Statistical Analysis Plan

Sponsor Name: Lumosa Therapeutics Co, Ltd.

Protocol Number: LT3001-205

Protocol Title: BRIGHT - A Phase II, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Multiple Doses of LT3001 Drug Product in Subjects with Acute Ischemic Stroke (AIS)

Protocol Version and Date: (DD-Mmm-YYYY): V8.1 (23-Apr-2025)

[redacted]

[redacted]

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	30-Jun-2025	[redacted]	Initial Release Version

I confirm that I have reviewed this document and agree with the content.

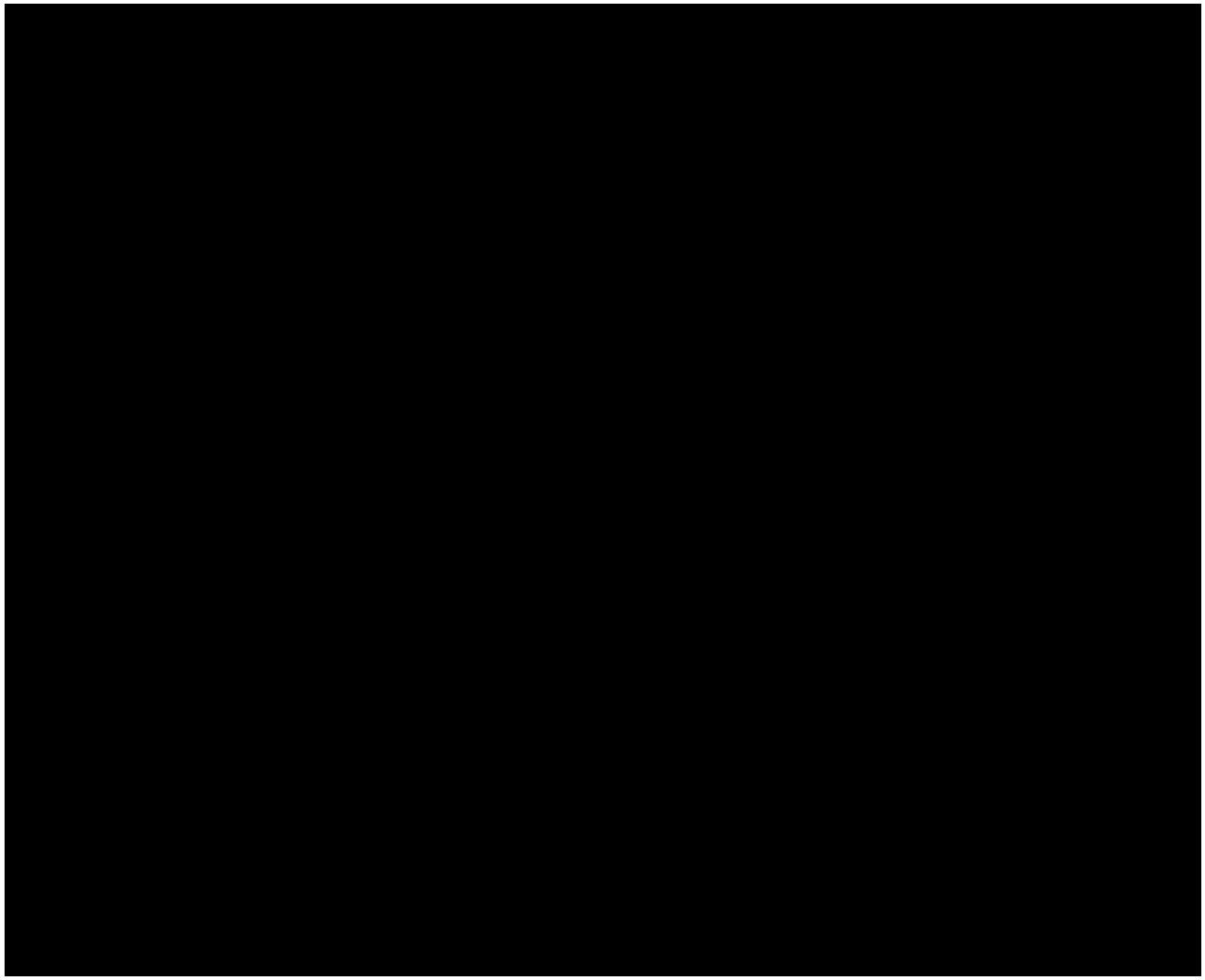


Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
aICH	Asymptomatic Intracranial Hemorrhage
AIS	Acute Ischemic Stroke
[redacted]	
[redacted]	
ANCOVA	Analysis of covariance
aPTT	Activated Partial Thromboplastin Time
ASPECTS	Alberta Stroke Program Early CT Score
[redacted]	
ATC	Anatomical Therapeutic Chemical
[redacted]	
CI	Confidence Interval
[redacted]	
[redacted]	
CRF	Case Report Form
CS	Clinically Significant
CT	Computed Tomography
CSR	Clinical Study Report
CTP	Computed Tomography Perfusion
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational Product
ITT	Intent-to-Treat
[redacted]	

Abbreviation	Description
Max	Maximum
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
[redacted]	
[redacted]	
MoCA	Montreal Cognitive Assessment
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
N/A	Not Applicable
NCS	Not Clinically Significant
NIHSS	National Institute of Health Stroke Scale
PP	Per Protocol
PT	Preferred Term
[redacted]	
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
sICH	Symptomatic Intracranial Hemorrhage
SOC	System Organ Class
SoC	Standard of Care
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
WOCBP	Women of Childbearing Potential
WHO	World Health Organization

2. Purpose

This statistical analysis plan (SAP) describes the planned statistical analyses and data presentations for study LT3001-205. The SAP is based on the Protocol Version 8.1, dated 23 Apr 2025.
Study measurements and assessments, planned statistical methods, and derived variables are summarized in this plan. Planned tables, figures, and listings are specified. All decisions regarding final analyses, as defined in this SAP document, have been made prior to locking the final database. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2.1. Responsibilities

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs).

