Statistical Analysis Plan

Sponsor Name: Lumosa Therapeutics Co, Ltd

Protocol Number: LT3001-201
Protocol Title: Protocol Title: A Phase IIa, Double-Blind, Single Dose, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, and Potential Efficacy of LT3001 Drug Product in Subjects with Acute Ischemic Stroke (AIS)

Protocol Version and Date: Version 2.1 17 Feb 2020

[redacted]

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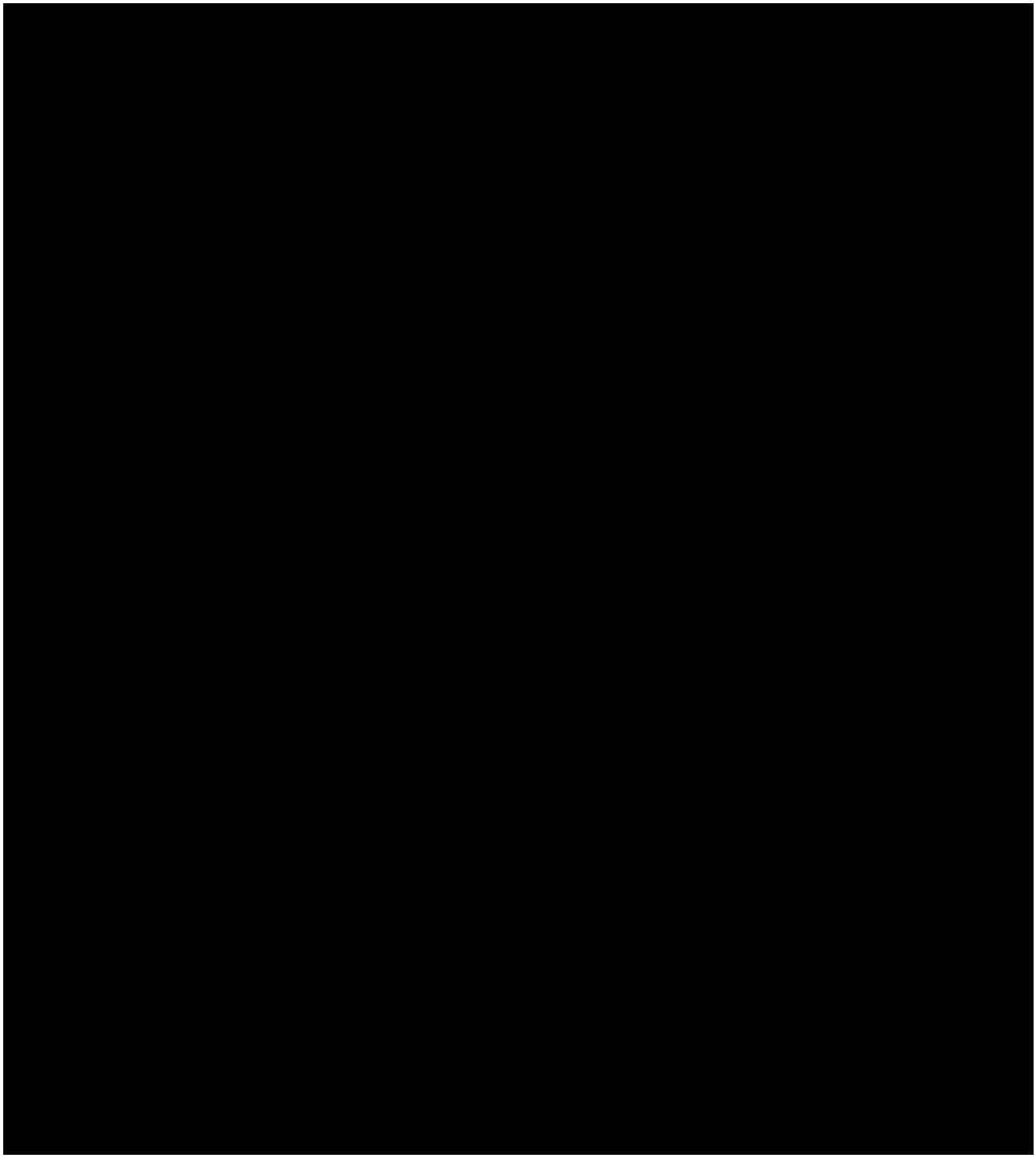
Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
V1.0	06-Mar-2020	[redacted]	Initial Release Version
V2.0	23-Mar-2021	[redacted]	Clarify determination of sample size Update analysis for secondary endpoints

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



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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
AIS	Acute Ischemic Stroke
AUC	area under the concentration-time curve
AUC_{0-t}	AUC from time zero to the time of the last quantifiable concentration
AUC_{inf}	AUC from time zero to infinity
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CL	Total Body Clearance (of Drug from Plasma)
C_{max}	Maximum Plasma Concentration
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ICF	Informed Consent Form
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
OR	Observational Research
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
sICH	Symptomatic Intracranial Hemorrhage

Abbreviation	Description
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, Listings
t_{max}	time to reach C_{max}
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

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

2.2. Timings of Analyses

The primary analysis of safety, efficacy, and pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the main phase of the study. Unless otherwise specified, the analysis includes all data collected in the database through the time of the database lock.

[redacted]

3. Study Objectives

3.1. Primary Objective

To determine the safety of a single dose [redacted] of LT3001 drug product administered intravenously (IV) in subjects with acute ischemic stroke (AIS).

