.1.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set	BIA-2093-213-T-1503020102-lbb-sum-ss.rtf
84	Table 15.3.2.1.3 Summary of Clinical Laboratory Tests: Coagulation – Safety Set	BIA-2093-213-T-1503020103-lbc-sum-ss.rtf
85	Table 15.3.2.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set	BIA-2093-213-T-1503020201-lbh-abnorm-ss.rtf
86	Table 15.3.2.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set	BIA-2093-213-T-1503020202-lbb-abnorm-ss.rtf
87	Table 15.3.2.2.2 Clinical Laboratory Tests: Incidence of Coagulation Abnormalities – Safety Set	BIA-2093-213-T-1503020203-lbc-abnorm-ss.rtf
88	Table 15.3.2.2.4 Clinical Laboratory Tests: Incidence of Thyroid Function Abnormalities – Safety Set	BIA-2093-213-T-1503020204-lbth-abnorm-ss.rtf
89	Table 15.3.2.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results from Baseline to Endpoint – Safety Set	BIA-2093-213-T-1503020301-lbh-shift-ss.rtf
90	Table 15.3.2.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results from Baseline to Endpoint– Safety Set	BIA-2093-213-T-1503020302-lbb-shift-ss.rtf

No	Table Identifier, Title	Output file
91	Table 15.3.2.3.3 Clinical Laboratory Tests: Shift Table of Coagulation Results from Baseline to Endpoint – Safety Set	BIA-2093-213-T-1503020303-lbc-shift-ss.rtf
92	Table 15.3.2.4.1 Clinical Laboratory Tests: Shift Table of Haematology Results from Baseline to Worst Post-Baseline Value – Safety Set	BIA-2093-213-T-1503020401-lbh-shift-wpb-ss.rtf
93	Table 15.3.2.4.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results from Baseline to Worst Post-Baseline Value – Safety Set	BIA-2093-213-T-1503020402-lbb-shift-wpb-ss.rtf
94	Table 15.3.2.4.3 Clinical Laboratory Tests: Shift Table of Coagulation Results from Baseline to Worst Post-Baseline Value – Safety Set	BIA-2093-213-T-1503020403-lbc-shift-wpb-ss.rtf
95	Table 15.3.2.5.1 Clinical Laboratory Tests: Incidence Clinically Significant Urinalysis Results (Local Dipstick) – Safety Set	BIA-2093-213-T-1503020501-lbu-local-ss.rtf
96	Table 15.3.2.5.2 Clinical Laboratory Tests: Incidence of Urinalysis Results (Central Laboratory) – Safety Set	BIA-2093-213-T-1503020502-lbu-central-ss.rtf
97	Table 15.3.2.6 Signs of Hyponatraemia – Safety Set	BIA-2093-213-T-1503020600-hyp-ss.rtf
98	Table 15.3.3.1.1 Summary of Vital Signs – Safety Set	BIA-2093-213-T-1503030101-vs-sum-ss.rtf
99	Table 15.3.3.1.2 Incidence of Vital Signs Abnormalities – Safety Set	BIA-2093-213-T-1503030102-vs-abnorm-ss.rtf
100	Table 15.3.3.2 Summary ECG Assessments – Safety Set	BIA-2093-213-T-1503030200-ecg-sum-ss.rtf
101	Table 15.3.3.3 Summary of Physical Examination Findings – Safety Set	BIA-2093-213-T-1503030300-pe-sum-ss.rtf
102	Table 15.3.3.4 Summary of Neurological Examination Findings – Safety Set	BIA-2093-213-T-1503030400-neuro-sum-ss.rtf
103	Table 15.3.3.5 Summary of EEG Assessments – EEG Analysis Subset	BIA-2093-213-T-1503030500-eeg-sum-ss.rtf

10.2 Listings

Appendix listings defined below will be provided in separate .rtf files for each output.