2.2. Timings of Analyses

The primary analysis of safety and efficacy is planned after all subjects complete all study periods (including the last scheduled follow-up visit) or terminate early from the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

An independent Data Safety Monitoring Board (DSMB) will be established to assess all data (including imaging data) of LT3001 drug product or placebo treatment. The DSMB will review safety and efficacy data when the first 30 treated subjects have completed study procedures on Day 7 or terminated the study prior to Day 7. Further description of the DSMB analyses can be found in the DSMB charter (Lumosa Therapeutics_LT3001-205_DSMB Charter). An unblinded team [redacted] will perform the analyses to maintain the blinding of the study. No interim analysis (IA) is planned for this study.

3. Study Objectives

3.1. Primary Objectives

To determine the safety of multiple doses of LT3001 drug product in subjects with AIS.

3.2. Secondary Objectives

To determine the efficacy of multiple doses of LT3001 drug product in subjects with AIS.

4. Study Design

4.1. Brief Description

This is a multicenter, double-blind, randomized, and placebo-controlled prospective Phase II clinical study, designed to evaluate LT3001 drug product versus placebo in subjects with AIS. The study is planned to take place in multiple countries. Subjects who participate in this trial should be treated with standard of care of AIS therapies when appropriate.

Approximately 200 eligible subjects will be randomized centrally 1:1 to LT3001 drug product or placebo with the stratification factors. Randomization will be stratified according to age, baseline NIHSS, and time of AIS symptoms onset to the 1st IP

Each eligible subject will The first dose of LT3001 drug product or placebo (1st IP) will be administered within 24 hours after stroke symptoms onset.

LT3001 drug product or placebo will be administered.

A Data Safety Monitoring Board (DSMB) will be formed to assess all data (including imaging data) of LT3001 drug product or placebo treatment. The DSMB will review safety and efficacy data when the thirtieth treated subject has completed study procedures on Day 7 or terminated the study before Day 7. The DSMB will meet after the data presentation and will issue recommendations relating to safety and study conduct. Unscheduled meetings will be recommended and initiated by the Sponsor or the Principal Investigators.

The participation for each subject is approximately 92 days from the Screening (Visit 1) to the last visit.

Study Design

[redacted]

4.2. Subject Selection

4.2.1. Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Subject has been diagnosed with AIS
2. Subject or if applicable subject's legally acceptable representative/ legally designated representative consents to participation by signing the informed consent form after receiving full information about the study.
3. Subject [redacted] is aged 18 to 90 years (inclusive) [redacted] is aged 18 to 80 years (inclusive) at the time of Screening (Visit 1).
4. Subject has an NIHSS of 4 to 25.
5. Subject [redacted] is able to receive the 1st IP within 24 hours after stroke symptoms onset [redacted]
6. Subjects who are women of childbearing potential, or men whose sexual partners are women of childbearing potential, are able and willing to use at least 1 highly effective method of contraception during the study until 3 months after the last dosing of IP administration.

Neuroimaging Inclusion Criteria:

1. Subject has adequate renal function, has no history of severe allergic reactions to contrast agents, and is able to undergo a contrast brain perfusion with either MRI or computed tomography (CT).
2. [redacted] the subsequent subjects must adhere to the following Mismatch Profile on MRI (perfusion is included) or CTP [redacted]**.

** The mismatch ratio is determined in real time by site routine practice (e.g., RAPID or similar software, or other similar analyses) based on the difference between the ischemic core lesion volume and the Tmax >6s lesion volume. If both a multimodal MRI and CTP are performed before enrollment, the later of the 2 scans is assessed to determine eligibility.

4.2.2. Exclusion Criteria

Individuals meeting any of the following criteria at Screening (Visit 1) or Baseline are ineligible to participate in this study:

1. During the current AIS episode, the subject has received or is scheduled to receive EVT and/or intravenous thrombolytic (e.g., recombinant tissue-type plasminogen activator) treatment based on the investigator's assessment of its potential benefit.
2. Subject has a pre-stroke disability (mRS >2).
3. Subject has Alberta Stroke Program Early CT Score of ≤5.
4. Subject has symptoms of suspected subarachnoid hemorrhage, even if CT is normal.
5. Subject has imaging evidence of acute intracranial hemorrhage, intracranial tumor (except meningioma without parenchymal mass effect), arteriovenous malformations, other central nervous system lesions that could increase the risk of bleeding, or aneurysm requiring treatment.
6. Subject has significant mass effect with midline shift.
7. Subject has pre-existing medical, neurological, or psychiatric disease that would confound the neurological or functional evaluations, e.g., seizures at onset of the current AIS, dementia.
8. Subject has current uncontrolled hypertension despite treatment: systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg before dosing at Screening (Visit 1).
9. Subject has hemorrhagic diathesis, coagulation factor deficiency or recent oral anticoagulant therapy with International Normalized Ratio >1.7 or activated partial thromboplastin time >1.5 times of upper limit of normal range at Screening (Visit 1).
10. Subject has received conventional heparin within 48 hours before the 1st IP administration, except for low dose subcutaneous conventional heparin or low molecular weight heparin at a preventive dose.
11. Subject has received one of the new oral anticoagulants within 48 hours before the 1st IP administration, e.g., dabigatran, apixaban, rivaroxaban, and edoxaban, except for dabigatran-treated subject who has been given a reversal agent, idarucizumab, before the 1st IP administration.
12. Subject has platelet count <100,000/mm3 at Screening (Visit 1).
13. Subject has blood glucose concentration <50 mg/dL or >400 mg/dL at Screening (Visit 1).
14. Subject has moderate or severe hepatic, renal, and/or active infectious disease at Screening (Visit 1) as judged by the investigator. Subject with confirmed COVID-19 or influenza infection can be enrolled at the investigator's discretion.
15. Subject is lactating, pregnant (pregnancy test required for all female subjects of childbearing potential), or planning to become pregnant during the study.
16. Subject has had history of sICH, prior AIS, myocardial infarction, or serious head trauma within 90 days before Screening (Visit 1).
17. Subject has had any major surgery within 90 days before Screening (Visit 1), e.g., intracranial or intraspinal surgery, coronary artery bypass graft, obstetrical delivery, organ biopsy.
18. Subject has had a bleeding event within 21 days before Screening (Visit 1), e.g., gastrointestinal hemorrhage.
19. Subject has puncture of noncompressible vessels within 7 days before Screening (Visit 1).
20. Subject has a history of severe allergic reactions to LT3001 or excipients.
21. Subject has participated in another investigational study and received IP within 30 days before Screening (Visit 1) or 5 half-lives (whichever is longer).
22. In the opinion of the Investigator, the subject has serious, advanced, or terminal illness that will prevent improvement or follow-up visits.
23. In the opinion of the Investigator, the subject is not appropriate for the study for any other reason.

4.3. Determination of Sample Size

[redacted]

4.4. Treatment Assignment and Blinding

The study is placebo-controlled to lessen the risk that events due to chance are falsely attributed to LT3001 drug product.

The study is randomized to control for factors known and unknown between the treatment groups.

The study is blinded so that the subjects, site staff administering the investigational product, and site staff conducting study assessments will not know which treatment a subject receives to allow assessment of the study objectives without bias.

Subjects will be randomly assigned to receive LT3001 drug product or placebo in a ratio of 1:1. The randomization will be stratified according to age[redacted], baseline NIHSS[redacted], and the time of AIS symptoms onset to the 1st IP[redacted]. The stratified randomization is to ensure similar risk distributions[redacted].

4.5. Administration of Study Medication

All subjects will receive the first dose of IP within 24 hours after stroke symptoms onset on Day 0 and will

be hospitalized for the care of AIS according to each study site's current standard of care. [redacted]

4.6. Study Procedures and Flowchart

Table 1 outlines the timing of procedures and assessments to be performed throughout the study.

Table 1 Schedule of Assessments

[redacted]

[redacted]

5. Endpoints

5.1. Primary Endpoint

The proportion of subjects with AEs, judged to be probably or definitely related to the IP within 90 days after the 1st IP administration.

5.2. Secondary Endpoints

Clinical efficacy outcomes:

1. Functional outcome

   a. The proportion of subjects achieve [redacted] mRS 0-1 [redacted]. The proportion of subjects achieve [redacted] mRS 0-2 [redacted].
   b. The proportion of subjects with independent functional outcome, defined as mRS ≤2 [redacted] after the 1st IP.
   c. The proportion of subjects with excellent functional outcome, defined as mRS ≤1 [redacted] after the 1st IP.
   d. The shift of proportion of subjects with each grade on mRS [redacted] from Baseline.

2. Neurological outcome

   a. The National Institute of Health Stroke Scale (NIHSS) [redacted] after the 1st IP [redacted].
   b. The proportion of subjects with neurological outcome improvement, defined as a decrease in NIHSS ≥4 points [redacted] from Baseline.
   c. The proportion of subjects with neurological outcome improvement, defined as a decrease in NIHSS ≥4 points or NIHSS of 0 to 1 point [redacted] from Baseline.
   d. The proportion of subjects with NIHSS ≤2 [redacted] after the 1st IP.
   e. The proportion of subjects with NIHSS ≤1 [redacted] after the 1st IP.
   f. Change in NIHSS [redacted] from Baseline.

3. The occurrence of recurrent stroke within 90 days after the 1st IP.

4. The change of cognition assessment by Montreal Cognitive Assessment (MoCA) [redacted] from Baseline [redacted].

Imaging outcomes:

1. The change of infarct volume [redacted] from Baseline by magnetic resonance imaging (MRI)/computed tomography perfusion (CTP).
2. The change of hypoperfusion lesion [redacted] from Baseline by perfusion-weight imaging MRI/CTP.