3.2. Secondary Objective(s)

a)To determine the tolerability of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS.

b)To determine the potential efficacy of a single dose [redacted] of LT3001 drug product administered IV in subjects with AIS.

[redacted]

3.3. Brief Description

This is a multicenter, double-blind, single-dose, randomized, and placebo-controlled prospective Phase IIa clinical study, designed to evaluate LT3001 drug product versus placebo/control in subjects with AIS.

There is only one dose of LT3001 drug product [redacted]. [redacted] Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo. Each eligible subject will receive a single dose of LT3001 drug product or placebo within 24 hours after stroke symptoms onset. LT3001 drug product or placebo will be administered via a [redacted]n IV infusion. The infusion will be stopped if an Serious Adverse Event (SAE) occurs during infusion.

[redacted]

The participation for each subject is approximately 92 days from the screening visit (Visit 1) to the last visit. The study design is illustrated in Figure 1.

[redacted]

3.4. Subject Selection

3.4.1. Inclusion Criteria

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

1. Subject or subject's legal representative consented to participation by signing the informed consent form (ICF) after receiving full information about the study.
2. Subject is aged 18 to 90 years, inclusive, at the time of Screening[redacted].
3. Subject has a NIHSS of 4 to 30.
4. Subject has a clinical diagnosis of AIS within 24 hours after stroke symptoms onset.
5. [redacted]
6. Subject is able to receive the investigational product (IP) within 24 hours after stroke symptoms onset.
7. Subjects are women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP, are able and willing to use at least 1 highly effective method of contraception during the study until 3 months after dosing of IP.

3.4.2. Exclusion Criteria

Individuals meeting any of the following criteria at Screening[redacted] or Baseline are ineligible to participate in this study:

1. Subject has been treated with rtPA and/or endovascular thrombectomy (EVT) during the current AIS.
2. Subject has a pre-stroke disability that requires help for activities of daily living[redacted].
3. Subject has imaging evidence of acute intracranial hemorrhage, intraparenchymal tumor, arteriovenous malformations, other central nervous system lesions that could increase the risk of bleeding, or aneurysm requiring treatment.
4. [redacted]
5. Subject has symptoms of suspected subarachnoid hemorrhage[redacted].
6. Subject has generalized seizure[redacted].
7. Subject has current uncontrolled hypertension [redacted].
8. Subject has International Normalized Ratio (INR) >1.7, abnormal activated partial thromboplastin time (aPTT) or platelet count <100,000/mm3.
9. Subject has blood glucose concentration <50 mg/dL or >400 mg/dL.

10. Subject is lactating, pregnant (pregnancy test required for all female subjects), or planning to become pregnant during the study.

11. Subject has received anticoagulants within 48 hours prior to treatment, e.g., direct oral anticoagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban), low molecular weight heparin (e.g., enoxaparin), fondaparinux.

12. Subject has received oral dual antiplatelet therapy and glycoprotein (GP) IIb/IIIa inhibitors within 48 hours prior to treatment.

13. Subject has had prior AIS, myocardial infarction, or serious head trauma within 90 days of Screening[redacted].

14. Subject has history of ICH within 90 days of Screening[redacted].

15. Subject has had any major surgery within 90 days of Screening[redacted], e.g., intracranial or intraspinal surgery, coronary artery bypass graft, obstetrical delivery, organ biopsy.

16. Subject with bleeding event within 21 days of Screening [redacted], e.g., gastrointestinal or hemorrhage.

17. Subject has puncture of noncompressible vessels within 7 days of Screening[redacted].

18. Subject has severe hepatic, renal, and/or active infectious disease at Screening[redacted].

19. Subject has participated in another investigational study and received IP within 30 days of Screening[redacted] or 5 half-lives (whichever is longer).

20. In the opinion of the Investigator, the subject is not appropriate for the study for any other reason.

3.5. Determination of Sample Size

Approximately 24 eligible subjects will be randomized 2:1 to LT3001 drug product or placebo. It is planned to have 24 subjects randomized, after which enrollment will stop.

3.6. Treatment Assignment & 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 study treatment (LT3001 drug product or placebo), 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 2:1.

At Screening[redacted] the Subject Number. This number will be associated with the subject throughout the study.[redacted]

[redacted]

The subjects will be centrally randomized at a study level. The treatment assignment will be determined by a randomization list prepared by the biostatistics group[redacted].