No	Listing Identifier, Title	Output file
Demographic and Study Population Data		
1	Listing 16.2.1.1 Patient Disposition – Randomised Set	BIA-2093-213-L-1602010100-disp-rs.rtf
2	Listing 16.2.1.2 Screening Failures – Enrolled Set	BIA-2093-213-L-1602010200-scr-fail-es.rtf
3	Listing 16.2.1.3 Patient Visits – Enrolled Set	BIA-2093-213-L-1602010300-visit-es.rtf
4	Listing 16.2.1.4 Exclusions from Analysis Sets – Randomised Set	BIA-2093-213-L-1602010400-excl-sets-rs.rtf
5	Listing 16.2.1.5 Patient Randomisation to Treatments – Randomised Set	BIA-2093-213-L-1602010500-rand-rs.rtf
6	Listing 16.2.1.6.1 Major Protocol Deviations – Full Analysis Set	BIA-2093-213-L-1602010601-dev-fas.rtf
7	Listing 16.2.1.6.2 Protocol Deviations related to COVID-19 – Enrolled Set	BIA-2093-213-L-1602010602-dev-covid-es.rtf
8	Listing 16.2.1.7 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set	BIA-2093-213-L-1602010700-incl-excl-es.rtf
9	Listing 16.2.1.8 Demographics – Enrolled Set	BIA-2093-213-L-1602010800-demo-es.rtf
10	Listing 16.2.1.9 (Primary) Stroke and Brain Imaging Details – Enrolled Set	BIA-2093-213-L-1602010900-stroke-brain-es.rtf
11	Listing 16.2.1.10 SeLECT and CAVE Scores – Enrolled Set	BIA-2093-213-L-1602011000-select-cave-es.rtf
12	Listing 16.2.1.11 Medical History – Enrolled Set	BIA-2093-213-L-1602011100-med-h-es.rtf
13	Listing 16.2.1.12 Medications – Enrolled Set	BIA-2093-213-L-1602011200-med-es.rtf
14	Listing 16.2.1.13 Therapies – Enrolled Set	BIA-2093-213-L-1602011300-ther-es.rtf
15	Listing 16.2.2.1 Exposure to IMP – Safety Set	BIA-2093-213-L-1602020100-exp-ss.rtf
16	Listing 16.2.2.2 Treatment Duration and Compliance – Safety Set	BIA-2093-213-L-1602020200-dur-compl-ss.rtf
17	Listing 16.2.2.3 IMP Accountability – Safety Set	BIA-2093-213-L-1602020300-acc-ss.rtf
Efficacy Data		
18	Listing 16.2.3.1 Seizure Screening Questionnaire – Enrolled Set	BIA-2093-213-L-1602030100-ques-seiz-es.rtf
19	Listing 16.2.3.2 Seizure Information after the Primary Stroke Occurrence – Enrolled Set	BIA-2093-213-L-1602030200-inf-seiz-es.rtf
20	Listing 16.2.3.3 Barthel Index – Enrolled Set	BIA-2093-213-L-1602030300-barthel-es.rtf
21	Listing 16.2.3.4 National Institutes of Health Stroke Scale (NIHSS)– Enrolled Set	BIA-2093-213-L-1602030400-nihss-es.rtf
22	Listing 16.2.3.5 Patient Health Questionnaire (PHQ-9) – Enrolled Set	BIA-2093-213-L-1602030500-phq9-es.rtf