3. The proportion of subjects with 90% reduction in hypoperfusion lesion [redacted] from Baseline by perfusion-weight imaging MRI/CTP.
4. The infarct volume [redacted] after the 1st IP by MRI/CTP [redacted].

Safety outcomes:

1. The occurrence of symptomatic intracranial hemorrhage (sICH) [redacted] after the 1st IP; clinical deterioration defined as an increase in the NIHSS of 4 points or more AND confirmed by MRI/CTP imaging – documentation.
2. The occurrence of asymptomatic intracranial hemorrhage (aICH) [redacted] after the 1st IP.
3. The occurrence of mortality due to any reason within 90 days after the 1st IP.
4. The number and severity of AEs within 90 days after the 1st IP.
5. The number of subjects with AEs within 90 days after the 1st IP.

6. Analysis Sets

6.1. Enrolled Population

All individuals who sign the ICF. The Enrolled Population will be used for all subject disposition analyses.

6.2. Safety Population

All randomized subjects who receive at least 1 dose of IP. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analysis of safety.

6.3. Intent-to-Treat (ITT) Population

All subjects who are randomized, irrespective of any deviation from the protocol or premature discontinuation. The treatment group assignment will be designated according to initial randomization. The ITT Population will serve as the primary basis for the analysis of efficacy [redacted].

6.4. Per-Protocol (PP) Population

All ITT subjects who are treated and complete study procedures through Day 30 without a major protocol deviation potentially impacting efficacy measurement [redacted]. The PP population will be used as supportive basis for analysis of efficacy [redacted].

6.5. Completers Population

All ITT subjects who are treated and complete study procedures through Day 90 without a major protocol deviation potentially impacting efficacy measurement [redacted]. The Completers population will be used as supportive basis for analysis of efficacy [redacted].

7. Estimands

Estimands approach is not applicable as this is an exploratory trials.

8. General Aspects for Statistical Analysis

8.1. General Methods

- Analysis will be carried out using SAS® (version 9.4 or newer, SAS Institiute Inc., Cary, NC). Templates for the summary tables, figures and subject data listings will be available separately.
- Data listings will include all data recorded for all enrolled and ITT subjects. Data will further be categorized by treatment group.
- Summary statistics will be presented by treatment group and overall (wherever applicable). For continuous variables, data will be summarized with the number of subjects (n), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.
- This is an exploratory study, i.e., all statistical comparison between the treatment groups is not confirmatory but of descriptive nature. Where appropriate, descriptive statistics may be presented with 95% confidence intervals (CIs).
- The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the recorded data. Measures of location (e.g., mean and median) will be reported to 1 degree of precision more than the recorded data, and measures of spread (e.g., standard deviation) will be reported to 2 degrees of precision more than the recorded data.
- The dictionary (MedDRA and WHODrug) version used will be specified in corresponding data display footnote.
- Only data from protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in summary tables but will be included in the listings.
- Any changes to the analyses that are not included in this SAP will be documented in the CSR.

8.2. Key Definitions

- Unless otherwise defined, baseline is defined as the last non-missing assessment prior to the first dosing.
- Study Day 1 is defined as the date on which a subject took the first dose of study drug**. Other study days are defined relative to Study Day 1.

  For assessments occurring on Day 1 or after, Study Day will be calculated as (date of assessment – date of first dose + 1). For assessments occurring before Day 1, Study Day will be calculated as (date of assessment – date of first dose).

[redacted]

8.3. Missing Data

Missing data will be imputed for the efficacy variables mRS and NIHSS as described in Section 10.1.

Missing or incomplete dates in safety data: In all listings, missing or incomplete dates will be left as they have been recorded. However, for calculation and sorting based on dates and for consideration in summary tables, the following method will be used: The most conservative approach will be systematically considered. For example, if the onset date of an AE/concomitant medication is missing or incomplete, it is assumed to have occurred during the study treatment, except if the partial onset date indicates differently. A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

Missing TEAE relationship will be imputed by 'related' for summary tables.

8.4. Visit Windows

Please refer to Section 4.6 for visit windows.

8.5. Subgroups

Efficacy endpoints will be summarized and statistically compared between the treatment groups in the subgroups of the variables used for [redacted]. As additional subgroup the [redacted] will be investigated, the comparison will be made for the overall treatment groups. Additionally, where applicable, comparative analyses will be performed with consideration of the [redacted]. Such subgroup summaries and analyses will be performed on the ITT population only.

9. Subject Disposition, Protocol Deviations, Demographic, Other Baseline Characteristics and Medication

9.1. Subject Disposition and Withdrawals

All individuals who sign the ICF will be included in disposition summary. The number of subjects who are screened, screen failed with reasons, randomized, number of subjects in each analysis set, number of subjects who excluded from each analysis set (including reasons for exclusion), number of subjects who completed the study treatment, who discontinued the treatment with reasons for treatment discontinuation, number of subjects who discontinued the study treatment but remained in the study [redacted], number of subjects who completed the study [redacted], who discontinued from the study with reasons for study discontinuation, death will be summarized by treatment group. All disposition data will be listed by subject and treatment group.