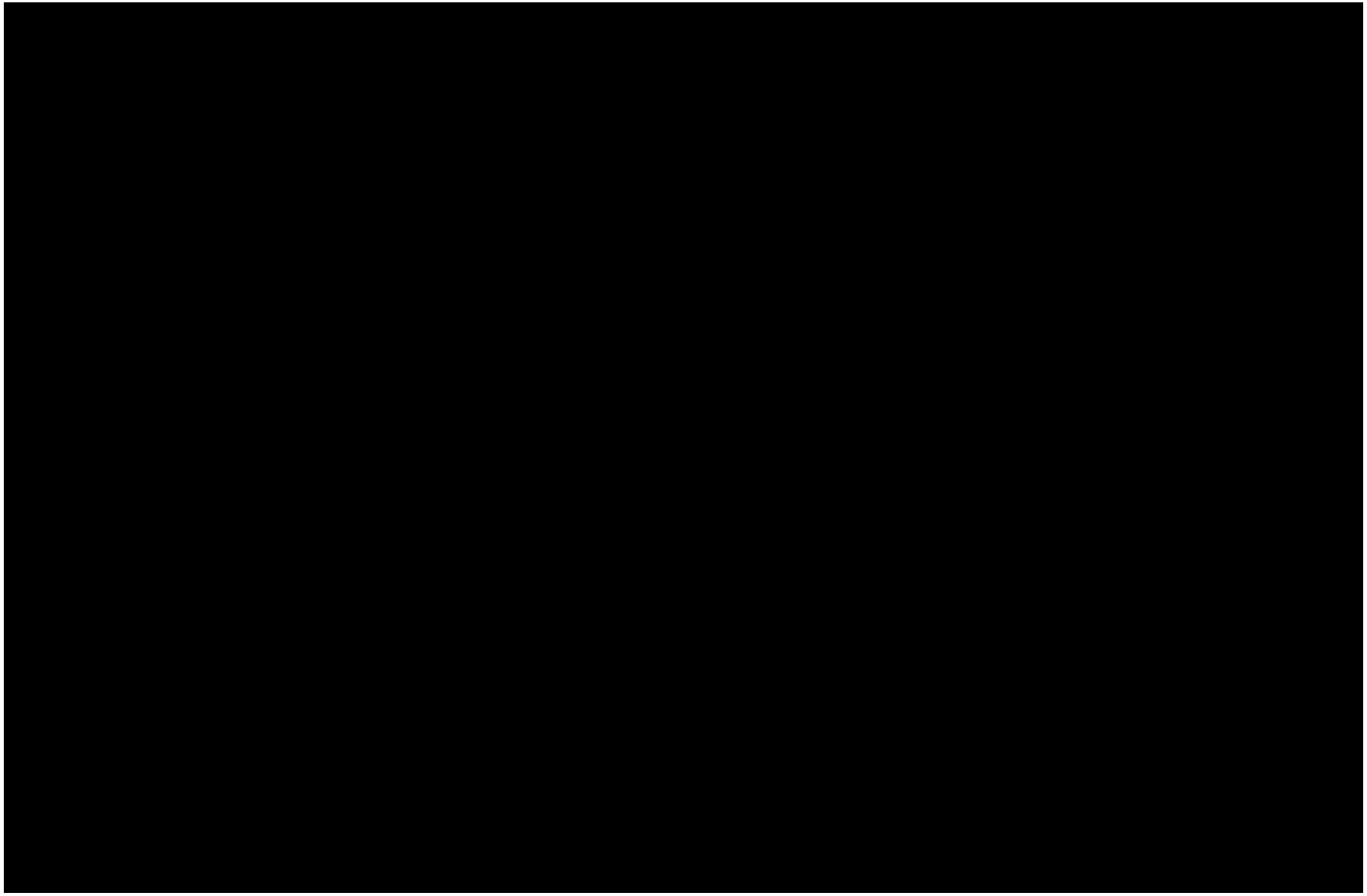
According to the randomization schedule as indicated in the Schedule of Assessments and in accordance with the pharmacy manual, [redacted] the Investigator or designee at the study site will be responsible to provide the Subject Number, [redacted] to the unblinded pharmacist or designee for the calculation of study treatment dosage. The unblinded pharmacist or designee will further confirm the Subject Number, [redacted] and the study treatment [redacted] and the dosage calculation, after which he/she will prepare the study treatment. Prepared study treatments will be identical in appearance and labeled in a blinded manner. Information included on the label includes the Protocol Number, Subject Number, Randomization Number, etc. No other study site personnel, subjects, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an Investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Medical Monitor must be obtained in such instances.

The Investigator must make every effort to contact the Medical Monitor prior to unblinding a subject. In the rare event that contact with the Medical Monitor is not possible prior to unblinding, the Investigator reserves the right to unblind in a true emergency, where subject safety is at immediate risk. The unblinding and its cause will also be documented in the electronic Case Report Form (eCRF) [redacted].

3.7. Administration of Study Medication

Subjects randomized to LT3001drug product will receive a single dose of LT3001 drug product [redacted] administered as a [redacted] IV infusion. Subjects randomized to placebo will receive placebo as a [redacted] IV infusion as well.

3.8. Study Procedures and Flowchart



[redacted]

4. Endpoints

4.1. Primary Endpoint

The primary endpoint of this study is the occurrence of symptomatic intracranial hemorrhage (sICH) within 36 hours after dosing -- clinical deterioration defined as an increase in the National Institute of Health Stroke Scale (NIHSS) of 4 points or more AND confirmed by computed tomography (CT)- or magnetic resonance imaging (MRI)- documented.

4.2. Secondary Endpoints

The secondary efficacy and safety endpoints are as follows:

- The occurrence of sICH [redacted].
- The occurrence of asymptomatic intracranial hemorrhage (ICH) [redacted].
- The occurrence of mortality due to intracerebral or other major bleeding complications [redacted].
- The occurrence of mortality due to any reason [redacted].
- The number and severity of AEs [redacted].
- The number of subjects with AEs [redacted].
- The occurrence of recurrent stroke [redacted].
- Functional outcome

  - The frequency and percentage of subjects with each grade on modified Rankin Scale (mRS) [redacted].

  - The frequency and percentage of subjects with mRS≤2 [redacted].
- Neurological outcome

  - Absolute change in NIHSS [redacted].

  - The proportion of subjects with NIHSS ≤2 [redacted].