No	Listing Identifier, Title	Output file
Safety Data		
23	Listing 16.2.4.1.1 Adverse Events: MedDRA Coding	BIA-2093-213-L-1602040101-ae-cod-es.rtf
24	Listing 16.2.4.1.2 Adverse Events: General – Enrolled Set	BIA-2093-213-L-1602040102-ae-es.rtf
25	Listing 16.2.4.2.1 Serious Adverse Events – Enrolled Set	BIA-2093-213-L-1602040102-ser-ae-es.rtf
26	Listing 16.2.4.2.2 AEs Leading to Discontinuation of IMP – Safety Set	BIA-2093-213-L-1602040102-disc-ae-es.rtf
27	Listing 16.2.4.2.3 AEs Leading to Death – Enrolled Set	BIA-2093-213-L-1602040203-death-ae-es.rtf
28	Listing 16.2.4.3.1 Laboratory Data - Haematology– Enrolled Set	BIA-2093-213-L-1602040301-lbh-es.rtf
29	Listing 16.2.4.3.2 Laboratory Data - Biochemistry– Enrolled Set	BIA-2093-213-L-1602040302-lbb-es.rtf
30	Listing 16.2.4.3.3 Laboratory Data - Coagulation– Enrolled Set	BIA-2093-213-L-1602040303-lbc-es.rtf
31	Listing 16.2.4.3.4 Laboratory Data - Thyroid Function– Enrolled Set	BIA-2093-213-L-1602040304-lbth-es.rtf
32	Listing 16.2.4.3.5 Laboratory Data - Clinically Significant Urinalysis Results (Local Dipstick) – Enrolled Set	BIA-2093-213-L-1602040305-lbu-local-es.rtf
33	Listing 16.2.4.3.6 Signs of Hyponatraemia – Enrolled Set	BIA-2093-213-L-1602040306-hyp-es.rtf
34	Listing 16.2.4.3.7 Laboratory Data - Urinalysis Parameters (Central Laboratory) – Enrolled Set	BIA-2093-213-L-1602040307-lbu-central-es.rtf
35	Listing 16.2.4.3.8 Pregnancy Tests – Enrolled Set	BIA-2093-213-L-1602040308-preg-es.rtf
36	Listing 16.2.4.4 Vital Signs – Enrolled Set	BIA-2093-213-L-1602040400-vs-es.rtf
37	Listing 16.2.4.5 Lead ECG Assessments – Enrolled Set	BIA-2093-213-L-1602040500-ecg-es.rtf
38	Listing 16.2.4.6 Physical Examination Findings – Enrolled Set	BIA-2093-213-L-1602040600-pe-es.rtf
39	Listing 16.2.4.7 Neurological Examination Findings – Enrolled Set	BIA-2093-213-L-1602040700-ne-es.rtf

10.3 Figures

Appendix figures defined below will be provided in separate .rtf files for each output.

No	Figure Identifier, Title	Output file
Demographic and Study Population Data		
1	Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Set	BIA-2093-213-F-1501010000-disp-es.rtf
2	Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set	BIA-2093-213-F-1501020000-asets-es.rtf
Efficacy Data		
3	Figure 15.2.1.1.1 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Full Analysis Set	BIA-2093-213-F-1502010101-tipp-fas.rtf
4	Figure 15.2.1.1.2 Tipping Point Analysis of Treatment Failure Rate within 6 Months after Randomisation – Per Protocol Set	BIA-2093-213-F-1502010102-tipp-pps.rtf
5	Figure 15.2.1.2.1 Time to First US after Randomisation – Full Analysis Set	BIA-2093-213-F-1502010201-time-us-fas.rtf
6	Figure 15.2.1.2.2 Time to First US after Randomisation – Per Protocol Set	BIA-2093-213-F-1502010202-time-us-pps.rtf
7	Figure 15.2.2.1 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by Barthel Index Total Score – Full Analysis Set	BIA-2093-213-F-1502020100-cum-inc-barthel-fas.rtf
8	Figure 15.2.2.2 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by Barthel Index Total Score – Per-Protocol Set	BIA-2093-213-F-1502020200-cum-inc-barthel-pps.rtf
9	Figure 15.2.3.1 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by NIHSS Total Score – Full Analysis Set	BIA-2093-213-F-1502030100-cum-inc-nihss-fas.rtf
10	Figure 15.2.3.2 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by NIHSS Total Score – Per Protocol Set	BIA-2093-213-F-1502030200-cum-inc-nihss-pps.rtf
11	Figure 15.2.4.1 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by PHQ-9 Total Score– Full Analysis Set	BIA-2093-213-F-1502040100-cum-inc-phq9-fas.rtf
12	Figure 15.2.4.2 Cumulative Incidence Curves of USs using Kaplan-Meier Curves by PHQ-9 Total Score– Per Protocol Set	BIA-2093-213-F-1502040200-cum-inc-phq9-pps.rtf
13	Figure 15.2.5.1 Overall Survival – Full Analysis Set	BIA-2093-213-F-1502050100-surv-fas.rtf
14	Figure 15.2.5.2 Overall Survival – Per Protocol Set	BIA-2093-213-F-1502050200-surv-pps.rtf

11. SIGNATURES

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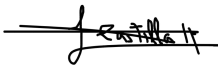
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