9.2. Protocol Deviations

Protocol deviations will be identified throughout the trial following the 'Protocol Deviation and Noncompliance Management Plan' [redacted]. Final definition of protocol deviations, categorization of protocol deviations into important / non-important, determination whether an important protocol deviation has an impact on the assessment of efficacy, and the determination of the populations will be finalized in the BDRM following [redacted] prior to database lock and unblinding.

All protocol deviations identified during the conduct of the trial will be listed, while only the important protocol deviations will be summarized by deviation category using the ITT population. The list of protocol deviations will be reviewed by the Sponsor, the medical monitor, and the study statistician and finalized before database lock. Exclusions from the PP population, if any, along with the rationale for the exclusion will be recorded in the protocol deviation file.

Important protocol deviations which potentially impact efficacy measurement will lead to exclusion from the PP population.

9.3. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be provided using the ITT population. These tabulations will include the following variables:

- Age (years)
- Age group
- Gender
- Subject's child bearing potential
- Race
- Weight (kg)
- Alcohol consumption history
- Smoking history

[redacted]

All demographic and baseline characteristics data will be listed by subject.

9.4. Medical History and Concomitant Illnesses

Medical history will include any pre-existing conditions, including AIS (the primary disease) as well as all prior significant illnesses, up to and including 1 year before Screening (Visit 1). Additional pre-existing conditions present at the time when informed consent is given and up to the time of the initiation of dosing [redacted] will be regarded as concomitant illnesses. All recorded medical history and concomitant illnesses verbatim terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

Medical history and concomitant illnesses data will be summarized by system organ class (SOC) and preferred term (PT) using the ITT population. Subject listings of medical history, concomitant illnesses, alcohol consumption history and smoking history will also be provided.

9.5. Medications

All recorded non-study medications will be coded using the dynamic version of the World Health Organization Drug Dictionary (WHODrug) Global B3 Mar 2025. WHODrug coding includes the Anatomical Therapeutic Chemical (ATC) classification levels and preferred name. All medications will be classified according to the study period in which its use occurred (i.e., Prior or Concomitant).

9.5.1. Prior Medication

All medications stopped before the 1st IP will be considered as prior medications. The incidence of prior medication use will be summarized by ATC level terms and preferred names using the ITT population.

9.5.2. Concomitant Medication

All medications started on the day of the 1st IP or afterwards and medications started prior to the 1st IP but continued after start of IP dose are considered as concomitant medications. Concomitant medications will be summarized by ATC level terms and preferred names using the ITT population.

Any medication reported more than one time will only be counted once per subject for each preferred name. All prior and concomitant medication use data will be listed by subject.

In case of incomplete stop date, the medication will be considered as prior only if this can be concluded without any doubt. All other cases of incomplete or missing stop dates will be considered concomitant medications.

9.5.3. Other Therapies

A listing of surgical procedures as captured in the CRF will be provided.

9.6. Study Drug Exposure

The total number of subject dosed, cumulative dose number, cumulative dose administered, planned cumulative dose (mg), relative dose intensity (%), relative dose intensity category and subject with at least one interrupted infusion, will be summarized descriptively for all subjects in safety population by treatment group. Also, all study drug administration data will be listed by subject.

10. Efficacy

All efficacy endpoints will be summarized and analyzed using the ITT population. Additionally, supportive analyses will be performed on the PP population and on the Completers population. Comprehensive listings of all efficacy data will also be presented by subject and visit.

All efficacy endpoints will be summarized using descriptive statistics by treatment group and by visit, as appropriate. Categorical endpoints will be summarized by treatment group by presenting the number and percentage of subjects in each category.

This is an exploratory study, i.e., all statistical comparison between the treatment groups is not of confirmatory but of descriptive nature. The statistical comparison of the efficacy endpoints based on mRS and NIHSS between treatment groups will be performed either after multiple imputation (MI) of missing data or will be analyzed [redacted]. For all other efficacy endpoints missing data will not be imputed prior statistical comparison, i.e. summaries and statistical analysis will use the observed data within ITT only.

10.1. Efficacy Endpoints for mRS and NIHSS and Analysis

10.1.1. Analysis of functional outcome based on mRS assessments

All binary response variables defined on mRS assessments at the respective visits will be summarized with the number and percentage of subjects with and without response by treatment group considering observed data of ITT. The difference of the proportions based on observed data of ITT between the treatment groups with the corresponding 95% confidence intervals (CIs) will be presented for the defined time points.

Comparison between the treatment groups will be performed for the binary response variables using the Chi-square test [redacted] at each defined timepoint separately and additionally [redacted].

Additionally, the comparison between the treatment groups at each timepoint and overall will be performed for the binary response [redacted]. The model will be performed for both categorizations of mRS, i.e., subjects with mRS ≤2 and subjects with mRS ≤1 [redacted]

[redacted].

The number and percentage of subjects in each score category of mRS will be presented for baseline and for the post-baseline time points [redacted] by treatment group for observed ITT population. A shift table will be presented by treatment with shifts from baseline to each defined post-baseline time point [redacted]

The [redacted] steps are described in section 10.1.3.

10.1.2. Analysis of neurological outcome based on NIHSS assessments

All binary response variables defined on NIHSS assessments at the respective visits will be summarized with the number and percentage of subjects with and without response by treatment group considering observed data of ITT. The difference of the proportions based on observed data of ITT between the treatment groups with the corresponding 95% CIs will be presented for the defined time points.