[redacted]

5. Analysis Sets

5.1. Enrolled Population

The Enrolled Population will include all individuals who sign the ICF. Unless specified otherwise, this population will be used for subject listings and for summaries of subject disposition.

5.2. Safety Population

The Safety Population will include 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.

5.3. Intent-to-Treat (ITT) Population

The ITT population will include 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.

5.4. [redacted]

[redacted]

5.5. Per-Protocol (PP) Population

The PP population will comprise all ITT subjects who complete study procedures through Day 90 without a major protocol deviation potentially impacting efficacy measurements. The PP population will also be used for the analysis of efficacy.

5.6. [redacted]

[redacted]

5.7. Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. The Sponsor, or its authorized designee, will report protocol deviations to the institutional review board/independent ethics committee and in accordance with applicable regulatory authority.

6. General Aspects for Statistical Analysis

6.1. General Methods

- The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided.
- Summary statistics will be presented by treatment group and overall. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation (SD), 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.
- The dictionary (MedDRA and WHODrug) version used will be specified in corresponding data display footnote.
- Unless otherwise stated, all listings will include all subjects in ITT Population, and all listings will be sorted by subject ID, treatment, and assessment date/time.
- For all percentage calculations, the denominator will be the number of subjects in the relevant population, unless otherwise stated.
- Only data from protocol scheduled visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables but will be included in the listings.

6.2. Key Definitions

- Baseline Value: unless otherwise defined, the last non-missing assessment prior to first dosing will serve as baseline value.

  Unknown, Not Done, Not Applicable and other classifications of missing data will not be considered when calculating baseline observations. However, valid categorical observations will be considered for baseline calculations.

- Study day: number of days since the study drug administration. Study day is calculated using the formula: Study day = date of assessment - date of first dosing

6.3. Missing Data

Missing data will not be estimated and/or imputed in any way. Adverse events(AEs) with missing onset dates will be included as treatment-emergent.

6.4. Visit Windows

Please refer to section 3.8. Study Procedures and Flowchart for visit windows.

7. Demographic, Other Baseline Characteristics and Medication

7.1. Subject Disposition and Withdrawals

Subject disposition will be summarized and listed.

The number and percentage of subjects in each population, completed and discontinued the study, together with the reasons for discontinuation (unacceptable toxicity or AE, subject withdrawal of consent, intercurrent illness, general or specific changes in the subject's condition, subject fails to adhere to the protocol requirements, lost to follow-up, pregnancy, study terminated, other) will be presented.

7.2. Demographic and Other Baseline Characteristics

Demographic data and baseline characteristics will be summarized and listed for ITT Population.

Demographic data including age (years), sex (male, female), child bearing potential (yes, no), race (asian, black or african American, white, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, other), ethnicity (Hispanic or Latino, Asian, Russian, Mixed Ethnicity, Not Reported, Unknown, Other) collected at study Screening will be summarized descriptively. Likewise, baseline characteristics including weight (kg) will also be summarized.

Age = (inform consent date - date of birth + 1) / 365.25 and truncated to complete years.

Weight (in kg) = weight (in lbs) * 0.4536

7.3. Medical History and Concomitant Diseases

Medical history and concomitant illnesses will be recorded at Screening[redacted]. Medical history and concomitant illnesses will be coded with Medical Dictionary for Regulatory Activities (MedDRA) dictionary and summarized by system organ class (SOC) and preferred term (PT) based on the ITT Population. Medical history will also include alcohol consumption and smoking history, if applicable.

Medical history will be summarized by SOC and PT for ITT Population.

Subject listing of medical history, alcohol consumption and smoking history will be provided.

7.4. Other Baseline Characteristics

Other baseline characteristics including pregnancy test will be listed only.

7.5. Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug). Prior and concomitant medications will be listed for ITT Population with the classification (prior and/or concomitant) identified.

7.5.1. Prior Medication

All medications stopped before first dosing will be considered as prior medications.

Prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) and PT for ITT Population and will be displayed in data listing.

7.5.2. Concomitant Medication

All medications stopped on or after first dosing will be considered as concomitant medications. Medications with missing stop date will be considered as concomitant medication.

Concomitant medications will be summarized by ATC and PT for ITT Population. Subjects who take the same medication (in terms of the PT) more than once will only be counted once for that medication.

Subject listing of concomitant medications will be provided.

7.5.3. Other Therapies

Surgical procedures will be captured in CRF.

Listing of surgical procedures will be provided.

8. Efficacy

Efficacy analyses will be conducted for the ITT population, evaluable population PP population and safety population. All statistical tests for secondary efficacy endpoints will be two-sided with α = 0.05.

8.1. Primary Efficacy Endpoint and Analysis

There will be no primary efficacy endpoint or analysis carried out for this study.

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Occurrence of Recurrent Stroke

The frequency and proportion of subjects who have a recurrent stroke will be reported by treatment group and overall.

8.2.2.

8.2.3. National Institute of Health Stroke Scale

The NIHSS is a standardized method to measure the level of impairment caused by a stroke and was developed by the National Institutes of Health. The NIHSS allows for objective comparison of efficacy across different treatments for stroke, including rehabilitation interventions.

The NIHSS is a brief and reliable stroke deficit assessment scale composed of 11 components and the numbers of grades for each component vary; however, for each component, a score of 0 is defined as normal while higher scores indicate increasing severity of impairment. The total score ranges from 0 (no deficit) to 42 (dead).

The total score and absolute change from baseline will be summarized . Data missing on the visit level will not be imputed, and no statistical inferences will be performed.

The proportion of subjects with NIHSS of 0-2 points will be presented by treatment group

8.2.4. Modified Rankin Scale

The mRS is a global disability scale that measures the overall independence of stroke patients. The level of disability following a stroke is assessed via a 7-point scale (0-6), where 0 is no limitation or symptom and 6 is death. It is expected that all subjects will have a baseline of 1 (no significant disabilities despite symptoms) up to 5 (severe disability, bedridden, incontinent, and requiring constant nursing care and attention).

[redacted]

For each shift table, missing values will not be included, so the denominator for percentages will be the number of subjects with a mRS score at both Baseline and the visit. No missing values will be imputed and no statistical inference will be performed on the shift tables.

The frequency and percentage of subjects with each grade on the mRS [redacted] will be presented by treatment group.

The frequency and percentage of subjects who achieve a score of 0-2 on the mRS [redacted] will be presented by treatment group. Comparisons by treatment group will be made [redacted]. No formal adjustment for multiple comparisons will be made.

The proportion of subjects with an increase in the mRS of ≥3 points, increase of 2 points, increase of 1 point, no increase/decrease, decrease of 1 point , decrease of 2 points and decrease ≥3 points from Baseline will be presented by treatment group [redacted]. No formal adjustment for multiple comparisons will be made.

[redacted]

[redacted]

[redacted]

[redacted]

10. Safety

10.1. Extent of Exposure

This is a single-dose study. A listing will be provided for IP administration.

10.2. Treatment Compliance

Not applicable to this study.

10.3. Adverse Events / Adverse Drug Reactions

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at Screening [redacted] worsens during the study, regardless of the suspected cause of the event.

Treatment-emergent AEs (TEAEs) are defined as events with onset dates on or after the start of the IP. AEs with missing onset dates will also be included as TEAEs.

AE will be coded with Medical Dictionary for Regulatory Activities (MedDRA) in place at the time of analysis and grouped by SOC and PT.

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.

All AEs will be included in data listings and listed by subject, along with information regarding onset, duration, relationship and severity to investigational product, action taken with investigational product, treatment of event, and outcome.

Drug-related AEs are defined as AEs with possible, probable, or definite relationship to study drug.

AEs are classified as mild, moderate and severe in intensity.

All AE summaries will be restricted to TEAEs only.

The number and percentage of subjects as well as number of events will be presented for TEAE summaries. For summaries by SOC, PT, and maximum intensity, a subject will be counted once at the highest intensity for which the event occurred at the SOC level and the highest intensity for each unique PT within that SOC level. Summaries by relationship to study drug will be handled similar to the summaries by intensity.

The following summaries will be provided.

- Overall summary of TEAEs by treatment group and overall
- TEAEs within 90 days by SOC and PT
- TEAEs within 90 days by SOC, PT and maximum intensity
- TEAEs within 90 days by SOC, PT and maximum relationship to study drug
- Drug-related TEAEs within 90 days by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs leading to study discontinuation by SOC and PT

All AEs will be listed with TEAE identified.

10.4. Laboratory Evaluations

Laboratory data including hematology, coagulation/clotting and clinical biochemistry will be summarized descriptively at each time point, [redacted] by treatment, using mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range. [redacted]

Subject listing of laboratory tests will be provided. Abnormal laboratory values will be flagged and will be identified in the listings. The abnormal laboratory values will also be presented in the listings.

[redacted]

[redacted]

10.5. Vital Signs

Vital signs includes body temperature (℃), pulse rate (beats/min), respiration rate (breaths rate/min), systolic and diastolic blood pressure (mmHg). Body temperature (℃) and respiration rate (breaths rate/min) will be collected [redacted]. Pulse rate (beats/min) and systolic and diastolic blood pressure (mmHg) will be collected at Screening (Visit 1), Visit 2 (Day 0), Visit 2-PK (5 min, 10 min, 15 min, 30 min and 1 hours after dosing), Visit 3 (24 Hours), on Visit 4 (Day 7), Visit 5 (Day 30) and at ET.

Vital signs will be summarized at each time point by treatment, using mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range. Shift table (normal, abnormal NCS, abnormal CS) will also be provided at each time point by treatment.

Subject listing of vital signs will be provided. Subjects with abnormal vital signs interpretation will be presented in the listings.

10.6. Electrocardiogram (ECG)

12-lead ECG including Ventricular Heart Rate (bpm), PR interval (msec), QRS interval (msec), QT interval (msec), QTcF interval (msec), QTcB interval (msec) will be summarized descriptively [redacted], by treatment, using mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point. The overall ECG interpretation (normal, abnormal NCS, abnormal CS) will also be summarized by treatment at each timepoint.

Subject listing of 12-lead ECG will be provided. Subjects with abnormal ECG interpretation will be presented in the listings.

10.7. Physical Examination

A complete physical examination (head, eyes, ears, nose, and throat; heart; lungs; abdomen; skin; cervical and axillary lymph nodes; and neurological [mental status, cranial nerve functions, motor and sensory function, cerebellar function, speech, gait] and musculoskeletal systems) will be performed [redacted].

[redacted]

Symptom-driven, limited physical examinations and neurological examinations will be performed as clinically indicated [redacted].

Subject listings of physical examinations and neurological examinations will be provided. Subjects with abnormal interpretation will be presented in the listings.