Comparison between the treatment groups will be performed for the definedbinary response variables using the Chi-square test [redacted] at each defined timepoint separately and additionally, [redacted]

Additionally, the comparison between the treatment groups at each timepoint and overall will be performed for the binary response variables [redacted]

The total score, subscores and change from baseline in NIHSS will be summarized at each defined time point by treatment group and overall on observed data of ITT [redacted]

[redacted]

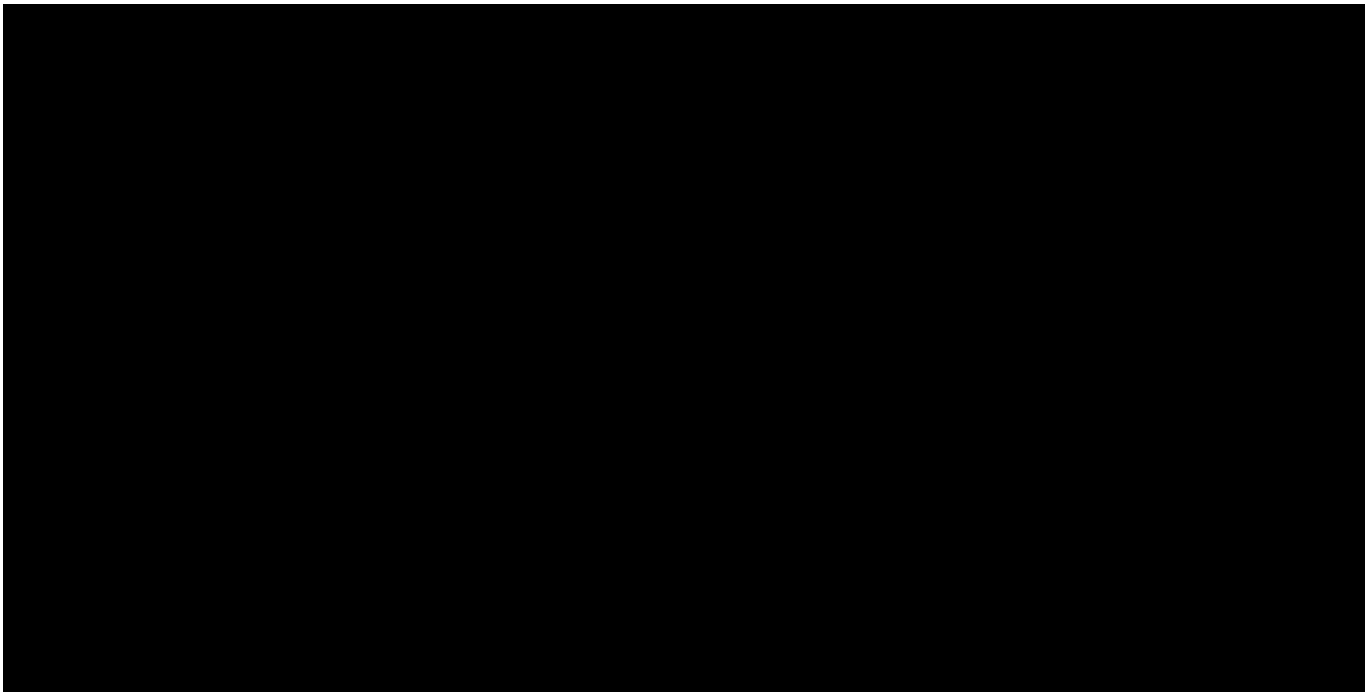
Comparison between the treatment groups will be performed for the continuous change from baseline variable [redacted] for each defined time point separately, [redacted].

The [redacted] are described in section 10.1.3.

10.1.3. General Multiple Imputation Approach

The primary analysis approach for mRS and NIHSS efficacy endpoints will consider the multiple imputation (MI) of missing data [redacted]

[redacted]



[redacted]

10.1.4. Supportive analyses:

The main analysis will be repeated on the PP and Completers populations as supportive analyses.

10.2. Further Efficacy Endpoints and Analysis

10.2.1 Occurrence of recurrent stroke within 90 days after the 1st IP:

The number and percentage of subjects who have a recurrent stroke within 90 days after the 1st IP will be presented by treatment group on the observed ITT. The difference of the proportions between the treatment groups with the corresponding 95% CIs will be presented. [redacted]

10.2.2. Montreal Cognitive Assessment (MoCA)

The MoCA total score and subscale will be summarized [redacted]

10.2.3. Change of infarct volume [redacted] from Baseline by MRI/CTP

The absolute and percentage change from baseline of infarct volume in MRI or CTP examination will be presented [redacted] by treatment group on observed ITT. Comparisons between treatments will be performed on observed ITT [redacted]

10.2.4. The infarct volume [redacted] after the 1st IP by MRI/CTP [redacted]

A comparison between the treatment group [redacted]

10.2.5. Change of hypoperfusion lesion [redacted] from Baseline

The absolute and percentage changes from baseline in hypoperfusion lesion in perfusion-weight imaging MRI or CTP will be summarized [redacted]

10.2.6. Proportion of subjects with 90% reduction in hypoperfusion lesion [redacted] from Baseline:

The number and percentage of subjects showing 90% reduction in hypoperfusion lesion [redacted] will be summarized by treatment group. The difference of the proportions between the treatment groups and the corresponding 95% CIs will be presented. Comparisons between treatment groups will be made on the observed data using the Chi-square test [redacted].

[redacted]

11. Safety

Safety analyses will be performed on the Safety population.

Safety will be assessed based on the incidence of AEs and changes in laboratory results, vital signs, and ECG parameters. For repeated safety assessments collected at scheduled time points, the last non-missing pre-dose value will be used as baseline, and the first non-missing value at each post-dose time points will be used in the analyses. However, all pre- and post-dose assessments including repeat assessments will be presented in data listings. Data collected at unscheduled visits will be included in data listings but will not be considered for analyses.

All safety summaries and analyses will be performed using observed data on the Safety population without imputation of any missing safety data.

11.1. Primary endpoint

Proportion of subjects with AEs, judged to be probably or definitely related to the IP within 90 days after the 1st IP.

The number and percentage of subjects with AEs, judged to be probably or definitely related to the IP within 90 days after the 1st IP will be presented by treatment group on the Safety population. The difference of the proportions between the treatment groups with the corresponding exact 95% Clopper Pearson CIs will be presented. [redacted]

11.2. Secondary safety endpoints

The occurrence of sICH and aICH [redacted] after the 1st IP will be assessed as part of the bleeding assessment.

- [redacted]
- [redacted]

A subject listing of bleeding assessment will be provided.

11.2.1. Occurrence of sICH [redacted] after the 1st IP

The number and percentage of subjects with sIC [redacted] after the 1st IP will be presented by treatment group and overall on the Safety population, and additionally within [redacted]

11.2.2. Occurrence of aICH [redacted] after the 1st IP

The number and percentage of subjects with aICH [redacted] after the 1st IP will be presented by treatment group and overall on the Safety population, and additionally within [redacted].

11.2.3. Occurrence of mortality due to any reason within 90 days after the 1st IP

The number and percentage of subjects who have died because of any reason within 90 days after the 1st IP will be presented by treatment group and overall for the Safety population [redacted].

11.2.4. Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present on or after the 1st IP administration [redacted], worsens during the study, regardless of the suspected cause of the event. AEs are defined as Treatment-emergent adverse events (TEAEs) in the SAP and TLFs.

An SAE is any untoward medical occurrence, in the view of either the Investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE.

Also, Related TEAE is an any event deemed possibly, probably or definitely related to treatment.

All AEs will be coded using the actual version of MedDRA dictionary to provide the system organ class (SOC) and preferred term (PT). Duration of the adverse event (AE) will be calculated and presented in days. Duration of the AE is defined as (AE end date – AE start date) + 1.

The number and percentage of subjects as well as number of events will be presented for TEAE summaries. An overall summary of TEAEs including the following categories will be presented:

- at least one TEAE
- at least one serious TEAE
- at least one related TEAE
- at least one TEAE leading to study drug withdrawal
- at least one TEAE with fatal outcome

A summary table of TEAEs by SOC and PT will be presented. Multiple instances of the TEAE in each SOC and multiple occurrences of the same PT are counted only once per subject. The denominator used for calculating the percentages will be the total number of subjects included in the safety population.

In addition, for each of the following, a summary of TEAEs will be produced at the subject level:

- Serious TEAEs by SOC and PT
- TEAEs by worst intensity by SOC, PT
- TEAEs by maximum relationship by SOC, PT
- TEAEs leading to study drug withdrawal

All AEs for each subject, including multiple occurrences of the same event, will be presented in full in a comprehensive listing sorted by subject number.

11.2.5. Laboratory Evaluations

The following laboratory tests at local laboratories will be performed at designated visits (See **Table 1**: Schedule of Assessments for timing and frequency):

[redacted]

For numeric laboratory results with a preceding '<' or '>', the sign would be ignored and the numeral alone would be considered as the result for summarizing purposes. The listing would, however, display the result as captured in the database.

[redacted]

Summary tables with actual and change from baseline values will be presented for hematology, serum chemistry and coagulation parameters, [redacted]

[redacted]

All laboratory data will be listed. Abnormal laboratory values will also be presented in separate listings.

11.2.6. Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature) will be summarized descriptively by parameter and visit. Similarly, changes from baseline will be summarized. Shift table will be presented at each post-baseline visit showing the number and percentage of subjects with normal, abnormal NCS or abnormal CS at baseline and post-baseline visit, where available. Vital signs data will be listed.

11.2.7. Electrocardiogram (ECG)

[redacted] eported and change from baseline values will be summarized by parameter and visit. Shift table for overall ECG interpretation will be presented at each post-baseline visit showing the number and percentage of subjects with normal, abnormal NCS or abnormal CS at baseline and post-baseline visits. ECG results along with abnormalities will be listed.

ECG parameters include heart rate, PR interval, and QT, QT correction Bazett formula (QTcB), QT correction Fridericia formula (QTcF) and a combination of the Q wave, R wave and S wave (QRS) intervals will be presented by normal, abnormal NCS or abnormal CS at each visit in listing.

11.2.8. Physical and Neurological Examination

[redacted]

[redacted]

A separate listing reporting the status, date of assessment, results and abnormal findings for each body system will be provided for physical examination.