10.8. Bleeding assessment

Th Bleeding assessment will be done by the Investigator or designee and categorized as sICH and asymptomatic ICH. The occurrence of sICH and asymptomatic ICH within 36 hours and 7 days after dosing will be recorded.

- [redacted]
- [redacted]

Subject listings of bleeding assessment will be provided.

10.9. Analysis of Primary Safety Endpoint

The frequency and proportion of symptomatic intracranial hemorrhage (sICH) within 36 hours of dosing will be reported by treatment group and overall. Comparisons by treatment group will be made [redacted] for the ITT [redacted].

10.10. Occurrence of sICH [redacted]

The frequency and proportion of sICH [redacted] will be reported by treatment group and overall. Symptomatic ICH will not be imputed for subjects missing either NIHSS score or CT/MRI examination so the denominator will be the number of subjects in whom sICH could be assessed. Comparisons of treatment group will be made [redacted]. No formal adjustment for multiple comparisons will be made. [redacted]

10.11. Occurrence of Asymptomatic ICH [redacted]

The frequency and proportion of asymptomatic ICH [redacted] will be reported by treatment group and overall. Intracranial hemorrhage will not be imputed for subjects missing either NIHSS score or CT/MRI examination at each visit so the denominator will be the number of subjects in whom ICH could be assessed. Comparisons of treatment group will be made [redacted]. No formal adjustment for multiple comparisons will be made. [redacted]

10.12. Occurrence of Mortality Due to Intracerebral or Other Major Bleeding Complications [redacted]

The frequency and proportion of subjects who have died due to intracerebral or other major bleeding complications [redacted] will be reported by treatment group and overall. Comparisons by treatment group will be made [redacted]

10.13. Occurrence of Mortality Due to Any Reason [redacted]

The frequency and proportion of subjects who have died due to any reason will be reported [redacted] by treatment group and overall. Comparisons of treatment group will be made [redacted] No formal adjustment for multiple comparisons will be made. [redacted]

10.14. Proportion of Subjects With NIHSS Change from Baseline

The proportion of subjects with an increase in the NIHSS of ≥4 points, increase of 1-3 points, no increase/decrease, decrease of 1-3 points and decrease ≥4 points from Baseline [redacted]. [redacted] No formal adjustment for multiple comparisons will be made.

11. Interim Analyses

No interim analyses are planned.

12. Changes from Analysis Planned in Protocol

- [redacted]

- Update definition of PP population from 'The PP population will comprise all ITT subjects who complete study procedures through Day 90 without a major protocol deviation.' to 'The PP population will comprise all ITT subjects who complete study procedures through Day 90 without a major protocol deviation potentially impacting efficacy measurements.'.

13. Reference List

1. ICH Guidance “E9 Statistical Principles for Clinical Trials.”

14. Programming Considerations

All tables, data listings, figures (TFLs), and statistical analyses will be generated using SAS® for Windows, Release 9.4 (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

14.1. General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in RTF format.
- Numbering of TFLs will follow ICH E3 guidance

14.2. Table, Listing, and Figure Format

14.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, 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 TFLs. 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., cm2, Cmax) 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.

14.2.2. Headers

- All output should have the following header at the top left of each page:
- Lumosa Therapeutics Protocol LT3001-201[redacted]

- Draft/Final Run <date>
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

14.2.3. Display Titles

- EachFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis set are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(ITT Analysis Set)

14.2.4. Column Headers

- Column headings are 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 set 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.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

14.2.5. Body of the Data Display

14.2.5.1. *General Conventions*

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

- Alphanumeric values are left-justified;

- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

14.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups 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
severe	0
moderate	8
mild	3

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%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups are included.
- An Unknown or Missing category are 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 are printed out to 1 more significant digit than the original values, and SDs are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

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

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Everyp-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. 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 should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of AE data are 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 PT), drugs (by ATC1 code), and AEs (by PT) are displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

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

14.2.5.3. *Listing Conventions*

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

- Missing data are 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 are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS 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

14.2.5.4. *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.

14.2.6. Footnotes

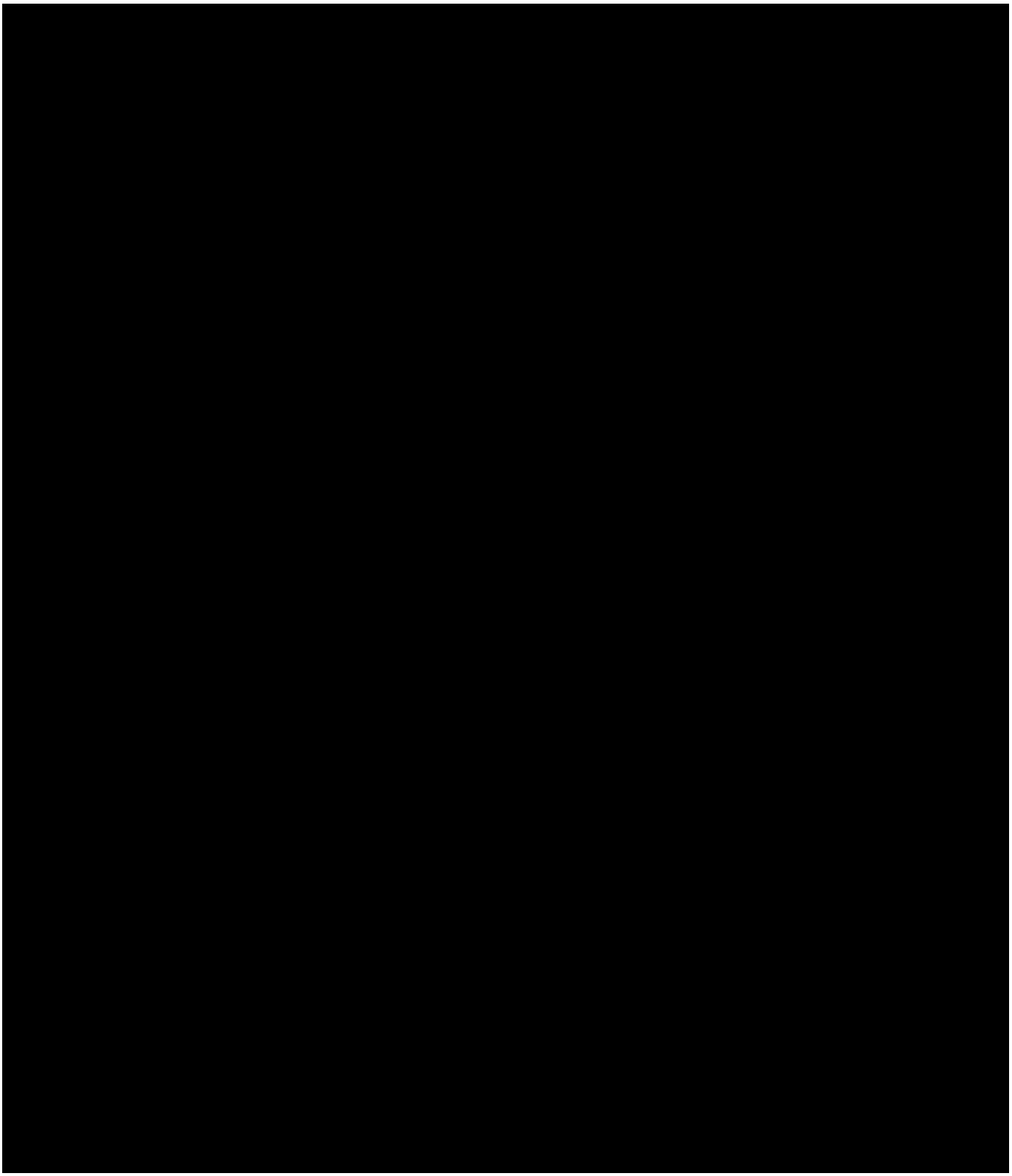
- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or listing. 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.
- 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, date the program was run, and the listing source (i.e., ‘Program : myprogram.sas Listing source: 16.x.y.z’).

15. Quality Control

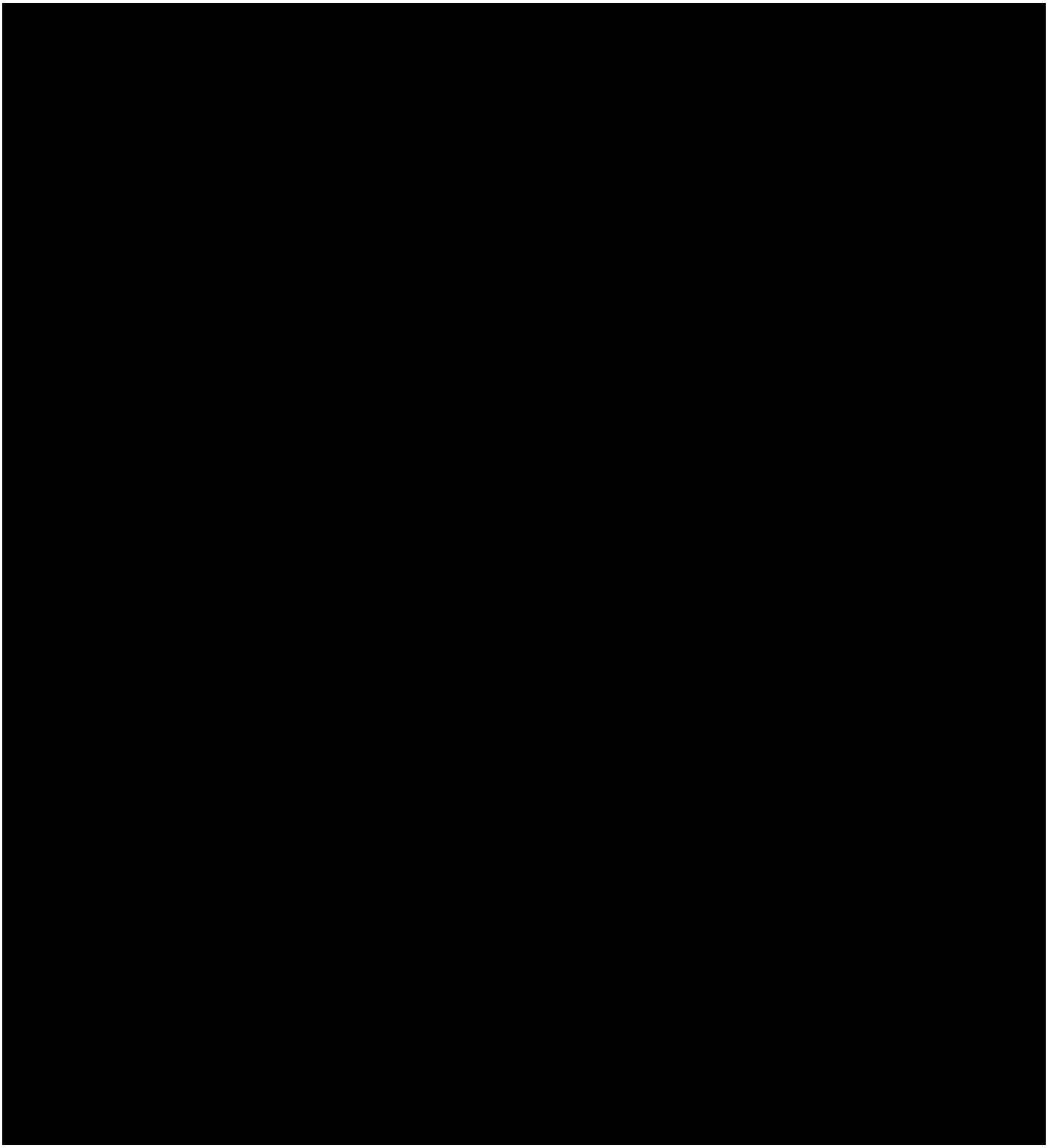
SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. [redacted]