A listing with neurological examination findings will also be provided.

12. Interim Analyses

No interim analysis is planned for this study.

13. Data Safety Monitoring Board (DSMB)

An independent DSMB will be established to assess all data (including imaging data) of LT3001 drug product or placebo treatment. The DSMB will review safety and efficacy data when thirtieth treated subjects have completed study procedures on Day 7 or terminated the study prior to Day 7. The DSMB will meet after the data presentation and will issue recommendations relating to safety and study conduct.

[redacted]

The DSMB TLFs will be a subset of the TLFs planned for final analysis. Refer to Sections 18, 19 and 20 for list of TLFs.

14. Changes from Analysis Planned in Protocol

Any changes to planned analyses, if applicable, will be cited in CSR along with the rationale for the change.

15. Reference List

1. Chuang-Stein C. Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal 1992; 26(1): 77-84.

2. Chuang-Stein C. Some issues concerning the normalization of laboratory data based on reference ranges. Drug Information Journal 2001; 35(1): 153-156.

16. Programming Considerations

All statistical computations and construction of tables, listings and figures will be performed using SAS® for Windows Version 9.4 or higher (SAS® Institute Inc., Cary, NC, USA), running on a Windows Server 2012 R2 Standard operating system.

The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

SDTM datasets will be created from the clinical database and external data, following the Study Data Tabulation Model Implementation Guide Version 3.2. Analysis will be based on ADaM datasets created from the SDTM datasets.

The below programming considerations will be followed unless already specified in the above text.

16.1. General Considerations

- One SAS program may create several outputs.
- Each output will be stored in a separate file
- Output files will be delivered in RTF format.
- Numbering of TLFs will follow International Conference on Harmonisation (ICH) E3 guidance.

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TLFs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for TLFs will have a minimum blank 1-inch margin on all 4 sides. No headers or footers will be present in this area.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified. Colours may be used in figures.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).

- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers

All outputs should have the Sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures will be internally paginated in relation to total length (i.e., page number will appear sequentially as “Page n of N”, where N is the total number of pages in the table). All outputs will have the following header at the top of each page:

Lumosa Therapeutics Co, Ltd. DSMB/Dry Run/Draft Run/Final Run
Protocol LT3001-205 Page n of N

16.2.3. Display Titles

Each TLF will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be followed. A decimal system (x.y and x.y.z) is used to identify TLFs with related contents. The title is centered and the study population is identified immediately following the title and enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Study Population)

16.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

- For numeric variables, include ‘unit’ in column or row heading when appropriate.

- Analysis population sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;
- Whole numbers (e.g., counts) will be right-justified; and
- Numbers containing fractional portions will be decimal aligned.

16.2.5.2. *Table Conventions*

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the minimum and maximum category are presented in the table, even if n=0 in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	3
moderate	8
severe	0

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- The same convention will be followed for data where categories are not ordered but are pre-specified on the CRF (e.g., Reasons for Discontinuation from the Study, Race, Ethnicity, etc.); thus, all possible responses available on the CRF will be presented in the table even if there are one or more categories with n = 0.
- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values will be output in the format: '0.xxx', where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then it will be presented as <0.0001. A p-value returned as >0.999 will be presented as >0.999.

- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8), 13 (5.4)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as '-'.

- Unless otherwise noted, the percentage of subjects will be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. Details about the selection of denominator will be described in footnotes or programming notes, as necessary.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, the subheading followed by '(cont)' will be printed at the top of each subsequent page. The overall summary statistics for the subheading will only be output on the first relevant page.

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups, subject number, visit/collection day, and visit/collection time.

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'N/A', with the footnote 'N/A = not applicable', whichever is appropriate.

- Dates will be printed in SAS DATE9.format ('DDMMMYYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'N/A', unless otherwise specified.
- All observed time values will be presented using a 24-hour clock HH:MM:SS or HH:MM format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the TLF. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when mutiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and the date the program was run (i.e., 'Program: myprogram.sas Date generated: ddMMMyyyy').

17. Quality Control

SAS programs are developed to produce outputs such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted]

[redacted] SAS Programming and Vaidation Plan describes the quality control procedures that are performed for all SAS programs and outputs. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the outputs by checking for their logic, efficiency and commenting and by review of the produced output.

18. Index of Tables

[redacted]

[redacted]

19. Index of Figures

Header	Figure Number	Name	Analysis Set
14.		FIGURES	
*	14.1.1.2	Subject Disposition	Enrolled Population
*	14.2.1.5.1	Modified Rankin Scale (mRS) [redacted]	ITT Population
*	14.2.1.5.2	Modified Rankin Scale (mRS) [redacted]	ITT Population
	14.2.1.5.3	Proportion of Subjects with mRS Score of 0-1 [redacted]	ITT Population
	14.2.2.5.1	NIHSS [redacted]	ITT Population
	14.2.2.5.2	[redacted]	ITT Population
	14.2.2.5.3	NIHSS [redacted]	ITT Population
	14.2.5.1.3	[redacted]	ITT Population

20. Index of Listings

[redacted]

21. Shells

Mock shells for tables, listings and figures will be created in a separate document as an attachment to the SAP which may be updated, revised and finalized separately from the SAP.

22. Appendices

N/A