[redacted] the QC procedures that are performed for all SAS programs and output. QC is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output."

16. Index of Tables

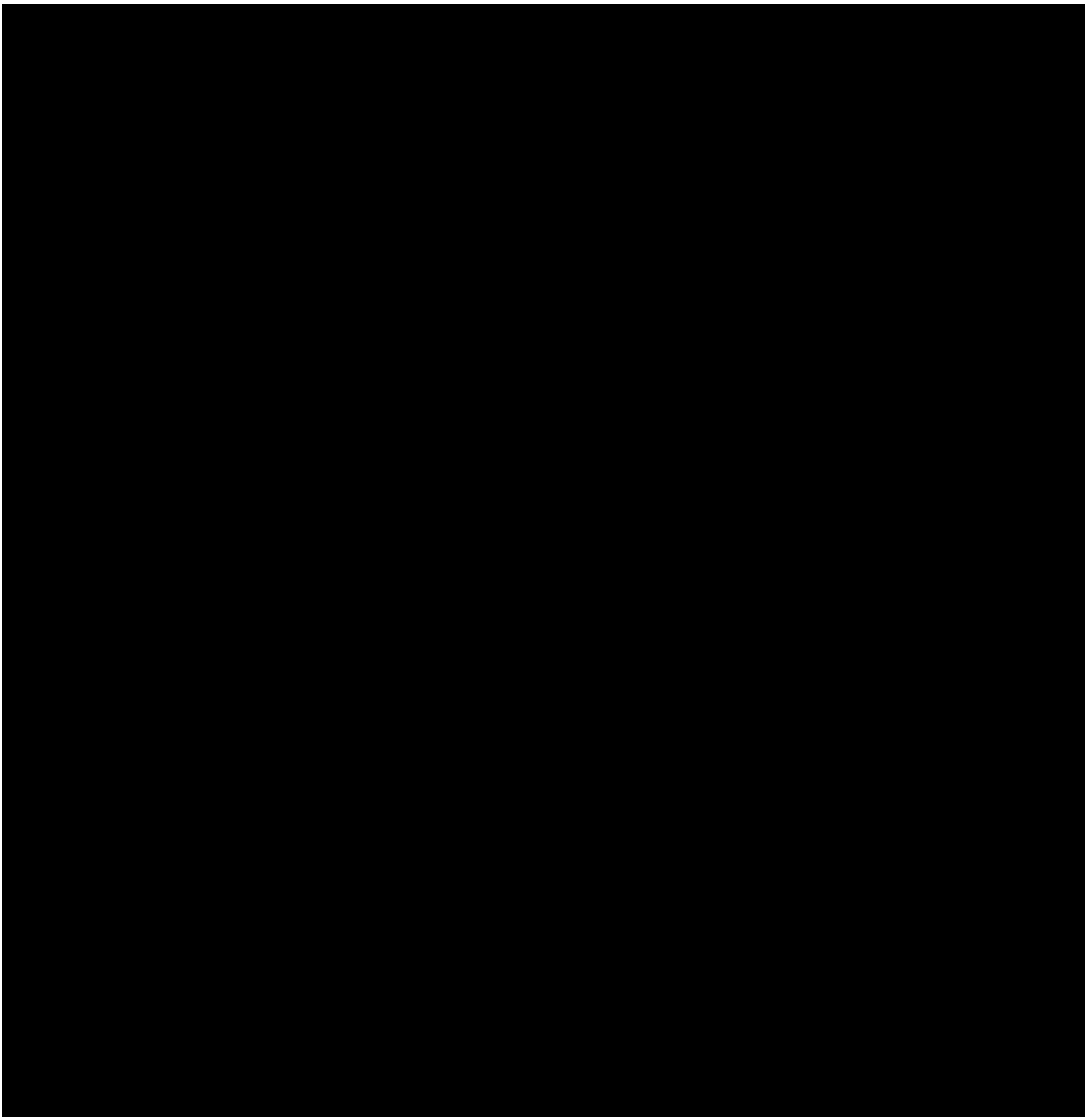


[redacted]



17. Index of Figures

18. Index of Listings



19. Shells

This table, figure and listing shells will in general be provided as a separate document.

20. Appendices

No appendics are available.